1. Results from the EU LiquiCaps study: a comparison between cases exposed to liquid laundry detergent and automatic dishwashing capsules


In 2015, a study on hazardous detergent mixtures contained in soluble packaging for single use (LiquiCaps study) was launched by the EU Commission to assess the effectiveness of the new safety measures on liquid laundry detergent capsules (LLDCs), implemented in June 2015 (Regulation No 1297/2014). Within the LiquiCaps study, cases of exposure to LLDCs and other liquid detergents in soluble capsules (OLDCs) were identified. The present contribution provides a comparison between cases exposed to different types of detergent capsules.

Methods: Detailed information on cases exposed to LLDCs and OLDCs between 1 August 2015 and 31 May 2016 were collected prospectively according to standardized procedures by the poison centers (PCs) of Utrecht, Milan, Dublin, Bratislava, Lisbon, and Göttingen. Distribution of cases by age (<1; 1–2; 3–4; ≥5 years) and severity of poisoning (none, low, moderate, high, according to the Poisoning Severity Score) for cases exposed to different types of capsule detergents were compared by using Pearson’s chi-squared test or Fisher’s exact test. A logistic regression model was used to measure the strength of the associations between detergent type and severity of poisoning by maximum likelihood estimates of the odds ratios (ORs) and related 95% confidence intervals (CIs), adjusted by age.

Results: A total of 882 cases of interest were identified, including 754 (75.9%) exposed to LLDCs, 123 (25.3%) to automatic dishwashing capsules (ADWCs), and 5 (0.5%) to other products (excluded). Distributions by age and severity of poisoning for cases exposed to LLDCs and ADWCs were different at a highly statistically significant level (p < 0.001, respectively). Age distribution was characterized as follows (LLDCs versus ADWCs): 5.8% versus 10.6% (<1 year), 51.7% versus 71.5% (1–2 years), 29.1% versus 6.5% (3–4 years), and 3.0 versus 9.8 (≥5 years). Among cases exposed to LLDCs, poisoning severity was none in 34.5%, low in 52.1%, moderate in 13.4%, high in one child aged <1 year who developed airway irritation and esophageal edema. Conversely, among cases exposed to ADWCs poisoning severity was none in 61.8%, low in 34.1%, and moderate in 4.1%. The odds of suffering moderate/high severity effects was four times higher for exposures to LLDCs in comparison to ADWCs (adjusted by age OR 4.5; 95% CI 1.6–12.6, p < 0.0001).

Conclusion: During the observation period, exposures to LLDCs continued to be more hazardous than those to ADWCs. Since both products contains highly hazardous ingredients, differences in formulation (ADWCs half liquid/half powder; LLDCs liquid) should be considered as main determinants of the reported findings.

2. Favorable acute toxicity profile of noscapine in children

Colette Degrandi, Jutta Trompetl, Andreas Vagt, Carola Seidel, Dagmar Prase, Claudia Zatloukal and Cornelia Reichert

In clinical use since 1960 as a centrally acting antitussive with no sedative or respiratory depressive properties. The maximal therapeutic dose for adults and children >12 years is 150 mg/day, for children 3–12 years 75 mg/day, and for children 0.5–3 years 37.5 mg/day divided in 3–6 doses. Noscapine seems to have a favorable side effect profile, but modern approval studies are lacking. The aim of the study was to determine the acute toxicity profile of noscapine in overdose, since available information is very limited.

Methods: Retrospective review of acute noscapine overdoses in children (<16 years) reported to six poison centres in Germany, Austria, and Switzerland. Included were cases with single-substance exposure, polysubstance exposure with co-ingestants of low toxicity (e.g., guaifenesin, plant extracts), sufficient evidence of exposure, a follow-up for at least 3 hours, and a high
Table 1. Age group, number of cases, dose, and severity of paediatric cases of noscapine ingestion reported to 6 poison centers in Germany, Austria and Switzerland.

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of cases</th>
<th>Dose (mg/kg)</th>
<th>Severity</th>
<th>Number of cases</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 y</td>
<td>12</td>
<td>4.5–45</td>
<td>No effect</td>
<td>11</td>
<td>0.7–7.5</td>
</tr>
<tr>
<td>&gt;1–5 y</td>
<td>47</td>
<td>7.5–250</td>
<td>Minor</td>
<td>37</td>
<td>0.5–19.2</td>
</tr>
<tr>
<td>6–13 y</td>
<td>11</td>
<td>108–200</td>
<td>Moderate</td>
<td>4</td>
<td>3.0–3.3</td>
</tr>
<tr>
<td>14–15 y</td>
<td>3</td>
<td>0</td>
<td>Minor</td>
<td>0</td>
<td>225–300</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
<td>–</td>
<td>Moderate</td>
<td>52</td>
<td>–</td>
</tr>
</tbody>
</table>

causality. Severity was graded according to the Poisoning Severity Score.

Results: Overall, 73 patients, 36 (49.3%) males, 33 (45.2%) females, 4 (5.4%) sex unknown; mean age 3.6 years (range 0.3–15 years), were included. The route of exposure was oral in 62 cases, and rectal in 11 cases (all children ≤5 years). No effects were reported in 52 cases, minor symptoms in 20 and moderate symptoms in one case. There were no severe cases, and no fatalities (Table 1). Minor signs consisted of mild gastrointestinal symptoms (n = 16), somnolence (n = 7), nervousness (n = 2), hypertension (n = 1), hypotension (n = 1), and tachycardia (n = 1). Moderate gastrointestinal symptoms (repeated vomiting, diarrhea) occurred in one case.

Conclusion: Overdose with noscapine up to 32 mg/kg in children is tolerated with no or only mild effects, apart from one case with moderate gastrointestinal symptoms. Therefore, observation at home seems reasonable after overdose of up to 32 mg/kg in children.

3. Toxicovigilance through social media: quantifying abuse-indicating information in Twitter data

Abeed Sarker, Graciela Gonzalez, Francis J. DeRoos, Lewis S. Nelson and Jeanmarie Perrone

Objective: The growing crisis of prescription medication (PM) abuse worldwide necessitates novel monitoring sources. Recent research suggests that social media may encapsulate an abundance of real-time information regarding PM abuse. We seek to validate the applicability of Twitter as a platform for monitoring PM abuse by quantifying the abuse information self-reported by users of different PMs and classes of PMs.

Methods: We collected data for 17 PMs belonging to four classes with known potential for abuse – opioids (5), benzodiazepines (4), atypical anti-psychotics (AAPs) (5), and stimulants (3) – from Twitter via its Streaming API, between April 2013 and February 2015. We used the medication trade and generic names, and their automatically generated common misspellings, as keywords for collection. Two annotators categorized a sample of English tweets from the collection into two classes, self-reported abuse and non-abuse, using established guidelines. Abuse-indicating tweets for each PM and class of PM were then quantified.

Results: Out of 13,966 tweets, 378 (2.71%) could not be categorized due to ambiguity. Of the 13,588 categorized tweets, 1967 (14%) indicated probable abuse. Stimulants had the highest volume of abuse-indicating posts (1199/1967; 61%), and the highest abuse to non-abuse ratio (21%). AAPs had the lowest ratio. Inter-annotator-agreement computed for 400 tweets showed substantial agreement (κ = 0.81). Table 1 summarizes the results.

Conclusion: Substantial amounts of self-reported abuse-indicating information were observed for each PM, suggesting that Twitter may serve as an important monitoring platform. Automated data categorization may enable continuous analysis of larger samples in near real time.

References


Table 1. Medication classes, generic names, volumes of Tweets annotated, and proportions of abuse-indicating tweets for individual and classes of medications.

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication</th>
<th>Abuse</th>
<th>Non-abuse</th>
<th>Total</th>
<th>Proportion (abuse to non-abuse ratio)</th>
<th>Class average for proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>Oxycodone</td>
<td>33</td>
<td>142</td>
<td>175</td>
<td>0.19</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
<td>4</td>
<td>181</td>
<td>185</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Hydrocodone</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>0.33</td>
<td>0.33</td>
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<tr>
<td></td>
<td>Tramadol</td>
<td>33</td>
<td>316</td>
<td>349</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Diazepam</td>
<td>53</td>
<td>481</td>
<td>534</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>Alprazolam</td>
<td>430</td>
<td>2633</td>
<td>3063</td>
<td>0.14</td>
<td>0.14</td>
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<tr>
<td></td>
<td>Clonazepam</td>
<td>27</td>
<td>252</td>
<td>279</td>
<td>0.10</td>
<td>0.10</td>
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<tr>
<td></td>
<td>Lorazepam</td>
<td>21</td>
<td>216</td>
<td>237</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>Atypical anti-psychotics</td>
<td>Olanzapine</td>
<td>73</td>
<td>1714</td>
<td>1787</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Asenapine</td>
<td>9</td>
<td>207</td>
<td>216</td>
<td>0.04</td>
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<tr>
<td></td>
<td>Risperidone</td>
<td>5</td>
<td>84</td>
<td>89</td>
<td>0.06</td>
<td>0.06</td>
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<tr>
<td></td>
<td>Quetiapine</td>
<td>63</td>
<td>476</td>
<td>539</td>
<td>0.12</td>
<td>0.12</td>
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<tr>
<td></td>
<td>Aripiprazole</td>
<td>11</td>
<td>279</td>
<td>290</td>
<td>0.04</td>
<td>0.04</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Adderall®</td>
<td>628</td>
<td>2755</td>
<td>3383</td>
<td>0.19</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Methylphenidate</td>
<td>8</td>
<td>159</td>
<td>167</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Lisdexamphetamine</td>
<td>563</td>
<td>1713</td>
<td>2276</td>
<td>0.25</td>
<td>0.21</td>
</tr>
</tbody>
</table>
4. Severe to lethal methanol poisoning after commercially available denatured ethanol “pink alcohol” abuse

Davide Lonatia, Sarah Vecchioa, Mara Garbiä, Virgilio Costanzob, Rosa Draisic, Maristella Rubbiania, Marta Crevaniä, Teresa Cocciñia and Carlo A. Locatelliä

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Objective: Consumption of surrogate alcohols may constitute a major public health problem, especially in relation to consumption of methanol. In Italy, methanol poisoning is relatively uncommon and results from unintentional/intentional ingestion. We describe severe cases of methanol poisoning in ethanol abusers.

Methods: Cases of methanol poisoning after ingestion of denatured ethanol (“pink alcohol”), referred to Poison Control Centre (PCC) were retrospectively evaluated (January 2005–September 2017) for: sex, age, ethnicity, modality of exposure, history of ethanol abuse, clinical manifestations/management, toxicological results, and outcome. The role of the alert/surveillance systems was evaluated.

Results: Twenty-seven patients (mean age 41.6 ± 8.1 years) were studied; 22/27 (82%) were Romanian; 4/27 (15%) Polish and 1 Ukrainian; 70% were women working as caregivers. Twenty-four cases (89%) were registered in Sicily. All patients were ethanol abusers. All cases presented at admission: mildly to complete unreactive bilateral mydriasis, metabolic acidosis (pH 6.8 ± 0.2) with moderate to severe hyperlactacidemia and hypotension. Coma was registered in 24/27 (88.8%), anuria in 12/27 (44%), respiratory failure in 11/27 (41%) and seizures in 4 cases. In 12 cases, nausea, vomiting, and severe ashenia were described during the week before the acute clinical manifestations. Ethanol was negative in all cases. Serum quantitative methanol concentrations were 142.2 ± 130.9 (10–420 mg/dL; performed in 18/27); 6 cases were positive (qualitative serum tests). In four cases, serum formate ranged from 57.7 to 73.6 mg/L (reference 5 mg/L). Supportive/dialytic treatment was performed in all cases. Antidote treatment was started in 21/27 (78%) with fomepizole (13/21), ethanol IV (6/21), or ethanol and then fomepizole (2/21). Reported sequelae were permanent mild visual disturbances (n = 3) and blindness (n = 1). Mortality rate was 85% (23/27), 35% and 52% during the first 48 and 96 hours, respectively (average 11.4 ± 17.6 days). History revealed that “pink alcohol” was mixed with alcohol to cheaply increase the percentage of ethanol. Ten rapid-alerts were forwarded by the PCC to National/Regional authorities and a syndromic surveillance system was implemented. Two different products (marketed in Italy, improperly labelled and/or packaged) were identified as source and contained methanol (29 to 70%).

Conclusion: Ingestion of methanol as a surrogate alcohol carries a high mortality (85%), mainly because of repeated exposure, late diagnosis and treatment. In the EU, industries that use alcohol for non-food purposes denature alcohol to make an undrinkable product limiting the abuse. If methanol is “erroneously” contained in pink alcohol, a real risk of lethal poisoning is present. Laboratory support has been essential to identify new cases. Syndromic surveillance systems activated by the PCC aid in the recognition of sources of methanol intoxication.

5. Morbidity and follow-up after acute poisoning by substances of abuse

Odd Martin Vallaersna, Dag Jacobsenb, Øivind Ekebergc and Mette Brekked

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Objective: To assess morbidity and follow-up in the first three months after acute poisoning by substances of abuse, through charting contacts with health services.

Methods: All patients 12 years and older treated for acute poisoning by substances of abuse at the main emergency outpatient clinic in Oslo, Norway, were included consecutively from October 2011 through September 2012. We collected data on gender, age, main toxic agent, suicidal intention, previous history of severe mental illness, and homelessness. Main toxic agent for a patient was defined as the most frequently diagnosed main toxic agent in that patient’s poisoning episodes. We retrieved information from national registries on fatalities during the study period, and on hospital admissions, outpatient contacts at specialist health services and consultations with general practitioners during the first 90 days after a poisoning episode.

Results: During one year, 1731 patients were treated for 2343 episodes of acute poisoning by substances of abuse. Median age was 33 years (IQR 23–46); 1136/1731 (66%) patients were male. There were 34/1731 (2%) deaths during the study period. Fatalities were most frequent among patients with one or more poisonings with suicidal intention 8/130 (6%), with a history of severe mental illness 8/183 (4%), or opioids as their main toxic agent 14/364 (4%). Multiple poisoning episodes were most frequent among patients with opioids as their main toxic agent 121/364 (33%), homeless patients 27/83 (33%), and patients with a history of severe mental illness 55/183 (30%). As another measure of morbidity, 508/1731 (29%) patients were admitted to a somatic hospital and 162/1731 (9%) were admitted to a psychiatric hospital. Concerning follow-up, 629/1731 (36%) patients had outpatient contacts at psychiatric and/or addiction specialist health services, an additional 517/1731 (30%) saw their general practitioner, leaving 585/1731 (34%) patients with no follow-up. Most patients with multiple poisonings were in follow-up (230/275 [84%]), as were patients with one or more poisonings with suicidal intention (118/130 [91%]), with a history of severe mental illness (158/183 [86%]), and with benzodiazepines (128/144 [89%]), or opioids (281/364 [77%]), as their main toxic agent. Homeless patients were frequently not in follow-up (32/83 [39%]).

Conclusion: Follow-up was more frequent among patients with increased morbidity, apart from the homeless. Thus, it seems that follow-up measures are targeted to those most in need. Still, however, the mortality rate calls for concern.
6. Impact of the UK Psychoactive Substances Act 2016 on Emergency Department presentations related to synthetic cannabinoid receptor agonists (SCRAs), cathinones and other new psychoactive substances

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**Objective:** In May 2016, the Psychoactive Substances Act (PSA) 2016 came into effect making it an offence to produce or supply new psychoactive substances (NPS) in the UK. The aim of this study was to determine the impact of the PSA on the drugs seen in Emergency Department (ED) presentations with acute NPS toxicity.

**Methods:** Our clinical toxicology database was searched for ED presentations to our inner city teaching hospital in London, UK with acute NPS toxicity in the 12-month periods pre- and post-introduction of the PSA (June 2015–May 2016 [defined as 2015/16], and June 2016–May 2017 [defined as 2016/17]). The following data were extracted: (i) demographics (age, gender); (ii) NPS(s) reported (subsequently categorised as, (i) synthetic cannabinoid receptor agonists (SCRA), (ii) cathinones, and (iii) “other NPS”); and (iii) month and year of presentation. Statistical comparisons were made using two-tailed t-tests for continuous variables, and Pearson’s test for correlation co-efficient.

**Results:** There were 1884 presentations with acute recreational drug toxicity over the two years, of which 447 (23.7%) self-reported use of NPS; 84% were male; mean±SD age was 33.1±9.4 years in 2015/16 and 35.3±9.2 years in 2016/17. There was no difference in the overall proportion of presentations involving an NPS in 2015/16 (n = 196 [22.3%]) and 2016/17 (251 [24.9%]); p = .48. There were a median of 16.3 (IQR: 15–19) NPS-related presentations per month in 2015/16 and 20.9 (IQR: 15.5–21.5) in 2016/17; there was no significant change in overall monthly NPS-related presentations between these periods (p = .15). However, median monthly SCRA-related presentations increased from 2015/16 (6.5 [IQR: 3.8–8.0]) to 2016/17 (15 [IQR: 10–17]); p = .004. Also, median monthly cathinone-related presentations decreased from 2015/16 (10 [IQR: 5.8–11.5]) to 2016/17 (4 [IQR: 1–6]); p = .001. There was no significant change in median monthly “other NPS” presentations from 2015/16 (1 [IQR: 0.8–2.3]) to 2016/17 (0 [IQR: 0–1]); p = .062. SCRAs as a proportion of NPS-related presentations increased (r = 0.90) whilst cathinones decreased over 2015/16 and 2016/17 (r = −0.82).

**Conclusion:** New psychoactive substances present law enforcement and front-line health services with unique challenges given their accessibility, wide variety, and potentially complex toxicodynamics. The Psychoactive Substances Act 2016 represents a major legislative effort in the UK to limit the availability and supply of these products. The burden of NPS use on this inner city ED remains large 12 months after this legislation has come into force, and the proportional growth of SCRA-related presentations and decrease in cathinone-related presentations points to evolving patterns of drug use within this population.

7. Investigation of the pharmacodynamic interaction involved in the respiratory depression attributed to diazepam/ buprenorphine combination

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\textsuperscript{a}Department of Medical and Toxicological Critical Care, Lariboisière Hospital, Paris-Diderot University, INSERM UMR1144, Paris, France; \textsuperscript{b}Molecular Imaging In Vivo, CEA, Paris-Saclay University, Orsay, France

**Objective:** Severe poisonings and fatalities have been attributed to buprenorphine (BUP) despite its ceiling respiratory effects, mainly if abused in co-ingestion with benzodiazepines. We previously showed that diazepam (DZP)/BUP combination induces severe respiratory depression in the rat, while each drug by itself does not. The objective of this study was to investigate the mechanisms involved in this drug-drug interaction using 11C-BUP positron emission tomography (PET) imaging and diaphragmatic electromyography (dEM) in the Sprague-Dawley rat.

**Methods:** 11C-BUP was administered intravenously, 30 mg/kg unlabeled BUP intraperitoneally and 20 mg/kg DZP subcutaneously. PET acquisition started with 11C-BUP PET injection, 15 minutes after DZP or its vehicle (VEH; n = 5/group) administration. Standardized Uptake Value (SUV)-normalized time activity curves (TACs) were generated and 11C-BUP binding potential (BPND, i.e., the ratio of the total receptor density [Bmax] on the equilibrium dissociation constant [KDI]) were modeled in different brain regions using a simplified reference tissue model with cerebellum as reference region. dEM, implanted under anaesthesia 7 days before the experiment, was recorded during 240 minutes in rats receiving VEH/VEH, DZP/VEH, VEH/BUP or DZP/BUP (n = 6/group). After filtering and half-wave rectification, the first 60 minute area under the curve (AUC) of diaphragm contraction and workload were determined and compared between the groups.

**Results:** TACs and 11C-BUP BPND were not different between the DZP/BUP and the VEH/BUP groups in all studied brain regions. Diaphragm contraction was significantly increased in the VEH/BUP group in comparison to the DZP/BUP group (p < .05). Diaphragm workload was significantly increased in the VEH/BUP group in comparison to the DZP/VEH and the DZP/BUP group (p < .05 and p < .01, respectively). DZP did not affect the 11C-BUP brain distribution and brain binding suggesting that DZP does not affect BUP transport across the blood brain barrier and BUP receptors density/affinity. BUP administration induced an increase in diaphragm contraction and workload. This increase was inhibited in the presence of DZP suggesting that DZP/BUP combination-induced respiratory depression is mostly related to DZP.

**Conclusion:** Respiratory depression related to DZP/BUP combination results from a pharmacodynamic drug-drug interaction.
8. Investigation of baclofen-induced neurorespiratory toxicity: characterization of tolerance development and withdrawal syndrome

Magali Chartier, Lucie Chevillard, Salma Tannous, Isabelle Malissin, Laurence Labat, Nadia Benturquia, Patricia Risède and Bruno Mégarbane

Department of Medical and Toxicological Critical Care, Lariboisière Hospital, Paris-Diderot University, INSERM UMRS1144, Paris, France

Objective: High-doses (up to 300 mg/day) of baclofen, a GABAB receptor agonist, are increasingly used to manage alcohol dependence, leading to increasing number of poisonings. Clinical studies pointed out the development of tolerance to baclofen-induced effects as well as the emergence of withdrawal syndrome in chronically baclofen-treated patients. Our objectives were to investigate the onset of tolerance to baclofen-induced neurorespiratory toxicity and to describe any withdrawal syndrome that may result after repeated baclofen treatment in Sprague-Dawley rats.

Methods: A high dose of baclofen (116mg/kg, equivalent to 80% of the lethal dose 50%) was administered by the intragastric route to rats repeatedly treated during 15 days with increasing doses of baclofen (acute-on-chronic poisoning) versus saline (acute poisoning). The neurorespiratory effects were studied using electroencephalography (EEG), plethysmography, and arterial blood gas analysis. Baclofen-induced EEG effects were graded using a specific scale developed for baclofen. Plasma baclofen quantification was performed using high-performance liquid chromatography coupled to mass spectrometry in tandem (HPLC-MS/MS) assay. The onset of withdrawal was studied using various behavioral tests.

Results: Acute-on-chronic baclofen poisoning in comparison to acute poisoning was responsible for significant time- and intensity-related decrease in sedation (p < .01), hyperthermia (p < .05), EEG alterations (i.e., epileptiform traces, burst suppression and tapered intensity waves) and respiratory depression (p < .001). Peak of effects were significantly delayed and duration of effects significantly shortened. Plasma pharmacokinetics showed accelerated baclofen elimination. The EEG effects/concentrations relationships clearly evidenced the development of tolerance to baclofen. In addition, the sudden baclofen discontinuation resulted in hyperlocomotion and non-anxiogenic withdrawal.

Conclusion: We demonstrated the development of pharmacokinetic and pharmacodynamic tolerance to baclofen-induced neurorespiratory toxic effects and onset of withdrawal syndrome after the cessation of repeated treatment, supporting the observations in humans. However, the molecular mechanisms remain to be investigated.

9. The development of analytical techniques for the cardiac glycosides in yellow oleander (Cascabela thevetia)

Eeman Cheema, Christopher Walker, Andrew Kicman, Fahim Mohammed, Indika B. Gawarammana and Paul I. Dargan

Faculty of Life Sciences and Medicine, King’s College London, London, United Kingdom; South Asia Clinical Toxicology Research Collaboration, University of Peradeniya, Kandy, Sri Lanka; Clinical Toxicology, Guy’s and St Thomas’ NHS Foundation Trust; Faculty of Life Sciences and Medicine, King’s College London, London, United Kingdom

Objective: Yellow oleander (Cascabela thevetia, previously Thevetia peruviana) self-poisoning is common in Sri Lanka and elsewhere in south Asia. There is currently no specific assay for the cardiac glycosides (thevetin A, thevetin B, neriifolin, and peruvoside) in yellow oleander. The aim of this study was to develop an analytical method for these glycosides in plant material and in serum samples from patients with yellow oleander poisoning.

Methods: Yellow oleander plant material (bark, leaves, flowers, seeds, and fruit) from Sri Lanka underwent solvent maceration to extract the glycosides and these were isolated from the crude extracts using a semi-preparative high-performance liquid chromatography (HPLC). Overall, 30 serum samples from 12 patients with yellow oleander poisoning in Sri Lanka were analysed using solid phase extraction (SPE) with digitoxin as the internal standard alongside a negative control (blank serum) and two positive controls spiked with all four glycosides at concentrations of 2 and 20 ng/mL. An ultra-high pressure liquid-chromatography tandem mass-spectrometric (UPLC-MS/MS) method using a triple quadrupole mass-spectrometer and electrospray ionisation (ESI) was used for both plant and serum analysis.

Results: LC-MS/MS enabled detection and identification of neriifolin, peruvoside, thevetin A, and thevetin B in extracts from plant material by comparison with authentic reference standards; there were differences in the proportions of glycosides in different plant parts. With the exception of the seed kernel, in which 87% of the detected glycoside was thevetin B, neriifolin was the most abundant glycoside and present as 67–70% of the detected glycosides in flowers, leaves, and roots. Analysis of the spiked serum samples enabled a limit of quantification of 1.0 ng/mL for all four glycosides. Application of this method for the analysis of the serum samples from patients with yellow oleander poisoning detected neriifolin in all samples at a concentrations up to 17.0 ng/mL; the other three glycosides were not detected in these patient serum samples.

Conclusion: We have developed an effective and sensitive LC-MS/MS method for the detection all four cardiac glycosides in yellow oleander, both in plant material and spiked human serum samples. Further work is required to investigate the reasons for not detecting thevetin A, thevetin B and peruvoside in serum samples despite these being present in the plant material ingested by patients with yellow oleander poisoning. The analytical method developed will enable future studies to characterise the pharmacokinetics of neriifolin in patients with yellow oleander poisoning and pharmaco-kinetic-pharmacodynamic study of current and potential future treatments for this patient group.

11. Early prognostic factors in colchicine intoxication

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Objective: Acute colchicine intoxication by ingestion of tablets or parts of Colchicum autumnale plant has a high mortality rate,
virtually 100% with doses higher than 0.8 mg/kg. Some prognostic factors of severity have been suggested, including the ingested dose and colchicine elimination kinetics. The aim of this study was to assess if some common clinical and laboratory factors can have an early (first 48 hours) prognostic value in acute colchicine poisoning.

Methods: We performed a retrospective analysis of our cases of colchicine intoxication. Inclusion criteria were the presence of severe gastroenteritis associated with alteration of one of the markers of cytolysis: lactate dehydrogenase (LDH), aspartate aminotransferase (AST), creatine kinase (CK). The intoxication was defined as severe if any of the following: (I) myelosuppression (platelets <100,000/mm³ and white blood cell count (WBC) <2000/mm³), (II) disseminated intravascular coagulation (DIC) (International Society on Thrombosis and Haemostasis [ISTH] definition), (III) hypokinetic cardiomyopathy, or (IV) adult respiratory distress syndrome (ARDS) with respiratory failure were present. Clinical and laboratory findings were evaluated within 48 hours after ingestion. p-Value, Student t-test, and Fisher’s exact test analysis were employed for statistical analysis.

Results: We included 53 patients (M/F 19/34), mean age 46.6 years (range 0.08–89) over a 20-year period. Thirty-one patients ingested medicated treatment (average dose 0.55 ± 0.30 mg/kg), and 22 ingested Colchicum autumnale, mistaken for edible vegetables including leaves (n = 11), bulb (n = 2), flowers (n = 8), and an unknown part (n = 1). Average time to admission was 12.4 ± 11.2 hours for drug, and 22 ± 19 hours for plant intoxications. According to the established criteria, 32/53 (60.4%) patients showed a moderate intoxication and 21/53 (39.6%) severe intoxication. Overall, mortality was 28.3% (15/53), but 71.4% (15/21) among patients with severe intoxication. By comparing serious versus moderate intoxications in the first 48 hours, statistically significant data were: (i) ingested dose of drug in mg/kg (0.71 ± 0.28 versus 0.38 ± 0.21 mg/kg; p = .001), (ii) increase at least one of the following AST, CK, LDH more than 4 times their normal values (p < .001), (iii) leukocyte level more than 18,000 (p > .001), and (iv) peak leucocytosis (23,712.7 ± 8577.2 versus 13,281.4 ± 3,256.5; p < .001).

Conclusion: Colchicine ingestion can lead to severe poisoning with a high-mortality rate. No specific antidote is available and treatment is only symptomatic. Early prognostic indicators, however, allow patient admission to the appropriate setting, and to undergo the best treatment to prevent and monitor the most serious complications. In our study, in addition to the ingested dose, early leucocytosis greater than 18,000 and the increase of one of the markers of cytolysis to more than 4 times the normal value were found to be significant prognostic indicators.

12. Illegal drug use in prison: results of urinary drug screening in patients hospitalized in a French Inter-Regional Secure Hospital Unit (UHSI)

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Objective: Prevalence of alcohol or drug use in prison was measured in a French national study and drug use disorder was diagnosed in 28% of study subjects [1]. There is little on the consequences of drug use in prisons on hospitalizations of inmates e.g., refusal of care, withdrawal syndrome, agitation and aggressiveness. In the Bordeaux UHSI a systematic urinary drug screening has been performed on admission for all inmates hospitalized since June 2011. We determined the prevalence of drug use among inmates hospitalized in this unit to evaluate the consequences of drug use on hospitalization of patients.

Methods: Retrospective monocentric study of patient files between 1 August 2012 and 31 December 2014. Variables studied: demographic data, drugs measured by cloned enzyme donor immunoadsorb (cannabis, cocaine, amphetamines, opioids except methadone, buprenorphine), treatment prescribed, consequences of drug use (withdrawal syndrome, refusal of care, need to prescribe psychoactive drugs). Statistical analysis is descriptive. Test results were considered for analysis only if performed at least 3 weeks after incarceration to avoid bias.

Results: Overall, 424 males (94.4%) median age 43 ± 14.7 years and 25 females (5.6%) median age 42 ± 12.7 years were hospitalized over the study period, with 726 urinary screens. Of these, 135 patients (30.1%) were positive for cannabis of which 66 (48.8%) were “high” as a result, 51 (11.4%) were on buprenorphine (16 were not under treatment), 36 (8%) were on opioids (3 were not under treatment), 2 (0.4%) were positive for cocaine and 6 (1.3%) were positive for amphetamine derivatives. Forty patients (8.9%) were positive for ≥2 drugs; 146 patients (32.5%) had negative results, and 73 (16.2%) refused screening. Consequences of hospitalizations: 21 patients exhibited cannabis withdrawal syndrome according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) criteria, all being “high” on test results. All patients under buprenorphine were unable to receive opioids for analgesia and buprenorphine had to be increased for pain relief.

Conclusion: Drug use in prison is a reality measured here by urine testing and not only by questionnaires as for most of papers published on the subject. Cannabis remains the most used drug in prison as in the general population, which causes difficulties during hospitalization with withdrawal syndrome, endangering caregivers and refusal of continued care in the hospital.

Reference


13. Correlation between cardiac symptomatology, troponin and echocardiogram in carbon monoxide poisoning: preliminary data in a prospective study

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Objective: Cardiac manifestations in carbon monoxide (CO) poisoning are well described, but there is a lack of data regarding their correlation with biomarkers, particularly high-sensitivity cardiac troponin (hs-cTn) and echocardiographic alterations.

Methods: An open, non-randomized, prospective study was conducted (EC approval 1088CE). All consecutive patients admitted...
to an Emergency Department-network and referred to a poison center between January 2014 and February 2017 were evaluated. Inclusion criteria: age > 12 years, CO-exposure and/or carboxyhemoglobin (COHb) > 5% (non-smokers) or > 10%. Exclusion criteria: smoke inhalation and/or burns. Case report form data: age, modality of exposure, CO-poisoning grading [Grade-1: asymptomatic; Grade-2: mild (nausea, vomiting, headache, vertigo); Grade-3: moderate (tachycardia, cardiac dyspnea, mild neurological symptoms, behavioral changes); Grade-4: severe (syncope, chest pain, hemodynamic instability, severe neurological manifestations)] [1], blood COHb, troponin increase, echocardiography (within 48 hours) and outcome. Patients were divided into group-A (cardiac manifestations), and group-B (non-cardiac manifestations). Patients with incomplete data were excluded.

Results: Seventy-four patients were included. Group A: 29 patients (mean age 44.9 ± 20.3 years); Grade-4: 15 cases (COHb 8.8–35.5%); Grade-3: 14 cases (COHb 9.3–41.7%). All accidentally exposed, except for one suicide attempt. CO-exposure was >12 hours in 6 cases. Troponin increase in 11/29 (38%); with hs-cTn increase. Two out 6 echocardiograms performed evidenced CO-related myocardial stunning (MS). In 62% (18/29), troponin were in range; one of 9 echocardiograms performed revealed MS. Group B: 45 (43.9 ± 20.4 years); Grade-4: 17 cases (COHb 7.3–35.8%); Grade-3: 7 cases (COHb 19.5–41.5%); Grade-2: 15 cases (COHb 6.1–38.0%); Grade-1: 6 cases (COHb 7.7–23.4%). All accidentally exposed, except for waterpipe use. CO-exposure was >12 hours in 7 cases. Troponin increase in 9/45 (20%). 5 had elevated hs-cTn. One of two echocardiograms performed evidenced MS. Seven echocardiograms performed in patients with troponin in range (36/45; 80%) were normal.

Conclusion: Cardiac symptomatology was reported in 39% of CO-poisoned patients. In this group, cTn was increased in 38% of the cases. cTn may also be positive in patients without cardiovascular manifestations (20%). One group-A patient with prolonged CO-exposure showed negative standard-cTn, but MS. All patients in group-B (non-cardiac manifestations) with negative cTns had normal echocardiograms (available in 7 cases). The hs-cTns seem to be a useful tool to identify cardiac damage. In patients without cardiac manifestation and negative cTn, echocardiogram should not be performed routinely. These results need to be confirmed in a larger case series.

Reference


14. What is the best antidote to reverse tramadol-induced neuro-respiratory toxicity in overdose? An experimental investigation in the rat

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Objective: Since the banning of dextropropoxyphene from the market, overdoses and fatalities attributed to tramadol, a World Health Organization (WHO) step-2 opioid analgesic, have increased markedly. Tramadol overdose results not only in central nervous system (CNS) depression attributed to its opioid properties but also in seizures, possibly related to non-opioidergic pathways, thus questioning the efficiency of naloxone to reverse tramadol-induced CNS toxicity. Our objective was to investigate the most efficient antidote to reverse tramadol-induced seizures and respiratory depression in overdose.

Methods: Sprague-Dawley rats overdosed with 75 mg/kg intraperitoneal (IP) tramadol were randomized into four groups to receive solvent (control group), diazepam (1.77 mg/kg IP), naloxone (2 mg/kg intravenous bolus followed by 4 mg/kg/h infusion) and diazepam/naloxone combination. Sedation depth, temperature, number of seizures and intensity, whole-body plethysmography parameters, and electroencephalography (EEG) activity were measured.

Results: Naloxone reversed tramadol-induced respiratory depression (p < .05) but significantly increased seizures (p < .01) and prolonged their occurrence time. Diazepam abolished seizures but significantly deepened rat sedation (p < .05) without improving ventilation. Diazepam/naloxone combination completely abolished seizures, significantly improved rat ventilation by reducing inspiratory time (p < .05), but did not worsen sedation. Based on the EEG study, tramadol-treated rats experienced electro-clinical seizures as soon as 5 min after the injection, characterized by spike-waves and polyspikes with progressive decreased frequencies and inter-critical phases of slow delta waves until the next crisis. After diazepam/naloxone injection, EEG waveforms comprised 8 Hz-alpha rhythms and slow-down theta rhythms of drowsiness. None of these treatments significantly modified rat temperature.

Conclusion: Diazepam/naloxone combination is the most efficient antidote to reverse tramadol-induced CNS toxicity. Our experimental data greatly encourage administering this combination rather than naloxone alone as first-line antidote in tramadol-poisoned patients as an alternative to tracheal intubation.

15. Effects of lipid emulsion on the pharmacokinetic and pharmacodynamic properties of metoprolol: a randomized, double-blind, placebo-controlled cross-over study

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Objective: Intravenous lipid emulsion (ILE) is used in the management of poisonings with cardioactive agents [1]. However, the evidence behind this therapy is based on a few animal studies and clinical case reports. There are no controlled human studies documenting efficacy or mechanism of action of the ILE dose recommended for toxicological emergencies. We therefore set out to investigate, (1) hemodynamic effects of ILE compared to saline placebo during metoprolol-induced hemodynamic depression and (2) effects of ILE on plasma metoprolol concentrations.

Methods: In this cross-over, participant-and-investigator blinded study, 10 healthy male participants received 60 mg metoprolol or matching saline placebo intravenously followed by a 1.5 mL/kg bolus + 0.25 mL/kg/min infusion for 15 min of 20% ILE or saline placebo in randomized order on four separate study days (saline + saline; saline + ILE; metoprolol + saline; metoprolol + ILE). We
explored several endpoints related to the effects of ILE alone and on metoprolol’s plasma concentration and cardio-inhibitory properties. Primary endpoint was change in heart rate from baseline compared between study days, 90 minutes after end of ILE/placebo-infusion. Hemodynamic endpoints were measured invasively through a radial arterial line and analyzed using a mixed model for repeated measurements.

Results: On metoprolol-days, average heart rates progressively increased after ILE administration and were 5.5 beats per minute (bpm) higher 90 minutes after infusion stop on days with ILE compared to saline placebo (95% CI 3.0–8.1 bpm, \( p < .001 \)). Average relative stroke volume was increased 4.1% (95% CI 1.0–7.3%, \( p < .001 \)) and average relative cardiac output was 10.0% (4.7–15.4%, \( p < .001 \)) higher after ILE compared to saline. Significant effects of ILE on heart rate and cardiac output were also present on days without metoprolol. Furthermore, there was a trend toward increased blood pressure on ILE-days (\( p > .05 \)). Area under the plasma metoprolol concentration versus time curves were similar between days (\( p = .78 \)). ILE was well-tolerated.

Conclusion: ILE increased heart rate and cardiac output independently of metoprolol administration, and demonstrated no major safety issues or effects on metoprolol pharmacokinetics. Hemodynamic effects occurred with delay, suggesting that slowly inserting metabolic effects or secondary catecholamine release caused by ILE are likely mechanisms behind our observations.

Trial registration: Clinicaltrials.gov: NCT02924454

Reference

16. Intentional acute valproate overdose: the role of gastroscopy for decontamination of the gastrointestinal tract

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Objective: Gastroscopy for the decontamination of the gastrointestinal tract of patients who have ingested medicines that can form concretions (gastric pharmacobezoars) has been emerging in recent years. With regard to gastroscopy, some authors maintain that hydroxypropyl methylcellulose (HPMC) may play a role for the formation of pharmacobezoars. There are single case reports or case series in the scientific literature, but to our knowledge, no studies focusing on valproate (VPA) intoxications and the possible formation of gastrointestinal agglomerates. To evaluate the role of gastroscopy in the gastric decontamination of patients with VPA overdose in the Pavia Poison Centre (PPC) case series.

Methods: All cases of intentional ingestion of valproic acid by adult patients in which gastroscopy for decontamination was performed from January 2007 to March 2017 were retrospectively reviewed.

Results: In total, 85 patients were included. In 82% (70/85) of the cases, valproate has been co-ingested with other drugs (co-ingestants), and in 40% (28/70) of the cases, there were drugs potentially able to form pharmacobezoars. The average latency from ingestion to the execution of the gastroscopy was 14 hours (range 1–156 hours); gastroscopy that documented pharmacobezoars was performed on an average after 16 hours, whereas negative gastroscopy after 13 hours. Gastroscopy was positive for bezoars in 59% (50/85) of the cases. The procedure was performed in an emergency for 56 patients with a positive result in 64% (36/56) of the cases. In 29 patients, the procedure was executed because of clinical deterioration, with positive results in 48% (14/29) of the cases. Valproate ingestion is more likely (64%, 45/70) to result in formation of concretions/bezoars if combined with co-ingestants. In addition, gastroscopy was positive in 62% (48/78) of cases in which HPMC is present. In most cases, it was not possible to assess the perception of the emergency physician about the possible effectiveness of gastric lavage (GL); in this group, gastroscopy was found to be positive in 57% (27/47) of the cases. When GL was considered ineffective for lack of material in the stomach, gastroscopy was positive in 71% (10/14) of the cases, and when GL was considered effective, gastroscopy was found to be positive in 69% (9/13) of the cases.

Conclusion: The perception of the efficacy of the gastric lavage may be erroneous in cases of ingestion of extended-release drugs. Gastroscopy for decontamination purposes in valproate intoxications seems effective in removing any bezoar. It is conceivable that decontamination with gastroscopy in valproate intoxications may become a more standard procedure.

17. Drug-specific risk of severe QT prolongation following acute drug overdose

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Objective: Severe QT prolongation (SQTP) is a strong predictor of adverse cardiovascular events in acute drug overdose [1], but drug-specific causes of SQTP in the setting of acute drug overdose remain unclear.

Methods: A prospective cohort study at >50 hospital sites across the US using ToxIC Registry data from 2015–2017. Inclusion criteria were adults (≥18 years) receiving medical toxicity consultation for acute (or acute-on-chronic) drug exposures. Cases lacking electrocardiogram (ECG), known cardiovascular medical history, or laboratory values were excluded. Medical toxicologists provided bedside consultation for each patient and independently reported the primary agent(s) responsible for drug toxicity, which was used for drug-specific QTc (correct QT) analysis. The primary outcome was SQTP, defined using the previously validated QTc cutpoint [1] of 500 ms. Drugs associated with SQTP were analyzed with chi-squared, odds ratios (OR), and 95% confidence intervals (CI). Assuming 10% drug class exposure and 10% baseline SQTP risk, we calculated the need to enrol 5138 patients to have 90% power to detect 50% increased risk.

Results: From 18,438 patients screened, 558 met inclusion criteria (49.6% female, mean age 38.9 years, 66.2% Whites, 13.7% Blacks, 1.8% Asians, 18.3% other/unknown, 9.9% Hispanic) with SQTP occurring in 469 (8.4%). Aside from Class III antidysrhythmics, sodium channel blockers, and potassium channel blockers, novel drugs associated with SQTP included cyclobenzaprine (OR
Table 1. Drugs with the highest risk of severe QT prolongation (SQTP) in 5588 ToxIC Registry patients.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Drug</th>
<th>SQTP/N (%)</th>
<th>Odds ratio with 95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>Haloperidol</td>
<td>5/18 (27.7)</td>
<td>4.2 (1.5–12)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Imipramine</td>
<td>3/11 (27.3)</td>
<td>6.2 (2.5–15)</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Lamotrigine</td>
<td>2/10 (20.0)</td>
<td>2.2 (1.0–4.5)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Quetiapine</td>
<td>1/16 (6.3)</td>
<td>2.1 (1.0–4.2)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Doxepin</td>
<td>2/10 (20.0)</td>
<td>9.1 (4.4–18.2)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Risperidone</td>
<td>7/14 (50.0)</td>
<td>13.2 (6.8–25.7)</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Lamotrigine</td>
<td>5/23 (21.7)</td>
<td>2.1 (1.0–4.3)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Clozapine</td>
<td>1/10 (10.0)</td>
<td>9.1 (4.2–18.9)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Venlafaxine</td>
<td>6/10 (60.0)</td>
<td>2.1 (1.0–4.2)</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Pregabalin</td>
<td>3/14 (21.4)</td>
<td>2.1 (1.0–4.3)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Quetiapine</td>
<td>1/10 (10.0)</td>
<td>2.1 (1.0–4.2)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Venlafaxine</td>
<td>3/11 (27.3)</td>
<td>2.1 (1.0–4.2)</td>
</tr>
</tbody>
</table>

3.6, 95% CI 1.8–7.1, trazodone (OR 2.9, 95% CI 2.0–4.1), clonazepam (OR 1.87, 95% CI 1.1–3.2), and oxycodone (OR 1.8, 95% CI 1.0–3.1). Table 1 summarizes drugs with significant associations with SQTP, which notably did not include lithium, ondansetron, or olanzapine.

**Conclusion:** In this large cohort, high risk drugs associated with SQTP were identified, including novel associations with clozapine, oxycodone, clonazepam, and trazodone. Implications for prescribing practices to prevent drug-induced QT prolongation require future study.

**Reference**


18. Clinical effects following 2C-B exposure: a case series of 20 patients

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**Objective:** After its legal ban in the late 1990s, the popularity of 2C-B (4-bromo-2,5-dimethoxyphenethylamine) is once again increasing in the Netherlands. From 2014–2016, the annual number of enquiries about 2C-B exposures to the Dutch Poisons Information Center (DPIC) was 22, 14, and 21, respectively. Despite its long history of abuse, data on health risks are limited. Therefore, we investigated the clinical effects following 2C-B exposure.

**Case series:** From January 2016 to June 2017, 20 cases of self-reported 2C-B exposure for whom the DPIC was consulted, were followed-up by telephone using standardized questionnaires with either the patient and/or physician. Predominantly, male patients were involved (80%, n = 16) with a median age of 21 years (range 13–26 years). In most cases (85%, n = 17), a median dose of 2 tablets (n = 13, range 1–5 tablets) containing 20 mg 2C-B (n = 10, range 13–21 mg) was ingested. Co-exposure to other illicit substances was reported in 55% of the cases (n = 11) including cannabis, lysergic acid diethylamide (LSD), gamma hydroxybutyrate (GHB), cocaine, amphetamine, 3,4-methylenedioxymethamphetamine (MDMA), and 4-fluoroamphetamine (4-FA).

Three of these patients also consumed alcohol (>2 units). Two patients combined 2C-B with alcohol only (>2 units). Reported clinical effects after mono-intoxications with 2C-B (n = 7) included mydriasis (n = 6), hallucinations (n = 6), hypertension (n = 3), tachycardia (n = 3), confusion (n = 3), agitation (n = 3), anxiety (n = 3), mucosal dryness (n = 3), enhanced perception (n = 3), nausea (n = 3), vomiting (n = 2), insomnia (n = 2), apathy (n = 2), dysphoria (n = 2), perspiration (n = 2), paleness (n = 2), and palpitations (n = 2).

There were single reports of redness, anorexia, diarrhea, muscle twitching, tremors, amnesia, dissociation, dizzi- ness, entactogenic effects, euphoria, sedation, tiredness, fainting, dysartrhia, headache, light-headedness, psychosis, elevated body temperature, tachypnea, paresthesia, and chest pain. One fatality was reported. This patient rapidly developed coma after an unknown number of 2C-B tablets and had convulsions soon after admission, followed by severe hyperthermia (42.6°C), tachycardia, and ECG abnormalities (ventricular fibrillation, prolonged QT interval, deep negative T-waves, pan-ischemia). Bradycardia and hypotension developed, finally resulting in fatal cardiac arrest. Toxicological analysis of urine was positive for MDMA and amphetamine. Analysis of blood samples is pending. In three non-fatal cases, left-over drug material was available for analysis and all drug samples contained 2C-B.

**Conclusion:** As the number of 2C-B intoxications is increasing, more data on clinical effects is required. Our data shows that most patients experience relatively mild symptoms following self-reported 2C-B exposure. Severe and life-threatening symptoms were only reported after co-exposure with other illicit substances. However, to improve conclusion validity, analytical confirmation in biological samples is needed.

19. Acute toxicity following analytically confirmed use of the novel psychoactive substance (NPS) methiopropamine: a report from the Identification Of Novel PsychoActive substances (IONA) study

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**Objective:** Methiopropamine is an NPS, which was first reported in 2011, but there are limited data on the pattern of acute toxicity associated with its use. It was controlled in the UK in November 2015. The UK Identification Of Novel Psychoactive substances (IONA) study collects biological samples from patients...
presenting with severe NPS toxicity to identify the NPS involved and link these to the clinical features documented. Here, we present 10 patients presenting with analytically confirmed methiopropamine use.

**Methods:** Adults (>16 years) presenting to participating UK hospitals with severe acute toxicity (based on pre-specified criteria) after suspected NPS use were recruited with consent or the agreement of a personal/professional representative. Clinical features were recorded on a structured data collection form and blood or urine samples were analysed using tandem mass-spectrometry.

**Results:** Of the 261 IONA patients with clinical and analytical information available recruited March 2015 to September 2017, methiopropamine was detected in 10 (3.8%); median age 23 (range 17–45) years and 8 were male, all presenting July 2015 to August 2016. In one patient, methiopropamine was the only drug detected; in three there was one additional drug detected, two had two additional drugs, two had three additional drugs, and two had five additional drugs detected. These included other NPS in 8 (5F-PB-22, FUB-NPB-22, FUB-PB-22, 5F-AKB-48, STS-135, MDMB-CHMICA, AM-1248, 5F-ABD hydrolisis metabolite, 25I-NBOMe, 2-aminoindane, 3F-phenmetrazine, ethylphenidate, and methylphenylphenidate) and conventional drugs/metabolites in 5 (methadone in 4, benzodiazepines in 3). Common features recorded included tachycardia (>100/min (n = 9), agitation (n = 6), confusion (n = 6), reduced Glasgow Coma Scale (GCS) (range 3–13, n = 4), hallucinations (n = 4), seizures (n = 3), hypertension (n = 3), palpitations (n = 3), and aggression (n = 3). Seven had a raised creatine kinase (CK) and in four, CK was >1000 IU/L. Two patients with CK >1000 IU/L had pyrexia (<39°C), hypertension, agitation, paranoia, and aggression requiring ICU admission for sedation and ventilation. One of these patients admitted to ICU had an acute kidney injury (creatinine 1058 μmol/L). Median length of hospital stay was 16 (range 2–185) hours; 9 were discharged without sequelae and one was transferred for in-patient psychiatric treatment.

**Conclusion:** Methiopropamine was detected in IONA patients over a 14-month period in 2015/16 but has not been detected since August 2016. The majority of the patients with confirmed methiopropamine use had also used other drugs; other NPS were particularly common. Raised CK was common but it is not possible to determine the degree to which this and other features could be contributed to by co-used substances.

20. An analytically confirmed non-fatal intoxication by the ultra-potent fentanyl analogue carfentanil in Sweden

Lisa Franzén

Olof Beck

Anders Helander

**Objective:** Carfentanil is one of the most potent opioids known, being about 100 times more potent than fentanyl. It has limited use in veterinary medicine as a fast and powerful tranquilizer for large animals. Recreational use of potent fentanyl analogues is an ongoing high-risk trend causing considerable concern worldwide and the number of new fentanyl reports to the European Monitoring Centre for Drugs and Drug Addiction has increased dramatically in recent years. During the first half of 2017, the number of detections of carfentanil in seizures and drug-related deaths has increased throughout Europe, but there are yet few published cases of poisoning. We present a severe, analytically confirmed non-fatal case of carfentanil poisoning in Sweden.

**Case report:** A 41-year-old male heroin addict was found unconscious (Glasgow Coma Scale [GCS] 3) at home with respiratory depression (respiratory rate 2/min) and oxygen saturation of 68%. After rapid intravenous (IV) administration of three 0.4 mg boluses of naloxone, he woke up and could inform the paramedics that he had, for the first time, taken carfentanil (0.025 mg nasally followed by 0.025 mg IV) about 3 hours earlier. About 8 hours earlier, he had also injected 0.5 g heroin. On arrival in the Emergency Department (ED), he was still awake with normal respiration and miosis. Soon after, however, his level of consciousness decreased and two additional boluses of naloxone were given. He was admitted to the intensive care unit and treated with naloxone infusion, initially 0.01 mg/kg/h, which was gradually lowered to 0.003 mg/kg/h. After a total of 40 hours, naloxone infusion was discontinued and he remained awake and stable. In a urine sample collected in the ED, both carfentanil and its metabolite norcarfentanil were analytically confirmed using liquid chromatography-high-resolution tandem mass spectrometry (LC-HRMS). He also tested positive for buprenorphine, methadone, heroin metabolites, benzodiazepines, and ethyl glucuronide.

**Conclusion:** The fact that the extremely potent fentanyl analogue carfentanil has appeared on the recreational drug scene should be cause for societal concern. Our case highlights the ability of carfentanil to cause life-threatening toxic symptoms, as the patient was completely knocked-out immediately after use and required naloxone treatment for almost two days.

22. New psychoactive substance (NPS)-induced toxicity requiring intensive care unit admission: a case series

Noémie Haloua, Isabelle Malissin, Jean-Claude Alvarez, Laurence Labat and Bruno Mégarbane

**Objective:** New psychoactive substances (NPS) are increasingly used on the recreational scene, despite a major risk of severe poisoning. Among the NPS, the synthetic cathinones have become popular amphetamine-like products representing a major health concern to date. Extremely limited data on NPS-poisoned patients admitted to the intensive care unit (ICU) have been reported. Our objective was to describe the clinical features, management, and outcome of NPS-poisoned patients admitted to the ICU. When available, pharmacokinetic data have been obtained.

**Methods:** Retrospective single center descriptive study including all NPS-poisoned patients admitted in one University Hospital ICU during 2011–2017. NPS use was based on the patient’s declaration and confirmed analytically if possible. The usual demographic, clinical, toxicological, and outcome data were collected from the medical records.

**Results:** Twenty-four NPS-poisoned patients (23 males/1 female; age: 34 years [18] (median [inter-quartile range]; chronic ethanol [77%] and drug [59%] consumers; including HIV-infected [58%] and depressive [25%] patients) were admitted to the ICU. The main declared compounds were methylenedioxyamphetamine (MDPV; n = 9), 4-methylmethcatinone (4-MEC; n = 6), 3-methyl methcatinone (3-MMC; n = 3) and 4-methyl methcatinone (4-MM; n = 3), more frequently used in drug mixtures sold as bath salts or in poly-intoxication with conventional illegal drugs.
Objective: Homelessness is reported to be increasing in the UK, with a homeless population of 254,500 (0.47%) estimated for England in 2016. Drug misuse is common in this population and there are concerns that there may be high use of novel psychoactive substances (NPS) as these may be cheap and easy to access. The UK Identification Of Novel psychoActive substances (IONA) study is a multicentre study characterising the NPS involved in episodes of severe toxicity and their associated clinical features. Here, we compare substances identified between homeless people and those who are not (controls).

Methods: The IONA study has ethical approval and is recruiting patients (≥16 years) presenting to 22 participating UK hospitals with severe acute toxicity (according to pre-defined definitions) after suspected NPS exposure, after informed consent (or the agreement of a representative in those lacking capacity). Clinical and demographic features including limited postcode were recorded using a structured data collection sheet. Blood and/or urine samples were analysed by liquid chromatography-tandem mass spectrometry. Proportions were compared between groups by chi-square testing.

Results: Analytical and clinical data were available for 275 patients; 27 (9.8%) reported themselves as homeless (median age 35 years, range 22–57, 87% males) and 248 did not (median age 32 years, range 16–61, 76% males). No significant differences (p > .05) were observed in the proportion of those with at least one sample positive for the following common substances (including metabolites) or groups: NPS overall (52% homeless versus 64% controls), conventional drugs overall (67% versus 71%), synthetic cannabinoid receptor agonists (SCRA) overall (48% versus 40%), NBOMe compounds (4% versus 10%), cathinones (0% versus 10%), methadone (44% versus 37%), cocaine (4% versus 18%), amphetamine (4% versus 13%), methamphetamine (4% versus 8%), MDMA (11% versus 13%), or diazepam (19% versus 25%). Two SCRs (or their metabolites) were found significantly more often in homeless patients; SF-ADB (41% versus 18%, p < .01) and FUB-AMB (26% versus 12%, p < .05).

Conclusion: Although there are uncertainties about estimates of the homeless population, they are disproportionately represented amongst these patients presenting to hospital with severe toxicity suspected to be NPS-related. No major drug group was found more commonly in the homeless, but the study lacks power due to the small homeless sample size. However, although SCRs overall were not found significantly more often in the homeless, two specific SCRs were more commonly identified. The reasons underlying these differences need further study.

24. Novel psychoactive substances (NPS) and emergency rooms (ER): a complicated relationship?

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Postgraduate School of Clinical Pharmacology and Toxicology, University of Milan, Milan, Italy; National Milan Poison Control Center, Niguarda Great Metropolitan Hospital, Milan, Italy; Department of Mental Health, Niguarda Great Metropolitan Hospital, Milan, Italy; Postgraduate School of Clinical Pharmacology and Toxicology, University of Genova, Genova, Italy; Biochemical Laboratory, Toxicology Section, Niguarda Great Metropolitan Hospital, Milan, Italy; Emergency Department, Niguarda Great Metropolitan Hospital, Milan, Italy

Objective: Despite their increasing availability, novel psychoactive substances (NPS) represent a critical problem in terms of analytical and clinical identification in the emergency room (ER), often due to non-specific symptoms, lack of collaboration between healthcare professionals and inadequate toxicological investigation techniques. The objective of our research is to examine all clinical records of patients with psychoactive substance intoxication among metropolitan ER patients.

Methods: We considered 1565 subjects accessing our ER and receiving a diagnosis of psychomotor agitation and substance intoxication over a 6-month period (July–December 2015). We excluded patients who had already received a primary psychiatric diagnosis of no substance abuse, as well as accidental or self-harm intoxications: 1294 cases were excluded. We analyzed data for 271 patients, considering the emergency department report, laboratory data, and psychiatry ward records (if present).

Results: Mean age in our sample was 39.7 years (SD 14.5); 63% of patients were Italian. Most patients were male (69%); among males, we recorded a double peak in age distribution of 18–29 and 40–49 years, accounting for 59% of cases. The majority of the patients (n = 112, 68%) arrived at the ER by ambulance. After ER evaluation and initial treatment, 122 (47%) were admitted to a psychiatry ward, with a mean length of stay of 11.1 days (SD 8.6). Diagnosis of intoxication was mostly clinically driven (only in 82 cases were toxicology tests on substances of abuse performed). The most common substance identified was alcohol (n = 12,947.6%) and 16 subjects were positive for tetrahydrocannabinol (THC), 18 for benzodiazepines, 6 for cocaine, and 1 for opioids. NPS abuse emerged only in 3 cases, 2 were suggestive of ketamine, and 1 positive for methamphetamine. One patient had reportedly taken methylenedioxyxypolyornerone (MDPV) but not tested. We detected 98 cases in which substance abuse was clinically suggestive but not tested: the most common symptoms were dissociative ideation, dangerous behavior and visual
hallucinations. Among these, 67 (68.4%) were admitted to a psychiatric ward; 46 were diagnosed with psychosis, and 12 with a manic episode.

**Conclusion:** In our sample, we could not find significant data regarding diagnosis of NPS intoxication, although it is an increasing problem in the Italian population. Clinical updates on the subject and a stronger collaboration between healthcare professionals are needed, as well as modern techniques for toxicological investigations. This, in addition to a complete and correct anamnesis collection when possible, would permit better diagnosis and treatment, and avoid unnecessary procedures.

### 25. 4-Fluoromethylphenidate (4F-MPH) abuse: an analytically-confirmed case

Marcello Di Tuccia, Pietro Papa, Giampietro Frison, Flavio Zancanaro, Antonella Valli, Davide Lonati, Eleonora Buscaglia and Carlo A. Locatelli

*Laboratory of Analytical Toxicology, Fondazione IRCCS Policlinico San Matteo-Pavia, Pavia, Italy; Laboratory of Environmental Hygiene and Forensic Toxicology, Department of Prevention, Azienda USL3 Mestre (Venezia), Mestre, Italy; *Pavia Poison Control Centre – National Toxicology Information Centre – Clinical and Experimental Lab, Toxicology Unit, Maugeri Clinical and Scientific Institutes IRCCS and University of Pavia, Pavia, Italy*

**Objective:** 4F-MPH is a methylphenidate analog that appeared on the Internet market as an alternative to other methylphenidate analogs (such as ethylphenidate). It was notified for the first time in 2015 as a new psychoactive drug [1]. Little is known about its pharmacology, but in vitro studies suggested that the addition of the fluorine atom makes 4F-MPH pharmacologically more potent than methylphenidate [2]. Moreover, bloggers report that it is considerably more potent than methylphenidate and ethylphenidate, with fewer uncomfortable side effects, such as anxiety and muscle spasm. We present a case of analytically confirmed 4F-MPH intoxication.

**Case report:** A 26-year-old female was admitted to the Emergency Department with severe psychomotor agitation, mild confusion and tachycardia (100 bpm); blood pressure, body temperature, and oxygen saturation were normal. Biochemical analyses were normal and urine immunochemical screening for opiates, cocaine, methadone, amphetamines, cannabinoids, and ethylphenidate was negative. She reported she had suffered from agitation, insomnia, and palpitations for a week, during which she sniffed a powdered named 4F-MPH acquired on the Internet. Symptoms improved after sedation with diazepam. Biological samples and the powder were sent to our lab for further toxicological analysis. The analyses were performed using 4F-MPH certified standard as reference (Chiron AS, Norway). The powder was analyzed by gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-tandem mass spectrometry (LC-HRMS) and biological samples by liquid chromatography-tandem mass spectrometry (LC-MS/MS) multiple reaction monitoring (MRM). Moreover, urine screening (GC-MS and LC-MS/MS) for new psychoactive drugs (i.e., cathinones, anticholinergics, dissociative/anaesthetics, trypamine derivatives, 2C and NBOMe-drugs, benzofurans, amphetamine derivatives) and prescription psychoactive drugs was performed. The substance identified in the powder was compatible with 4F-MPH: the methods do not distinguish between the isomers, but to date no other isomers have been notified. 4F-MPH was also detected in blood and urine. No other psychoactive drugs were detected.

**Conclusion:** This is the first analytically confirmed case of abuse of 4F-MPH. The symptoms presented by the patient are reasonably attributed to abuse of 4F-MPH, as intoxication with ethylphenidate is characterized by a similar clinical picture [3].

### 26. Diffuse ST elevation on electrocardiogram (ECG) consistent with pericarditis secondary to smoking “K2”

Muhammad Masood Khalid, Rayhan Tariq, Ahmed Mamdouh Taha Mostafa, Rita McKeever and Richard Hamilton

*Emergency Department, Division of Medical Toxicology, Drexel University College Of Medicine, Philadelphia, United States; Department of Anesthesia, Drexel University College Of Medicine, Philadelphia, United States; Department of Emergency Medicine, Drexel University College Of Medicine, Philadelphia, United States*

**Objective:** Synthetic cannabinoid (SCs) are compounds based on indole and indazole scaffolds with various side chains that are agonists at the cannabinoid 1 and 2 (CB1/CB2) receptors. A number of cardiovascular effects subsequent to SC use have been reported, including tachycardia, tachy- and bradydysrhythmias, myocardial ischemia, and myocardial infarction. To our knowledge, this is the first case series to report transient ECG changes consistent with pericarditis after smoking “K2.”

**Case reports:** Case 1. A 26-year-old male with a history of substance abuse was brought to the Emergency Department (ED) after being found somnolent. He admitted to “K2” use, denied other co-ingestions, and denied chest pain. On physical examination, the patient had injected conjunctiva. Initial vital signs included blood pressure 116/77 mmHg, respiratory 16/minute, temperature 36.8 °C, heart rate 102 bpm, and oxygen saturation 95% (room air). His ECG revealed diffuse ST elevations with PR depression without any reciprocal changes. Laboratory studies including serial troponins were negative. A bedside ultrasound showed no evidence of pericardial effusion. He received ibuprofen and left against medical advice. He returned to the ED 10 hours later stating he felt generalized weakness. Repeat ECG was normal. His vital signs, physical examination, laboratory studies including an additional troponin were all negative. Analysis of a serum sample obtained on this visit demonstrated the presence of AB-FUBINACA and ABD-FUBINACA. Case 2. A 22-year-old male was brought to the ED after being found unresponsive. He stated he smoked “K2,” denied any other co-ingestions, and denied chest pain. His physical examination revealed conjunctival injection. His initial vital signs included blood pressure 86/49 mmHg, respiration 18/minute, heart rate 63 bpm, and temperature 36.7 °C. His ECG demonstrated diffuse ST elevations without PR depression. Laboratory studies including serial troponins were negative.

### References


Bedside ultrasound demonstrated no evidence of pericardial effusion. He was admitted for one day, his vital signs normalized, and a repeat ECG demonstrated benign early repolarization. Analysis of a serum sample obtained on this visit demonstrated the presence of AB-FUBINACA.

**Conclusion:** In both cases, the ECGs were consistent with pericarditis, and this was confirmed by cardiology consultation. The diagnosis of pericarditis requires two of the following: chest pain consistent with pericarditis, typical ECG changes; pericardial friction rub, or a non-trivial pericardial effusion. These patients only had ECG changes. Furthermore, the SCS abused in these patients have been encountered in prior patients without the ECG changes of pericarditis. Further investigation is warranted to elucidate the effect of SCS on the heart.

27. Acute intracerebral haemorrhage following the use of synthetic cannabinoids and cathinones

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Center of Toxicology, Vilnius University, Vilnius, Lithuania

**Objective:** Synthetic cannabinoids and synthetic cathinones are the two biggest groups of new psychoactive substances and are currently popular drugs of abuse [1]. Toxicity with these substances can be associated with severe adverse events. We present two cases of intracerebral haemorrhage following the use of synthetic cannabinoids and cathinones.

**Case series:** Case 1. An 18-year-old man with no history of drug abuse was brought to the Emergency Department (ED) by ambulance after charged from the hospital. Case 2. A 40-year-old man without no history of drug abuse was brought to the ED by ambulance after charged from the hospital.

**Results:** We reviewed a specific database of patients with acute recreational drug toxicity from 1 October 2013 to 30 April 2017. The cases of acute intoxication caused by a recreational drug (in this case, cannabis associated with or without alcohol) were included. We reviewed a specific database of patients with acute recreational drug toxicity from 1 October 2013 to 30 April 2017. The chi-square test was used to analyze categorical data.

**Methods:** An observational study of medical records of patients presenting to an Emergency Department of a tertiary hospital. Any patient presenting to the Emergency Department with symptoms of acute intoxication caused by a recreational drug (in this case, cannabis associated with or without alcohol) were included. We reviewed a specific database of patients with acute recreational drug toxicity from 1 October 2013 to 30 April 2017. The chi-square test was used to analyze categorical data.

**Results:** Of a total of 740 patients treated for recreational drug presentations, 220 (30%) included cannabis. In 140, cannabis was the only substance without taking into account ethanol. In 12 cases, the concomitant consumption of alcohol was not reported and therefore, the remaining 128 were analyzed. Of these 128, 77% were male. Overall, 80 patients (62%) had consumed alcohol, as well as cannabis. Clinical characteristics and physical examination were compared in both groups (Table 1).

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Cannabis without alcohol (n = 48)</th>
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<tr>
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<td>Palpitations</td>
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<td>p = .0589</td>
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28. Acute cannabis presentations: clinical characteristics and the effect of ethanol co-ingestion

Juan Ortega Pérez, Christopher Yates, Catalina Homar Amengual and Jordi Puiguriguerr Ferrando

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**Objective:** Despite popular consideration as a non-problematic drug in acute intoxication, cannabis plays an important role in Emergency Department presentations arising from recreational drugs [1]. In this study, we analyze the clinical characteristics of acute cannabis intoxications with or without alcohol and compare these two modalities.

**Methods:** An observational study of medical records of patients presenting to an Emergency Department of a tertiary hospital. Any patient presenting to the Emergency Department with symptoms of acute intoxication caused by a recreational drug (in this case, cannabis associated with or without alcohol) were included. We reviewed a specific database of patients with acute recreational drug toxicity from 1 October 2013 to 30 April 2017. The chi-square test was used to analyze categorical data.

**Results:** Of a total of 740 patients treated for recreational drug presentations, 220 (30%) included cannabis. In 140, cannabis was the only substance without taking into account ethanol. In 12 cases, the concomitant consumption of alcohol was not reported and therefore, the remaining 128 were analyzed. Of these 128, 77% were male. Overall, 80 patients (62%) had consumed alcohol, as well as cannabis. Clinical characteristics and physical examination were compared in both groups (Table 1).

**Table 1.** Clinical characteristics and physical examination of users taking cannabis with and without ethanol.

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Objective: We present a case of severe amphetamine poisoning associated with a prolonged dyskinetic syndrome.

Case report: A 29-year-old man swallowed a sealed bag containing 5 g of amphetamines when arrested by the police. He was tense, nervous, at times confused, with heart palpitations and involuntary movements of the limbs. He was admitted to the Clinic of Toxicology of UMHATEM "N.I.Pirogov", Sofia, Bulgaria.

Conclusion: In this severe amphetamine poisoning, the clinical picture was dominated by prolonged dyskinetic syndrome. High doses of benzodiazepines over a prolonged period were required for management. Against this background, the patient has no gross cognitive impairment.

30. Fatalities related to dextromethorphan abuse

Blazena Caganova, Silvia Plackova and Igor Batora
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Objective: Dextromethorphan (DXM) is a centrally-acting cough suppressant, structurally similar to opioids, and sold over-the-counter in many countries. At recommended doses, the drug produces few adverse effects, however, when abused in large quantities (>2 mg/kg), it has been associated with dissociative effects similar to ketamine and phencyclidine. Massive ingestions may be associated with serious toxicity. Since 2012, increasing recreational use of DXM has been reported to the National Toxicological Information Centre (NTIC) in Slovakia.

Methods: All cases of DXM overdose were extracted from the NTIC database from January 2008 to December 2016. Data were evaluated for demographic and clinical factors.

Results: We studied the outcome of 72 cases of DXM overdose. The median age of patients was 15 years (range 1–55 years). Recreational abuse prevailed with 70.8%; accidental ingestion occurred in 22.2% and a suicide attempt in 6.9%. The median ingested dose was 250 mg (range 15–2700 mg). There were no symptoms or signs of toxicity in 15 cases (20.8%), minor toxicity occurred in 44 patient (61.1%), moderate in 10 (13.9%) and serious in 1 (1.4%). Clinical features included drowsiness (22.8%), ataxia (22.2%), nausea or vomiting (19.4%), mydriasis (13.8%), tachycardia, hypertension (11.1%), blurred vision (8.3%), agitation (8.3%), nystagmus (5.6%), tremor (5.6%), and coma (2.8%). In total, 55.5% of the patients were treated in a healthcare facility. The median length of hospital stay was 3 days (range 1–5 days).

Conclusion: In this single case of DXM abuse, two men aged 22 and 55 years died after ingestion of tablets containing DXM for recreational purposes. Toxicological analysis revealed high concentrations of DXM. The cause of death was determined to be acute dextromethorphan intoxication. Both deceased had a history of drug abuse.

31. Gabapentin and the potentiation of opioid effects: two cases

Timothy J. Wiegand and Kenneth Conner
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Objective: Gabapentin, readily available both via prescription and illicitly, is not typically considered a “narcotic” by prescribers. Non-medical use has become increasingly common in the US and Europe [1] where abuse is associated with both illicit use of opioids and with use of methadone in opioid treatment/substitution programs. It is also abused by patients receiving buprenorphine. Individuals report taking high doses of gabapentin to reduce opioid tolerance and enhance intoxication [2]; some report that high doses can negate the ceiling-effect of buprenorphine. We present 2 cases in which patients were hospitalized after taking gabapentin in order to potentiate an opioid. These
cases are presented to illustrate this phenomenon and to highlight a concerning trend.

**Case reports:** Case 1. A 33-year-old male was found obtunded at a party after he reportedly injected heroin earlier in the evening. He was bradypneic (6 breaths/minute) and hypoxic (80% oxygen saturation) when the emergency medical services (EMS) arrived. Naloxone 2.8 mg was administered in incremental doses reversing bradypnea and hypoxia, although the somnolence remained. He later developed pulmonary edema. After two days in intensive care, he was extubated and admitted taking 7 tablets of gabapentin prior to using heroin to potentiate its effect. Case 2. A 27-year-old male receiving buprenorphine in an outpatient program was brought to the Emergency Department after his parents found him breathing but obtunded. He was given naloxone by the EMS with slight response (groans). Over the next 8 hours, he awakened and reported taking 6 × 600 mg tabs of gabapentin and a double dose 2 × 8/2 mg buprenorphine/naloxone before going to bed. He described taking this combination to experience sedation and euphoria.

**Conclusion:** Gabapentin is abused by opioid users in order to potentiate intoxication or to mitigate opioid tolerance. This effect appears to be similar to potentiation seen by other sedative-type medications such as benzodiazepines, which increases the risk of central nervous system depression, coma, respiratory depression, and fatal overdose. Consideration should be given to scheduling gabapentin and more appropriately screening/monitoring patients receiving gabapentin prescriptions, in particular, if they have an opioid use disorder.

**References**


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### 32. Saturday night abscess: a brachial plexus abscess in an intravenous drug user

Jonathan De Olano, Aaron Rothstein, Larissa Laskowski, Mary Ann Howland, Susi Vassallo and Rana Biarya

**Objective:** Brachial plexopathies are rarely caused by infectious etiologies. We report a case of a patient who presented to the Emergency Department (ED) for brachial plexus neuritis due to an intramuscular abscess and myositis in the setting of recent intravenous methamphetamine use and ingestion of 3,4-methylenedioxymethamphetamine (MDMA). Naloxone 2.8 mg was administered in incremental doses reversing bradypnea and hypoxia, although the somnolence remained. He later developed pulmonary edema. After two days in intensive care, he was extubated and admitted taking 7 tablets of gabapentin prior to using heroin to potentiate its effect.

**Case report:** A 57-year-old man with a history of human immunodeficiency virus (HIV) (undetectable viral load and CD4 of 800), and polysubstance use disorder, presented to the ED reporting three days of numbness and inability to move his left arm. The evening prior, he ingested GHB and intravenous administration of methamphetamine in a left antecubital vein after being sober for three months. Unable to recall the rest of the events that evening, the patient awoke the following morning on the floor of his apartment, supine with his left arm immobile and flexed above his head. Initial vital signs were normal. On physical examination, the patient had normal heart sounds without murmurs. Neurologic exam of his left upper extremity revealed decreased sensation throughout and 0/5 strength of his deltoid muscle and all muscles distally; the rest of his neurologic exam was normal. Laboratory studies revealed a normal white blood cell count (7 × 10^3/mm^3), normal electrolytes, and creatine phosphokinase of 490 IU/L. Brain computerized tomography was unremarkable. Magnetic resonance imaging (MRI) of the cervical spine and brachial plexus showed focal myositis with a 1.7 × 1.5 cm intramuscular abscess within the levator scapulae, focal myositis of the left middle scalene with adjacent brachial plexus neuritis lateral to the scalene triangle, and myositis affecting the left upper intercostal muscles. The patient had limited drainage of the abscess by interventional radiology, and was treated empirically with intravenous antibiotics. Cultures grew Propionibacterium acnes and Staphylococcus warneri with broad sensitivity. The patient was discharged on hospital day seven with a two-week course of amoxicillin/clavulanic acid and outpatient occupational therapy. At his six-month neurology follow-up, the patient had 4/5 and 5/5 strength to all left upper extremity muscle groups.

**Conclusion:** We present a case of a complete brachial plexopathy from an abscess in the setting of recent methamphetamine intravenous injection. High-risk patients, such as intravenous drug users, with acute brachial plexus palsies may warrant appropriate imaging diagnostic studies to exclude infectious etiologies.

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### 33. Analytically confirmed recreational use of oberacetam (Noopept®) in the UK

Heather Jarman, Philip Moss, Michael D. Dunn, Simon L. Hill and Simon H. L. Thomas

**Objective:** Oberacetam (Noopept®, N-phenylacetyl-L-prolylglycine ethyl ester, GVS-111, CAS Number 157115-85-0) is a proline-containing dipeptide nootropic agent developed in Russia and reported to have memory enhancing, anxiolytic, and neuroprotective actions after oral use [1]. Although not licensed as a medicine in the European Union, it is promoted for sale on websites that claim the substance boosts memory and recall. There are media reports of increasing use of Noopept as a “smart drug” by British students. Little information is available about its human toxicity. Here, we present a patient who developed toxicity requiring hospital admission following analytically confirmed recreational use of oberacetam with other drugs.

**Case report:** A 21-year-old male presented to a hospital in London with palpitations after snorting oberacetam powder purchased via the internet (www.intellimeds.net), together with cocaine. He had also reported taking excess amounts of risperidone and duloxetine. Admission observations included sinus tachycardia (134/min) with frequent ectopics, mild hypotension (BP 99/56 mmHg) and drowsiness (Glasgow Coma Scale 14). An electrocardiogram, arterial blood gases, and hematologic and biochemistry screens showed no other significant abnormalities. The heart rate had fallen to 116/min after 1.75 hours and to 99/min after 5.25 hours. The following day, he developed facial spasm and twitching, which resolved over 24 hours and was thought to be a dystonic reaction to risperidone. As use of a novel psychoactive substance (NPS) was suspected, the patient was entered and treated empirically with interventional radiology, and was treated empirically with intravenous antibiotics. Cultures grew Propionibacterium acnes and Staphylococcus warneri with broad sensitivity. The patient was discharged on hospital day seven with a two-week course of amoxicillin/clavulanic acid and outpatient occupational therapy. At his six-month neurology follow-up, the patient had 4/5 and 5/5 strength to all left upper extremity muscle groups.

**Conclusion:** We present a case of a complete brachial plexopathy from an abscess in the setting of recent methamphetamine intravenous injection. High-risk patients, such as intravenous drug users, with acute brachial plexus palsies may warrant appropriate imaging diagnostic studies to exclude infectious etiologies.
analysed by liquid chromatography-tandem mass spectrometry and confirmed the presence of oberacetam, cocaine, and its metabolites and risperidone, as well as diazepam and its metabolites.

**Conclusion:** This case confirms the recreational use of oberacetam by snorting, although the clinical features observed (tachycardia, ecotropes, drowsiness, dystonia) probably relate to reported co-use of other substances. Clinical toxicologists and poison centres should be aware of the use of oberacetam and further data collection is needed to characterize its toxic effects.

**Reference**


**34. Clinical effects and analytical implications of the use of Sceletium tortuosum and cannabis: a case report**

Anna Celentano, Marco Morina, Adriano Masarin, Attilio Negri, Cecilia Gechtmans, Rossana Borghin, Fabrizio Sesana, and Franca Davanzo

**Objectives:** Sceletium tortuosum (ST), known as “kanna,” is a South African plant used by native people as a painkiller and to alleviate hunger; due to its features, it has gained popularity for its psychoactive effects, generally because of synergistic interaction observed with other psychoactive substances, including Cannabis sativa (CS), which patients are potentially unaware of. Following the involvement of our Poison Control Center in a case of ST intoxication and considering the current availability of “smart” drugs lacking toxicological profiles and laboratory standards, we want to highlight risks of ST use, especially when combined with CS. Moreover, we underline the difficulty of the determination of ST’s active principles on biological matrices, as analytical methods are unavailable in most hospitals.

**Case report:** A 16-year-old male presented to the Emergency Room (ER) in June 2015 with psychomotor agitation, restlessness, abdominal pain, and panic attacks. He admitted daily use of cannabis and reported a similar episode one year before. He was treated with lorazepam after neuropsychiatric evaluation. He returned to ER two days later for worsening anxiety. A more accurate anamnesis clarified that the patient purchased on the Internet and used ST three days prior to the first presentation, which was smoked and snorted. A urine toxicology screen demonstrated tetrahydrocannabinol (THC) use (≥100 ng/mL), but no data on ST were available, due to the impossibility to detect it with standard laboratory tests.

**Conclusion:** A daily assumption of 50–100 mg of ST may cause a significant improvement in mood disorders and anxiety symptoms. However, in the first week of use, a worsening in anxiety symptoms may occur; furthermore, a powerful synergy with CS could expose patients to serious risks of traumatic flashbacks and hyperesthesia. Similarly, exaggerated responses may occur with concurrent use of antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs). Cross-reactivity reactions with tetrahydrocannabinol seem unlikely, due to the steric hindrance of the substituent group of mesembrine.

**37. Cerebrovascular ultrasound changes in opium addicted and non-addicted ischemic stroke patients**

Omid Mehrpour, Seyed Mohammad Mousavi Mirzaei, Abolfazl Talebi, Alireza Amirabadizadeh and Samaneh Nakhaee

**Objective:** Stroke is one of the leading causes of morbidity and mortality worldwide [1]. It has been noted, in addition to known risk factors of ischemic stroke, other factors such as substance use are also involved in the development or exacerbation of the atherosclerotic process [2,3]. The aim of the present study was to compare cerebrovascular ultrasound changes in addictive and non-addict ischemic stroke patients.

**Methods:** In this cross-sectional study, ischemic stroke patients admitted to the Vali-Asr Hospital (Birjand, Iran) in 2017 were enrolled. A transcranial doppler (TCD) was performed in all patients and the findings were compared between addicts and non-addicts. Opium dependency was determined based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria. Data were analyzed by SPSS software (version 19) using Student’s t-test and p values of .05 or less were considered as the statistical significant levels.

**Results:** A total of 115 patients were enrolled in the study, of which 40 (34.7%) were addicted to opium and 75 patients (65.3%) were non-addicts. The median [IQR] number of atherosclerotic plaques were significantly higher in opium-dependent patients compared to the non-dependent group ((3 [1–4] versus 1.5 [1–3], z = 1.98, p = .008). There was no statistical significant differences in median [IQR] number of calcified arteries ((2 [1–3] versus 1 [1–2]), z = 1.39, p = .16), percentage of vascular stenosis in left (35 [15–50] versus 35 [10–48], z = 0.36, p = .72), and right (27 [14.25–42.5] versus 32 [15.1–50], z = 0.71, p = .48) sides between the addicted and non-addicted patient.

**Conclusion:** The results showed that the pattern of vessel stenosis was different between opium addicted and non-addicted ischemic stroke patients. Further studies are recommended to evaluate the possible effects of opium consumption parameters such as dosage, duration, and route of opium consumption on these findings.

**References**


38. Low Glasgow Coma Scale (GCS) due to gammahydroxybutyrate (GHB) intoxication is not an indication for intubation

Lidwien Van Helmond and Femke Gresnigt
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Objective: The approach to management of gammahydroxybutyrate (GHB)-related presentations is variable [1]. In particular, opinions regarding the indications for intubation after GHB overdose vary [1–3]. The objectives of this study are to describe the clinical profile of a comatose GHB-intoxicated population and to determine if supportive care without endotracheal intubation in the Emergency Department (ED) is safe without complications.

Methods: Retrospective chart review of all patients presenting to a tertiary urban ED with a reduced level of consciousness related to suspected GHB or gammabutyrolactone (GBL) intoxication between April 2011 and December 2014.

Results: A total of 209 patients with a reduced level of consciousness due to GHB intoxication were included. Mean age was 30.5 years (SD 7.67) and 84% were male. More than 75% of the patients had a Glasgow Coma Scale (GCS) less than 9 with a median GCS of 6 [IQR 3–8]. The most frequently seen and potentially life-threatening symptoms were airway obstruction (22%), hypoxia (12%), hypothermia (14.8%), bradycardia (8.1%), hypotension (6.7%), bradypnea (5.7%), and vomiting (5.3%). Four patients (1.9%) were intubated and three were admitted to the intensive care unit. In total, 206 patients were observed in ED while monitoring rhythm, pulse rate, respiratory rate, saturation, and capnography and were discharged from the ED after a mean stay of 156 minutes [IQR 120–212]. There were no deaths and none of the patients had signs of aspiration pneumonia or returned to our ED due to complications.

Conclusion: Supportive care, monitoring of vital signs and neurologic state, and non-invasive airway management was sufficient to prevent major adverse events. This conservative management has led to a low rate of intubation and a low rate of hospital admissions. Major complications were already evident after primary survey. Our study shows that it is safe to observe patients with a reduced level of consciousness due to GHB intoxication in the ED when complications like airway obstruction and hypoxia can be treated adequately without intubation.

References


39. Illegal drug overdoses in Ljubljana, Slovenia

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Centre for Clinical Toxicology and Pharmacology, University Medical Centre Ljubljana, Ljubljana, Slovenia

Objective: The aim of this study was to evaluate illicit drug overdoses at the University Medical Centre Ljubljana (UMCL), Slovenia.

Methods: A retrospective study conducted at the internal medicine emergency units, UMCL, the primary city hospital in Ljubljana (population 400,000 inhabitants). All patients admitted to the internal medicine emergency units poisoned with illicit drug(s) between 2010 and 2016 were included. They had documented exposure to illegal drugs according to the patient’s history or/and urinary semi-quantitative screening by immunoassay for opiates, tetrahydrocannabinoids, met/ampheptamines, and cocaine and/or urine/serum drug measurement by liquid chromatography/mass spectrometry.

Results: A total of 23,000–24,000 patient examinations were conducted yearly at the units between 2010 and 2016. In 2016, the number of illicit drug-related acute emergencies accounted for 0.64% of all emergencies handled by the units, whereas in 2010, 2011, 2012, 2013, 2014, and 2015, this proportion was 0.24%, 0.19%, 0.20%, 0.36%, 0.54%, and 0.61%, respectively. Table 1 lists the illicit drugs that caused acute emergencies in adult patients treated at UMCL.

Conclusion: Illicit drug-related acute emergencies accounted for 0.2–0.6% of all patients treated between 2010 and 2016. In the past few years, an increase in the number of heroin and cocaine-induced acute emergencies was observed along with an ever-increasing number of cannabis poisonings. In the last three years,
cannabinoids have been the most commonly found illicit drug. Since 2013, we recorded a significant increase in gamma-hydroxybutyrate (GHB) poisoning. The number of poisonings with amphetamine-type stimulants has remained unchanged in recent years. However, a marked increase was observed in 2016. Poisonings with new psychoactive substances (NPS) are constantly increasing, of which synthetic cathinones have prevailed in recent years. Consequently, a national system for continuous monitoring of NPS poisonings (SONDA project) was developed in 2016.

40. Hyperthermia in sympathomimetic/serotonergic substance of abuse poisoning: a case series

Erica Garbelli\textsuperscript{a,b}, Valeria M. Petrolini\textsuperscript{a}, Teresa Coccinia\textsuperscript{a}, Sarah Vecchio\textsuperscript{a}, Pietro Papa\textsuperscript{b}, Davide Lonati\textsuperscript{a} and Carlo A. Locatellia\textsuperscript{a}

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Objective: Hyperthermia is one of the most serious and feared toxic effects of substances of abuse (SOA) with sympathomimetic/serotonergic effects. Unlike fever, the body heat increase is due to either central or peripheral mechanisms, and is not responsive to common antipyretic drugs. We present a case of a patient with hyperthermia after recreational drug use.

Methods: A retrospective study evaluating patients needing emergency medical care after the use of sympathomimetic/serotonergic substances and referred to our Poison Control Center. Inclusion criteria were hyperthermia (temperature > 39°C) and at least two of (i) alteration in consciousness, (ii) rhabdomyolysis, and/or (iii) excitatory neuromuscular manifestations.

Results: Sixteen male patients aged 16–44 years were enrolled over a 6-year period (2011–2016). Overall, mortality was 56.2\% (9/16): survivors recovered completely. Clinical manifestations that caused admission to hospital were characterized in most cases by early onset of hyperthermia and alteration in consciousness. Not all clinical data are available for a patient who died soon after admission with a body temperature of 41.7°C. Among the other 15, rhabdomyolysis was present in 15/15 (100\%), excitatory neuromuscular manifestations in 12/15 (80\%), and acute renal failure in 11/15 (73.3\%). Lethal cases worsened within hours or few days to multi-organ failure, coagulation disorders including disseminated intravascular coagulation (DIC), and finally irreversible hemodynamic failure. Toxicological analysis performed for each patient revealed sympathomimetic/serotonergic substances in 12/15 patients. No sympathomimetic/serotonergic SOA was found despite the history of consumption in 3 cases. The detected sympathomimetic/serotonergic SOA were cocaine (8/16), 3,4-methylenedioxymethamphetamine (MDMA) (16/16), amphetamines/methamphetamine (4/16), APB (1/16), paramethoxyamphetamine (PMA) (1/16), levamisole, tetrahydrocannabinol (THC), heroin, tramadol, methadone, ethanol, and ketamine were also detected in 6 of these patients. In 6/16 cases, more than one sympathomimetic SOA was found.

Conclusion: Hyperthermia occurring in sympathomimetic/serotonergic SOA poisoning is frequently lethal. The patients have the same clinical features as seen in neuroleptic malignant syndrome (NMS), and severe NMS typical complications (renal and liver failure, multi-organ failure, and DIC). The clinical management of both NMS and hyperthermia due to substances of abuse is the same, and may include specific therapy with dantrolene. Similarities between the two syndromes suggest shared pathophysiologic mechanisms. Idiosyncratic occurrence hints at individual predisposing factors that require investigation.

41. Acute health problems due to recreational drug use in patients presenting to an urban Emergency Department in Switzerland

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Objective: To describe the frequency and variety of acute medical problems due to recreational drug use in patients presenting to an Emergency Department in Switzerland during a 15-month period with a focus on novel psychoactive substances.

Methods: Retrospective analysis within the Euro-DEN Plus project of cases presenting from May 2016 to July 2017 at the Emergency Department of the University Hospital of Bern. Cases with symptoms/signs consistent with acute toxicity were retrieved using a comprehensive full-text search algorithm. Isolated ethanol intoxications were excluded.

Results: During the study period, 292 of the 56,303 Emergency Department attendances were included. The mean patient age was 33 years (range 16–65) and 70\% were male. Alcohol co-ingestion was reported in 47\% and use of more than one recreational drug simultaneously occurred in 32\% of the cases. The most frequent cases were related to cocaine (42\%), cannabis (26\%), and heroin (18\%). Excluding opioids and benzodiazepines, prescription drugs used recreationally were antidepressants (n = 4), dextromethorphan (n = 3), methylphenidate (n = 2), and antipsychotics (n = 1). The reported herbal substances included damiana and ayahuasca (1 case each). Urine drug screening immunoassay was available in 160 patients (55\%). In this subset based on urine screening, the most frequently detected substances were cocaine (80 times), cannabis (79 times), and benzodiazepines (68 times). There were four intoxications with novel substances involved; two cases with 2,5-dimethoxy-4-bromophe-nethylamine (2C-B) use (immunoassay in one case not performed and in the other case positive for amphetamines [co-ingested] and benzodiazepines [iatrogenic]), one case with 4-acetoxy-dimethyltriptamine (4-Aco-DMT) use (immunoassay positive for benzodiazepines [iatrogenic]), and one case of carfentanil (detected with liquid chromatography-mass spectrometry, immunoassay negative). Overall, 51\% of the patients had impaired consciousness (Glasgow Coma Scale (GCS) < 15) upon presentation and/or pre-hospital, 19\% were unconscious (GCS < 8). Other frequent symptoms were agitation (32\%), anxiety (29\%), and tachycardia (28\%). Severe complications included one fatality (patient was found unconscious with a needle in arm, immunoassay positive for opiates and cannabis), two acute myocardial infarctions, as well as psychosis and seizures in 37 and 21 cases, respectively. Most patients (55\%) were discharged home, 21\% were referred to psychiatric care and 13\% were admitted to intensive care.
Conclusion: Although new generations of recreational drugs are flooding the market, the usual suspects such as cocaine and cannabis are still dominating when it comes to hospital admissions with presentations mainly characterized by central nervous system depression, sympathomimetic toxicity, and/or psychiatric disorders.

42. One-year experience with the Paris supervised injection site: drugs used and safety analysis

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Objective: In 2016, the first French supervised injection site (SIS) was opened in Paris. SIS is a legally-sanctioned, medically-supervised facility designed to reduce nuisance from public drug use, providing a hygienic and stress-free environment allowing intravenous injection and inhalation of illicit recreational drugs. Collaboration was set up between the SIS and the neighboring hospital to manage the medical complications resulting from drug use. Our objective was to describe the drug user profiles, the drugs used and events requiring medical intervention, transfer to the Emergency Department and admission to the Intensive Care Unit (ICU).

Methods: We conducted a prospective observational study including all patients who visited the SIS during the last 10 months (October 2016 to August 2017). The collection of the usual anonymous demographic, medical, and toxicological data was performed by the care-givers and social workers in charge of the drug users. Data were declarative and no analytical confirmation was available except for the patients admitted to the ICU.

Results: During 10 months, 818 drug users (F/M sex ratio 0.13; median age 38 years (21–69); patients without resources (40%), without medical insurance (27%), with unstable housing/homelessness (52%)) visited the SIS for drug injection or inhalation, representing 50,060 drug uses including 14,587 inhalations and 35,473 injections by 180 drug users/day. Drug users had no addictionology (48%) or socio-medical (27%) follow-up. They were infected by hepatitis virus C (44%) and/or HIV (5%). They declared they continued injecting in a public space (52%), sharing material (13%), and needles/syringes (47%). The injected/inhaled drugs in the SIS were Skenan\textsuperscript{a} (morphine, 42.6%), crack (43.0% including a third of injections), methadone (6.3%), buprenorphine (6.1%), heroin (1.2%), and cocaine (0.89%). These drugs were self-administered by polydrug users declaring concomitantly consuming crack (72.0%), illicit morphine (68.5%), cocaine (34.8%), ethanol (33.7%), cannabis (33.4%), heroin (29.9%), illicit methadone (20.4%), benzodiazepines (13.6%), and illicit buprenorphine (9.5%). Forty-five patients required a paramedical intervention in the SIS resulting in 17 calls to the Emergency Department and 15 hospital admissions including 2 transfers to the ICU in relation to opioid overdose. No cardiac arrest and no death occurred.

Conclusion: SIS visits for recreational drug self-administration rapidly became popular among drug users. Illicit morphine (Skenan\textsuperscript{a}) represents the most commonly self-administered drug. SIS seems safe, highlighting the effectiveness of the collaboration set up with the neighboring hospital.

43. Presentations to the Emergency Department with misuse of benzodiazepines and Z-drugs: profiling and relation to sales data

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Objective: Non-medical use of benzodiazepines and Z-drugs is common; however, there is limited information available on the extent of harm related to this in Europe, as well as the relationship between misuse and availability. We describe presentations to the Emergency Department (ED) in Europe related to the recreational use of benzodiazepines and Z-drugs and compare regional differences in these presentations with legal drug sales of benzodiazepines and Z-drugs within each country.

Methods: ED presentations with recreational misuse of benzodiazepines and Z-drugs were obtained from the Euro-DEN dataset for the period from October 2013 to September 2015; data extracted included demographics, clinical features, reported co-used drugs, and outcome data [1]. Sales figures obtained by QuintilesIMS\textsuperscript{’} (Atlanta, Georgia) were used to compare regional differences in the proportion of benzodiazepines and Z-drugs in the ED presentations and legal drug sales across Europe.

Results: Over the two years, there were 2,119 presentations to the Euro-DEN project associated with recreational use of benzodiazepines and/or Z-drugs (19.3% of all Euro-DEN presentations). Presentations with 25 different benzodiazepines and Z-drugs were registered in all countries, most (1809/2340 registered benzodiazepines and Z-drugs, 77.3%) of which were prescription drugs. In 24.9%, the type of benzodiazepine was unknown. Where the benzodiazepine/Z-drug was known, the most frequently used benzodiazepines and Z-drugs were respectively clonazepam (29.5% of presentations), diazepam (19.9%), alprazolam (11.7%), and zopiclone (9.4%). The proportions of types of benzodiazepines/Z-drugs related to ED-presentation vary between countries. We note a moderate (Spain, UK, Switzerland) to high positive (France, Ireland, Norway) correlation between ED-presentations and sales data (Spearman Row’s correlation 0.66–0.80, $p < .005$), with higher correlation in countries with higher ED presentation rates.

Conclusion: Presentations to the ED associated with the non-medical use of benzodiazepines and/or Z-drugs are common, with differing proportions of types of benzodiazepines and/or Z-drugs between countries. There is a moderate to high correlation with the sales data, with higher correlation in countries with higher ED presentation rates. However, they are not the only explanation for a variation in use and benzodiazepines or Z-drug related ED presentations.
44. Doctors’ awareness and perception of prescription medicine misuse in Singapore

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**Objective:** To establish the level of awareness and perception of prescription medicine misuse among doctors working in the Emergency Department (ED) in Singapore.

**Methods:** An online questionnaire was emailed to doctors working in six Singapore EDs. Demographic data (age, gender and job designation), awareness of prescription medicine misuse in their practice, whether they suspected their patients misused prescription medicines and whether they required help in managing such patients were collected. The drugs surveyed were benzodiazepines, Z-drugs (zopiclone/zolpidem), opioid analogues, codeine-containing cough-mixtures, prescription stimulants, pregabalin, gabapentin, and baclofen.

**Results:** Overall, 102 doctors completed the survey: 55.9% male, median (IQR) age 38 (25–55) years; 24.5% medical officers/residents, 22.5% resident physicians (fellows), and 54.5% consultants. The majority of respondents (76.5%) were concerned about misuse of prescription drugs by their patients, and 86.3% were aware that they might be prescribing to patients who were misusing medicines. Codeine-containing cough-mixtures were the most common medicine that doctors thought their patients were misusing (Table 1). In total, 80.8% of the respondents felt they needed help to deal with patients who were prescription medicine misusers and 65.7% indicated that more training in this area was required: 15.1% preferred face-to-face training, 37.9% preferred online training, and 47.0% were keen for both face-to-face and online training. Implementation of clinical guidelines on management of these patients, online resources, and a hotline and online training were preferred online training, and 47.0% were keen for both face-to-face and online training. Implementation of clinical guidelines on management of these patients, online resources, and a hotline and online training. Implementation of clinical guidelines on management of these patients, online resources, and a hotline and online training. Implementation of clinical guidelines on management of these patients, online resources, and a hotline and online training. Implementation of clinical guidelines on management of these patients, online resources, and a hotline and online training. Implementation of clinical guidelines on management of these patients, online resources, and a hotline and online training.

**Conclusion:** The majority of doctors surveyed were aware that their patients could be misusing prescription medicines and that they needed help/training to deal these patients. These findings will be used to improve training to help doctors manage such patients, to ensure that their prescribing is appropriate and to decrease the risk of prescription medicine misuse.

<table>
<thead>
<tr>
<th>Drug</th>
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<th>No</th>
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<tr>
<td>Benzodiazepines</td>
<td>64.7%</td>
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</tr>
<tr>
<td>Z-drugs (zopiclone, zolpidem)</td>
<td>45.1%</td>
<td>54.9%</td>
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<tr>
<td>Opioid analogues</td>
<td>83.3%</td>
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</tr>
<tr>
<td>Baclofen</td>
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<td>35.3%</td>
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45. Intentional opioid exposures with benzodiazepine co-ingestants in the US and Europe as reported to the RADARS\textsuperscript{a} System Global Toxicosurveillance Network

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**Objective:** This study aimed to determine what proportion of intentional exposures involving opioids also included a benzodiazepine as reported to participating Reserched Abuse, Diversion and Addiction-Related Surveillance (RADARS\textsuperscript{a}) System Global Toxicosurveillance Network (GTNet) poison centres in the United States and Europe.

**Methods:** GTNet was established in 2011 as a means of collaboration between countries to provide information about prescription drugs involved in acute health events as reported to participating poison centres worldwide, including intentional and unintentional exposures. Intentional exposures involving prescription opioids from 2012 through 2016 were analyzed from participating poison centres in Italy (Milan), Germany (Göttingen), France (Paris), and the US (Poison Center Program; 50 of 55 regional poison centres). We examined the percentage of intentional exposures by country that also involved a benzodiazepine. In addition, we examined the percentage of opioid and benzodiazepine co-ingestion intentional exposures that were misuse/abuse exposures.

**Results:** Of the 4 countries evaluated, the US had the highest percentage of opioid intentional exposures that were misuse/abuse exposures. In the US (Poison Center Program; 50 of 55 regional poison centres), the percentage of opioid and benzodiazepine co-ingestion intentional exposures that were misuse/abuse exposures was reported as misuse/abuse exposures.

**Conclusion:** Differences across countries may reflect differences in populations utilizing poison centres (general population versus medical providers), prescribing patterns within each country, and the extent of opioid misuse within each country.

46. A nine year retrospective review of trends in oral anticoagulant enquiries to the UK National Poisons Information Service

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**Objective:** To determine what proportion of queries to the UK National Poisons Information Service (NPIS) in the nine years from April 2008 to March 2017 were related to oral anticoagulants and what proportion of these related to warfarin.

**Methods:** All 13,905 anticoagulant-related queries to the NPIS databases were reviewed: 8,097 (58.7%) were for warfarin, 2,421 (17.6%) for dabigatran, and 3,387 (24.7%) for other oral anticoagulants.

**Results:** Of the 8,097 warfarin-related queries, 61.8% were for queries relating to bleeding (4,205; 51.9%) and 23.5% for queries relating to anticoagulant-related drug–drug interactions (1,923; 23.7%). The remaining 14.7% referred to other queries.

**Conclusion:** The most frequent warfarin-related queries were related to bleeding and drug–drug interactions.

**Reference**

47. Prevention of direct oral anticoagulant prescription errors using obligatory prerequisite review by clinical pharmacists

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**Objective:** To evaluate the effectiveness of obligatory prerequisite review by clinical pharmacists in order to identify and prevent direct (novel) oral anticoagulant prescription errors.

**Methods:** A single medical center retrospective review of all direct oral anticoagulant prescriptions reviewed by clinical pharmacists from 1 January 2012 to 31 December 2016. Primary outcome was percentage of inappropriate and erroneous prescriptions. Secondary outcomes were percentage of prescription errors per direct oral anticoagulant, types of errors, and pharmacist interventions.

**Results:** During the study period, 2612 direct oral anticoagulant prescriptions were reviewed by clinical pharmacists before the medications were dispensed. Of which 530 (20.3\%) were inappropriate or erroneous. There was a significant reduction in the annual percentage of errors since the introduction of the first direct oral anticoagulant in 2012 (42.3\%) until the end of the study period (16.4\%), $p < .0001$, chi-squared test. There was no significant difference in the error percentage between the different direct oral anticoagulants within each year. Main types of the errors were contraindications for direct oral anticoagulants due to reduced renal function or presence of a significant mitral disease and inappropriate dose. Pharmacist interventions included dose correction (50\%), recommendation for avoiding any direct oral anticoagulant (35.7\%) and anticoagulant substitution (14.3\%).

**Conclusion:** The obligatory prerequisite review by clinical pharmacists of direct oral anticoagulant prescriptions was effective in identifying and preventing a significant number of errors. The annual reduction in the percentage of errors may be attributed to the growing physicians' knowledge and experience with direct oral anticoagulants and the effect of the clinical pharmacists' continuous review and feedback. Yet, even in the last studied year, the error ratio was 1 to every 6 prescriptions. Thus, the need for the obligatory review remains relevant. It is advised to implement obligatory prerequisite review of anticoagulant prescriptions or any high-alert medication prescriptions preferably by clinical pharmacists as an effective measure to prevent serious medication errors.

48. Idarucizumab in a clinical toxicology setting: the Italian experience

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**Objective:** The monoclonal antibody idarucizumab, available in Italy since April 2016, is used to reverse the anticoagulant effect of dabigatran. Clinical indications are (i) major bleeding, and/or (ii) necessity of urgent surgery in dabigatran-treated patients. There are no specific indications for its use in overdose cases. We describe the Poison Control Centre experience and activity related to the first uses of idarucizumab in Italy.

**Methods:** All dabigatran-related calls for potential idarucizumab indication were prospectively evaluated (April 2016 to September 2017). Data about patients, intoxication circumstances, clinical manifestations, adverse drug reactions (ADRs), and outcome were analyzed.

**Results:** In total, 16 cases were included (62.5\% male), aged between 47 and 91 years. All patients took dabigatran in chronic therapy. In 11/16 cases, PCC treatment with idarucizumab was indicated; 7/11 presented spontaneous major bleeding (4/7 cerebral, 3/7 gastrointestinal); 3/11 required urgent surgical intervention; 1/11 was an intentional overdose (presenting with hematuria at the PCC evaluation). In all, 11 patients idarucizumab was administered intravenously, at the recommended dose of 2 vials (1 vial 2.5 g/50 mL), without adverse drug reactions. In 7/11 cases, the antidote was supplied by our PCC. Hematuria resolution was registered in the only case of intentional overdose; no bleeding complications were registered for the patients that needed surgical treatment (3/11 cases). Concerning the 7/11 cases with spontaneous major bleeding, 6 cases (4 cerebral bleeding, 2 gastrointestinal bleeding) improved and, 1/7 died (cerebral bleeding). In 3 of the 5 patients that were not-treated with idarucizumab, the antidotal treatment was not employed because of the low bleeding risk of a superficial cut lesion (1 case) and the possibility of postponing the surgical intervention.
(2 cases); 1/5 gastrointestinal bleeding spontaneously resolved, 1/5 patient died before antidotal treatment. In 2/5 cases, the antidote was, nevertheless, supplied on-site by PCC.

**Conclusion:** The PCC, as with other antidotes, plays a key role in giving expert indications and in supplying antidote if hospitals are lacking. A greater number of patients is needed to further evaluate the safety and efficacy of the antidote in reversing dabigatran-related major bleeding, and to confirm the apparent usefulness in preventing bleeding in case of surgery.

**Acknowledgement:** Support of Boehringer Ingelheim Italia S.p.A.

### 49. Reversible dabigatran-induced neutropenia after a single dose

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**Objective:** Dabigatran is a novel oral anticoagulant frequently used in clinical practice to prevent stroke and systemic embolism. Among the adverse drug reactions (ADR) reported, neutropenia is not described. We report a case of rapid onset dabigatran-induced neutropenia development.

**Case report:** A 68-year-old man was admitted to the cardiac intensive care unit because of atrial fibrillation. His therapy included bisoprolol 1.25 mg, ramipril 5 mg, and low-molecular weight heparin. After some days of therapy, the cardiologist indicated a switch from heparin to dabigatran. Consequently, heparin was stopped and patient started dabigatran 110 mg for the first time at 9 pm. Two hours later (11 pm), the patient manifested chills, sweat, fever, and general malaise. At this time, biochemistry showed decreased white blood cell count (WBC) (2400/µL), with 480/µL neutrophils, while the other laboratory tests were normal (including hemoglobin, platelets, and coagulation). Compared with biochemistry tests routinely performed before, in the morning, a significant decrease in total WBC (morning value 8960/µL) with a drastic reduction in neutrophils (morning value 5600/µL) was observed. No difference in other tests was registered. Considering the rapid onset of the neutropenia, an immune-mediated drug-induced neutropenia was suspected, and hydrocortisone was administered, dabigatran was discontinued and low-molecular weight heparin was started again. The clinical manifestations improved overnight and, by the next afternoon, laboratory tests showed an amelioration of WBC (5700/µL) and neutrophils (3200/µL). Anti-neutrophil antibodies were not investigated (not available in the laboratory). He was treated for the following days with heparin, without re-onset of neutropenia.

**Conclusion:** Pathogenesis of drug-induced neutropenia is not completely understood; mechanisms hypothetically involved are immunologic or due to damage to myeloid cell line (onset after chronic exposure) [1]. Neutropenia is not commonly reported as an dabigatran-induced ADR [2], but in this case, the other drugs were not considered responsible because of the rapid onset after dabigatran administration, the resolution with drug discontinuation, the reintroduction of heparin without complications and the long-term therapy with ramipril and bisoprolol. An immune mediated pathophysiology was suspected due to the rapid onset and improvement, but, in order to perform a more accurate diagnosis, the determination of anti-neutrophil antibodies is strongly recommended.

### References


### 50. Erroneous administration of the dabigatran antidote idarucizumab during surgery: case report and lessons learned

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**Objective:** To describe a case of erroneous administration of the dabigatran antidote idarucizumab during surgery and the learned lessons.

**Case report:** A 91-year-old male with abdominal perforation secondary to obstructive cholangitis was scheduled for urgent surgery. He was treated regularly with apixaban 2.5 mg twice daily for the prevention of systemic embolism and stroke due to atrial fibrillation. Last administration of apixaban was 20 hours prior to surgery. Coagulation and liver parameters were within the normal ranges. Factor Xa activity was not evaluated, although the test was available. During the operation, increasing blood oozing from exposed tissues was evident. Following an immediate telephone consultation with a hematologist, the anesthesiologist sent a prescription for prothrombin complex concentrate with the caption “IV PCC 4000 units” to the blood bank, where coagulation factors and anticoagulant antidotes are stored for emergency use. The dose was not properly adjusted to the patient weight. The blood bank technician accidentally took idarucizumab (Praxbind®) instead of prothrombin complex concentrate (Beripure®); the abbreviation PCC misled her. She noticed that this medication strength is in grams, contrary to the written dose on the prescription, and called the hematologist. During their conversation, the medication names were not mentioned, thus the error was missed and the wrong medication was dispensed. The anesthesiologist received the idarucizumab shortly after; he had no previous experience with it. He noticed the wrong name and dose, but presumed that there was a good reason for dispensing this medication and that it was probably adequate. He administered the medication without any further enquiry. The surgery was completed without major bleeding due to proper mechanical control of the blood oozing. The patient recovered from his acute illness.

**Conclusion:** Impaired knowledge and procedures regarding antidotes for direct oral anticoagulants caused a potentially life-threatening medication error. These medications carry high risk for error as they are relatively new, rarely used and in stressful situations, and require knowledge and expertise. Several interventions for improved practice are recommended: prerequisite hematologist, pharmacist, or toxicologist consultation regarding the use of anticoagulant antidotes in patients undergoing urgent invasive interventions; using proper laboratory tests for anticoagulant activity evaluation; prohibiting abbreviations in prescriptions; using formatted prescription forms based on approved protocols for anticoagulant antidotes; using the read-back technique for proper oral communication; involving pharmacists in the dispensing process; double-checking before administration;
and providing continuous education of relevant medical personnel to improve knowledge and awareness.

51. Apixaban and rivaroxaban ingestion in cats and dogs

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Objective: Apixaban and rivaroxaban are selective direct factor Xa inhibitors, used in human medicine for the prevention of thromboembolic events. Rivaroxaban is used in veterinary medicine in the management of thrombotic syndromes; the dose in dogs is 0.5–1.1 mg/kg daily. We reviewed feline and canine cases of accidental apixaban and rivaroxaban ingestion to evaluate clinical signs and outcome.

Methods: A retrospective study of cases of apixaban and rivaroxaban ingestion in cats and dogs reported to the VPIS between 2013 and August 2017. All cases with known outcome and returned veterinary surgeon follow-up (via postal questionnaire) were included.

Results: There were 34 canine cases (apixaban 9, rivaroxaban 25). The dose of apixaban ingested was estimated in 8 cases and ranged from 0.06–1.54 mg/kg (mean 0.5 mg/kg). One dog had co-ingested fluoxetine (1.2 mg/kg) and another tizanidine (0.26 mg/kg). Of the 9 dogs, 8 remained clinically well; clotting parameters were reportedly measured in two cases. One dog developed pyrexia and prolonged prothrombin time (20 seconds, reference 15 seconds) and activated partial thromboplastin time (26 seconds, reference 14 seconds) and abdominal pain, and anorexia occurred in 14.9% (n = 7), 11.6% (n = 5), 9.3% (n = 4) and 7.0% (n = 3) of animals, respectively. Two animals developed bradycardia. Tremors were commonly observed, with weakness/hypotonia (16.3%, n = 7), twitching/muscle fasciculations (11.6%, n = 5), collapse (9.3%, n = 4), paralysis (7.0%, n = 3), and recumbency (2.3%, n = 1) also reported. One animal went into shock, was comatose, and subsequently died. In general, the duration of clinical effects was 24–48 hours, but longer in severe cases. In one incident involving four adult guinea pigs that were inadvertently fed foxglove by the owner’s children, all four animals developed clinical effects, which varied in severity: one animal was shaking mildly and developed tremors, one developed hypotonia of the head and forelegs, another showed paralysis of the forelimbs, head hypotonia, and laboured respiration, and the fourth animal was lethargic, anorexic, had hypotonia, severe tremors, and laboured respiration. The animals all recovered following supportive care in 24 hours, 48 hours, 72 hours, and 72 hours, respectively. Overall, 29 guinea pigs fully recovered (61.7%), 12 animals (25.5%) died, and five (10.6%) were euthanized. Deaths occurred “suddenly” within 12 hours post-exposure (n = 4), or 24–36 hours after ingestion following ill effects (n = 4). One animal with clinical effects died 7 days post-exposure. The time of death was not recorded in three cases. Overall, treatment protocols were largely supportive, principally involving the use of fluid therapy, nutritional support (e.g., syringe feeding), and analgesia.

Conclusion: As in humans, apixaban and rivaroxaban are generally well tolerated in cats and dogs following acute ingestion. There is a risk of bleeding, however, after ingestion of a large quantity, although this quantity remains unknown.

52. Digitalis species (foxglove) ingestion in 47 domestic guinea pigs (Cavia porcellus)

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Objective: Foxglove (Digitalis species) contains cardiotonic glycosides, which typically cause gastrointestinal effects, cardiac arrhythmias, and electrolyte imbalance. The objective was to examine the typical clinical signs and outcome of foxglove exposure in guinea pigs.

Methods: A retrospective study of foxglove ingestion in domestic guinea pigs reported to the VPIS between December 1986 and September 2017.

Results: Following the ingestion of foxglove, clinical effects were observed in all but one animal (97.9%, n = 46/47). Typically, the quantity ingested was unknown, but the smallest stated amount ingested to cause clinical effects was half a leaf. The earliest onset of signs, where reported, was 2 hours post-exposure. The most common signs were lethargy (34.0%, n = 16), tremor (29.8%, n = 14), ataxia (27.7%, n = 13) and tachycardia (21.3%, n = 10). Gastrointestinal effects including inappetence, diarrhea, abdominal pain, and anorexia occurred in 14.9% (n = 7), 11.6% (n = 5), 9.3% (n = 4) and 7.0% (n = 3) of animals, respectively. Two animals developed bradycardia. Tremors were commonly observed, with weakness/hypotonia (16.3%, n = 7), twitching/muscle fasciculations (11.6%, n = 5), collapse (9.3%, n = 4), paralysis (7.0%, n = 3), and recumbency (2.3%, n = 1) also reported. One animal went into shock, was comatose, and subsequently died. In general, the duration of clinical effects was 24–48 hours, but longer in severe cases. In one incident involving four adult guinea pigs that were inadvertently fed foxglove by the owner’s children, all four animals developed clinical effects, which varied in severity: one animal was shaking mildly and developed tremors, one developed hypotonia of the head and forelegs, another showed paralysis of the forelimbs, head hypotonia, and laboured respiration, and the fourth animal was lethargic, anorexic, had hypotonia, severe tremors, and laboured respiration. The animals all recovered following supportive care in 24 hours, 48 hours, 72 hours, and 72 hours, respectively. Overall, 29 guinea pigs fully recovered (61.7%), 12 animals (25.5%) died, and five (10.6%) were euthanized. Deaths occurred “suddenly” within 12 hours post-exposure (n = 4), or 24–36 hours after ingestion following ill effects (n = 4). One animal with clinical effects died 7 days post-exposure. The time of death was not recorded in three cases. Overall, treatment protocols were largely supportive, principally involving the use of fluid therapy, nutritional support (e.g., syringe feeding), and analgesia.

Conclusion: Foxglove is commonly found across Great Britain, growing in the wild and in gardens. In this case series, only one animal remained asymptomatic. In the symptomatic cases, clinical effects were predominantly lethargy, tremor, ataxia, and tachycardia. The overall fatality rate was 36.2%.

53. Ferric phosphate molluscicide exposure in dogs: low risk of poisoning

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Objective: Ferric phosphate is present in some slug and snail killers, in concentrations of 1% (amateur products) or 3% (professional products); the remainder comprises a cereal filler such as bran or wheat. Ferric phosphate exposure in animals is expected to be less severe than with ferrous salts of iron as it is practically insoluble in water and lipids and has low oral bioavailability. These products are described on the packaging as safe for pets and children. We reviewed canine cases of ferric phosphate ingestion to evaluate clinical signs and outcome.

Methods: A retrospective study of cases of ferric phosphate ingestion in dogs reported to the VPIS between 1996 and September 2017. All cases with exposure to ferric phosphate as a single agent and known outcome with returned veterinary surgeon follow-up (via postal questionnaire) were included.
Results: There were 37 cases of ferric phosphate molluscicide ingestion in dogs. Of these 37 dogs, 16 (43%) remained asymptomatic; the quantity ingested in most cases was unknown, but where reported, ranged from a few grams to 550 g. Treatments given in asymptomatic dogs were emesis (n = 10), IV fluids (n = 2), gasproctectants (n = 2), adsorbants (n = 1), or none (n = 5). Overall, 21 (57%) dogs developed signs; the quantity ingested in these cases was again mostly not reported, but where known, ranged from a few grams to 550 g. Signs reported were diarrhea (n = 11), vomiting (n = 11), lethargy/depression/dullness (n = 5), abdominal tenderness/pain (n = 2), coloured stools (n = 2), hyperesthesia (n = 2), ataxia (n = 1), collapse (n = 1), shaking (n = 1), hematemesis (n = 1), melena (n = 1), and leukocytosis (n = 1). One animal developed liver damage with elevated liver enzymes and jaundice. Treatments given in symptomatic dogs were IV fluids (n = 13), analgesia (n = 4), gasproctectants (n = 3), prescriptio/bland diet (n = 3), emesis (n = 3), antiemetics (n = 2), antibiotics (n = 4), and probiotics (n = 1). Investigations were undertaken in few cases; biochemistry (n = 2), hematology (n = 1), urea and electrolytes (n = 1), and liver function tests (n = 1).

Of the 21 dogs that developed symptoms, 20 recovered fully. Recovery time, where known, ranged from a few days to several weeks. The case of the dog that developed liver damage was ongoing at the time of follow-up.

Conclusion: Ferric phosphate molluscicide ingestion presents a low risk of poisoning to dogs. Diarrhea and vomiting are the most commonly reported features of poisoning and may be caused by the cereal filler rather than the iron content and significantly elevated blood iron levels are not expected.

54. Exposure to Ornithogalum plants: a cause of blindness in small animals?

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Objective: Several Ornithogalum species are grown as ornamental plants. In some species, cardiac glycosides have been identified. Poisonings in small animals are rare. Here, we present two suspected Ornithogalum poisonings.

Case reports: Case 1: The Dutch Poisons Information Center (DPIC) was consulted by a veterinary ophthalmologist concerning a 4-month-old, otherwise healthy Labrador retriever dog (9 kg) with a sudden decrease in vision starting less than one day ago. Upon ocular examination, menace response and dazzle reflex were absent in both eyes. Both pupils were dilated and direct and consensual pupillary light reflexes were absent. Ophthalmoscopy revealed moderate hyperreflection of the tappeal area and a moderately swollen optic nerve head in both eyes. The medical history revealed that the dog was seen playing with Ornithogalum arabicum bulbs and ingestion of these bulbs could not be excluded. Soil containing many of these bulbs was used as fertilizer on the land of the pup owner. Another Labrador retriever pup (10 weeks old) of the same owner was euthanized two months earlier because of its poor clinical condition due to severe hemorrhagic diarrhea. According to the owner, this pup had acutely gone blind as well. Case 2: A 2-year-old Dachshund (5.8 kg) was presented with acute blindness starting one week earlier. Prior to the blindness, this dog was seen playing with an Ornithogalum arabicum plant, followed by vomiting (×1) and watery diarrhea for three days. The menace response and dazzle reflex were absent in both eyes and bilateral mydriasis was noted in the now otherwise healthy dog. The direct pupillary light reflex was absent in the left eye and sluggish and incomplete in the right eye. The results of chromatic pupillary light reflex testing suggested that intrinsically photosensitive retinal ganglion cell function was present in both eyes, while rod and cone photoreceptor function was absent in the left eye and reduced in the right eye. Ophthalmoscopy showed corresponding, asymmetrical signs of retinal degeneration and pale optic nerve heads.

Conclusion: Retinal degeneration and associated visual impairment may be an underestimated risk in exposure to cardiac glycosides containing plants belonging to the genus Ornithogalum.

55. Non-accidental poisoning of domestic and wild animals in Ferrara Province, Italy

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Objective: The purpose of this paper is to describe our experience of animal poisoning after the Italian Legislative Decree of 18 December 2008 prohibiting the use of poisoned baits.

Methods: Since 2008, the Ferrara region of the Lombardy and Emilia Romagna Experimental Zootechnic Institute (IZSLER) had received 465 samples for testing for toxic or harmful substances. These were 256 suspected baits, 152 carcasses and gastric contents of pets, and 55 carcasses of wild animals. Baits had been subjected to an inspection and then, if necessary, directed to the chemical laboratory for toxicological analysis. A necropsy was carried out on the carcasses and, on the basis of the findings, organs were taken for chemical analysis.

Results: In total, 166 samples (35.7%) were positive for the presence of toxic/harmful substances. The most frequent toxins were rodenticides (36.1%), followed by carbamate/organophosphate pesticides (16.9%), carbarates (11.4%), and chlorinated pesticides (9.0%). In 7.2% of the baits, foreign bodies (spikes or needles) were found and 3.0% of the positive samples contained strychnine. The carcasses or the gastric contents of pets were mainly dogs (53.3%) and cats (46.7%). Between the pets, there were 31 (38.2%), poisoned dogs and 26 (36.6%) poisoned cats. The toxic agents responsible for these poisonings were anticoagulant rodenticides (31.4%) in the dogs, and anticoagulant rodenticides (19.1%) and carbarates (19.1%) in the cats. Of the wild animals 41.8% tested positive for poison; pesticides were the most commonly encountered toxic substance, while in synanthropic animals, the most common toxins found were anticoagulants.

Conclusion: Many toxic substances are easy to find in the market, but in five cases, strychnine was also detected and it has been banned for years. The Decree requires the involvement of the Official Veterinary Service and of the official laboratory in suspected cases but this is often neglected, so the number of cases reported to the Judicial Authority is certainly lower than actual
cases. Although a good diagnostic rate was achieved by the laboratories, the improvement margins remain wide and it is therefore very important to collaborate among the different organisations, in our case, the Forensic Toxicology Laboratory at the University of Ferrara, the Pavia Poison Control Centre, and the Institute of Legal Medicine, Catholic University of Sacred Heart, Rome, to increase the number and categories of toxic substances that can be identified.

56. Successful management of acute kidney failure in a dog following calcipotriol ingestion

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**Objective:** Calcipotriol intoxication in dogs is quite rare, but it can cause mineralization and necrosis of multiple organs including the kidneys [1]. Calcipotriol is highly toxic to dogs; the acute minimal toxic dose can be as low as 10 µg/kg and acute lethal dose is 65 µg/kg [2]. We report a case of toxic acute kidney failure after ingestion of calcipotriol in a dog, which was successfully treated with intermittent hemodialysis.

**Case report:** A Bedlington terrier, 1-year-old, 9.8 kg chewed and ingested up to 30 g of Daivobet® ointment (containing calcipotriol 50 µg/g and betamethasone 0.5 mg/g). The ingested dose of calcipotriol was therefore up to 1500 µg (153 µg/kg). Emesis was induced after approximately 2 hours, with a small amount of ointment found in the vomitus. The first symptoms manifested the next day with depression, anorexia, vomiting, and polyuria. The first blood analysis revealed hypercalcemia (3.54 mmol/L, reference 2.2–3.0) and hyperphosphatemia (3.43 mmol/L, reference 0.8–2.2). The dog was treated with intravenous fluids, furosemide, and maropitant but its condition deteriorated. Blood analysis (urea 43.4 mmol/L [reference 3–10], creatinine 904 µmol/L [reference 30–140]) and urine specific gravity (1.008) revealed acute kidney failure on the 3rd day. The dog was transferred to a veterinary clinic with hemodialysis facilities and intermittent hemodialysis was started on the same day. Six hemodialysis sessions were performed on the 3rd, 4th, 5th, 6th, 9th, and 11th days. The first two of 0.5 and 1 hour duration were performed with 0.8 m² low-flux dialyzer, and the next four of 1.5 hours duration each, with 0.2 m² high-flux dialyzer. Mannitol infusion was used for dis-equilibrium syndrome prevention, and heparin for anticoagulation. Blood flow up to 70 ml/min (7 ml/kg/min) was reached without hemodynamic instability. The renal function started to improve from the 12th day and no further hemodialysis was necessary. The dog is under long-term observation. Azotemia is improving gradually; on the 21st day urea was 18.1 mmol/L, creatinine 449 µmol/L, and urine specific gravity 1.017.

**Conclusion:** There are few cases of canine intoxication by vitamin D reported in the literature. We describe one case of calcipotriol toxicity. Our case demonstrates that hemodialysis for pets can significantly improve outcome.

**References**


57. 5-Fluorouracil ingestion in dogs

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Veterinary Poisons Information Service (VPIS), London, United Kingdom

**Objective:** 5-Fluorouracil (5-FU) is used, typically as a 5% cream, for topical treatment of solar and actinic keratoses, and superficial pre-malignant and malignant skin lesions in humans. 5-FU disrupts DNA replication by inhibiting the synthesis of thymidine pyrimidine deoxyribonucleoside base in rapidly dividing cells. Overdose results in gastrointestinal signs, neurological effects, and then bone marrow suppression. We reviewed the clinical signs and outcome of accidental 5-FU ingestion in dogs.

**Methods:** A retrospective study of cases of 5-FU ingestion in dogs reported to the VPIS between 1993 and September 2017. All cases with exposure to 5-FU as a single agent and known outcome with returned veterinary surgeon follow-up (via postal questionnaire) were included.

**Results:** In total, 33 cases of 5-FU ingestion by dogs were reported. Four dogs remained asymptomatic (12.1%). In the symptomatic dogs (87.9%), most developed neurological, gastrointestinal, cardiovascular, or respiratory complications. Active bleeding and coagulopathies were also frequently reported. The most predominant sign was vomiting (57%, n = 19); convulsions occurred in 17 dogs (51.5%). Three dogs had evidence of bone marrow suppression, one died, one was euthanized (despite treatment with filgrastim) and one survived. In the symptomatic animals that survived, treatment of 5-FU was largely supportive, principally involving the use of emetics, activated charcoal and aggressive intravenous fluid therapy. Anticonvulsants and gastro-protectants were also used. Overall, 7 dogs died (21%), 14 were euthanized (42%), and 8 made a full recovery (24%). The dose ingested in surviving dogs was only estimated in one case and was 0.8 mg/kg. The overall fatality rate in symptomatic cases was high (72.4%), and the most common signs reported in these dogs were vomiting (87.5%), convulsions (50%), and bleeding complications (37.5%). Time to death was reported in 3 cases and was 11.5, 16.5, and 72 hours. The dose was estimated in three dogs that died and was 2.5, 3.3–6.7, and 4.8–9.5 mg/kg. Time to euthanasia was reported in 7 cases with a mean of 15 hours and range of 4 to 32 hours; euthanasia was typically due to progression of signs and poor prognosis. The dose ingested was estimated in 6 dogs that were euthanized with a mean of 5.4 mg/kg and a range of 2.2–8.3 mg/kg.

**Conclusion:** The prognosis in dogs that ingest 5-FU cream is very poor; almost three-quarters of dogs that developed signs in this small case series died or were euthanized. In symptomatic cases, the clinical effects were predominantly vomiting and convulsions. Treatment is supportive.

58. Clitocybe rivulosa poisoning in dogs

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**Objective:** Mushroom poisonings are rarely reported in dogs. *Clitocybe rivulosa* contains muscarine, a quaternary ammonium compound structurally similar to acetylcholine. Muscarine competes with acetylcholine for receptors in the autonomic nervous system.
system, causing mainly parasympathetic effects. We present three cases of confirmed Clitocybe rivulosa poisoning in dogs. The mushrooms were identified by a professional mycologist, specialized in identifying mushrooms from photographs sent via email with additional description of the habitat and geographic area. 

**Case series:** Case 1: A 5-month-old, 4 kg, mixed breed dog ingested one mushroom in the garden and developed ptysialism, tremors, and diarrhea within 1–2 hours. On arrival at the veterinary clinic, he was lethargic with profuse diarrhea. Mushrooms growing in the same area were identified as Clitocybe rivulosa by the expert mycologist. The dog was given an emetic, producing several pieces of mushroom. Further treatment consisted of antiemetic followed by activated charcoal and IV crystalloid fluids. The dog made a gradual improvement and was discharged without sequelae 24 hours after ingestion. Case 2: A 4.5–month-old, 5 kg, Norwegian Elkhound developed profuse diarrhea 1–2 hours after ingestion of one mushroom, identified as Clitocybe rivulosa. Additional vital signs included profuse ptysialism and severe vomiting. At the owner’s request, the dog was further observed at home with gradual improvement over the next two days. Case 3: A 6-month-old, 6.6 kg French Bulldog ingested one Clitocybe rivulosa, identified by the mycologist. Ten minutes after ingestion, the dog developed diarrhea, ptysialism, tremors, and vomiting. On arrival at the veterinary clinic 1.5 hours after ingestion, he was hypothermic (37.3 °C) with pale mucous membranes and ptysialism. Treatment consisted of activated charcoal and IV crystalloid fluids for 5 hours. The dog had persistent pale mucous membranes, but was discharged at the owner’s request. At the follow-up examination the next morning, he had made a full recovery. The mushroom collected from the garden was submitted for further analysis and verified as Clitocybe rivulosa by microscopic analysis.

**Conclusion:** Muscarinic mushroom poisoning in dogs can lead to rapid onset of effects requiring urgent veterinary attention. Treatment of Clitocybe rivulosa and other muscarinic mushrooms in asymptomatic dogs consists of induction of emesis and administration of activated charcoal. Symptomatic and supportive treatment includes IV fluid administration, an antiemetic and oxygen. Atropine is the specific antidote for muscarine, and could have been administered in these cases. We present a case series of 6 dogs with confirmed mushroom poisoning with elevated amylase and/or lipase activity.

**Table 1.** Presentation of six cases of mushroom poisoning in dogs.

<table>
<thead>
<tr>
<th>Age, weight, breed</th>
<th>Mushroom ingested</th>
<th>Amount ingested</th>
<th>Clinical signs</th>
<th>Amylase (U/L)</th>
<th>Lipase (U/L)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-Weeks-old, 5.8 kg English Springer Spaniel</td>
<td>Lactarius trivialis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pieces of one mushroom</td>
<td>Ptyalism, diarrhea, lethargy, tremors, tachycardia</td>
<td>&gt;2500</td>
<td>&gt;6000</td>
<td>Full recovery two days after ingestion</td>
</tr>
<tr>
<td>3-months-old, 6 kg Whippet</td>
<td>Inocybe sp.</td>
<td>Unknown amount</td>
<td>Ptyalism, vomiting, lethargy, tremors</td>
<td>&gt;2500</td>
<td>&gt;6000</td>
<td>Full recovery next morning. One week after ingestion normal lipase and slight elevated amylase (1429 U/L)</td>
</tr>
<tr>
<td>2-Months-old, 1 kg Chihuahua</td>
<td>Inocybe dulcama&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Unknown amount</td>
<td>Ptyalism, diarrhea, lethargy, tachycardia (160/min)</td>
<td>2091</td>
<td>5297</td>
<td>Full recovery 11 hours post-exposure. One week after ingestion normal lipase and amylase</td>
</tr>
<tr>
<td>5-Months-old, 1.4 kg Maltese</td>
<td>Hypholoma fasciculare</td>
<td>One mushroom</td>
<td>Vomiting, bloody diarrhea, lethargy, hypothermia, tremors</td>
<td>1659&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NA</td>
<td>Full recovery in 24 hours</td>
</tr>
<tr>
<td>13-Weeks-old, 11 kg Golden retriever</td>
<td>Inocybe sp.</td>
<td>One mushroom</td>
<td>Ptyalism, vomiting, watery diarrhea, abdominal pain, lethargy, anorexia, reduced urinary control, polyuria</td>
<td>Normal</td>
<td>1690</td>
<td>Reduced general condition for 3 days. Full recovery 5 days after ingestion</td>
</tr>
<tr>
<td>3-Months-old, 6.7 kg English Setter</td>
<td>Unknown</td>
<td>Unknown amount</td>
<td>Profuse ptysialism, diarrhea, vomiting, lethargic, anemia, hypothermia, dyspnea</td>
<td>&gt;2500</td>
<td>&gt;6000</td>
<td>Normal lipase and reduction in amylase (1112 U/L) the next day. Full recovery 3 days after ingestion with normal amylase and lipase values</td>
</tr>
</tbody>
</table>

NA: Not analysed.

*Verified with microscopic analyses.

<sup>b</sup>Blood sample taken the day after ingestion.
60. Back-calculation of the peak plasma concentration and proteomic analysis 50 years following 2,3,7,8-tetrachloro-dibenzo-p-dioxin exposure

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Objective: To estimate the peak 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) in 1965–1968 during herbicide trichlorophenoxy-acetic acid production and examine proteomics in the last 8 survivors of the incident 50 years after their occupational intoxication. TCDD analysis was first available 30 years after exposure (1996) and actual TCDD half-life is 13–20 years.

Methods: Examination of 8 men (72 ± 2 years) and 7 male controls (66 ± 16 years) included TCDD in plasma, densitometry of the body fat, internal examination, and proteomics of the exhaled breath condensate (EBC) by mass spectrometry and comparison with human proteins database uniprot.org. The peak TCDD concentration was estimated using the physiologically based pharmacokinetic model by Emond [1].

Results: The mean TCDD concentration was 180 ± 136 pg/g blood lipids (median 112 pg/g). The control group had median 12 pg/g. Mean TCDD body deposit in the patients was 4.95 ± 3.7 µg. The back-calculated TCDD plasma concentration in the group of patients may have reached 35,000 to more than 350,000 pg/g fat. More than 400 proteins have been quantified in the EBC of the patients. Proteomics found 7 proteins overexpressed compared to the control group (p < 0.05): serine protease inhibitor S, protein 3 filament-A, acylamino-acid-releasing enzyme, suprabasin, puromycin-sensitive aminopeptidase, serpin B273, and Rab GDP dissociation inhibitor beta. On the other hand, transthyretin, mucin-5B, transaldolase, alpha-1-antitrypsin, cystatin-S, glycodelin, apolipoprotein D, and cystatin-SN were lower in EBC, originating in the lungs and airways.

Conclusion: Fifty years after intoxication, the TCDD plasma concentration is still more than 10-fold higher than in the general population and several metabolic long-term impairments are present. The back-calculated TCDD concentration ranks these patients as the highest occupationally exposed group. A high percentage of subjects suffer from diabetes, skin, neurological and/or cardiovascular disorders. Involved proteins play a role in cell-cell contacts and adherent junctions during the development of blood vessels, heart and brain, skin and hair morphogenesis and anti-inflammatory protection. Their role in TCDD exposure needs to be studied more deeply. Several patients have already died due to cancers, and TCDD is a proven human carcinogen. No antidote is available to increase TCDD elimination and only symptomatic treatment is used. Due to the long half-life, further health impairments can be expected in the future.

Acknowledgement: Q25/LF1, Q29/LF1.

Reference


61. Diffuse alveolar damage (chemical pneumonitis) after inhalation of nitrogen oxides fumes by an electroplating worker

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Objective: To report a case of an electroplating worker who developed diffuse alveolar damage (DAD) after short-term inhalation of nitrogen oxides (NOx) generated from a highly concentrated nitric acid solution.

Case report: A 44-year-old non-smoker and previously healthy man was admitted at our emergency room (ER) complaining of dyspnea initiated abruptly 3 hours before, associated with productive cough, headache, and myalgia. At examination, he had tachycardia (130 bpm), hypoxemia (oxygen saturation 80%), and diffuse alveolar cracks. His oxygenation improved with non-invasive ventilation, bronchodilators, and systemic corticosteroids. He reported to have been working during the day cleaning metallic pieces with sequential baths of sodium hydroxide and nitric acid, prior to dipping the pieces in the electroplating bath. Due to a recent change in the work process, he had to use a deeper container into which he plunged the pieces in the nitric acid solution during which his whole face was exposed to the surface of the solution, inhaling continually the acidic fumes for 3 hours. There was no exhaust system. He left the workplace without symptoms, and the initial respiratory ailments started at night, around 8 hours post-exposure. Thoracic X-ray and high-resolution computed tomography (HRCT) on arrival showed diffuse bilateral alveolar filling represented by ground glass opacities and septal thickening. Oral prednisone was started and given for three days, followed by inhaled corticosteroids after hospital discharge. After 2 months, he was asymptomatic (oxygen saturation 97%), with normal X-ray, but with obstructive defect at spirometry, that persisted after 6 months of follow-up (FEV1/FVC = 0.67 and FEF25–75% = 61%).

Conclusion: NOx are gases with a very low-water solubility penetrating very deeply into the airways reaching terminal bronchioles and alveolar space. At this anatomical level, NOx cause diffuse alveolar damage (DAD) after short-term inhalation of nitric oxides (NOx) generated from a highly concentrated nitric acid solution.
respiratory condition. The lasting obstructive defect may be due to persistent bronchiolitis in this case.

62. Peracetic acid exposures reported to the Dutch Poisons Information Center

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Objective: In hospitals, peracetic acid (PAA) is often used to disinfect hands or instruments before medical procedures. Due to decomposition of PAA in a watery solution, PAA solutions always contain acetic acid and hydrogen peroxide. Typical concentrated PAA solutions contain 40% peracetic acid, 40% acetic acid, 5% hydrogen peroxide, and 13% water. As a disinfectant, PAA concentrations usually vary from 0.1–1%. Although its omnipresence as a disinfectant and the large quantities in which PAA is produced, little is reported about acute intoxications with PAA. We provide an overview of the PAA exposures reported to the Dutch Poisons Information Center (DPIC), including a recently reported severe PAA intoxication.

Case series: Since 2008, the DPIC has been consulted about 32 incidents of PAA exposure; the routes involved were inhalation (n = 17), eye (n = 11) and dermal (n = 6). In 17 cases, symptoms were present upon consultation and consisted of irritation of the throat (n = 6), eyes (n = 6), respiratory tract (n = 2), and skin (n = 1) as well as dyspnea (n = 3), coughing (n = 1), and nausea (n = 2). Four incidents occurred in a hospital, of which one incident is described in detail. An emergency room physician consulted the DPIC for a presumed leakage of acetic acid in their hospital. Later that day, it turned out that a mentally confused temporary employee had intentionally spilled 5 L of PAA (unknown concentration). After inhalation, two patients were immediately admitted to the Emergency Department with severe respiratory symptoms, He suffered severe mucous membrane damage to the upper respiratory tract, but recovered without sequelae. Fifteen other employees developed minor symptoms that spontaneously resolved upon cessation of the exposure. The employee was prosecuted for attempted murder and manslaughter.

Conclusion: In most cases, after inhalation of PAA, the symptoms were mild, mainly consisting of irritation of mucous membranes of upper airways and eyes. However, as the last case demonstrates, spillage of a large quantity or high concentration of PAA may cause severe and life-threatening conditions. Careless use of PAA might pose a serious health risk, for instance, in hospitals where PAA is commonly used.

63. Comparison of occupational poisoning cases reported to the German Federal Institute for Risk Assessment (BfR) and enquiries to the Poisons Centres in Germany

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Objective: On the basis of the national Chemicals Act, the German Federal Institute for Risk Assessment (BfR) receives reports on poisonings with chemical substances or products from physicians. Over 90% of the incoming reports describe accidents at the workplace, which are made by the German Social Accident Insurance Institution after completion of the patient’s treatment.

Methods: Occupational poisoning cases documented at BfR were compared to other reports from German Poisons Centres.

Results: From the occupational sector, 13,182 poisoning cases were reported to the BfR from 2014 to 2016. In all cases, a product categorization was assigned; 94% of the agents involved were categorized to the 2nd level, 74% were categorized up to level 3, 62% has a product category of level 4, and 30% of level 5. In 11,897 cases, the toxic agent was classified as chemical substance or product, in 681 cases as a medicine and in 139 cases as a pesticide. In the cases related to chemical substances or products, accidents with cleaning agents were most frequent (n = 3077), followed by exposures to exhaust gases (n = 1472), building materials (n = 1185) and disinfectants (n = 1097). In the 13,182 poisoning cases, eye exposure occurred 8002 times (61%), dermal exposure in 2887 cases (22%), and inhalation exposure 2231 times (17%). Oral poisoning was only documented in 83 cases (0.6%). Overall, 90% of the cases reported to the BfR occurred in the professional environment. In German Poisons Centres data, only 2.5% of all enquiries are occupational. In the majority of cases, minor symptoms appeared (11,243 cases or 85%), moderate symptoms were observed in 856 cases (6.5%) and severe symptoms in 14 cases (0.1%). In 553 cases (4.2%), there were no symptoms reported and in 501 cases, the grade of severity could not be evaluated.

Conclusion: In Germany, cases of poisoning are documented by the BfR and Poisons Centres. However, the case reports differ considerably in the etiology. The BfR cases are mostly from the professional sector and in the German Poison Centres data, most documented cases reflected private exposures. Both datasets might be merged in a national monitoring of poisonings to obtain an overview of occupational poisoning events in Germany.

64. Occupational lead exposure and multiple organ dysfunction: a case series

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Objective: The paper describes five cases of metallurgical industry workers diagnosed with occupational lead poisoning. Clinical presentation, occupational exposure data, laboratory findings, and treatment during hospitalization are provided.

Case series: The research was conducted in the period 2010–2015 in Copşa Mică, Romania, a region intensely polluted with heavy metals (Pb, Cd, Cu, Zn) due to nonferrous ore extraction and metallurgical processing. Contamination of the workplace and prolonged and severe environmental pollution has a great health impact on population living in this area [1]. Five males aged 37–55 years, with an occupational exposure to heavy metals of 14–35 years, were hospitalized in a labor medicine clinic, presenting signs of hematological, nervous, renal, hepatic, or gastrointestinal damage. All patients had mild or moderate anemia and elevated lead exposure biomarkers: blood lead concentrations ranged from 47.4 to 78.1 μg/dL, urinary lead excretion per 24 hours from 106.2 to 575 μg, and δ-aminolevulinic acid concentrations in urine from 14.3 to 30.25 mg/L. One patient has gingival pigmentation (Burton’s line), a typical sign of chronic lead
poisoning [2]. The treatment included chelating therapy, vitamins and symptomatic therapy.

**Conclusion:** Chronic lead poisoning results in different dose-related clinical manifestations, anemia, and the increased lead levels in the blood and urine of occupationally exposed patients.

### References


### 65. The impact of www.poisoncentre.be and social media on the number and characteristics of calls to the Belgian Poison Centre

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**Objective:** We examined whether the Belgian Poison Centre (BPC) website and social media have influenced the number and type of telephone calls to the BPC.

**Methods:** The BPC launched a renewed website in 2014 and introduced a Facebook page and Twitter account in 2015. We analyzed the use of www.poisoncentre.be, the BPC Facebook page and Twitter account during 2014–2016 and investigated if there was a difference between 2011–2013 and 2014–2016 in the number and type of calls to the BPC. Furthermore, we examined the probability of first consulting the Internet for patients with unintentional poisonings before calling the BPC in a survey. All unintentional cases (n = 485) from 1045 calls to the BPC during 7 days in February/March 2016, were included. In the week following the call, 404 patients were contacted by telephone.

**Results:** Between 2011 and 2016, the number of calls to the BPC increased from 52,848 to 55,255 (+4.6%). Exposure calls increased from 43,656 to 47,568 (+9.0%) while information calls decreased from 9192 to 7686 (-16.4%). The evolution towards a higher proportion of exposure calls largely took place after renewing the BPC website, introducing Facebook and Twitter, with 5.2% more exposure calls and 14.6% less information calls (2013–2016). The revised website www.poisoncentre.be resulted in an increase in the number of users 2013–2016 (861,875 to 1,083,383 [+25.7%]), sessions (948,293 to 1,221,936 [+28.9%]) and frequented pages (1,584,253 to 1,799,499 [+13.6%]). The average number of consulted pages/session was 1.6 (1.5–1.8), the session duration 1 minute 5 seconds (57 seconds–1 minute 24 seconds) and the proportion of returning visitors 12.6% (10.7–13.6%). In 2016, BPC reached 404 followers on Twitter and 601 on Facebook. From the survey, we know that 9/404 (2.2%) callers first consulted the Internet before calling the BPC.

**Conclusion:** The number of people calling the BPC rose slightly with more calls for exposures and fewer requests for information. The stay on www.poisoncentre.be is short, with a small number of pages visited and a high number of new visitors. The number of Facebook and Twitter followers is low. These results suggest that people still use the BPC telephone in emergency situations and consult other communication tools when they are looking for information. Further research is needed to determine whether this trend is continuing and to identify the influence of Internet.

### 66. Agomelatine-related toxicity reported to the Victorian Poisons Information Centre

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**Objective:** Depression is a common mental illness with more than 300 million people estimated to be suffering from the condition [1]. Agomelatine is a novel antidepressant available for the treatment of major depressive disorder in Australia and the European Union. It is indicated for adults and the recommended therapeutic dose is 25–50 mg daily [2]. Agomelatine is believed to work as a 5-HT2c receptor antagonist and a melatonin (MT1 + 2) receptor agonist, increasing dopamine and noradrenaline activity, and resynchronising circadian rhythm to improve mood and sleep quality, respectively [3]. Currently, there is limited information regarding agomelatine toxicity in overdose. This study aims to define the epidemiology of agomelatine poisoning and specifically describe the symptoms of overdose by examining data from the Victorian Poisons Information Centre (VPIC).

**Methods:** This was a retrospective review of agomelatine-related calls to the VPIC between June 2013 and February 2017. The VPIC database was interrogated for the terms “agomelatine”, “Valdoxan®”, and “antidepressant”, and relevant call records were extracted. Information including patient demographics, reported symptoms, ingested dose, poisoning severity scores, and intent (overdose, misuse, therapeutic error, accidental ingestion) were examined. In this study, “overdose” refers to intentional deliberate self-harm and “misuse” encompasses the terms “diversion”, “off-label use”, and “recreational abuse”.

**Results:** There were 87 agomelatine-related calls to VPIC during the study period. Most calls were related to overdose (n = 62, 71.3%). The youngest age reported in overdose was 15 years old. The majority were polydrug overdoses (n = 47, 75.8%). In sole agomelatine overdoses, most patients were asymptomatic (60%), however, calls occurred within 1 hour of ingestion. Other callers developed drowsiness (26.6%), dizziness (6.7%) or nausea (6.7%) at a median of 1 hour (IQR 1.3) post-ingestion. All cases that developed drowsiness were managed supportively without the need for intubation.

**Conclusion:** Results from this study suggest that sole agomelatine ingestion can result in drowsiness, dizziness, or nausea. More severe toxicity has been reported with polydrug overdose. Further research into drug-drug interactions and long-term agomelatine use could contribute to future safety data.

### References


67. Being Paracelsus: the toxicology educational card game

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**Objective:** Undergraduate toxicology students are frequently overwhelmed by the volume and complexity of information they are expected to learn [1]. Healthcare-based educational games enhance the communication, social interaction, and critical thinking skills of the students [2]. The objective of this study was to introduce a fun, alternative learning technique to (i) assess student learning and (ii) to assess student satisfaction with the learning experience.

**Methods:** The card game centred on poisoning scenarios and the treatment thereof. Two decks of cards were developed; one set with the poisoning exposure and the other with treatment. Students needed to pair the poisoning exposure with the correct treatment. If they do not have the matching card, they were required to collect another card. Any other group member with a matching card could yell “Paracelsus” to play. Twenty-one 5th year medical students voluntarily agreed to participate in the game. The students were given relevant toxicology literature to aid them in the game. Three staff members from the Tygerberg Poisons Information Centre supervised the students. After the game, they were asked to anonymously complete a questionnaire.

**Results:** Students indicated that the card game was a competitive and engaging non-lecture approach to teaching toxicology. All students indicated that Paracelsus immersed them in course material and they would recommend this type of learning above didactic teaching. However, students need basic toxicology lectures before playing. Groups should be limited to 10 participants, for larger groups could have an influence on the level of participation. Supervision by toxicologists are initially necessary but once students have mastered the game, they can self-facilitate and thereby increase peer-to-peer learning [3].

**Conclusion:** The game was an effective adjunct to toxicology lectures. This can lead to significant increases in toxicology assessment marks. A process of computerising this game should be undertaken and further research should focus on the incorporation of this type of game in the different fields of medical studies.

**References**


68. Inadvertent instillation of electronic cigarette liquid as eye drops

Eleri Thomasa, Sally M. Bradberryb, Euan A. Sandilandsc, Simon H. L. Thomasd and John P. Thompsona

**Objective:** In May 2016, a new European Tobacco Products Directive (TPD) 2014/14/EU was initiated [1]. This mandated the placement of clearly labelled safety warnings and details of ingredients on e-liquid containers, which were required to be child-resistant and tamper evident. Other measures included a capacity restriction of liquid in electronic-cigarette tanks (2 mL) and refill containers (10 mL), in addition to limiting nicotine concentration to ≤20 mg/mL. Prior to May 2016, the toxicity profiles of e-liquids varied considerably; manufacture and quality control measures employed by companies were inconsistent. Poorly labelled containers of various sizes, including small 10–15 mL dropper bottles, were being used to package e-cigarette solutions and were potentially liable to be confused with medicinal drops. We determine the nature of the enquiries to the NPIS concerning ocular exposures to e-cigarette liquids.

**Methods:** Telephone enquiries to UK National Poisons Information Service (NPIS) regarding accidental instillation of e-liquid solution into the eyes were analysed retrospectively for the period December 2012 to March 2017.

**Results:** The NPIS received a total of 72 enquiries reporting ocular exposure to e-cigarette liquid, 26 concerning accidental administration into the eye. All were acute exposures and affected 14 females and 12 males. Only two cases were reported during 2012–2014. Eight cases were documented annually between 2015 and 2017. Five patients (19%) were aged under 19 years, 19 patients (73%) were aged between 20 and 70 years and two patients were of unknown age. The Poison Severity Scores (PSS) indicated that 92% of enquiries had either nil (PSS0) or minor (PSS1) features but moderate (PSS2) toxicity was documented in one and in one the PSS was unknown. A third of patients (34%) exhibited single key features: conjunctivitis (n = 5), eye pain (n = 2), or irritation (n = 2). Conjunctivitis or irritation was combined with other features in all other cases. Seven patients (27%) remained asymptomatic, 17 (65%) had a maximum poison severity score of 1, one had a maximum PSS of two and one had an unknown severity score.

**Conclusion:** Whilst ocular exposure to electronic cigarette liquid generally causes only minor features, the risk of accidental ocular exposure could be further reduced if the packaging were to be of a different design from medicinal/therapeutic eye drops.

**Reference**


69. Inhalant abuse in New Zealand: are the warnings being taken in?

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**Objective:** Inhalant abuse in the young has been a concern in New Zealand for a number of years, with several deaths reported by coroners. The aim of this study was to utilise Poisons Centre
data to assess current practices around such abuse, and its reported effects in teenagers and younger children.

**Methods:** All poisons call records concerning intentional inhalation of volatile substances by under-20-year-olds for the 10-year period between mid-2006 and mid-2016 were reviewed. The enquiries were classified according to type of products used, and the symptomatology (if any) at the time of the call. Our recorded descriptions and assessments of the incidents were also reviewed.

**Results:** There were 169 calls regarding 179 subjects over this period. Males were involved in 117 cases (65.4%), females in 56 cases (31.3%), with gender uncertain in 3.3%. The highest number of cases involved 13-year-olds, and the youngest children were a 4-year-old and a 24-month-old. Details of product used was provided in 143 (84.6%) of calls. The most commonly used product was petrol (n = 46), followed by fly spray (n = 33) and deodorant (n = 28), with fewer cases of butane (n = 9), air freshener (n = 5), glue (n = 5), hair spray (n = 4), and lighter fluid (n = 4). Other products (including “solvent”) were involved in 9 calls. Symptoms at or around the time of the call were reported in 76 (42.5%) of the subjects. The most common were vomiting (n = 20), drowsiness (n = 15), dizziness (n = 12), “drunk”/“out of it” (n = 10), nasal/throat irritation (n = 10), feeling “high” (n = 6), unconsciousness (n = 6), headache (5), and abdominal pain (n = 5). There were 30 further references to symptoms or effects, including agitation, dyspnea, hallucinations, and syncope. There was no significant yearly trend. Gasoline was implicated more than in an earlier (2003–2004) NZ Poisons Centre study [1].

**Conclusion:** Inhalational abuse of volatile hydrocarbons remains a significant practice in New Zealand. Common household products remain the most abused substances in the young population studied. The adverse effects are various and some serious. However regulation of these products as a way of reducing harm would not be feasible. Therefore, other strategies for harm reduction, such as targeted education and cognitive behavioural therapy, need to be considered.

**Reference**


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**70. Baclofen exposures reported to the UK National Poisons Information Service (NPIS) over 12 years (2005–2017)**

Pardeep S. Jagpal\(^[1]\), Mark Pucci\(^[1]\), Euan A. Sandilands\(^[2]\), John P. Thompson\(^[3]\), Simon H. L. Thomas\(^[4]\) and Sally M. Bradberry\(^[1]\)

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**Objective:** To investigate cases of baclofen poisoning reported to the UK National Poisons Information Service (NPIS). Baclofen is a gamma-aminobutyric acid (GABA) receptor agonist with a well-established role in the treatment of spasticity. In recent years, there has been growing interest in its potential for the treatment of alcohol and gamma hydroxybutyrate/gamma butyrolactone (GHB/GBL) dependence and withdrawal. National Health Service (NHS) Digital prescription data demonstrate a significant rise in the number of issued primary care prescriptions for baclofen in England from 540,195 in 2005 to 1,000,026 in 2015 [1]. We investigated whether this was mirrored by an increase in the number of poisonings reported to the UK NPIS.

**Methods:** A retrospective analysis of UK NPIS enquiry data between January 2005 and 31 July 2017.

**Results:** We identified 545 enquiries regarding 530 patients. There was an increase from 15 enquiries in 2005 to 47 in 2016. The majority (54%) originated from primary care facilities, but there were 195 (36%) from hospitals, involving 186 patients; 128 patients co-ingested baclofen with other pharmaceuticals and were excluded from subsequent analysis. In the 58 hospital patients (35 adults and 23 children) exposed, based on history, to baclofen only (three declared co-ingestion of alcohol), the maximum poisoning severity score (PSS) [2] was moderate in 15 (26%) and severe in 25 (43%). The predominant route of exposure was ingestion (n = 52) and median reported ingested dose was 175 mg (IQR 57.5–295 mg). There was a significant positive correlation (r = 0.47, p = 0.006) between reported dose ingested and severity of poisoning. Reduced consciousness was reported in 46 of 58 (79%) patients with 15 of 58 (26%) requiring intubation and ventilation. Nine cases were followed up with a complete recovery documented in eight. No deaths were reported. Other features reported included respiratory insufficiency (20%), myoclonus (8.6%), and seizures (3.5%).

**Conclusion:** There has been a substantial increase in the number of enquiries to the NPIS relating to baclofen poisoning over the last 12 years. Severe toxicity requiring high dependency care is common.

**References**


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**71. A review of the methods and efficiency of follow-up of enquiries to the UK National Poisons Information Service (NPIS) in 2016**

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**Objective:** The operating policy of the UK National Poisons Information Service (NPIS) requires the Specialist in Poisons Information (SPI) receiving telephone enquiries to follow-up cases where the Poisoning Severity Score (PSS) [1] is severe (PSS3) or where enquiries were referred to a consultant toxicologist. The
aim of the study was to review methods, efficiency, and outcome of follow-up.

Methods: All case records with a PSS3 and those referred to a consultant toxicologist from 1 January 2016 to 31 December 2016 inclusive were extracted from the UK Poisons Information Database (UKPID) and analysed retrospectively.

Results: During the study period, the NPIS handled a total of 45,408 enquires, of which 2171 (4.8%) fulfilled the inclusion criteria (2009 consultant referrals and 162 PSS3 enquires not referred). Follow-up was not carried out in 884 (41%) enquires for the following reasons: deemed unnecessary by the SPI or consultant (n = 279), duplicate enquires about the same patient (n = 270) or not appropriate for other reasons including enquires from paramedics, general practitioners, and the public service helpline (n = 231). In 104 records, no reason for lack of follow-up was documented. Of the 1287 enquires that were followed-up, documentation of a definitive outcome was achieved in only 800 (62%). These outcomes were: complete recovery in 44% (n = 566), ongoing features of poisoning in 7% (n = 90), sequelae in 2% (n = 26), features unrelated to poisoning in 2% (n = 27), and death in 7% (n = 91). Follow-up techniques varied between the four NPIS units and included telephone, postal questionnaire, email or a combination. During the study period, telephone alone was the most frequently used method (n = 702) with an outcome recorded for 83% (n = 585). In total, 431 postal questionnaires were sent out and 139 returned, a response rate of 32%.

Conclusion: Follow-up data are informative for SPIs, clinicians, and end-users of the service. Outcome data are essential for governance and may contribute to the assessment of treatments for which there is a minimal evidence base. In this study, telephone follow-up was the most effective method of obtaining outcome data for poison enquiries but was time-consuming. This may explain the suboptimal completion of follow-up through to a definitive outcome. Ways to improve the efficiency of follow-up data collection, possibly using web-based methods, should be explored.

Reference


72. Wonder chemistry: exposures related to chemistry sets, 2008–2017

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Objectives: Chemistry sets have been popular toys for decades. Nowadays, these kits are safer than before but still contain potentially harmful chemicals, if they are not carefully handled. Based on online research, there are currently 47 products marketed as chemistry sets or educational toys based on chemistry in Italy. We report a retrospective case series of human exposures reported to a Poison Centre (PPC) from January 2008 to October 2017.

Methods: All cases of intoxication including “chemical or chemistry set” as a keyword were collected from PPC archives from January 2008 until October 2017.

Results: Overall 45 cases of intoxication linked to chemistry sets were included; 37 cases involved patients aged 0–18 years (78% under 10 years) and 8 involved adults. Ingestion was the most frequent route of exposure (35 cases) followed by ocular contact (5 cases), and dermal contact (3 cases). Inhalation occurred in one case with one case of concurrent ocular and dermal contact. In 29 cases, a single compound was involved and in 16 cases, multiple substances. A total of 16 chemicals were reported: copper sulphate was most frequently involved (28 cases) followed by tartaric acid (12 cases), sodium carbonate (11 cases), citric acid (4 cases), potassium alum (4 cases), ferrous sulfate (3 cases), and food coloring (3 cases). Another 9 substances (chalk, calcium carbide, calcium hydroxide, hydrogen peroxide, strontium aluminate, potassium ferrocyanide, potassium nitrate, sugar, and cleaner base) accounted for 1 case each. Overall, 36 cases were referred to the Emergency Department, 6 cases were managed at home and 3 cases were referred to a general practitioner. Classification of cases based on the Poison Score System (PSS) highlight a predominance of minor clinical symptoms (25 cases with PSS1) or asymptomatic (15 PSS0). Five cases were considered as PSS2: 2 cases of ingestion, 2 cases of dermal contact, and a case of ocular contact. Copper sulphate alone or in mixture, appeared in four of five cases (2 cases alone and 2 cases in mixture with tartaric acid, sodium bicarbonate, potassium nitrate, and sugar). Another PSS2 case involved calcium carbide alone. Main clinical manifestations were: 2nd degree burns (facial area), vomiting (copper sulphate ingestion), and visual disturbances.

Conclusion: Intoxication by chemicals in chemistry sets are a rare but potentially harmful event. These kits should only be used under adult supervision and experiments should be performed following instructions and wearing appropriate protective equipment.

73. Specialist in poison information (SPI)-initiated toxicology consults: trends from a regional poison center

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Objective: Regional poison centers (RPC) in the US utilize certified and certification-eligible specialists in poison information (CSPi and SPI, respectively) to handle the majority of calls. CSPis provide recommendations and medical management advice to callers for a wide variety of exposures based on regional poison center guidelines. Toxicologists are usually available in most centers for second opinions, formal requests, recommendations for exposures outside the knowledge or comfort level of the C/SPIs, or in clinical grey areas where no standard recommendation can be made. Our RPC has a standard operating procedure (SOP) in place for when calls should be escalated to the medical or clinical toxicologist; however, it is unclear at our center how closely this SOP is followed and if medical toxicologists are being consulted appropriately. We sought to determine this.

Methods: We queried our RPC’s case management system for all cases flagged with a toxicologist (medical/clinical toxicologist or fellow) consultation between the dates of 1 January 2015 to 31 December 2015. Because of the high volume of consults returned, we looked at a certain percentage of the total number of cases. Cases notes were reviewed for substances involved and documented reason for toxicologist consult.

Results: Overall, 6330 consults involving a toxicologist or fellow were identified. We reviewed the case notes of 284, of these
cases, 65% involved a single ingestion. Of the documented cases reviewed, 55% followed our poison center's SOP, while 16% had no documented or discernible reason for toxicologist consultation and 29% had other documented cause for consultation. Of these other causes, a specific caller question (49%), C/SPI-specific question (25%), informal case review with toxicologist (19%), poly-substance ingestion (6%), and ingestion thought to be more toxic than it actually was (1%) were listed as reasons for consultation.

**Conclusion:** These data indicate that of our RPC cases that were escalated, just over 50% of these consults were performed appropriately, according to criteria from the SOP. The majority of the consults that were performed that did not meet SOP criteria involved specific questions regarding exposures in which the C/SPI did not know the answer. While calls to medical/clinical toxicologists and fellows are required in certain situations, we hope to share these data with our C/SPI staff to promote appropriate consultation per our SOP, as well as identify areas of training or development where we can expand the role of C/SPIs in managing exposures to the best of their abilities.

### 74. Dangerous experiments with drugs against dry cough

Eliška Lacinová, Jíří Hlusička, Lucia Neuschlova, Lucie Lischková, and Sergey Zakharov

**Objective:** Over the past years, an increased number of dextromethorphan (DXM) intoxications have been reported to the National Toxicology Information Center (TIC). Therapeutic doses of DXM act as a centrally acting antitussive while in toxic doses, it acts as a dissociative hallucinogen [1]. The aim of our study was to analyse data on DXM abuse in the Czech Republic over the last 5 years.

**Methods:** Retrospective analysis of data from TIC database from January 2012 to August 2017.

**Results:** The TIC received 237 calls associated with DXM poisoning over the study period. In 2017, the number of intoxications increased clearly compared to earlier years: 77 calls during the first 8 months compared to 45 calls in 2016. An increase in the number of intoxications in the 12–17-year-old age group was approximately 8 times (with 5 consultations in 2012 compared to 47 consultations during first 8 months in 2017). The most common cases were intoxications with the monocomponent drug Stopex® available as an over-the-counter pharmaceutical. Over the past 3 years, intoxications with Stopex® were 8 times more frequent than intoxication with the syrup. The information on DXM abuse was provided by TIC to the State Institute for Drug Control to initiate a change in registration. As a result, on 15 August 2017, the registration of solid ingredient formulations containing dextromethorphan was changed from over-the-counter to prescription only by the national authority. There are still over-the-counter drugs containing DXM available in the form of syrup and polycrystalline influenza medications.

**Conclusion:** Abuse of DXM carries the risk of acute intoxication as well as the complications of chronic exposure. Change in the dispensing of the most hazardous group of drugs containing DXM was a result of toxicovigilant activities of the TIC and cooperation with national authorities. However, the issue of possible abuse of other forms of DXM remains open and needs to be investigated to prevent the negative effects of mass abuse by adolescents.

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### Reference


### 75. The role of the UK National Poisons Information Service (NPIS) in the diagnosis of death in poisoned and non-poisoned patients

Emma Moyns, Hayley Williams, Mark Pucci, Euan A. Sandiland, John P. Thompson, Simon H. L. Thomas, and Sally M. Bradberry

**Objective:** To investigate the number and nature of enquiries to the UK National Poisons Information Service (NPIS) concerning the diagnosis of death in poisoned and non-poisoned patients.

**Methods:** A retrospective analysis of UK NPIS enquiries between 1 January 2004 and 1 June 2017 was undertaken for enquiries containing the terms "brain dead", "brain death", "brain stem", "brainstem", or "stem testing". Since enquiries seeking assistance interpreting thiopentone concentrations appeared frequently, a further search was undertaken for all enquiries relating to "thiopentone" or "thiopental" to retrieve any additional cases pertinent to the study.

**Results:** The original search retrieved 187 enquiries, of which 95 were deemed relevant. Further 8 enquiries were identified by the second search, giving a total of 103 enquiries for assessment. These involved 86 patients. The cause was thought to be toxicological in 64 patients and non-toxicological in 22. Reasons for enquiry to the NPIS (more than one were allowed per case) were regarding: how the presence of drugs affects brainstem reflex tests ($n = 26$); kinetics and metabolism of drugs ($n = 24$); toxicological causes of brainstem signs ($n = 20$); requests for laboratory analysis ($n = 16$); interpretation of quantitative analytical results ($n = 10$); suitability for organ donation ($n = 7$); and withdrawal of active treatment ($n = 6$). The median age of those with a suspected toxicological cause of death was 30 years (IQR 20.8–63.3); 68.8% were male. Agents involved were: single drug of abuse ($n = 14$), single prescribed drug ($n = 14$), mixed prescription drugs ($n = 10$), toxic alcohol ($n = 6$), mixed drugs of abuse ($n = 7$), combination of prescribed drugs and drugs of abuse ($n = 3$), other ($n = 5$), and unknown ($n = 5$). Stimulant drugs were the most commonly implicated single drug of abuse ($n = 8$), followed by opioids ($n = 5$). The median age of the non-toxicological causes of brainstem death was 23 (IQR 15.5–47); 65.2% were male. The most common causes were: traumatic head injury ($n = 7$), stroke ($n = 4$), hypoxic encephalopathy secondary to cardiac arrest ($n = 3$), status epilepticus ($n = 1$), hanging ($n = 1$), and unknown ($n = 6$).

**Conclusion:** The NPIS serves as a vital role in the management of poisoned patients but can also assist in the diagnosis of death in both the poisoned and non-poisoned patients. In this study, the majority of enquiries about the diagnosis of death involved
Conclusions: Poisons management.

We developed the app to cement its position as a vital tool in frontline clinical scenarios. We aim to build on this positive feedback to provide a comprehensive and reliable source of evidence-based poisons information both online and offline to healthcare professionals at the point of care. Our objective was to establish user expectations and requirements of this facility, and to improve our understanding of how the product is currently being used with a view to strategic development to meet our users' needs.

Methods: We invited all UK-based National Health Service (NHS) users with current subscriptions at 31 July 2017 (8600) to complete a short email questionnaire. We compared satisfaction scores for the app with those previously received for use of TOXBASE online [1].

Results: Overall, 489 (6%) responses were received; not all respondents answered every question. The app was used for "routine enquiries" 80%, "triage decision" 58%, "complex enquiries" 50%, "education" 55%, and for "maintaining local protocols" 12%. Most users (84%) reported multiple types of use. Only 3% of the respondents used the app "daily", 22% "a few times a week", 28% "weekly", and 47% "less often". Respondents described the typical locations where they used the app: around 50% of app users are ambulance personnel [2] thus 48% of users reported using the app out of hospital in the community setting. Hospital location in respect to the patient was noted as "at the bedside" (15%) and "away from the patient" (4%). Some reported using the app in multiple scenarios (27%). User satisfaction: Using the app in multiple scenarios (27%). User satisfaction with current subscriptions at 31 July 2017 (8600) to complete a short email questionnaire. We compared satisfaction scores for the app with those previously received for use of TOXBASE online [1].

Conclusions: The TOXBASE app is highly thought of amongst our user group and users have confidence in the information provided. This data demonstrates its versatility within a variety of clinical scenarios. We aim to build on this positive feedback to develop the app to cement its position as a vital tool in frontline poisons management.

References


77. Comparison of liquid laundry detergent pods and other laundry detergent exposures in children: an 11 month survey in Austria

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Poisons Information Centre, Vienna, Austria

Objective: In a prospective study, the Poisons Information Centre (PIC) analysed exposures to liquid laundry detergent pods in children by telephone follow-up and compared the results with exposures to other laundry detergents.

Methods: From August 2016 to June 2017, all PIC consultations regarding liquid laundry detergent pod exposure in children were followed-up by telephone to evaluate the outcome. Data regarding other laundry detergents were extracted from the database.

Results: There were 84 cases of accidental exposures with liquid laundry detergent pods in children aged 9 months to 6 years. The route of exposure was oral (n = 69), ocular (n = 6), and other (n = 9). Thirteen cases were excluded due to loss of follow-up. Of the remaining 71 cases, 49 patients (69%) had symptoms, in 22 cases (31%), there were no symptoms. In 45 cases (63%), the symptoms were mild: nausea, vomiting (1–4 times), diarrhea, irritation of the eyes, exanthema, and coughing. In 3 cases (4.2%), the symptoms were moderate: prolonged vomiting (5–6 times), intense irritation of the eyes and blepharospasm. In one case (1.4%), the symptoms were severe. A 2-year-old child ingested only a small amount of liquid laundry detergent pod and immediately vomited five times. The child was coughing so badly that hospital admission was advised. In the hospital, a bronchoscopy and suction of foamy liquid was performed. In addition, the child had diarrhea 3 times. The child was discharged after 2 days of hospitalisation without complications. Regarding other laundry detergents, the PIC documented 262 cases in the same observation period. The age ranged from 2 months to 13 years. Ingestion alone was the most common route of exposure (n = 228). Ocular exposure occurred in 6 cases, and other exposures in 28 cases. In 232 cases (88.5%), there were no symptoms and in 30 cases (11.5%), mild symptoms were present: nausea, vomiting (1–3 times), and irritation of the eye. No cases with moderate or severe symptoms were documented.

Conclusion: Accidental exposures to liquid laundry detergent pods in children caused mild symptoms in 63%, moderate symptoms in 4.2%, and severe symptoms in 1.4% of the cases. In contrast, for other laundry detergents, mild symptoms were documented only in 11.5% and no moderate or severe symptoms occurred. Liquid laundry detergent pods tend to cause symptoms more frequently and with higher severity than conventional laundry detergents.

76. User experience of the TOXBASE app


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Objective: The TOXBASE app (for iOS/Android) provides up-to-date, evidence-based poisons information both online and offline to healthcare professionals at the point of care. Our objective was to establish user expectations and requirements of this facility, and to improve our understanding of how the product is currently being used with a view to strategic development to meet our users' needs.

Methods: We invited all UK-based National Health Service (NHS) users with current subscriptions at 31 July 2017 (8600) to complete a short email questionnaire. We compared satisfaction scores for the app with those previously received for use of TOXBASE online [1].

Results: Overall, 489 (6%) responses were received; not all respondents answered every question. The app was used for “routine enquiries” 80%, “triage decision” 58%, “complex enquiries” 50%, “education” 55%, and for “maintaining local protocols” 12%. Most users (84%) reported multiple types of use. Only 3% of the respondents used the app “daily”, 22% “a few times a week”, 28% “weekly”, and 47% “less often”. Respondents described the typical locations where they used the app: around 50% of app users are ambulance personnel [2] thus 48% of users reported using the app out of hospital in the community setting. Hospital location in respect to the patient was noted as “at the bedside” (15%) and “away from the patient” (4%). Some reported using the app in multiple scenarios (27%). User satisfaction: Using the app in multiple scenarios (27%). User satisfaction with current subscriptions at 31 July 2017 (8600) to complete a short email questionnaire. We compared satisfaction scores for the app with those previously received for use of TOXBASE online [1].

Conclusions: The TOXBASE app is highly thought of amongst our user group and users have confidence in the information provided. This data demonstrates its versatility within a variety of clinical scenarios. We aim to build on this positive feedback to develop the app to cement its position as a vital tool in frontline poisons management.

References


78. Results from the EU LiquiCaps study: a comparison between cases of poisoning aged <5 years and exposed to laundry detergents


Objective: Liquid laundry detergent capsules (LLDCs) are highly concentrated detergents in water-soluble packaging intended for single use. Accidental exposures to LLDCs have been associated with moderate and high severity poisonings, particularly among children. From June 2015, mandatory safety measures were implemented in Europe (Regulation (EC) No 1297/2014) to prevent hazardous exposures to LLDCs. This contribution provides a comparison between cases of poisoning aged <5 years and exposed to LLDCs and traditional laundry detergents (TLDs) during an 8 month period following the implementation of the new rules. Prospective data collection and analyses were carried out within the study on hazardous detergent mixtures contained in soluble packaging for single use (LiquiCaps Study) launched by the European Commission.

Methods: Detailed information on cases aged <5 years and with clinical effects associated with exposure to laundry detergents occurred between 1 October 2015 and 31 May 2016 were collected according to standardized procedures by the poison centers (PCs) of Utrecht, Milan, Prague, Dublin, Bratislava, Lisbon, and Göttingen. Distributions by age (<1, 1–2, 3–4 years) and severity of clinical effects (low, moderate, high) according to the Poisoning Severity Score (none, low, moderate, high). Pooled data were estimated as mean daily number of cases/month and number of cases/million units sold per month. A change point analysis was used to identify changes of national exposure rates that were estimated as mean daily number of cases/month and number of cases/million units sold per month. A change point analysis was used to identify changes of national exposure rates.

Results: Among the identified cases of poisoning, 109 (25.3%) were exposed to TLDs and 321 (74.7%) to LLDCs. The two exposure groups showed highly statistically different distributions (p < .001) by age and severity of clinical effects. Age distributions were as follows (TLDs versus LLDCs): 6.5% versus 7.2% (<1 year), 78.7% versus 58.6% (1–2 years), and 14.8% versus 34.3% (3–4 years). Among TLDs-related poisonings, severity of clinical effects was low in 95.3% and moderate in 4.7%. Conversely, among LLDCs-related poisonings, severity was low in 78.5%, moderate in 21.5%, and high in one case suffering airway irritation and esophageal edema. The odds of moderate/high severity effects was six times higher among cases exposed to LLDCs than to TLDs (adjusted by age OR 6.0; 95% CI 2.3–15.4, p < .001).

Conclusion: During the observation period, LLDC-related poisonings continued to be more frequently reported and more severe than those referred to TLDs. If confirmed in subsequent investigations, these observations suggest that further efforts are needed to reduce LLDC’s intrinsic toxicity and their attractiveness/accessibility to children.

79. EU LiquiCaps study: an evaluation of impact of Regulation (EU) No 1297/2014 on frequency of exposure to liquid laundry detergent capsules and poisoning severity


Objective: In April 2015, the European Commission launched a study on hazardous detergent mixtures contained in soluble packaging for single use (LiquiCaps study) to assess, among other things, the impact of Regulation (EC) No 1297/2014 on the frequency of exposure to liquid laundry detergent capsules (LLDCs) and poisoning severity. We reported the results concerning these objectives.

Methods: Information on exposures to LLDCs between 1 August 2015 and 31 May 2016 were collected prospectively according to standardized procedures by the PCs of Utrecht, Milan, Prague, Dublin, Bratislava, Lisbon, and Göttingen. National exposure rates were estimated as mean daily number of cases/month and number of cases/million units sold per month. A change point analysis was used to identify changes of national exposure rates. Severity of poisoning was assessed according to the Poisoning Severity Score (none, low, moderate, high). Pooled data were analysed by using two logistic regression models to estimate the strength of the association between bi-monthly exposure periods, clinical effects (none; at least one) and severity of poisoning by odds ratios (ORs) estimates adjusted by age.

Results: No statistically significant changes in national exposure rates were observed. In total, 740 cases were identified. Among them, 86.6% were aged <5 years. Poisoning severity was none in 34.8% of the cases, low in 52.0%, moderate in 13.2%. One child aged <1 year developed high severity effects (airway irritation and esophageal edema). No statistically significant associations...
were observed between being exposed in different sub-periods, clinical effects and moderate/high severity poisoning.

**Conclusion:** The reported observations do not exclude that significant changes might have occurred outside the study period. In fact, safety measures intended to improve labelling, prevent accessibility (child-impeding lids), and reduce visibility (opaque outer-packaging) of LLDCs had been introduced in Europe by major companies (MCs) well before they became compulsory. In Italy, an abrupt 50% reduction of exposure rates had been detected in December 2012, four months after the introduction of opaque outer-packaging by a MC, while stable rates were observed in the subsequent two-year period, although this measure, along with others, became compulsory in June 2013 by a ministry decree [1]. No indications are provided on effectiveness of the measures intended to prevent/lower exposure in case of capsules accessed and, consequently, to reduce frequency and severity of poisoning in case of contact. A retrospective extension of the observation period is needed to make the study more informative.

**References**


**80. Use and safety of mood stabilizers and antipsychotic drugs during pregnancy: the experience of the Florence Teratology Information Service**

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**Objective:** About 15% of pregnant women suffer from a psychiatric illness [1]. The psychiatric conditions are often worse during pregnancy and post-partum, which are extremely vulnerable periods, especially when medical treatments are discontinued [2].

**Methods:** Eighty-one pregnant women affected by severe psychiatric conditions, such as psychosis, bipolar and major depressive disorders, in treatment with lithium, mood stabilizers, or antipsychotics were referred to the Florence Teratology Information Service (TIS), during the year 2014. A follow-up was performed 3 months after the estimated date of delivery through a telephone interview in order to collect information about childbirth, neonatal outcome, and drug management during pregnancy. A subsequent follow-up was performed after 12–24 months in order to investigate maternal psychological and physical wellbeing, breastfeeding, and child development.

**Results:** About 80% of patients were treated with more than one psychotropic drug, (mode 3 different drugs), and the most prescribed was valproic acid (32%). During pregnancy, 25% of the patients continued unchanged psychiatric therapy, whereas 42% modified the number or drug posology and 33% completely discontinued their treatment. The analyzed population had a high rate of elective termination of pregnancy (11%), a higher risk of preterm delivery (14%) and transitory neonatal complications (15.7%) compared to general population. Psychological distress during pregnancy was twice as high in patients who discontinued their therapy as in continuously treated patients.

**Conclusion:** This study showed that in pregnant psychiatric patients, therapy changes should be performed before pregnancy and psychotropic drug association are minimized. Drugs associated with a high rate of malformations or neurodevelopment disorders such as valproic acid and carbamazepine should be avoided in women who are planning a pregnancy and/or of childbearing age. Folic acid supplementation should be mandatory at least three months before conception. A multidisciplinary team approach should be preferred and the possibility of breastfeeding tailored to each patient.

**References**


reporting minor symptoms (PSS 1). Thirteen patients (2.1%) experienced moderate symptoms (PSS 2) while six (0.9%) reported severe symptoms (PSS 3). No fatalities were reported. Of those who reported minor symptoms (n = 234), the most common features were vomiting (20.5%), nausea (12.8%), eye irritation (12.8%), cough (12.0%), and headache (9.0%). Clinical features in 6 patients experiencing severe toxicity included dyspnea (n = 3), central nervous system depression (n = 3), vomiting (n = 2), and pneumonia (n = 2).

Conclusion: The majority of patients with petroleum distillate exposure were either asymptomatic or experienced mild symptoms only, but serious toxicity can occur and appropriate assessment and monitoring is essential. Exposure most commonly occurs accidentally in a residential setting and commonly involves children.

82. Poisoning in the elderly: characterization of exposures reported to the Dutch Poisons Information Center

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Objective: Aging of the population is a worldwide phenomenon and one of the greatest challenges for healthcare. The aim of this study was to gain insight on exposures reported to the Dutch Poisons Information Center (DPIC) involving elderly patients, in order to help prevent future intoxications.

Methods: Enquiries to the DPIC from 2006 to 2016 involving patients >65 years old were selected from the database. Data on patient characteristics and exposures were analysed.

Results: The annual number of enquiries to the DPIC on patients >65 years old more than doubled from 852 in 2006 (2.6% of total enquiries) to 1851 in 2016 (4.5% of total enquiries). Exposures in 2016 were analysed in more detail. In 2016, 58% of elderly patients were female, and one-third were >80 years old. The product groups most often involved were medication (74%), household products (9%), and cosmetics (4%). Drugs involving the central and peripheral nervous system (44%) and cardiovascular agents (26%) were most frequently taken in overdose. In 73% of the cases, drug overdose was unintentional. The severity of the exposures to medication was estimated using dose and body weight (mg/kg), and was none/mild in 64% of the cases, moderate/severe in 11%, and unknown in 25%. In 63% of the cases, it was advised to observe the patient at home, whereas in 22%, evaluation by a (family) physician, and in 15% hospital admission were recommended. The most remarkable trend in the past years was the large increase in the number of enquiries on novel oral anticoagulants (NOACs). Exposures to rivaroxaban increased from 1 in 2013 to 22 in 2016, apixaban increased from 0 in 2013 to 7 in 2016, and dabigatran increased from 2 in 2013 to 9 in 2016. All exposures to NOACs resulted from medication errors, mostly due to taking an extra dose during therapeutic use.

Conclusion: The number of enquiries to the DPIC about elderly patients has strongly increased over the last decade. Pre-hospital triage and treatment of poisoning can be challenging in this population. The elderly may be more susceptible to toxic effects, due to underlying medical conditions, and the use of concurrent medication. The majority of medicinal overdoses in older people are unintentional. A multidisciplinary approach, involving education and monitoring by general practitioners, pharmacists, nursing home staff, and home care providers, may prevent medication errors caused by memory impairment, or improper use or storage of medication.

83. Carbon monoxide poisoning: data from the UK National Poisons information Service (NPIS)

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Objective: To assess the incidence and severity of carbon monoxide (CO) exposure in patients in the UK following accesses to TOXBASE® and calls to NPIS.

Methods: Data were collected from NPIS call records, TOXBASE® accesses, and follow-up questionnaires (1 July 2015 to 30 June 2017) regarding patients with suspected CO exposure.

Results: Data were collected on 1627 patients (71% adults ≥13 years, 1156), 19% children [≥12 years, 312]). Of these, 1546 (95%) were non-house fire related with only 81 (5%) associated with house fires. Table 1 demonstrates the poisoning severity scores (PSS) versus intentionality for suspected non-house fire CO exposures. The majority of patients (930, 62.3%) with unintentional exposures were asymptomatic or experienced mild symptoms (PSS 0 or 1). Only 1.2% reported severe features. Conversely, 26.4% of intentional exposures experienced severe features and 3.8% fatal outcome. Similarly, a greater proportion of patients exposed to CO in house fires experienced severe (12.4%) or fatal (4.9%) outcomes, likely compounded by additional factors (e.g., cyanide, thermal injury, etc.). Admission pre-treatment carbon monoxide (COHb) concentrations were available in 424 (27.4%) patients. Regression analysis using a non-linear ordinal (PSS) indicates a positive correlation between COHb concentration and symptom severity (r² = 0.93). In patients where COHb concentration confirmed exposure, common clinical features included headache (38.6%), nausea (16.5%), dizziness (15.1%), reduced Glasgow Coma Scale (13.7%), and fatigue (13.0%). When signs were categorized by body system, 53.5% were neurological, 20.1% gastrointestinal, 10.9% cardiovascular, 8.4% respiratory, 4.8% musculoskeletal, and 2.3% metabolic.

Conclusion: Data are presented on CO exposures reported to the NPIS over a 2-year period. The majority were unintentional, often resulting in mild non-specific symptoms. However, fatalities did occur. Intentional or house fire-related exposures were associated with greater severity. Data comparing initial COHb concentration and symptom severity suggests a correlation and warrants further exploration.

Table 1. Poisoning severity score with respect to exposure type and measured carboxyhaemoglobin (COHb) concentrations (data from the UK National Poisons Information Service, 2015–2017).

<table>
<thead>
<tr>
<th>NPIS Poisoning Severity Score (PSS)</th>
<th>Non-house fire related (n = 1546)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unintentional</td>
<td>Self-harm (intentional)</td>
</tr>
<tr>
<td>% COHb (n = 424) (mean ± SD)</td>
<td></td>
</tr>
<tr>
<td>None (PSS 0)</td>
<td>310 (20.8) 14 (26.4) 5.15 ± 6.8</td>
</tr>
<tr>
<td>Minor (PSS 1)</td>
<td>620 (41.5) 16 (30.2) 5.55 ± 6.65</td>
</tr>
<tr>
<td>Moderate (PSS 2)</td>
<td>77 (5.2) 4 (7.6) 13.18 ± 11.68</td>
</tr>
<tr>
<td>Severe (PSS 3)</td>
<td>18 (1.2) 14 (26.4) 25.33 ± 7.31</td>
</tr>
<tr>
<td>Fatal (PSS 4)</td>
<td>3 (0.2) 2 (3.8) 30 ± NA</td>
</tr>
<tr>
<td>Uncertain</td>
<td>468 (31.2) 3 (5.7) 7.18 ± 7.58</td>
</tr>
</tbody>
</table>

Values in parentheses indicate % of total exposures for that category.
84. Oral methotrexate exposure: a 15-year survey of Austrian Poisons Information Centre cases

Tara Arif, Susanna Dorner-Schulmeister and Kinga Barteczka-Mino
Poisons Information Centre, Vienna, Austria

Objective: Methotrexate (MTX) is an antineoplastic drug, which is also used in autoimmune/rheumatic diseases. The aim of this study was to analyse circumstances and symptoms after oral exposure with MTX alone.

Methods: A retrospective and descriptive review of enquiries to the Austrian Poisons Information Centre concerning only oral MTX exposures from 2002 to 2016 was conducted.

Results: In total, 54 patients with oral MTX exposures were extracted from the database. In the paediatric group, 13 children (5 girls, 8 boys; 2 to 11 years of age) were involved. In 11 cases, the intake was accidental, 2 patients received a second dose of their medication from their parents as a therapeutic error. None of the children had any symptoms. The other patients were over the age of 15 years (n = 41; 11 males, 30 females). In 29 cases, the intake was due to therapeutic error, in 9 cases, exposures were intentional and in 3 cases unknown. Symptoms occurred in 20 out of the 41 cases: anaemia (n = 3), leucopenia (n = 2), thrombocytopenia (n = 2), pancytopenia (n = 7), coagulopathy (n = 1), gastrointestinal bleeding (n = 2), nausea (n = 4), vomiting (n = 3), diarrhea (n = 4), ulceration in gastrointestinal tract (n = 6), stomatitis (n = 6), liver failure (n = 3), fever (n = 3), and sepsis (n = 2). We describe two patients with sepsis. A 40-year-old female was hospitalized after intentional intake of 55 mg MTX. Her symptoms were: fever, diarrhea, painful oral, perianal and vaginal mucosal lesions, gastrointestinal bleeding with hemorrhagic gastritis and duodenal ulcer, sepsis, and pancytopenia. Hypertension required treatment with nitroglycerin, urapidil, and verapamil. The ECG showed intermittent atrial fibrillation and narrow complex tachycardia. She also developed abscesses in the gluteal area. The patient was discharged after 2 months. An 86-year-old female patient received MTX 10 mg daily for 8 days instead of 2.5 mg/week due to a therapeutic error. Her presentation included vertigo, nausea, fever, renal failure, elevated liver enzymes, and pancytopenia. She was treated with calcium folinate. The patient died after 9 days of hospitalization in the intensive care unit due to bone marrow suppression leading to sepsis.

Conclusion: Therapeutic error often causes MTX intoxication due to inaccurate administration by pharmacists, or an incorrect or misleading prescription. The lack of knowledge of the medication often puts the life of patients at risk and results in enormous medical problems in an already health-impaired patient. Clear instructions to patients or family members are necessary.

85. Massive lead poisoning from a gunshot with high soft lead charge


Objective: To report a case of unusually rapid onset of lead poisoning after a special ammunition gunshot.

Case report: A 38-year-old man with no history of lead poisoning was shot. The bullet blew through a door before reaching the victim, fragmented, and resulted in a riddling of 60 secondary projectiles in the victim. Initial lesions mainly concerned the left chest, left shoulder, and left brachial plexus. The first blood lead level (BLL) was collected on day 7 after the wound and analysed by graphite furnace atomic absorption spectrometry. BLL was 1048 µg/L (French reference value in exposed adult men <200 µg/L), with a peak to 1566 µg/L on day 11. Symptomatology was a sensation of extreme fatigue, constipation, and peripheral neurologic involvement of the left ulnar. Other markers on day 11 were slight anemia (hemoglobin 11.6 g/dL), erythrocyte protoporphyrin level (1.911 µmol/L) and urine delta-aminolevulinic acid (13 µmol/mL of creatinine). Two subcutaneous metallic residues and a hair sample were sent for analysis by inductively coupled plasma mass spectrometry to confirm the presence of lead: they confirmed that lead was present in the residues (817 and 841 mg per gram), there was a recent incorporation of lead in hair (63 ng/mg in the end and 119 ng/mg in the basis), and the lead in the hair was from the same origin as the bullet (isotopic ratios were the same Pb 206/Pb 207 = 1.17, Pb 208/Pb 207 = 2.44, Pb 208/Pb 206 = 2.08). Several chelation treatments with succimer and sodium calcium edetate together with surgical extraction of lead fragments did not prevent clinical and biological signs of chronic lead poisoning.

Conclusion: This special ammunition contained 30 g inert soft lead not protected with a metallic envelope. It is not intended to be used directly on living targets. Such a rapid, high, and massive contamination is linked to a pure and important lead charge of the cartridge not protected by a metallic envelope, the presence of “soft lead”; which is more prone to fragmentation than “hard lead”, and the location of the lead fragments in the body, especially in the pleura and near the shoulder joint. The presence of a substantial lead store in the body is now responsible for chronic lead poisoning, probably for the rest of the patient’s life.

86. Metal release from spinal arthrodesis: two cases with titanium-alloy implant failure and local metal release but mild elevation of serum concentrations

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Objective: No published data have extensively investigated spinal titanium-alloy implant functioning, presence/absence of local...
metal release, local histopathological findings and systemic blood metal concentrations taken together [1]. We report two cases of spinal titanium-alloy implant failure describing serum metal concentrations and local findings.

**Case reports:** Case 1: A 58-year-old male was referred to the Emergency Department (ED) after falling at work. Spine X-ray showed an L1 fracture, and spinal stabilization and D11-L3 fusion with USS-Low-Profile-system (DePuy-Synthes) was performed. After six months, dorso-lumbar pain appeared. A computerised tomography (CT) scan showed dislocation of the caudal implant-screws with peripheral bone reabsorption. Vertebral implant removal, and L1, L2, L3 vertebroplasty was performed. Scar-like tissue with metallic pigmentation around the dislocated screws were present intraoperatively. Toxicological blood analysis showed aluminum 6 µg/L (reference 1–6 µg/L), titanium 5 µg/L, tantalium 0.08 µg/L (reference <0.1 µg/L), and niobium 0.1 µg/L. After six months, the patient reported occasional lumbar pain with vertebral stability on magnetic resonance imaging (MRI).

Case 2: A 41-year-old female presented to the Neurosurgical Department with cervical pain and serous dehiscence from an occipital decubitus lesion. Ten years before, a surgical fusion for atlanto-axial instability in rheumatoid arthritis was performed. She underwent cranio-vertebral implant removal (Oasys-occipito-cervical-system-Striker) and occipital skin plastic surgery. Scar-like tissue with metallic pigmentation around the dislocated screws was sampled. Histopathology revealed fibrous tissue, sinovial tissue with faint fibrosis, phlogosis, and pigmented material deposition. Toxicological blood analysis showed chromium 1 µg/L (reference 0.1–0.2 µg/L), cobalt 0.3 µg/L (reference 0.05–0.3 µg/L), molybdenum 2.6 µg/L (reference 0.2–1 µg/L), and titanium 12 µg/L. After one month, she reported occasional cranio-vertebral pain with vertebral segment stability at X-ray.

**Conclusion:** Metal spinal implants may be involved in several complications including implant corrosion, local metal release, and increases in systemic blood metal concentrations. In our patients, there was implant failure with local metal release at histopathology. Blood metal concentrations were within the reference values or under the reported concentrations for these metals in patients with well-functioning spinal implants. Systemic metal release from failed spinal implant may result in low serum concentrations compared to the well described literature on metal-on-metal hip implanted patients. This suggests that serum metal monitoring may be an inadequate surrogate “marker” for spinal implant functioning, development of inflammatory local reactions or spinal metallosis.

**References**


87. Biochemical effects of lead in exposed workers with respect to liver and kidney function tests

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**Objective:** Lead (Pb) has been one of the most widely used metals due to its useful properties [1]. Contact with lead and its compounds within different conditions and circumstances can result in lead poisoning, this can occur in the process of lead production and use or in non-occupational lead poisoning, present in everyday life [2]. Lead is known to affect organs and various systems of an organism [3]. The present study attempts to assess the impact of lead exposure on the liver and renal function indices of exposed workers.

**Methods:** In this prospective cohort study, 100 adults with occupational lead exposure (blood lead levels [BLL] > 10 µg/dL) were compared with 100 age- and gender-matched normal healthy subjects (BLL < 10 µg/dL). Biochemical concentrations of BLL, blood urea, creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were recorded for subsequent analysis. Data were analyzed by SPSS software (version 19) using Mann-Whitney U-test and logistic regression model. p Values of <0.05 less were considered as the statistical significant levels.

**Results:** The mean BLLs were significantly higher in the exposure group compared to the controls (51.36 ± 44.72 versus 4.17 ± 1.97, p = 0.002). The median [IQR] serum urea (36 mg/dL [27–223.25]), creatinine (0.9 mg/dL [0.8–1]), ALT (27 mg/dL [16–49]) and AST concentration (30 mg/dL [20–42]) were significantly (p < 0.01) higher in the study subjects than the comparison group (30 [27–35.75], 0.8 [0.7–0.9], 22 [22–29.75], and 20 [18–24] mg/dL, respectively). Logistic regression analyses for BLL were significantly associated with serum urea (OR 95% CI: 1.02 [1.001–1.05], p = 0.04) and AST concentration (OR 95% CI: 1.08 [1.03–1.13], p = 0.001).

**Conclusion:** These results indicate that people with occupational lead exposure are at risk of developing renal and liver impairment. Early screening and regular monitoring of industrial workers is urgently needed to prevent long-term adverse effects of lead exposure.

**References**


88. A national survey of the level of knowledge of orthopedic surgery residents regarding systemic cobalt toxicity associated with total hip arthroplasty

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**Objective:** Metallosis, specifically systemic cobalt toxicity, following total hip arthroplasty is an important clinical concern. Cobalt-containing arthroplasty implants are known to release cobalt ions over time and elevate both serum and urine cobalt
concentrations. Systemic adverse effects from elevated cobalt concentrations have been reported to include cardiomyopathy, hypothyroidism, polycythemia, deafness, visual loss, and peripheral neuropathy. Biological surveillance of cobalt ion burden, and monitoring of symptoms is necessary to confirm clinical suspicions regarding toxicity as it is impossible to predict, which patients will develop adverse effects. A non-specific clinical presentation in conjunction with lack of physician awareness may lead to under-recognition of the problem. Currently, there is no information regarding the level of education orthopedic surgery residents receive during training regarding systemic cobalt toxicity following total hip arthroplasty. The objective of this study was to identify the level of knowledge of orthopedic trainees regarding this topic.

Methods: An electronic survey was distributed to 4022 resident trainees currently enrolled in an Accreditation Council of Graduate Medical Education and American Osteopathic Association approved orthopedic surgery residency training program.

Results: A total of 261 resident physicians completed the survey (response rate 6.4%). Responses were equally distributed among postgraduate years (PGY) 1 through 5. Overall, 113 respondents reported that cobalt-containing prosthesis were used in over 50% of cases and metal-on-polyurethane was the most common type of implant used. Over a third of respondents (38.3%) reported they never received any education regarding systemic cobalt toxicity and 8.8% were completely unaware of the problem. When asked to report their level of knowledge on the topic, only a small percentage (6.9%) felt they were able to educate others and 46.7% reported they did not know any specific details regarding the adverse effects of cobalt related to hip arthroplasty. Most respondents (80%) stated they never screen at-risk patients for toxicity. If a case did present itself, 21.5% were unsure who they would consult to assist in managing the patient. The majority of orthopedic resident physicians (63.8%) expressed interest in receiving more education regarding this topic.

Conclusion: Orthopedic surgery resident trainees have limited knowledge regarding systemic cobalt toxicity associated with total hip arthroplasty. These results demonstrate an opportunity for medical toxicologists to assist in orthopedic surgery training by providing education regarding arthroplasty metallosis.


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Objective: Mercury-containing measuring devices (barometers, manometers, sphymgomonometers, and thermometers) have been used for many years in domestic and professional settings. European legislation on chemicals led to a ban on their sale to the general public in April 2009 and for professional use in April 2014. The objective of this study was to characterise exposures related to mercury-containing measurement devices, in terms of circumstances, symptoms experienced, and severity as reported to the UK National Poisons Information Service (NPIS).

Methods: Telephone enquiries relating to mercury-containing measurement devices recorded in the UK Poisons Information Database were analysed for the period 1 January 2008 to 31 December 2016.

Results: During the study period, there was a total of 581 enquiries received relating to mercury-containing measurement devices; 84% related to thermometers, 12% to barometers, 3% to sphymgomonometers, and 1% to manometers. There was a 30% decline in calls relating to exposures from mercury-containing measurement devices between 2008 and 2016. Exposures were usually accidental (95%) and primarily occurred in the home (88%), followed by work (6%), schools (2%), general practitioner surgeries (1%), nursing/care homes (1%), other (1%), and public areas (1%). The majority of exposures were amongst females (57%) and were common in children <10 years old (30%), with children <5 years old accounting for 22% of exposures overall. Ingestion (45%), inhalation (35%), and skin contact (17%) were the predominant routes of exposure. The majority of patients (88%) were asymptomatic (Poisoning Severity Score (PSS) 0); 17% experienced minor symptoms (PSS 1) and 0.3% experienced moderate symptoms (PSS 2); no patients experienced severe (PSS 3) or fatal (PSS 4) outcomes. Of the 105 patients that reported symptoms, 56% experienced only one symptom, 33% two symptoms, and 11% three or more symptoms. The most commonly reported symptoms were: headache (4%), paraesthesia (2.4%), taste disturbance (2.1%), nausea (1.7%), coughing (1.5%), dizziness (1.5%), pharyngitis (1.4%), malaise (1%), abdominal pain (0.9%), and chest pain (0.9%).

Conclusion: There has been a decline in calls to the UK National Poisons Information Service relating to mercury exposures from measuring devices between 2008 and 2016. Exposures were accidental and asymptomatic in the majority of cases.

90. Occupational lead poisoning – similarities and differences: two case reports

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Objective: We present two cases of occupational lead poisoning in patients of the same age working at the same workplace, but with significant differences in blood lead levels (BLL), clinical manifestations, and outcomes.

Case reports: Two previously healthy patients were engaged in cutting lead-coated bridge beams without adequate personal protective equipment. About 3 weeks after starting the work, they experienced the first symptoms. In the next 5 weeks, they underwent medical examinations in local hospitals, but symptoms progressed. Case A: A 45-year-old male was transferred to the Department of Clinical Toxicology from a local hospital where he was examined due to anemia and progressing abdominal pain. He presented with malaise, nausea, obstipation, abdominal pain, generalized bone and muscular pain and weight loss (about 10 kg). Physical examination showed bluish pigmentation on gingival tissue and blood pressure was 160/100 mmHg. Other exams were normal. Laboratory tests revealed anemia (hemoglobin 77.8 mg/L) and basophilic stippling of erythrocytes. Blood lead level was 285.03 μg/dL. His symptoms improved after a 5-day course of chelation treatment with dimercaprol and sodium calcium...
91. Severe symptoms following “heavy metal detoxification”

Anne Stürzebecher, Mandy Gollmann, Gesine Liebetrau, Maike Borchers, Wolfram Pönisch, David Hellinger, Thomas Ernst and Dagmar Prasa

Objective: Many natural health professionals and alternative practitioners offer therapies for “heavy metal detoxification”, which often contain chelators in non-therapeutic doses as well as other antioxidants, such as alpha-lipoic acid (ALA). ALA is used traditionally as an antioxidant and for treatment of diabetes, neuropathy, and AIDS. To date, it is marketed as a dietary supplement and pharmaceutical drug. We report on five cases of severe neuropa-thy as patient A. After the second course, the BLL was 45.12 μg/dL, but quadruplaemia had not improved. The amount of lead eliminated in urine during the first and second course was 33.27 mg and 24.64 mg, respectively.

Conclusion: Despite the similar duration of exposure, the patients developed different clinical manifestations and outcome. Patient B had a lower BLL and better elimination of lead, but had more severe intoxication than patient A, which could be explained by unrecognized individual factors. Occupational lead poisoning is still a serious health risk in developing countries and physicians should be aware of the risk. Delayed diagnosis can cause irreversible harm with permanent sequelae.

92. Intracorporeal bullets: screening for lead poisoning and setting up of a medical follow-up

Pierre Brun, Régis Bédé, Claire Masson-Samoyault, Estelle Sudre, Nahid Sarram-Nadjimi, Mareme Kandji and Sophie Gronb-Monnoyeur

Objective: In France, possession of a gun is strictly forbidden except for hunting. Metallic bullets may cause lead poisoning after progressive dissolution when in contact with acidic corporal fluids. People with a criminal history have a high risk of having retained bullets in the body; in a study of arrested people from 11 US towns, 21% had been shot at some point [1]. We examined the risk of lead poisoning from intracorporeal bullets in patients hospitalized in the Secure Unit of Bordeaux University Hospital.

Methods: Retrospective monocentric study of patients presenting with intracorporeal bullets between 1 May 2008 and 1 December 2016. Socio-demographic characteristics, nature of the intracorporeal bullets, precise location on imaging, blood lead concentrations and clinical or biological signs suggestive of lead poisoning were collected. Statistical analysis is descriptive.

Results: Overall, 22 patients (1.1% of the patients admitted in the unit during the study period), all men, with a mean age of 47 ± 13.5 years were recorded. In the 4 patients who had blood lead concentrations measured less than 40 days after the ballistic trauma, only one showed clinical and biological signs of acute lead poisoning with a maximum blood lead concentration of 1566 μg/L, and evolved to chronic lead poisoning, despite double chelation and surgical extraction of lead fragments. In the other 3 patients, blood lead concentrations increased during the first 3 weeks to concentrations < 450 μg/L and then decreased to less than the general population concentration (< 100 μg/L in France) without symptoms of lead poisoning. In the 15 patients with intracorporeal lead for more than 40 days, the average blood lead concentration was 78.3 ± 51.4 μg/L. When several blood lead concentrations were performed, they showed a stable or decreasing trend. None showed symptoms of lead poisoning.

Conclusion: After one year, unless the patient shows symptoms of lead poisoning or something happens to cause a change in blood lead concentration, there is no need for further examination, except to have a blood lead concentration measured as a reference value for the follow-up. Patients with intracorporeal lead projectiles therefore require a notification in their medical file in order not to overlook a current or future risk of lead poisoning, even several years after the trauma.
Reference


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Objective: In Morocco, scorpion envenomation in children is a real health problem, but there is a lack of data about spider bites among young people. Thus, we have conducted a study to describe patterns of spider bites in children reported to the Moroccan Poison Control Centre (CAPM).

Methods: Data for this study were extracted from the medical records of CAPM from 2000 to 2012. The data included sex, age distribution, the outcome, and local and systemic effects.

Results: A total of 59 cases were reported. The accidents were mostly seen during spring and in the afternoon. The male/female ratio was 2.5. The mean age was 6.3 years (34 cases aged from 5–13 years old). Local symptoms were observed in 59.3% of the cases, including local pain, edema, redness, and itching. Systemic symptoms were observed such as nausea, vomiting, abdominal pain, weakness, sweating, dyspnea, tachycardia, priapism, and hyperthermia. The outcome was favorable in 90% cases.

Conclusion: The number of spider bites remains underestimated in Morocco even if the envenomation is responsible for systemic symptoms. A prospective study including the identification of the spider species is needed to determine the incidence and risk of spider bites.

94. How often do snakebite patients receive prophylactic steroids or antihistamines before Fab antivenom?

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Objective: Fab antivenom (CrobFab®, BTG International) is the principal antivenom for crotalid snakebites in North America. In spite of evidence that hypersensitivity reactions to Fab antivenom are infrequent and mild, the manufacturer’s prescribing information warns, “severe hypersensitivity reactions may occur,” and “emergency medical care (e.g., epinephrine, intravenous antihistamines and/or albuterol) should be readily available”. We sought to determine the frequency of pre-treatment of crotalid snakebite victims with steroids or antihistamines before Fab antivenom.

Methods: We searched our Poison Control Center (PCC) database from 2011 through 2016 for patients with a crotalid snakebite. We reviewed the PCC call records for treatments given (antivenom, steroids, antihistamines, or salbutamol). We excluded PCC records without available text or indicators of treatment.

Results: The PCC recorded 1037 enquiries about snakebite during the six-year period (average 173 per year). Of these, 186 of the cases had an evaluable record for further analysis. Copperhead snakes (Agkistrodon contortrix) predominated in our state. Of the 186 evaluable cases records, 139 patients received Fab antivenom, and 47 patients did not receive Fab antivenom. Among the 139 patients who received Fab antivenom, 15 (11%) received antihistamines alone (including one patient who took diphenhydramine before arriving at the hospital), and one received steroids alone before Fab antivenom, and nine (6%) received both diphenhydramine and steroids. There were 114 patients who had no recorded use of steroids or antihistamines. No patient received salbutamol. No patient had anaphylaxis following Fab antivenom regardless of the presence or absence of pre-treatment. Of the 47 who did not receive Fab antivenom, three (6%) received antihistamines alone, one received steroids alone, and one received both antihistamine and steroids. Forty-two cases had no recorded use of steroids or antihistamines.

Conclusion: A minority of cases had documented pre-treatment with diphenhydramine or steroids before receiving Fab antivenom. Because specialists in poison information (SPIs) may not elicit pre-treatment information from callers, these proportions may underestimate the frequency of pre-treatment. Pre-treatment appeared to have no effect on outcome.

95. A misuse of snakebite antitoxin may be life-threatening for patients: a French case of European Vipera species envenomation treated with ViperaTAb®

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Objective: Due to a current shortage of Viperav®, the French authorities decided to import and recommend the use of ViperaTAb®, another antitoxin to treat Vipera berus envenomation [1]. In south west France, the main species is represented by Vipera aspis. Data regarding the efficiency of ViperaTAb® in the treatment of V. aspis bites are scarce, and the misuse of such antivenom could be life-threatening for patients [2].

Case report: A 61-year-old man was bitten by Vipera species in south west France. Upon admission to the Emergency Department, two hours after the bite, he had a local edema on the forefinger of the left-hand with moderate pain. The envenomation was evaluated as grade I (minor envenomation) that only requires a 24-hour monitoring. Nevertheless, the patient was given a single dose (i.e., two vials) of ViperaTAb®. As he did not present any other envenomation symptoms six hours after the bite, he was discharged. He returned to the Emergency Department 24 hours later with extensive edema up the arm, a hematoma, and lymphangitis. Blood tests showed an increase in C-reactive protein (CRP) (23 mg/L), leucocytosis (21000/mm³), mild rhabdomyolysis (275 UI/L) and a coagulopathy with increased D-dimer (5140 ng/mL). The Poison Control Center was contacted and they advised administration of two successive doses of ViperaTAb® at an interval of at least four hours. Symptoms began to decrease 12 hours after the second antivenom dose.

Conclusion: This case illustrates that envenomation treatment requires a close monitoring for 24 hours, even if the symptoms seems to stop evolving. The simultaneous use of the two types of antidotes on French territory could be responsible for medical
97. Spiders bites in Italy: data collection of a Poison Control Center

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Objective: Toxicological requests to our Poison Control Center (PCC) for spider bites have increased over the last two years. Biting of a human is an incidental event, occurring when the spider is involuntarily touched or crushed. In most cases, consequences of the bite resolve in a relatively short time, without any complications; nevertheless some species’ bites can lead to relevant medical issues.

Methods: Analysis of PCC data about all spider enquiries was performed from 1 January 2015 to 31 December 2016. The PCC uses a specific protocol: in case of a suspected spider bite data are collected on which part of the body is involved, if there is pain, the time-lapse between the bite and the appearance of the injuries, their characteristics and photographic documentation of the bite.

Results: During the study period, 301 spider bite enquiries were collected. Among these, 239 were clinical cases, 36 information and 26 were recalls. The data collection involved 135 females and 101 males and 3 of unknown gender. In total, 154 patients were treated in the hospital, 42 at home and 43 unknown. Overall, 171/239 cases were followed-up successfully (71.5%). The bite area involved was the hand (n = 78), lower limbs (n = 50), arms (n = 28), and other (n = 83). Signs of local edema, irritation, and hyperemia were frequently reported. Clinical effects included: hyperemia (n = 133), localized edema (n = 118), pain (n = 91), itching (n = 58), vesicles (n = 23), diffuse edema (n = 15), hyperthermia (n = 14), paresthesia (n = 5), and a measles-like rash (n = 2). In 89/171 cases with complete follow-up severity was classified as minor (37.2%), 56 as moderate (23.4%), 14 as severe (5.8%), no symptoms were present in 11 cases (4.6%) whereas 69 cases could not be graded on the basis of the dataset (28.9%). The spider was seen in 48 cases (20%) and was identified by an entomologist in 22 cases (9.2%). Spider bites were most commonly reported in July (n = 39) and August (n = 39).

Conclusion: Diagnosis is not easy when the spider is not seen and symptoms, such as pain, itching, and edema, appear after a lag of some hours or even days. Nevertheless, the evolution of a central blister into necrotic tissue following a bite from *Loxosceles* species, and possible superinfection, rapidly worsen. Aiming to inform and generate awareness on these dangers, the PCC prepared a brochure to describe all dangerous spiders of medical interest and updated its web page making contents available for download and publishing notices to citizens and healthcare professionals.
98. Wave biomechanotherapy for the rehabilitation of patients bitten by *Vipera berus*

Yury Ostapenko, Amayak Badalyan, Yury Goldfarb, Mikhail Potshkheria, Vladislav Shcetkin and Elena Chukina

*Research and Applied Toxicology Center of Medical and Biological Agency, Moscow, Russian Federation; †Sklifosovsky Research Institute for Emergency Medicine, Public Healthcare Institution of Moscow Healthcare Department, Moscow, Russian Federation; ‡ Russian Medical Academy of Postgraduate Education, Federal Public Educational Institution of Additional Professional Postgraduate Education of Russian Federation Healthcare Ministry, Moscow, Russian Federation*

**Objective:** *Vipera berus* bites are the most common snake bites in Russia and apart from general poisoning symptoms, local early massive or rapidly-spreading edema is often a symptom of *Vipera berus* bites, which seriously complicates the course of rehabilitation. Therefore, elimination of local complications is an important goal of treatment. We evaluated the effectiveness of wave biomechanotherapy (WBMT), a biomechanical automated massage treatment, in patients bitten by *Vipera berus*.

**Methods:** Changes in clinical and laboratory parameters were compared in 25 patients with a *Vipera berus* bite. Ten received WBMT in the complex of therapeutic measures (study group) and 15 patients were treated without WBMT (comparison group). All patients underwent the same basic treatment including damaged limb immobilization, forced diuresis, and symptomatic therapy. The WBMT procedures started on the 3rd day after admission to the hospital and exclusion of venous thrombosis by ultrasound dopplerography. The BIOM-WAVE (http://biomwave.com, Russia) was used and the compression cuff was placed on the injured limb. The procedure was carried out in the “traveling wave” mode, going from the distal to the proximal limbs at a speed up to 5 m/s, and in the “biomechanical resonance” mode with air vibrations frequency in the cuff 5–20 Hz in a limited area during 30 minutes 4–7 times a day. WBMT efficacy was assessed by clinical and laboratory data, as well as by measurement of the swelling perimeter.

**Results:** in patients treated with WBMT overall well-being improved, painlessness decreased, body temperature and heart rate normalized, edema, redness, hemorrhages decreased, and skin sensitivity was restored. On the third day of WBMT treatment, the lower extremity edema perimeter significantly decreased by an average 4.5 cm. At the initial laboratory study, all patients had multidirectional disorders of almost all hemorheological indices, deviations from the norm were 6.2 ± 1.2 m/s, 11 ± 1.4 g/dL, 73%. There were a moderate leukocytosis, and significantly increased indices of endotoxins. The use of WBMT resulted in more pronounced correction of these abnormalities than in the comparison group. The hospitalization period was 6.0 ± 0.9 days for patients in the WBMT group and 8.9 ± 1.2 days in the comparison group.

**Conclusion:** The use of WBMT for treatment of patients with a *Vipera berus* bite is highly effective and results in a significant reduction in the duration of hospitalization (median 33%).

Table 1. Laboratory results at admission and follow-up in a patient with an asymptomatic pulmonary hemorrhage after a bite from a Bothrops species snakebite.

<table>
<thead>
<tr>
<th>Laboratory results</th>
<th>Time in hours from the time of the bite (T0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (reference &gt;12–16 g/dL)</td>
<td>T4</td>
</tr>
<tr>
<td>Platelets (reference 150000–400000/mm³)</td>
<td>7000</td>
</tr>
<tr>
<td>INR (reference &lt;1.3)</td>
<td>&gt;11</td>
</tr>
</tbody>
</table>

99. Asymptomatic pulmonary hemorrhage on chest computed tomography (CT) after Bothrops species snakebite

Eduardo M. De Capitani, Carla F. Borrasca-Fernandes, Camila C. Prado, Elza Maria, F. P. Cerqueira and Fábio Bucaretchi

*Campinas Poison Control Center, School of Medicine, University of Campinas, São Paulo, Brazil; †Computed Tomography Division, CDE – Center for Diagnosis by Images, Campinas, São Paulo, Brazil*

**Objective:** To report an envenomation caused by *Bothrops* species snakebite with asymptomatic pulmonary hemorrhage detected on chest CT.

**Case report:** A 49-year-old man was admitted to our Emergency Department approximately 4 hours after a snake bite, with induced edema of the right hand up to distal part of the arm, local pain, and ecchymosis and bleeding from self-inflicted linear wounds with a knife (hands, left leg, and foot). He also showed signs of drunkenness, and mentioned that he had cut himself in an attempt to “extract the snake venom” after the bite. The offending snake was not brought for identification. The main laboratory features at admission revealed coagulopathy (INR >11) and severe thrombocytopenia (Table 1). Clinical and laboratory features suggested a lance-headed pit viper bite (*Bothrops* species), and he was treated with IV Bothropic antivenom (6 vials, Butantan Institute, Brazil), and transfusion of red blood cells, fresh frozen plasma, and platelets. A chest CT performed at the time of admission showed bilateral patchy ground glass opacities compatible with alveolar fillings. The patient had no hemoptysis or any other respiratory symptoms upon admission or during follow-up. He was discharged at day 4; follow-up revealed full recovery of thrombocytopenia, and improvement of hemoglobin level (day 8) and of the chest image (day 16).

**Conclusion:** Systemic hemorrhage, such as gingival bleeding, is not uncommon after envenomation by *Bothrops* snakes. In contrast, gross hematuria, pulmonary symptomatic hemorrhage, or central nervous system bleeding are uncommon. The chest images were considered to have been caused by pulmonary hemorrhage secondary to the hemostatic disturbances associated with the envenomation, such as coagulopathy, thrombocytopenia, and direct venom hemorrhagic activity on vessel walls (hemorrhagic metalloproteinases). Since routine chest X-ray is not taken in such cases, the real frequency of asymptomatic pulmonary hemorrhage is probably underestimated.
100. *Naja mossambica* snakebite in Kentucky

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**Objective:** The Mozambique spitting cobra (*Naja mossambica*) is indigenous to South East Africa [1] and due to high morbidity and mortality, the World Health Organization considers envenomation by this species to be of the highest medical importance [2]. The venom is profoundly cytotoxic and causes neurologic and cardiac effects [3,4]. There are few case reports describing cases outside Africa. We present a patient bitten in North America who had positive response when treated with the SAIMR Polyvalent Snake antivenom.

**Case report:** A 58-year-old male was attempting to milk a Mozambique Spitting Cobra when the snake’s fang scratched his left index finger. The patient’s own supply of SAIMR Polyvalent Snake antivenom was started approximately 110 minutes later (an infusion rate of 50 mL/hour), prior to arrival at our facility. On arrival, he had ascending paresthesia, which began at his feet and extended to his mid-thigh area. He had bilateral lower extremity limb fasciculation present and intermittent jerking in those extremities. There was notable erythema and swelling from the bite site up the left forearm. Initial vital signs were within normal limits and he was able to protect his airway. He had begun to develop rash and hives that were believed to be secondary to the antivenin, and was given diphenhydramine, famotidine, and methylprednisolone and therapy was continued. Coagulation studies, electrocardiogram, and cardiac markers all remained within normal limits. He received 5 vials of the antivenom and the rate was titrated up to 150 mL/hour, at which time, progression of his paresthesia stopped. He was discharged 24 hours later with full resolution of parasthesias. His left index finger had a puncture site but no redness; swelling was reduced along with return of full range of motion and no signs or symptoms of necrosis.

**Conclusion:** Limited clinical experience with the Mozambique spitting cobra envenomations exists outside of the native geographical area. Our patient experienced significant improvements after treatment with SAIMR Polyvalent Snake antivenom and was discharged approximately 24 hours after the initiation of treatment.

**References**


101. Microangiopathic hemolytic anemia and acute kidney injury following *Bothrops jararaca* snakebite

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**Objective:** To report envenomation by the pit viper *Bothrops jararaca* that evolved with microangiopathic hemolytic anemia (MHA) and severe acute kidney injury (AKI).

**Case report:** A 56-year-old woman with controlled hypertension was transferred from a primary hospital to our Emergency Department approximately 7 hours after being bitten by *B. jararaca* on the distal left leg. She developed edema extending from the bite site to the proximal thigh, associated with intense radiating local pain (grade 10; pain scale 0–10), local paresthesia and ecchymosis at the bite site. Laboratory features upon admission included coagulopathy (WBCT20 > 20 min), thrombocytopenia (7600 platelets/mm\(^3\)) and slight increase in serum creatinine (1.58 mg/dL) (Table 1). Upon admission, the patient received bothropic antivenom (120 mL, intravenously). During outcome, she developed intravascular hemolytic anemia and severe AKI (Kidney Disease: Improving Global Outcomes [KDIGO] stage 3) associated with thrombocytopenia and blood smears on days 6 and 9 showing fragmented red cells; all these features were compatible with MHA. No red blood cell transfusion, renal replacement therapy, or plasmapheresis was done. She showed progressive improvement from D10 and was discharged on D20; complete recovery of hemoglobin concentrations occurred during follow-up (D50).

**Conclusion:** MHA with or without AKI has been described after snakebites in India and Sri Lanka (*Hypnale* species) and Australasia (*Pseudonaja* species, *Oxyuranus scutellatus* and *Notechis scutatus*). Acute anemia, even without local or systemic hemorrhage, is common after bites by *Bothrops* species (30–50% of the cases); however, MHA has not routinely been screened as a possible etiology of anemia in these cases. Confirmed fatal MHA causing multiple cerebral, myocardial, and mesenteric infarctions has been described after *Bothrops lanceolatus* snakebite, the venom of which may cause systemic thrombotic complications, in contrast to other *Bothrops* species. To our knowledge, this is the first confirmed report of MHA with severe AKI following *B. jararaca* snakebite.

**Table 1.** Relevant laboratory results in a patient bitten by *Bothrops jararaca*.

<table>
<thead>
<tr>
<th>Days (D)</th>
<th>D1(7 h after bite)</th>
<th>D3</th>
<th>D5</th>
<th>D7</th>
<th>D10</th>
<th>D19</th>
<th>D24</th>
<th>D50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (reference 12–16 g/dL)</td>
<td>14.5</td>
<td>11.6</td>
<td>10.0</td>
<td>8.7</td>
<td>7.8</td>
<td>9.2</td>
<td>10.3</td>
<td>12</td>
</tr>
<tr>
<td>Haptoglobin (reference 30–200 mg/dL)</td>
<td>–</td>
<td>–</td>
<td>&lt;7.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Platelets (reference 150–400 × 10(^3)/mm(^3))</td>
<td>76</td>
<td>101</td>
<td>70</td>
<td>65</td>
<td>157</td>
<td>334</td>
<td>344</td>
<td>255</td>
</tr>
<tr>
<td>INR (reference &lt;1.3)</td>
<td>1.02</td>
<td>1.02</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>20-min whole blood clotting test (WBCT20): (reference &lt;20 min)</td>
<td>&gt;20</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Creatinine (reference &lt;1.2 mg/dL)</td>
<td>1.58</td>
<td>5.06</td>
<td>6.33</td>
<td>6.9</td>
<td>5.37</td>
<td>1.3</td>
<td>1.29</td>
<td>0.83</td>
</tr>
</tbody>
</table>


102. Is antivenom treatment for *Naja kaouthia* bites always necessary in high care hospitals?

Marieke A. Dijkman, Dylan W. De Lange, Irma De Vries

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**Objective:** The monocellate or monocled cobra (*Naja kaouthia*) is commonly held in captivity by amateur herpetologists. It is responsible for most venomous exotic snakebites incidents in the Netherlands. It can induce (severe) local effects and post-synaptic neurotoxicity. In the Netherlands, antivenoms are kept on stock in the National Serum Depot. After successful treatment, including mechanical ventilation, of a severely envenomated patient for whom no antivenom was ordered, we questioned whether antivenom treatment is always necessary for *Naja kaouthia* bites, especially in high care hospitals. More specifically, what would be the reduction in duration of mechanical ventilation between patients treated with and without antivenom?

**Methods:** Analysis of case reports and case series concerning *Naja kaouthia* bites treated with and without antivenom available in the English medical literature (PubMed; search terms: *Naja kaouthia* bites, cobra bites, antivenom, respiration). Cases were included when data concerning the duration of mechanical ventilation were available. Also, three unpublished Dutch cases with sufficient data were included.

**Results:** One case report and 4 case series involving 31 patients treated without antivenom and 21 patients with antivenom were retrieved. The mean time until intubation was 4.1 hours (range 2–7 hours) in patients treated without antivenom and 4.8 hours (range 2–10 hours) in patient treated with antivenom. The mean duration of intubation was 50 hours (range 44–72 hours) without antivenom and 13.6 hours (range 10–24 hours) with antivenom. Treatment with specific *Naja kaouthia* antivenom reduced the mechanical ventilation duration by approximately 1.5 days.

**Conclusion:** Antivenom to treat (post-synaptic) neurotoxicity is life-saving when administered outside hospital and in areas with poor medical facilities. If high care facilities are available, it seems that post-synaptic neurotoxicity can be treated without antivenom. In clinically stable and mechanically ventilated patients, decisions about whether to administer antivenom can be based not only on risks of adverse reactions, but also on cost-benefit aspects. Antivenoms vary in price from <100 Euro to >2500 Euro per vial and often many vials are necessary. These costs are not covered by health insurance, and paid by the hospitals. Alternatives for expensive antivenom treatment could be anticholinesterase following pre-treatment with atropine, which can hasten neurological improvement and thereby shorten ventilation duration and intensive care unit stay. The total hospital stay is mainly determined by severity of the local effects. The neutralising effect of specific *Naja kaouthia* antivenom on the severity of the local effects is not well investigated and remains questionable.

Reference


103. Psychoactive synthetic cathinones elicit mitochondrial myotoxicity by different mechanisms

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**Objective:** We have shown previously that synthetic cathinones, stimulant psychoactive substances that are derivatives of cathinone, can be hepatotoxic [1]. In the clinical setting, besides hepatotoxicity, synthetic cathinones can also affect skeletal muscle. In the current study, we investigated possible mechanisms of myotoxicity of six synthetic cathinones.

**Methods:** We used C2C12 myoblast (a mouse myoblast cell line that can be differentiated into tubes) as a model for muscle cells. We determined cell membrane integrity (release of adenylate kinase), adenosine triphosphate (ATP) content, mitochondrial superoxide production, and mitochondrial oxygen consumption (with a Seahorse XF24 analyzer) after exposure for 24 hours. In addition, we also determined the effect on the mitochondrial membrane potential after exposure for 24 hours and during acute exposure. For assays with incubations for 24 hours, the cell supernatant was removed and replaced by buffer (assay in the absence of toxicant) and assays with acute incubations were performed in the presence of the toxicants. We investigated the following substances: 3-methylmethcathinone (3-MMC), 4-methyl methcathinone (4-MMC, mephedrone), methylene, 3,4-methylenedioxy-pyrrolidinovalerophenone (MDPV), α-pyrrolidinosalverophenone (α-PVP), and naphyrone.

**Results:** After an incubation of 24 hours, methylene, MDPV, α-PVP and naphyrone started to deplete the cellular ATP content at lower concentrations (20 to 500 μM) than that causing membrane damage (50 μM to 1 mM), suggesting mitochondrial toxicity. In comparison, 4MMC and 3MMC started to deplete the cellular ATP pool at identical (200 μM) and higher concentrations (500 versus 200 μM), respectively, than concentrations causing membrane damage. The compounds investigated also impaired mitochondrial oxygen consumption by C2C12 myoblasts starting at concentrations similar to that causing ATP depletion. As a consequence, after an incubation of 24 hours, all compounds investigated increased mitochondrial reactive oxygen species (ROS) production compared to control incubations, starting at concentrations similar to that causing ATP depletion. Surprisingly, after an incubation of 24 hours, the mitochondrial membrane potential was not affected for the compounds investigated. However, after an incubation of 1 hour, all compounds studied significantly decreased the mitochondrial membrane potential.

**Conclusion:** Synthetic cathinones showed two types of toxicity: acute toxicity in the presence and toxicity after incubation for 24 hours in the absence of the toxicants. Acute toxicity is probably related to direct inhibition of components of the respiratory chain whereas long-term exposure may affect structure and/or composition of enzyme complexes of the respiratory chain.

Reference

104. The dissociative new psychoactive substances diphenidine and methoxphenidine interact with monoaminergic transporters and receptors

Dino Luethia, Marius C. Hoener and Matthias E. Liechti

Objective: Diphenidine, and its methoxylated derivative, methoxphenidine are new psychoactive substances (NPS) that have recently appeared on the illicit drug market. These NPS mediate their dissociative psychoactive effects via potent N-methyl-D-aspartate receptor antagonism [1]. In the current study, we investigated whether interactions with monoaminergic transporters and receptors could contribute to their psychoactive properties.

Methods: We assessed the inhibition of human monoamine transporters for norepinephrine (NET), dopamine (DAT), and serotonin (SERT) in human embryonic kidney (HEK) 293 cells stably expressing the respective transporters. We treated the cells with various concentrations of the test substances and vehicle control before adding 3H-labeled norepinephrine, dopamine, or serotonin to initiate uptake transport. To assess for substrate-type monoamine release, we preloaded the NET, DAT, or SERT expressing HEK 293 cells with neurotransmitter before adding the test substances and vehicle control. In addition, we assessed binding affinities to monoamine receptors using cell membrane preparations expressing the respective receptors.

Results: Diphenidine was an equipotential inhibitor of the NET and DAT with IC50 values of 3.3 and 3.4 μM, respectively. Methoxphenidine inhibited the NET at 7.8 μM but was a weak inhibitor of the DAT and SERT (IC50: 65 and 741 μM, respectively). Neither NPS caused substrate-type efflux of any monoamines. Diphenidine and methoxphenidine bound to adrenergic and serotonergic receptors in the range of 3–11 μM but they did not bind to dopaminergic or trace amine-associated receptors in the investigated concentration range.

Conclusion: Diphenidine was an inhibitor of the NET and DAT, whereas methoxphenidine was mainly an inhibitor of the NET. Both drugs bound to adrenergic and serotonergic receptors. These results suggest that monoamine transporter and receptor interactions could contribute to the psychoactive properties of diphenidine and methoxphenidine.

Reference


105. Changes with time in analytically confirmed exposure to novel psychoactive substances (NPS) in patients with severe clinical toxicity in the UK


Objective: The Identification Of Novel psychoActive substances (IONA) study is a multicentre study characterising the NPS involved in episodes of severe toxicity and their associated clinical features. Here, we report changes with time in the NPS identified up to September 2017 and related these to changes in legal control status in the UK and in particular, the May 2016 Psychoactive Substances Act (PSA, enacted 26 May 2016).

Methods: With ethical approval, patients (≥16 years) presenting to 22 participating hospitals with severe acute toxicity (according to pre-defined definitions) after suspected NPS exposure were recruited with informed consent (or in those lacking capacity the agreement of a relative/representative). Demographic and clinical features were recorded using a structured data collection sheet and blood and/or urine samples analysed by liquid chromatography-tandem mass spectrometry. Temporal changes were examined by comparing 4 arbitrary time periods.

Results: Clinical and analytical data were available for 261 patients (median age 32 years, range 16–61) including 211 (81%) males. NPS were detected in at least one sample from 165 (63%), conventional drugs of misuse from 184 (70%), both from 107 (41%) and neither in any samples from 19 (7%) patients. The most common conventional drugs of misuse (or their metabolites) identified were methadone (n = 99), diazepam (n = 65), cocaine (n = 45), MDMA (n = 33), amphetamine (n = 31), and methamphetamine (n = 21). Common NPS groups were synthetic cannabinoid receptor agonists (SCRA), NBOMe compounds, and cathinones (Table 1). Prevalence has reduced for SCRAs overall (from late 2016), cathinones (from early 2017) and methiophene (from early 2016). Changes for individual SCRAs included...
reductions for MDMB-CHMICA and increases for 5F-ADB, 5F-NPB-22 and FUB-AMB (all from early 2016).

**Conclusion:** Patterns of NPS identified in patients with severe toxicity have changed during the study. Legal controls, including the PSA, may explain some but not all of the changes observed, but other factors must also be important.

### 106. Under-estimation of new psychoactive substance use in patients presenting with acute recreational drug toxicity to the emergency department


**Objective:** There has been a significant increase in the availability of new psychoactive substances (NPS) globally; however there is limited data available on the prevalence of acute toxicity associated with the use of NPS. The aim of this study was to determine how commonly NPS were detected in a cohort of patients presenting to the Emergency Department (ED) with acute recreational drug toxicity.

**Methods:** We conducted a prospective study enrolling consecutive adults presenting to an inner-city ED in London, UK with acute recreational drug toxicity. Ethical approval was granted for surplus serum samples that were taken as part of routine clinical care to be anonymised and sent for comprehensive drug screening. Samples were prepared by liquid/liquid extraction and screened using ultra performance liquid chromatography (UPLC) with time-of-flight mass spectrometry and measured against a database containing >1400 drugs/metabolites. High-resolution accurate mass-spectrometry tandem-liquid-chromatography (HRAM-LCMSMS) was used to analyse synthetic cannabinoid receptor agonists (SCRAs). Gas chromatography-mass spectrometry (GC-MS) was used for gammahydroxybutyrate (GHB) detection. For the purpose of this study, new psychoactive substances (NPS) were drugs reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) Early Warning System (EWS) since 2003; established (classical) recreational drugs were the amphetamines, cocaine, heroin, cannabis, ketamine, LSD, and GHB.

**Results:** Plasma samples were available for analysis from 191 patients, 153 (80.1%) were male and the median age was 32 years (range 18–65 years); 177 (92.7%) samples had sufficient plasma for detailed SCRA analysis. Established drugs were detected in 142 (74.3%) and NPS in 89 (46.6%) presentations. Mephedrone was the most commonly detected drug overall (66, 74.1% of NPS), present in over one-third (34.6%) of all presentations. The other commonly detected NPS were para-methoxymethyl-phenethamine (PMMA) (27, 14.1% of NPS) and synthetic cannabinoid receptor agonists (SCRAs) (16, 9.0% of the 177 samples analyses for SCRA). NPS that were less frequently detected were ethylone (6, 3.1%), methiopropamine (4, 2.1%), methylene (4, 2.1%), phenazepam (3, 1.6%), ethylphenidate (2, 1.0%), alphapyrrolidinopentiophenone (1, 0.5%), etizolam (1, 0.5%), dimethyllone (1, 0.5%), and butylone (1, 0.5%). Of the 89 presentations in which one or more NPS were detected, only 49 (55.0%) patients reported use of an NPS.

**Conclusion:** A wide range of NPS were analytically confirmed in almost half of this series of individuals presenting to an ED in London with acute recreational drug toxicity. However, only half of those in whom one or more NPS was detected self-reported NPS use.

### 107. Four-year surveillance trends of new psychoactive substances in London, UK using pooled urine analysis

John R. H. Archer, Paul I. Dargan, Simon Hudson, Nicholas E. Webb, Elizabeth Biswell and David M. Wood

**Objective:** In April 2016, the UK introduced the Psychoactive Substances Act, which made it an offence to import, distribute or sell NPS. A number of NPS have also been controlled under...
existing drugs legislation. Despite this, surveys suggest continued use of cathinone NPS, with increasing concerns regarding the use of synthetic cannabinoids receptor agonists (SCRAs). This study determined trends of cathinone and SCRA detection in pooled urine samples taken from urinals in central London, UK.

**Methods:** Anonymised pooled urine samples were collected from street urinals in central London, UK on the first Saturday of each month from July 2013 to June 2017. Samples were analysed using full-scan accurate mass high-resolution liquid-chromatography tandem mass-spectrometry (LC-MS/MS). Data are expressed as 6-monthly mean (± standard deviation) of urinals positive per month or percentage range of detection over a defined period for the drug indicated.

**Results:** Cathinones: Over the 4-year period, 14 cathinones were detected at variable frequencies. Mephedrone was the most commonly detected with a 6-monthly average frequency of 41.3% (±21%) July–December 2013; 55.6% (± 20.9%) January–June 2014; 63.5% (± 2.3%) July 2014–December 2014; 62.8% (± 28.7%) January 2015–June 2015. Subsequently, there was a downward trend: 24% (± 18.8%) July 2015–December 2015 (not detected in 2 months); 6.7% (± 7%) January–June 2016 (not detected in 3 months). In July 2016, it was detected in 16.7% of the urinals; it was then not detected in any urinals August 2016 to June 2017. During this period, the predominant cathinone detected was 4-chloro-N-ethylcathinone: 52.1% (± 20%) August–December 2016 and 38.3% (± 18%) January–June 2017.

SCRA detection and variety has increased since cathinones. SCRA detection and variety has increased since 2012 until 15 September 2017 for calls concerning exposures to designer benzodiazepines and benzodiazepines not registered in the Netherlands.

**Conclusion:** Analysis of pooled urine samples has demonstrated the variability of NPS used in London; in particular the significant decline in the detection of mephedrone and increase in other cathinones. SCRA detection and variety has increased since January 2016 and warrants further triangulation with data from other indicators to assess changes over time.

### 108. An increasing number of cases involving designer benzodiazepine exposures reported to the Dutch Poisons Information Center

Antoinette J. H. P. Van Riel, Annette J. J. Nuitgen-Van Lonkhuyzen, Irma S. Van Den Hengel-Koot and Irma De Vries

Dutch Poisons Information Center, University Medical Center Utrecht, Utrecht, Netherlands

**Objective:** The addictive properties of prescription benzodiazepines are well known. Alongside, more restrictions regarding repetitive prescriptions for benzodiazepines, there is an increase in (illegal) online availability of both prescription benzodiazepines and designer derivatives of benzodiazepines [1]. In our study, we investigated trends in the number of calls concerning illegal benzodiazepines and designer benzodiazepines to the Dutch Poisons Information Center (DIPC).

**Methods:** The DIPC database was searched retrospectively from 2012 until 15 September 2017 for calls concerning exposures to designer benzodiazepines and benzodiazepines not registered in the Netherlands.

**Results:** In total, 48 cases were identified, concerning 44 patients (52% female and 48% male). The median age of the patients was 26 years (range 2.5–61 years, including 2 children aged 2.5 and 3 years). In 2017, we received 6 separate reports about the abuse of four different designer benzodiazepines by the same patient. The 19 different substances reported and their regulatory status in the Netherlands are listed in **Table 1**. Symptoms reported were consistent with benzodiazepine use; 38 out of 44 patients (86%) showed signs of central nervous system depression.

**Conclusion:** The number of enquiries to the DIPC about uncontrolled (not listed) designer benzodiazepines rose from one in the three years 2012–2014 to at least 32 in the next three years (2015–2017). Incidentally, there are reports of list II scheduled benzodiazepines too, but no rise was observed in that category.

### Table 1. Enquiries involving designer benzodiazepines reported to the Dutch Poisons Information Center (DIPC) from 2012 to September 2017.

| Benzodiazepine | TOTAL | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 up to September | Legal status | Registered outside Netherlands?
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazolam</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>Not listed</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Diclozepam</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>1</td>
<td>Not listed</td>
<td>No</td>
</tr>
<tr>
<td>Pyrazolam</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>Not listed</td>
<td>No</td>
</tr>
<tr>
<td>Flunitrazolam</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>Not listed</td>
<td>No</td>
</tr>
<tr>
<td>Flubromazolam</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>Not listed</td>
<td>No</td>
</tr>
<tr>
<td>Flubromazine</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>Not listed</td>
<td>No</td>
</tr>
<tr>
<td>Flubromazepam</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>Not listed</td>
<td>No</td>
</tr>
<tr>
<td>Meclonazepam</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>Not listed</td>
<td>No</td>
</tr>
<tr>
<td>Epizolam</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>Not listed</td>
<td>No</td>
</tr>
<tr>
<td>Deschloroetizolam</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>Not listed</td>
<td>No</td>
</tr>
<tr>
<td>Etizolam</td>
<td>13</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td></td>
<td></td>
<td>Not listed</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mexazolam</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>Not listed</td>
<td>Yes</td>
</tr>
<tr>
<td>TOTAL (not listed)</td>
<td>32</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>7</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenzazepam</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>List II</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Nordazapam</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>List II</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Tetrazepam</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>List II</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Estazolam</td>
<td>2</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td>List II</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Pinazepam</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>List II</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Medazepam</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>List II</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Cloxazolam</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>List II</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Cliozepam</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>List II</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>TOTAL (list II)</td>
<td>25</td>
<td>6</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL (All)</td>
<td>57</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>16</td>
<td>10</td>
<td>17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**List II:** List II of the Dutch Opium Act, listing “soft drugs” that are considered to carry a lower health risk than “hard drugs” like cocaine, amphetamines and opiates; for example hallucinogenic mushrooms are also scheduled on List II.
109. Clinical characteristics of new designer benzodiazepines: intoxication cases from the Swedish STRIDA project

Matilda Bäckberg, Madeleine Pettersson Bergstrand, Lisa Franzén, Olof Beck and Anders Helander

Unit for Drug Prevention, The Public Health Agency of Sweden, Stockholm, Sweden; Karolinska Institutet and Karolinska University Laboratory, Stockholm, Sweden; Swedish Poisons Information Centre, Stockholm, Sweden

Objective: Benzodiazepines are among the most widely prescribed drugs, but also one of the most common drug groups misused. In Sweden, all medicinally approved benzodiazepines are placed under control as narcotic substances. Notifications of unclassified benzodiazepines appearing on the online market for new psychoactive substances (NPS) has grown over the last years, but bioanalytical and clinical data related to these substances are limited.

Methods: To characterize the pattern of NPS benzodiazepine toxicity and misuse in Sweden, the STRIDA project database was searched for all suspected NPS benzodiazepine-related exposures from January 2012 to December 2016. The data collected includes age, gender, intended and actual substance exposure, co-ingestion of drugs, pertinent clinical signs, and treatment. Urinary screening for benzodiazepines was done by immunoassay. For confirmation, a multi-component liquid chromatography-tandem mass spectrometry (LC-MS/MS) method, which was continuously updated to cover the latest set of NPS benzodiazepines, was used. Clinical data were retrieved from medical and poison centers.

Results: Of 2443 STRIDA cases, 867 patients screened positive for benzodiazepines. The number of confirmed exposures to NPS benzodiazepines was 113; the average age of patients was 29.2 (range 13–57) years, and 78% were men. Etizolam was the first NPS benzodiazepine identified (March 2011), and it was followed, in order of appearance, by diclazepam, pyrazolam, flubromazepam, meclonazepam, flubromazolam, clonazolam, and 3-hydroxyphenazepam. All substances were unregulated when they were first detected. Sixteen patients tested positive only to one or more benzodiazepines, whereas 97 had also administered stimulants (23%), depressants (28%), dissociative drugs (4%), or substances from several groups of drugs (31%). Use of NPS benzodiazepines was only rarely self-reported (28%). The main clinical sign in patients exposed solely to NPS benzodiazepines, or in combination with conventional benzodiazepines, was central nervous system (CNS) depression, which was reported in 67% of the cases. Two patients were deeply unconscious on arrival to the hospital, three responded positively to flumazenil treatment, and 33% of the patients were observed in the intensive care unit.

Conclusion: Benzodiazepine intoxication may result in significant CNS depression and need for intensive care monitoring and support. However, the NPS benzodiazepines may not be distinguished from prescription benzodiazepines by the standard drug screening methods used in clinical settings. To identify these novel recreational drugs, targeted confirmatory analysis based on LC-MS/MS is required.

110. Synthetic cannabinoid receptor agonist (SCRA) availability on darknet drug markets: changes during 2016–2017

Andrew Scourfield, Catherine Flick, Jack Ross, Natalie Thurtle, Darryl Stellmach, John R. H. Archer, David M. Wood and Paul I. Dargan

Objective: Changes in legislation in many countries have impacted supply routes of new psychoactive substances such as SCRAs; with increasing anecdotal evidence of supply over the darknet. The aim of this study was to determine the profile of SCRA availability on the darknet during 2016–2017.

Methods: Darknet drug markets were identified using an index database with markets added as they emerged. The Tor Browser was used to access the markets and SCRAs identified using product listing through a custom-programmed script with manual data filtering to exclude errors. Data were collected at two-monthly intervals between August 2016 and April 2017 from item listings/product description were chemical name or brand, formulation, weight, cost (bitcoin, which was converted to Euro using the exchange at that time), name and market place origin and vendor details.

Results: Overall, 12 identified markets listed SCRAs for sale during the time period. The largest number of darknet SCRA listings by country of origin were China (198–245 items per time-point), UK (54–131), US (37–102), Netherlands (29–62), and Germany (6–63). Across all time points combined, there were 2434 listings for SCRAs by their chemical formula/name, 1190 as powder or crystal, 1092 as smoking preparations, 97 as topical oil, 34 as vape preparations in October 2016, although there was a steady reduction over time to 29 listings in April 2017. Compounds consistently available across time-points were FUB-AMB (mean 39 listings), 5F-NPB-22 (32), NM-2201 (24), MAB-CHMINACA (23), FUB-AKB (19) and THU-2201 (14). Some SCRA were unavailable in August and October 2016 but available in December 2016 and February and April 2017: 5F-CUMYL-4CN-PINACA (mean 20 listings), 5F-MDMB-2201 (11), JWH-210 (3), UR-144 (2). SCRA available in 2016 but not 2017 were SGT-25 and EAM-2201.

Conclusion: Large quantities of SCRA products are available over the darknet, in particular powder and crystal SCRAs from China with price per gram reducing with increased weight. The market appears to be volatile with changes in the SCRA available on the darknet over time; monitoring would enable clinicians and policymakers to be aware of products potentially available to users to ensure targeted risk assessment.
111. 5F-MDMB-PINACA on the streets: case series of 17 poisonings

Csaba Pap
Department of Emergency Medicine and Clinical Toxicology, Péterfy Hospital, Budapest, Hungary

Objective: 5F-ADB (also known as 5F-MDMB-PINACA) is a synthetic cannabinoid from the indazole-3-carboxamide family. This substance was first identified in 2014 from post-mortem samples taken from a total of 10 people who had died from unexplained drug overdoses in Japan. In Hungary, it was first reported at the beginning of 2015 and has been scheduled since April 2015. We report a cluster of 17 cases of 5F-ADB abuse and describe the characteristics of their clinical picture, treatment, and evolution.

Case series: In the middle of August 2017 during a 36-hour period, 17 patients were found unconsciously lying on the platform at tram stops or on the pavement in small segregated area in Budapest. One man was dead, and the others were admitted to our department. On site, they were assessed with the Richmond Agitation and Sedation Scale (RASS); 2 patients were found with severely (RASS-5), 8 with moderately (RASS-4 or -3) and 6 with mildly (RASS-1 or -2) reduced level of consciousness. Two had vomited and 3 showed transient extrapyramidal symptoms. Based on the history, all patients had inhaled the smoke of a herbal mixture called “magic smoke”. Ethanol was co-ingested in 2 patients (12.5% of cases) and there were no other co-ingestants. There were 13 men and 3 women. The average age was 25.12 (range 15–37) years. On admission, examination revealed mild central nervous system (CNS) depression in 11 patients and moderate CNS depression in 2 patients. Other findings were confusion (12.5%), agitation (18.75%), mild tachycardia (18.75%) with a heart rate between 100 and 120 bpm, mild systolic hypertension (18.75%) with a blood pressure between 140 and 160 mmHg, and mydriasis (25%). We took blood and urine samples for toxicological analysis at the time of admission. During the hospitalization, there were no episodes of bradyarrhythmia, seizures, elevated temperature, or other complications. As for therapy, 11 patients were administered IV fluids and 3 patients were given IV midazolam. The length of stay averaged 9.3 (range 1–72) days. All patients were discharged. According to the Poison Severity Score, 12.5% of patients were given IV midazolam. The length of stay averaged 11.5 days. According to the Poison Severity Score, 12.5% of patients were given IV midazolam. The length of stay averaged 11.5 days.

Conclusion: Toxicity following the poisoning caused by novel cannabinoid-type designer drugs is unpredictable. 5F-MDMB-PINACA can cause a short period of moderate to severe CNS depression followed by transient confusion and agitation.

112. Acute synthetic cannabinoid receptor agonist (SCRA) toxicity: a case series of 442 patients presenting to a regional poisons treatment centre

Konstantin M. Brusinaa, Yulia V. Kraevab, Maria A. Gofenburgc, David M. Woodc and Paul I. Darganc

aKaplan Medical Centre, Rehovot, Israel; bRegional Poisoning Treatment Centre, Sverdlovsk Regional Psychiatric Hospital, Yekaterinburg, Russian Federation; cClinical Toxicology, Guy’s and St Thomas’ NHS Foundation Trust; Faculty of Life Sciences and Medicine, King’s College London, London, United Kingdom

Objective: Over 170 synthetic cannabinoid receptor agonists (SCRAs) have been reported in Europe. We describe here the pattern of acute toxicity following analytically confirmed SCRA use.

Methods: Data on all acute recreational drug toxicity presentations to the Sverdlovsk Regional Poisoning Treatment Centre, Russia, were prospectively collected from January 2015 to December 2016 inclusive. Urine samples collected at Emergency Department (ED) presentation were analysed by gas chromatography quadrupole mass-spectrometry and gas-chromatography with flame-ionization. Data was extracted on presentations where one or more SCRA was detected and analysed using Excel; significance was calculated by Pearson’s chi-squared test.

Results: There were 442 presentations in which one or more SCRA was detected; 408 (92.3%) were male; median age 21 (IQR 16–28) years. There were 11 SCRAs detected: AB-PINACA-CHM (288 presentations), AB-FUBINACA (n = 98), MDMB(N)-BZ-F (n = 65), PB-22F (n = 15), MDMB(N)-2201 (n = 9), THJ-2201 (n = 6), AB-PINACA (n = 4), AB-PINACA-F (n = 4), THJ-2201 (n = 4), MDMB-BZ-F (n = 2), MDMB(N)-CHM (n = 2). In 90 (20.4%), more than one SCRA was detected. Clinical features are outlined in Table 1. Psychosis was more common with MDMB(N)-BZ-F compared to Lone MDMB(N)-BZ-F.

Table 1. Clinical features of analytically confirmed acute synthetic cannabinoid receptor agonist (SCRA) toxicity including all SCRAs, lone SCRAs, and the 3 most common lone SCRAs presenting to the Sverdlovsk Regional Poisoning Treatment Centre, Russia (2015–2016).

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>All SCRA cases (n=442)</th>
<th>SCRA with no alcohol/other drugs (n=327)</th>
<th>Lone AB-PINACA-CHM (n=189)</th>
<th>Lone AB-FUBINACA (n=48)</th>
<th>Lone MDMB(N)-BZ-F (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>36.7%</td>
<td>34.9%</td>
<td>32.3%</td>
<td>27.1%</td>
<td>53.1%</td>
</tr>
<tr>
<td>Agitation/aggression</td>
<td>26.2%</td>
<td>27.5%</td>
<td>38.1%</td>
<td>0</td>
<td>15.6%</td>
</tr>
<tr>
<td>Seizures</td>
<td>17.2%</td>
<td>16.8%</td>
<td>19.0%</td>
<td>12.5%</td>
<td>15.6%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2.9%</td>
<td>3.1%</td>
<td>5.3%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Confusion</td>
<td>21.5%</td>
<td>23.9%</td>
<td>29.1%</td>
<td>10.4%</td>
<td>15.6%</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>18.8%</td>
<td>9.3%</td>
<td>11.6%</td>
<td>0</td>
<td>12.5%</td>
</tr>
<tr>
<td>Coma (Glasgow Coma Scale &lt;8)</td>
<td>12.0%</td>
<td>8.6%</td>
<td>7.4%</td>
<td>14.6%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>0.5%</td>
<td>0.6%</td>
<td>0.5%</td>
<td>0</td>
<td>3.1%</td>
</tr>
<tr>
<td>Bradycardia (&lt;60 bpm)</td>
<td>14.0%</td>
<td>15.3%</td>
<td>18%</td>
<td>12.5%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Tachycardia (&gt;120 bpm)</td>
<td>9.3%</td>
<td>8.6%</td>
<td>7.9%</td>
<td>12.5%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Hypotension (systolic ≤90 mmHg)</td>
<td>7.0%</td>
<td>6.4%</td>
<td>5.8%</td>
<td>6.4%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Hypertension (systolic ≥180 mmHg)</td>
<td>1.4%</td>
<td>1.2%</td>
<td>1.1%</td>
<td>2.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>9.3%</td>
<td>7.6%</td>
<td>10.6%</td>
<td>8.3%</td>
<td>0%</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothermia (&lt;36 °C)</td>
<td>7.2%</td>
<td>6.1%</td>
<td>7.4%</td>
<td>2.1%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Hyperthermia (≥39 °C)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
both AB-PINACA-CM and AB-FUBINACA (p < .05). Confusion was more common with AB-PINACA-CM than AB-FUBINACA (p < .05). One (0.2%) patient was discharged directly from the ED; 388 (88.0%) of the 441 patients admitted were admitted to critical care and 55 (14.2%) required intubation and ventilation. Two AB-FUBINACA cases had serious outcomes: (i) coma, shock, and acute injury with death in critical care 47 hours after admission; and (ii) resuscitated after pre-hospital cardiac arrest but developed persistent vegetative state.

**Conclusion:** In this series of 442 presentations with analytically confirmed acute SCRA toxicity, the most common clinical features seen were more stimulant/sympathomimetic in nature (psychosis, agitation, and seizures) than typically expected with cannabinoids. Drowsiness/coma was also common in keeping with previously reported acute third generation SCRA toxicity.

### 113. Back from irreversibility after drug-induced cardiovascular toxicity treated with massive catecholamine doses

Amandine Bouchet, Sébastian Voicu, Isabelle Malissin, Nicolas Péron, Nicolas Deye and Bruno Mégarbane
Department of Medical and Toxicological Critical Care, Lariboisière Hospital, Paris-Diderot University, INSERM UMR514, Paris, France

**Objective:** Maximal dosage thresholds for catecholamine infusion are associated with an almost 100% fatality rate in patients presenting with cardiovascular failure of non-toxic causes including sepsis. In contrast, little is known regarding such thresholds in poisoning while survivors have been reported, despite receiving massive catecholamine doses. Our objectives were to test the validity in poisoning of the thresholds determined in non-poisoned patients and evaluate the survival rate, catecholamine-attributed complications, and predictive factors of death in poisoned patients receiving massive catecholamine doses.

**Methods:** We performed a retrospective study including all poisoned patients admitted to our intensive care unit (ICU) during a 13-year period (2003–2016), who received massive catecholamine doses, i.e., epinephrine > 1.25 µg/kg/min (5 mg/h), norepinephrine > 2.5 µg/kg/min (10 mg/h) and/or isoproterenol > 1.25 µg/kg/min (5 mg/h), to treat cardiovascular failure. The usual demographic, clinical, and outcome data were collected. Univariate analysis was performed with Mann-Whitney and chi-squared tests.

**Results:** Overall, 246 poisoned patients (representing 25% of the poisoned patients admitted in the ICU and receiving catecholamine infusion during this period) were included. The patients (56% females/44% males, age 47 years [36; 57]; median [percentiles 25; 75]) were poisoned in relation to self- (88%) or accidental overdose (12%). In total, 117 patients (48%) survived. The toxicants involved were calcium-channel inhibitors (35%), beta-blockers (30%), vasodilators (15%), and sodium-channel blockers (10%). The mortality rate was significantly correlated with the epinephrine infusion rate. The maximal infusion rates associated with survival were 12.5 µg/kg/min (50 mg/h) epinephrine, 35 µg/kg/min (140 mg/h) norepinephrine and 6.25 µg/kg/min (25 mg/h) isoproterenol. Catecholamine-attributed complications (11%) included limb (6%) and mesenteric ischemia (4%). Based on univariate analysis, the other predictive factors of death were the onset of cardiovascular arrest (p < .0001), female sex (p = .03), decreased Glasgow Coma Score (p = .0001), cardiogenic shock (p = .004), extracorporeal membrane oxygenation (ECMO) requirement (p = .003), mechanical ventilation (p = .01), elevation in plasma lactate (p < .0001), creatinine (p = .009), transaminases (p < .0001) and creatine phosphokinase (p < .0001), as well as prothrombin time (p < .0001), platelets (p < .0001), arterial pH (p < .0001), and PaO2/FiO2 ratio (p = .008).

**Conclusion:** Surviving drug-related cardiovascular failure requiring major catecholamine doses overwhelming the usual thresholds associated with irreversibility (i.e., fatality rates of 100%) in non-toxic situations is achievable.

### 114. Clinical effectiveness of a shorter 12 hour acetylcysteine (SNAP) protocol in routine clinical practice


**Objective:** To evaluate the effectiveness of a protocol using a modified 12-hour intravenous N-acetylcysteine (NAC) regimen based on the SNAP study [1].

**Methods:** A clinical protocol using a modified 12-hour NAC regimen (“SNAP regimen”) was introduced in mid-2016 in two UK hospitals for all patients requiring treatment for a paracetamol overdose. The SNAP regimen comprises intravenous NAC 100 mg/kg over 2 hours, then 200 mg/kg over 10 hours before end-of-infusion blood sampling. NAC treatment was discontinued if all the following criteria were met: INR < 1.4 AND ALT < ULN (upper limit of normal); ALT < 2 × ULN and not more than doubled from admission; paracetamol concentration < 10 mg/L. NAC was continued at 200 mg/kg over 10 hours in patients who did not meet these criteria, providing NAC 500 mg/kg over 22 hours compared to the standard regimen (300 mg/kg over 21 hours). An additional blood sample was taken at least 24 hours post-ingestion to allow discharge when the initial end-of-infusion sampling occurred earlier than 24 hours post-ingestion. A prospective audit of patients treated with the SNAP protocol over a 12-month period was conducted and compared with data collected from previous audits of patients treated with the 21-hour regimen licensed in the UK. Statistical analysis was performed by a two-tailed Fisher’s exact test.

**Results:** Data were available for 500 patients treated with the SNAP protocol and 413 patients treated with the 21-hour NAC regimen. Treatment with an antihistamine for anaphylactoid reaction was reported for 28 (6.8%) patients in the 21 hour NAC regimen group compared with 8 (1.6%) in the SNAP treatment group (p < .01). Extended NAC treatment (more than 300 mg/kg) was needed in 46 (11.1%) patients in the 21 hour group and 56 (11.2%) with the SNAP protocol. Peak ALT > 3 × ULN and peak ALT > 1000 occurred in 41 (10%) and 17 (4.1%) patients with the 21-hour regimen versus 48 (9.6%) and 18 (3.6%) with the SNAP protocol. None of the 257 patients who had NAC discontinued after the second infusion required re-institution of NAC treatment on the basis of results from the blood sample taken at least 24 hours after overdose.

**Conclusion:** Treatment using the SNAP protocol resulted in significantly fewer patients requiring treatment for anaphylactoid reactions and showed similar effectiveness in preventing liver injury in an selected patient population with paracetamol overdose. These findings require confirmation in larger cohorts of patients.
115. A nationwide Danish study of the impact of a new 2-bag N-acetylcysteine dosing regimen on paracetamol overdose morbidity and mortality

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Objective: In Denmark, all suspected overdoses of paracetamol are treated with N-acetylcysteine (NAC). The 36 hour 3-bag regimen changed to a 20-hour 2-bag regimen in 2013 to simplify treatment, reduce the risk of medication errors, and the number of adverse reactions. However, due to concerns of reduced efficiency of the 2-bag regimen, we examined the nationwide morbidity and mortality of paracetamol overdoses after the implementation of the 2-bag NAC regimen compared to the 3-bag regimen.

Methods: The study population consisted of all patients in Denmark admitted with a diagnosis of paracetamol poisoning from 1 January 2010 to 31 December 2012 (3-bag period) and 1 July 2013 to 30 June 2016 (2-bag period) allowing for a 6 month run-in period. Outcome data were extracted from the Danish National Registers. Logistic regression was used to calculate the crude odds-ratio and odds-ratio adjusted for pre-existing alcoholic liver disease, age, attempted suicide, and co-ingestants.

Results: In total, 16,928 cases were identified; there were 29% fewer cases during the 2-bag period compared to the 3-bag period. The mean age was slightly higher in the 2-bag period (32.7 versus 30.4 years, \( p < .001 \)). No signs of decreased efficiency were seen (Table 1). The median length of stay declined significantly from 2 to 1 day (\( p < .001 \)). The adjusted mean length of stay was reduced by 35% (95% CI: 33–37%, \( p < .001 \)).

Conclusion: After implementation of the 2-bag regimen, no increase in morbidity or mortality were noted. In contrast, a decrease in both the number of paracetamol poisonings and risk of developing toxic liver disease was seen. This is likely due to other factors than the 2-bag regimen, such as the implementation of pack size restriction for over-the-counter analgesics in September 2013.

Table 1. Occurrences of selected outcomes in paracetamol overdoses 3 years before and after implementation of the 2-bag acetylcysteine regimen in Denmark.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>3-Bag (n=9878)</th>
<th>2-Bag (n=7050)</th>
<th>Crude odds-ratio (95% confidence interval)</th>
<th>p-Value</th>
<th>Adjusted odds-ratio (95% confidence interval)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In hospital deaths</td>
<td>69 (0.70%)</td>
<td>51 (0.72%)</td>
<td>1.04 (0.72–1.49)</td>
<td>.84</td>
<td>0.80 (0.54–1.16)</td>
<td>.24</td>
</tr>
<tr>
<td>Referrals to tertiary liver unit</td>
<td>263 (2.2%)</td>
<td>155 (2.2%)</td>
<td>0.82 (0.67–1.00)</td>
<td>.056</td>
<td>0.84 (0.68–1.03)</td>
<td>.09</td>
</tr>
<tr>
<td>Liver transplants</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Toxic liver disease</td>
<td>307 (3.1%)</td>
<td>170 (2.4%)</td>
<td>0.77 (0.64–0.93)</td>
<td>.007</td>
<td>0.76 (0.62–0.93)</td>
<td>.007</td>
</tr>
<tr>
<td>Acute and subacute hepatic failure</td>
<td>67 (0.68%)</td>
<td>50 (0.71%)</td>
<td>1.05 (0.72–1.51)</td>
<td>.81</td>
<td>1.00 (0.68–1.45)</td>
<td>.99</td>
</tr>
<tr>
<td>Albumin dialysis</td>
<td>7 (0.07%)</td>
<td>3 (0.04%)</td>
<td>0.60 (0.13–2.16)</td>
<td>.46</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Acute dialysis</td>
<td>70 (0.70%)</td>
<td>39 (0.55%)</td>
<td>0.78 (0.52–1.15)</td>
<td>.21</td>
<td>0.76 (0.51–1.14)</td>
<td>.19</td>
</tr>
</tbody>
</table>

116. The predictive value of opioid co-ingestion for acetaminophen-induced hepatotoxicity

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Objective: Abuse and misuse of acetaminophen (paracetamol)-opioid combination drugs can lead to acetaminophen-induced hepatotoxicity, for which the Rumack–Matthew nomogram may not be applicable. We investigated acetaminophen-opioid co-ingestion as a risk factor for acetaminophen-induced hepatotoxicity and mortality.

Methods: A prospective cohort of acetaminophen exposures were enrolled over 18 months at a network of over 40 urban hospitals affiliated with one PCC. Patients were enrolled upon report to the PCC and data was collected regarding demographics, exposure details, laboratory markers, and management (application of the nomogram, acetylcysteine, activated charcoal, prolonged observation, hospitalization, intensive care unit [ICU], renal replacement therapy, and liver transplant). Co-ingestion was identified by a combination of clinical history (verbal report, pills, bottles, and drug paraphernalia), opioid toxidrome, response to naloxone, and urine toxicology. The primary outcome was mortality, and secondary outcomes were: transaminases >1000 U/L, or positive King’s College Criteria.

Results: Out of the 677 patients with acetaminophen poisoning, 166 were acetaminophen-opioid exposures (mean 33 years, 36% male, mean acetaminophen concentration 74 µg/L, median AST 30 U/L, mean AST 369 U/L, 62% intentional self-harm, 21% multiple acetaminophen products, 66% nomogram inapplicable), and 511 were without opioid co-ingestion (mean 33 years, 25% male, mean acetaminophen concentration 74 µg/L, median AST 30 U/L, mean AST 368 U/L, 72% intentional self-harm, 2% multiple

Reference

117. Acetaminophen repeated supratherapeutic-dose toxicity among children under five years old: efficacy of N-acetylcysteine in Monrovia, Liberia


Objective: This study investigates the efficacy of N-acetylcysteine (NAC) in the treatment of acetaminophen repeated supratherapeutic dose among children weighing less than 10 kilograms with severe hepatotoxicity.

Methods: A retrospective case series included children admitted with severe acetaminophen hepatotoxicity to Barnesville Junction Teaching Hospital (BJTH) in Monrovia, Liberia between August 2016 and June 2017. Some cases were misdiagnosed and thereby were not treated with NAC, enabling us to conduct a cohort analysis comparing survival trends between children receiving treatment and the ones who did not. We developed a new NAC dosage regimen due to the severity of the hepatotoxicity, by distributing the dose over three days to provide 600 mg/kg in total. To prevent adverse effects related to rapid infusion, including anaphylactoid reactions, we decreased the speed of infusion with a reduced loading dose (100 mg/kg instead of 150 mg/kg over 2 hours).

Results: The series included 109 patients; 86% aged two years old and less. Case-fatality accounted for 53% of the admitted patients. In total, 16/109 children (15%) did not receive NAC during hospitalization; 14/16 (88%) of which died. In addition, 44/93 (47%) of the children receiving NAC died during hospitalization. Two-thirds of the children finished treatment of NAC according to the protocol (three-day course). Multivariate analysis adjusted for severity factors, and potential confounders showed an increased hazard when NAC was not administered (hazard ratio 5.24, 95% CI 2.23–12.42). Finishing NAC with the three-day treatment regimen was associated significantly with survival (hazard ratio 0.015, 95% CI 0.005–0.047). Receiving NAC in less than 24 hours of hospitalization was the only protective factor emerging at 35% lower risk of death than the ones who did not receive NAC (risk ratio 0.65, 95% CI 0.48–0.90). Delayed treatment showed no significant association with death. No adverse effects were observed among any of the children.

Conclusion: The three-day NAC dosage regimen resulted in increased rate of survival in acetaminophen supratherapeutic-dose severe hepatotoxicity among children weighing less than 10 kg. Decreasing the speed of infusion prevented occurrence of adverse effects of NAC. The high frequency of admission of acetaminophen-intoxicated children at BJTH in Monrovia highlights a heavy public health burden not just specific to Liberia, but possibly also to other countries with unrestricted access to medicines. The little evidence on treatment of acetaminophen supratherapeutic dose toxicity among children highlighted in this study dictates the change of diagnostic algorithms and treatment protocols in all low resource settings when encountering such a toxidrome.

118. Fishkeeping: a high risk sports activity? The underestimated threat of zoanthids

Martin Ebbecke, Jakob Strube, Nadja Struß and Andreas Schaper

Objective: Zoanthids (Zoanthidea) are increasingly popular residents in advanced hobbyists’ aquariums. These animals look beautiful, but have one crucial disadvantage – they are extremely poisonous. Some zoanthids contain palytoxin, a highly toxic Na+-K+-ATPase binding substance. In accordance with their growing popularity, the number of intoxications with these animals is rising in Northern Germany.

Methods: For the period 2000–2017, all cases with accidental exposure to zoanthids kept in aquaria were identified. Conditions and route of exposure, symptoms, severity, and ToxIndex were analysed.

Results: During the analysis period, GIZ-Nord Poisons Centre observed an increasing number of incidents with zoanthids. Overall, 39 cases were identified that met inclusion criteria. In all cases, the exposure occurred while cleaning the aquarium. The route of exposure was dermal 56%, dermal and inhalation 13%, and inhalation only 23%. According to the Poisoning Severity Score, 62% had minor, 33% moderate, 3% severe symptoms, and 2% were not well documented. No fatalities occurred. Signs reported were shivering 38% of the patients, fever 33%, dyspnea 33%, nausea or vomiting 26%, muscle weakness 26%, dizziness 13%, exanthema 13%, and muscle cramps or fibrillation 10%. In 10% of the cases, children were involved. The ToxIndex is defined as the sum of all cases classified as lethal, severe, or moderate in relation to the number of all exposure cases. This index for contact with zoanthids was quite high at 36%.

Conclusion: Zoanthids are widely sold unregulated in aquarium shops without warnings about their toxicity or guidelines for their storage and care. Because of the specific symptoms, we believe that our data represent only the tip of an iceberg. They show that zoanthids carry an unacceptably high risk for fishkeepers. The national surveillance authorities in Germany were informed. Due to their numerous contacts to the public and to health professionals, European Poisons Control Centres play a key role in toxicovigilance. All these centres should analyse their cases with zoanthids and in case of similar results, establish an EU-wide initiative to regulate trade with these poisonous animals.
119. Hyperbaric oxygen effectively reduces harmful effects of carbon monoxide in mixed but not in neuronal cell cultures

Manja Mlakar, Klara Bulc Rozman, Miran Brvar and Damijana M. Juric

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Objective: Carbon monoxide (CO) causes neural and glial apoptosis, leading to delayed and progressive neurological sequelae. Brain cell damage could be prevented by hyperbaric oxygen (HBO). Due to the central role of astrocytes in maintaining neuronal function, we investigated the hypothesis that HBO therapy by preserving the viability and neurotrophic activity of astrocytes may exert beneficial effect on acute CO poisoning-induced impairment of neuronal cells as well.

Methods: Primary cultures of fetal rat neurons (neuronal cell culture) or neurons and astrocytes (mixed cell culture) were exposed for 1–12 hours to 3000 ppm CO and 24 hours normoxia or were exposed for 5 hours to 3000 ppm CO and during 24 hours normoxia at different time periods (0–7 hours after CO) incubated for one hour in HBO. Cell viability was determined by measuring the metabolic activity, intracellular level of adenosine triphosphate (ATP), lactate dehydrogenase (LDH) activity, and mitochondrial membrane potential. Triggering of apoptosis was determined by measuring caspases-3/7 activity and neurotrophic activity by measuring nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) or neurotrophin-3 (NT-3) secretion levels by ELISA.

Results: In both neuronal and mixed cell cultures impaired celluar respiration caused by CO provokes a progressive decline of viability (42/51% decline regarding non-exposed cells, respectively), loss of mitochondrial membrane potential (40/35% decline, respectively) and ATP level depletion (40/35% decline, respectively) accompanied by caspase-3/7 activation (400/220% increase, respectively) and no LDH changes. The maximal response was seen after 5 hours in CO. NGF secretion levels in neuronal and mixed cell culture progressively declined (by 30%) with time in CO. In neurons, a 23% decrease of NT-3 secretion was observed, but no change in BDNF levels. HBO exhibited profound benefit in providing mitochondrial protection, increased viability, and ATP concentration and decreased caspase-3/7 activity up to the levels of the control non-exposed cells in a time-dependent manner in mixed culture but only partly in neuronal cells. Increased neurotrophin levels were observed in mixed cell cultures when exposed to HBO after CO with the secretion of NGF, BDNF, or NT-3 being significantly (130, 140 and 150%, respectively) higher than in untreated cells. In neuronal cells, HBO after CO affected only BDNF causing 150% increase regarding the control.

Conclusion: HBO effectively and time-dependently reduces harmful effects of CO in mixed cell cultures but not in neuronal cell cultures. This suggests astrocytes have a key role in supporting survival and function of neurons after acute CO poisoning and HBO treatment.

120. Investigation of paracetamol metabolites to compare efficacy of acetylcysteine regimens in paracetamol overdose

Anselm Wong, Natalie Homer, James W. Dear, Kay Weng Choy, James Doery and Andis Graudins

Monash and Austin Toxicology Units, Monash and Austin Health and Department of Medicine, School of Clinical Sciences, Monash University, Victoria, Australia; Edinburgh Clinical Research Facility, Queen’s Medical Research Institute, Edinburgh, United Kingdom; Pharmacology, Toxicology and Therapeutics, University/BHF Centre for Cardiovascular Sciences, University of Edinburgh, Edinburgh, United Kingdom; Monash Pathology, Monash Health, Victoria, Australia; Monash Toxicology Unit and Emergency, Monash Health and Department of Medicine, School of Clinical Sciences, Monash University, Victoria, Australia

Objective: Circulating CYP450-metabolites have been investigated previously to ascertain risk of liver injury. We investigated the clinical safety of an abbreviated 12-hour IV acetylcysteine protocol (200 mg/kg over 4 hours, 50 mg/kg over 8 hours) with a control group, 20-hour regimen (200 mg/kg over 4 hours, 100 mg/kg over 16 hours) in patients with acute paracetamol poisoning and low-risk of liver injury (NACSTOP-trial) using paracetamol metabolites to predict liver injury.

Methods: A convenience sample, treated with acetylcysteine, following paracetamol overdose was recruited from NACSTOP. Patients with normal ALT at presentation and low paracetamol (<20 mg/L) and normal ALT after 12 hours of acetylcysteine were included. Two comparative groups not enrolled in NACSTOP, with acute liver injury (ALI: ALT >50 IU/L and double baseline) or hepatotoxicity (ALT >1000 IU/L), were also included. Paracetamol metabolites (APAP-Cys, APAP-GSH, APAP-Mer, APAP-Sul, APAP-Glu) were assayed. Sum CYP-metabolite percentage (CYS, Mer, GSH)/Total metabolites was calculated.

Results: Paracetamol metabolites were examined in 40 patients; eight received the 12-hour regimen and 21 received 20-hours of acetylcysteine (NACSTOP-control). Nine patients with ALI and two with hepatotoxicity were also recruited. The overall median age was 22 years (IQR 18,32) and 70% were female. Median acetylcysteine duration was 13 hours in those receiving the 12-hour regimen, 20 hours in the NACSTOP-control and ALI groups and 60 hours in those with hepatotoxicity. Median times to starting acetylcysteine were 6 hours (IQR 5.5,12), 6.5 (5.6,11), 9 (5.5,16), 21 (12,31); median peak ALT was 13 IU/L (IQR 10,20), 19 (14,22), 67 (59,94), 8983 (2365,15601); and presentation sum CYP-metabolites percentage 2.5, 3.0, 2.8, 14.9 in the abbreviated, NACSTOP-trial, ALI and hepatotoxicity groups, respectively. There was also a significant difference between presentation sum CYP-metabolite percentage in those with and without hepatotoxicity (p < .01).

There was no significant difference in CYP-metabolite percentage in those not developing any liver injury (NACSTOP patients). ROC-AUC on presentation using ALI as an outcome was APAP-GSH 0.58 (95% CI 0.37,0.78), APAP-Mer 0.66 (0.45,0.86), APAP-Cys 0.58 (0.35,0.8), APAP-Sul 0.65 (0.45,0.85), APAP-Glu 0.59 (0.38,0.81), ROC-AUC for sum CYP/total metabolite 0.61 (0.42,0.81), APAP Cys/Sul ratio 0.61 (0.39,0.82), and paracetamol concentration 0.66 (0.47,0.84). Paracetamol metabolites and ratios were similar in the ability to predict ALI on presentation.

Conclusion: Patients with increased sum CYP-metabolite percentage on presentation were more likely to develop hepatotoxicity. Paracetamol metabolite concentrations were similar in groups with low-risk of hepatotoxicity and these may be useful to compare efficacy of acetylcysteine regimens.
121. Blood lactate prognostic implications in acetaminophen supratherapeutic-dose toxicity among low weight children


Objective: The aim of the study was to investigate the use of venous blood lactate measurement to predict poor prognosis among children with severe hepatotoxicity attributed to acetaminophen repeated supratherapeutic dose ingestion in low-resource settings.

Methods: We retrospectively analyzed 97 children with acute liver failure attributed to acetaminophen poisoning admitted to Barnesville Junction Teaching Hospital (BJTH) for pediatrics in Monrovia, Liberia between August 2016 and June 2017. Venous blood lactate rapid measurement used in this study was obtained upon admission to hospitalization before administration of N-acetylcysteine (NAC).

Results: The mean age of the children admitted was 14.6 months, 52% of which died during hospitalization. Eighty-four (87%) children received NAC during hospitalization. The median lactate was significantly higher among the deceased children than the discharged patients (10.7 mmol/L [IQR 7.4–15.7] versus 6.1 mmol/L [IQR 4.1–8.5], p-value < .001, respectively). Multivariate analysis adjusted for treatment and severity factors showed a 6% increased risk of death with every unit increase of blood lactate (Risk Ratio 1.06 95% CI 1.03–1.08). The optimal cut-off obtained from receiver operating characteristic (ROC) analysis was 7.3 mmol/L with a sensitivity of 80% and specificity of 70% (area under curve = 0.78). Notably, the 3.5 mmol/L cut-off for lactate, previously established, had a sensitivity of 94% and a specificity of 15% in our sample.

Conclusion: In low-resource settings, venous blood lactate measurement as a rapid test can accurately identify children who are at risk of death from acetaminophen poisoning. Lactate cut-off measurements previously established seem to have low specificity in predicting poor prognosis among children with acetaminophen repeated supratherapeutic-dose poisoning.

122. The role of oxidative stress in acute methanol intoxication: oxidative lipid damage and subsequent neuroinflammation

Jiri Hlusicka, Daniela Pelclova, Sergey Zakharov and Petr Kacer.

Objective: The mass methanol intoxication that occurred in the Czech Republic in 2012 gave us the opportunity to measure the concentrations of lipid peroxidation markers and leukotrienes in acutely intoxicated patients.

Methods: Blood serum samples were collected from 28 patients hospitalized with acute intoxication and from 36 survivors two years after discharge. In these samples, concentrations of 4-hydroxy-trans-2-hexenal (HHE), 4-hydroxynonenal (HNE), malondialdehyde (MDA), and leukotrienes LTB4, LTC4, LTD4, LTE4 were measured using the method of liquid chromatography-electrospray ionization-tandem mass spectrometry.

Results: The maximum acute serum concentrations of all three lipid oxidative damage markers were higher than the follow-up serum concentrations: HNE 71.7 ± 8.0 ng/mL versus 35.4 ± 2.3 ng/mL; p < .001; HHE 40.1 ± 6.7 ng/mL versus 17.7 ± 4.1 ng/mL; p < .001; MDA 80.0 ± 7.2 ng/mL versus 40.9 ± 1.9 ng/mL; p < .001, peaking 3–4 days after admission. The survivors without methanol poisoning sequelae demonstrated higher acute serum concentrations of the markers than the patients with sequelae. A correlation between the markers and leukotrienes concentrations was established: HNE correlated with LTC4 (r = 0.663), LTD4 (r = 0.608), LTE4 (r = 0.771), LTB4 (r = 0.717), HHE correlated with LTC4 (r = 0.713), LTD4 (r = 0.676), LTE4 (r = 0.819), LTB4 (r = 0.746), MDA correlated with LTC4 (r = 0.785), LTD4 (r = 0.735), LTE4 (r = 0.814), LTB4 (r = 0.674); all p ≤ .001. Lipid peroxidation markers correlated with anion gap (r = −0.428, −0.388, −0.334; p = .026, .045, .080 for HNE, HHE, MDA, respectively). The follow-up serum concentrations of lipid oxidation markers measured in survivors with and without visual/neurological sequelae two years after discharge did not differ.

Conclusion: Our results show that lipid oxidative damage plays an important role in the mechanisms of toxic brain damage caused by acute methanol poisoning. The acute concentrations of the three biomarkers were elevated in comparison with the follow-up concentrations. Neuronal membrane lipid oxidation and leukotriene-mediated neuroinflammation in acute methanol poisoning seem to be a part of the neuroprotective mechanisms preventing damage caused by the direct cytotoxic effect of formic acid [1]. The elevation of lipid oxidation markers was moderate, adaptive, and transient. No cases of persistent elevation were registered among the survivors two years after discharge.

Acknowledgement: Supported by the Ministry of Health of the Czech Republic (AZV), grant No. 16–27075A, the Project 43/16/ RP2P, and the Projects PROGRES Q25 and Q29 of Charles University in Prague.

Reference

123. Chronic retinal neurodegeneration following acute methanol exposure: four-year prospective study in a cohort of 42 survivors of methanol poisoning

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Objective: To study the character and dynamics of chronic structural changes of ocular retina after acute methanol poisoning and its association with key toxicological and biochemical parameters, clinical features, and treatment modalities.

Methods: A four-year prospective study in a cohort of 42 survivors of methanol poisoning. Examination included standard ophthalmic tests, optical coherence tomography with retinal nerve fibers layer estimation (RNFL), visual evoked potentials (VEP), and magnetic resonance imaging (MRI). The variables were compared by unpaired Student’s t-test. The exploratory factor analysis on Spearman and Pearson correlations between RNFL thickness and studied parameters was used.

Results: Clinical examination of survivors was performed three times during the study period: 49.9 ± 0.6 months, 25.0 ± 0.6 months, and 49.9 ± 0.5 months after discharge from the hospital. On admission to the hospital, the mean serum methanol concentration was 1.43 ± 0.47 g/L, arterial blood pH 7.17 ± 0.07, base deficit 16.5 ± 3.5 mmol/L, and formic acid 0.60 ± 0.15 g/L (CI95%). Half of the patients had severe metabolic acidosis (arterial blood pH ≤ 7.20) on admission, 10 patients were admitted in coma, and 20 patients presented subjective signs of visual damage on admission ranging from blurred vision to complete blindness (n = 3). Significant decrease of mean global RNFL thickness in both eyes comparing the control group (ocular dexter/sinister [OD/OS]) from 88.3 ± 5.5/84.9 ± 6.4 µm to 83.3 ± 7.1/80.4 ± 7.7 µm versus 98.5 ± 3.9/96.8 ± 4.1 µm in controls; p < 0.001) was registered with dramatic decrease in temporal segments of retina during the study period (OD/OS from 59.9 ± 5.3/55.1 ± 4.9 µm to 56.8 ± 5.9/53.6 ± 5.8 µm versus 75.0 ± 5.8/71.1 ± 4.0 µm in controls; p < 0.001), but not in nasal segments. The rate of RNFL decrease in all segments was higher than the physiological one. The most significant changes in RNFL thickness were registered in the group of patients with severe methanol poisoning (arterial blood pH on admission lower than 7.2). The patients, who had abnormal RNFL findings on the first examination in 2013, had the most significant RNFL decrease in the following years. An association was present between the dynamics of RNFL loss over the four years and admission laboratory parameters of arterial blood pH (r = -0.507; p < .001), base deficit (r = -0.498; p = .001), anion gap (r = 0.420; p = .01), creatinine (r = 0.577; p < .001), and lactate (r = 0.416; p = .02).

Conclusion: Acute methanol-induced damage of neuronal ganglion cells of ocular retina can lead to chronic retinal neurodegeneration in severely poisoned patients with further loss of visual functions over at least four years after discharge from the hospital.

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124. Attitudes towards research among adult acute toxicity admissions

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Objective: Poisoning, particularly drug overdose, is a major cause of hospital admission in Scotland. Clinical trials involving this patient group are rare but are being performed. This study aims to establish the willingness and capacity of toxicity patients to engage in research, identify the principal reasons why patients are unable to participate, and investigate types of research patients would participate in.

Methods: We performed a matched case-control study of adult patients admitted to Edinburgh Royal Infirmary Emergency Department (ED) and Acute Medical Unit (AMU) over 10 weeks from 24 July to 6 October 2017. Toxicology patients’ ability to consent was assessed. Suitable patients were matched with age and gender controls admitted for general medical conditions. Information was collected on demographic data, previous medical history and details of the current admission. Questionnaires were conducted asking patients if they were willing to participate, hypothetically, in a variety of study designs. Perceived barriers to participation in research were also addressed.

Results: Overall, 149 toxicity admissions were assessed for eligibility (AMU = 104, ED = 45); 109 were excluded mainly because the patient was too drowsy or inappropriate to approach (26%). The remaining 40 patients (55% female) (AMU = 31, ED = 9) and matched controls (AMU = 23, ED = 17) were included in the analysis. The most common drugs resulting in hospital attendance were paracetamol (58%) and opioid analgesics (23%). Around half of the presentations also involved alcohol and around three-quarters had a significant mental health history. Table 1 summarises the patients’ willingness to participate in different aspects of research.

Table 1. Frequency of patients’ willingness to participate in different types of research.

<table>
<thead>
<tr>
<th>Study type</th>
<th>Toxicology (n = 40)</th>
<th>Controls (n = 40)</th>
<th>Unpaired difference and 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient interview</td>
<td>36 [90]</td>
<td>38 [95]</td>
<td>UD: −0.05 95% CI: −0.18544−0.07994</td>
</tr>
<tr>
<td>Outpatient interview</td>
<td>26 [65]</td>
<td>26 [65]</td>
<td>UD: 0 95% CI: 0–0.20139–0.201392</td>
</tr>
<tr>
<td>Study using patient data</td>
<td>39 [97.5]</td>
<td>38 [95]</td>
<td>UD: 0.025 95% CI: 0.008494–0.141864</td>
</tr>
<tr>
<td>Waste samples study</td>
<td>39 [97.5]</td>
<td>39 [97.5]</td>
<td>UD: 0 95% CI: 0–0.10583–0.105832</td>
</tr>
<tr>
<td>Fresh blood samples study</td>
<td>26 [65]</td>
<td>29 [72.5]</td>
<td>UD: −0.075 95% CI: −0.26731–0.12517</td>
</tr>
<tr>
<td>Phase I drug trial</td>
<td>20 [50]</td>
<td>24 [60]</td>
<td>UD: −0.1 95% CI: −0.30135–0.113621</td>
</tr>
</tbody>
</table>
Conclusion: Only 28% of unselected acute toxicology patients would be suitable for recruitment into research studies that require individual patient consent. Of those patients potentially suitable for participation in research, their willingness to participate was comparable with other acute medical patients.

125. What are the exact mechanisms involved in tramadol-induced seizures in overdose? An experimental investigation in the rat

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Objective: Since dextropropoxyphene withdrawal from the market, overdoses and fatalities attributed to tramadol, a WHO step-2 opioid analgesic drug, have increased markedly. Besides central nervous system depression, tramadol overdose may result in seizures, usually included in the related serotonin syndrome. However, the serotonergic mechanism of tramadol-induced seizures has been recently questioned. Aiming to identify the mechanisms involved in seizures related to tramadol overdose, we investigated the effects of various specific pretreatments on tramadol-induced seizure onset and alterations in brain monoamines in the rat.

Methods: Sprague-Dawley rats were randomized into five groups (n = 6/group) to be pretreated with various agonists/antagonists before receiving 75 mg/kg tramadol intraperitoneally: 1.77 mg/kg IP diazepam; 2 mg/kg IV bolus followed by 4 mg/kg/h infusion naloxone; 10 mg/kg IP cyproheptadine, and 15 mg/kg IP fexofenadine. Seizure severity was graded according to the modified Racine Score [1]. We measured neurotransmitter concentrations in the frontal cortex using high-performance liquid chromatography coupled to fluorimetry or radioenzymatic assay, as required. We used positron emission tomography-computed tomography to investigate interactions of tramadol with γ-aminobutyric acid (GABA)ₐ receptors. The effects of treatments on seizures were compared using two-way analysis of variance followed by multiple comparison tests with Bonferroni’s correction. The areas under the curves of the effects on monoamine concentrations and the binding potentials in the PET-imaging study were compared two-by-two using Mann-Whitney U-tests.

Results: Diazepam abolished tramadol-induced seizures, in contrast to naloxone, cyproheptadine, and fexofenadine pretreatments. Interestingly, despite seizure abolishment, diazepam significantly enhanced tramadol-induced increase in the brain serotonin (p < 0.01), histamine (p < 0.01), dopamine (p < 0.05) and norepinephrine (p < 0.05) while no significant modifications were observed with the other tested pretreatments. Based on positron emission tomography imaging using 11C-flumazenil fixation in the rat brain, we demonstrated molecular interaction between tramadol and GABAₐ receptors not related to a competitive mechanism between tramadol and flumazenil on the benzodiazepine binding site. Our findings clearly ruled out the involvement of serotonergic, opioidergic, histaminergic, dopaminergic, and norepinephrine pathways in tramadol-induced seizures while strongly suggesting tramadol-induced specific allosteric change in GABAₐ receptors that could contribute to seizure onset in overdose.

Conclusion: Tramadol-induced seizures in overdose are mainly related to the GABAergic pathway.

Reference


126. Investigation of intravenous lipid emulsion on quetiapine pharmacokinetics in the rat: is the lipid sink theory valid?

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Objective: The effectiveness of intravenous lipid emulsion (ILE) to reverse quetiapine-induced toxicity in acute overdose is controversial. The exact involved mechanisms of ILE action are also unknown. Our objective based on the “lipid sink” theory, was to assess the influence of ILE on quetiapine pharmacokinetics in a rat model of quetiapine intoxication.

Methods: Sprague-Dawley rats were randomized in two groups: 20% Intralipid® versus 0.9% sodium chloride (1.5 mL/kg followed by 0.25 mL/kg/min infusion during 30 minutes; n = 5/measure- ment time), 5 minutes after the IV administration of quetiapine (20 mg/kg). The level of rat sedation was graded using a usual scoring system. Concentrations of total plasma quetiapine, nor-quetiapine, and 7-hydroxyquetiapine and unbound-to-lipid quetiapine were measured using a liquid chromatography-tandem mass spectrometric assay. A three-compartmental model was performed to calculate the parameters of quetiapine pharmacokinetics.

Results: Our analytical method was successfully validated according to the European Medicines Agency criteria. No significant differences between the two groups were observed regarding the pharmacokinetic parameters despite moderate entrapment of quetiapine in the ILE and mild improvement in the rat sedation level (p < 0.5).

Conclusion: Intralipid® was able to entrap quetiapine but no “lipid sink” effect was observed on the pharmacokinetic parameters of quetiapine to explain its possible clinical effects. The exact mechanisms of ILE effectiveness, if any, to reverse quetiapine toxicity remains to be established.

127. The effects of cannabinoids on astrocytic viability and neurotrophic activity

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Objective: The phytocannabinoid tetrahydrocannabinol (THC) is the primary psychoactive compound in cannabis. Cannabidiol...
(CBD) is another major constituent of the plant. Synthetic cannabinoids, such as cumyl-PINACA (SGT-24), bind to cannabinoid receptors and give similar effects to cannabis. Abuse of cannabinoids can result in different adverse central nervous system (CNS) effects. Astrocytes are important glial cells in the CNS, capable of actively supporting neuronal survival and function. Astrocytes represent a main cellular source of neurotrophins nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), that have emerged as key regulators of neural circuit development, synaptic plasticity, and higher cognitive functions. The aim of this study was to evaluate THC, CBD, and SGT-24 effects on astrocyte viability and neurotrophic activity.

Methods: The exposures of primary cultures of neonatal rat cortical astrocytes to 5 µM THC, 1 µM CBD, and 1 µM SGT-24 for different time periods (2-24 hours) were followed by determination of cell viability, assessment of membrane integrity, cellular adenosine triphosphate (ATP) measurement, detection of caspase 8, 9, and 3/7 activity and determination of the cellular contents and secreted amounts of NGF, BDNF, and NT-3.

Results: THC, CBD, and SGT-24 decreased astrocytic metabolism and viability by gradual suppression of ATP concentration and metabolic activity. THC, CBD, and SGT-24 triggered the extrinsic pathway of apoptosis by activation of caspase 8 (173, 183, and 170% regarding non-exposed cells, respectively), intrinsic pathway of apoptosis by activation of caspase 9 (180, 183, and 140% regarding non-exposed cells, respectively) and activation of executive caspase 3/7 (210, 200, and 190% regarding non-exposed cells, respectively). The exposure did not result in necrosis. THC, CBD, or SGT-24 time-dependently suppressed neurotrophic activity. The BDNF concentration decreased by 45% in SGT-24 exposed astrocytes and 30-34% in THC and CBD exposed astrocytes, compared to non-exposed astrocytes. The NGF concentration decreased by 28% in SGT-24 and 38% in THC- and CBD-exposed astrocytes. NT-3 decreased by 61% in CBD and 44 and 36% in THC and SGT-24 exposed astrocytes, respectively.

Conclusion: Phytocannabinoids (THC and CBD) and synthetic cannabinoid (SGT-24) cause time-dependent cytotoxic effects and trigger apoptosis of neonatal astrocytes, but not necrosis. Cannabinoids exposure results in decline of synthesis and secretion of astrocytic BDNF, NGF, and NF-3, that could represent a serious risk to the developing brain.

128. Mechanisms of toxicity involved in metamizole-associated neutropenia

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Objective: Metamizole (dipyrone), a non-opioid analgesic prodrug, can cause life-threatening neutropenia. Currently, the mechanisms underlying metamizole-induced neutropenia are poorly understood [1,2]. Since certain features are compatible with direct metabolic toxicity on circulating cells and/or their precursors, our objective was to investigate the mechanism of cytotoxicity in neutropenia caused by the main metamizole metabolites N-methyl-4-aminoantipyrine (MAA), N-formyl-4-aminoantipyrine (FAA), 4-aminoantipyrine (AA), and N-acetyl-4-aminoantipyrine (AAA).

Methods: We treated promyelocytic HL60 cells and neutrophil granulocytes with increasing concentrations of metamizole metabolites (from 1 µM to 200 µM) with or without hydrogen peroxide (H2O2), biological modifiers, iron compounds, an iron chelator and/or radical scavengers. As a marker of cytotoxicity, we assessed the adenylyl kinase release and the adenosine triphosphate (ATP) content, which reflect cell membrane integrity and cellular energy metabolism, respectively, in HL60 cells and neutrophil granulocytes.

Results: MAA, FAA, AA, and AAA did not affect cell membrane integrity or cellular ATP content in HL60 cells or neutrophil granulocytes. H2O2 (100 µM) depleted the ATP content of HL60 cells by >90% after 24-hour of incubation and showed minor cell membrane toxicity, which was significantly increased by MAA and AA, but not by FAA and AAA. In granulocytes, H2O2 neither affected the ATP pool, nor increased cell membrane toxicity of MAA. Neither the myeloperoxidase inhibitor PF1355 nor the hydroxyl radical scavenger dimethylthiourea decreased the toxicity of MAA in the presence of H2O2. In the presence of Fe2++H2O2 or of hemin (containing Fe3+), cell membrane toxicity of MAA and AA was increased in HL60 cells, but not in neutrophil granulocytes. The toxicity could almost completely be prevented by the iron chelator EDTA or the radical scavengers, glutathione, or N-acetylcysteine.

Conclusion: We showed that MAA and AA alone are not toxic for HL60 cells or neutrophil granulocytes but require Fe2+ and H2O2 or hemin to exhibit cytotoxicity. We suppose that MAA and AA are reductants that are oxidized to a cytotoxic radical by H2O2 and Fe2+ via a Fenton reaction or by the Fe3+ contained in hemin. As in vitro cytotoxicity was observed in the promyelocytic HL60 cells but not in neutrophil granulocytes, this adverse reaction may affect only granulocyte progenitor cells.

References


129. Mitochondrial toxicity and oxidative stress induced by methylene blue and toluidine blue in mammalian cells

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Objective: The phenothiazine dyes toluidine blue (TB) and methylene blue (MB) are clinically used mainly for the treatment of methemoglobinemia, for intra-operative staining purposes and in vasodilatory shock (MB). In Germany, where TB is preferred to MB for the correction of methemoglobinemia, there have been several cases of life-threatening cardiac arrhythmias following the intravenous administration of TB [1]. Despite their widespread use and well described cell-protective effects at low concentrations (<1 µM), little is known about the therapeutic range and toxicity mechanisms of these agents at higher concentrations (>5 µM) expected in clinical use. This in vitro study aimed at comparing the effects of TB and MB on several metabolic endpoints, with indigo carmine (IC) as a non-phenothiazine dye for reference.
Methods: Human lung adenocarcinoma cells (A549) and mouse fibroblast cells (L929) were treated with various concentrations of the three dyes. The mitochondrial membrane potential (MMP), adenosine triphosphate (ATP)-content, reactive oxygen species (ROS) production, and total glutathione concentrations were measured.

Results: MB and TB significantly decreased the MMP after 75 minutes and 4 hours at concentrations >50 µM, with the exception of fibroblasts treated 75 minutes with MB. ATP-content decreased significantly at concentrations >100–500 µM. In A549 cells, the EC50 for ATP content reduction was significantly lower for TB than MB. At concentrations >50 µM, TB significantly increased ROS production in both cell lines after 20 minutes. No significant ROS production occurred after MB exposures; neither dye affected glutathione concentrations. IC did not notably affect any of the parameters. Low-dose MB and TB pretreatment of fibroblasts significantly reduced ROS production induced by hydrogen peroxide.

Conclusion: High-dose MB and TB exposures decreased MMP and ATP-content, suggesting mitochondrial toxicity. Since fluctuations in cardiac MMP can lead to arrhythmias [2], mitochondrial dysfunction could contribute to the cardiovascular effects of TB. High-dose effects were in contrast to low-dose exposures, which reduced oxidative stress generation in fibroblasts. MB appeared less toxic than TB in most of the measured endpoints, and might constitute a safer treatment for methemoglobinemia. For intra-operative staining purposes, IC might be a more suitable alternative.

References

130. Neurotoxicity of cathinones: effects on in vitro neuronal activity

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Objective: The number of new psychoactive substances (NPS) is increasing annually, while data on pharmacological and toxicological effects is limited. We have previously shown that neuronal cultures grown on multi-well micro-electrode arrays (mwMEAs) can be applied as an in vitro screening tool to rapidly determine effects of drugs on neuronal activity. Here, we report the effects of several “classic” illicit drugs and NPS of the cathinone class on neuronal activity.

Methods: mwMEAs were used to measure neuronal activity in primary rat cortical neurons. The mean spike rate (MSR) of these neurons was determined before (baseline) and during drug exposure to investigate the effects of acute exposure (30 minutes) to several drugs on neuronal activity. The effects of cocaine, amphetamine, 3,4-methylenedioxymethamphetamine (MDMA), methylene, methylenedioxypyrovalerone (MDPV), and alpha-pyrrolidinopseudoephedrine (alpha-PVP) were investigated at different concentrations (1 µM to 1 mM), including concentrations relevant for human recreational exposure.

Results: Following exposure, all drugs rapidly and concentration-dependently decreased neuronal activity, although with different potencies. Of the “classic” drugs, cocaine most potently inhibited neuronal activity (IC50 11 µM), while amphetamine and MDMA only inhibited activity at a higher concentration (IC50 110 and 106 µM, respectively). Of the cathinones, MDPV and alpha-PVP potently inhibited neuronal activity, with IC50 values of 24 and 20 µM, respectively. In contrast, methylene inhibited activity far less potent with an IC50 value of 218 µM. At high drug concentrations, activity was completely abolished.

Conclusion: Inhibition of neuronal activity by cocaine, amphetamine, and MDPV occurs at concentrations close to the estimated human brain concentrations following recreational doses of these drugs. MDMA, methylene, and alpha-PVP inhibit neuronal activity at higher concentrations. With respect to the chemical structure of these drugs, the presence of a pyrrolidine ring in MDPV and alpha-PVP appears to increase the potency of drugs to inhibit neuronal activity. Our data shows that mwMEA recordings of cortical neurons are a suitable tool to investigate drug-induced neurotoxicity, which also provides an integrated approach that covers multiple modes of action. Possibly, structure-activity relationships could be applied in the future to aid in the risk assessment of emerging NPS.

131. Investigation of the neurorespiratory effects of buprenorphine/ethanol combination in the rat: evidence for a pharmacodynamic drug-drug interaction

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Objective: Acute poisons characterized by life-threatening central nervous system depression sometimes leading to death due to asphyxia have been attributed to the combination of buprenorphine (BUP) and ethanol. However, the exact mechanism of BUP/ethanol interaction remains unknown. The present work aimed to characterize the respiratory effects resulting from BUP/ethanol combination and investigate the effects of ethanol on the brain distribution of BUP and its main active metabolite, norbuprenorphine (NBUP).

Methods: The effects on ventilation of IV BUP (30 mg/kg) after the intragastric administration of ethanol (3 g/kg) were studied in Sprague-Dawley rats, using diaphragmatic electromyography, arterial blood gas analysis, and blood lactate concentration measurements. In situ cerebral perfusion was performed to investigate the effects of ethanol on the rat blood-brain barrier integrity by using [14C]-saccharose (0.08 µCi/mL) and [3H]-diazepam (0.15 µCi/mL) and to measure the effects of ethanol on the brain distribution of BUP and NBUP. BUP and NBUP concentrations were measured in the brain tissue and in the perfusates using liquid chromatography coupled to mass spectrometry in tandem (LC-MS/MS).

Results: In the presence of ethanol, BUP-induced respiratory depression occurred rapidly after the exposure (as soon as 5 min), evidenced by significant alterations in rat respiratory frequency and cycle amplitude (p < 0.01), resulting in marked and sustained respiratory acidosis (p < 0.01) and hypoxemia (p < 0.001). In situ cerebral perfusion showed preserved blood-brain-barrier integrity.
following ethanol infusion and confirming the absence of ethanol-induced differences in brain concentrations of BUP and NBUP as directly measured in the brain tissues.

**Conclusion:** We demonstrated a significant interaction between BUP and ethanol in the rat, resulting in respiratory depression in the rat. The diaphragmatic electromyography analysis of BUP/ethanol-induced respiratory effects supported a pharmacodynamic drug-drug interaction. No significant alteration in BUP and NBUP distribution in the brain were found. Additional experimental investigations are required to definitely rule out any possible pharmacokinetic interaction between BUP and ethanol.

### 132. Advanced electrocardiogram (ECG) analysis in the amitriptyline-poisoned pig treated with coated activated charcoal hemoperfusion (CAC-HP)

Tejs Jansen\(^a\), Lotte C. G. Hoegberg\(^a\), Thomas Eriksen\(^b\), Christian Haarmark\(^c\), Kim P. Dalhoff\(^d\) and Bo Belhage\(^a\)

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**Objective:** Coated activated charcoal hemoperfusion (CAC-HP) does not reduce the plasma concentration in amitriptyline-poisoned pigs. The aim of this non-blinded randomised controlled animal trial was to determine, if CAC-HP reduces the pathological ECG changes caused by amitriptyline poisoning.

**Methods:** Fourteen female Danish Land Race pigs (mean weight 27.7 kg, range 20–35 kg, CAC-HP group and 24.4 kg, range 18–35 kg controls). All pigs were administered amitriptyline 7.5 mg/kg infused over 20 minutes. Both groups were given standard care with orally instilled activated charcoal. The intervention group was randomised to 4 hours of CAC-HP. After a 1-hour redistribution phase, the pigs were euthanized and within 20 minutes vitreous humour, liver, ventricle and septum of the heart, diaphragm, fat, and brain tissue were collected. Amitriptyline and nortriptyline concentrations were quantified by ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS).

**Results:** No significant differences between treatment arms were found when analysing amitriptyline data (independent sample t-test) (F = 0.580–5.707, df 12, p > .347). For the nortriptyline concentration, a difference in the brain tissue (F = 1.315, df 12, p < .05), and fat tissue (F = 11.64, df 9, p = .045) were the only significant findings.

**Conclusion:** No clinical significant differences in amitriptyline or nortriptyline concentrations were found in the examined tissues. Four-hour treatment with CAC-HP did not affect the accumulation of amitriptyline and nortriptyline in tissues from different organs.

### 133. Amitriptyline accumulation in tissues after coated activated charcoal hemoperfusion: a randomized controlled animal poisoning model

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**Objective:** Amitriptyline poisoning is common and the drug acts on the central nervous and cardiovascular systems. In toxic concentrations, amitriptyline possess the ability to cause life-threatening complications. Treatment is supportive care. The use of extracorporeal clearance techniques, such as coated activated charcoal hemoperfusion (CAC-HP) has not been investigated and we sought to determine whether CAC-HP reduces the accumulation of amitriptyline and the active metabolite nortriptyline in various tissues in an experimental pig model.

**Methods:** A non-blinded randomised controlled animal trial including 14 female Danish Land Race pigs (mean weight 27.7 kg, range 20–35 kg, CAC-HP group and 24.4 kg, range 18–30 kg, controls). All pigs were administered amitriptyline 7.5 mg/kg infused over 20 minutes. Both groups were given standard care with orally instilled activated charcoal. The intervention group was randomised to 4 hours of CAC-HP. After a 1-hour redistribution phase, the pigs were euthanized and within 20 minutes vitreous fluid, liver, ventricle and septum of the heart, diaphragm, fat, and brain tissue were collected. Amitriptyline and nortriptyline concentrations were quantified by ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS).

**Results:** No significant differences between treatment arms were found when analysing amitriptyline data (independent sample t-test) (F = 0.580–5.707, df 12, p > .347). For the nortriptyline concentration, a difference in the brain tissue (F = 1.315, df 12, p < .05), and fat tissue (F = 11.64, df 9, p = .045) were the only significant findings.

**Conclusion:** No clinical significant differences in amitriptyline or nortriptyline concentrations were found in the examined tissues. Four-hour treatment with CAC-HP did not affect the accumulation of amitriptyline and nortriptyline in tissues from different organs.

### 134. Evaluation of the hepatoprotective functions of *Schizophillum commune* in mice with experimental hepatitis caused by carbon tetrachloride

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Objective: We studied the effect of extract of Schizophillum commune (SC), a fungus, on the transport system of serum albumin with experimental hepatitis caused by hepatotoxic carbon tetra-chloride (CTC).

Methods: White male mice (line Af, n = 20) weighing 20–22 g, were divided into the following groups (n = 5 each): control (group 1); CTC 5 mL/kg as a 50% solution in sunflower oil injected once in the skin fold of the neck (group 2); aqueous extract of SC (AES) 0.5 mL (preventive oral)/day for 6 days before the injection of CTC and for 2 days after injection; the animals were removed on the 3rd day (group 3); and AESC 0.5 mL (preventive oral)/day for 6 days before the injection of CTC and for 6 days after CTC injection; the animals were removed on the 7th day (group 4). The effect on serum albumin indicators was evaluated using a set of reagents, PROBE-Albumin (Russia), a spectrofluorimeter CM 2203 Solar (Belarus), and a published method [1]. The parameters measured were total albumin concentration (TAC, the number of albumin molecules), effective albumin concentration (EAC, the number of unoccupied binding sites of albumin), reserve albumin binding (RAB = EAC/TAC 100%), which reflects the degree of structural modification of the protein and the Index of Toxicity (IT = TAC/EAC-1), which characterizes the filling of albumin centers by toxic ligands.

Results: The values of the total concentration of albumin were in the normal range for all groups analyzed. In group 2, the IT increased by 51% when compared to controls. However, the use of AESC according to the scheme 6 + 2 (group 3) decreased the IT by 11% when compared to group 2; and the use of AESC according to the scheme 6 + 6 (group 4) decreased IT by 29% when compared to group 2.

Conclusion: CTC is hepatotoxic and causes structural and functional changes in serum albumin in mice. The indicator “Index of Toxicity” is informative and can be proposed as a marker for assessing the degree of severity of toxic hepatitis and a measure of the influence of therapeutic agents on the process of hepatic recovery. Aqueous extract of Schizophillum commune possesses hepatoprotective activity and can be recommended for further study of its pharmacological properties with the aim of creating drugs.

Reference

135. Effect fingerprinting of cathinones: lessons from in vitro data

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Objective: New psychoactive substances (NPS) are involved in many Emergency Department visits. Effects on several molecular targets have been reported, although literature is scattered and pharmacological profiles are lacking. A summary of the effects of a specific NPS, a “fingerprint”, could aid risk characterization. Therefore, we obtained effect fingerprints of the largest group of NPS, cathinones, on in vitro neuronal modes of action.

Methods: A PubMed search for English-written literature published up to 1 October 2017 was performed. Effect concentrations (e.g., half maximal inhibitory and effective concentrations IC50 and EC50) for neuronal targets of methedrone, 4-methylmethcathinone (4-MEC), pentedrone, methylene, methylenedioxypyvalerone (MDPV), and alpha-pyridylidinovalphonene (alpha-PVP) are reported and related to human relevant concentrations.

Results: At human relevant concentrations, cathinones inhibit and reverse monoamine transporters. Of all cathinones, MDPV most potently inhibits and reverses the dopamine transporter (DAT), with an IC50 value of 4 nM and EC50 of 1 nM. Remarkably, four studies reported MDPV-induced monoamine release via DAT: two reported limited release at 1 nM and two reported no release at 100 µM. Notably, pentedrone and alpha-PVP do not reverse transporters. Effects on neurotransmitter receptors are scarce and mostly involve binding data. Mephedrone, 4-MEC, pentedrone, methylene, MDPV, and alpha-PVP show no or low-binding affinity for dopamine (D1, D2, D3), serotonin (5-HT1A, 5-HT2A, 5-HT2C), alpha-adrenergic, beta-adrenergic, and muscarinic acetylcholine receptors at low-micromolar concentrations. Functional data, i.e., activation or inhibition of receptors, is rare and only reported at higher concentrations. The only functional reported effects are activation of the serotonin 5-HT1A receptor (Kd–60–120 µM) and inhibition of the 5-HT2A receptor (Kd–50–250 µM) by mephedrone, methylene, and MDPV. However, one article reported activation of the 5-HT1A receptor by mephedrone (IC50 0.4 µM). Higher effect concentrations for receptors than for transporters suggests that receptors are less important targets. However, when effect concentrations are related to human relevant concentrations, specific receptors were identified as relevant targets. For example, activation of the 5-HT1A receptor by MDPV and inhibition of the 5-HT2A receptor by mephedrone occurs at concentrations relevant for human exposure. Surprisingly, effects on other neurotransmitter receptors or ion channels have not yet been reported.

Conclusion: The obtained effect fingerprints show many data gaps and large differences in effect concentrations between different studies. Also, more functional data should be obtained for targets other than monoamine transporters. Nevertheless, effect fingerprints can identify targets relevant for human exposure, when related to human relevant concentrations.

136. Effects of active and passive smoking on serum oxidative stress biomarkers in psychiatric patients

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Objective: Recent research cited in the biomedical literature indicates that both active and passive smoking can cause changes in the redox cell balance, which causes the onset or worsening of various pathological conditions. In this study, we aimed to explore the association between serum oxidative stress biomarkers and systemic cotinine concentrations in young subjects who smoked cigarettes.

Methods: We evaluated the cotinine serum concentrations as well as serum glutathione (GSH) concentrations, the advanced oxidation protein products (AOPP), and the antioxidant capacity measured as ferric-reducing antioxidant potential (FRAP) in 76 patients recruited from a psychiatry clinic.

Results: The study subjects were divided into 3 groups according to serum cotinine concentrations: a low-level cotinine group (3.44 ± 0.15 ng/mL serum; n = 25), a medium-level cotinine group (15.86 ± 20.54 ng/mL serum; n = 26) and a high-level cotinine group (91.71 ± 6.57 ng/mL serum; n = 25). Unexpectedly, we
137. Biomarkers of endothelial dysfunction in acute cocaine drug overdose

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Objective: Abuse of stimulant drugs, such as cocaine and amphetamines, has been associated with increased risk of developing adverse cardiovascular medical consequences, some of which can be ascribed to thrombus formation and endothelial dysfunction. Previously, it has been shown that chronic cocaine use produces endothelial dysfunction, and that biomarkers of endothelial dysfunction may rise and fall in the setting of cocaine exposure and abstinence [1]. Here, we study the association between cocaine drug overdose in humans and the following serum markers of endothelial dysfunction: endothelin-1 (ET-1); regulated upon activation normal T-cell expressed and secreted (RANTES); and soluble inter-cellular adhesion molecule-1 (sICAM-1).

Methods: This prospective cohort study enrolled consecutive adult patients with acute drug overdose over a one-year period at two urban tertiary care hospitals. Drug exposures were classified according to urine drug toxicology as follows: cocaine, opioids, cannabinoids, and other. Serum was drawn at the bedside upon presentation to the Emergency Department as part of clinical care, and waste specimens were saved in the lab, frozen at −80 °C and stored for biomarker analysis. Endothelial biomarkers were analyzed using ELISA kit assays (Rand D Systems, Inc., Minneapolis, MN, USA) according to the manufacturer's instructions.

Results: Over the study period, serum from 144 patients was available for analysis, of whom there were 30 cocaine (10 cocaine only), 67 opioids (30 opioids only), 22 cannabinoids (8 cannabinoids only), and 85 other drugs (controls). Mean RANTES (pg/mL) was 7366 for controls, 7658 for cocaine, 8970 for opioids, and 7267 for cannabinoids (all p = NS). Mean ET-1 (pg/mL) was 20.95 for controls, 14.58 for cocaine, 30.56 for opioids, and 13.8 for cannabinoids (all p = NS). Mean sICAM (ng/mL) was 200.2 for controls, 1014 for cocaine (p < .01), 328.7 for opioids only (p = .03), and 298.6 for cannabinoids (p = NS).

Conclusion: Acute cocaine overdose was associated with endothelial dysfunction demonstrated by highly elevated sICAM-1. This novel finding may facilitate future studies of treatments for cocaine and other stimulant abuse, because biomarker surrogates are currently needed to demonstrate cocaine abstinence. Furthermore, early risk stratification for cocaine and other stimulant overdose may help detect and prevent adverse cardiovascular medical consequences of drug overdose. Predictive utility of endothelial biomarkers for the occurrence of adverse cardiovascular events requires further study.

Reference

138. Pharmacovigilance: a 4-year Poisons Information Center pilot survey of atypical antipsychotics

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Dutch Poisons Information Center, University Medical Center Utrecht, Utrecht, Netherlands

Objective: Retrospective evaluation of information acquired from Poisons Center databases provides an excellent opportunity for pharmacovigilance. A survey of the Dutch Poisons Information Center (DPIC) database was performed, focusing on the frequency and severity of intoxications with atypical antipsychotics.

Methods: All mono-intoxications from 2013–2016 with the atypical antipsychotic drugs quetiapine, risperidone, olanzapine, aripiprazole, and clozapine were extracted from the DPIC database. Severity of intoxications was estimated using the DPIC dose-effect value, which are based on medical literature and toxicological experience. The DPIC uses higher exposure limits for frequent clozapine users (due to tolerance) than for children and non-clozapine users. The number of registered antipsychotic users was derived from the Dutch National Health Care Institute.

Results: The relative number of consultations to the DPIC in relation to the registered number of users was 0.16% on average for quetiapine, risperidone, olanzapine, and aripiprazole. For clozapine, however, this percentage was considerably higher, averaging 0.45%. Moreover, the proportion of potentially severe intoxications was considerably higher, with 79.9% of all clozapine intoxications classified as moderate/severe, compared to 31.2% for the other atypical antipsychotics. Moderate/severe clozapine intoxications were especially frequent in children and non-clozapine users, with 86.3% compared to 10.9% for frequent clozapine users (Table 1).

Conclusion: Substantial differences were found between the frequency and estimated severity of clozapine intoxications versus other atypical antipsychotic drugs. Clozapine causes relatively more intoxications in relation to registered users compared to other antipsychotic drugs, and more severe intoxications in children and non-clozapine users compared to frequent clozapine users. These results may be used to improve medicine safety information provided to patients, urging safe storage to reduce the risk of accidental poisoning of relatives and co-residents. In a broader perspective, prospective PIC database surveys may contribute to pharmacovigilance and stimulate safer medicine use, using benefit-risk balances regarding the prescription of drugs.
139. Unexpected toxicity of cannabidiol (CBD) oil health products

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Johanna J. Nugeteren-Van Lonkhuyzen,
Laura Hondebrink, Saskia J. Rietjens, Irma De Vries and Antoinette J. H. P. Van Riel

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Objective: Cannabis sativa contains dozens of cannabinoids, including psychoactive cannabinoids like tetrahydrocannabinol (THC), and non-psychoactive cannabinoids, like cannabidiol (CBD). Many people believe that CBD has health-promoting effects. In the Netherlands, CBD products are available over-the-counter (OTC). The number of enquiries about CBD to our Poisons Center had increased. Therefore, we aimed to investigate the adverse effects caused by CBD-containing health products.

Methods: The database of the Dutch Poisons Information Center (DPIC) was queried for enquiries on human exposures to CBD products from November 2013 to September 2017. The acquired data was analysed statistically.

Results: The DPIC was consulted on 57 patients who were exposed to a CBD product (1 in 2015; 22 in 2016; 34 in 2017). Twenty-three patients (40%) reported that the CBD product also contained THC and/or other concomitant exposures. These cases were excluded. The remaining 34 included patients (60%) reported exposure to products supposedly containing CBD only. Their median age was 43 years (IQR: 32–76 years) and gender was equally distributed. CBD was mainly used for (palliative) pain management (21%), as a sleeping aid (24%) or as a sedative (6%). CBD products were often received from family or friends (32%), but also bought OTC (9%) or online (15%). In one case, the CBD oil was prepared at home. Exposure in adults (n = 30) was mainly to the intended dose (n = 24), however, 6 patients (18%) were accidentally exposed to an overdose due to a dosing error. The ingested dose varied from 2 drops to 15 mL (e.g., content of an entire bottle). Of the 34 included patients, only 6 were asymptomatic during the enquiry. Notably, psychoactive effects were reported in 10 patients (29%), including anxiety (n = 6), confusion (n = 1) or hallucinations (n = 4). Other reported symptoms included palpitations (n = 4), tachycardia (n = 3), dizziness (n = 5), sleepiness (n = 7), gastrointestinal distress (n = 6), and perspiration (n = 4). Most enquiries originated from general practitioners (65%), but enquiries were also made from Emergency Departments (18%) and paramedics (17%).

Conclusion: Remarkably, psychoactive effects were reported after using products supposed to contain CBD only, while CBD is not a psychoactive substance. The presence of THC in OTC CBD products is illegal in the Netherlands. However, the occurrence of psychoactive and cardiovascular effects indicates the presence of THC in these products. Therefore, the quality of CBD products that are available OTC is questionable and should be monitored more carefully.

140. Thirty years of inpatient toxicology deaths

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Objective: Death from intentional self-poisoning once in hospital is rare in the Western world. We aimed to identify the number of inpatient deaths within our unit over a 30-year period and to provide a clearer description of whether the death was related to the poisoning or due to a non-related event.

Methods: All admissions to a tertiary referral toxicology unit between 1987 and 2016 were reviewed for death whilst an inpatient. Patient records, coronial reports, and autopsy results were then reviewed for each death.

Results: There were 21,067 admissions over the 30-year period, with 90 (0.43%) inpatient deaths; 69 cases had a coronial report, whilst 21 did not (two were not referred to the coroner, 5 were yet to be completed, and 14 could not be found). Of the 90 deaths, 6 deaths were secondary to the effects of hanging and were excluded, resulting in 84 (0.40% from admission rate) deaths associated with poisonings. Of these, 76 deaths occurred as a direct result of self-poisoning, whilst 8 deaths were secondary to medical conditions, 3 cases of pulmonary embolism, one each from asthma, coronary occlusion, sepsis, cancer related death, and chronic obstructive pulmonary disease (COPD). Of the 76 poisoning deaths, 47 (62%) were male, with a median age of 47 years (IQR: 32–70 years), compared to the overall admission rates of 12,795 (61%) female with a median age of 32 years (IQR: 24–48 years). Garden shed poisons were ingested by 18 (14%) patients (of which 16 were male), 16 (12%) ingested narcotic drugs and 5 (4%) used gas. The remaining 37 ingestions were a mix of therapeutic medications (Table 1).

Conclusion: The overall inpatient mortality from intentional self-poisoning is low at 0.36%. Older males completed suicide at a higher rate than females, and tended to use garden shed poisons more than females.

Table 1. Average yearly frequency and estimated severity of intoxications for the most commonly used atypical antipsychotics in the Netherlands (2013–2016).

<table>
<thead>
<tr>
<th>Quetiapine</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Aripiprazole</th>
<th>Clozapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registered users</td>
<td>90,527</td>
<td>49,412</td>
<td>43,442</td>
<td>19,816</td>
</tr>
<tr>
<td>Intoxications</td>
<td>209.3</td>
<td>72.0</td>
<td>54.3</td>
<td>29.5</td>
</tr>
<tr>
<td>Intoxication versus registered users (%)</td>
<td>0.23</td>
<td>0.14</td>
<td>0.13</td>
<td>0.14</td>
</tr>
<tr>
<td>No/mild intoxication (%)</td>
<td>56.0</td>
<td>60.2</td>
<td>54.0</td>
<td>88.9</td>
</tr>
<tr>
<td>Moderate/severe intoxication (%)</td>
<td>40.4</td>
<td>37.6</td>
<td>38.2</td>
<td>8.6</td>
</tr>
<tr>
<td>Frequent users</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>No/mild intoxication (%)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Moderate/severe intoxication (%)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Children/non-users</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Registered users: 90,527 49,412 43,442 19,816 11,960
Intoxication: 209.3 72.0 54.3 29.5 52.0
Intoxication versus registered users: 0.23 0.14 0.13 0.14 0.45
No/mild intoxication: 56.0 60.2 54.0 88.9 9.2
Moderate/severe intoxication: 40.4 37.6 38.2 8.6 79.9
Frequent users: n/a n/a n/a n/a 63.6
Moderate/severe intoxication: n/a n/a n/a n/a 10.9
Children/non-users: n/a n/a n/a n/a 13.7
Moderate/severe intoxication: n/a n/a n/a n/a 86.3
141. Coroners' Reports to Prevent Future Deaths related to poisoning in England and Wales: relevance to toxicosurveillance

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Objective: To establish whether Reports to Prevent Future Deaths (PFDs) made by Coroners in England and Wales include useful information on the prevention or management of poisoning by medicines and drugs of abuse.

Methods: We examined 500 sequential coroners’ PFDs in the public domain \cite{1} by pre-defined criteria to identify those in which medicines played a part, and to collect information on coroners’ concerns \cite{2}. Here, we examine those cases related to poisoning and drugs of abuse.

Results: We found 99/500 PFDs (relating to 100 deaths) that expressed concerns about legal or illegal drugs or their supply or administration. Twenty-five were clearly related to poisoning or drugs of abuse or both. Of the seven related to poisoning by medicines, one described a woman with severe malnutrition given a standard dose of paracetamol; all the others concerned opioids with or without psychotropic drugs. Fentanyl caused death in one case because a damaged patch released an excessive dose and in another because a patient took a hot bath while wearing a patch. A patient with stage 4 kidney failure was poisoned by codeine administered in full dose; and two patients were given supplies of dangerous medicines, despite having previously taken overdoses. Of the 18 cases related to drugs of abuse, 8 involved persons in prison or police custody; 8 reported that drug regulation of e-cigarette fluid, or cannabinoids, amphetamine or fentanyl derivatives was inadequate; and five concerned heroin or methadone. In one case, a prisoner hanged himself in his cell, and a synthetic cannabinoid, [Black] Mamba, was detected in post-mortem specimens, but the coroner was unable to say whether this had affected the deceased’s state of mind. In another case, a 17-year-old boy became psychotic after taking cannabis and ecstasy, discharged from hospital, relapsed, and jumped into a river.

Conclusion: Coroners’ PFDs contain relevant information on deaths by poisoning. They generally reflect concerns already expressed by others. The fentanyl patch cases led to regulatory action, and the law on synthetic drugs of abuse (“legal highs”) has changed, \cite{3} although we are unable to assess how influential Coroner’s PFDs were in changing the law.

References


142. Oral alkaline pH drops: risk of chemical injuries

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Objective: Alkaline pH drops claim to contribute to a healthy lifestyle by restoring the acid-base homeostasis of the body. There is no scientific evidence that these alkaline pH drops have any beneficial effects. The drops contain sodium hydroxide, potassium hydroxide, and additives like minerals and zinc gluconate. The recommended use is to drink a few drops mixed in water several
times a day. Undiluted, these drops have a pH of approximately 14 and therefore cause burns upon direct tissue contact. To assess the actual health risks, all enquiries involving alkaline pH drops reported to the Dutch Poisons Information Center (DPIC) were retrospectively analysed.

**Case series:** The DPIC was first consulted about exposure to alkaline pH drops in March 2013. Thereafter, the annual number of these exposures increased from 1 in 2013, 3 in 2014, 9 in 2015, 10 in 2016, and 6 up to September 2017. In all 29 cases (2 children, 27 adults, 72% female) ingestion, eye or skin contact with the undiluted product occurred. Eighteen cases concerned eye exposures. Most of these exposures were caused by accidental exchange with eye drops or fluids for contact lenses. The reported symptoms were irritation, conjunctivitis and corneal damage, dry eyes, lacrimation, edema, blurred vision, and a facial skin burn. Eight patients ingested pure drops. In two cases, the alkaline drops were mistaken for vitamin D drops or homeopathic drops. All patients reported symptoms, ranging from irritation, pain, tongue burns, erosions, and edema in the mouth, throat and/or stomach, to nausea and headache. There were two skin exposures. One of these was a prolonged exposure caused by a leaking bottle in a pocket. Both skin exposures led to pain, edema, chemical burns, and necrosis. One child was found with an empty bottle that was reportedly only half full. However, this child did not develop symptoms, so it is probable there had not been any exposure.

**Conclusion:** Alkaline pH drops can lead to severe local burns when misused or mistaken for other products. In our registration, symptoms only occurred in these settings and not when used according to instructions, regulatory measures are difficult. However, it is worrisome that these kinds of products, without any scientific evidence or medical benefit, are available in the market. Public awareness and at least a change in packaging and/or warnings on the bottle may help prevent these unfortunate mistakes.

### 143. The epidemiology and severity of scorpion envenoming in South Africa: data from the Tygerberg Poisons Information Centre over a 10 year period

**Carine J. Marks**, **Dmitrij Sachno**, **Gert J. Muller**, **Helmut Reuter**, **Cheryllyn Wium**, **Catharina E. Du Plessis** and **Daniel J. Van Hoving**

**aClinical Pharmacology, Stellenbosch University, Cape Town, South Africa; bEmergency Medicine, Stellenbosch University, Cape Town, South Africa**

**Objective:** Scorpions are widely distributed in South Africa, especially in the arid Western regions [1]. Identification is difficult and can often only be done by an expert. It is therefore important for the treating physician to be guided by symptoms and signs to assess the severity of the envenomation. The aim of this study was to analyse South African epidemiological data of scorpion stings and envenomation as processed by the Tygerberg Poisons Information Centre (TPIC).

**Methods:** A retrospective analysis was conducted on data with regard to scorpion sting as processed by the TPIC over a 10-year period (1 January 2005 to 31 December 2014). Collected data were entered onto a standard Microsoft Excel® spreadsheet. Descriptive statistics are presented for all variables.

**Results:** During the study period, 52,163 consultations were processed by the TPIC, of which 740 (1.4%) cases involved scorpion stings. Of these, 141 (19.1%) cases were deemed serious envenomations. Antivenom was recommended to be administered in 131 (93%) of these cases. The majority of stings occurred in adults (>20 years of age) (n = 518, 70%) and during the warmer summer months, from October to March, with a peak in January (n = 127, 17.2%) and February (n = 118, 15.9%). The greatest number of calls were received from healthcare professionals (n = 485, 65.5%). In 356 (48.1%) cases of scorpion envenomation, a call to the TPIC was made within six hours of the sting occurring. Most scorpion sting consultations per population originated from the Western Cape (6.9 stings/100,000 people) and the Northern Cape (2.1 stings/100,000 people) provinces [2]. Identification of the relevant scorpion was done in 2% (15/740) cases by positive morphological examination.

**Conclusion:** Although the incidence of severe scorpionism is relatively low (141/52163; 0.3%) compared to other acute poisoning exposures, serious systemic effects can cause high morbidity and mortality due to respiratory failure [3]. Healthcare professionals, the general public, and tourists should be aware of this. For optimal treatment, a Poisons Centre should be contacted.

### References


### 144. Human H1-antihistamine exposures reported to the Poisons Information Centre Erfurt from 2007 to 2016

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**Poisons Information Centre Erfurt, c/o HELIOS Klinikum Erfurt GmbH, Erfurt, Germany**

**Objective:** In Germany, the use of first-generation H1-antihistamines (FGH1AH) in children under the age of 3 years is criticised by the Federal Institute for Drugs and Medical for a higher risk of experiencing adverse effects and in adults for the risk of abuse and suicide attempts [1,2]. In this context, we investigated all human H1-antihistamine exposures registered by the Poisons Information Centre (PIC) Erfurt for differences between first- and second-generation H1-antihistamines (SGH1AH).

**Methods:** The changes in frequencies, circumstances of exposure, symptoms, symptom severity, age groups, and substances involved in all H1-antihistamine related enquiries to the PIC Erfurt were retrospectively analysed from 2007 to 2016 and compared between FGH1AH and SGH1AH exposures.

**Results:** In total, 4371 cases of H1-antihistamine exposures with 2596 monexposures were registered. Cases of FGH1AH (n = 4013) and SGH1AH (n = 324) exposures increased from 364 and 22 cases in 2007 to 430 and 47 in 2016, respectively. In FGH1AH cases, diphenhydramine (n = 1258) and promethazine (n = 992) and in SGH1AH cases cetirizine (n = 193) and loratadine (n = 85) were most frequently involved. Age groups in FGH1AH exposures were more often adults (78.1%) and less frequently children (21.7%) compared to SGH1AH exposures (adults 27.8%;...
children 72.2%). The proportion of exposures with abuse and suicidal intention was higher in FGH1AH (29.6% and 62.0%) than in SGH1AH (0% and 24.1%), whereas the proportion of accidental exposures was lower (13.5% versus 58.6%). FGH1AH exposures were more often symptomatic (mild 48.2% versus 22.8%; moderate 7.6% versus 3.4%, severe 3.4% versus 0.3%) than SGH1AH. In all cases with moderate symptoms, 66.7% in babies, 90.5% in toddlers, and 57.1% in schoolchildren were caused by diphenhydramine although over all age groups, the most cases with moderate (43.5%) and severe (51.1%) symptoms were caused by diphenhydramine.

**Conclusion:** Cases with FGH1AH seem to be accompanied by an increased health risk in all age groups in comparison with SGH1AH exposures. The study shows that there is a higher risk, especially for children, developing moderate to severe symptoms after misuse of over-the-counter H1-antihistamines and the necessity of regulation.

**References**


145. Poisoning in the UK: what is the true incidence?

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**Objective:** Poisoning in the UK is common with over 160,000 people attending UK Emergency Departments annually and many more are managed in primary care. Estimating the true incidence is challenging. TOXBASE® is the primary information resource for healthcare professionals managing poisoned patients in the UK; in 2016/2017, there were 1,651,369 TOXBASE® accesses (page loads). Access data has been used as a surrogate marker to estimate poisoning incidence but not all TOXBASE® accesses relate to patient management. TOXBASE® users were surveyed as to their reasons for accessing the TOXBASE® database to provide a more accurate estimate of the incidence of poisoning in the UK.

**Methods:** TOXBASE® users were surveyed on two separate weeks (5–11 September and 26 September to 2 October 2017) using a two-question survey every time they accessed an entry. Users were asked whether their access related to patient management and if so, whether it was the first time TOXBASE® was viewed, or if their access was not patient-related. Survey responses were exported into Excel; unique user responses were identified through exclusion of duplicate accesses for a user within an hour. Unique user responses were analysed with access data for the same period.

**Results:** Data demonstrate that at least 19% of all TOXBASE® accesses during the study period related directly to individual patients (Table 1).

**Conclusion:** In 2016/2017, this would equate to 313,760 patients for which a TOXBASE® referral was required. It is important to note the true number of patients for which a TOXBASE® referral was required is likely to be higher than that calculated from these survey data as: 46% of users chose not to respond; healthcare professionals familiar with managing poisoned patients may not have accessed TOXBASE®, and unique telephone enquiries and accesses made via the TOXBASE® app were not included.

146. Epidemiology of acute metformin poisoning in children: a 5 year study

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**Objective:** To analyse the epidemiology of acute metformin poisoning in a pediatric Toxicology Department.

**Methods:** All cases of acute metformin poisoning admitted to the Emergency Clinical Hospital for Children Grigore Alexandrescu, Bucharest, Romania in a 5-year period (2012–2017) were analysed. The data extracted were age and gender distribution, intention, complications, and evolution.

**Results:** There were 37 cases. Gender distribution was 27 girls (73%) and 10 boys (27%). Age distribution was 1–5 years 11 cases (29.7%), 5–10 years 1 case (2.7%), 10–14 years 3 cases (8%), and 14–18 cases 22 cases (59.4%). The youngest age was 1 year and 6 months in a child with accidental poisoning. In 8 cases (22%), there was multi-drug poisoning and metformin was taken with antidepressants. For the circumstance of poisoning, there were 24 cases (64.8%) of intentional and 13 cases (35.2%) of accidental poisoning. Ten patients (27%) developed lactic acidosis (values of lactate in the blood above 4–5 mmol/L), and 8 of them received supportive treatment and recovered. Three adolescents (who ingested a high dose) developed increased concentrations of serum creatinine, urea, and lactate. Of these three, one patient recovered with supportive treatment, and two required hemodialysis [1]. Of these patients, one fully recovered and the other died with multi-organ failure.

**Table 1.** TOXBASE® user survey responses to determine whether access related to patient management or was for another reason (e.g., educational purposes or multiple accesses for a single patient).

<table>
<thead>
<tr>
<th>User</th>
<th>TOXBASE® Access (UK only, excluding educational)</th>
<th>Unique user access (% of overall TOXBASE® accesses)</th>
<th>Unique patient related accesses (% of overall TOXBASE® accesses)</th>
<th>Unique patient related first accesses (% of overall TOXBASE® accesses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital users</td>
<td>31,032</td>
<td>17,662</td>
<td>9715</td>
<td>6015</td>
</tr>
<tr>
<td>All others (e.g., general practitioner, telephone triage services)</td>
<td>15,370</td>
<td>8581</td>
<td>3852</td>
<td>2755</td>
</tr>
<tr>
<td>Total</td>
<td>46,402</td>
<td>26,243 (56.5%)</td>
<td>13,567 (29.2%)</td>
<td>8770 (18.9%)</td>
</tr>
</tbody>
</table>

In total, 26,243 unique user accesses were identified; 54% (14,250) answered the first question. Overall, 13,567 (95.2%) were patient-related enquiries and 683 (4.8%) accesses were for educational or other reasons. In addition, 8770 respondents (64.6%) indicated it was their first TOXBASE® access in relation to that patient, 4017 (29.6%) indicated it was not their first visit and 780 (5.8%) did not complete the second question.
Conclusion: Acute metformin poisoning has become an important cause of admission in a pediatric toxicology department [2] as more people are diagnosed and treated for diabetes mellitus.

References


147. Epidemiology of intentional poisoning in children admitted to a toxicology department

Simona Stanca, Madalina E. Petran and Coriolan Ulmeanu
Pediatric Poisoning Centre, Emergency Clinical Hospital for Children Grigore Alexandrescu, Bucharest, Romania

Objective: An epidemiological study of intentional poisoning cases admitted in the toxicology department of a children's hospital over a 9-month period.

Methods: A retrospective study including all cases of suicide attempt or intentional poisoning admitted in the Toxicology Department, Emergency Clinical Hospital for Children Grigore Alexandrescu, Bucharest, Romania from January to September 2017. Etiology, gender and age groups, severity criteria, coma, and psychiatric associated disorders were considered [1].

Results: There were 188 cases of intentional poisoning recorded over the study period. There were 131 girls (69%) and 57 boys (31%). Age group ratio: under 14 (11–14 years old) 25 (13%) and 14–18 years old 163 (87%). The youngest patient was 11 years and had taken a multidrug overdose. Etiology: 56 cases of multi-drug poisoning (30%), 32 with ethanol (17%), 4 with alcohol and drugs (2%), 7 with alcohol and abuse substances (3.7%), 32 with neurotropic drugs (17%), 16 with non-steroidal anti-inflammatory drugs (NSAIDs) (8.5%), 18 with other drugs (9.5%), 11 with chemicals (5.8%) and 12 with abuse substances (6.3%). Two adolescents were pregnant and 18 patients were diagnosed with psychiatric disorders (9.5%). Of these, there were 13 girls (72%) and 5 boys (28%). Altered consciousness (coma) was present in 24 cases (13%) involving 11 girls (45%) and 13 boys (55%). Coma etiology as was follows: 58% ethanol (14 cases), 37% drugs (9 cases), and 4% pesticides (an organophosphate insecticide 1 case).

Conclusion: Intentional poisoning is a major cause of admission in an emergency hospital. Ethanol and abuse substances represent an increasing health problem in adolescents, so close monitoring of this age group is a real necessity [2].

References


148. Medication poisoning in children: Moroccan Poison Control and Pharmacovigilance Centre data

Narjis Badranea, Ahlam Meftahb, Naima Raлемa, Abdelmajid Soulaymanib and Rachida Soulaymani Bencheikhab
aCentre Anti Poison et de Pharmacovigilance du Maroc, Rabat, Morocco; bGenetics and Biometry Laboratory, Faculty of Sciences, University Ibn Tofail, Kenitra, Morocco

Objective: Medications are the most common substances involved in pediatric poisoning [1]. The aim of our study was to describe the epidemiological features of medication poisoning in children (0–15 years old) identified by the Moroccan Poison Control and Pharmacovigilance Centre (CAPM) from 2013 to 2014.

Methods: A retrospective study from January 2013 to December 2014 of all cases of medication poisoning in children reported to the CAPM was conducted. The data included circumstances of poisoning, sex, age distribution, drugs involved in the poisoning cases and outcome. Poisonings in the fetus and the newborn of an intoxicated mother were excluded from this study.

Results: The CAPM collected 2513 medication poisoning cases in children (41.7% of all medication intoxications) over the study period. Emergency Departments notified more than 90% of the cases. The average age was 4.3 years ±1.3 (66.7% of children were aged from 1–5 years). Sex-ratio (M/F) was 1.3. The drugs implicated in the largest number of poisoning cases were psychotropic drugs (18%) and contraceptives (11.7%). The poisoning occurred inadvertently in 2096 (83.4%) cases while 120 (4.8%) patients (90 cases involving girls) attempted suicide. In total, 76.9% of patients were followed up after emergency treatment, 17.23% were hospitalized, and two children died.

Conclusion: Easy availability of medicines is the major risk factor for acute childhood poisoning, which demands increasing public awareness. It is necessary to start prospective studies in Morocco to elucidate the risk factors of suicide in young children, especially girls.

Reference


149. Racial and ethnic characteristics in cases of intentional pharmaceutical exposure with concern for toxicity

Alexa Camarena-Michelb and Benjamin Hattenb
bEmergency Medicine, Denver Health Medical Center, Denver, United States; bSection of Medical Toxicology, Department of Emergency Medicine, University of Colorado School of Medicine; On behalf of the Toxicology Investigators Consortium (ToxIC), Aurora, United States

Objective: There is little data examining intentional pharmaceutical ingestion characteristics across different ethnic and racial groups. Intentional pharmaceutical behaviors may be impacted by various sociocultural and biological factors. It is prudent to
Conclusion: Given the dearth of available data, this represents rates of death were observed when comparing hispanics (0.3%) versus non-hispanics with regards to reasons for intentional use: attempt at self-harm, misuse/abuse or no attempt at self-harm, therapeutic use (such as bradycardia after verapamil use) or other. This data were evaluated with regards to Hispanic and non-Hispanic patients as well as 8 racial groups including Asian, Black/African, American Indian/Alaska Native, Caucasian, Native Hawaiian or Pacific Islander, Mixed or other. Descriptive statistics were used to present basic epidemiology and chi-squared testing was performed to compare groups.

Results: Data from 3410 cases from 2017 were queried in the ToxIC database. Intentional pharmaceutical exposures were examined and there was found to be a correlation between reasons for intentional drug use (self-harm 69% versus 76%, misuse/abuse 19% versus 11% and therapeutic effect 6% versus 8%, p = 0.013) and being non-Hispanic (n = 1811) or Hispanic (n = 251). Moreover, when different racial groups were queried, there was a statistically significant correlation between various racial groups and reasons for intentional pharmaceutical use (p = 0.018). Similar rates of death were observed when comparing Hispanics (0.3%) and non-Hispanics (1.0%) and between the 8 racial categories (range 0–2%).

Conclusion: Given the dearth of available data, this represents an initial examination of racial and ethnic characteristics in cases of intentional pharmaceutical exposures. In the data analyzed, there are significant differences between racial groups and Hispanics versus non-Hispanics with regards to reasons for intentional pharmaceutical ingestion. However, survival is similar. Future work will be undertaken to explore racial and ethnic differences within the entire ToxIC dataset (2010–2017).

152. Epidemiology of acute poisoning in Uganda: an 8-year analysis

Stephen A. Hardinga, Rana Biaryb, Robert S. Hoffmana, Samuel Malings, Mark Bisanzo, Steven A. Hardings, Stacey Chamberlaina, Bradley Dreiffusa, Heather Hammerstedta, Melissa Langevint, Sara Nelsona, Usha Periyanayagama and Brian Rickea

Objective: To present a descriptive retrospective analysis of patients acutely poisoned in two hospital sites in Uganda between 2009 and 2017.

Methods: Data was abstracted from a quality assurance database developed by the Global Emergency Care Investigators Collaborative, a non-governmental organisation (NGO) providing emergency care training to physicians in Uganda. The database included all patient visits from two hospital sites: one rural NGO hospital (Karoli Lwanga Hospital) from 2009–2015, and one urban regional referral hospital (Masaka Regional Referral Hospital) from 2014–2017. All cases of poisoning were extracted. The data reviewed included gender, age, specific poison, study site (urban/rural), three-day patient outcomes, and suicidal intent.

Results: Overall, 60,312 cases were examined; 33,171 patients were male, and 27,141 were female. Of these, 628 visits were due to poisoning etiology. Over a third of patients (34.8%) were younger than 5 years, 13.9% were 5–12 years, 34.4% were 12–18 years, 16.2% were between 18–64 years old, and 0.006% were more than 65 years. Suicidal intent was involved in 23.8% of poisonings. Organophosphate poisoning (OP) was the most common diagnosis (29.6%) and was most prevalent (68/186) in the 12–18 age group and 60% of OP exposures occurred in the rural site. Of these, 186 OP exposures, 86% were due to a suicidal intent. There were 16 fatalities in the OP group (8.5% mortality rate). The second most common poison diagnosis was amitraz (cow-tick) with 117 cases (18.6%), of these, 97.4% were in the rural setting. 41.8% were due to suicidal intent, with 9 fatalities (7.7% mortality rate). Other diagnoses included: chloroform, kerosene, paraffin, pesticide, rat poison, and unknown/unclear. The total number of deaths from poisonings was 36 (5.7%).

Conclusion: We present an epidemiologic review of two hospital sites, one urban and one rural, in Uganda. Toxicologic causes represented approximately 1% of all hospital visits. This remains a significant public health burden, given the high resources required to care for poisoned patients. This information can characterize the prevalence of exposure and evaluate areas for preventive interventions. The differences between rural and urban centers can target toxic-specific public health interventions and focus resource allocations. Given the large number of pesticide poisonings, identification of highly toxic compounds may reduce morbidity and mortality through either regulation or discontinuation of high-risk pesticide supplies. Lastly, identifying emerging toxicologic threats can both improve management of future cases, and translate into interventions elsewhere.

153. Usage of extracorporeal treatment in Hungary

Csaba Papat

Department of Emergency Medicine and Clinical Toxicology, Péterfy Hospital, Budapest, Hungary

Objective: Based on the EXTRIP (Extracorporeal TReatments In Poisoning) recommendations extracorporeal treatment (ECTR) is recommended in severe acetaminophen, barbiturate, carbamazepine, lithium, metformin, methanol, phenytoin, salicylate, thallium, theophylline, and valproic acid poisoning. The preferred mode of ECTR is intermittent hemodialysis. We examined trends and indications for use of ECTR in poisoning at our department in light of EXTRIP recommendations.

Methods: Patients treated with hemoperfusion (HP) or hemodialysis (HD) for severe intoxications at our department between January 2013 and December 2016 were analyzed retrospectively. Patients severely poisoned with the above-mentioned substances with typical symptoms and elevated serum concentrations were enrolled. Patients intoxicated by ethylene glycol were excluded. The following parameters were recorded: age, ingested amount, type of ECTR, indication for ECTR, adverse effects of ECTR, and outcome of poisoning.

Results: In the study period, we had no patients poisoned by methanol, phenytoin, salicylate, or thallium requiring ECTR. Overall, 34 patients received ECTR (HD 23, HP 12; one patient received both). In 2013, we treated 7 patients with HP, in 2014 one patient with HP and 3 patients with HD, in 2015 three patients with HP and 12 patients with HD, and in 2016, we treated one patient with both HP and HD and 7 patients with HD. HP was given for barbiturates (n = 4), theophylline (n = 3), acetaminophen (n = 2), and valproic acid (n = 2), carbamazepine (n = 1), and HD for lithium (n = 14), carbamazepine (n = 4), metformin (n = 2), theophylline (n = 2), and valproic acid (n = 1). The indications for ECTR were markedly elevated serum concentrations in acetaminophen poisoning, deep coma, hypotension, hypothermia, and respiratory failure with barbiturates, rising serum concentration and/or shock and prolonged coma with...
carbamazepine, severe acidosis after metformin, serum concentra-
tion exceeding 100 mg/L and severe symptoms with theophylline,
elevated serum concentration, shock and brain edema with val-
proate, and slurred speech, ataxia, fasciculations, memory loss,
and apathy in chronic lithium intoxication. Thrombocytopenia
occurred in 7 cases after HP, and one patient required a transfu-
sion. One patient developed pneumothorax after HD. Four
patients died (barbiturate 1, lithium 1, theophylline 1, metformin
1) and 21 patients completely recovered. Nine were transfered
(mainly to psychiatry) with sustained mild symptoms (lithium 6),
psycho-organic syndrome (theophylline 1, valproic acid 1) and
mildly elevated transaminases (acetaminophen 1).

Conclusion: Use of HP has decreased over the past 2 years, while
patients receiving HD has increased. With regard to the indica-
tions for ECTR in severe poisonings, our treatment protocols have
been consistent with EXTRIP recommendations except for lithium
intoxication where we have our own recommendations.

154. The NACSTOP trial: a multi-
centre, cluster, controlled trial
investigating the early cessation of N-
acetylcysteine in paracetamol
overdose

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Richard McNultyd, Shaun L. Greenee,
Zeff Koutsogiannise, Naren Gunjaf and
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Australia; eAustin Toxicology Service, Austin Health, Victoria,
Australia; fWestern Sydney Toxicology Service and Sydney Medical
School, University of Sydney, NSW, Australia; gMonash Toxicology
Service, Monash Emergency and School of Clinical Sciences,
Monash Health and Monash University, Victoria, Australia

Objective: Paracetamol poisoning is treated with intravenous N-
acetylcysteine (NAC). However, current standard of care takes a
"one-size-fits-all" approach. We aimed to determine if NAC can be
safely ceased after 12 hours of treatment in patients with
paracetamol poisoning and a low risk of developing hepatotox-
icity (ALT < 40 IU/L and paracetamol < 20 mg/L).

Methods: This is an ongoing multicentre, open-label cluster-con-
trolled pilot trial at six emergency departments in Australia.
Recruitment began February 2016. Inclusion criteria: single or
controlled pilot trial at six emergency departments in Australia.

Conclusion: Of 337 paracetamol overdoses receiving NAC, 75 have
been recruited so far. Median age 23 years (IQR 12,23) and 80%
female. Median time to commence NAC was seven hours post-
overdose (IQR 6,12). There was no difference in median peak ALT
(25 versus 19 IU/L) or median peak INR (1.2 versus 1.2) between
intervention and control groups, respectively. No patients devel-
oped hepatic injury or hepatotoxicity in either group. All patients
with an ALT <40 IU/L at 12 hours maintained this level at 20
hours post-initiation of NAC. No patients receiving the abbrevi-
ated regimen required restarting of NAC. Median duration of
NAC was significantly shorter in the intervention group (13 versus
20 hours, p < .0001). No patients re-presented with liver injury at
telephone follow-up 14-days post-discharge.

Conclusion: An abbreviated 12-hour NAC regimen is feasible and
likely safe for those at low risk of developing hepatotoxicity after
paracetamol overdose, and may decrease duration of hospital
stay.

155. Acute liver failure of unclear
cause? Paracetamol adducts make the
diagnosis

Michael E. Mullinsa and Laura P. Jamesb

aEmergency Medicine, Washington University School of Medicine,
Saint Louis, United States; bClinical Pharmacology and Toxicology,
Arkansas Children’s Hospital, Little Rock, United States

Objective: To illustrate the utility of paracetamol adducts assay
in a child with acute liver injury of unclear cause.

Case report: A 2-year-old girl came to the Emergency
Department (ED) when her condition worsened with 2 days of
lathargy, vomiting, and fever after 2 weeks of apparent viral
infection. Her history included perinatal anoxic brain injury result-
ing in cerebral palsy, failure to thrive (8.8 kg), recurrent ear infec-
tions, and a gastrosotomy tube for feeding and medications. Her
mother reported treating her fever with “one mill” (1 mL) of para-
acetamol elixir (160 mg/5 mL) with each dose. Abnormal laboratory
values in the ED included white blood cells 27.18 × 10⁹/L (78%
cytocytes), sodium 150 mmol/L, CO₂ 16 mmol/L, BUN 46 mg/dL,
and glucose 30 mg/dL (1.7 mmol/L). Her urinalysis and cerebral
spinal fluid were non-diagnostic. The ED did not order liver
enzymes or coagulation studies. Upon admission, her AST and
ALT were 8989 and 6338 IU/L with an INR of 4. The paracetamol
concentration was 55 µg/mL. Repeat AST and ALT were 5136 and
5646 IU/L. She underwent transfer to a regional liver transplant
center, where the intensive care team consulted both gastro-
enterology and toxicology. She was given IV N-acetylcysteine
(NAC) after transfer. Her AST and ALT after transfer were 4087 IU/
L and 1831 IU/L with INR 2.17. Paracetamol was < 5 µg/mL. Nasal
swab testing confirmed adenovirus by polymerase chain reaction
(PCR). The gastroenterology consultants concluded that she had
acute hepatitis caused by adenovirus. Her mother continued to
insist that the paracetamol dose was “one mill” (about 32 mg or
almost 4 mg/kg). Toxicology remained concerned for paracetamol
toxicity, and she continued on IV N-acetylcysteine. Hepatic ultra-
sound was normal. Organic acid screening for metabolic or mito-
dochondrial disorders was normal. Rapid consultation with a
research laboratory specializing in paracetamol protein adducts
led to testing of the original blood for paracetamol adducts by
high performance liquid chromatography with electrochemical
detection (HPLC-EC). Four samples all showed APAP-cysteine
adduct concentrations of 11 to 12 nmol/mL (normal ≤1.0 nmol/
ml). Subsequently, when asked to demonstrate 1 mL with water,
the mother filled a medicine cup with 7 mL. This volume of para-
cetamol would contain 224 mg (or about 25 mg/kg).
**Conclusion:** Paracetamol protein adduct testing identified the cause in a case of liver injury of unclear etiology.

### 156. Unintentional paracetamol overdose: 3-year analysis of patients admitted for treatment with acetylcysteine to a toxicology unit in the UK

Janice M. Pettie\(^a\), Margaret A. Dow\(^a\), Karen Osinski\(^a\), Elizabeth Macrae\(^b\), Eibhlin Brogan\(^b\), Mary Dalglish\(^b\), Euan A. Sandilands\(^a\) and James W. Dear\(^b\)

\(^a\)Clinical Toxicology Unit and National Poisons Information Service, Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom; \(^b\)Clinical Toxicology Unit, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom

**Objective:** Paracetamol (acetaminophen) is commonly taken as a single agent or in many combination products. Paracetamol is safe when taken as directed, but accidental or deliberate overdose can cause hepatotoxicity. In patients treated with acetylcysteine (NAC) for an unintentional paracetamol overdose, our aim was to determine the incidence of overdose, reason for paracetamol use, reason why the recommended dose was exceeded, and frequency of hepatotoxicity.

**Methods:** Data were obtained from (1) our inpatient paracetamol overdose database and (2) discussion with the patient about overdose of paracetamol from 28 July 2014 to 27 July 2017.

**Results:** In the 3-year period, 1812 patients received NAC treatment for paracetamol overdose. Of these, 246 (14%) were due to an unintentional overdose. The reasons for paracetamol use were: dental pain (n = 99, 40% of total unintentional overdose); musculoskeletal pain (n = 54, 22%); abdominal pain (n = 30, 12%); other pain (n = 31, 12%); and viral symptoms (n = 24, 10%). Six patients ingested excess co-codamol for the codeine content. The reason the recommended dose was exceeded was available in 180 patients. The reasons were: unaware excess may cause harm (n = 76, 42%); unaware multiple products contained paracetamol (n = 58, 32%); unaware of recommended dose (n = 36, 20%); unaware of the frequency of dosing in a 24-hour period (n = 27, 15%). Admission blood results demonstrated that 61 patients had an ALT > 50 IU/L and 16 had an INR of > 1.3. Six patients had a peak ALT > 1000 IU/L.

**Conclusion:** Hospitalisation for treatment of an unintentional paracetamol overdose is common. Dental pain was the single most common cause for overdose. A small number of our patients developed hepatotoxicity, although all recovered. These findings highlight the need for a public health approach to reduce unintentional overdose. Clearer labelling of products and educational initiatives by dentists, doctors, nurses, and pharmacists about safe dosage, use of multiple products and the dangers associated with exceeding the maximum daily dose is required.

### 157. Delayed absorption of paracetamol due to co-ingestion of a bezoar-forming pharmaceutical

Katrin Faber\(^a\), Martin Walter\(^b\), Christine Rauber-Lüthy\(^c\), Tobias Huebner\(^c\), Hugo Kupferschmidt\(^a\) and Katharina E. Hofer\(^a\)

\(^a\)National Poisons Centre, Tox Info Suisse, Associated Institute of the University of Zurich, Zürich, Switzerland; \(^b\)Department of Internal Medicine, Kantonsspital Muensterlingen, Muensterlingen, Switzerland; \(^c\)Department of Anesthesiology and Intensive Care, Kantonsspital Muensterlingen, Muensterlingen, Switzerland

**Objective:** Altered toxikokinetics have been reported in paracetamol overdose, and several factors including large ingestions, poor solubility, and the co-ingestion of gut-slowing medications such as opioids or anticholinergic agents, may be involved [1]. We present two comparable paracetamol overdoses in the same patient, but with different co-ingestants resulting in different pharmacokinetic patterns of paracetamol.

**Case report:** A 48-year-old female with major depression and ethanol abuse presented at the Emergency Department twice within 8 months with intentional ingestion of 65 g paracetamol each time. See Table 1 for details of each admission. Absorption of paracetamol varied remarkably in the two episodes with a maximum plasma concentration after 6 hours and 12 hours, respectively. Consistent with the consequences of bezoar formation, the patient experienced typical signs of quetiapine toxicity (coma, hypotonia) at the time of the delayed paracetamol peak, and the phenomenon of “line-crossing” in the nomogram was observed in this episode. Elimination of paracetamol was comparable, and followed expected patterns in both episodes. Each overdose resulted in severe hepatotoxicity, despite early decontamination and prolonged antidotal treatment with N-acetylcysteine. The patient recovered without sequelae, and was discharged home 8 and 9 days after admission, respectively.

**Conclusion:** Delayed absorption of paracetamol may occur when co-ingested with bezoar-forming pharmaceuticals such as certain

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**Table 1. Co-ingestants, pharmacokinetic parameters of paracetamol, hepatic values, and clinical course in two episodes of paracetamol ingestion in the same patient.**

<table>
<thead>
<tr>
<th>Episode</th>
<th>Parameters</th>
<th>Co-ingestants</th>
<th>Hepatic Values</th>
<th>Clinical Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Paracetamol dose</td>
<td>65 g (1 g tablets, IR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Co-ingestants</td>
<td>2.5 g quetiapine (XR*)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 g quetiapine (IR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pipamperone (IR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ethanol (1.42%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Activated charcoal (hours after ingestion)</td>
<td>1 g/kg (1 h), MDAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NAC onset of therapy</td>
<td>1 h after ingestion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial paracetamol concentration (time after ingestion)</td>
<td>606 µmol/L (6 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximal paracetamol concentration (time after ingestion)</td>
<td>2097 µmol/L (12h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial aspartate aminotransferase (AST)</td>
<td>16 U/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peak AST (time after ingestion)</td>
<td>9221 U/L (80 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symptoms at presentation</td>
<td>Drowsiness</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Signs and symptoms during clinical course</td>
<td>Late and progressive impairment of consciousness to GCS 9, and hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Paracetamol dose</td>
<td>65 g (1 g tablets, IR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Co-ingestants</td>
<td>1 g quetiapine (IR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>800 mg tramadol (XR)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>1.3 g diclofenac (XR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Activated charcoal (hours after ingestion)</td>
<td>1 g/kg (2.5 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NAC onset of therapy</td>
<td>2.5 h after ingestion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial paracetamol concentration (time after ingestion)</td>
<td>2061 µmol/L (4 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximal paracetamol concentration (time after ingestion)</td>
<td>2532 µmol/L (6 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial aspartate aminotransferase (AST)</td>
<td>19 U/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peak AST (time after ingestion)</td>
<td>6607 U/L (8 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symptoms at presentation</td>
<td>Drowsiness, hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Signs and symptoms during clinical course</td>
<td>Rapid deterioration to GCS 7, oxygen saturation 82%; patient regained consciousness with naloxone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)known to form bezoar [2].

extended release quetiapine products [2]. In these cases, an adaptation of gastrointestinal decontamination strategy, monitoring of paracetamol concentration with repeated determinations, and adjustment of the N-acetylcysteine treatment regimen should be considered [1].

References


158. Paracetamol overdose in pregnancy: a case report

Dóra O. Jakab, Csaba Pap, Ágnes Bakos, Viktor A. Ágoston and István Elek
Emergency Department and Clinical Toxicology, Péterfy Sándor Street Hospital-Clinic and Accident-Emergency Centre, Budapest, Hungary

Objective: Paracetamol is a frequently used pain-killer in pregnancy. We present a case with severe paracetamol intoxication in the second trimester of pregnancy.

Case report: A 22-year-old woman in the 24th week of pregnancy was presented to her local Emergency Department after taking 20 tablets of 500 mg paracetamol because of lower abdominal pain 24 hours previously. The patient had severe nausea, vomited several times, and complained of right upper quadrant abdominal pain 24 hours previously. The patient started to recover. Meanwhile, her serum bilirubin started to increase and she developed icterus. The patient had a negative pregnancy reaction rates in NAC-treated patients using the traditional 3-bag regimen (150 mg/kg in the first hour) versus a reduced bolus rate of 50 mg/kg in the first hour. Search terms in PubMed and Embase were (“paracetamol” AND “acetylcysteine”) AND “adverse”. Peer-reviewed human research comparing the two protocols and reporting adverse reaction rates were included. A meta-analysis comparing adverse reaction rates to NAC between the traditional 3-bag protocol and a 2-bag protocol was conducted.

Results: Our systematic review returned 804 articles after duplicates were removed. Three studies remained after exclusion criteria were applied, with a total of 1283 patients (481 using the 2-bag protocol and 802 using the 3-bag) [1–3]. We included the SNAP study, which although a different design with a shorter 12-hour protocol, it also had an initial NAC infusion rate of 50 mg/kg/h in the 2-bag protocol [2]. All 3 studies found a decrease in adverse reactions that favoured the 2-bag protocol (odds ratio 0.36, 95% CI 0.24, 0.54). The combined result is nearly a 3-fold lower risk of adverse reaction to NAC with the reduced initial bolus rate of 50 mg/kg in the first hour compared with the traditional 3-bag protocol of 150 mg/kg in the first hour.

Conclusion: An initial rate of 50 mg/kg/h NAC infusion results in a reduction in adverse reactions even in studies, which underestimate the true rate of adverse reactions (especially for undocumented transient, minor events). The meta-analysis further supports the finding that a lower initial rate of NAC infusion results in a reduction in adverse reactions even in studies with differing methodologies. In light of these findings, a review of NAC infusion guidelines is warranted.

References

160. Non-anion gap acidosis in significant salicylate poisoning: mind the non-gap!

Elie Harmouche, Mark Su and William Chiang

Objective: Both acute and chronic salicylism constitute a significant cause of morbidity and mortality in poisoned patients. While some authors have suggested that there is no need to screen for salicylate toxicity in the absence of a history or an anion gap acidosis, here we present a case of non-anion gap acidosis in a patient with significant salicylate poisoning.

Case report: A 59-year-old man with no known significant past medical history was brought to the Emergency Department with one minute with shallow respirations, temperature of 37.3 °C, blood pressure 129/79 mmHg, heart rate 81 bpm, and oxygen saturation 94% on room air. Venous blood gas analysis showed: pH 7.4 and pCO2 28 mmHg. Initial blood tests revealed: sodium 135 mmol/L, potassium 4.6 mmol/L, chloride 105 mmol/L, bicarbonate 19 mmol/L, blood urea nitrogen 19 mmol/L, creatinine 132 µmol/L, glucose 6.7 mmol/L, and anion gap 11 mmol/L (normal range 8–16 mmol/L). He was intubated and a subsequent arterial blood gas showed: pH 7.14 and pCO2 77 mmHg. Blood salicylate concentration obtained on initial screening was 0.61 mmol/L (therapeutic < 0.22 mmol/L). Intravenous bicarbonate infusion was started, he was given multi-dose activated charcoal and hemodialysis performed. He was extubated five days after admission and medically cleared on day 7 of admission.

Conclusion: Significant salicylate ingestion is a well-recognized cause of elevated anion gap metabolic acidosis. Sporer et al. suggested that there is no need to screen for salicylate ingestion in the absence of an anion gap acidosis [1]. However, here we demonstrate the presence of a non-anion gap metabolic acidosis associated with a clinically severe salicylate ingestion. There are multiple explanations for this phenomenon. Multiple chemistry analyzers including the one used at our hospital uses a proprietary ion-sensitive chloride electrode. With this analyzer, salicylate concentrations of 0.145 mmol/L and more than 0.43 mmol/L are known to cause a 4% and 15% false increase in chloride concentrations, respectively. This can erroneously cause a normal or even negative anion gap. In addition, acute salicylism occasionally causes proximal renal tubular dysfunction that can contribute to a non-anion gap acidosis. Clinicians should be compulsive about screening for salicylates in undifferentiated poisoned patients as routine chemistry tests may be insufficient to show salicylate toxicity.

Reference


161. Poisonings with two new antiepileptic drugs: lacosamide and perampanel

Romain Torrents, Bastien Domange, Katharina Von Fabeck, Corinne Schmitt, Susanna Davoust, Mathieu Gliaza, Audrey Boulamer, Luc De Haro and Nicolas Simon

Objective: Lacosamide is a third-generation antiepileptic drug that was first introduced into clinical practice in 2008 [1]. Perampanel is among the latest new antiepileptic drugs approved in more than 45 countries, including the US and Europe [2]. We report four cases of poisoning with these new antiepileptic drugs: three with lacosamide, including a child, and one with perampanel.

Case series: One patient developed central nervous system signs after 280 mg of lacosamide whereas another remained well after 1400 mg. A 6-year-child also developed mild central nervous system signs after 300 mg. Recovery occurred within 24 hours after lacosamide whereas a 16-year-old male had agitation lasting 5 days after ingestion of perampanel (Table 1).

Conclusion: Few cases of poisonings with these antiepileptic drugs are described. Perampanel can induce drowsiness and agitation similar to our case report, but it can also cause dysarthria, mild tiredness, misperception, disorientation, and misjudging of situations [3]. Lacosamide can induce drowsiness, nausea, dizziness, and ataxia, in addition to heart rhythm disorders, and death has been reported after ingestion of 7 g [4]. Those four observations allow us to better understand the toxicity of two new antiepileptic drugs and to improve the management of such cases.

References


Table 1. Four cases of poisoning with new anti-epileptic drugs.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Drug</th>
<th>Circumstances</th>
<th>Clinical presentation</th>
<th>EKG</th>
<th>Blood concentration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>M 6 years</td>
<td>Lacosamide</td>
<td>Accidental 300 mg</td>
<td>Drowsiness, nausea, ataxia, dizziness</td>
<td>Normal</td>
<td>22.44 µg/mL</td>
<td>Recovered without sequelae after 24 hours of medical care</td>
</tr>
<tr>
<td>F 43 years</td>
<td>Lacosamide</td>
<td>Self-poisoning 1400 mg</td>
<td>Asymptomatic</td>
<td>Normal</td>
<td>Not done</td>
<td>Recovered without sequelae after 24 hours of medical care</td>
</tr>
<tr>
<td>F 44 years</td>
<td>Lacosamide</td>
<td>Self-poisoning 280 mg</td>
<td>Drowsiness, Glasgow Coma Scale (GCS) 14, diplopia</td>
<td>Normal</td>
<td>Not done</td>
<td>Recovered without sequelae after 24 hours of medical care</td>
</tr>
<tr>
<td>M 16 years</td>
<td>Perampanel</td>
<td>Self-poisoning 112 mg</td>
<td>Drowsiness, agitation</td>
<td>Normal</td>
<td>Not done</td>
<td>Persistent agitation requiring sedation and medical care for 5 days</td>
</tr>
</tbody>
</table>
Globally, polypharmacy increases the risk of ADRs, which is why the importance of timely, evidence-based surveillance cannot be understated. The surveillance system in place has been instrumental in identifying the problem of polypharmacy and its associated ADRs. The surveillance system has been successful in identifying the problem and providing solutions to mitigate it. The identification of ADRs is critical in reducing the incidence of polypharmacy-related ADRs. The surveillance system has been successful in identifying the problem and providing solutions to mitigate it. The identification of ADRs is critical in reducing the incidence of polypharmacy-related ADRs.

References

164. Estimation of the dialysis time for patient with extremely high ethylene glycol concentration

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Objective: Intermittent haemodialysis is the most efficient method of rapidly lowering serum ethylene glycol and toxic metabolites. Adequate calculation of the duration of dialysis can shorten the treatment time significantly. We describe a case with an extremely high serum ethylene glycol concentration where the dialysis time was calculated with a modified equation [1].

Case report: A 49-year-old alcoholic man was brought in our department from a local hospital by ambulance. He ingested 0.5 L of ethylene glycol and alcohol in order to commit suicide. On admission to our hospital, he was awake, but disoriented. His vital signs were blood pressure 150/90 mmHg, heart rate 100/min and temperature 36.3 °C. A blood gas analyzer showed pH 7.356, pCO₂ 45 mmHg, pO₂ 59.2 mmHg, bicarbonate 24.6 mmol/L, and potassium 4.07 mmol/L. The ethylene glycol and ethanol serum concentrations in a sample received from the local hospital were 240.59 mmol/L and 1.66%, respectively. He was given 10% ethanol solution 2 mL/kg/hour, thiamine, pyridoxine, folic acid intravenously and 3 hours after admission haemodialysis was initiated. Owing to his extremely high serum concentration, we reduced the target toxin concentration to 3 mmol/L. We calculated the dialysis duration (T) according to modified equation from Hirsch et al. [1] T(hour) = −V ln(3/A) /0.06k, where V (47 litre) is the Watson estimate of total body water, A is the initial toxin concentration (154.28 mmol/L) and k is 80% of the manufacturer specified dialyser urea clearance (255.2 mL/min) at the initial observed blood flow rate. The calculated dialysis time was 12 hours. During the dialysis, the patient became agitated, necessitating sedation, endotracheal intubation, and mechanical ventilation. There were no other complications. At the end of the dialysis, the serum ethylene glycol concentration was 4.47 mmol/L. The antidotal therapy was continued for one day. After stopping the alcohol therapy, he had alcohol withdrawal symptoms and required treatment for bronchitis, but his renal function remained intact. He was discharged from intensive care on the 5th day after admission.

Conclusion: Using the modified equation provides a good estimation of the required dialysis time in cases of ethylene glycol poisoning. It seems a better approach than serum ethylene glycol concentrations when antidotal therapy is not necessary and could reduce treatment time and costs.

Reference

165. Epidemiology of organ failure in poisoned patients: a 16-year experience of an Italian Intensive Care Unit

Roberto Zoppellaria, Evelina Fortinia, Ilaria Farinellia, Giulia Dallocchioa, Anna Pinamontia, Angela Ricci Frabattistab, Anna Talaricoc and Rosa M. Gaudioc

Objective: Poisoning can induce organ failure and require admission to the Intensive Care Unit (ICU). We studied ICU usage in poisoned patients and the related features.

Methods: A 16-year (1 July 2001 to 30 June 2017) prospective study including all patients admitted to our adult ICU with a main diagnosis of acute poisoning. We defined three criteria for ICU admission: the presence of vital function impairment (group 1), the perception that significant organ dysfunction could appear in asymptomatic patients on the basis of toxicokinetics or toxicodynamics (group 2), a clinical judgment for intensive observation in mildly symptomatic patients (group 3).

Results: Poisoned patients admitted to ICU over the study period totalled 171 (2.8% of admitted patients) and 57% involved miscellaneous agents. All toxic agents were confirmed by toxicological laboratory analysis. The number of patients in each group was 135 for group 1, 13 for group 2 and 23 for the third. The average length of ICU stay (in days) was 3.9, 2.1, and 1.5 (p < .01 compared to group 1 with Wilcoxon test), respectively. Fifteen patients died: three for paraquat ingestion, five due to a delay between poisoning and resuscitation (two 85-year-old patients for neurodepressant brain injury, one patient for heroin overdose, one for ethylene glycol, one for metoprolo), one for aspiration pneumonia as a consequence of an organophosphate ingestion, one for metoprolol ingestion, two due to hydrochloric acid ingestion and three with metformin intoxications. For group 1, the poisons involved were mainly benzodiazepines, which were found at toxic concentrations in 65 patients. The main causes for impairment of vital functions were respiratory failure requiring ventilatory support (84.4%), severe cardiovascular toxicity (5.2%), neurological dysfunction with a Glasgow Coma Scale <11 (7.4%) and metabolic failure (2.2%). Group 2 toxins were paracetamol (n = 3), acetaminophen (n = 2), digoxin (n = 2), paraquat (n = 2), ethylene glycol (n = 2), metoprolol (n = 1), and hydrochloric acid (n = 1); paraquat, metoprolol, and hydrochloric acid caused death. All patients in group 3 had a good recovery and only one required ventilatory support owing to aspiration pneumonia.

Conclusion: A rational approach to ICU use is described: many poisonings (78.9%) presented an immediate life-threatening nature, while for patients who were asymptomatic or minimally symptomatic at admission, a short ICU stay was chosen for observation and treatment due to an unpredictable clinical course.

166. Clinical features and pharmacokinetic analysis in acute olanzapine poisoning in patients admitted to the intensive care unit

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Objective: Olanzapine, an atypical second generation antipsychotic drug, is increasingly prescribed due to its effectiveness in chronic psychosis with improved tolerance in comparison to the first generation antipsychotic drugs. Whereas side-effects are well-reported, acute poisonings remain less well documented.

Methods: We conducted a retrospective single-center descriptive study including all patients admitted to the intensive care unit (ICU) of a University Hospital between January 2000 and June...
Objective: To review a case series of four patients with intoxication considered for extracorporeal membrane oxygenation (ECMO)-treatment with emphasis on long-term survival.

Case series: Four patients presented with severe intoxication after ingestion of cardiovascular drugs or tricyclic antidepressants. The first three patients presented with hemodynamic shock resistant to conventional therapy and ECMO was initiated. All of these patients survived intensive care and were eventually discharged from the hospital. At 1-year follow-up, two of the patients were reported dead with suspected out-of-hospital overdose as the cause of death. Our fourth patient suffered uncontrollable seizures and cardiovascular collapse. Owing to a previous difficult psychiatric history, the patient was declined ECMO and did not survive (Table 1).

Conclusion: The efficacy and short-term survival of intoxicated patients treated with ECMO is considered to be satisfactory [1,2]. In our intensive care unit data and previous researches, the difference between in-hospital and long-term mortality of intoxicated patients is notable (1–2% and 9–11%, respectively) even though most are young and somatically healthy [3]. It is essential to take into account the patient’s psychiatric health and possible effect on long-term survival prior to making a decision on the use of resource-consuming ECMO. The cost-effectiveness of ECMO in this patient group is a matter in need of further evaluation.

References

Table 1. Treatment and outcome in 4 patients with severe intoxication treated with or without extracorporeal membrane oxygenation (ECMO).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Substance</th>
<th>Previous suicide attempts</th>
<th>Conventional treatments given</th>
<th>Cardiopulmonary resuscitation</th>
<th>ECMO</th>
<th>ICU</th>
<th>Dialysis</th>
<th>Recovery to discharge</th>
<th>1 Year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 y, male</td>
<td>CCI, BB, nicotine</td>
<td>1</td>
<td>Glucagon, calcium, norepinephrine, adrenaline, vasopressin</td>
<td>Yes</td>
<td>2 days</td>
<td>10 days</td>
<td>Yes</td>
<td>Yes</td>
<td>Death</td>
</tr>
<tr>
<td>45 y, female</td>
<td>CCI, BB, ACEI</td>
<td>6</td>
<td>Glucagon, calcium, norepinephrine, adrenaline</td>
<td>No</td>
<td>1.5 days</td>
<td>3 days</td>
<td>Yes</td>
<td>Yes</td>
<td>Death</td>
</tr>
<tr>
<td>33 y, female</td>
<td>CCI, BB, ACEI</td>
<td>3</td>
<td>Glucagon, calcium, insulin/dextrose, norepinephrine adrenaline, atropine, vasopressin, pacemaker Adrenaline</td>
<td>Yes</td>
<td>4 days</td>
<td>13 days</td>
<td>Yes</td>
<td>Yes</td>
<td>Alive</td>
</tr>
<tr>
<td>27 y, female</td>
<td>TCA</td>
<td>23</td>
<td>Adrenaline</td>
<td>Yes</td>
<td>None</td>
<td>0 days</td>
<td>No</td>
<td>No</td>
<td>Death</td>
</tr>
</tbody>
</table>

CCI: calcium channel inhibitor (amlodipine); BB: beta blocker (metoprolol, propranolol); ACEI: angiotensin converting enzyme inhibitor (ramipril); TCA (amitriptyline).
in comparison to first generation drugs. Only few data regarding NGAD poisoning have been published. Our objective was to report the clinical and biological toxicities attributed to NGAD overdose and, where possible, describe NGAD pharmacokinetics.

**Methods:** We conducted a retrospective single-center descriptive study including all NGAD-poisoned patients admitted to the intensive care unit (ICU) of a University Hospital over 10 years (2007–2017). The usual demographic, clinical, toxicological, and outcome data were collected from the patients’ records. Non-compartmental pharmacokinetics modeling was obtained using WinNonlin v. 5.1 software, Certara.

**Results:** Twenty-one patients (9 males/12 females, aged 44 years [33; 51]) (median [percentiles 25, 75]; depressive patients, 76%) were included in the study. The NGADs included were lamotrigine (n = 10, 48%), levetiracetam (n = 5, 24%), topiramate (n = 4, 19%), lacosamide (n = 1, 5%) and oxcarbazepine (n = 1, 5%). Most cases involved a multi-drug ingestion (n = 20, 95%). On ICU admission, patients presented consciousness impairment (33%; Glasgow coma score 11 [3; 15]), hypotension (systolic blood pressure 104 mmHg [99; 119]) with gastrointestinal symptoms (n = 6, 28%), seizures (n = 4, 19%), vertigo (n = 3, 14%), fatigue (n = 2, 9%), agitation (n = 2, 9%), headache (n = 1, 5%), diplopia (n = 1, 5%), nystagmus (n = 1, 5%) and myoclonus (n = 1, 5%). Biological disturbances included increased plasma lactate concentrations (2.9 mmol/L [1.5; 5.9]), moderate hypoxemia (PaO2/FiO2 242 [160; 398]), mild hypokalemia (3.2 mmol/L [2.6; 3.7]), mild increased alanine aminotransferase (49 IU/L [28; 99]) and rhabdomyolysis (creatine phosphokinase 271 IU/L [65; 653]).

Management included mechanical ventilation (n = 16, 76%), catecholamine infusion (n = 8, 38%), and 8.4% sodium bicarbonate infusion (n = 5, 24%). One lacosamide-intoxicated patient died in relation to membrane-stabilizing effects resulting in acute cardiac failure. Limited alterations in the pharmacokinetic parameters (half-life and clearance) were observed in comparison to the pharmacological situation, highlighting the important consequences of poisoning-induced organ failure.

**Conclusion:** Despite marked safety at pharmacological doses, NGAD overdose may result in life-threatening poisoning requiring ICU admission and even fatality. The pharmacokinetic parameters seem more related to the blood volume and organ functions in the poisoned patient rather than to the ingested NGAD dose.

**170. Acute amitriptyline and clomipramine poisoning in the intensive care unit: clinical presentation and pharmacokinetic modelling**

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**b**Toxicology Laboratory, Lariboisière Hospital, Paris-Descartes University, Paris, France

**Objective:** The tricyclic antidepressants, amitriptyline (AMI), and clomipramine (CLO), are responsible for severe poisonings with anticholinergic encephalopathy, seizures, and cardiotoxicity attributed to membrane stabilizing effects. Their prescriptions have decreased over 30 years following the marketing of the serotonin reuptake inhibitor (SRI) antidepressants. Our objective was to report a series of AMI and CLO poisonings in the era of SRI supremacy with description of the clinical manifestations and pharmacokinetic data.
Methods: We conducted a retrospective single-center descriptive study including all AMI- and CLO-poisoned patients admitted to an intensive care unit (ICU) in a University Hospital over a 16-year period (2000–2016), evidenced by plasma AMI and CLO concentrations in the toxic ranges. Non-compartmental analysis of AMI and CLO pharmacokinetics was performed using WinNonlin v. 5.1 software from Certara. Comparisons were performed using chi-squared and Mann–Whitney tests as required.

Results: Sixty patients (age 49 years [42; 75]; 68% females/32% males; [75% with past depression history]) were included. AMI and CLO overdose resulted from self-ingestion in a suicide attempt. AMI (dose 1.5 g [1.0; 2.6]; plasma concentration 0.7 mg/L [0.4; 1.4]) was responsible for 3 times more intoxications than CLO (dose 3.0 g [1.6; 5.6]; plasma concentration 0.7 mg/L [0.5; 1.4] with 72% versus 28%). The patients presented consciousness impairment (Glasgow coma score 3 [3; 9]), tonic-clonic seizures (12%), mydriasis (23%), QT lengthening (55%), and QRS enlargement (50%) on the electrocardiogram (ECG). AMI was responsible for a significantly deeper coma (p < .0001) but fewer seizures than CLO (p = .02). Three patients (5%) died. Based on a univariate analysis, factors associated with death were cardiac arrest onset (p = .003), elevated plasma lactate concentration (p = .005), low arterial pH (p = .007), reduced PaO2/FiO2 ratio (p = .007), and prothrombin ratio (p = .008), increased aspartate aminotransferase (p = .009), alanine aminotransferase (p = .01), and serum creatinine concentration (p = .01) as well as marked catecholamine infusion rate (p = .02). The pharmacokinetic study showed significant increase in AMI (43 h versus 24 h) and CLO (55 h versus 21 h) elimination half-lives in overdose compared to pharmacological conditions, highlighting the contribution of organ failure to the delayed elimination of both toxicants.

Conclusion: Cases of AMI and CLO poisoning did not disappear and are still responsible for significant morbidity and mortality. AMI was responsible for longer coma with fewer seizures in comparison to CLO. AMI and CLO elimination half-lives were significantly prolonged in overdose due to organ failure.

171. Cardiac arrest following severe autointoxication with chloroquine

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Objective: We present a patient with successful treatment in the acute phase of severe intoxication with chloroquine.

Case report: A 27-year-old female called the emergency services and reported a suicide attempt with medication. Prescribed medications were clonidine, dextroamphetamine, flurazepam, and propoxyphene. Later, the family reported that she frequently bought medicines online. Upon arrival of the paramedics, she was fully conscious with normal vital signs. While entering the ambulance, she became asystolic and cardiopulmonary resuscitation (CPR) was performed for 19 minutes. Upon arrival to the hospital, very broad QRS-complexes (326 ms) were observed, in all probability because of an intoxication caused by an unknown substance. Sodium bicarbonate 100 mL 8.4% and lipid emulsion 20% (100 mL bolus followed by 400 mL infusion) were administered via an intravenous needle. Shortly after arrival, she lost circulation again and CPR was restarted according to protocol with addition of 950 mg calcium gluconate by the intraosseous route. Shortly after this, her hemodynamics status stabilized and cardiac contractility improved. It is possible that the first dose of lipid emulsion remained in the bone marrow compartment. Results of toxicological analysis showed a severe intoxication with chloroquine (concentration 3 hours after ingestion 16.1 mg/L; toxic: >0.5 mg/L) and a positive benzo diazepines blood test. High-dose diazepam was added based on literature reports, resulting in further improvement of cardiac contractility and it became possible to cease treatment with vasopressors. Alkalisation was restarted as soon as potassium stabilised after supplementation. After 60 hours, cardiac conduction normalised and therapy with sodium bicarbonate and diazepam was discontinued. On day 7 of intensive care treatment, she was weaned from mechanical ventilation. A few days later, she was transferred to a nursing home for further treatment.

Conclusion: In this case, we were challenged with a severe intoxication with prescription medication that was illegally bought online. Successful treatment with sodium bicarbonate and intravenous lipid emulsion was started before the substance was identified.

172. Kinetics of hydroxychloroquine following massive overdose

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Objective: Management of hydroxychloroquine overdoses is based on chloroquine toxicity. We report a patient with a massive overdose manifested by profound hypokalemia and ventricular dysrhythmias and describe hydroxychloroquine kinetics following the highest serum concentration recorded in the literature.

Case report: A 20-year-old woman (60 kg) with a history of depression presented to the Emergency Department one hour after ingesting 36 g of hydroxychloroquine. Vital signs were systolic blood pressure 66 mmHg/palpation, heart rate 115/min, respiratory 18/min, oxygen saturation 100% (room air), and glucose 5.1 mmol/L. She was given normal saline fluids and epinephrine intravenously (40 µg twice), and intubated. Diazepam (2 mg/kg IV) was administered via an intravenous (400 µg twice), and intubated. Diazepam (2 mg/kg IV) was administered via an intravenous infusion rate (p = .02). The pharmacokinetic study showed significant increase in AMI (43 h versus 24 h) and CLO (55 h versus 21 h) elimination half-lives in overdose compared to pharmacological conditions, highlighting the contribution of organ failure to the delayed elimination of both toxicants.

Conclusion: Cases of AMI and CLO poisoning did not disappear and are still responsible for significant morbidity and mortality. AMI was responsible for deeper coma with fewer seizures in comparison to CLO. AMI and CLO elimination half-lives were significantly prolonged in overdose due to organ failure.
Serial hydroxychloroquine concentrations over the first 24 hours demonstrated apparent first order elimination with a half-life of 11.6 hours (previously reported 15.5–31 hours in overdose). After 200 mEq of potassium chloride in the first 12 hours, her potassium normalized (4.0 mmol/L). During that time, she had multiple episodes of non-sustained ventricular tachycardia requiring lidocaine. Serial ECGs demonstrated continued widening of her QRS and QTc even with normal serum potassium and magnesium concentrations. The ECG normalized 36 hours post-ingestion. She was extubated on hospital day 3 and recovered fully.

**Conclusion:** We present a case of a massive hydroxychloroquine overdose treated successfully with early intubation, epinephrine, high-dose diazepam, aggressive electrolyte repletion, and lidocaine. Abnormal cardiac conduction and dysrhythmias were present even after correction of electrolyte abnormalities. The half-life of hydroxychloroquine was 11.6 hours, which was shorter than previously described and is likely explained by a two-compartment model of hydroxychloroquine and represents the distribution phase of the drug into tissue and not true elimination from the body.

### 173. Intentional injection with high dose insulin degludec resulting in prolonged hospitalization and suspected insulin edema

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**Objective:** Insulin degludec (IDeg) is a novel insulin with an ultra-long action exceeding 42 hours at therapeutic doses. IDeg forms soluble multihexamers in subcutaneous tissue from which a constant release into the blood is achieved. Insulin edema is a rare condition that can affect patients after the introduction or escalation of insulin treatment. Insulin edema leads to fluid retention but pathologic glycogen accumulation may also be involved [1]. According to our knowledge, there are no case reports describing overdose with IDeg or insulin intoxications resulting in insulin edema. We present a case with suspected insulin edema and prolonged need for large quantities of IV glucose after an IDeg overdose.

**Case report:** In a suicide attempt, a 33-year-old non-diabetic woman injected 3000–6000 units of her partner’s IDeg. Equipped with a blood glucose meter, she managed to avoid severe hypoglycemia for 5 days by an almost constant intake of fast-acting carbohydrates. Eventually, she could not stay awake and worried about her recent weight gain of 11 kg, so she called the ambulance service. On initial presentation, hypoglycemia with blood glucose of 1.3 mmol/L (23.4 mg/dL) was present. Boluses of 30% glucose were given about her recent weight gain of 11 kg, so she called the ambulance service. On initial presentation, hypoglycemia with blood glucose of 1.3 mmol/L (23.4 mg/dL) was present. Boluses of 30% glucose were given.

**Conclusion:** Eventually, she could not stay awake and worried about her recent weight gain of 11 kg, so she called the ambulance service. On initial presentation, hypoglycemia with blood glucose of 1.3 mmol/L (23.4 mg/dL) was present. Boluses of 30% glucose were given. Eventually, she could not stay awake and worried about her recent weight gain of 11 kg, so she called the ambulance service. On initial presentation, hypoglycemia with blood glucose of 1.3 mmol/L (23.4 mg/dL) was present. Boluses of 30% glucose were given.

In non-diabetic patients, glucose-stimulated endogenous insulin release may contribute to prolonged symptoms. We also describe the first suspected case of insulin edema syndrome after acute insulin overdose.

**Reference**


### 174. Insulin overdose: a systematic review of case reports with focus on clinical course, complications and experimental treatment option

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**Objective:** Large overdose of insulin can lead to protracted poisoning and encompass a risk of severe hypoglycemia, but there is little evidence to guide clinicians on how to treat these patients. We aimed to systematically search, compile, and review the existing case reports on insulin overdose with a focus on clinical course and treatment options.

**Methods:** We systematically searched (PubMed, Embase, Cochrane, and PROSPERO databases for case reports on insulin overdose published between 1986 and 2017. We excluded autopsy reports, non-English language manuscripts, and case reports published only as conference abstracts. We extracted data for analysis including: age, sex, diabetes, co-morbidity, insulin-pharmacokinetic variables, arrival symptoms, variables on hospitalisation, treatment (IV glucose, glucagon, octreotide, surgical incision, hydrocortisone, and other), acute complications, and long-term complications.

**Results:** Of the 1523 published articles, we included data from 37 manuscripts including 40 cases of insulin overdoses. Of these cases, 83% (n = 33) concerned solo insulin overdoses with a median, total insulin dose of 900 international units (IU) (range 26 to 4,800 IU) and all but one case requiring hospitalisation (n = 39). Median hospitalisation time was 96 hours (range 12–721 hours) with about one-third requiring admission to the intensive care unit (n = 14). First-line treatment was intravenous (IV) glucose treatment in 92% (n = 36) of cases. In addition, we identified several adjunctive treatment options such as the use of glucagon IV or intramuscular (IM), octreotide IV or IM, surgical excision, hydrocortisone IV, and oral intake of complex carbohydrates. The most prevalent complications were intermittent, cerebral impairment (n = 26), and hypokalemia in 43% (n = 17) of cases with a median of 3.1 mmol/L (range 2.2–3.5 mmol/L). Other complications included lowered plasma concentrations of calcium, magnesium, and phosphate, various forms of hepatotoxicity (storage hepatomegaly, acute hepatitis) or cardiac conduction disturbances (QT prolongation, arrhythmias, perhaps secondary to electrolyte disturbances). Long-term consequences were rare with only one case of lasting, hypoglycemic encephalopathy, and one death.

**Conclusion:** Following massive insulin overdose, in-hospital treatment with IV glucose may be needed for days and up to a week. Monitoring of electrolytes, hepatic, and cardiac function is important. Experimental treatment options (i.e., administration of complex oral carbohydrate, glucagon, glucocorticoid, and surgical excision) may be considered in addition to glucose administration. Finally, even cases with a clinical presentation of severe hypoglycemia and neurologic complications may have a favorable outcome with appropriate pre- and in-hospital treatment.
175. Refractory bradycardia and heart rate-dependent hypotension following verapamil and telmisartan overdose responding to emergency transvenous cardiac pacing

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Objective: Verapamil overdose can result in life-threatening shock, which may be exacerbated by refractory bradycardia and rate-dependent poor cardiac output. Emergency cardiac pacing has been rarely reported to effectively increase heart rate and blood pressure (BP). We report a case of electrical cardiac pacing-responsive hypotension in a mixed overdose.

Case report: A 65-year-old female with chronic obstructive pulmonary disease (COPD) and hypertension, presented 12 hours after overdose, including extended-release verapamil (7.2 g) and telmisartan-hydrochlorothiazide (1680/525 mg). She presented with pulse 30 bpm and systolic BP 80 mmHg, peripherally vasodilated. Haemodynamic status deteriorated on arrival, with profound bradycardia (20/min) and episodes of pulseless electrical activity (PEA)-asystolic arrest requiring intermittent external cardiac massage. Resuscitation included endotracheal intubation, crystalloid resuscitation, atropine, calcium, glucagon, adrenaline, and isoprenaline boluses, vasoactive agents (adrenaline, noradrenaline, and isoprenaline) and high-dose insulin/eglycaemia. Bedside transthoracic echocardiogram demonstrated good cardiac contractility, suggesting peripheral vasodilation and heart rate-dependent hypotension. Bradycardia (20–30/min) with rate-related hypotension (80/35 mmHg) persisted despite pharmacotherapy. Transcutaneous cardiac pacing improved heart rate and BP (103/45 mmHg) and a transvenous pacing wire was inserted with good capture. Mean arterial pressure was maintained >65 mmHg with paced-rate of 80/min and noradrenaline and vaso-pressin infusions. End organ perfusion also improved with cardiac pacing. BP fell when pacing rate was reduced. She recovered from her overdose, but died 9 days later from unrelated respiratory sepsis.

Conclusion: There is limited literature on emergency cardiac pacing in the treatment of calcium-channel-blocker overdose-related hypotension or peri-arrest bradycardia [1]. In our case, significant hemodynamic compromise resulted from verapamil-induced bradycardia and hypotension from the combination of verapamil and telmisartan-induced peripheral vasodilation. Bedside echocardiography identified good ventricular contractility and assisted in the identification of vasodilatory shock. Despite multiple inotropes, pressors, and chronotropes, improvement in BP only occurred when electrical-pacing increased heart rate. Failure of pacing-capture is reported with verapamil poisoning, however, pacing alone will not correct negative inotropic or vasodilatory components of intoxication [1–3]. This case describes significant vasodilatory shock in a mixed verapamil/telmisartan overdose compounded by verapamil-induced bradycardia. Emergency cardiac pacing may be considered a part of the tailored multi-modal approach to treatment of severe cardiovascular poisoning.

References


176. Levosimendan as a potential calcium channel blocker antidote: a systematic literature review

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Objective: Calcium channel blockers (CCB) remain amongst the most challenging pharmaceuticals to treat in overdose due to potent toxic effects on the cardiovascular system, and are associated with significant morbidity [1]. We performed a systematic literature review to determine whether the myocardial calcium sensitizer levosimendan may have a role in managing CCB poisoning.

Methods: Ovid MEDLINE, Ovid Embase, and Google Scholar were interrogated using the following “exploded” category plus keyword search: ("Levosimendan" or "Simdax") and ["calcium channel blocker" or "verapamil" or "diltiazem" or "nifedipine" or "amlodipine"]). In total, 546 relevant entries were retrieved; entries that did not consider levosimendan in CCB overdose were excluded, resulting in 22 entries for inclusion.

Results: Five papers reported levosimendan use in human (n = 6) CCB overdose, 4 papers reported animal models and 13 entries were classified as correspondence, commentary, or existing reviews of levosimendan efficacy. In human cases, ingested CCBs included amlodipine (n = 3; 250 mg, 500 mg, 630 mg), verapamil (n = 2; 480 mg, 16000 mg) and diltiazem (n = 1; 3360 mg). Levosimendan loading doses ranged between 0–24 µg/kg via bolus with infusion doses between 0.1–2 µg/kg/minute. No adverse reactions were reported following levosimendan administration and survival occurred in all patients. Recorded improvements in blood pressure (n = 3) were outweighed by improvements in heart rate (n = 5) consistent with animal models. In Wistar rat models treated with verapamil, no improvement in blood pressure was reported following levosimendan administration although heart rate increased. In two reports (n = 35, n = 60) levosimendan was suggested to be actively detrimental to managing hypertensive shock due to vasodilatory effects, consistent with levosimendan contraindications in therapy. Calcium salts outperformed levosimendan in one report, and a Landrace pig model showed an improvement of left ventricular pressure infused over 60 minutes (+38% LV dP/dt, control -31%) in addition to increased survivability.

Conclusion: Levosimendan in human CCB poisoning has optimistic consensus regarding its efficacy based on human data, though reported patients were intensively managed with conventional CCB treatments such as vasopressors, inotropes, and insulin/dextrose regimes for up to 8 days prior, and often during levosimendan administration. In controlled animal studies, consensus ranged from improved survivability in pigs to increased mortality in rats, though the latter is disputed in medical correspondence. Levosimendan requires further reports of its use if it is to be considered as a potential CCB antidote.
177. Chronic digitalis poisoning treated with anti-digoxin Fab fragments: a critical analysis of treatment indications and patient outcome

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Objective: Due to major limitations in digitalis indications, incidence of digoxin poisoning has constantly decreased and is almost limited to accidental chronic digoxin overdose in the elderly. Despite demonstrated effectiveness, the indications, regimen dosage, and usefulness of anti-digoxin Fab fragments to reverse chronic overdose remain controversial. Our objectives were to describe the management of digoxin-overdosed patients admitted in the intensive care unit (ICU) and evaluate their outcome according to treatment strategy.

Methods: We conducted a retrospective observational study including all digoxin-intoxicated patients admitted to a University Hospital ICU between 2000 and 2016. The usual demographic, clinical, toxicological, and outcome data were collected from the records. Treatments including the dose regimen of anti-digoxin Fab fragments were decided by the physicians in charge. We analyzed the indications and modalities of the antidote administration and determined the predictive factors of death.

Results: In total, 49 patients (13 males/36 females, aged 83 years [73; 88] (median [percentiles 25; 75]), with past cardiac history (100%), renal failure (71%), and liver failure (4%); daily digoxin dose 250 µg [125; 250], plasma digoxin concentration 4.10 nmol/L [3.33; 5.68]) were included in the study. On ICU admission, patients presented nausea/vomiting (53%), diarrhea (41%), confusion (33%), visual disturbances (18%), dizziness (16%), consciousness impairment (12%), agitation (12%), delirium (4%), and headaches (2%). On admission, serum creatinine concentration was 145 µmol/L [105; 226] and serum potassium concentration 4.6 mmol/L [4.1; 5.3]. Electrocardiogram (ECG) showed slowed atrial fibrillation (47%), type I (20%), II (18%), III (8%) atrioventricular block and ventricular arrhythmias (2%). Patient management included anti-digoxin Fab fragments infusion (57%) with molar (31%), dose 160 mg [80; 160] or semi-molar (27%, dose 80 mg [80; 80]) dose regimen as well as mechanical ventilation (33%, duration 3 days [2; 6]), catecholamine infusion (47%) and hemodialysis (18%). The main observed complications were aspiration pneumonia (14%) and hospital-acquired infections (29%). Eight patients (16%) died in the ICU, mainly in relation to multi-organ failure. Based on an univariate analysis, only the presence of neuro-respiratory (p = .02), renal (p = .02), and liver (p = .05) failure on admission was predictive of death. Survival did not differ in relation to the serum digoxin concentration on admission or to the Fab dose administered (molar versus semi-molar).

Conclusion: Despite optimal management in the ICU, digoxin overdose is still responsible for life-threatening morbidities and a high-mortality rate. If possible, early anti-digoxin Fab administration at semi-molar dose regimen seems an effective strategy to avoid organ failure that may develop while waiting for molar neutralization as the usual recommendation in textbooks.

178. Delayed QTc prolongation after supratherapeutic loperamide use to treat chronic diarrhea associated with irritable bowel syndrome

James B. Leonarda, Denise Coucha and Hong K. Kimb

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Objective: Loperamide, a phenylpiperidine opioid, is a widely available over-the-counter antidiarrheal medication. Misuse and abuse of loperamide is associated with cardiac conduction abnormalities (QRS and QTc prolongation) and dysrhythmias. We present a case of a delayed QTc prolongation after ingestion of supratherapeutic loperamide doses to treat chronic diarrhea from irritable bowel syndrome (IBS).

Case report: A 59-year-old female with a history of IBS presented to the Emergency Department with elevated blood pressure (BP), sweating, and feeling unwell. For IBS-associated chronic diarrhea, she took 5 tablets of 2 mg loperamide, three times a day (TID) for 10 days followed by 15 tablets TID for an additional 7 days; she reported withdrawal symptoms when missing her doses. Her last dose was 2 hours prior to presentation. Vital signs were temperature 36.7 °C, heart rate 79/min, blood pressure 178/120 mmHg, respiratory rate 16/min and oxygen saturation 98%. Physical exam was normal except for diaphoresis. Initial electrocardiogram showed a ventricular rate of 66/min, QRS 100 msec and QTc 429 msec. Laboratory investigations were only notable for white blood cell of 12.9 × 109/L, platelet 367 × 109/L [73; 170], magnesium 1.7 mg/dL, AST 43 U/L, and ALT 44 U/L. QTc prolongation occurred 7 hours after the last loperamide dose and reached 570 msec at 17 hours post-ingestion. Serial QTc and QRS intervals are displayed in Table 1. Cardiac conduction abnormality resolved after 2 days.

Conclusion: Loperamide’s effect on cardiac conduction is well described. The majority of symptomatic patients in published case reports experienced prolonged QRS/QTc intervals or dysrhythmias at the time of presentation. Delayed QTc prolongation has not been previously reported. In our case, QTc prolongation was delayed and peaked 17 hours after the last dose of loperamide. Patients using supratherapeutic doses of loperamide with normal cardiac conduction may require serial electrocardiograms and cardiac monitoring for up to 17 hours.

<table>
<thead>
<tr>
<th>Time since dose</th>
<th>QTc (msec)</th>
<th>QRS (msec)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 h</td>
<td>429</td>
<td>100</td>
<td>66</td>
</tr>
<tr>
<td>7 h</td>
<td>471</td>
<td>104</td>
<td>62</td>
</tr>
<tr>
<td>10 h</td>
<td>559</td>
<td>96</td>
<td>58</td>
</tr>
<tr>
<td>17 h</td>
<td>570</td>
<td>106</td>
<td>57</td>
</tr>
<tr>
<td>20 h</td>
<td>524</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>23 h</td>
<td>493</td>
<td>104</td>
<td>63</td>
</tr>
<tr>
<td>27 h</td>
<td>473</td>
<td>102</td>
<td>61</td>
</tr>
<tr>
<td>36 h</td>
<td>481</td>
<td>92</td>
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</tr>
<tr>
<td>41 h</td>
<td>486</td>
<td>98</td>
<td>67</td>
</tr>
<tr>
<td>49 h</td>
<td>448</td>
<td>94</td>
<td>72</td>
</tr>
</tbody>
</table>

Table 1. Electrocardiogram changes due to supratherapeutic loperamide dosing.
179. Colchicine poisoning presenting with acute myocardial infarction and secondary cardiogenic shock

Francis Grossenbacher a, Vanessa Champenois b, Veronique Pinel-Petit a, Quentin Marion a, Carole Carole b, Yohann Cazaubon c and Jean Marc Malinovsk y d

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Objective: Colchicine poisoning can induce CS, which has been survived in a patient managed with extracorporeal life support (ECLS) [1]. After acute myocardial infarction (AMI) 4.2–8.6% of patients develop CS, with percutaneous coronary intervention (PCI) as the recognised management [2]. Colchicine is used in acute pericarditis as an anti-inflammatory agent. We report a patient with colchicine poisoning presenting with acute myocardial infarction and secondary cardiogenic shock.

Case report: A 55-year-old male presented to our Emergency Department, 25 hours (day 2) after ingesting 40 mg of colchicine (Colchimax®) with alcohol. He was a strong alcohol and tobacco user taking colchicine 1 mg daily for gout. On admission, he complained of gastrointestinal signs. Vital signs were blood pressure 140/102 mmHg, heart rate 60/minute, oxygen saturation 86%, temperature 34.5 °C. Blood gases showed pH 6.96, pO2 38 mmHg, and pCO2 58 mmHg. Laboratory findings were anionic gap 25.4, white cells 34.7 × 10⁹/L, platelets 299 × 10⁹/L, glucose 6 mmol/L, lactate 15.96 mmol/L, prothrombin time Quick test 41%, Factor V 18%, white cells 34.7 × 10⁹/L, platelets 299 × 10⁹/L, glucose 6 mmol/L, creatinine 389 µmol/L, and potassium 5.5 mmol/L. Electrocardiography showed acute inferior ST segment elevation myocardial infarction (STEMI) and anterior mirror; troponin was 1038 ng/L and pro-brain natriuretic peptide (proBNP) 8541 pg/mL. Cardiogenic shock (CS) occurred two hours later, necessitating admission to the intensive care unit (ICU). Cardiac ejection fraction was estimated at 10%. Dobutamine and ECLS were performed but Fab anticolchicine was not administrated due to excessive delay. The admission colchicine concentration was 19 mg/L (a dose/weight of 0.57 mg/Kg). He died from multi-organ failure on day 3. Autopsy showed hemorrhagic suffusion of the epicardium, cerebral, and gastrointestinal tract hemorrhage and severe multisvessel coronary disease (highly obstructive multi-stenosis) with no previous cardiovascular event.

Conclusion: In our patient, colchicine-induced multiorgan failure requiring ICU admission was considered a priority. PCI was not performed as the colchicine-induced major disturbances of hemostasis were expected to have had an anticoagulant action. A PCI could have been useful in reducing ischemic myocardial damage and decreasing the risks of CS due to AMI and colchicine poisoning in this patient. We recommend cardiology advice on arrival in ICU for patients withcolchicine poisoning.

References


180. Severe cardiovascular failure in relation to beta-blocker poisoning: predictive factors, pharmacokinetics and effect/concentration relationships

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aDepartment of Medical and Toxicological Critical Care, Lariboisière Hospital, Paris-Diderot University, INSERM UMRS1144, Paris, France; bToxicology Laboratory, Lariboisière Hospital, Paris-Descartes University, Paris, France

Objective: Beta-blockers, the most frequent drugs involved in cardiotoxicant poisonings, may be responsible for severe toxicity. Our objectives were to describe the toxic features and investigate the prognosticators of death in severe beta-blocker poisonings; to study beta-blocker pharmacokinetics (PK) at the elevated ingested doses in comparison to the reported values at pharmacological doses; and to analyze the usefulness of the Vasoactive Inotropic Score (VIS) as a pharmacodynamic (PD) parameter in relation to the plasma concentrations.

Methods: Prospective single-centre study including all severely beta-blocker-poisoned patients admitted to a University Hospital intensive care unit (ICU) in 2007–2016 and treated with catecholamines. We performed a univariate analysis of prognostic factors using chi-squared and Mann–Whitney tests and modeled the PKs and PK/PD relationships.

Results: One hundred and fourteen patients (64 females/50 males; age: 49 years [38–58] (median [percentiles 25–75]); Simplified Acute Physiology Score (SAPS) II: 51 [37–63]) were included. A multidrug ingestion was involved in 87% of the cases including co-ingested cardiotoxins in 37% of the cases. Thirteen patients presented sudden cardiac arrest, 15 required veno-arterial extracorporeal membrane oxygenation (ECMO) and nine died. The predictive factors of death or ECMO requirement on admission were cardiac arrest onset (p < .001), stabilizing membrane effects on the electrocardiogram (ECG) (p = .05), hyperlactatemia (p = .005), liver cytolysis (p < .001), altered prothrombin index (p = .02), VIS (p = .01) and SAPS II scores (p = .004). In contrast, the plasma concentration of the beta-blocker agent was not predictive of the final outcome. Propranolol PK fitted a mono-compartmental population PK model well with first-order absorption and elimination. This model clearly showed the ability of ECMO to allow the metabolic and renal clearance of the toxicant. A non-compartmental PK approach was used for the other beta-blockers. No significant correlation was found between the VIS and the plasma concentrations of the different beta-blockers.

Conclusion: Beta-blocker poisonings admitted to the ICU are responsible for major morbidities and even fatalities. The main prognosticators include cardiac arrest onset, membrane stabilizing effect on the ECG and the paradoxical elevation in blood lactate concentration. Although not correlated to the plasma concentrations of the beta-blocker, the VIS is able to predict ECMO requirement or death.
181. Carbon monoxide poisoning in pre-hospital and Emergency Department hospital settings: critical issues on correct evaluation and proposal of a clinical procedure

Stefano Rosa, Davide Lonati, Azzurra Schicchi, Francesco Salinaro, Stefano Perlini and Carlo A. Locatelli

Objective: Carbon monoxide (CO) poisoning is underestimated, as unspecific clinical manifestations can make diagnosis difficult, especially in a pre-hospital setting. We investigated the management of CO-poisoning in the pre- and intra-hospital setting, according with Italian Guidelines, and the Poison Control Centre’s (PCC) role.

Methods: Patients with confirmed CO-poisoning admitted to a tertiary-emergency department (ED) were retrospectively evaluated (January 2013–February 2017); demographic data, clinical management, follow-up, and outcome were collected. Cases were graded as Grade-1: asymptomatic with carboxyhemoglobin concentrations (CoHb) suggestive of exposure (>5% non-smokers, >10% smokers); Grade-2: mild (nausea, vomiting, headache, vertigo); Grade-3: moderate (tachycardia, dyspnea, mild neurological symptoms, behavioral changes); Grade-4: severe (syncope, chest pain, electrocardiogram (ECG) abnormalities, hemodynamic instability, severe neurological manifestations). Grade-0 was assigned to pre-hospital asymptomatic patients with undetermined COHb.

Results: Sixty-three patients were studied (mean age 40.8 years; 7 months–91 years). Pre-hospital: Forty patients (64%) were rescued by emergency medical service (EMS); in 22/40, the diagnosis was made by ambient CO-detectors. Main clinical manifestations were nausea (31%), headache (27.5%), severe asthenia (19.6%), syncope (17.6%), and coma (1 case). Patients were assigned to Grade-3/4 (39%), Grade-2 (24%), and Grade-0/1 (37%). ED: Main clinical manifestations were nausea (25%), headache (23.6%), vertigo (20.3%), asthenia (19.6%), and chest pain (8.5%); Grade-3/4 (27%) and Grade-2 (27%). Considering only CoHb concentration (unavailable in pre-hospital), 78% of Grade 0/1 were assigned to Grade-1. Cardiac troponin was increased in 9.8% of the cases; echocardiogram was performed in 6.5%. Hyperbaric therapy was performed in 33/63 patients (53.2%). Six patients graded as 3/4 in pre-hospital setting received 24 hours of normobaric oxygen. The PCC-toxicologist was called in 49.2% of the cases, and an optimal protection for rescuers, which is strongly recommended. GI symptoms + syncope + headache and GI + chest pain + headache may be a “sentinel triad” in pre-hospital and EDs, respectively. Our data evidence a risk of clinical undervaluation of the severity in ED-hospital grading: 6 patients were under-graded, and did not receive appropriate treatment. A correct overall evaluation requires consideration of both pre-hospital and ED grading, emphasizing the worst sign/symptoms presented. Toxicological follow-up is indicated in all cases of CO-poisoning and to detect and manage DNS.

182. Carbon monoxide exposures and hyperbaric oxygen therapy: a review of the ToxIC Registry

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Objective: Carbon monoxide (CO) is one of the most common causes of fatal poisonings worldwide. A complication of sublethal CO toxicity is the development of delayed neurologic sequelae (DNS). Hyperbaric oxygen (HBO) therapy is a frequently utilized treatment for acute CO toxicity and prevention of DNS. Currently, it is difficult to predict the subset of CO-poisoned patients that will develop DNS, and thus receive the most benefit from HBO therapy. While several clinical indications have been proposed in the medical literature, no consensus exists. We reviewed the Toxicology Investigators Consortium (ToxIC) Case Registry to identify if any clinical parameter, among CO-poisoned patients, predicted the use of HBO therapy.

Methods: A retrospective search of the ToxIC Registry was performed during the time period 1 January 2010 to 1 July 2016 to identify patients with CO exposure and those whom received HBO. Demographic and clinical parameters were collected and analyzed using descriptive statistics, chi-squared analysis, and logistic regression.

Results: A total of 475 patients were reported to have a carbon monoxide exposure. The most common age range was 19–65 years old (63.7%) and 75% of patients were 19 years or older. A slight majority of patients were male (54.3%) and 9 females were pregnant. Most exposures were classified as unintentional and environmental (77.5%). CO was an isolated exposure in 83.1% cases. Most patients were symptomatic (86.3%). Neurological symptoms were present in 37.6% of the cases with coma/central nervous system depression being the most commonly reported (29.4%). Approximately 25% of the cases received hyperbaric oxygen (HBO) therapy. There were 7 deaths with carbon monoxide exposures with only one of them receiving HBO. Chi-square analysis showed no correlation between HBO use and gender, age greater than 65, intubation, pregnancy, or death. There was a significant association between coma/CNS depression and HBO use. Logistic regression did not demonstrate an association between carboxyhemoglobin concentration and use of HBO therapy. There were 7 additional cases where HBO was used in non-CO exposures, with 85% cases involving hydrogen peroxide.

Conclusion: Medical toxicologists were more likely to use HBO therapy for the treatment of CO toxicity, if patients presented with CNS depression/coma. Further research into the benefits of HBO therapy and prevention of DNS is needed.

183. Lisdexamfetamine overdose in adolescents and adults: experience in Sweden

Eva Backman, Karin Feychting and Jonas Höjer

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Objective: The sympathomimetic drug lisdexamfetamine was introduced in Sweden in 2013 for treatment of attention deficit hyperactivity disorders (ADHD). Since then, the prescription rate of lisdexamfetamine has increased and an increasing number of inquiries related to overdose of lisdexamfetamine has been observed. The aim of this study was to assess the acute toxicity.
of lisdexamfetamine in human overdose. A retrospective survey of hospital case records received by the Swedish Poisons Information Centre (Swedish PC) from the introduction in 2013 to 31 August 2017 was carried out.

**Case series:** During the survey period, the Swedish PC was consulted in 559 cases regarding lisdexamfetamine overdose in adults and adolescents. Of these, 20 cases of single drug overdose with lisdexamfetamine could be analysed in detail by studying hospital case records. The age of the patients varied from 12 to 58 years and half were aged 12–19 years; there were 13 females and 7 males. Sixty percent of the patients were documented to have lisdexamfetamine on prescription. Ingested dose ranged from 150 mg to 2100 mg (average 647 mg; median 512.5 mg). The reasons for overdosing were intentional (18/20) and therapeutic error (2/20). The severity of poisoning was graded according to the Poisoning Severity Score (PSS) [1]. Nine patients within the dose range 150–1500 mg developed mild symptoms (PSS 1) and 11 patients within the dose range 190–2100 mg had moderate symptoms (PSS 2). There were no severe cases and no fatalities. The most frequent symptoms were tachycardia (16/20), hyperactivity/restlessness/anxiety (10/20), mydriasis (7/20), mild-to-moderate hypertension (7/20), dizziness (6/20), chest pain/tightness of the chest (5/20), hallucinations (4/20), tremor (3/20), nausea (3/20), tachypnea (3/20), and dyspnea (3/20). Occasionally, hyperventilation, muscle fasciculations, hyperreflexia, mild fever (<38 °C), flushing, vomiting, agitation, paranoia, psychosis, mild central nervous system depression, sweating, ST segment depression, hypokalemia as well as elevated troponin, lactate, creatine kinase, and myoglobin levels were observed. Treatment with activated charcoal was performed in four patients and in six patients benzodiazepines (diazepam or oxazepam) were administered for sedation.

**Conclusion:** In this limited material, all cases of lisdexamfetamine poisonings were graded as mild to moderate. There was no clear dose-effect response to predict the severity of poisoning in the presented dose range. No unexpected symptoms of this sympathomimetic drug were observed.

**Reference**


### 184. Duloxetine overdose

Michael Keegan, Joyce M. Cooper and Geoffrey K. Isbister
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**Objective:** Duloxetine is a commonly used antidepressant that is a serotonin and norepinephrine reuptake inhibitor. In this study, we aimed to investigate the frequency and severity of the clinical effects following duloxetine overdose.

**Methods:** A retrospective review of duloxetine overdoses (>120 mg) admitted to a tertiary toxicology unit between March 2007 and January 2017. Demographic information, details of ingestion (dose, co-ingestants), clinical effects, investigations (electrocardiogram [ECG] parameters including QT interval), complications (serotonin toxicity, seizures, and cardiovascular effects), length of stay (LOS), and intensive care unit (ICU) admission were extracted from a clinical database.

**Results:** There were 48 duloxetine overdoses, median age 38 years (interquartile range [IQR]:25–49 years); 34 (71%) were female. The median dose was 840 mg (range 180–2820 mg).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Duloxetine alone (n=35)</th>
<th>Duloxetine plus co-ingestants (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range; IQR)</td>
<td>41 (20–52; IQR:40–50)</td>
<td>30 (17–60; IQR:24–48)</td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>10 (3%)</td>
<td>24 (69%)</td>
</tr>
<tr>
<td>Dose ingested (mg), median (range)</td>
<td>840 (360–1260)</td>
<td>720 (180–2020)</td>
</tr>
<tr>
<td>Number of co-ingestants</td>
<td>–</td>
<td>3 (1–6)</td>
</tr>
<tr>
<td>Length of stay (hours), median (range; IQR)</td>
<td>11 (0.7–78; IQR:3–15)</td>
<td>20 (9–216; IQR:13–33)</td>
</tr>
<tr>
<td>Glasgow Coma Score 15</td>
<td>10 (77%)</td>
<td>18 (51%)</td>
</tr>
<tr>
<td>Glasgow Coma Score 10–14</td>
<td>3 (23%)</td>
<td>11 (31%)</td>
</tr>
<tr>
<td>Glasgow Coma Score ≤9</td>
<td>0</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>Systolic blood pressure &gt;140 mmHg</td>
<td>6 (46%)</td>
<td>11 (31%)</td>
</tr>
<tr>
<td>Tachycardia (heart rate &gt;100 bpm)</td>
<td>2 (15%)</td>
<td>20 (57%)</td>
</tr>
<tr>
<td>Abnormal QT internal</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Serotonin toxicity</td>
<td>1 (8%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Thirteen patients ingested duloxetine alone and 35 co-ingested a median of 3 other medications (Table 1). Tachycardia occurred in 22 (46%) patients and mild hypertension (systolic blood pressure >140 mmHg) in 17 (35%); no patients had hypotension or arrhythmias. One patient had an abnormal QT, but was tachycardic (119 bpm) and co-ingested quetiapine, mirtazapine, and diazepam. Serotonin toxicity occurred in two patients: one ingested 360 mg duloxetine alone, and the other ingested duloxetine 400 mg, desvenlafaxine 2700 mg, and temazepam 50 mg, and also had a seizure. Glasgow Coma Score (GCS) was <15 in 20/48 patients (42%) and GCS <9 in six patients (13%), all co-ingesting other medications. One patient developed priapism. The median LOS was 16.7 hours (range 0.7–33 hours) and five (10%) patients were admitted to the ICU (four requiring intubation), all due to toxicity from co-ingested drugs.

**Conclusion:** Duloxetine overdose caused similar clinical effects (serotonin toxicity and cardiovascular effects) in frequency and severity to other serotonin noradrenaline reuptake inhibitors in overdose, except it did not cause seizures. Co-ingestion of other medications occurred in the majority and resulted in more severe toxicity.

### 185. Delayed resolution of amitriptyline toxicity associated with CYP2D6 deficiency

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**Objective:** We present a case of delayed resolution of amitriptyline toxicity with elevated serum amitriptyline and nortriptyline concentrations 96 hours post-ingestion in a patient with CYP2D6 deficiency.

**Case report:** A 44-year-old Caucasian female presented to the Emergency Department (ED) three hours after ingesting approximately 60 capsules of 75 mg amitriptyline in a suicide attempt. The patient was alert on arrival with blood pressure 105/53 mmHg, heart rate 95 beats/minute, temperature 36.2 °C, and oxygen saturation 97% (room air). An initial electrocardiogram (ECG) exhibited normal sinus rhythm with a QRS of 96 hours post-ingestion in a patient with CYP2D6 deficiency.
the intensive care unit (ICU). The sodium bicarbonate infusion was discontinued at 24 hours. An ECG performed 30 hours post-ingestion showed typical features of TCA toxicity for the first time with terminal R in AVR, prolongation of QRS and QTc intervals. The patient was restarted on sodium bicarbonate infusion for 24 hours with frequent doses of magnesium sulfate. Total serum tricyclic antidepressant concentrations 96 hours post-ingestion were: total 808 ng/mL (reference 80–200 ng/mL), amitriptyline 224 ng/mL, and nortriptyline 584 ng/mL. On day six, the patient’s ECG showed normal intervals with sustained improvement in QTc and QRS intervals. The patient remained intubated for 10 days and had resolution of central nervous system symptoms on day 12. Genotype testing designated the patient as a poor metabolizer, homozygous with CYP2D6 *4/*4.

**Conclusion:** The primary enzyme responsible for amitriptyline metabolism is CYP2D6 and 5–10% of Caucasians have reduced or absent activity of this enzyme [1,2]. Poor metabolizers and individuals deficient in CYP2D6 may manifest delayed resolution and thus a protracted course of amitriptyline toxicity secondary to a prolonged elimination half-life.

**References**


### 186. Severe central nervous system depression and acute respiratory distress syndrome in severe nisoldipine toxicity

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**Objective:** Severe encephalopathy, loss of protective airway reflexes, and development of acute respiratory distress syndrome (ARDS) has previously been reported with non-dihydropyridine calcium channel antagonist (CCA) toxicity. However, development of severe central nervous system (CNS) depression and ARDS is not well reported with dihydropyridine CCA toxicity. The purpose of this report is to present a case of massive nisoldipine ingestion that resulted in severe CNS depression, aspiration pneumonitis, ARDS, and death.

**Case report:** A 44-year-old male presented after being found obtunded adjacent to an empty prescription bottle of nisoldipine. No other substances or prescription bottles were found on the scene or in the patient’s possession. The patient was emergently intubated upon arrival to the Emergency Department secondary to severe lethargy and loss of protective airway reflexes. Vomiting was evident around the patient’s oropharynx. Initial vital signs included a blood pressure of 75/44 mmHg and heart rate of 61 bpm. Sinus bradycardia was noted on the electrocardiogram (ECG). A standard urine drug screen was negative for all substances, and a serum ethanol concentration was undetectable. Bedside echocardiogram demonstrated hyperdynamic ejection fraction. Despite parenteral administration of calcium gluconate boluses, glucagon, and normal saline boluses, the patient’s diastolic blood pressure declined to 20 mmHg. Norepinephrine, vasopressin, and calcium gluconate infusion were initiated and mean arterial pressure improved to 65 mmHg, albeit with very wide pulse pressures. Despite initial clinical improvement after 48 hours, including the weaning of vasopressors, the patient subsequently developed severe ARDS, increasing oxygen requirements, and refractory hypotension. On hospital day 4, the patient developed anuric renal failure necessitating continuous renal replacement therapy, and he subsequently expired on hospital day 5.

**Conclusion:** While not well reported in the literature, this severe case of nisoldipine toxicity is particularly noteworthy, given the degree of obtundation. Encephalopathy secondary to CCA toxicity has been postulated to result from cerebral vasodilation through inhibition of L-type calcium channels. Furthermore, despite initial improvement in hemodynamic parameters, the patient subsequently expired after developing severe ARDS. Other authors have proposed that verapamil can cause inhibition of prostaglandin synthesis, resulting in disruption of pulmonary capillary vasculature’s integrity, leading to ARDS. A similar mechanism is possible for nisoldipine toxicity. Additional research is needed to further understand the possible mechanisms behind nervous system and pulmonary toxicity in nisoldipine toxicity.

### 187. Using pesticide-poisoned patients as potential organ donors

**Umesh Mistry**<sup>a</sup>, **Paul I. Dargan**<sup>b</sup> and **David M. Wood**<sup>b</sup>

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**Objective:** The gap between the number of patients on transplant waiting lists and patients receiving transplants is growing. There is increasing use of solid organs following deaths from toxicins such as cocaine, carbon monoxide, and cyanide. Use of donors who have died following pesticide exposure remains controversial. This study reviews the literature related to transplant from this group.

**Methods:** A literature search was undertaken on PubMed using the following key words: “insecticide”, “pesticide”, “rotenoid”, “organophosphate”, “carbamate”, “poisoning”, “toxicity”, “overdose”, “intoxication”, “injection”, “organ donation or procurement”, “transplant”, “allograft transplant”, and “expanded criteria organ donation”; 21 specific pesticides/insecticides were also added to the search; the index for EAPCCT/NACCT meeting abstracts 2008–2017 was also searched. Potential publications identified were reviewed and if they described human donation/transplantation of one or more solid organ(s), the following was extracted: compound(s) ingested; donor demographics; organ(s) transplanted; and graft function at follow up.

**Results:** Ten papers were identified describing 17 fatalities (1999–2017) where organ donation occurred following exposure to a pesticide (aldicarb 4 cases, parathion 1, malathion 1, carbosulfan/carbamate 1, organophosphate 8, carbamate 1, brodifacoum 1). No further cases were identified from review of EAPCCT/NACCT abstracts. Donors were aged 12–50 (25.9 ± 12.2) years. There were 38 organs transplanted: 28 kidneys, 7 livers and 3 hearts (Table 1). Of the 34 recipients with outcome reported, 2 (5.9%) patients died, 2 (5.9%) had graft failure dysfunction, and 32 (88.2%) had good graft function at follow-up. Overall, survival with good graft function was 96%, 67%, and 71% for transplanted kidneys, hearts, and livers, respectively.

**Conclusion:** There is an increasing need to identify additional potential donor pools. Review of the published literature suggests that solid organ donation following exposure to a pesticide is associated with good short-to-medium-term graft organ
Table 1. Summary of cases of organ donation from pesticide-poisoned donors.

<table>
<thead>
<tr>
<th>Organ Exposure</th>
<th>Number of organs transplanted</th>
<th>Follow-up outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney Aldicarb</td>
<td>6</td>
<td>Alive with “good graft function” at 7–17 months.</td>
</tr>
<tr>
<td>Parathion</td>
<td>2</td>
<td>One with serum creatinine 1.67 mg/dL (148 µmol/L) at 3 months; 1 with delayed graft failure due to early humoral rejection requiring hemodialysis at 3 months.</td>
</tr>
<tr>
<td>Malathion</td>
<td>2</td>
<td>Alive with “good graft function” at 12 months.</td>
</tr>
<tr>
<td>Carbofuran/Carbamate</td>
<td>2</td>
<td>Alive with good graft function at 12 months. Serum creatinine of 1.0 mg/dL (88 µmol/L) and creatinine clearance of 71 mL/min/1.73 m² in right transplanted kidney. Serum creatinine of 0.9 mg/dL (80 µmol/L) and creatinine clearance of 68.6 mL/min/1.73 m² in left transplanted kidney.</td>
</tr>
<tr>
<td>Organophosphate</td>
<td>16</td>
<td>Twelve “excellent renal function” at 13–62 months; 4 not reported.</td>
</tr>
<tr>
<td>Heart Aldicarb</td>
<td>2</td>
<td>Alive with “good graft function” at 17 and 22 months.</td>
</tr>
<tr>
<td>Carbamate</td>
<td>1</td>
<td>Died 24 hours post-transplantation due to acute left ventricular dysfunction.</td>
</tr>
<tr>
<td>Liver Aldicarb</td>
<td>4</td>
<td>Three alive with “good graft function” at 7–17 months; 1 died post-transplant due to primary non-function.</td>
</tr>
<tr>
<td>Parathion</td>
<td>1</td>
<td>Alive at 3 months but had recurrent ascites requiring treatment.</td>
</tr>
<tr>
<td>Malathion</td>
<td>1</td>
<td>Alive with “good graft function” at 12 months.</td>
</tr>
<tr>
<td>Brodifacoum</td>
<td>1</td>
<td>Alive with “good graft function” (defined as normal liver function and coagulation studies) at 15 months.</td>
</tr>
</tbody>
</table>

function following transplantation, particularly for transplanted kidneys.

188. Predicting outcomes in aluminum phosphide poisoning using a risk-prediction nomogram

Esmaeil Farzaneh, Samaneh Nakhaee, Alireza Amirabadizadeh, Omid Mehrpour and Shiva Shabrang

Objective: Aluminum phosphide (AIP) is a toxic agent with high lethality rate [1,2]. The aim of this study was to determine clinical and laboratory findings for predicting the medical outcome of AIP-poisoned patients.

Methods: This is a prospective study of AIP poisoned patients from 2010–2015 in Ardabil, Iran. In the study period, all patients with confirmed diagnosis of AIP poisoning were included. Clinical data, scoring systems, and clinical outcomes were compared between surviving and non-surviving patients. Univariate analysis (Mann–Whitney or t-test), multiple logistic regression, receiver operating characteristic (ROC) curve analysis, Pearson correlation test, STATA/SE 13.0, and the nomolog software were performed.

Results: A total of 68 AIP poisoned patients were included, of which 36 died. From the multiple logistic regression analysis, it was determined that 4 factors were significant for predicting mortality including Glasgow coma score (GCS) (OR [95% CI] 0.24 [(0.09–0.63), p = .003], systolic blood pressure (SBP) (OR [95% CI] 0.91 [0.84–0.97], p = .006), urinary output (UOP) (OR [95% CI] 0.99 [0.98–0.99], p = .04), and serum bicarbonate (OR [95% CI] 0.7 [0.56–0.93], p = .01). We developed a four-variable risk-prediction nomogram for predicting the risk of mortality and identifying high-risk patients. A Simplified Acute Physiology Score II (SAPS II) score greater than 24.5, Acute Physiology and Chronic Evaluation II (APACHE II) score greater than 8.5, Sequential Organ Failure Assessment (SOFA) score greater than 7.5, and, SBP of < 92.5 mmHg, bicarbonate < 12.9 mEq/L, UOP < 1725 mL/day, and GCS < 14.5 predicted AIP mortality.

Conclusion: The results of our study showed that SBP, GCS, UOP, and serum bicarbonate are the best prognostic factors of mortality in AIP poisoned patients. According to the area under the ROC curve, the APACHE II score compared with SOFA and SAPS II can better discriminate between non-survivors and survivors. Physicians could use this simple nomogram to identify patients with acute poisoning at risk of death immediately after presentation, and optimize patient management to prevent mortality and to identify the patient who initially looks well and then goes on to have a fatal outcome. For high risk patients, some invasive procedures such as intraaortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO) could be considered.

References


189. Severe suicidal self-poisoning with massive dose of potassium ferricyanide: risk of life-threatening hyperkalemia and acute renal failure

Lucie Lischkova, Daniela Pelclova, Jiri Hlusicka, Tomas Navratil, Vaclav Kadlec and Sergey Zakharov

Objective: We describe a rare case of intentional ingestion of a massive dose of potassium ferricyanide in a suicide attempt with life-threatening hyperkalemia and acute renal failure as complications.

Case report: A 37-year-old male with a history of chronic alcohol abuse and social adaptation failure ingested 80 g of pure potassium ferricyanide (approximately 770 mg/kg) in a suicide attempt. In animals, the lethal oral dose (LD₅₀) in mice is 1600 mg/kg. The patient reported vertigo as the first sign and six episodes of diarrhea two hours after ingestion. He was transported to the intensive care unit 8 hours after ingestion conscious and spontaneously ventilating, with Glasgow Coma Scale (GCS) 15. On the electrocardiogram (ECG) tall “tent” T-waves in V3–V6 and progressive flattening of P-waves were registered. Serum
concentrations of potassium of 7.2 mmol/L, urea of 7.1 mmol/L, and creatinine of 162 µmol/L indicated development of acute renal failure. As the serum potassium continued to rise (7.4 mmol/L) over the next few hours and there was risk of acute renal failure, intermittent hemodialysis was performed in combination with insulin therapy. A proton pump inhibitor (PPI) was administered intravenously to increase gastric pH and to treat the irritation of gastrointestinal tract. The condition of the patient stabilized and he was discharged on day 4 of hospitalization.

Conclusion: Massive ingestion of potassium ferricyanide may be a life-threatening condition due to severe hyperkalemia refractory to treatment, but not due to significant release of free cyanide anions. A combination of insulin therapy with intermittent hemodialysis is indicated in these cases. Administration of a PPI intravenously might have an effect on the stability of ingested chemical. Gastrointestinal decontamination should be considered if a massive dose has been ingested and the patient presents soon after ingestion.

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190. Lactation in beta-thalassemia major: is deferasirox compatible? The first case with clinical data and breastmilk concentrations

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Objective: Deferasirox (DFX) is an orally bioavailable iron-chelating agent. It is used in chronic iron overload due to transfusional therapy in beta-thalassemia or sickle-cell disease. DFX is excreted in the milk of lactating rats [1] and its high apparent volume of distribution (14.4 L/kg) and protein binding (99%) make this drug theoretically of low concentration in human milk. The safety of breastfeeding for patients with thalassemia major receiving deferasirox (DFX) therapy is debated [2]. At present, with the exception of few animal data, no human cases or laboratory data involving lactation with this drug are available. We describe the clinical course of a newborn exclusively breastfed by a beta-thalassemic mother on DFX therapy. Iron status of the infant during lactation and DFX breastmilk concentration were evaluated.

Case report: A 28-year-old woman with beta-thalassemia major treated with blood transfusions, delivered a healthy baby. Due to potential transfusion-related iron overload, DFX oral therapy (35 mg/kg/day) was started one week after delivery. Breastfeeding was started and iron status monitored. Blood tests in the infant at 1, 10, 30 days after starting DFX revealed normal ferritin of 190, 218, 96 ng/mL (normal 22–275) and sideremia of 101, 77, 71 µg/dL (normal 60–170). In the first month, growth (41 percentile) and length-curve were normal. DFX breastmilk concentration was analyzed by adapting a validated high-performance liquid chromatography method described for plasma [2]. Donors provided “blank” human breastmilk to prepare calibration standards. No measurable DFX concentrations were found.

Conclusion: Our case, exclusively breastfed by the mother on chronic DFX therapy, presented a normal growth curve and iron status during lactation. The DFX milk concentration was evaluated on a sample at 2 hours after therapy, within the range of time to expect a serum peak (1.5–4 hours) and was <0.1 mg/L (below the detection limit). Despite the limitation of a single case, DFX seems to be compatible in breastfeeding, does not modify the newborn growth curve and iron status and seems to be excreted in a very low concentration in breastmilk.

Acknowledgement: The authors acknowledge mothers and the Leche League Italia for the collection of the “blank” samples.

References


191. Liquid bromine ingestion: a rare entity

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Objective: To present the outcome and the evolution in a case of acute ingestion of liquid bromine in a 17-year-old adolescent.

Case report: A 17-year-old male patient was transferred from a regional hospital to our unit after acute ingestion of liquid bromine for suicidal purpose. At admission, he presented altered general status, dysphonia, hematemesis, severe edema of the lips and tongue, and intense abdominal pain. Laboratory findings showed metabolic acidosis (pH 7.21) with hyperchloremia (112 mmol/L), acute inflammatory syndrome (C-reactive protein [CRP] 13 mg/dL, fibrinogen 715 mg/dL), leucocytosis (112 mmol/L), and biological status slowly improved but he continued to present very severe damage to the digestive tract comparable to that observed following ingestion of a strong acid.

Endoscopy revealed erosions and false membranes covering the esophageal wall, marked hyperemia and edema, with gastric stasis and blood clots that covered the gastric mucosa, duodenal bulb with ulcers, and false membranes suggestive of severe caustic lesions. Abdominal ultrasound showed thickened gastric wall and gastric stasis. The patient received aggressive intravenous hydration, partial parenteral nutrition, ceftiraxone, hemostatics, antisecretories, and analgesia. In evolution, he presented abundant sialorrhea, hematemesis with hematocritia, bilious vomiting, diarrhoea, fever, and intense epigastric pain requiring morphine administration. He continued receiving partial parenteral nutrition, gradually shifting to solid food and symptomatic treatment. During the next 4 weeks, the clinical and biological status slowly improved but he continued to present massive bilious vomiting. A repeat abdominal ultrasound showed massive gastric and duodenal stasis raising suspicion of duodenal stenosis that was confirmed by a second digestive endoscopy, which revealed amelioration of the caustic esophageal and gastric lesions. Unfortunately, follow-up examination was not possible since the patient and the family solicited to be discharged.

Conclusion: Acute ingestion of liquid bromide is an extremely rare entity because of its physical characteristics, but it can cause very severe damage to the digestive tract comparable to that observed following ingestion of a strong acid.
192. A patient with dimethoate poisoning requiring prolonged decontamination

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Emergency Department, Singapore General Hospital, Singapore

Objective: We report a case of dimethoate poisoning with persistent skin contamination, despite prolonged decontamination. Case report: A 27-year-old depressed gardener consumed dimethoate at his workplace. This was witnessed and an ambulance called immediately. At the scene, paramedics noted he was drowsy and diaphoretic, but otherwise hemodynamically stable with 100% oxygen saturation. He was evacuated with a prehospital stand-by activation message to the receiving Emergency Department (ED) to prepare for a critically ill patient. En route, he vomited multiple times and was drenched in vomitus with a pungent odour. On arrival at the ED reception area, his vital signs were stable but Glasgow Coma Scale (GCS) was 10, with excessive salivation and crepitations in the lungs bases. In view of the gross external contamination from the vomitus, the hospital decontamination shower was activated for decontamination prior to entry into the hospital. Staff donned protective suits and proceeded to disrobe and bag all of his clothing before showering him for 10 minutes using soap and water. Post-decontamination, a chemical agent monitor (CAM) was used to screen for residual chemicals as per hospital decontamination protocol. The chemical alarm was triggered around the left mastoid region and he had targeted re-showering for another 5 minutes. On repeat scanning, the CAM alarm triggered just below the left breast. He was re-showered for another 5 minutes before finally being cleared. Decontamination took a total of 20 minutes, excluding preparation time of the showers. He received atropine (2.4 mg total dose) and was started on pralidoxime 1 g followed by an infusion for 24 hours. He became more responsive and was admitted to the ICU for monitoring where he continued to improve over the next 24 hours. He made an uneventful recovery and was discharged 5 days later.

Conclusion: The chemical terrorism incident in Tokyo [1], demonstrated the high incidence of secondary exposures amongst healthcare workers as a result of lack of casualty decontamination. This case report suggests that effective decontamination takes time. Extrapolating this experience to mass casualty incidents, rapid decontamination of casualties in the field or hospital may have limitations. Measures to ensure effectiveness of decontamination are important to ensure staff and patient safety [2].

References

193. A case of copper acetoarsenite poisoning

Helga Ruus Lorentzen, Kristin Opdal Seljetun, Tarjei Skeide Rønning, Ane Cecilie Dale and Fridtjof Heyerdahl

Objective: Copper acetoarsenite (Paris green), an inorganic, trivalent, arsenic compound, is a highly toxic emerald-green crystalline powder. Inorganic arsenic compounds can produce symptoms shortly after ingestion with the gastrointestinal tract, heart, brain, and kidneys as primary targets. We describe the clinical course and management of a large ingestion of copper acetoarsenite with an unexpectedly benign outcome.

Case report: A 41-year-old (72 kg) man with history of drug abuse was admitted to the hospital two hours after ingesting 20 g of Paris green in a suicide attempt. On arrival, he was tachycardic (120–180/min) and tachypneic (respiration 30/minute) with abdominal pain, nausea, and retching. Blood pressure was 97/54 mmHg and oxygen saturation 97% (room air). Initial electrocardiogram (ECG) revealed QT prolongation (QTc 529 ms), which remained moderately prolonged for two weeks. Notable biomarkers were pro-brain natriuretic peptide (proBNP) 1458 pmol/L and troponin T 24 ng/L, elevated INR (1.5), lactate dehydrogenase (215 U/L) and ALT (141 U/L). Hematological parameters revealed thrombocytopenia (111 × 10^9/L) and anemia (hemoglobin 9.6 g/dL). The Poison Control Centre suggested treatment with unithiol (2,3-dimercapto-1-propanesulfonic acid, DMPS). Due to the patient’s reluctance for treatment and the severity of the poisoning, he was sedated and intubated. Gastric lavage was performed about two hours after ingestion and unithiol initiated to enhance removal of the toxic substance. The arsenic concentration in urine was 196 µg/mL one day post-exposure, declining over the next days to 12.8 µg/mL (day three), 0.72 µg/mL (day six), and 168 µg/mL (day nine). Background level for arsenic in urine is 30–50 µg/mL [1]. The patient was discharged 15 days after ingestion with no neurological sequela and normal biochemistry values.

Conclusion: Ingestion of copper acetoarsenite is harmful and can cause serious poisoning. Our patient had typical early symptoms associated with acute arsenic and copper poisoning, with abdominal pain, nausea, and retching. The elevation in cardiac biomarkers was probably caused by arsenic’s direct cardiotoxic effect. Early treatment with aggressive gastric decontamination, unithiol, supportive care, and close monitoring of the patient can reduce the severity of a potentially lethal intoxication.

Reference

194. HydroxoSavêe: empiric prehospital cyanide treatment with hydroxocobalamin in house fire patients

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Objective: Despite the known risk of cyanide toxicity in house fires and the well demonstrated benefit of hydroxocobalamin in cyanide poisoning, many first responders do not routinely administer hydroxocobalamin. In addition, there is a paucity of data regarding prehospital hydroxocobalamin use. We present two cases in which hydroxocobalamin administration at the scene of a house fire appeared to prevent death in one patient.
**Case series:** Case 1: A 52-year-old woman with no known significant past medical history was found unresponsive in front of a house fire. Intravenous (IV) access was established and the patient was intubated on scene by Emergency Medical Services (EMS) personnel. Hydroxocobalamin 5 g, was administered IV on scene. On arrival to the Emergency Department, she was tachycardic (118 bpm) and hypertensive (220/97 mmHg). Initial blood gas analysis showed pH 6.9, PCO₂ 57 mmHg, HCO₃⁻ 14 mEq/L, and a lactate 13 mmol/L. She was given sodium thiosulfate 12.5 g IV. Her carboxyhemoglobin level was 36.9% and she was transferred for hyperbaric oxygen therapy. Although the patient’s hospital course was complicated by pneumonia, she was extubated on day 5 of admission and later discharged with no reported neurological complications. Case 2: Concurrently, another patient, a 64-year-old man with a prior history of seizure disorder and prior cerebrovascular accident was pulled from the same building on fire. He was found to be in cardiac arrest with pulseless electrical activity. He was given hydroxycobalamin 5 g IV and thiosulfate 12.5 g IV in addition to epinephrine 1 mg twice on scene by EMS, with return of spontaneous circulation. His carboxyhemoglobin level was >20% and a head computed tomography showed evidence of anoxic brain injury. Unfortunately, he expired in the Emergency Department shortly after presentation. A pre-hospital blood sample was obtained and tested for cyanide, revealing a concentration of 24 μmol/L (toxic range >20 μmol/L).

**Conclusion:** Cyanide poisoning from house fires is well recognized. Hydroxocobalamin has a proven efficacy as a cyanide antidote when administered in a timely fashion. However, a large number of EMS systems in the US do not carry hydroxocobalamin or any other cyanide antidote. Here, we report on the administration of pre-hospital hydroxocobalamin after a house fire in two patients, one with a confirmed toxic cyanide concentration. These cases should lead to a discussion about EMS antidote stocking of hydroxocobalamin and the need for future research on this subject.

### 195. Dermal exposure to hydrofluoric and sulfuric acid treated with yogurt

Cicily E. Little, Matt Mink and Ryan Chuang

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**Objective:** Dermal exposures to hydrofluoric acid (HF) may be underappreciated due to delayed onset of symptoms and few external physical findings. Prehospital treatment with a calcium source while en route to medical care may offer some pain relief until definitive care can be accessed.

**Case report:** Thirty minutes after using a decanted automotive aluminum cleaner diluted with an unknown amount of water (Autotemp AQUA LUM Aluminum Cleaner®; HF 3–7%, sulfuric acid 7–13%, detergents 1–5%), a 26-year-old female developed pain and tingling to her entire right hand rated at 5/10. Despite multiple hand washings, the pain remained 5/10 at the time of initial call to the local poison center. The estimated travel time to the nearest medical facility was one hour. Due to escalating pain and extended time until medical assessment, the Specialist in Poison Information recommended the topical application of any calcium-containing product available in the home. Activia Strawberry Vanilla Yogurt® was placed in a dishwashing glove and applied to the hand. Pain decreased to 3/10 with improvement in the tingling sensation within 5 minutes. Family followed up with the poison center 80 minutes later enquiring if hospital assessment was still required due to improvement in pain. They were directed to continue to proceed to the nearest healthcare facility. On arrival to the Emergency Department, pain relief (1/10) was achieved with application of calcium gluconate gel. Complete resolution of pain was achieved after 24 hours following standard 4 hours on/hour off calcium gluconate gel application.

**Conclusion:** HF exposures result in delayed onset of severe pain following low percentage exposures. The yogurt product used had 128 mg calcium/100 g with the average amount of calcium in yogurt being 142.22 mg calcium/100 g compared to 2.5% calcium gluconate gel, which contains 232 mg of elemental calcium. We cannot discount sulfuric acid as contributing to symptoms, nor the cooling effect of the yogurt in the improvement of pain. Application of the calcium gluconate gel at the hospital with even more pain relief suggests HF as the primary cause of symptoms. Yogurt is a possible source of calcium that can be applied dermally in non-hospital settings for improvement in pain following HF exposure prior to standard care of calcium gluconate gel in a medical setting.

### 196. Healthcare professionals’ experience in HAZMAT preparedness and responses in Thailand

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**Objective:** To evaluate Thai healthcare professionals’ experience in HAZMAT preparedness and responses.

**Methods:** A survey using self-administered questionnaires was performed at HAZMAT training courses provided by one of the authors (TJ) from August 2015 to September 2017.

**Results:** Of 325 questionnaires distributed, 270 responses (83.1%) were received. The median age was 31.0 years (IQR 28–34), most respondents were female (74.4%), and were from hospitals in non-industrial areas (77.8%). Some 46.7% of the respondents were in charge of HAZMAT preparedness and responses. A total of 82 HAZMAT incidents were identified through the responses, including 30 fatal incidents (36.6%). Most incidents involved chemical spills or explosions in industrial premises. The number of deaths and injuries concerning each incident ranged from 1 to 13 and to over 100, respectively. The majority of incidents (76.6%) involved decontamination. While an after-action review (AAR) was performed in 88.2% of the incidents, only 55.9% of the respondents indicated that HAZMAT response drills were conducted in their hospitals. Most respondents (83.7%) rated their hospital’s performance in HAZMAT responses as either “needs improvement” or “acceptable”. Further, while 89.2% of the respondents indicated that personal protective equipment (PPE) was available at their hospitals, only 43% indicated that fit-test was provided, and surprisingly, 38.8% of respondents indicated there were no designated decontamination areas in their hospitals. Antidotes concerning HAZMAT and most commonly stocked at respondents’ hospitals included pralidoxime (41.5%), methylene blue (29.4%), sodium nitrite (26.4%), and sodium thiosulfate (22.3%), despite the Thailand National Antidote Program [1]. Most respondents (91%) considered there were insufficient HAZMAT training courses available in Thailand, while 89.8% of respondents indicated they have consulted with the poison center for HAZMAT or other poisoning at least once. Being in hospitals located in industrial areas was associated with having experience in HAZMAT responses (OR 4.6, 95% CI 2.5, 8.5) compared to being in hospitals located in non-industrial areas.

**Conclusion:** The majority of Thai healthcare professionals in this study were not satisfied with the response to HAZMAT incidents...
provided by their hospitals. The areas for improvement include establishing designated decontamination areas, and conducting HAZMAT drills, PPE fit-tests, and other HAZMAT training.

Reference


197. Extraordinary mobilizations of Botulinum-Anti-Toxin from the National Stockpile to the Emergency Department: an efficient and versatile system for the provision of emergency antidotes

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Objective: Botulinum toxins are the most potent poisons known, and they can be used as a biological weapon. In Italy, botulinum-antitoxin (BAT) serum (250 mL vial of trivalent equine antitoxin against botulinum toxins A, B, E) is supplied by Ministry of Health (MoH) and from January 2017 is included in the extraordinary endowment of antidotes for chemical, biological, and radionuclear events (named “SNA”), due to the more frequent terrorist alerts. Nevertheless, botulism is relatively frequent in Italy, especially the food-borne form (approximately 50% of all European cases) due to the consumption of improperly home-canned foods [1]. Thus, BAT (located in the SNA stockpiles throughout Italy) can be rapidly mobilized in case of botulism through a specific procedure requiring (i) a preliminary clinical evaluation by the Pavia Poison Control Centre (PPCC), and then (ii) an on-time authorization by the MoH. We evaluate the BAT extraordinary mobilizations (BAT-EM) from SNA stockpiles over a 10-month period.

Methods: We investigated all BAT-EMS authorized/made in the period January–October 2017. For each mobilization (i) the clinical evaluation of the botulism case (e.g., form, severity, quantity of BAT vials), (ii) the National Health System (NHS) hospital location and (iii) the SNA stockpile involved were assessed.

Results: BAT-EMS from the SNA stockpile to an NHS hospital was performed 11 times (for 17 patients), and all cases was due to clinical suspicion of food-borne botulism. In 2 cases (involving 1 and 3 patients, respectively) the BAT was not administered as the intoxication was related to ingestion of vegetables contaminated with anticholinergic pesticides. BAT-EM for food-borne botulism intoxication involved 3 SNA stockpiles (Rome 8/11, Pavia 2/11, Taranto 1/11 located in 3 different Italian regions) for 10 different NHS hospitals located in 9 Italian regions. All the treated patients (13/17) received 2 vials of BAT (recommended dose; 10/13), except for 3/13 patients who received 1 vial/patient due to a mild clinical picture.

Conclusion: The distribution of SNA stockpiles throughout Italy ensures a rapid and efficient supply of BAT. SNA was established for unconventional events, but is an essential facility in order to obtain BAT in cases of botulism due to non-terrorist origin. The current organization of the SNA combines clinical toxicological expertise and antidote supply in order to maintain diagnostic and therapeutic appropriateness.

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Reference


198. Hallucinations and seizures: what are the most likely causes?

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Objective: A wide range of toxic agents can provoke hallucinations and seizures. In these clinical conditions, the identification of their cause can be difficult.

Methods: A retrospective chart review was performed on a selection of human exposure calls to our Poison Center. Patients who experienced hallucinations or seizures between 1 January 2016 and 31 December 2016 were included. Patients with symptomatology that was not attributable were excluded. Data were analyzed to identify trends in age and gender distribution, the most frequently involved agents and circumstances, and the relationship between these factors.

Results: Overall, 52 patients experienced hallucinations: 63.5% \((n = 33)\) males, 30.8% \((n = 16)\) females, 5.8% \((n = 3)\) unknown gender. The main circumstances were abuse 42.3% \((n = 22)\), adverse drug reaction in therapy/self-prescription (ADR/SP) 23.1% \((n = 12)\), and mental incapability 9.6% \((n = 5)\). The main agents were substances of abuse 30.8% \((n = 16)\), anticholinergic drugs 9.6% \((n = 5)\), multiple categories 9.6% \((n = 5)\), and plants 9.6% \((n = 5)\). Anticholinergic drugs were the main cause of hallucinations \((50\% n = 4)\) among children aged 0–5 years, whereas substances of abuse were the main cause \((40.0\% [n = 4]; 66.7\% [n = 4]; 63.6\% [n = 7])\) in patients aged 11–15, 16–20 and 21–40 years, respectively. ADR/SPs were predominant in patients aged less than 10 years of age and more than 61 years. Abuse prevailed in those aged 11 and 40 years. Seizures occurred in 35 patients 60.0% \((n = 21)\) males and 40.0% \((n = 14)\) females. The main circumstances were self-harm 48.6% \((n = 17)\), abuse 22.9% \((n = 8)\) and medical errors 8.6% \((n = 3)\). The most frequently involved agents were multiple categories 22.9% \((n = 8)\), substances of abuse 20.0% \((n = 7)\), antidepressants 8.6% \((n = 3)\), insulin 5.7% \((n = 2)\), and carbon monoxide 5.7% \((n = 2)\). The main causes were substances of abuse among patients aged 21–40 years, multiple categories and antidepressants among those aged 41–60 years. Abuse was one of the main circumstances for 16–40 year old patients, and self-harm for those between 21–60 years old, reaching 83.3% \((n = 10)\) among patients >41 years old.

Conclusion: More than 50% of patients experiencing hallucinations and 22.9% of those experiencing seizures are <20 years old. Substances of abuse in adults and anticholinergic drugs
(atropine) in children were identified as the main cause of hallucinations. Seizures were most likely provoked by self-harm with ingestion of multiple agents or antidepressants in patients >40 years, whereas substances of abuse are the most common agents in younger patients >16 years old.

200. Definition and treatment of benzodiazepine-resistant ethanol withdrawal syndrome

Hugo Langlois, Monique Cormier, Saif Al Ghafri, Eric Villeneuve, Robert S. Hoffman, Cristina Longo, and Sophie Gosselin

Objective: To determine the most common definition of benzodiazepine-resistant ethanol withdrawal syndrome (EWS) and assess practice variations in the use of phenobarbital for those patients.

Methods: We conducted a four-part, 25 questions online cross-sectional survey to assess different components of the evaluation and management of patients with EWS. The survey was conducted from 5 July to 18 September 2017 and deployed by email via administrators to the membership of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT), the Asia Pacific Association of Medical Toxicology (APAMT), the American Academy of Clinical Toxicology (AACT), and the Canadian Association of Emergency Physicians (CAEP). This study reports on two series of questions, which evaluated the definition of benzodiazepine-resistant EWS and use of phenobarbital in those patients. Respondents noted their preference for three common definitions for benzodiazepine-resistant EWS among Hack [1], NCT01652326 [2], and R.E.B.E.L. MD [3]. This study was approved by McGill University Health Centre Research and Ethics Board.

Results: Overall, 356 individuals responded to the survey. Response rate was low but difficult to quantify due to cross membership. Participants were mostly physicians (82.3%) specializing in emergency medicine (73.0%), aged 30–49 years (67%) with a range of experience. Clinicians were mostly practicing full-time (89.0%) in North America (91.8%), with 99% routinely treating EWS. The most popular definitions of benzodiazepine-resistant EWS were: high benzodiazepine dosage (65.2%); seizures (24.4%); and persistent tachycardia (16.3%). Only 52 (14.6%) reported that a high score on an EWS assessment tool indicated benzodiazepine resistance. Preferences were split among available definitions: Hack (28.0%); NCT01652326 (29.7%); and R.E.B.E.L. MD (28.0%). Phenobarbital was used most commonly for seizures (41.6%) or a high benzodiazepine dosage (28.9%). Only 14 (3.9%) used phenobarbital for a high severity score or persistent tachycardia.

Conclusion: This survey demonstrates wide practice variations in the definition and treatment of benzodiazepine-resistant EWS. However, we observed that high benzodiazepine dosage appears to be an important criterion for defining benzodiazepine resistance. A systematic review and consensus statement could help to guide optimal therapy.

201. Practice variation in the initial treatment of patients with ethanol withdrawal syndrome (EWS)

Hugo Langlois, Monique Cormier, Saif Al Ghafri, Eric Villeneuve, Robert S. Hoffman, Cristina Longo, and Sophie Gosselin

Objective: To determine practice variations in the initial management of patients with ethanol withdrawal syndrome (EWS).

Methods: We conducted a four-part, 25 questions online survey to assess different components of the evaluation and management of patients with EWS. The survey was conducted from 5 July to 18 September 2017 and deployed by email via administrators to the membership of the EAPCCT, APAMT, AACT, ACMT, and the Canadian Association of Emergency Physicians (CAEP). This study reports on two series of questions, which evaluated the initial management of patients with EWS. This study was approved by McGill University Health Centre Research and Ethics Board.

Results: Overall, 356 individuals responded to the survey. Response rate was low but difficult to quantify due to cross membership. Participants were mostly physicians (82.3%) specializing in emergency medicine (73.0%), aged between 30–49 years (67%) with a range of experience. Clinicians were mostly practicing full-time (89.0%) in North America (91.8%), with 99% routinely treating EWS. Participants indicated that diazepam (58.7%) and lorazepam (34.0%) were their preferred first-choice benzodiazepines for the treatment of EWS, with the Clinical Institute Alcohol Withdrawal Assessment Scoring Guidelines (CIWA-Ar) (50.6%) and modified CIWA-Ar (21.3%) the most commonly used scoring tools to evaluate severity in these patients. The Richmond Agitation Sedation Scale (RASS) was only used by 36 (10.1%) clinicians, with 47 (13.2%) indicating they do not use a tool to score their EWS patients, but prefer clinical assessment. Most participants (75.8%) administer thiamine to all patients with EWS, while others indicated in comments they only give thiamine when malnourishment was suspected. When indicated, the most common regimen used was 100 mg daily (44.7%) administered intravenously (IV) for a short duration. With regard to other adjuvants, only 72 (20.2%) of the participants reported administering IV multivitamins routinely to patients with EWS, while parenteral magnesium was given more frequently for those patients with low magnesium concentrations (55.6%), ECGs demonstrating a prolonged QT interval (37.9%) and seizures (17.1%). When indicated, the most commonly reported regimen was a single dose of 2 g IV
202. An outbreak of foodborne botulism in Rome, Italy

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Objective: Foodborne botulism is caused by consumption of preformed Clostridium botulinum toxins (BoNT) in food. Although rare events, botulism outbreaks, especially those involving commercially prepared products, represent a public health emergency, given the potential for a large number of cases [1].

Case series: In November 2016, a 71-year-old male (Case 1) presented to Umberto I Emergency Department (ED) with a 5-day history of diplopia, xerostomia, and constipation. He was afibrile with normal vital signs. Neurological examination confirmed left and right diplopia in the lateral vision, with no deficit in muscles tone, coordination, and osteotendon reflexes. He was held for further tests; the symptoms did not resolve. The Poison Control Center was alerted 2 days later, and a detailed anamnesis and food history revealed a meal consumed 10 days earlier with four friends in a public eatery. One of them was already hospitalized elsewhere for head trauma following a sudden fall, and showed severe weight loss (Case 2). Botulism was considered and then strongly suspected when informed by the local health department of a confirmed case in a patient who ate at the same restaurant on the same day. The remaining three diners were evaluated in our ED shortly after. Two (Case 3 and 4) reported dysphagia, diplopia, and constipation, associated with ptosis in one case. One patient was asymptomatic and discharged. An industrial preparation of vegetables in oil, used as a sandwich filling, was considered the most likely source. Trivalent-Equine-Antitoxin (TEqA, 750 IU-anti-A, 500 IU-anti-B, 50 IU-anti-E per mL) was administered. There was no progression of clinical signs and no one required mechanical ventilation. BoNT-producing clostridia, identified as type B, were detected in fecal samples. Patients were discharged after 12 (Case 1), 19 (Case 2) and 23 days (Case 3 and 4), respectively. In total, the outbreak produced 5 confirmed cases.

Conclusion: This report allows the following considerations: (i) mildly symptomatic botulism cases may escape recognition; (ii) clinicians should be trained to consider a diagnosis of botulism: an initial suspicion may lead to identification of other cases originally misdiagnosed; (iii) collaboration of medical and public health professionals is key to link multiple suspected cases to a common exposure. In summary, secondary prevention, which includes rapid identification, epidemiologic linkages of cases, and control of outbreaks resulting from contaminated food, is beneficial to prevent further spread and reduce morbidity and costs.

Reference


203. Probable case of botulism: treating with a grain of salt

Susanna M. Signoretti, Michele S. Milella, Paolo Boldrini, Bruna Auricchio, Fabrizio Anniballi and M. Caterina Grassi

Objective: Foodborne botulism is caused by ingestion of neurotoxins of Clostridium botulinum. Confirmed diagnosis is based on isolation of toxin in patient and/or food samples, but there are also cases with suggestive clinical symptoms associated with negative laboratory testing and responsive to specific antitoxin therapy.

Case report: On December 2016, a 39-year-old woman was admitted in a clinical department of Policlinico Umberto I for diarrhea and dysarthritis. Antibiotic and antiviral therapy was prescribed. Neurological exam was normal, and computerised tomography (CT) scan, magnetic resonance imaging (MRI), and cerebrospinal fluid analysis were negative. Three days later, symptoms progressed with the onset of ptosis, mydriasis, ophthalmoplegia, diplopia, xerostomia, dysphagia, and constipation, and the Poison Control Center was alerted. Foodborne botulism was suspected based on the anamnestic data, symptom onset and exclusion of other possible conditions. Rectal swabs were taken and Trivalent-Equine-Antitoxin (TEqA, 750 IU-anti-A, 500 IU-anti-B, 50 IU-anti-E per mL) was requested. Food samples consisting of oil industrial preparations of meat and vegetables in spreadable paste (paté) consumed regularly by the patient were sent for laboratory analysis. Antitoxin was then administered with a slow and progressive clinical amelioration over 48 hours. Culture of food samples revealed the presence of toxin producing Clostridium, while patient samples were negative. In the following days, ocular symptoms continued to improve, although a nasogastric tube was positioned for nutrition as liquid and solid dysphagia persisted. Fourteen days later, dysphagia for liquids and constipation resolved. Gradual improvement of symptoms continued over one month and she was discharged with a persistent diplopia. Two outpatient ophthalmological examinations at two and three months showed a gradual resolution of diplopia. On telephone follow-up, the patient reported facial muscles weakness four months after recovery.

Conclusion: This case allows the following considerations: (i) given that bacterial isolation in food does not constitute a valid laboratory diagnostic criterion; presence of clinical and epidemiologic criteria may define a probable botulism case [1]; (ii) neuromuscular sequelae several years after the critical phase have been reported [2], and may escape recognition if long-term follow-up sessions are not scheduled.
204. Finger prick capillary microRNA-122 is a biomarker of paracetamol hepatotoxicity

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**Objective:** Paracetamol overdose is the most common cause of acute liver failure in Western countries. Several strategies have been used to define the risk of acute liver injury (ALI) and to decide whether to treat patients with N-acetylcysteine (NAC). Despite such strategies, a small proportion of patients will still develop liver damage because their hepatotoxic risk is underestimated [1]. To improve risk stratification, new markers are currently under investigation. MicroRNA-122 (miR-122) has recently been demonstrated to be a marker of liver injury following paracetamol overdose. We have previously demonstrated that capillary miR-122 faithfully reflects the venous concentration [2]. This study was undertaken to confirm the reliability of capillary miR-122, measured in a finger prick blood drop, as a biomarker of paracetamol induced ALI. Capillary miR-122 promises to facilitate rapid point-of-care diagnosis with minimal sample preparation.

**Methods:** Thirty-eight patients with paracetamol overdose were enrolled in this study. All patients were treated with the SNAP 12-hour NAC regimen (300 mg/kg body weight). Ten hours after beginning NAC, a capillary blood drop was obtained through a finger prick. miR-122 was measured by quantitative polymerase chain reaction in collected samples. Results were compared with alanine aminotransaminase (ALT) activity. miR-122 was also compared between patients without liver injury (ALT < 50 IU/L), with borderline liver injury (ALT 50–100 IU/L) and with ALI (ALT >100 IU/L). Non-normal data comparisons were made using the Mann–Whitney U test. Pearson’s correlation test was used for correlation analysis. Results were considered significant when \( p < 0.05 \).

**Results:** Capillary miR-122 was positively correlated with ALT measured at 10 hours and at 20 hours after commencing NAC \(( r = 0.83, \; p < 0.0001; \ r = 0.96, \; p < 0.0001 \text{, respectively})\). MI-122, measured after 10 hours of NAC treatment, was significantly higher in patients who developed ALI (ALT >100) at 10 \(( n = 2, \; p = 0.0036)\) and 20 hours \(( n = 2, \; p = 0.0062)\) after beginning of NAC treatment.

**Conclusion:** Our data support the reliability of capillary miR-122 as a predictive marker of liver damage caused by paracetamol overdose and confirm its utility as a simple and minimally invasive diagnostic test when collected by finger prick.

**References**


205. Acute kidney injury in Australian snake envenoming: common, multifactorial and somewhat avoidable (ASP-26)

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**Objective:** To describe the frequency and severity of acute kidney injury (AKI) resulting from Australian snake envenoming and the effect of antivenom.

**Methods:** The is an ongoing prospective observational study of snakebite patients Australia-wide. Data was extracted from a database including demographics, snake type, clinical syndromes, serial creatinine measurements, and treatment (antivenom, dialysis). AKI was defined according to the RIFLE (Risk, Injury, Failure, Loss of kidney function, and end-stage kidney disease) criteria. Baseline serum creatinine was taken as the lowest recorded or upper limit of normal for age, whichever was lowest.

**Results:** Overall, 1962 patients were recruited between 2001 and 2017. Of these, 982 (50%) were envenomed, 289 patients (29%) developed AKI. According to RIFLE criteria patients were classified as: risk 156 (54%), injury 59 (20%), and failure 74 (26%). For the 133 patients with moderate or severe AKI (RIFLE: Injury/Failure), the median age was 45 years (IQR 30–58; range 2–81), 13 (10%) patients were <18 years old, 95 (71%) were male and 24 (18%) were snake handlers. Most commonly causing snake types were brown snake (43%), tiger snake (14%), taipan (11%), and rough-scaled snake (3%). Renal replacement therapy was used in 13 patients. In the 120 non-dialysed patients, the median peak serum creatinine was 261 µmol/L (IQR 154–465; range 54–1383) with a median time to peak serum creatinine of 37 hours (IQR 18–90; range 1.1–474 hours). Death occurred in 10 patients. Co-existing/causative features of envenoming included venom induced consumption coagulopathy (VICO) (68%), microangiopathic hemolytic anemia (MAHA) (51%), partial VICO (24%), myotoxicity (24%), hemodynamic instability/major bleeding (11%) and anticoagulant coagulopathy (3.8%). Patients with RIFLE Injury/Failure received antivenom a median of 5 hours post-bite (IQR 3.3–7.5 hours; \( n = 127 \)), which was significantly longer than both those who did not develop AKI (median 4.1 hours; IQR 2.7–6 hours; \( n = 570 \)) and those who were only at risk (median 3.6 hours; IQR 2.2–5.6; \( n = 135, \; p < 0.0002; \) Kruskal–Wallis Test). There was a reduction in the proportion of patients developing more severe injury when antivenom was given within 2 hours (11.2% versus 15.9%; difference,4.7%; 95% confidence interval [CI] 1% to 13%) and within 4 hours (11.1% versus 19%; difference 7.9%; 95% CI 3% to 13%). The number of patients treated with dialysis was less when antivenom was given within 2 hours (1 versus 11) and 4 hours (2 versus 10). The median length of stay in the 123 patients with RIFLE Injury/Failure that survived to discharge was 183 hours (IQR: 87–336 hours).

**Conclusion:** AKI is a common and often unrecognised syndrome associated with multiple other venom effects. Early antivenom
appears to be associated with a decreased frequency and severity of AKI.

206. Role of norepinephrine transporter gene variations in the cardiostimulant effects of 3,4-methylenedioxyamphetamine (MDMA)

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Objective: MDMA (ecstasy) is used recreationally and frequently leads to sympathomimetic toxicity. MDMA produces cardiovascular and subjective stimulant effects that were shown to partially depend on the norepinephrine transporter (NET)-mediated release of norepinephrine and stimulation of α1-adrenergic receptors [1,2]. Genetic variants, such as single-nucleotide polymorphisms (SNPs), of the NET gene (SLC6A2) or α1-adrenergic receptor gene (ADRA1A) may explain interindividual differences in the acute stimulant-type responses to MDMA in humans.

Methods: We characterized the effects of common genetic variants of the SLC6A2 gene (rs168924, rs47958, rs1861647, rs2242446, and rs36029) and ADRA1A gene (rs1048101) on cardiovascular and subjective stimulation after 125 mg MDMA administration in 132 healthy subjects (64 male, 68 female) in a pooled analysis of 8 double-blind, placebo-controlled studies. Differences in maximal effects (MDMA-placebo) were analyzed using one-way analyses of variance (ANOVs) with genotype as between-subject factor. The area under the MDMA plasma concentration-time curve from 0–6 h was included as covariate in the ANOVAs, and p-values were Bonferroni corrected for the six SNPs.

Results: Carriers of the GG genotype of the SLC6A2 rs1861647 SNP presented higher elevations of heart rate and rate-pressure product after MDMA than subjects with one or no G alleles (mean ± SD increase: +23 ± 15 versus +15 ± 14 bpm and +555 ± 2831 versus +4016 ± 2895 mmHg·bpm, respectively; F1,128 = 8.92, p = .02 and F1,128 = 7.81, p = .04, respectively). Subjects with the CC genotype of the SLC6A2 rs2242446 SNP presented higher elevations of the rate-pressure product after MDMA administration compared with the T-allele group (+24 ± 11 versus +17 ± 9 mmHg; F1,129 = 7.41, p = .04). Subjects with the AA genotype of the SLC6A2 rs36029 SNP presented higher elevations of mean arterial pressure and rate-pressure product after MDMA administration than carriers of the G allele (+23 ± 10 versus +16 ± 9 mmHg and +5458 ± 2972 versus +4272 ± 2873 mmHg·bpm, respectively; F1,129 = 9.83, p = .01 and F1,129 = 7.28, p = .047, respectively). The SLC6A2 rs168924 and rs47958 SNPs and ADRA1A rs1048101 SNP did not alter the response to MDMA.

Conclusion: Genetic polymorphisms of the SLC6A2 gene weakly moderated the acute cardiovascular response to MDMA in controlled studies and may play a minor role in adverse cardiovascular events when MDMA is used recreationally. ADRA1A rs1048101 polymorphism did not moderate MDMA effects.

References

207. The potential utility of microRNA for comparing efficacy of acetylcysteine regimens in paracetamol overdose

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Objective: MicroRNA (miR)-122 expression increases, and miR-483 decreases with paracetamol liver injury. We compared the clinical safety of an abbreviated 12 hour IV acetylcysteine protocol (200 mg/kg over 4 hours, 50 mg/kg over 8 hours) with a 20-hour regimen (200 mg/kg over 4 hours, 100 mg/kg over 16 hours) in patients with low risk of liver injury after acute paracetamol poisoning (NACSTOP-trial).

Methods: A convenience sample of patients treated with acetylcysteine following paracetamol overdose was recruited from NACSTOP. Patients with a normal ALT at presentation and low paracetamol (<20 mg/L) and normal ALT 12 and 20 hours from the start of acetylcysteine were included. Two comparative groups not enrolled in NACSTOP with acute liver injury (ALI: ALT >50 IU/L and double baseline) or hepatotoxicity (ALT >1000 IU/L) were also included. miR-122 expression (quantification cycle, Cq), miR-483 and a miR-ratio (2^-deltaCq miR-122/483) were determined from patient samples. Cq results are inversely proportional to miR-expression.

Results: Of the 38 patients, eight received the 12-hour (abbreviated) and 20 received the 20-hour (control) NACSTOP acetylcysteine regimens; seven patients with ALI and three with hepatotoxicity were also included. The overall median age was 22 years (IQR 18,32) and 70% were female. Median acetylcysteine duration was 13 hours in those receiving the abbreviated regimen, 20 hours in the control and ALI groups and 60 hours in those with hepatotoxicity. Median time to starting acetylcysteine was 6 hours (IQR 5.5,12), 6.5 (5.6,10.5), 7 (5.12), 24 (12,31); median peak ALT was 13 (IQR 10,20) IU/L, 20 (14,22), 83 (61,100), 2365 (2035,15601); and median peak miR-122 Cq was 29.6 (IQR 28.7,31.0), 29.7 (28.6,32.7), 29.0 (23.1,32.4), 23.7 (21.1,23.8) in the abbreviated, control, ALI, and hepatotoxicity groups, respectively. There was no significant difference in median peak ALT or miR-122 Cq between abbreviated and control NACSTOP groups (p >.05). There was no difference in presentation median miR-122 Cq value (30.1 [IQR 28.9,31.5]; 30.9 [29.3,31.5]; 28.9 [25.8,33.6]; 26.2 [23.8,31.6]) in the abbreviated, control, ALI, and hepatotoxicity groups, respectively (p = .28). However, there was a significant difference in presentation median miR-ratio in the abbreviated (1.8 [IQR 0.5,4.4]) + control (1.8 [0.4,3.6]) compared to the hepatotoxicity group (34.6 [6.1,52.1]) (p <.02).

Conclusion: Presentation and peak miR-122 and miR-122/483 ratios were similar in those with low risk of developing hepatotoxicity. The miR ratio may be a better predictor of hepatotoxicity.
208. Relative risk of combining benzodiazepine with opioids based on National Poison Data System (NPDS) exposure outcome data

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**Objective:** The hazard of the use of opioids along with benzodiazepines or other central nervous system depressants compared to opioids alone has been reported, based on prescribing pattern mortality, US Veteran’s Administration, and Drug Abuse Warning Network (DAWN) data. NPDS data was not included in these analyses. On 31 August 2016, the US FDA announced new prescription guidelines cautioning against the concomitant prescribing of opioids and benzodiazepines and the requirement for a “black boxed warning” in drug labeling of prescription opioid pain and cough medicines, and benzodiazepines. Our objective was to quantify the hazard of concomitant opioid and benzodiazepine exposure based on NPDS outcome data.

**Methods:** We tabulated NPDS closed, human, exposures to opioids, and opioid + benzodiazepine by year (2000–2016). More serious outcomes (MSO = Medical outcome of moderate, major or death) and total exposures were determined by individual opioid class generic code, benzodiazepine, and opioid + benzodiazepine. Total exposures were corrected for the relative decline in less serious exposures compared to MSO exposures. A morbidity index (morbidity), defined as 1000*MSO/Total exposures, was calculated for each exposure group using SAS JMP 12.0.1. Relative risk and confidence intervals [CIs] for opioid + benzodiazepine to opioid only were calculated using StatsDirect 3.1.11.

**Results:** Overall, 791,667 exposures were identified, of which 130,463 (16.3%) were MSOs and 43,851 (5.47%) involved opioid + benzodiazepine. The morbidity index (morbidity), defined as 1000*MSO/Total exposures, was calculated for each exposure group using SAS JMP 12.0.1. Relative risk and confidence intervals [CIs] for opioid + benzodiazepine to opioid only were calculated using StatsDirect 3.1.11.

**Conclusion:** NPDS opioid alone and opioid + benzodiazepine combinations revealed a more than doubling of morbidity and clearly supports the mortality reports. NPDS exposure outcome data and a simple morbidity index can be readily calculated and followed over time using this near real-time nationwide database.

**Table 1.** The morbidity for 12 of the most commonly reported opioids and each opioid + benzodiazepine group in National Poison Data System (NPDS) exposure outcome data (2000–2016).

<table>
<thead>
<tr>
<th>Opioid name</th>
<th>Morbidity index</th>
<th>Relative risk [95% CI]</th>
<th>Opioid + benzodiazepine</th>
<th>More serious exposures</th>
<th>Total exposures (corrected)</th>
<th>Opioid only</th>
<th>More serious exposures</th>
<th>Total exposures (corrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin</td>
<td>380.5</td>
<td>362.2</td>
<td>1.05</td>
<td>[1.00, 1.10]</td>
<td>1294</td>
<td>3401</td>
<td>11,805</td>
<td>32,588</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>410.0</td>
<td>275.9</td>
<td>1.49</td>
<td>[1.31, 1.67]</td>
<td>167</td>
<td>407</td>
<td>1949</td>
<td>7063</td>
</tr>
<tr>
<td>Methadone</td>
<td>447.9</td>
<td>262.6</td>
<td>1.71</td>
<td>[1.65, 1.76]</td>
<td>2822</td>
<td>6300</td>
<td>8063</td>
<td>30,705</td>
</tr>
<tr>
<td>Tramadol</td>
<td>184.6</td>
<td>151.6</td>
<td>1.22</td>
<td>[1.14, 1.29]</td>
<td>875</td>
<td>4740</td>
<td>12,514</td>
<td>82,535</td>
</tr>
<tr>
<td>Morphine</td>
<td>321.8</td>
<td>127.4</td>
<td>2.53</td>
<td>[2.37, 2.69]</td>
<td>781</td>
<td>2427</td>
<td>4066</td>
<td>31,920</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>209.1</td>
<td>117.4</td>
<td>1.78</td>
<td>[1.59, 1.99]</td>
<td>302</td>
<td>1445</td>
<td>1443</td>
<td>12,294</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>284.1</td>
<td>103.3</td>
<td>2.75</td>
<td>[2.63, 2.87]</td>
<td>2102</td>
<td>7398</td>
<td>6257</td>
<td>60,553</td>
</tr>
<tr>
<td>Oxycodone + paracetamol</td>
<td>229.9</td>
<td>84.6</td>
<td>2.72</td>
<td>[2.59, 2.85]</td>
<td>1833</td>
<td>7974</td>
<td>6050</td>
<td>71,492</td>
</tr>
<tr>
<td>Hydrocodone + Paracetamol</td>
<td>208.8</td>
<td>75.7</td>
<td>2.76</td>
<td>[2.67, 2.84]</td>
<td>4570</td>
<td>21,891</td>
<td>14,199</td>
<td>187,524</td>
</tr>
<tr>
<td>Codeine + paracetamol</td>
<td>192.3</td>
<td>65.7</td>
<td>2.93</td>
<td>[2.66, 3.22]</td>
<td>397</td>
<td>2065</td>
<td>2453</td>
<td>37,360</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>180.5</td>
<td>44.7</td>
<td>4.04</td>
<td>[3.3, 4.92]</td>
<td>107</td>
<td>593</td>
<td>335</td>
<td>7495</td>
</tr>
<tr>
<td>Codeine</td>
<td>128.4</td>
<td>31.1</td>
<td>4.13</td>
<td>[3.05, 5.53]</td>
<td>42</td>
<td>327</td>
<td>369</td>
<td>11,855</td>
</tr>
</tbody>
</table>

**Conclusion:** Serotonin toxicity is a relatively common following an SSRI or SNRI overdose, and the risk increases with dose ingested. Consistent with the pharmacology, monoamine oxidase inhibitor
co-ingestion increases the risk markedly, while co-ingestion of two antipsychotics that have 5-hydroxytryptamine (5-HT₂) antagonist activity, decrease the risk.

210. Large inter-batch variation in acute adverse reactions to Indian polyvalent antivenom

Anjana Silva⁵, Nuwan Premawardene⁵, Anoma Bandaranayake², Sisira Siribaddana³ and Geoffrey K. Isbister⁶

¹Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka, Anuradhapura, Sri Lanka; ²Internal Medicine Unit, Teaching Hospital Anuradhapura, Anuradhapura, Sri Lanka; ³Clinical Toxicology Research Group, University of Newcastle, Newcastle, Australia

Objective: Acute adverse reaction to antivenom is a major concern with snakebite treatment. We investigated the frequency and contributory factors to adverse reactions to antivenom.

Methods: A prospective 14-month cohort study of snakebites in a tertiary hospital in Sri Lanka. Detailed information on snakebite, antivenom treatment (Bharat Serums and Vaccines Ltd or VINS BioProducts Ltd), adverse reactions and premedication were recorded.

Results: Of 776 snakebites, 266 (34%) received 383 antivenom doses. Of these, 137 received a single dose while 93 received 2 or more doses. Overall, 360 doses were VINS antivenom from nine different batches and 21 were Bharat antivenom from two batches, and two doses were a combination. There were 324 (84%) 20-vial doses and the remainder were 10-vial doses (500 mL of normal saline given intravenously over 1 hour). Acute adverse reactions occurred after 139 (36%) antivenom doses administered to 122 (46%) patients. Reactions occurred a median of 20 minutes (range 3–150 minutes, IQR 10–30 minutes) after commencement of antivenom, for a median duration of 15 minutes (IQR 10–30 minutes; range 5 minutes to 3 days). Acute adverse reactions included hypotension (systolic blood pressure < 90 mmHg; 60%), chills (56%), rigors (54%), hypoxia (SpO₂ < 92%; 31%), nausea (17%), vomiting (17%), urticarial rash (17%), and wheezing (8%). Severe anaphylaxis occurred in 98/139 (71%) adverse reactions. Seven patients had persistent hypotension for two antivenom treatments, and two doses were a combination. There were 324 (84%) 20-vial doses and the remainder were 10-vial doses (500 mL of normal saline given intravenously over 1 hour). Acute adverse reactions occurred after 139 (36%) antivenom doses administered to 122 (46%) patients. Reactions occurred a median of 20 minutes (range 3–150 minutes, IQR 10–30 minutes) after commencement of antivenom, for a median duration of 15 minutes (IQR 10–30 minutes; range 5 minutes to 3 days). Acute adverse reactions included hypotension (systolic blood pressure < 90 mmHg; 60%), chills (56%), rigors (54%), hypoxia (SpO₂ < 92%; 31%), nausea (17%), vomiting (17%), urticarial rash (17%), and wheezing (8%). Severe anaphylaxis occurred in 98/139 (71%) adverse reactions. Seven patients had persistent hypotension for 3 days requiring continuous inotropes, likely causing one fatality. A marked inter-batch variation in acute adverse reaction rates was observed for nine batches of VINS antivenom (median 52%; IQR 30–66%; range 21–94%), and 8% and 22% for two Bharat batches. There was no association between age, sex, snake type and antivenom use, and the occurrence of reactions (Table 1). Subcutaneous adrenaline, hydrocortisone, and chlorpheniramine were given in 17%, 70%, and 56% of the cases, respectively as pre-medication, which was not associated with a decrease in reactions (p > .05, Fisher’s exact test).

Conclusion: Life-threatening antivenom reactions remain a major concern with Indian antivenom. Marked inter-batch variation in reactions means that further post-marketing surveillance of individual batches is required.

211. Pre-workout supplements: the new trend

Chantal C. J. Roelen⁴, Antoinette J. H. P. Van Riel⁴, Bastiaan J. Venhuis⁵, Pauline M. Verputten⁶ and Irma De Vries⁴

⁴Dutch Poisons Information Center, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands; ⁵National Institute for Public Health and the Environment, Bilthoven, Netherlands

Objective: Annually, the Dutch Poisons Information Center (DPIC) handles approximately 100 consultations regarding slimming, sports, or bodybuilding supplements. These supplements contain stimulating ingredients and some are adulterated with illegal substances [1]. Currently, the so-called pre-workout supplements are trending and the health risks associated with these products were investigated. Usually, these products are powders to be mixed with water before use. According to the labelling, they mostly contain caffeine, green tea, vitamins, proteins, and various herbal ingredients. They are supposed to increase energy, focus, and endurance, and are typically taken just before a workout.

Methods: All telephone inquiries to the DPIC in the last three years were analyzed. From January 2016 onwards, samples of products were requested for analysis by the National Institute for Public Health and the Environment (RIVM).

Case series: In 2015, 2016, and 2017 (up to September) the DPIC was consulted for 4, 17, and 15 cases, respectively, involving 36 patients (75% male). The median age of intentional users was 22 years (range 15–37 years). Three children (≤2 years) had accidentally taken the supplement. Adverse effects were reported after taking the recommended dose (n = 13) or even half of this (n = 2). In 18 cases, overdoses were taken, mostly twice the recommended dose (n = 9), but up to 30 times. Reported symptoms included dizziness, agitation, anxiety, dilated pupils, hyperventilation, dyspnea, syncope, tremor, fever, tachycardia, hypertension, chest pain, and hallucinations. Seven patients required hospital care. The onset of symptoms was within a few minutes to hours after ingestion, whilst in 16 cases, they began during the workout. The pre-workout supplements were mostly purchased online. Between January 2016 and September 2017, 6 samples were obtained. Two samples have been analyzed so far and showed higenamine and 1,3-dimethylamylamine (1,3-DMAA). Both ingredients are prohibited by the World Anti-Doping Agency (WADA) and are associated with rhabdomyolysis and serious cardiovascular complications, respectively [2].

Conclusion: The use of pre-workout supplements is increasingly popular, but can give rise to severe adverse effects, often occurring during exercise. This setting may further increase the cardiovascular risks associated with these supplements. In some samples, forbidden substances, such as 1,3-DMAA were found.

Table 1. Characteristics of patients with and without reactions to Indian polyvalent antivenom.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Adverse reactions (n = 122)</th>
<th>Nil reactions (n = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: median (IQR)</td>
<td>42 (32–51) years</td>
<td>40 (27–48) years</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>79 (65%)</td>
<td>106 (73%)</td>
</tr>
<tr>
<td>Bite-to-antivenom delay: median (IQR)</td>
<td>3.6 (2.8–5.6) hours</td>
<td>3.7 (2.8–4.8) hours</td>
</tr>
<tr>
<td>Past history of snakebite</td>
<td>11 (9%)</td>
<td>17 (12%)</td>
</tr>
<tr>
<td>Biting species: Russell’s viper</td>
<td>87 (71%)</td>
<td>103 (72%)</td>
</tr>
<tr>
<td>Peak serum Russell’s viper venom concentration: median (IQR)</td>
<td>326 (48–1112) ng/mL</td>
<td>326 (36–599) ng/mL</td>
</tr>
</tbody>
</table>
References


212. A new concentration of a pediatric ibuprofen suspension available for purchase: analysis of the impact on therapeutic errors

Hayley M. Vergan, Attilio Negri, Adriana M. Tomoig, Fabrizio Sesana, Angelo R. Travaglia and Franca Davanzo

Objective: Nurofen® febbre e dolore (fever and pain) is a drug in suspension form containing ibuprofen, which is widely used in children. It has been marketed in two different dosages, 100 mg/5 mL and 200 mg/5 mL, in similar packaging. The 200 mg/5 mL concentration was authorised by the Italian Medicines Agency (AIFA) in December 2014. Our aim is to evaluate any increase in therapeutic errors by analysing the number of telephone calls, regarding this drug, received at our Poison Control Centre after the introduction of the new dosage.

Methods: We queried poison centre “Nurofen febbre e dolore” therapeutic error cases from 1 January 2014 to 30 June 2017. The data collected includes: demographic data, suspension concentration, circumstances, and symptoms.

Results: In total, 249 enquiries about therapeutic errors with “Nurofen febbre e dolore” were retrieved. Mean age of the patients was 5.3 years, and the majority of them (67.5 %) were under 6 years of age. In 2014, when only the 100 mg/5 mL formulation was on sale, we registered 32 errors. There were 54 errors in 2015 and 107 in 2016. Comparing the first half of each year, errors increased from 2014 to 2016, whilst in 2017 errors were in line with 2016. Overall, the main errors were dosing mistakes (88%). Since 2015, when both formulations became available, there were 217 errors, while 131 involved the new concentration medication. Almost two-thirds (62%) of the errors that occurred with the 200 mg/5 mL formulation were because it was mistaken for the 100 mg/5 mL product. In 23% of these cases, the mistake was made at home, in 35% errors were attributable to healthcare professionals because of lack of clarity in prescription or indications. In 42%, the reason for the errors was not identifiable. Overall, only 8 children reported symptoms, with nausea, vomiting, abdominal pain, heartburn, and haematochezia (maximum degree of severity according to the Poison Severity Score was 2).

Conclusion: Placing a pharmaceutical product on the market with a different concentration, but with the same name and similar packaging to another medication can cause confusion both in healthcare professionals and medication end-users as well, therefore increasing therapeutic errors. This medication has low toxicity, so the errors observed did not cause serious clinical symptoms. We believe that a greater diversification of the packaging would help avoid errors, and that better communication by health workers at the time of prescription and sale is needed.

213. Acute pediatric poisoning in Slovakia: changes over the years

Silvia Plackova, Blazena Caganova, Olga Otrubova, Jaroslav Kresanek and Igor Bator

Objective: The National Toxicological Information Centre (NTIC) in Bratislava responds to approximately 5000 enquiries every year from all over Slovakia. With the aim to obtain more information about the structure of poisoning in children, we performed a retrospective analysis of all enquiries in children in the years 2007 and 2016.

Methods: Acute poisonings in 2016 were analysed for age, sex, intent of exposure, substances ingested and clinical severity. We compared our data with previous data from the year 2007, i.e., 10 years ago.

Results: In 2016, the number of all enquiries increased by 69% compared to 2007. Consultations by the general public increased fourfold. In 2016, the NTIC was consulted about 2684 children, a 100% increase compared to more than 10 years ago. The majority of cases (1834 children, 68.3%) were under five years of age with peak age three. Most of the cases were accidental (93%). Suicidal cases (7%) occurred in children over the age of 10, except for two 8-year-old children. In the age group 11–18 years, suicidal intoxications by medicaments prevailed, mostly involving girls. Intoxications with psychoactive substances (0.7%) were represented mainly by amphetamines and plant-derived drugs. Despite the fact that the number of enquiries increased in 2016, symptoms of intoxication occurred only in 21.6% compared to 31.5% in 2007. In 2016, pharmaceuticals were the most frequent agent of poisoning (38%), however, their representation dropped by 7% compared to 2007. Dimetindene, colecalciferol, ibuprofen, potassium permanganate, and paracetamol were the substances most frequently ingested in children under 5 years of age in 2016 and 2007. In 2007, the number of household cleaning products made up 15%, and in 2016, their number almost doubled (29%). We also observed an increase in consultations about plants. The most frequently ingested plants in 2007 were Datura stramonium, Dieffenbachia, and Atropa belladonna while in 2016, Zamioculcas zamiifolia, Taxus baccata, and raw fruit of Sambucus nigra were common.

Conclusion: Medicines are still the most frequent cause of acute poisoning in children. Compared with the previous years, the number of poisonings with household cleaning products has significantly increased. The types of indoor plants have changed as a reflection of new houseplant trends. In order to minimize intoxications, all preventive measures against poisoning should be taken including preventive strategies of education at national level, especially in drug and household product storage.
214. Unintentional pediatric exposures to prescription medications in Europe as reported to the RADARS® System Global Toxicosurveillance Network

Zachary R. Margolin1, Stevan G. Severtson2, Samantha J. Leroy3, Laura J. Fischer4, Jody L. Green5, Bruno Mégarbana6, Antoine Villa7, Andreas Schaper8, Martin Ebbecke9, Fabrizio Sesana10, Simon H. L. Thomase and John P. Thompsonf

1Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, Denver, Colorado, United States; 2Centre Antipoison et de Toxicovigilance de Paris, Hospital Fernand Widal, Paris, France; 3GIZ-Nord Poisons Centre, University Medical Centre Göttingen, Göttingen, Germany; 4Poison Control Centre of Milan, Asst Grande Ospedale Metropolitano Niguarda, Milan, Italy; 5Newcastle Unit Poison Centre, National Poisons Information Service (Newcastle), Newcastle, United Kingdom; 6Cardiff Unit Poison Centre, National Poisons Information Service (Cardiff), Cardiff, United Kingdom

Objective: To determine drug products most commonly mentioned in unintentional, pediatric exposures within France, Germany, Italy, and the UK as reported to the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System Global Toxicosurveillance Network (GTNet).

Methods: GTNet was established in 2011 as a means of collaboration between countries to provide information about prescription drugs involved in acute health events as reported to participating poison centres worldwide, including intentional and unintentional exposures. Data collected on prescription opioids, stimulants, sedatives, benzodiazepines, and GABA analogues from participating poison centres in GTNet were analyzed from 2012 through 2016. Unintentional exposures involving children 5 years of age and younger reported to participating poison centres in Italy (Milan), the United Kingdom (Birmingham, Cardiff, Edinburgh, Newcastle), Germany (Göttingen), and France (Paris) are presented. The UK provides medical management advice to healthcare providers only, while the other poison centres also offer services to the public.

Results: In France, there were 372 pediatric exposures to prescription drugs of interest reported between 2012 and 2016. Codaene was the most common substance mentioned (n = 66, 17.7%) followed by alprazolam (n = 63, 16.9%), zolpidem (n = 48, 12.9%), and tramadol (n = 36, 9.7%). In Germany, there were 382 pediatric exposures to prescription drugs of interest reported between 2012 and 2016. Methylphenidate (n = 68, 17.8%) was the most common substance mentioned followed by codeine (n = 61, 16.0%), lorazepam (n = 44, 11.5%), diazepam (n = 24, 6.3%), and tramadol (n = 24, 6.3%). In Italy, there were 709 pediatric exposures to prescription drugs of interest reported between 2012 and 2016. Alprazolam (n = 200, 28.2%) was the most common substance mentioned followed by lorazepam (n = 193, 27.2%), diazepam (n = 71, 10.1%), and lormetazepam (n = 68, 9.6%). In the UK, there were 489 pediatric exposures to prescription drugs of interest reported between 2012 and 2016. Codaene (n = 105, 20.5%) was the most common substance mentioned followed by tramadol (n = 97, 19.0%), diazepam (n = 39, 7.6%), gabapentin (n = 38, 7.4%), and morphine (n = 38, 7.4%).

Conclusion: Between 2012 and 2016, there is variation in the most common drug products mentioned in pediatric exposures reported to poison centres across France, Germany, Italy, and the UK.

References


216. Cholinergic crisis in a toddler after accidental pyridostigmine intoxication

Johanna Nordmark Grass and Birgitta Jonsson
Swedish Poisons Information Centre, Stockholm, Sweden

Objective: Pyridostigmine is a carbamate cholinesterase inhibitor in clinical use for the treatment of myasthenia gravis. Inhibition of cholinesterase increases the concentration of acetylcholine in the synaptic cleft stimulating both muscarinic and nicotinicergic transmission. This can cause devastating cholinergic toxicity in insecticide or nerve gas poisoning. Pyridostigmine has a short half-life (0.5–3 hours), however, and this may explain why very few cases of overdoses have been reported. We present a case of pyridostigmine intoxication in a child causing a life-threatening cholinergic toxidrome.

Case report: A 2.5-year-old, previously healthy, boy accidentally ingested his mother’s pyridostigmine, which she was taking for myasthenia gravis. At the time of detection, 19 tablets (60 mg tablets = 1140 mg) were missing and the boy admitted intake. Thirty to sixty minutes after the suspected ingestion, the boy’s condition deteriorated. He vomited and lost his muscular tonus. When presenting at the hospital (1–2 hours after ingestion) he was awake but tetraplegic. He was drooling, had increased bronchial secretions and miosis but intact respiratory muscle function and was circulatory stable with heart rate of 90 beats per minute. He was promptly administered two consecutive doses of 0.2 mg of atropine. The airway secretions rapidly cleared and no respiratory support was needed. Seven hours after ingestion, his limb motor function had returned but some dysphagia persisted. Twelve hours after ingestion, he was discharged, completely recovered.

Conclusion: To our knowledge, the only previously described pyridostigmine overdoses are in a case series in adult patients with mild symptoms [1]. Here, we report a case with severe intoxication causing tetraplegia in a pediatric patient. Even though the symptoms were dramatic on admission, the patient only needed a few doses of atropine and no respiratory support. The rapid resolution of symptoms is probably due to the fast elimination and to the fact that >40% of cholinesterase needs to be inhibited for symptoms to emerge [2]. However, the case illustrates that without proper supportive therapy, pyridostigmine poisoning may be life-threatening in the pediatric population.

217. Pronounced hyperchloremic acidosis after salt dough ingestion in a toddler

Ellen Norrhäll, Jenny Westerbergh and Jonas Höjer
Swedish Poisons Information Centre, Stockholm, Sweden

Objective: Home-made salt dough is commonly used as plaything for children in homes and preschools. Recipes for dough can easily be found on the Internet and one gram of such dough
humans, ages/infant (birth-23-months-old)/preschool child (2–5 years-old), language/english. EAPCCT and NACCT conference abstracts 2007–2016 and hand-searched cross-references were also included. The outcomes of interest were exposure, dose-effect relationship, relevant laboratory data, and survival/death.

**Table 1.** Data extraction of 51 records on vitamin D poisoning in children, including 138 patients.

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Number of patients (n)</th>
<th>Calcium, ion (mmol/L)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Calcium, total (mmol/L)</th>
<th>25-OH vitamin-D (nmol/L)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Parathyroid hormone (pg/mL)</th>
<th>Nephrocalcinosis (%)</th>
<th>Outcome (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6</td>
<td>44</td>
<td>112.000–1,600,000</td>
<td>75.7–2,236</td>
<td>29</td>
<td>2.52 (n = 1/13)</td>
<td>&lt;LOQ-9.5 (n = 4)</td>
<td>Yes, 20</td>
</tr>
<tr>
<td>&gt;6–12</td>
<td>29</td>
<td>1,100,000–2,400,000</td>
<td>150–51,339</td>
<td>44</td>
<td>3.31 (n = 11/13)</td>
<td>&gt;150 (n = 3/13)</td>
<td>Yes, 11</td>
</tr>
<tr>
<td>&gt;12–18</td>
<td>17</td>
<td>75.0–149.0</td>
<td>150–1,149</td>
<td>51</td>
<td>3.30 (n = 16/22)</td>
<td>&gt;150 (n = 4/30)</td>
<td>Yes, 11</td>
</tr>
<tr>
<td>&gt;18–24</td>
<td>5</td>
<td>75.0–149.0</td>
<td>20–51,339</td>
<td>51</td>
<td>3.30 (n = 16/22)</td>
<td>&gt;150 (n = 4/30)</td>
<td>Yes, 11</td>
</tr>
<tr>
<td>&gt;24</td>
<td>13</td>
<td>75.0–149.0</td>
<td>20–51,339</td>
<td>51</td>
<td>3.30 (n = 16/22)</td>
<td>&gt;150 (n = 4/30)</td>
<td>Yes, 11</td>
</tr>
<tr>
<td>Not reported</td>
<td>30</td>
<td>6,000,000–18,200,000</td>
<td>150–2,400,000</td>
<td>150</td>
<td>3.04 (n = 8/22)</td>
<td>&lt;3.0 (n = 23/23)</td>
<td>Yes, 11</td>
</tr>
</tbody>
</table>

Values are range and p = reported/not reported cases. Calcium concentrations are reported either calcium-total or calcium-ion. "<LOQ" is upper-LLOQ only in 19 cases, 8L, international units. LLOQ: limit of quantification, NR: not reported.

**Conclusion:** In August 2014, the UK’s National Poisons Information Service raised a warning regarding the extensive use of play dough among toddlers. It said that there had been no fatalities in children so far, but there were reports of pets being poisoned [1]. The marked laboratory metabolic disturbances recorded in the present case, despite the former possibly life-saving massive intake of tap water at home, shows that severe sodium chloride poisoning may be caused in toddlers by extensive ingestion of play dough.

**Reference**


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**218. Pediatric vitamin D poisoning: a review of the literature**

Lotte C. G. Hoegberg<sup>a</sup> and Soeren Boegevig<sup>b</sup>

<sup>a</sup>Department of Anesthesiology and Intensive Care and The Danish Poisons Information Center, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark; <sup>b</sup>Department of Clinical Pharmacology and The Danish Poisons Information Center, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark

**Objective:** During the vitamin D poisoning outbreak in Denmark in 2016, involving more than 100 infants exposed to an erroneously manufactured product, a thorough review of existing knowledge on vitamin D poisoning was urgently needed to consolidate risk assessment and optimize the treatment algorithm. This review aims to evaluate the toxic profile of vitamin D.

**Methods:** Medline and Embase were searched from inception to 3 October 2017 using the search terms “vitamin D” or “cholecalciferol” and “poisoning,” “poison,” “intoxication,” “overdose,” “risk” or “hypercalcaemia.” Filters included species/humans, ages/infant (birth-23-months-old)/preschool child (2–5 years-old), language/english. EAPCCT and NACCT conference abstracts 2007–2016 and hand-searched cross-references were also included. The outcomes of interest were exposure, dose-effect relationship, relevant laboratory data, and survival/death.
Results: The 153 records retrieved were screened for relevance. Toxicology details could be extracted from 51 records, including 138 patients; of these 95 were aged <2 years-old, 13 were 2–5 years-old, and 30 were children/infants of non-reported age (Table 1). The causes of poisoning were erroneous dosing of standard commercial products or therapeutic dosing of erroneously manufactured products. Data was heterogeneous in character with a great variation in reported details. Nephrocalcinosis was described in 63% (45/71) of the cases where this information was available. Fatal cases (6 patients) were only reported in children <2 years-old.

Conclusion: Severe vitamin D toxicity has been reported since the identification of vitamin D as an essential dietary supplement, but fatal cases were rare and only reported in cases from 1936–1952. Inappropriate use of standard vitamin D products or the use of highly concentrated products lead to excess vitamin D dosing and development of non-specific toxic symptoms. If early suspicion of vitamin D overdose is not recognised as the cause of symptoms, there is a risk of continued exposure followed by progression of severe poisoning.

219. Put a stopper on the dropper: a case of severe hypercalcemia with bilateral medullar nephrocalcinosis due to supratherapeutic vitamin D supplementation

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Objective: The American Academy of Pediatrics recommends 400 IU/day of vitamin D supplementation for all breastfed infants. As with other infant medications, dosing is often provided in drops or mL amounts instead of exact units. We report an infant with failure to thrive (FTT) due to severe symptomatic hypercalcemia from repeated supratherapeutic administration of over-the-counter (OTC) vitamin D.

Case report: A 6-week-old boy presented to his pediatrician with FTT. He was born at 41 weeks via cesarean section and was briefly admitted for suspected chorioamnionitis. Breastfeeding began upon discharge. At one week of life, his pediatrician recommended initiating 1 mL of vitamin D supplementation daily. The brand, formulation, and location for purchase were not specified. The family, unaware of different formulations, purchased an OTC vitamin D preparation containing 5000 IU/drop. Instructed to give 1 mL daily, the parents removed the dropper from the bottle and used a 1 mL syringe from a previous prescription. Over the next five weeks, the child failed to gain weight despite a normal appetite; the pediatrician recommended supplementing his feeds with formula. At six weeks, he was 0.5 kg below birth weight and was referred to the Emergency Department for FTT. stool and urine output were appropriate. There was no family history of FTT or gastrointestinal pathology, and no known prenatal drug exposures. Initial laboratory testing revealed a serum calcium 4.24 mmol/L (17 mg/dL). Upon further questioning, the higher concentration supplement was discovered. The 30 mL supplement bottle was brought to the hospital (4.5 million IU per bottle); roughly 80% of the bottle had been administered over 5 weeks for a total dose of approximately 3.6 million IU. Additional studies revealed a serum vitamin D concentration above the upper limit of detection 240 nmol/L (96.0 ng/mL) and creatinine 53 µmol/L (0.6 mg/dL). Renal sonogram demonstrated bilateral medullar nephrocalcinosis. The patient received intravenous fluids, calcitonin, and pamidronate with gradual improvement of his calcium; he gained 1 kg over his 8-day admission and was discharged without known sequelae.

Conclusion: Severe hypercalcemia can occur with repeated supratherapeutic vitamin D administration. We recommend writing prescriptions for vitamin D in exact doses (milligrams or IUs) rather than by volume and counseling patients and families regarding appropriate administration of all medications.

220. Pediatric vitamin D poisoning: diagnostic and treatment algorithm update

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Objective: An erroneously manufactured vitamin D product containing 150 µg/droplet was identified in Denmark in July 2016 after an infant developed severe vitamin D poisoning. The dose recommended (5 drops/day) contained 750 µg (30,000 IU) compared to 10 µg (400 IU)/day in other products. Neither concentration nor dosing recommendations were stated on the product. More than 340 bottles were sold from March–July 2016 and during the first days of the outbreak, we realized that national and international diagnostic and treatment guidelines were suboptimal in the outbreak process and for triage of the high number (>100) of exposed infants. The signs of vitamin D poisoning are non-specific (muscular weakness, nausea, vomiting, constipation, weight loss/failure to thrive). In severe hypercalcemia symptoms, progress to polyuria, thirst, fever, and possibly nephrocalcinosis, and calcium may reach life-threatening concentrations. 25-OH-vitamin D is formed by transformation of vitamin D2 + D3, and calcium may reach life-threatening concentrations. 25-OH-vitamin D and calcitriol is reduced in infants. The later inactivation capacity of 25-OH-vitamin D and calcitriol is reduced in infants. High 25-OH-vitamin D concentrations itself are probably harmless, but elevated concentrations may lead to hypercalcemia. The aim with the current algorithm was to consolidate risk assessment and optimize treatment by updating the diagnostic and treatment algorithm on vitamin D poisoning.

Methods: The updated diagnostic and treatment algorithm was based on a literature review (PubMed, Medline, and cross-references) aiming to evaluate the toxic profile of vitamin D, and considerations of the dose and appearance of signs in the patients identified during the 2016 outbreak.
**Results:** As initial clinical symptoms were non-specific, the diagnostic algorithm was based primarily on the clinical biomarkers; serum calcium and 25-OH-vitamin D. The serum calcium concentration was divided into subgroups: <1.32 mmol/L, 1.33–1.49 mmol/L, 1.50–1.59 mmol/L, and >1.60 mmol/L. Criteria for further triage to either no further observation/treatment, general pediatric units (three observation/treatment levels), or highly specialized pediatric units, depended on the serum calcium followed by 25-OH-vitamin D and possibly related symptoms. Children with obvious life-threatening symptoms are referred directly to specialized units. Repeated measurements of initial and other specific biomarkers and diagnostics in 4-day intervals were important due to the lipophilic properties of vitamin D.

**Conclusion:** To prevent delay in commencement of appropriate and specific treatment, initial admission to healthcare facilities able to handle all parameters in the diagnostic algorithm is essential for the identification of infants potentially at risk of severe vitamin D poisoning. Specific treatment needs should be met in highly specialized pediatric units only.

### 221. Clinical and biological issues in acute mushroom poisoning in children: a 3-year retrospective study

**Irina M. Ciomaga**, **Violeta Streanga**, **Aniela L. Rugina**, **Otilia E. Frasinariu**, **Cristina Jitareanu** and **Nicolai Nistor**

*University of Medicine and Pharmacy “Grigore T. Popa”, Iasi, Romania; Pediatric Poisoning Centre, Emergency Clinical Hospital “Sfînta Maria”, Iasi, Romania*

**Objective:** To analyze specific clinical and biological issues in acute mushroom poisoning in children.

**Methods:** We performed a three-year retrospective study of the acute mushroom poisoning cases registered in a pediatric poisoning centre using the data from medical records and taking into consideration the following criteria: age, gender, home environment, treatment, and clinical outcome.

**Results:** Overall, 72 children with acute mushroom poisoning were admitted to our centre between 2013 and 2016. There was a high incidence in the age group of 1–5 years (47.2%) and in the children from rural areas (80.5%). Classification of the patients in a specific syndrome was based on the latency period from the ingestion to the onset of the clinical and biological changes. Most patients \( n = 65, 90.3\% \) presented with a short latency syndrome. Out of these, the majority \( n = 50, 69.4\%, p < .001 \) had gastrointestinal syndrome. Out of the 25 children with a long latency syndrome, 3 developed the phalloid syndrome and 3 cases of gyromitrin syndrome (each representing 4.1%). Electrolyte imbalances, transaminase elevations \( n = 7, ALT 2100 \pm 1300 \text{ U/L, AST 3000} \pm 1310 \text{ U/L} \) and altered clotting factors \( n = 3 \) were the most frequent biological disturbances. Blood urea nitrogen was increased in 12 children and creatinine was increased in 3 cases. Treatment consisted of gastric lavage and activated charcoal in all cases, rehydration in 50 cases (69.4%) and hydroelectrolytic rebalancing in 20 cases (27.7%). Transfused quantities of fresh frozen plasma were performed in 7 cases. All 3 children with phalloid syndrome received high dose of penicillin G and sildarmin. No death was recorded and all the patients recovered completely.

**Conclusion:** Despite many prevention campaigns, mushroom poisoning still remains a entity in children’s pathology in our country [1]. In most common cases, the signs are mild but there are some situations, especially the phalloid syndrome, which can be life-threatening [2].

### 222. Dangers of pediatric compounding: toxicity from a compounded solution

**Mark Layer**, **Adina Sheroff**, **Iris Sheinhait**, **Michele Burns** and **Rebecca Brucoleri**

*Massachusetts Rhode Island Poison Center, Boston, United States; Boston Children’s Hospital, Boston, United States*

**Objective:** To describe a case of an unintentional ingestion of a large volume of a compounded solution causing QT prolongation, metabolic alkalosis, hypokalemia, hypernatremia, and aspiration. The solution contained omeprazole, which is a relatively benign agent in overdose and there are few treatment recommendations beyond supportive care. Compounded pediatric prescriptions, however, are solutions with suspension ingredients, which can have potentially serious sequelae.

**Case report:** A 16-month-old girl with a complex cardiac history presented the morning after discharge from a tertiary pediatric hospital for suspected aspiration and subsequent respiratory distress. The caregiver described administering what she thought were enteral feeds through a gastro-jejunal tube for a total volume of 70 mL. The patient began retching, had diarrhea, and there was concern she had aspirated. At this point, it was discovered a compounded omeprazole suspension 2 mg/mL, not enteral feeds, had been given with an estimated total dose of 140 mg. On arrival, she was found to have coarse lung fields, oxygen saturation of 73% (on room air from a baseline of 85–90%), a respiratory rate of 60/minute and sequential chest X-rays were taken. An electrocardiogram (ECG) demonstrated QRS 109 msec and prolonged QTc of 638 msec with a baseline junctional rhythm of 84 bpm. Laboratory testing was notable for venous pH 7.53 and serum sodium 152 mEq/L, potassium 2.82 mEq/L, and carbon dioxide 39 mEq/L. On discussion with the compounding pharmacy, 18 omeprazole capsules had been opened and mixed with sterile water with 15.12 g bicarbonate; the omeprazole capsules notably contained talc as an inactive ingredient. She was treated with supportive care including nasal cannula oxygen and potassium chloride via enteral solution. After 24 hours, her ECG demonstrated QRS 90 msec and QTc 439 msec; her serum abnormalities resolved, and her respiratory status gradually improved. She was discharged with a minimal oxygen requirement (0.06–0.25 liters/minute by nasal cannula) with no delayed renal effects from omeprazole in her subsequent follow-up.

**Conclusion:** We present a case of an unintentional ingestion of a large volume of a compounded solution containing sodium bicarbonate and talc resulting in QT prolongation, metabolic alkalosis, hypokalemia, hypernatremia, and aspiration. Talc aspiration has been reported to result in serious pulmonary toxicity and likely contributed to her clinical picture [1]. In cases of overdose with compounded medication, it is important that the toxicities of other ingredients be anticipated.

### References


Conclusion: and esophagitis. The adhesive nature and the occlusive qualities of this coating provides the salicylic acid enough surface contact time to cause lesions and prevents dilution and removal of the acid. Salicylic acid is a relatively weak organic acid with a pKₐ of 2.97. Toxicity from absorption of salicylic acid, ether or other ingredients is unlikely considering the small volumes ingested. We present a case series of pediatric ingestions of a wart remover containing 155 mg/mL salicylic acid in collodion.

Case series: The Poison Centre records of five children ingesting a wart remover containing collodion were reviewed. Age, ingested volume, reported symptoms, and clinical course are shown in Table 1. The children developed gastrointestinal burns and esophagitis. Coating formation also occurs when collodion is exposed to water. The adhesive nature and the occlusive qualities of this coating provides the salicylic acid enough surface contact time to cause lesions and prevents dilution and removal of the acid. Salicylic acid is a relatively weak organic acid with a pKₐ of 2.97. Toxicity from absorption of salicylic acid, ether or other ingredients is unlikely considering the small volumes ingested. We present a case series of pediatric ingestions of a wart remover containing 155 mg/mL salicylic acid in collodion.

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Reference


223. Severe irritation after collodion-based wart remover ingestion in children: a case series

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Objective: Wart removers may contain collodion and salicylic acid. Collodion is a mixture of nitrocellulose, ether and alcohol, which forms a hydrophobic coating after evaporation of the solvents. Coating formation also occurs when collodion is exposed to water. The adhesive nature and the occlusive qualities of this coating provides the salicylic acid enough surface contact time to cause lesions and prevents dilution and removal of the acid. Salicylic acid is a relatively weak organic acid with a pKₐ of 2.97. Toxicity from absorption of salicylic acid, ether or other ingredients is unlikely considering the small volumes ingested. We present a case series of pediatric ingestions of a wart remover containing 155 mg/mL salicylic acid in collodion.

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Table 1. Age, ingested volume, reported symptoms and clinical course of five children after ingestion of small quantities of a collodion-based wart remover.

<table>
<thead>
<tr>
<th>Age</th>
<th>Ingested volume</th>
<th>Reported symptoms</th>
<th>Clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 m</td>
<td>5 mL</td>
<td>Stomatitis, mucosal edema, sialorrhrea, grade 2 esophagitis.</td>
<td>Intubation, mask ventilation. Length of hospital stay 5 days. Recovered.</td>
</tr>
<tr>
<td>2 y</td>
<td>3 mL</td>
<td>Burns (mouth, throat, nose), edema of the lips, sialorrhrea, sore throat.</td>
<td>Recovered.</td>
</tr>
<tr>
<td>2 y</td>
<td>Unknown</td>
<td>Burns (mouth, skin), emesis, grade 2 esophagitis.</td>
<td>Parenteral nutrition. Length of hospital stay: 13 days (infectious complications). Recovered.</td>
</tr>
<tr>
<td>2 y</td>
<td>5 mL</td>
<td>Burns (mouth), grade 2 esophagitis.</td>
<td>Recovered.</td>
</tr>
<tr>
<td>3 y</td>
<td>5 mL</td>
<td>Burns (mouth), edema of the lips, sialorrhrea, grade 2 esophagitis.</td>
<td>Nasogastric tube feeding. Length of hospital stay 11 days. Recovered.</td>
</tr>
<tr>
<td>6 m</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

224. Pediatric extracorporeal cardiopulmonary resuscitation in the emergency room for intentional propafenone intoxication

Irene Salfaa, Sara Cairolib, Mara Pisanic, Bianca Goffredob, Jessica Serafinellia, Matteo Di Nardoc, Leonardo Genuinid, Corrado Cecchettd and Marco Maranod
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Objective: The use of drugs in suicide attempts is becoming more and more frequent among adolescents. In recent years, pediatric intentional suicide cases with propafenone have been reported [1,2]. We document a pediatric case of propafenone-induced heart failure in an adolescent girl successfully rescued with an “early” deployment of veno-arterial extracorporeal membrane oxygenation (VA ECMO) in the emergency room of a secondary hospital, along with data regarding serum propafenone concentrations.

Case report: A 16-year-old girl was admitted to the Emergency Department of a secondary hospital one hour after an overdose of 1.8 g of propafenone with progressive loss of consciousness and cardiotoxicity. The patient was managed with mechanical ventilation, sodium bicarbonate and inotropic support. Although maximal medical therapy was administered, severe hypotension with an ejection fraction of 20% and bradycardia alternating with pulseless electrical activity (PEA) persisted due to severe cardiac dysfunction. Femoral VA ECMO was rapidly started by the pre-alerted hospital ECMO team. Toxicological screening showed propafenone concentrations 4.9 mg/L at 6–7 hours post-presentation, falling to 0.02 mg/L at 50–51 hours post-presentation. The patient was monitored daily with a cardiac ultrasound and electrocardiogram (EKG). After four days, VA ECMO was stopped with complete recovery of cardiac function and no brain damage.

Conclusion: Propafenone, in pediatric patients, even when administered at therapeutic dosages (10–15 mg/kg/day) can be pro-arrhythmic. Propafenone overdose has no specific treatment or antidote. The consequent cardiovascular failure is generally a severe but transient condition; therefore there is a strong rationale for using extracorporeal life support, considering that both cardiac and respiratory function can be supported by ECMO while waiting for the drug to be eliminated. According to our experience, even though evidence is still limited to small case reports, we believe that the “early” deployment of extracorporeal cardiopulmonary resuscitation (ECPR) can be an effective and relatively safe second-line support to manage severe cases of poisoning-induced cardiac failure unresponsive to maximal medical therapy. We document a pediatric case of propafenone-induced heart failure in an adolescent girl successfully rescued with an “early” deployment of (ECPR) in the emergency room of a secondary hospital, along with data regarding serum propafenone concentrations.

References

225. Adolescent poisoning in Edinburgh: a 10 year analysis

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Objective: Poisoning in adolescents is less well understood than other age groups. Currently in Edinburgh, patients aged 13 years and over are treated under adult services. From 2018, patients up to the age of 16 years will be admitted under pediatrics. Our objective was to investigate adolescent poisoning admissions in Edinburgh and assess the potential impact of the transfer of these patients from adult to pediatric services.

Methods: We conducted a 10-year retrospective analysis of data for patients aged 13 to 16 years admitted with self-poisoning (±alcohol) to the Royal Infirmary of Edinburgh (1 January 2003 to 31 October 2013). Routine data collection ceased after this date and was unavailable for analysis. Data analysed included gender, age, social deprivation category (Scottish Index of Multiple Deprivation [SIMD]), agent ingested, length of stay and discharge destination.

Results: Over the study period, 981 admissions were recorded (75% female) with a mean (95% confidence interval) annual admission rate of 98.1 (74.2, 122.0). This represented 759 patients, 94% (70.2, 97.9) of whom were female. The majority of which (626, 82.5%) were admitted once; 133 (17.5%) patients recorded two or more admissions. A significant difference in admission rate between the most deprived areas (SIMD-1) and least deprived areas (SIMD-5) was observed (SIMD-1 195 (25.7%); SIMD-5 135 (17.8%); p = .0004). There was no statistical difference between months although admissions reduced during periods of school holiday. There was no variation according to day of the week. The majority of admissions (654, 66.6%) resulted from ingestion of a single agent. Agents most commonly ingested included paracetamol and combination products (643, 65.5%), non-steroidal anti-inflammatory drugs (NSAIDs) (186, 18.9%), antidepressants (104, 10.6%), aspirin (68, 6.9%), benzodiazepines (50, 5.1%), antibiotics (42, 4.2%), and antihistamines (41, 4.2%). Recreational drugs accounted for 132 (13.5%) admissions with ecstasy (48, 48.4%) being the most common. Nine patients required critical care admission. Four hundred and ninety-four patients (50.4%) were discharged within 24 hours; 937 (95.5%) within 48 hours. The majority (882, 89.9%) were discharged home with other destinations including psychiatric services (25, 2.5%), self-discharge (24, 2.4%), admitted to another hospital ward (13, 1.33%), police custody (9, 0.92%), unknown (28, 2.76%).

Conclusion: Adolescent poisoning in Edinburgh accounts for 98.1 (74.2, 122.0) admissions per year with many more presentations to the Emergency Department. Admissions are commonly of short duration and low severity, with few requiring critical care. The agents involved are similar to that seen in adults with medications frequently found in the household being most common.

References


226. Pudendal block sub partu may induce transient neonatal methemoglobinemia

Daniela Acquarone and Simone Lippmann

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Objective: It is conceivable that post-partum cyanosis in a newborn is caused by respiratory or cardiac dysfunction or the development of sepsis. Here, we report a case of a newborn with post-partum cyanosis which, after exclusion of other causes, was suspected to have been caused by toxic methemoglobinemia.

Case report: A 6-hour-old newborn was admitted to the neonatal intensive care unit with a pale gray central cyanosis, and oxygen saturation of 85–90%, without overt signs of dyspnea. Pulmonary and cardiac causes were excluded and there was no detection of inflammatory signs. As a possible cause of the generalized cyanosis, methemoglobinemia with a maximal methemoglobin of 32% was detected. After 17 hours of oxygen delivery, the methemoglobin declined to 3%; no further therapeutic measures were necessary. The most likely explanation for the methemoglobinemia was the application of 20 mL prilocaine 1% to the mother while performing a pudendal nerve block nine minutes before birth.

Conclusion: In comparison to other local anesthetics, prilocaine has the advantage of fewer neurological and cardiac side effects. On the other hand, prilocaine passes well through the placenta and can cause methemoglobinemia in the newborn [1–4]. In post-partum cyanosis after delivery under pudendal anesthesia, a toxic genesis has to be considered.

References


227. Electroencephalogram (EEG) alterations during tetrahydrocannabinol (THC) ingestion in children: a case series

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Pavia Poison Control Centre – National Toxicology Information Centre – Clinical and Experimental Lab, Toxicology Unit, Maugeri Clinical and Scientific Institutes IRCCS and University of Pavia, Pavia, Italy

Objective: In medical literature and our experience cases of unintentional cannabis ingestion in pediatric population (<8 years) are described. Acute clinical manifestations include cardiac and
Objective: Serious neurological manifestations (prolonged coma, requiring respiratory support) occur at a period of neuropsychiatric development, and it could be important to determine if some alterations correlate to symptoms, which can be instrumentally evaluated, and to assess possible long-term sequelae. We describe three clinical cases of children with EEG alterations after accidental ingestion of analytically confirmed cannabis.

Case series: Case 1. A 9-month-old baby was admitted to the Emergency Department (ED) after the parents reported ingestion of dog food. At presentation, he showed consciousness impairment, mydriasis, fixed gaze, general hypotonia with mild nape rigidity; he cried when awakened with painful stimuli. His vital signs were normal, except for mild temperature elevation (37.3 °C). Blood analysis revealed rhabdomyolysis and leukocytosis. Three hours after admission, urine toxicological analysis revealed THC positivity. On admission, an encephalic echography was normal and an EEG showed "left central asymmetry". The baby was discharged the following day in good condition. Case 2. An 18-month-old girl was admitted to the ED with a false history of ingestion of her father’s valerian pills. She presented with consciousness impairment; at physical examination she had rigidity of the arms and neck. Her vital signs were normal, except for tachycardia (170 bpm). Blood analysis was normal. Thirty minutes after admission, urine toxicological analysis was positive for THC. She remained in the ED for monitoring. The following day, because of persistent consciousness impairment, she underwent EEG, which showed a "sleepy rhythm, with cortical activity when stimulated". She was transferred to pediatric division and about 13 hours after admission, she had recovered completely, and was discharged. Case 3. An 18-month-old boy was admitted at the ED because the grandparents were unable to awake him from an afternoon nap. The physical presentation revealed consciousness impairment, mydriasis, and hypotonia. Blood analysis was normal. Two hours after admission, an EEG revealed "frontal symmetric abnormal activity". Soon after, urine toxicological analysis was positive for THC. The following day, the baby was discharged, after complete clinical recovery.

Conclusion: There are no scientific data reporting specific EEG alterations related to THC ingestion in children. Our cases support the hypothesis of peculiar EEG alterations. A prospective study is needed to better correlate EEG patterns to symptoms and to neuropsychiatric long-term sequelae.

228. Pediatric exposures involving opioid medications in New Zealand

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Objective: Opioid overdose has become more prevalent in recent years as the use of opioid medications has increased. In New Zealand, codeine-combination products were reclassified as pharmacist-only medications in 2010. This study aims to examine whether the change in classification coincided with any changes in trends and to characterize pediatric poisoning to opioid medications using data reported to the New Zealand National Poisons Centre (NZNPC).

Methods: Telephone enquiries to NZNPC involving exposures to opioid medication in children (0–5 years) from 1 January 2005 to 31 December 2015 were reviewed. Ingestions of opioid medications alone and opioid-combination products were included. Cases with other co-ingestants were excluded. Data on patient age, substances involved, symptoms, and number of medical referrals were collated and evaluated.

Results: Between 2005 and 2015, there were 2221 calls to NZNPC concerning children 0–5 years with exposures to opioid medications (1484 involved single opioid medications, 22 multiple opioid medications, and 715 opioid-combination medications). Children aged 1 and 2 years were responsible for the majority of enquiries (22.8% and 42%, respectively). Comparatively, 1952 calls involved adults (>18 years). The number of calls per year increased from the beginning of the study period with 178 calls in 2005 to a peak of 256 incidents in 2009. From 2010, enquiries declined to 162 calls in 2015. Codeine was the most common medication (36% of incidences), followed by opioid-combination medications (34%), pholcodine (9.5%), and tramadol (7%). Buprenorphine, dextromethorphan, dihydrocodeine, methadone, morphine, loperamide, oxycodone, and pethidine each accounted for <5% of cases. Overall, 94% of children were asymptomatic at the time of call; however, medical attention was still required in 50% of the cases. Symptoms commonly reported were drowsiness (31%), vomiting (20%), and lethargy (10%). Although codeine was the most common substance prompting medical assessment overall, a higher frequency (>85%) of referrals were due to dihydrocodeine, methadone, morphine, and oxycodone exposures. Medical evaluations were recommended when the child was deemed to be at risk of developing toxicity.

Conclusion: This study revealed that children <5 years were at higher risk of opioid exposures. Poisonings peaked in 2009 before declining, coinciding with the reclassification of codeine to pharmacist-only in 2010. Although most children were asymptomatic at the time of call, but a high proportion were referred for medical evaluation due to the risk of developing toxicity. Awareness and poison prevention strategies should be implemented to ensure medications are kept out of reach of children in order to minimize exposures.

229. Escitalopram overdose in children and adolescents

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Objective: Information on the toxicity of escitalopram in pediatric patients is limited. The aim of this study is to provide more data about toxicity and clinical effects in escitalopram overdoses.

Methods: In a retrospective multicentric study, cases of acute overdose of escitalopram in children and adolescents were analysed. Inclusion criteria were children and adolescents up to 17 years, single substance ingestion, defined dose, and documented follow-up for at least 9 hours. Severity of symptoms was assessed according to Poisoning Severity Score.

Results: A total of 45 cases met the inclusion criteria. Patients involved were 3 babies (0.25–0.75 years), 8 toddlers (1.25–4 years), 8 schoolchildren (6–13 years), and 26 adolescents (14–17 years). Doses ranged between 5–10 mg (0.6–3.8 mg/kg) in babies, 10–40 mg (0.7–6.3 mg/kg) in toddlers, 7.5–100 mg (0.2–2.6 mg/kg) in schoolchildren, and 30–1500 mg (0.6–30.0 mg/kg) in adolescents. In 55.6% of the cases, the circumstance was self-harm, especially in the adolescents (92%). Nevertheless, 31.1% of all patients remained asymptomatic and more than half of the children and adolescents (55.6%) developed only mild symptoms. Moderate to severe symptoms were only observed after intentional ingestion. The clinical features of escitalopram poisoning...
are characterized by mydriasis (22.6%), nausea (19.4%), vomiting (19.4%), dizziness (16.1%), tachycardia (16.1%), QT prolongation (16.1%), stupor (12.9%), and tremor (12.9%). In isolated cases, two adolescents developed, amongst other symptoms, coma and seizure at doses of 1000 mg and 1500 mg, respectively. **Conclusion:** Most cases of escitalopram overdose in this study resulted in no or only mild effects (86.7%). Moderate symptoms were not recorded in babies, toddlers, and schoolchildren. There is no correlation between dose and severity of symptoms. Currently, there are limited data and studies of escitalopram toxicity, particularly in this age group. Therefore, further investigations are necessary for a comprehensive and conclusive assessment of the toxicity of escitalopram in children and adolescents.

### 230. Analysis of Croatian Poison Control Centre consultations involving poisonings in preschool children (2007–2016) as a basis for poisoning prevention action

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**Objective:** Croatian Poison Control Centre (CPPC) is planning an educational intervention addressing secure storage of poisons in households, which is acknowledged as good practice for poison prevention in children [1]. Since there is no national registry of poisoning incidents in Croatia, we used CPPC data to identify the most frequent causative agents involved in poisonings of preschool children, and the agents responsible for severe poisonings. Results will serve as a focus for our educational intervention.

**Methods:** Data collected from telephone consultations for accidental poisoning incidences involving preschool children (1–5 years of age) during the 10-year period 2007–2016 were analyzed regarding subject characteristics, causative agent, route of exposure and symptoms reported at the time of the call.

**Results:** There were 6710 cases of accidental exposure of preschool children during the study period. Reported median age was 2 years (IQ 1.5–3 years), and boys were involved in 59% of the cases with known age. Ingestion was by far the most prevalent route of exposure (91%). Overall, the most prevalent causative agents were household chemicals (47%) and medications (35%). Other causes included plants (6% of total), pesticides (5%), and industrial chemicals (3%). Among household chemicals, the most prevalent were detergents and cleaning agents (37%), cosmetics (17%), and silica gel (7%). Among medications, the most prevalent were non-steroid anti-inflammatory drugs and analgesics (21%) followed by psychoactive (15%) and cardiovascular drugs (13%). Only 93 children (1% of total) had severe symptoms, such as serious disturbances of the central nervous system, corrosive injuries of the gastrointestinal tract, or severe respiratory symptoms, at the time of the call. Medications were stated as a cause in 41% of these cases (mostly psychoactive, 55%) and household chemicals in 30% (mostly detergents and cleaning agents, 36%, and products containing corrosive concentrations of acids or alkali, 32%).

**Conclusion:** Although CPCC data do not comprise all poisoning incidences in Croatia, results of this study indicate that education of parents of preschool children should focus on cleaning agents, cosmetics, non-steroid anti-inflammatory drugs, and other analgesics. Additional attention should be given to psychoactive drugs and corrosive household chemicals as possible causes for severe health consequences.

### References


232. Epidemiology of acute unintentional poisoning in children: a 3-year retrospective study

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Objective: To analyze the epidemiology of unintentional poisoning in children.

Methods: We performed a three-year retrospective analysis of cases with acute unintentional poisoning admitted to a pediatric poison centre. Data from the medical records included: substance involved, age, gender, home environment, and outcome.

Results: Out of the total of 1720 poisoned children admitted between January 2014 and December 2016, 480 (25%) unintentional poisonings were registered. Of these, there were 322 cases (67%) with non-drug poisoning and 158 patients (33%) with drug poisoning. The majority of children with non-drug poisoning were in the age group 0–2 years (78 cases, 24.2%). The most frequently involved substances were: household products (66 cases, 20.4%), followed by carbon monoxide (63 cases, 19.5%), nitrates/nitrates (34, 10.5%), cholinesterase inhibitors (30, 9.3%), other insecticides (26, 8.1%) and petroleum products (18, 5.5%). Non-drug poisoning more commonly involved males (24.9% versus 15.2%, p = .045) and children from urban area (32.2% versus 15.9%, p < .002). Of the 158 cases with drug poisoning, 49 children (31.2%) were aged age 2–3 years. The drugs most frequently involved were: anticonvulsants (30 cases, 18.9%), non-steroidal anti-inflammatory drugs (17, 10.7%), paracetamol (16, 10.1%) and antiemetics (13, 8.2%). The distributions of gender and home environment were homogeneous (p > .05). There were only 3 deaths (0.62%), involving cholinesterase inhibitors (n = 2) and smoke inhalation (n = 1).

Conclusion: Unintentional poisoning remains an important child health problem representing a significant percentage of children’s intoxications [1]. The fact that the most commonly involved agents in our study were drugs, household products, carbon monoxide, and insecticides should be considered the starting point in the development of a poisoning prevention program in children under five years of age [2]. The outcome in the majority of the cases with unintentional poisoning is favorable, mortality being low.

References


233. Acute benzodiazepine poisoning in children: a 2-year retrospective study

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Objective: To analyze the specific issues of acute benzodiazepine poisoning in children.

Methods: We performed a 2-year retrospective study of children with acute benzodiazepine poisoning admitted in a regional pediatric poisoning centre using the medical records and taking into consideration the following criteria: modality of intoxication (accidental or voluntary), symptoms, treatment and evolution.

Results: Out of the total of 1167 poisoned cases admitted in our centre, 63 children (5.4%) with acute benzodiazepine poisoning were registered during the studied period (January 2014 and December 2015). The number of voluntary poisonings was almost double that of accidental poisonings (41/22). Poisoning in girls prevailed in both types of poisoning (a total of 70%), but the difference was statistically significant only for voluntary poisoning (p < .001). Voluntary poisoning had a slight predominance in children from rural areas, but the difference was statistically insignificant. The symptoms were mainly those of central nervous system depression with somnolence (62.1%), ataxia (43.2%), vertigo (35.1%), and slurred speech (29.7%). Coma was found in 5 cases (7.9%). A urinary screen test, was positive for benzodiazepines in 82% of the cases. Decontamination measures were performed in 52 patients (82.5%) that were admitted early after the ingestion. In 38 cases (60%), symptomatic and supportive treatment was given; the antidote (flumazenil) was needed in only 2 patients. In all, 41 children with voluntary intoxication, a psychological and psychiatric examination was performed according to the protocol implemented in the department. A depressive episode was found in 16.2% of the cases and tense intra-family relationships in 13.5%.

Conclusion: The number of cases with acute benzodiazepine poisoning has decreased in the last few years, but it continues to be common in pediatric poisoning cases [1,2]. The symptoms were mild or moderate and the outcome favorable in most cases [1]. Compared to adults, in children with voluntary poisoning, only a small percentage (16.2%) were diagnosed with psychiatric pathology with the intoxication being considered a suicide attempt.

References

234. Is slime dangerous? Data from the French Poison Centers
Françoise Giraud, Ingrid Blanc, Cécilia Solal, French Poison Control Centers and Magali Labadie

Objective: Slime is a home-made playdough, made in small amounts and used to allow children to experience different textures. It is becoming increasingly popular. It is also cheap and easy to make at home, although manufactured products can be bought. It is made from the polymerisation of polyvinylalcohol (contained in some adhesives) with boric acid. Different admixtures can be added such as soap, food colourings, detergents, etc. The objective of this study was to determine toxicity from exposure to this new substance used in play, using data from the French Poison Control Centers.

Methods: Telephone enquiries to the French Poisons Information Service regarding “slime” were analysed retrospectively for the period January 2010 to 6 October 2017.

Results: There were 38 enquiries relating to 41 patients, 6 between 2010 and 2016, and 32 in 2017. The sex ratio was 0.6 and the average age 8 years old (SD ±7.7, range 0.8–42 years). Cases mostly occurred in the northern half of France (24 out of 38). Overall, 20 cases remained asymptomatic and the other 21 were of low severity. Most cases (n = 34) involved oral contact and/or ingestion, 6 had skin contact, and 1 involved inhalation. The 6 patients who had skin contact had cutaneous lesions ranging from simple irritation to more severe lesions (eczema, hand burns, nail damage). Of the 31 cases of ingestion, 14 had vomiting and/or abdominal pain, which resolved without treatment.

Conclusion: Exposures to slime were frequent in 2017. Accidental ingestion of slime does not appear to cause serious toxicity, but prolonged skin contact results in prolonged and more pronounced symptoms. It was not possible to study the severity of these cutaneous signs according to the recipe used for the manufacture of this slime.

235. The etiological spectrum and social impact on adolescents with acute poisoning
Ana Oglinda, Liliana Schirca, Victoria Lupu, Tatiana Sertinean, Cristina Casian, Mihai Casian and Viorela Nitescu

Objective: To assess the etiological spectrum and the social impact of acute intoxications in adolescents.

Methods: We performed an 18-month retrospective study of the adolescents with acute poisoning admitted in our hospital, using data from medical records and taking into consideration the following criteria: type of substance, treatment, and length of hospital stay.

Results: Overall, 182 adolescents with acute poisoning were registered during the studied period, which was 36.6% of the total number of children admitted with poisoning to our hospital. Regarding the modality of poisoning, the following distribution was noted, there were 119 voluntary poisonings and 63 accidental poisonings. The following agents were involved: medicines 62 cases (34.1%), new psychoactive substances, and other drugs of abuse 50 patients (27.5%), alcohol in 35 adolescents (19.2%), insecticides 19 (10.4%), carbon monoxide 8 (4.4%), irritant spray 4 (2.2%) and other substances 4 (2.2%). Out of the 182 patients, 103 (56.6%) received medical care in the Emergency Department (ED) and 79 (43.4%) in the Intensive Care Unit (ICU). In total, 26 adolescents received antidote treatment, in 8 cases (carbon monoxide and opiates poisoning) this occurred during the prehospital stage and in 18 cases at presentation to the emergency department. The length of stay in the ED was 0.78 ± 0.25 days and the length of hospitalization was 3.4 ± 1.9 days. Psychological evaluation and psychiatric exam were performed in all adolescents with voluntary poisoning, highlighting that out of the 119 cases with voluntary poisoning, 45 were suicidal attempts. In 147 cases, the impact on school activity was studied, these adolescents registering 419 days (1896 hours) of absence from school, the duration of which is directly proportional to the length of hospitalization, which is determined by the severity of intoxication.

Conclusion: Medicines followed by drugs of abuse and alcohol, are the most frequent agents implicated in adolescent poisoning. The social impact is difficult to measure and is directly proportional to poisoning severity.

236. Acute poisoning in children and adolescents in Vojvodina, Serbia
 Vesna Mijatović, Aleksandra Stojadinović, Katarina Katić and Isidora Samojlić

Objective: Acute poisoning in children and adolescents represents a challenge not only for pediatricians, but is also a public health issue [1]. Currently, the need for the establishment of the Regional Poison Control Center (with pediatric subdivision) of Vojvodina (with a population of 2 million, nearly 27% of Serbia’s population) has been discussed by the authorities. To assess this need, an evaluation of patients treated for acute poisoning at the Institute for Health Protection of Children and Youth of Vojvodina (IHPCYV) between 2012 and 2015 was undertaken.

Methods: In the study period, data were collected from the patient medical records at the IHPCYV.

Results: Medical records of 678 self-poisoned patients were examined. Among them, 47% were children, while 53% were adolescents. The mean age of children and adolescents was 2.8 ± 1.8 years and 15.4 ± 1.7 years, retrospectively. Boys predominated in the following age categories: 4–6 years (62.3%), 7–10 years (63.2%), 11–17 years (60.6%), while domination of girls was registered in the early adolescent age category (66.7%). Seasonality was not observed. Xenobiotics were taken orally by most of the patients (89.0%). Agents most commonly ingested by children were medicines (52.0%) and household products (32.7%). Alcohol was the most prominent agent in adolescents and was detected in blood of 55.0% of them, while medicines was in second place (31.2%). Considering medicines toxicologically confirmed in blood, those used in the treatment of neurological, cardiovascular, and gastrointestinal disorders were most frequently detected (26.2%, 9.4%, and 5.6%, respectively). The mode of poisoning was accidental in 52.4% patients. Adolescents were most likely to have intentional (suicidal) poisoning (33.4%). The most frequent cause of a suicide attempt among them was conflict in the family (37.2%), followed by school problems (23.1%). The outcome was recovery and discharge in 100% of the
cases. Clinical toxicologists from the National Poison Control Center provided professional support by telephone, if they were contacted by pediatricians from IHPCYV.

**Conclusion:** All the poisonings were successfully managed. More thorough discussion should be organized before the potential foundation of a pediatric subdivision within the Regional Poison Control Center in Vojvodina.

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**Reference**


237. Evolution of the epidemiological profile of pediatric poisoning in 20 years at the Emergency Department of a General Hospital

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**Objective:** To describe the characteristics of pediatric toxic exposures and evaluate the impact of preventive measures to avoid them.

**Methods:** The study population were all patients under 14 years old attending the Emergency Department collected in the database of a Unit of Clinical Toxicology due to potentially toxic exposures. We studied this population in the period from 1996 to 2015.

**Results:** There were 971 cases, 5% of the total 21,111 acute poisonings attending the Emergency Department over the study period. The mean age of the children was 4.18 (SD ±3.96) years. The cases were evenly distributed among sexes. We found two defined clusters of population in terms of age distribution with 689 cases under 4 years old (71%) and 159 over 10 years old (16%). There were 689 cases of poisoning related to domestic accidents, 76 cases involving abuse of drugs and 27 cases were suicide gestures. All children in the two last situations were over 10 years old. Most (83%) of the cases were oral exposures. The yearly distribution ranged between 34 and 77 cases without any significant trend.

**Conclusion:** Pediatric intoxications have not decreased in number in spite of the preventive measures and campaigns addressing the risks of poisoning in this population. On the other hand, the cases show a very low risk, probably due to these preventive measures.

238. Strong alkali ingestion in children: a 2-year retrospective study

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**Objective:** To analyze a group of pediatric patients admitted in a toxicology department for acute exposure to strong alkalis.

**Methods:** We performed a 2-year retrospective study that collected data from the medical records of 30 patients admitted in a pediatric toxicology department between April 2015 and March 2017 for acute exposure to caustic agents with the chemical properties of strong alkalis.

**Results:** The majority of cases were in the age group 1–5 years. There were 22 boys and 8 girls; 93% of the cases were accidental exposures. Oven cleaning solutions were the most commonly ingested product, followed by degreasing products for motor vehicles. Sodium hydroxide was involved in most cases and calcium hydroxide in a limited number of cases. Only 64% of the patients experienced symptoms at admission. Of these, the majority (73.3%) had mouth, lips, and/or perioral lesions. Other symptoms were dysphagia (30%), sialorrhea (47%), vomiting (50%), fever (13%), and tachycardia (3%). For injury staging, we used endoscopy 24–48 hours after ingestion. Most cases had grade 2 injuries (40%), followed by grade 1 lesions (34%). Grade 3 lesions were present in one case; no patient showed grade 4 lesions. Half of the patients that were asymptomatic at admission had grade 1 or 2 esophageal injury. Patients received intravenous fluids, systemic antibiotics, corticosteroids, antisecretory, and antiemetic agents, as appropriate. Corticotherapy was prescribed in those cases with grade 2 and 3 injury, which explains the longer hospitalization time of those who received this treatment (mean 4.8 days), than those without injuries or with grade 1 lesions (mean 2.4 days). Mean hospitalization period overall was 3.6 days. There was a direct correlation between the number of days spent in the hospital and the severity of the injuries.

**Conclusion:** The results obtained in this study reflect the reality of our country at this time. Our results are similar to those published by other authors in other countries, which indicates that these intoxications occur in populations with similar profiles. The most frequently encountered patient profile in this study was a male aged 1 to 5 years, who had accidentally ingested a sodium hydroxide-containing oven cleaner. Efforts should be made to establish a legal framework to limit the availability of caustic products on the market and also to educate the population to keep these substances out of reach of children.

239. Poisoning with cholinesterase-inhibiting insecticides: experience from two pediatric poisoning centres

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**Objective:** To outline the specific aspects of the etiology and evolution in cases with acute cholinesterase-inhibiting pesticide poisoning admitted in two pediatric emergency hospitals.

**Methods:** We performed a five-year retrospective study, of children with acute poisoning from cholinesterase-inhibiting insecticides admitted in two pediatric poisoning centre taking into
consideration: etiology, demographics (age, gender, home environment), toxin-induced organ dysfunction, medical treatment, length of hospitalization, and evolution.

**Results:** Overall, 60 patients with acute insecticide poisoning were registered between 2012 and 2016. There were 32 boys and 28 girls, of which 53 (88.3%) were from a rural area and 7 (11.7%) from an urban area. Mean age was 6.6 years; most of the children belonging to the age group 0–5 years (n = 34, 56.7%), followed by children aged 12–18 years (n = 17, 28.3%). In total, 44 cases (73.3%) were accidental exposures, while 16 (26.7%) were self-poisonings. The main insecticide involved was diazinon (n = 41, 68.3%). Carbofuran was involved in 9 cases (15%) and in 10 cases, the substance remained unknown. Five of the children presented renal failure, of which 2 evolved to death and 20 had hepatic failure, with 6 deaths (30%). In 23 children, varying degrees of coma occurred, of which 5 (21.7%) died. In total, 21 patients (51.7%) were admitted to the intensive care unit; the median length of stay was 5.1 days. The average length of total hospitalization was 8.4 days. All of the patients received antidotal treatment with atropine; in 38 cases high doses (up to 3 g, 3000 vials of 1 mg) were necessary. In 13 cases, cholinesterase reactivators (obidoxime) were added. For 32 of the patients, gastrointestinal decontamination by gastric lavage and activated charcoal was performed; all were blue is the specific antidote for intoxication with nitrates and leads to a more rapid recovery than vitamin C alone.

**Conclusion:** Diazinon is the most common cause of cholinesterase-inhibiting insecticides poisoning, associated with severe evolution and a high mortality rate [1]. The presence of toxic organ injury increases the severity of acute poisoning, mortality being higher when renal, hepatic, or neurological dysfunctions occur [1,2].

**References**


240. “Blue Baby Syndrome” and drinking water

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**Objective:** A study to determine the risk factors of acute nitrate intoxication in children presenting to a hospital in the Nord-Est Region of Romania.

**Methods:** A descriptive analysis of children presenting to the emergency pediatric department of a university hospital, 2012–2016. The data were extracted from emergency unit consultation records, hospital electronic database, emergency cards, and clinical observation sheets. Data collected included: patient age, environment of origin, type of feeding, seasonal variations, social status, severity of intoxication, co-morbidities, and treatment. The case series includes patients with methemoglobinemia from well water [1,2], that may not meet water standards. Individual sources of water are not tested in Romania because it requires the owner’s request and payment of a fee (approximately 65 euros). The cases were divided into two groups depending on the treatment given: Group A (2012–2014) included 51 children who received methylene blue IV [3] ± vitamin C IV and Group B (2015–2016), which included 14 children who received only vitamin C IV. This change in protocol occurred because methylene blue was not available in Romania at the time. Inclusion criteria were: methemoglobinemia measured by co-oximetry with values ≥10% to ≤70%. Exclusion criteria were: sepsis, previous treatment and feeding with spinach, beet, or carrots.

**Results:** There were 65 children aged 14 days to 36 months with nitrate intoxication. Most children (81.5%, n = 53) were from a rural environment and the remainder (18.5%, n = 12) from urban areas where the source was potable water. Most cases (73.8%) occurred in the spring when fertilizers infiltrate groundwater following the melting of snow or rain. The risk factors identified were age ≤4 months (64.6%), milk formula feeding (42%), and both breast milk and milk formula feeding (28%). The median duration of hospitalization for Group A was 2 days and for Group B was 7 days. All the children recovered.

**Conclusion:** Intoxication with nitrates in rural patients is a major health problem in the Nord-Est Region of Romania. Methylene blue is the specific antidote for intoxication with nitrates and leads to a more rapid recovery than vitamin C alone.

**References**


241. Determination of mothball composition in the home using carbonated sodas

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**Objective:** In-home determination of mothball composition utilizing a saturated solution of salt has been previously published [1]. In our poison center’s experience, many callers are unwilling to make this solution. Our recommendations are observation in a healthcare facility for all patients with suspected glucose-6-phosphate dehydrogenase (G6PD) deficiency for greater than half an unknown or naphthalene mothball. The objective of this study was to identify commonly available liquids in the household that can differentiate between paradichlorobenzene and naphthalene mothballs.

**Methods:** We randomly numbered 8 sets of naphthalene or paradichlorobenzene mothballs and had observers (trained Certified Specialists in Poison Information) record whether they thought each set of mothballs was paradichlorobenzene or naphthalene. We then asked these observers to record whether mothballs floated or sank in several liquids. The liquids tested include Sprite®, Diet Pepsi®, Coca Cola®, 7-UP®, Dr. Pepper®, canned Minute Maid Lemonade®, household bleach, tap water, fat free milk, 1% milk, 2% milk, and whole milk. All of the colas were carbonated at the time of testing and had bubbles. Approximately 4 ounces (115 mL) of each liquid was poured into individual cups...
before whole mothballs were added to liquids marked with a unique identifier. Each cup contained one type of mothball and one type of liquid. For any of the liquids where one type of mothball floated and the other sank, smaller pieces of the mothball that sank were tested. The institutional review board (IRB) determined this to be Non-Human Subjects Research.

**Results:** Determination of the type of mothball by sight was 57% accurate. Both naphthalene and paradichlorobenzene mothballs sank in all liquids except for the Sprite®, Diet Pepsi®, Coca Cola®, 7-UP®, and Dr. Pepper®. Naphthalene mothballs floated in Sprite®, Diet Pepsi®, Coca Cola®, 7-UP®, Dr. Pepper®, while whole paradichlorobenzene mothballs sank in these liquids, but partial mothballs that were less than a third of a full mothball floated.

**Conclusion:** Naphthalene mothballs float in the tested carbonated sodas, while paradichlorobenzene mothballs sank, making these carbonated sodas an acceptable triage tool for differentiating between naphthalene and paradichlorobenzene mothballs.

**Reference**


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**242. Ocular injuries from head lice shampoos containing a mixture of mineral oil and detergents: a consecutive case series**

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**Objective:** Due to health concerns related to insecticide-based pediculicides, there is growing demand for head lice treatments with a physical mode of action. These shampoos may contain mineral oils or enzymes, which act by destroying the insect exoskeleton. Eye irritation and corneal abrasion have been described after contact with a shampoo containing peppermint oil, detergents, glycerol, and protease enzymes, and the enzymes were the presumed causative agents [1]. The aim of this study was to investigate ocular injuries associated with lice shampoos containing a mixture of mineral oil and detergents.

**Methods:** A retrospective review of ocular exposures in humans to lice shampoos containing mineral oils and detergents reported to our Poisons Centre between June 2012 and July 2017 with good evidence of exposure and high causality. The severity of observed symptoms was graded according to the Poisoning Severity Score.

**Results:** A total of 15 patients, 4 adults (mean age 38 years, range 30–49 years) and 11 children (mean age 5.9 years, range 1.9–13.2 years) were included. The severity of the eye injuries was classified as minor in 8 cases and moderate in 7 cases. Eye reactions occurred immediately in all patients, and persisted despite prompt irrigation with water (n = 12). Reported ocular signs and symptoms in the 15 patients consisted of eye irritation (n = 6), conjunctivitis (n = 5), ocular pain (n = 5), lid swelling (n = 4), red eyes (n = 3), blepharospasm (n = 2), epiphora (n = 2), foreign body sensation (n = 2), visual disturbance (n = 2) and photophobia (n = 1). Four patients presented with corneal abrasion, 3 after prompt eye irrigation. Most patients (n = 13) had delayed presentation for medical examination (range 2.5–16 hours, mean 7 hours), and the poisons centre was never contacted (n = 15) immediately after the exposure. Medical treatment involved repeated eye irrigation (n = 9), artificial tears (n = 3), antibiotic eye drops (n = 3), Vit-A cream (n = 2), paracetamol (n = 1), and corticosteroids (n = 1). No sequelae were reported.

**Conclusion:** This case series highlights the risk of ocular injuries from lice shampoo containing a mixture of mineral oil and detergents. Although the mechanism of action remains unclear, it is possible that this particular mixture may result in a strong adherence of the chemicals to the eye surface. Therefore, it is essential to increase consumer knowledge about possible hazards of these shampoos and the need for prompt and copious eye irrigation with water.

**Reference**


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**243. Isopropyl alcohol overdose masquerading as ethylene glycol toxicity**

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**Objective:** Although isopropyl alcohol may be classified as a “toxic alcohol”, isopropyl alcohol is rarely associated with significant toxicity. If ingested, isopropyl alcohol classically causes ketosis without acidosis. We present a case of a massive isopropyl alcohol that presented with acidosis, acute kidney injury and elevated lactate mimicking ethylene glycol toxicity.

**Case report:** A 49-year-old man with a history of alcohol abuse, head trauma, status post-craniotomy, and peptic ulcer disease, was brought to the Emergency Department by the emergency medical services (EMS) after being found next to a bottle of 70% isopropyl alcohol. He was initially unresponsive to deep sternal rub and his initial vital signs were blood pressure 108/60 mmHg, heart rate 157/min, respiratory rate 45 breaths/min, temperature 37°C, oxygen saturation 90% on room air, and point-of-care blood glucose 15 mmol/L (270 mg/dL). The patient’s initial venous blood gas showed a pH 7.26, pCO2 35 mmHg, bicarbonate 15 mEq/L, and lactate 12.6 mmol/L. Other remarkable labs included an anion gap 22 mEq/L, BUN 10 mmol/L (28 mg/dL), creatinine 186 μmol/L (2.1 mg/dL) up from a baseline creatinine of 79.6 μmol/L (0.9 mg/dL), osmol gap of 115 mOsm/kg and a urine analysis that was qualitatively positive for ketones. The patient was intubated for obtundation. Owing to the inability to rapidly obtain serum toxic alcohol concentrations and the laboratory abnormalities, the patient was treated empirically with fomepizole. He was also placed on norepinephrine for hypotension. His chest X-ray was unremarkable and computed tomography head showed prior craniotomy, cerebral volume loss but no acute disease. In the medical intensive care unit, he underwent emergent dialysis and had a second session the following day. Three days later, the initial isopropyl alcohol and acetone concentrations obtained on hospital presentation returned at 48 mmol/L (288 mg/dL) and 43 mmol/L (250 mg/dL) respectively. The patient was extubated on hospital day three and ultimately discharged to a long-term rehabilitation facility.

**Conclusion:** While typically associated with central nervous system depression and ketosis without acidosis, very large ingestions of isopropyl alcohol may result in findings consistent with possible ethylene glycol toxicity. Obtaining prompt toxic alcohol...
serum concentrations could prevent the use of fomepizole in atypical presentations. Furthermore, hemodialysis may be useful for patients with severe isopropyl alcohol toxicosis in shock.

**244. Eye burns due to liquid laundry detergent capsules distributed as promotional gift via mailshot letter**

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**Objective:** Liquid laundry detergent capsules in water-soluble packaging for single use have become increasingly popular among European consumers, as they are easy to use and are a simple solution for busy households. The International Association for Soaps, Detergents, and Maintenance Products introduced a voluntary product stewardship programme in 2012 recommending the implementation of several voluntary safety measures. Mandatory safety measures were adopted at the EU level (Regulation No 1297/2014) to try and address the issue from 1 June 2015 onwards. Nevertheless, the growing use and popularity of these capsules has been associated with an increase in the number of accidental poisonings, mainly involving small children.

**Methods:** Analysis of case reports received from hospitals and a national survey of stakeholders.

**Results:** The German Federal Institute for Risk Assessment (BfR) received 2 reports (within the legal requirement § 16e Chemical Acts) from the Pediatric Clinic Frankfurt Höchst, Germany, about cases of ocular exposure by a new brand of liquid laundry detergent capsules on the German market. The capsules had been distributed by promotional gift via mailshot letter at the beginning of May 2017. Two girls, 3 and 10 years old, were exposed and hospital treatment was needed for 6 and 8 days, respectively. They developed extensive corneal abrasion classified as moderate (using the Poisons Severity Score). One child still suffered from pain and revisited an ophthalmic hospital in June 2017. For both children, care under an ophthalmologist continued until at least August 2017. After having received the reports, the BfR started a national survey involving hospitals, poison centres, national institutions, and industry to determine the impact of this promotional exercise. The mailshot letters had been distributed in the greater area of Munich at the beginning of May 2017 (approximately 1.1 million households) and the Rhein Main Area between 10 and 20 May 2017 (approximately 1.1 million households). Overall, 15 cases involving the new product were registered from the start of mailshot letters in Hessen (10 May) until 20 May 2017. In 5 cases, the promotional gift was registered as cause of poisoning. In total, a rate of 2 to 6 cases per 1 million doses distributed was calculated.

**Conclusion:** Despite newly implemented safety measures from industry, liquid laundry detergent capsules turned out to be a poisoning risk that must be monitored continuously. It is important in keep on raising parent’s awareness of the hazards of this product to ensure that products are kept out of the reach of children.

**246. Managing superglue exposure: a sticky subject**

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**Objective:** Superglue, sold in small tubes of around 10–20 g, is a commonly used adhesive containing cyanoacrylate, which is also present in nail glues and medical adhesives. The aim of the study was to look at cases reported to the UK National Poisons Information Service (NPIS) to determine the types of exposures to superglue and analyse the poisoning severity and demographic trends.

**Methods:** Enquiries to the NPIS were analysed retrospectively for 1 January 2010 to 31 December 2016 inclusive.

**Results:** There were 466 enquiries regarding cyanoacrylate adhesives: 0.14% of overall calls to the NPIS. Enquiries (47%) were about ingestion, 26% skin contact, and 24% eye contact. Most of the queries regarding ingestion (66%) and skin contact (43%) were in children under 5 and most these were asymptomatic. There were 24 calls (19%) regarding skin contact that described burns or redness to the affected area. With eye exposures, 6% occurred in children under 5 years, with 27% of the cases involving the 10–19 age group, and 18% in patients aged 20–29 years. Most (78%) eye contact queries were classed as asymptomatic. The majority of eye symptoms were classed as minor and included symptoms such as eye pain, redness, and irritation. There were three cases of ear application and two of nasal application.

**Conclusion:** Superglue is considered low toxicity by ingestion as it rapidly hardens on contact with air and the solid product is pharmacologically inert. This process can, however, cause an exothermic reaction so skin contact to the product can cause burns as well as skin-skin adhesion. Overall, 19% of calls regarding skin contact described redness or burns and in 13% adhesion was an issue. Eye, nose, and ear contact may be problematic due to the small size of the bottle being similar to that of some medicinal creams or drops. Superglue may cause skin burns and eye injury, although most cases were minor and supportive care was all that was required. Therapeutic error from mistaken packaging may be an issue, which would benefit from further more detailed exploration on circumstances of exposure.

**247. Aspiration and dermal lesions after disinfectant detergent exposure in a toddler**

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**Objective:** In relation to the total number of calls to the Poisons Information Centre (PIC) in Austria, enquiries regarding biocidal
products are relatively rare, but they have increased with 630 persons in 2015 and more than 700 persons in 2016. Nevertheless, the number of human intoxications seems to be low. We report a case of exposure in a child with a commercially available disinfectant detergent after pouring it over his head. **Case report:** A healthy 1.5-year-old boy accidentally poured a disinfectant detergent over his head and thereby ingested a small amount. The ingredients were quaternary ammonium compounds (3.85%), non-ionic surfactants (under 5%), and fragrances. His mother induced vomiting immediately and the child vomited twice. At the hospital, laryngeal spasm with inspiratory stridor and drooling was predominant. Chest X-ray was unremarkable. The child was treated with epinephrine inhalation, intravenous cortisone, and the eyes were rinsed thoroughly. The condition of the child did not improve. Bronchoscopy and esophagoscopy under general anesthesia were performed. Multiple mucosal lesions, supraglottic airway edema, and irritation in the right bronchus were noted. The child was intubated subsequently. On the following day, laryngoscopy was performed, and showed the edema had diminished, but copious amounts of mucus secretion were still present. In addition, antibiotics and NSAIDs were administered. The child was extubated after 24 hours and no further respiratory problems occurred. The next day, dermal lesions of the neck, thorax, and shoulder (3–4% surface of the body) were noticed, and in some areas, epidermal detachment occurred. The lesions were successfully treated with topical antimicrobial dressings containing silver. The child was discharged after 3 days without any further symptoms. **Conclusion:** This case shows that respiratory problems can occur as a consequence of induced vomiting after ingestion of a commercially available disinfectant detergent. Even low quaternary ammonium concentrations can lead to dermal lesions if contact is prolonged. Therefore, in addition to other treatments, after contact with a significant amount of disinfectant and/or detergent, the whole body surface of the child should be inspected and thoroughly decontaminated.

### 248. Cerebellar infarction following accidental inhalation of toluene-containing paint

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**Objective:** We report a case of atypical cerebellar infarction following accidental inhalation of toluene mixed paint. **Case report:** An unconscious 57-year-old housewife with hypertension arrived at our Emergency Department by ambulance. She had been rescued from a basement (30 m³) 12 hours after exposure to a paint containing toluene (34%). On arrival, she was comatose (E1V1M3) with a mild fever (37.4°C). Physical examination showed chemical burns on her buttocks and rales on the left lung. Initial arterial blood gas analysis with 15 L/minute of oxygen showed a pH of 7.142, PCO2 of 47.3 mmHg, and PaO2 of 204.7 mmHg. She received endotracheal intubation and mechanical ventilation. Laboratory tests showed elevated white blood cells (26.9 x 10^3/L), C-reactive protein (0.18 mg/dL), glucose (238 mg/dL), and creatinine kinase (1389 U/L). Supportive management including hydration and antibiotics were given. At 5.5 hours after arrival, she became responsive to verbal commands. On day 3, after removal of the endotracheal tube, she began to complain of an occipital headache without neurologic abnormalities. Brain magnetic resonance angiography (MRA) performed on day 6 showed a tiny acute infarction on the right cerebellar hemisphere. Urinary hippuric acid concentrations (reference range, ≤2.5 g/g creatinine) were measured serially from 74 hours (3.9) after hospital arrival to 218 hours (0.5). She was discharged on day 14. **Conclusion:** A high incidence of renal tubular acidosis in inhalant abusers suggests chronic toluene exposure causes an inability of the distal tubule to excrete hydrogen ion [1]. We suggest this is why our patient did not show renal failure and hypokalemia. Since toluene has a short elimination half-life of 3–6 hours, most patients recover rapidly, as shown in our case. Measurement of blood toluene and urinary cresol concentrations are useful in confirming toluene intoxication [1]. However, we serially measured urinary hippuric acid concentrations and confirmed toluene intoxication. Compared with prior findings of bilateral involvement or reversibility, the MRA in this case showed atypical findings [2]. This housewife, who was not a worker or chronic abuser, had an atypical cerebellar infarction after exposure to nearly fatal concentrations of toluene (>45,000 mg/m² estimated based on the basement volume and quantity of paint used).

**References**


### 249. Risk evaluation of caustic chemicals used as household cleaning products

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**Objective:** To evaluate the risk of the contact with chemical caustic products commercialized as household cleaning agents and frequently used in the domestic setting in our country. **Methods:** The study population was defined as the patients attending the Unit of Clinical Toxicology due to caustic exposure in the period from 1996 to 2015. The unit serves a population of 300,000 people. The aim of the study was to verify the risk variability determined by the intentionality of the poisoning and the type of agent. For the purpose of this study, the caustic agent is defined by its ability to produce caustic injuries in the membrane of contact by the oral route. **Results:** A contact with a potential caustic agent was present in 558 cases representing a 2.6% of the total 21,111 acute poisonings attending the Emergency Department. The age of the patients was 38 (SD ±25.3) years. The patients were evenly distributed by sex. There were 111 (20%) pediatric cases (≤14 years old) and 83.7% were under 7 years old. All these cases were domestic accidents, and the main agents involved were bleach (47.7%) and ammonia (10.8%); 9% were attributed to caustic detergents. There were no severe or fatal cases among this group. In the population over 14 years old, the number of cases was 447. Of these, 346 were accidents, among which 270 (60.4%) were domestic accidents involving patients with a mean age of 48.5 years and 52 (11.6%) were occupational accidents, involving patients with a mean age of 37.7 years. There were 101 (22.6%) cases involving suicidal gestures and these patients had a mean age of 50 years. The more prevalent agents among accidental
cases were bleach, caustic soda, and caustic detergents. In the suicidal cases, the more frequent products were bleach (40.6%) and salfuman (hydrochloric acid) 14.8%. A total of 16 patients died (2.9%), 15 of them were suicides. The mean age of the lethal cases was 72 years. The main agent involved in patients with a fatal outcome was salfuman, accounting for 12 cases.

**Conclusion:** In spite of the widespread presence of caustic agents among cleaning agents in the household, our cases demonstrate that the accidents related to them are not particularly severe and that the main risk is produced by suicidal gestures, particularly related to the domestic availability of salfuman (HCl). The pediatric cases are not unusual but do not present any particular threat in terms of morbimortality.

### 250. Intoxications with food supplements: an underestimated risk?

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**Objective:** Food supplements are subjected to less stringent laws than pharmaceuticals in Europe. EU legislation defines categories of approved substances, labeling, and permissible health claims. However, food supplements do not require approval, and only in some EU countries, including Germany, is registration compulsory. Despite the requirement of Directive 2002/46/EC, no binding upper intake limits (UL) have been established to date. As a result, even after administration according to the distributor’s recommendations, considerable overdosage may occur. The German Federal Institute for Risk Assessment (BfR) maintains a case database for various types of intoxications reported by physicians. Four cases of intoxications possibly related to food supplements were selected to illustrate risk factors.

**Case reports:**

**Case 1:** A 78-year-old woman took vitamin D3 according to the distributor’s specification (10,000 IU/day) over a long period (EFSA recommendation for UL is 100 μg/day [4000 IU/day]). She developed acute renal failure with massive hypercalcaemia.

**Case 2:** A 63-year-old woman took a selenium-containing food supplement according to the label over two months. She developed hair loss. Blood analysis detected 562 μg/L selenium (reference value in Germany 60–80 μg/L). The analysis revealed an approximately 8-fold higher content of selenium in the capsules than the declaration on the package. Case 3: A 37-year-old woman developed restless legs syndrome after using melatonin over nine months. In Germany, melatonin is a prescription drug if sold as a pharmaceutical and only approved for short-term treatment (maximum three weeks). The allowance as food supplement is under discussion in Germany. Case 4: A 64-year-old woman took a food supplement with glucosamine and chondroitin for years. She developed liver damage indicated by massive elevation of transaminases, which might possibly be related to the product. Corresponding reports have already been recorded by the European Medicines Agency (EMA) for similar products sold as pharmaceuticals. For food supplements, there is no corresponding toxicovigilance system in Germany.

**Conclusion:** In the EU, the distributor has sole responsibility for the safety of food supplements. In certain cases, even dosage in accordance with the label may lead to considerable side effects. Since there is no standardized reporting procedure in Germany for the registration of side effects by dietary supplements, a high number of unreported cases can be assumed. By establishing a national monitoring of poisonings in Germany with systematic case collection by poison information centers, the toxicovigilance of many products, including food supplements could be considerably improved.

### 251. Clozapine increases the incidence of pneumonia compared to risperidone and to no antipsychotic medication in the general hospital population

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**Objective:** Clozapine demonstrates superior efficacy in certain severe mental illnesses [1], but it comes with a comparatively heavy burden of toxicity. In addition to receptor-based side effects and metabolic derangements, clinical experience in hospital psychiatry suggests that clozapine therapy may be associated with acute lung infections [2]. We sought to determine whether the incidence of pneumonia in patients taking clozapine was more frequent compared to those taking risperidone or no atypical antipsychotics at all prior to admission to acute hospital.

**Methods:** A retrospective, case-matched study of 465 general medicine patients over a 25-month period from 1 July 2010 to 31 July 2012. Detailed electronic medical records were analyzed to explore the association between use of two atypical antipsychotics and incidence of pneumonia. Keyword searches of pharmacy records identified patients taking antipsychotic medications, and those patients’ hospital admissions were searched by diagnosis for incidence of pneumonia. Fisher’s exact test was used for comparing baseline patient characteristics. To quantify relationships between incidence of pneumonia and use of anti-psychotic medications compared to non-use, SPSS Version 22.0 was employed to calculate odds ratios with 95% confidence intervals.

**Results:** Of the 155 patients in the clozapine group, 54 (34.8%) had documented pneumonia compared to 22 (14.2%) in the risperidone group and 18 (11.6%) in the general population group. Clozapine, when compared to the general population, was associated with increased risk of pneumonia (OR, 4.07; 95% CI, 2.25–7.36; p < 0.001). There was no significant increase in risk of pneumonia associated with the use of risperidone (OR, 1.26; 95% CI, 0.65–2.45). A minimum of 17 (31.5%) of the pneumonias in clozapine patients were attributed to aspiration.

**Conclusion:** Clozapine use is associated with increased risk of pneumonia that may be related to immunologic factors or side effects of sedation, drooling, and extrapyramidal motor problems that make aspiration more likely [3], although causative mechanisms require further investigation. Prescribers should use caution in choosing candidates for clozapine therapy and reassess the balance of clinical benefits against risks of toxicity and lung infection over time.

**References**


252. Pediatric adverse reaction from eltrombopag: pharmacokinetic and pharmacogenetic evaluation

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Objective: Idiopathic thrombocytopenic purpura (ITP) is an hematological disease characterized by isolated thrombocytopenia without secondary causes. Eltrombopag, an oral thrombopoietin receptor agonist, is approved in patients over 1 year with chronic ITP unresponsive to first-line therapy (corticosteroids, immunosuppressant drugs or splenectomy). Upper respiratory tract infections, diarrhea, and increased transaminases are the most common side effects. The maximum dosage is 75 mg/day [1,2].

Case report: A 3-year-old Caucasian girl, with chronic ITP in treatment with eltrombopag, was admitted to a pediatric intensive care unit (PICU) due to acute onset of altered consciousness, oliguria and vomiting. Brain computerised tomography (CT) scan was negative and abdominal scan revealed mild hepatomegaly. Blood tests showed hyperlactacidemia, metabolic acidosis, hyperammonemia, hypoglycemia, mild hypertransaminasemia, increased lactate dehydrogenase, and bilirubin associated with severe coagulopathy (INR 9.16 [reference 0.92–1.14], aPTT 70.3 seconds [reference 28.6–35.79], aPTTr 2.41 [reference 0.91–12.9], fibrinogen 67 mg/dL [reference 162–401], antithrombin III < 20%). Infectious and metabolic causes were excluded. Suspecting an iatrogenic complication despite a dosage of 50 mg/day, eltrombopag plasma concentrations were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and were extremely high (387.5 µg/mL, reference 5.1–7.1). Pharmacogenetic analysis of genes involved in eltrombopag metabolism (UGT1A1, CYP1A2, CYP2C8 and transport (ABCG2)) was performed. The patient was homozygous in UGT1A1*28 and in CYP2C8*3 genes and heterozygous in ABCG2 genes, explaining reduced metabolism and possibly intracellular accumulation of the drug, respectively. Eltrombopag was discontinued with rapid clinical improvement and, later, restarted at a lower dose with drug concentration monitoring.

Conclusion: We describe an insidious onset of eltrombopag toxicity, in a patient affected by ITP given a standard dosage but who was a carrier of variants in essential genes for drug metabolism and transport. Ertrombopag is generally well tolerated in pediatric population. In clinical practice, a complex assessment of interactions between metabolic effects and individual susceptibility of specific drugs is required through a pharmacokinetic and a pharmacogenetic approach. Thus, it would be more correct to decide the dosage for each child considering their ability to metabolize the drug, instead of using a standard dosage range. So, we could distinguish a specific patient’s susceptibility before administering a specific drug, avoiding the risk of adverse events and choosing a tailored therapy.

253. Renal dysfunction is associated with a higher risk of cardiotoxicity following anti-cancer therapy among female patients with early breast cancer

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Objective: Previous studies have found that long-term use of anti-cancer therapy may cause cardiotoxicity, which could lead to increased medical cost and poor quality of life. Renal dysfunction is common in cancer patients, however, its impact on anti-cancer therapy-related cardiotoxicity is largely unknown because clinical trials often exclude patients with renal dysfunction. The aim of this study was to investigate whether renal dysfunction at baseline might be associated with increased risk of cardiotoxicity following anti-cancer therapy among female patients with early breast cancer, the result of which could be to aid better choice of anti-cancer therapy and monitoring of adverse drug events.

Methods: This study was a nested case-control study that employed electronic medical charts and the Cancer Registry of Taipei Veterans General Hospital (TVGH) to identify female patients with incident early breast cancer, who were admitted to TVGH and received anti-cancer therapy between 2009 and 2013. Patients’ medical records were independently reviewed by two researchers to identify incident cases of cardiotoxicity (e.g., cardiomyopathy, congestive heart failure, and coronary artery disease). Up to 4 randomly selected controls were matched to each case on age (±3 years). Information on demographics, lifestyle, comorbidities, current cancer regimen, and estimated glomerular filtration rate (eGFR) were then collected and analyzed. We used conditional logistic regression analysis to explore the association between renal dysfunction and the risk of cardiotoxicity.

Results: The case-control study comprised of 55 incident cases of cardiotoxicity and 220 age-matched controls. The crude odds ratio (OR) of developing cardiotoxicity was 1.90 (95% CI 1.03–3.51) for renal dysfunction group (eGFR < 90 mL/min/1.73 m²), compared with normal renal function group (eGFR ≥ 90 mL/min/1.73 m²). After adjusting for potential confounders, the adjusted OR for renal dysfunction was 2.04 (95% CI 1.09–3.84). Moreover, the adjusted OR for patients with mild (eGFR 60–89 mL/min/1.73 m²) and moderate-to-severe renal dysfunction (eGFR < 60 mL/min/1.73 m²) was 1.95 (95% CI 1.01–3.75, p = 0.046) and 2.72 (95% CI 0.88–8.40, p = 0.072), respectively (test for trend, p = 0.072).

Conclusion: Among female patients with early breast cancer, renal dysfunction at baseline may be associated with a higher
risk of cardiotoxicity. Therefore, appropriate evaluation of renal function and management of patients with renal dysfunction may be needed before prescribing anti-cancer therapy to reduce the incidence of cardiotoxicity.

254. Hydrochlorothiazide-induced non-cardiogenic pulmonary edema: a severe life-threatening adverse reaction

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Objective: Hydrochlorothiazide (HCTZ) is a diuretic drug, frequently used in antihypertensive therapy. Most common adverse reactions are electrolyte and dysmetabolic disturbances, erectile dysfunction, and vertigo. HCTZ-induced acute interstitial pneumonitis is a rare but reported event [1]. The only identified predisposing factor is a history of similar reaction to hydrochlorothiazide or another thiazide diuretic. We present a case of a severe adverse reaction to HCTZ.

Case report: A 78-year-old woman was admitted to the Emergency Department with cyanosis, sinus tachycardia (127 bpm), hypotension (90/40 mmHg), dyspnea and diffuse pulmonary rales. Symptoms occurred immediately after accidental ingestion of a telmisartan/hydrochlorothiazide (40/12.5 mg pill) (her son’s therapy) instead of her antihypertensive drug. Anaphylactic shock was suspected, and hydrocortisone and adrenaline was promptly administered, without improvement. Rapid worsening of her clinical condition necessitated intubation, mechanical ventilation with continuous positive airway pressure, and adrenaline infusion to provide hemodynamic support. Arterial blood gas revealed a respiratory acidosis (pH 6.9, pCO\textsubscript{2} 82 mmHg), chest X-ray evidenced interstitial pneumonitis with severe pulmonary edema, and echocardiographic assessment reported normal cardiac function. Biochemistry showed increase of procalcitonin (100 ng/mL), leukocytosis, and disseminated intravascular coagulopathy. The clinical picture suggested, initially, a sepsis overlapped on an anaphylactic shock, but no infection focus was found. The history revealed that, four years ago, the patient developed an allergic reaction (rash and laryngospasm) after ingestion of hydrochlorothiazide. Consequently, considering the patient’s history and another described case report [2], the diagnosis of HCTZ-induced acute allergic interstitial pneumonitis with pulmonary edema was established. Treatment included sedation and mechanical ventilation, amines, antibiotics, and fresh frozen plasma and human coagulation factors. During the following days, laboratory tests showed a slow amelioration with progressive decrease of procalcitonin and leucocytes, normalization of the coagulation profile. Nevertheless, the severity of the respiratory dysfunction only permitted extubation 10 days later; the patient was discharged without sequelae 20 days after admission.

Conclusion: HCTZ-induced pulmonary edema is a severe adverse reaction. This clinical manifestation is typically associated with increased procalcitonin, and could mimic septic shock. It is important to suspect the correct etiology if a rapid onset of this clinical picture is not associated with cardiac failure or infectious focus, and if predisposing factors are known.

References

255. A hard stop: clozapine withdrawal causing serotonin syndrome

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Objective: Clozapine is an atypical antipsychotic that is used primarily for refractory schizophrenia. Clozapine exhibits not only dopaminergic effects, but also has antimuscarinic properties and a strong affinity for the 5-hydroxytryptamine (5-HT\textsubscript{2}) receptors in the brain. Here, we present an unusual case of serotonin toxicity associated with clozapine withdrawal.

Case report: A 22-year-old man with a history of bipolar disorder presented to the Emergency Department with altered mental status. Vital signs upon arrival were blood pressure 137/57 mmHg, heart rate 129/min, respiratory rate 20/min, and temperature, 37.7 °C. Physical examination demonstrated a depressed mental status as well as rigid tone with hyperreflexia and clonus in the lower extremities. The patient was admitted to the intensive care unit (ICU) for management of presumed serotonin toxicity. His hospital computerised tomography (CT) scan and cerebral spinal fluid studies were negative for evidence of structural or infectious etiologies. On further questioning, it was discovered that the patient had recently stopped taking his clozapine. No other medications, including over-the-counter or supplements, or drugs of abuse were reported. In the ICU, he continued to exhibit muscular rigidity, despite the administration of lorazepam and benztrpine. He was restarted on clozapine while in the ICU and his symptoms began to improve. He was medically cleared on day 14 of admission.

Conclusion: Here, we present an unusual case of presumed serotonin toxicity triggered by clozapine withdrawal. In the literature, there are few reports of this phenomenon [1]. It is hypothesized that clozapine use downregulates 5-HT\textsubscript{2} receptors and discontinuation of clozapine leads to up-regulation of the 5-HT\textsubscript{2} receptors. This can predispose to serotonin toxicity, especially when a selective serotonin re-uptake inhibitor (SSRI) or another serotonergic agent is involved. Case reports suggest that symptoms occur as soon as 24 hours after stopping. While this mechanism has been reported in other drugs with serotonin receptor activity like clomipramine [2], reports of serotonin toxicity in clozapine withdrawal without a serotonergic agent on board is rarely reported.

References
256. Fatal liver failure after therapeutic doses of paracetamol in a Duchenne patient: a case report

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Objective: Paracetamol is a widely used drug with a good safety profile in normal doses. However, increased risk of paracetamol toxicity in patients with muscular dystrophies has been described, but the mechanism of toxicity is unknown. Further, genetic polymorphisms have not been mapped in these cases. We present a case report of acute liver failure following therapeutic doses of paracetamol in a Duchenne patient where pharmacogenetic analyses were conducted.

Case report: A 30-year-old man with Duchenne muscular dystrophies was admitted to hospital due to dyspnea. Previous literature found increased toxicity in other dystrophies and atrophies as well, supporting the lack of glutathione as a major cause in a possible multi-factorial etiology.

Case report: A 30-year-old man with Duchenne muscular dystrophy was electively admitted for a tracheostomy. On admission, alanine aminotransferase (ALT) was slightly elevated at 101 U/L and he had low creatinine (7 µmol/L) consistent with low-muscle mass. Paracetamol was initiated as analgesic therapy after the tracheostomy. Over the next four days, he was given 10 doses of 1 g paracetamol and 9 doses as 0.5 g in combination with 30 mg codeine (total 14.5 g). Five doses of paracetamol were given as 1 g intravenous infusion and the rest as oral doses. On day five, he developed gastrointestinal symptoms with nausea and vomiting. He had dark and reduced diuresis and was transferred to the intensive care unit with a possible subileus. Routine blood samples revealed severe liver failure with ALT 8921 U/L, INR 4.3, lactate dehydrogenase 5754 U/L, bilirubin 48 µmol/L and ammonium 207 µmol/L. Serum paracetamol was elevated, peaking at 282 µmol/L on day five. N-acetylcysteine infusion was initiated. Over the next few days, he became unconscious and was ventilated. He developed circulatory failure requiring vasopressors and increasing respiratory failure. On day 11, all active treatment was stopped, and the patient died the same day. He was not given any other hepatotoxic medications and there were no drug interaction that could explain his liver failure. Pharmacogenetic analysis showed that the patient was an inherent CYP2D6 poor metabolizer, while no other abnormalities in the tested enzyme-metabolizing genes were found.

Conclusion: This case supports the hypothesis that patients with Duchenne muscular dystrophy are at increased risk of liver failure on normal doses of paracetamol. CYP2D6 likely plays a minor role in the metabolism of paracetamol to N-acetyl-p-benzoquinoneimine (NAPQI), and as the patient was a CYP2D6 poor metabolizer, a small amount of NAPQI would actually be expected in this case. Previous literature found increased toxicity in other dystrophies and atrophies as well, supporting the lack of glutathione as one major cause in a possible multi-factorial etiology.

257. Black hairy tongue (BHT) associated with use of amoxicillin: three case reports

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Objective: BHT is an acquired benign condition characterized by the appearance of hypertrophied and elongated filiform papillae on the dorsum of the tongue. Conditions associated with BHT include smoking, excessive coffee/black tea consumption, poor oral hygiene, trigeminal neuralgia, and xerostomia and the use of antidepressants and antibiotics, such as penicillin, aureomycin, erythromycin, doxycycline, and neomycin. BHT's etiology is still debated, although it may involve an alteration of oral flora, along with anatomical conditions, functional limitations, and environmental factors. Few antibiotic-induced adverse reactions causing BHT have been reported, and the incidence on data sheet is listed as "not known": we highlighted 3 cases linked to amoxicillin-clavulanate in the Italian population in the last 3 years.

Case reports: A 59-year-old female smoker, 53 kg, was prescribed oral amoxicillin + clavulanate 875 + 125 mg twice daily for a dental implant. She was already on chronic therapy with lormetazepam and had received the same antibiotic therapy previously with adverse effects. On the first day of treatment, she reported general malaise and severe headache, followed by repeated episodes of diarrhea during the second day. After the fifth dose, her tongue appeared hypertrophic and hyperpigmented. She was diagnosed with BHT and treatment was suspended; the symptoms resolved after 5 days (Naranjo Adverse Drug Reaction Probability Scale score 4). A 7-year-old female of 27 kg was prescribed oral amoxicillin + clavulanate 400 + 75 mg/5 mL for a bronchiolitis (65 mg/kg/day in two doses). On the 12th day of therapy, after salbutamol was added to her therapy, she developed BHT. Symptoms regressed after treatment discontinuation (Naranjo Score 8). Our third case, a 38-year-old male who was taking oral amoxicillin + clavulanate 875 + 125 mg twice daily for an oral infection, was diagnosed with BHT after his second dose, after he attended the Emergency Room. As in the other cases, therapy was discontinued and tongue dyschromia disappeared (Naranjo Score 4).

Conclusion: In our literature review through a MEDLINE search, we could not find any amoxicillin-associated case report of BHT, while linezolid, penicillin, and erythromycin were more common. In two of our cases, the adverse drug reactions were classified as "possible" on the Naranjo Scale, and the third one was listed as "probable". In our first patient, potential other factors included drug-drug interactions, smoking, and poor oral hygiene. In all three cases, suspension of therapy was sufficient to resolve the BHT.

258. Multi-organ failure and Takotsubo cardiomyopathy after off-label use of baclofen for treatment of alcohol addiction: a case report

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Objective: Treatment of alcohol-dependence with high doses of baclofen up to 400 mg/day has gained increasing public attention and is even mentioned in a French guideline as second-line therapy. Here, we report a case with severe adverse effects.
Case report: A 47-year-old female was found in her apartment with Glasgow Coma Scale (GCS) 12, fiddling movements, and stable vital signs. Relatives reported the patient having commenced baclofen therapy for alcoholism after supervision by a specialized doctor; the last telephone contact was 36 hours earlier. She presented with multiple bruising on legs and arms, dehydrated, and feverish (38.6 °C). Cranial computerised tomography (CT) scan and abdominal sonography were unremarkable. With deteriorating GCS, she was intubated and mechanically ventilated. Relevant laboratory results were: creatinine 5.9 mg/dL (1.1), creatine kinase (CK) 51,720 U/L (<140), procalcitonin (PCT) 24.6 ng/mL (<0.1), lactate 7 mmol/L (<2.4), ALT 1385 U/L (10–35), troponin T 15.62 ng/mL (<0.014), pro-brain natriuretic peptide (proBNP) 5778 pg/mL (<158), alcohol negative, ethylglucuronide positive. The electrocardiogram (EKG) showed ST elevations in lead II, III, AVF, and V4-V6. Coronary angiography showed normal coronary arteries, transesophageal echocardiography revealed left ventricular dys-function (ejection fraction 30%) with apical ballooning, consistent with Takotsubo syndrome. Baclofen concentration in serum was 962 μg/L on admission and 439 μg/L 17 hours later. Despite fluid resuscitation, she remained anuric and needed intermittent hemodialysis for 3 weeks. For suspected aspiration, she received empirical antibiotic treatment. The patient was extubated on day 7 but had to be re-intubated because of pulmonary edema due to cardiac and renal dysfunction. Further complications were cather-sepsis with candida and delirium after final extubation 4 weeks after admission. The patient denied a suicidal intended overdose of baclofen, but reported having started a baclofen therapy with increasing doses over 1 week, at last 8 × 25 mg 2 days before her discovery. She reported amnesia for the day before her admission, however, violence as cause for the hematoma was excluded. After 6 weeks, she was discharged home with minor and spontaneously improving left ventricular dysfunction and normal renal function. 

Conclusion: This clinical course presumably resembles a delirium caused by supratherapeutic doses of baclofen and consecutive falls causing hematomas, traumatic rhabdomyolysis with renal failure, and a Takotsubo cardiomyopathy. Takotsubo cardiomyopathy is a rare complication of delirium during alcohol withdrawal. In this case, we suppose the Takotsubo syndrome was due to emotional stress and adrenergic surge in a delirium induced by baclofen. This case demonstrates potential risks of uncontrolled baclofen therapy at supratherapeutic doses.

259. Drug-induced hepatitis after exposure to Nuvaring® (etonogestrel/ethinyl estradiol vaginal ring) in a patient with Gilbert’s syndrome

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Belgium Poison Center, Brussels, Belgium

Objective: Nuvaring® (etonogestrel/ethinyl estradiol vaginal ring) was introduced in 2003 as a contraceptive. It has the safety profile of oral hormonal combined contraceptives. Adverse effects on the liver are considered rare [1]. Gilbert’s syndrome is a congenital disorder characterized by impaired glucuronyltransferase. It is defined by chronic elevated non-conjugated bilirubinemia with symptoms limited to fluctuating mild jaundice. We present a case of a drug-induced hepatitis in a patient with Gilbert’s syndrome.

Case report: A female patient presented to a general practitioner (GP) with complaints of icterus, high concentrations of bilirubin, elevated liver enzymes (AST 300 U/L) and localized eruption on the fingers. She reported recent repeated skin contact with Clean Tabs®, a medical device used to clean braces and/or dentures. The GP contacted the Belgium Poison Center to discuss a possible link between her symptoms and the Clean Tabs® exposure. She had ruled out food supplementation and foods as possible causes. Serum serology tests had all been negative. Although the skin irritation could easily be explained by the composition of Clean Tabs®, it could not be linked to the liver symptoms. Further anamnesis about the patient’s medication revealed that she had been using Nuvaring® as a contraceptive for 6 months. A liver biopsy was performed and showed a drug-induced hepatitis. Treatment with Nuvaring® was stopped and liver enzymes normalized within two weeks. The patient was later diagnosed with Gilbert’s syndrome, which explained her bilirubinemia, but not the abnormal liver enzyme values. A rechallenge was started 8 months later. A first blood test after 3 weeks’ use revealed no abnormalities. We will follow-up in later months.

Conclusion: This is the first report of a drug-induced hepatitis with Nuvaring® (etonogestrel/ethinyl estradiol vaginal ring) coinciding with the presence of Gilbert’s syndrome. Although reports of embolism are available for Nuvaring®, no case reports of hepatic side effects caused by a combination of Gilbert syndrome and Nuvaring® or Nuvaring® alone could be found [2].

References


260. Dexrazoxane for rapid extended livedo reticularis-like skin reaction due to systemic epirubicin diffusion during transcatheter arterial chemoembolization (TACE) for hepatocellular carcinoma

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Objective: Skin reactions after transcatheter arterial chemoembolization (TACE) with anthracyclines are rare, mostly limited to small areas [1]. No data involving dexrazoxane (a topoisomerase-II catalytic-cycle inhibitor) to treat skin reactions due to anthracycline systemic diffusion after TACE are reported. We describe a case where dexrazoxane was administered for an extended livedo reticularis-like reaction after TACE with epirubicin.

Case report: A 56-year-old man underwent TACE to treat one nodular hepatocellular carcinoma in hepatic segment 1. Hematological and hepato-pancreatic evaluation before the procedure was normal. Ethiodized-oil and epirubicin 50 mg were infused through a segmental artery, starting from the left hepatic artery, feeding the carcinoma. Ethiodized-oil, epirubicin 25 mg, and embolizing microspheres were then administered through an anatomical variation from the right renal artery. Immediately
after, right side pain and a livedo reticularis-like skin reaction from right flank to hypochondrium occurred. NSAIDs, opioids, chlorpheniramine were administered without success. A possible adverse reaction due to epirubicin diffusion was suspected. Dexrazoxane (1000 mg/m²) was administered 8 hours after TACE followed by 1000 mg/m² on day 2 2500 mg/m² on day 3. Laboratory results during the first week showed elevated liver enzymes (ALT 443 IU/L, AST 1189 IU/L), increased D-dimer (14,459 ng/mL), anemia (hemoglobin 8.6 g/dL), neutropenia (leukocytes 1.07 × 10⁹/L, neutrophils 0.49 × 10⁹/L), and thrombocytopenia (22.0 × 10⁹/L). On the fourth day, abdominal computerised tomography (CT) scan evidenced hyperdensity in right lower pulmonary lobe, right hepatic segments, thickening of the abdominal wall with right basal pleural effusion. He underwent thoracic drainage, received blood transfusion, and granulocyte-colony-stimulating-factor. During the third and fourth week, abdominal pain resolved, with progressive improvement of the pleural effusion, normalization of hematological-hepatic parameters and a complete skin resolution at one month after TACE. Heart function remained normal. Alopecia manifested on day 21 as a late systemic effect of epirubicin.

**Conclusion:** Adverse skin reactions related to anthracycline diffusion during TACE are mostly nodular spotted-like skin eruptions limited to peri-/supra-umbilical areas occurring after 1–30 days and resolving up to several months later [1]. In our patient, hematological and systemic epirubicin-related effects manifested. However, despite the initial presentation, a good clinical outcome was observed. Systemic administration of dexrazoxane could have played a role in resolution of the skin manifestation, heart protection, and reduction of hepatic and hematological effects.

**Reference**


### 261. Auditory and visual hallucinations after oral administration of amoxicillin: Hoigne’s Syndrome?

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**Objective:** Antibiotics are commonly used and usually well tolerated drugs. However, in sporadic circumstances, some classes including cephalosporins, quinolones, and trimethoprim-sulfamethoxazole have been linked to the development of transitory neurotoxicity or psychotic symptoms. This case report describes the onset of hallucinations after administration of oral amoxicillin.

**Case report:** A 7-year-old boy, weighing 24.8 kg, was admitted to the Emergency Department with a recent anamnesis of visual and auditory hallucinations after starting a therapy with an adequate dose of oral amoxicillin (5 g/100 mL oral suspension) 10 mL twice a day (1 g/day) for a febrile episode. Two hours after the administration of a single first dose, he began to develop auditory hallucinations: he could hear voices scolding him. He experienced at least three episodes in 24 hours. During this period, the patient experienced an episode of visual hallucinations, he could see a person far away from him. Soon after the last auditory hallucination episode, at admission, the patient was apyretic and in good general conditions, alert and eupneic. His pharynx was hyperemic. The physical examination did not detect any pathological cardiac or pulmonary sounds. The neurological assessment did not find any underlying disorder: the cranial nerve exam, Mingazzini, Romberg, and finger-nose-finger tests were all negative, his pupils were isocoric and isocyclic. Blood test results were white blood cells 4000 cells/mm³ and polymerase chain reaction (PCR) 0.06 mg/dL. Amoxicillin was promptly suspended. No therapies were administered. After 10 hours he remained apyretic (temperature 36 °C) and asymptomatic. After 18 hours of observation, he was discharged asymptomatic.

**Conclusion:** In this case, psychotic symptoms appeared for the first time after the administration of amoxicillin and resolved completely, without the need for any therapy, after its suspension. The patient did not experience any further hallucinatory episode during the observation period. Moreover, there was no evidence of underlying neurological or psychiatric pathology. The hypothesis of a causal effect is supported by the finding in literature of a similar rare case reported as a variant of Hoigne’s syndrome [1]. Although rare, serious psychotic events including auditory and visual hallucinations are possible after administration of oral amoxicillin. Even in the absence of predisposing factors or pre-existing psychiatric illness, considering the possibility of drug-induced acute psychosis in similar cases can be helpful.

**Reference**


### 262. The use of subcutaneous hyaluronidase in the treatment of dextrose 50% (D50) soft tissue extravasation

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**Objective:** Dextrose 50% (D50) is sometimes administered by prehospital personnel for the treatment of hypoglycemia. It is hypertonic and should only be administered by a central or large peripheral vein. Emergency Medical Services (EMS) across the US use D50 as initial dextrose fluid but are recently adopting a protocol of using D10 due to safety concerns and various other reasons. We present a patient who accidentally received 3 ampules of D50 subcutaneously.

**Case report:** A 32-year-old male, with diabetes mellitus, hypertension, and seizure disorder was brought to the hospital after he was found unresponsive. He received glucagon and D50 by the EMS, which was accidently injected subcutaneously due to non-functioning IV lines. Upon arrival, he had a swollen (Table 1) and tender right arm. Initial vital signs were temperature 35.8 °C, blood pressure 156/85 mmHg, oxygen saturation 99% (room air), heart rate 67/min and respiratory rate 18/min. Pain score at arrival was 8/10. His right arm was swollen and tender from the
Table 1. The measurements of both upper extremities in a patient following subcutaneous injection of dextrose 50% in the right arm.

<table>
<thead>
<tr>
<th>Location</th>
<th>Normal left arm</th>
<th>Right arm (on presentation)</th>
<th>Right arm (next day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist</td>
<td>19 cm</td>
<td>20.5 cm</td>
<td>20 cm</td>
</tr>
<tr>
<td>Mid-forearm</td>
<td>21 cm</td>
<td>26 cm</td>
<td>24 cm</td>
</tr>
<tr>
<td>Elbow</td>
<td>30.5 cm</td>
<td>36.5 cm</td>
<td>34 cm</td>
</tr>
<tr>
<td>Mid arm</td>
<td>31.5 cm</td>
<td>37 cm</td>
<td>32 cm</td>
</tr>
<tr>
<td>Deltoid insertion</td>
<td>32 cm</td>
<td>32 cm</td>
<td>32 cm</td>
</tr>
</tbody>
</table>

263. Analysis of the cases of anaphylactic and anaphylactoid drug reactions: a retrospective study

Julia V. Radenkova-Saeva and Rayna D. Stoyanova
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**Objective:** To present the results of a six-month retrospective study of anaphylactic and anaphylactoid adverse drug reactions in patients admitted to the Toxicology Clinic, Department of Adult Toxicology, UMHATEM “N.I.Pirogov” Sofia, Bulgaria.

**Methods:** The records of the Toxicology Clinic, Department of Adult Toxicology, were reviewed retrospectively for all hospitalized patients due to anaphylactic and anaphylactoid reactions, caused by medicines, during a six-month period, 1 January 2017 to 30 June 2017. The methods used included clinical observations and laboratory investigation.

**Results:** The number of patients, hospitalized in the department, due to anaphylactic and anaphylactoid reactions, caused by medicines was 96 during the study period. There were 36 men (37%) and 60 women (63%), median age 48, (range 18–78) years. The main groups of drugs involved antibiotics 47 patients (40.9%), analgesics and antipyretics 13 patients (13.5%), non-steroidal anti-inflammatory drugs (NSAIDs) 12 patients (12.5%), other drugs 24 patients (25.0%). Penicillins were the antibiotics most commonly involved in anaphylactic or anaphylactoid adverse drug reactions in 20 patients (43%), followed by the lincomamide clindamycin 11 (23%), cephalosporins 4 (8.5%), quinolones 4 (8.5%), macrolides 4 (8.5%), and other antibiotics 4 (8.5%). Anaphylactic shock was observed in 14.6% of the patients (14 cases). Angioedema with swelling on the face and neck, eyelids, lips, tongue, or throat was seen in 42 patients (43.8%). All of the patients had cutaneous/mucus membrane symptoms.

**Conclusion:** Our data show that antibiotics are the most common cause of anaphylactic and anaphylactoid adverse drug reactions in adults.

264. Choreiform movements in a patient after routine bilateral sacroiliac joint injections with lidocaine

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**Objective:** Typically, toxicity due to lidocaine occurs secondary to inadvertent intra-arterial injection following intramuscular or intravenous (IV) administration. To our knowledge, there are no cases reported in the peer-reviewed medical literature discussing neurologic or motor side effects after intra-articular (IA) injection of lidocaine. We report a patient with choreiform movements after receiving routine bilateral sacroiliac joint injections with lidocaine and triamcinolone at an outpatient facility.

**Case report:** A 52-year-old female with a history of lower back pain presented to the Emergency Department (ED) for rapid, repetitive, jerky, and well-coordinated involuntary choreiform movements two minutes after receiving bilateral IA sacroiliac joint injections with lidocaine and triamcinolone under fluoroscopy. On presentation to the ED, the patient was hypertensive, tachycardic, and tachyplenic. Upon examination, the patient was alert, oriented, and having generalized rhythmic choreiform movements lasting 45 minutes. She received IV normal saline, lorazepam, and diphenhydramine with resolution of her uncontrolled choreiform motor activity. She had been receiving lower back injections at the same facility for several years, without these symptoms in the past. Her serum lidocaine concentration was 1 µg/mL (reference normal 1.5–5.0 µg/mL) and computed tomography of the brain was normal. The patient remained asymptomatic in the ED and was later discharged after observation.

**Conclusion:** We present a case demonstrating lidocaine toxicity following fluoroscopy-assisted bilateral IA sacroiliac joint injection with lidocaine and triamcinolone. Factors that may contribute to systemic local toxicity following percutaneous administration include inadvertent intravascular injection, acidosis, and hepatic dysfunction. The serum lidocaine concentration in this case was below that characteristically associated with systemic lidocaine toxicity and we postulate that diffusion directly from the IA space to the central nervous system (CNS) may have mediated toxicity. Utilizing the Adverse Drug Reaction Probability Scale, the patient’s response to IA lidocaine injection receives a score of 6, making this reaction probable. Although typically considered safe, IA lidocaine injection of the SA joint may result in choreiform movements. Physicians performing this procedure should be aware of this potential complication.

265. Mitomycin C adverse reaction after intravesical instillation

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**Objective:** Mitomycin C is an antibiotic isolated from the broth of Streptomyces caesposus, which has been shown to have antitumor activity due to the selective inhibition of the DNA
Further iron concentrations were 76 µmol/L (426 µg/dL), after the initial concentration was 101 µmol/L (567 µg/dL). An iron concentration performed 6 hours after the initial concentration one hour after the iron infusion was 233 µmol/L (1301 µg/dL), at which time, she complained of mild dizziness and abdominal pain. Her vital signs were blood pressure 125/65 mmHg, heart rate 71/min; respiratory rate 18/min, temperature 35.9°C with an oxygen saturation of 100% on room air. Her blood glucose was 9.1 mmol/L (163 mg/dL). The patient had no vomiting and a normal anion gap. Despite the high iron concentration after mitomycin intravesical instillation, systemic absorption of mitomycin C after bladder instillation is demonstrated, and is significantly correlated with the extent of bladder resection, with a plasma concentration ranging from 5.64 to 49.25 ng/mL. The peak plasma concentration is reached within the first 40–60 minutes. Reported adverse effect have occurred in 35% of the patients after intravesical instillation, and this includes nausea, fatigue, and dysuria, but neurological effects are not mentioned in any study. Thus, this case shows that systemic absorption of mitomycin instilled into the bladder may also cause neurological effects.

266. Intravenous iron overdose: treat the patient not the number

Rana Biarya, Li Li and Robert S. Hoffman

Objective: We report a patient with a 5-fold overdose of intravenous iron sucrose. Although the patient’s initial iron concentration was very elevated, the patient had minimal symptoms and her hepatic function remained normal with only supportive care.

Case report: A 53-year-old man with a bladder tumor staged as T2, was subjected to a third instillation of mitomycin after TURBT. During mitomycin administration, the patient manifested a syncopal episode without total loss of consciousness; furthermore, he reported retro-orbital pain and unilateral blurred vision. A computed tomography (CT) scan of the brain and eyes was performed immediately and was negative. The patient had no bladder perforation, the symptomatology regressed in approximately 30 minutes, and he was discharged after a few hours.

Conclusion: After intravenous administration, mitomycin C is rapidly cleared from the blood; the time required to half the serum concentration after a 30 mg bolus injection is 17 minutes. Metabolism is primarily in the liver, but also in the other tissues. Systemic absorption of mitomycin C after bladder instillation is demonstrated, and is significantly correlated with the extent of bladder resection, with a plasma concentration ranging from 5.64 to 49.25 ng/mL. The peak plasma concentration is reached within the first 40–60 minutes. Reported adverse effect have occurred in 35% of the patients after intravesical instillation, and this includes nausea, fatigue, and dysuria, but neurological effects are not mentioned in any study. Thus, this case shows that systemic absorption of mitomycin instilled into the bladder may also cause neurological effects.

Reference


267. Prevention of mushroom poisonings in populations of foreign origin in Norway

Christina Olsen, Helga Ruus Lorentzen and Kristin Opdal Seljetun

Norwegian Poisons Information Centre, National Institute of Public Health, Oslo, Norway

Objective: The Norwegian Poisons Information Centre (NPIC) has seen an increasing trend of people of foreign origin being overrepresented in the severe cases of mushroom poisonings. A retrospective analysis of all mushroom enquiries to the NPIC was undertaken for the years 2011–2017. The results demonstrated that people with non-Norwegian background accounted for 70% of serious poisonings after ingestion of toxic mushrooms following misidentification. NPIC have initiated measures to reduce mushroom poisonings in this population.

Methods: In cooperation with the NPIC, the Norwegian Health Department provided financial support to local mushroom societies to arrange free mushroom courses for people of foreign origin. The NPIC produced an illustrated brochure of the most poisonous mushrooms in Norway translated into 19 languages. The brochures are available online, free of charge. In the autumn of 2015, the NPIC launched a low-cost Facebook campaign in English focusing on the possibility of misidentifying poisonous mushrooms as edible mushroom species. The advertisements were directed towards people originating from Thailand, Poland, China, or Russia, and linked to the brochures in their own language. In 2017, the advertisements were targeted towards people with Thai or Polish background. In addition, the Thai advertisement was translated to their own language.

Results: The local mushroom societies arranged 48 mushroom courses free of charge during the period 2011–2016. The courses focussed on the most poisonous mushrooms in Norway commonly misidentified with edible mushrooms in other countries. Overall, 911 people of foreign origin from more than 45 nationalities participated. The proportion of Thai users who shared or commented on the Facebook advertisement increased by 2.4 when the advertisement was translated to Thai.
Conclusion: Mushroom courses free of charge for people with non-Norwegian background proved popular. They are an important step in educating this group, and preventing serious poisonings. The illustrated brochure in 19 languages, together with mushroom courses, is an important tool to increase awareness of the geographical differences between mushrooms in different parts of the world. Tailored Facebook advertisements have the potential to reach specified groups at a relatively low price. With a clear and simple message, there is a huge potential in reducing health and hospital costs. The increased success of the Thai advertisement suggests that advertisements in a native language feel more personal and involving. The extra charge of the translation was quickly earned back with a higher success rate.

268. Mushroom poisoning in Finland: review of enquiries received by the Finnish Poison Information Centre (FPIC) in 2014–2016

Terhi Lampinen
Poison Information Centre, HUH Emergency Medicine and Services, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Objective: To describe the epidemiology of mushroom poisoning in Finland between 2014 and 2016.

Methods: Telephone calls related to acute mushroom poisoning were retrospectively retrieved from the FPIC database and analyzed.

Results: A total of 2325 enquiries (2% of all enquiries) concerning any kind of mushroom were received. Of these, 1837 enquiries related to acute human exposure to a poisonous or unidentified mushroom were included in this study; 488 calls concerning non-poisonous mushrooms were excluded. The number of enquiries per year was 624 in 2014, 543 in 2015, and 670 in 2016. There was variation in crop abundance every year and it also affected the annual calls to FPIC. Seasonal variation was divided between May and October 96% (n = 1756) and between November and April 4% (n = 81), (peak in September 37% (n = 672)). Although, mushroom picking is more popular among people living in Eastern Finland, most enquiries were received from Northern Finland. In adults, there were 12 enquiries/100,000 inhabitants from the Lapland region while the mean value of the whole Finland. In adults, there were 12 enquiries/100,000 inhabitants per year.

Conclusion: A child tasting an unidentified mushroom was the most common case in this data. Although, there are only a few poisonous mushrooms in Finland and severe poisonings are relatively uncommon, there is always a concern that a toxic species is involved. Potentially, severe cases should not be missed. The quick and reliable identification of the mushroom together with an early administration of activated charcoal and referral to the hospital with the required treatment facilities are important.

269. High-dose magnesium sulphate in the treatment of aconite dysrhythmia

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Objective: Stimulated by the review [1] in which magnesium sulphate received a marginal assessment in the treatment of aconite-induced dysrhythmia, we want to highlight the positive experience with this treatment in our department.

Case series: Seven cases were recruited from our poison control centre where advice was given to other hospitals with a follow-up. Four additional patients were treated in our intensive care unit. All patients were treated with magnesium sulphate and all survived. In the 11 cases, 8 involved suicide attempts and 3 were attempted murders. All the patients had ingested Aconitum napellus. The cases are summarized in Table 1.

Conclusion: Magnesium sulphate was used successfully in the treatment of dysrhythmias due to aconite poisoning. The dosage used was between 1.5 to 8 g as a bolus followed by a continuous infusion dependent on the severity of the dysrhythmia. In two patients, amiodarone failed to restore sinus rhythm whereas magnesium sulphate or the combination of both did so.

Reference

Table 1. Eleven cases of aconite-induced dysrhythmia treated with magnesium sulphate.

<table>
<thead>
<tr>
<th>Circumstance</th>
<th>Dosage of poison</th>
<th>Electrocardiogram</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicidal</td>
<td>15 g of dried leaves</td>
<td>VT, bigeminy, bundle block</td>
<td>Amiodarone, cardioversion, 8 gMg²⁺+K⁺</td>
</tr>
<tr>
<td>Suicidal</td>
<td>200 mL of pickled bulb in ethanol</td>
<td>SVT plus polytopic VES</td>
<td>5 gMg²⁺+12 g/24 h + K⁺</td>
</tr>
<tr>
<td>Suicidal</td>
<td>Unknown amount of seeds</td>
<td>SVT plus polytopic VES</td>
<td>4 gMg²⁺+5 g/24 h + K⁺</td>
</tr>
<tr>
<td>Attempted murder</td>
<td>Unknown amount in coffee powder</td>
<td>Bradycardia 40 b/min. AV-block III</td>
<td>2 gMg²⁺+5 g/24 h</td>
</tr>
<tr>
<td>Attempted murder</td>
<td>Unknown amount in coffee powder</td>
<td>Bradycardia 45 b/min. AV-escape rhythm</td>
<td>1.5 gMg²⁺+4.2 g/24 h</td>
</tr>
<tr>
<td>Suicidal</td>
<td>Handful of flowers</td>
<td>Polytopic VES, intermediate bundle block</td>
<td>Mg²⁺ unknown dosage</td>
</tr>
<tr>
<td>Suicidal</td>
<td>4 roots</td>
<td>Polytopic VES</td>
<td>3.5 gMg²⁺+3g/24h</td>
</tr>
<tr>
<td>Suicidal</td>
<td>1 bulb</td>
<td>Polytopic VES</td>
<td>2 gMg²⁺+2.5g/24h</td>
</tr>
<tr>
<td>Attempted murder</td>
<td>Concentrate in praline</td>
<td>VT + VES</td>
<td>Amiodarone, cardioversion, 4 Mg²⁺+6 g/12 h + K⁺</td>
</tr>
<tr>
<td>Suicidal</td>
<td>Chopped bulb</td>
<td>Bradycardia, QTc prolongation 514 msec</td>
<td>4 gMg²⁺+2 g/24 h</td>
</tr>
<tr>
<td>Suicidal</td>
<td>1 whole plant</td>
<td>VES, QTc prolongation 500 msec</td>
<td>2 gMg²⁺+7 g/24 h</td>
</tr>
</tbody>
</table>

VT: ventricular tachycardia; SVT: supraventricular tachycardia; VES: ventricular extrasystole.
270. Neurological symptoms after consumption of earthballs (Scleroderma species): a retrospective case series

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Objective: At the EAPCCT meeting 2016, we presented a case of gastrointestinal and bizarre neurological symptoms (sudden transient blindness, hallucinations, and depression) after consumption of the earthball Scleroderma cepa [1] (=index case, included in this study). Although, mycological field guides mention neurological symptoms vaguely [2] and one case with neurological symptoms is reported in a German mycological journal [3], this information is not readily accessible in medical databases such as Pubmed or Web of Science to date. Therefore, a working group of Swiss and German Poison Information Centers (PIC) conducted a retrospective investigation of PIC cases of human ingestions of Scleroderma species.

Methods: Data from five German and the Swiss PIC from 2002 to 2017 were analyzed for human ingestions of "Scleroderma" or "Kartoffelbovis" (German synonym for Scleroderma species). Symptomatic cases were evaluated for symptoms, and their severity, according to Poisoning Severity Score (PSS), outcome, and latency from ingestion to start of symptoms.

Results: Overall, 230 cases of self-reported human ingestions with Scleroderma were identified; 81 (35%) developed symptoms. Among the symptomatic cases, 74 patients reported gastrointestinal symptoms, among them vomiting (n = 46) and diarrhea (n = 4); 24 cases had only minor upper gastrointestinal symptoms. One or more neurological symptom was reported in 19 cases with vertigo (n = 15), visual disturbances (n = 5), and headache (n = 4); the index case had hallucinations, diplopia and achromatopsia. According to PSS, 68 cases had minor, 13 moderate symptoms, and none was severe or lethal. In total, 149 cases of ingestion developed no symptoms.

Conclusion: Ingestion of Scleroderma species may cause not only gastrointestinal symptoms, but also neurological symptoms (mostly vertigo and headache) in about 23% of the symptomatic cases. Neurological symptoms have been described in the mycological literature, but not in the commonly accessible medical literature. Neither a specific toxin nor the pathophysiology is known. A prospective investigation of such cases with better case assessment including identification of the earthballs by mycologists is necessary and a better communication between mycologists and medical staff and implementation of mycological journals into medical databases such as Pubmed are desirable.

References

271. Kratom: natural painkiller or herbal enemy?

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Objective: Mitragyna speciosa, colloquially known as kratom, is endemic to tropical Southeast Asia. The primary active alkaloids and μ receptor agonists are mitragynine and 7-hydroxymitragynine and the latter has 13-fold higher opioid receptor potency than morphine [1]. Knowledge of these components has led to kratom’s marketing as an analgesic for chronic pain, reliever of opioid withdrawal symptoms, and anxiolytic. However, little formal study regarding the possible dangers of kratom use has occurred.

Methods: Data was obtained from the Toxicology Investigators Consortium (ToxIC) case registry maintained by the American College of Medical Toxicology since 2010. Participating sites include over 50 locations in the US and three international locations. A descriptive analysis of this registry was conducted to report the epidemiology of kratom exposure.

Results: There were 15 exposures reported to ToxIC from April 2013 to August 2016. No analytic confirmation was performed. Of these exposures, 14 of 15 (93%) were male. The median age was 36 years with a range of 17 to 57 years. All exposures were oral in the form of tea, capsules, pills, or powder. In 8 of 15 (53%) cases, kratom was ingested with at least one other substance. None of the cases were self-harm attempts. One death was reported with co-ingestion of quetiapine, lamotrigine, and paroxetine. When combined with alcohol, one patient developed cholestatic liver injury, while another developed multi-organ injury attributed to hypoxia after isolated kratom use. Among patients for whom data was available, the most commonly reported signs and symptoms included hypertension (2/10), tachycardia (3/10), seizures (2/11), agitation (3/11), respiratory depression (2/9), and central nervous system depression (6/11). In total, 40% of the patients received therapy with naloxone, sodium bicarbonate, and/or benzodiazepines.

Conclusion: To date, most published literature on kratom consists of case reports [2], introducing confounding factors regarding lack of quality control and drug interactions. This study provides systematically collected population data, highlighting the epidemiology of kratom exposures and potential adverse effects. At minimum, the available information suggests extreme caution when using kratom products, especially with other substances. Further studies are needed to investigate the efficacy and safety, including addiction potential of kratom.

References
272. Analytically confirmed aconitine poisoning as a result of mistaking monkshood leaves for lovage

Maren Hermanns-Clausen, Renate Katlein, Ioana Ionascu and Volker Auwärter

Objective: Monkshood (Aconitum napellus) is a popular garden plant in Europe, although it is considered to be the most toxic European plant. The toxic alkaloid aconitine is found in all plant parts. Aconitine leads to persistent opening and activation of voltage-dependent sodium channels resulting in severe cardiac and neurological toxicity. The lethal dose in adults is 2–6 mg, and it may be contained in as little as 1 g of fresh leaves of Aconitum napellus. We report an acute accidental poisoning in two adults, who ingested a few leaves of Aconitum napellus, which they mistook for lovage (Levisticum officinale).

Case reports: An elderly couple ate noodles with a sauce made with fresh herbs from the garden, which had been picked by the husband. Thirty minutes after the dinner, the couple contacted the emergency medical services because of perioral and oral paresthesias spreading over the whole body. Both patients felt restless and dizzy. On admission to the hospital, the blood pressure of the 69-year-old woman (patient 1) was 70/40 mmHg. An electrocardiogram revealed sinus bradycardia (40/minute) and bigeminy. The therapy consisted of supportive care, administration of intravenous fluids, and benzodiazepines. After eight hours, the symptoms resolved, and the patient was discharged the next day. Vital signs of her 71-year-old husband (patient 2) were unremarkable on arrival in the Emergency Department but within 30 minutes, he developed pronounced hypotension and ventricular rhythm disturbances, namely ventricular ectopy, bigeminy, and trigeminy. Intravenous fluids and catecholamines were applied. The symptoms completely resolved over 7 hours. In the blood serum samples obtained on admission, aconitine was identified by liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS) analyses (1.8 ng/mL patient 1; 2.0 ng/mL patient 2). The couple later reported that Aconitum napellus was growing within close proximity of Levisticum officinale in the garden.

Conclusion: Accidental poisoning by confusing the leaves of edible plants (such as parsley) with monkshood has been reported before. Risk of confusion is probably higher before the flowers of aconitum emerge. Poisonous plants such as Aconitum napellus should not be planted in close proximity to edible herbs to avoid the possibility of confusion.

273. Accidental ingestion of outdoor mushrooms in children: a 1-year survey of the Austrian Poisons Information Centre

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Objective: The Poisons Information Centre (PIC) usually receives 70 to 80 enquiries per year regarding accidental ingestion of mushrooms by children while being outdoors. Since 2016, the PIC cooperates with mycologists to identify mushrooms. Mycologists are contacted if more than 1 cm² has been ingested. In such cases, the PIC obtains either a photograph of the mushroom from the caller by email or other instant-messaging services together with a description of the habitat and geographic area or the mycologist inspects the mushroom directly. The aim of this study was to determine the symptoms after accidental ingestion of mushrooms with the help of telephone follow-up.

Methods: A prospective study of all cases involving mushrooms accidentally ingested by children while outdoors over a 1-year period was conducted. Telephone follow-up with family members was performed at least 24 hours after the ingestion.

Results: In total, there were 70 cases of exposure in children aged 8 months to 12 years (39 boys, 31 girls). Four cases without follow-up were excluded. In the remaining 66 cases, 40 mushrooms were not identified, 6 mushrooms were identified by family members (Panaeolina foeniseeci, Scleroderma), 20 mushrooms were identified with the help of mycologists: Coprinellus micaceus, Panaeolina foeniseeci, Mycena spp., Amanita rubescens, Panaeolus papilionaceus, Lycoperdon perlatum, Leucoagaricus barssii, Inocybe spp., Hypholoma lateritium, Macrolepiota procera, Coprinus spp., Hypholoma fasciculare. In 2 cases, the mushroom could not be identified exactly by the mycologist, but highly poisonous mushrooms could be ruled out. In 3 out of 66 cases, hospital admission was advised because of the suspicion of intoxication with muscarine-containing mushrooms (Inocybe spp.) of more than 1 cm² in size. In all 66 cases, telephone follow-up was performed at least 24 hours after the ingestion. The 3 hospitalized children remained asymptomatic. Only two children had mild gastrointestinal symptoms (vomiting, diarrhea, abdominal discomfort) after the ingestion of Panaeolina foeniseeci. All other children had no symptoms regardless of the amount ingested.

Conclusion: In our study, most of the mushroom exposures in children during outdoor play were harmless or resulted in only mild gastrointestinal disturbances and the children could be observed at home. Nevertheless, co-operation with mycologists to identify mushrooms is important in order to avoid unnecessary hospital admissions.

274. Poisonous smoothie: acute gastroenteritis from crushed cherimoya seeds

Nadja Strusz, Gabriele Schulze, Annette Groeneveld and Martin Ebbecke

Objective: Annona cherimola (cherimoya) is a tropical fruit from the custard apple family (Annonaceae) with a creamy texture and an aromatic taste that makes it an ideal ingredient for smoothies. The 1–2 cm sized smooth black seeds are poisonous, however, containing alkaloids like caffeine, reticulin, anonain, liriodenin, and lanuginosin. If the seeds are pureed with the pulp, the beverage becomes toxic and can cause symptoms such as headache, sweating, severe vomiting, and diarrhea and abdominal cramps within an hour. After eye contact with the crushed seeds, corneal ulceration, photosensitivity, and even blindness can occur.

Methods: All cases involving cherimoya over a four-year period (2011–2015) were identified that met the following criteria: certain ingestion of Annona cherimola smoothie with crushed up seeds in humans. Ingested amount, severity, and duration of symptoms, ToxIndex, age distribution and seasonal distribution were analysed.

Results: Over the study period, an increasing number of cases with Annona cherimola intoxications were identified. Of the 14 cases that met the inclusion criteria, 8 of them could be followed
successfully. Altogether, 21 persons were affected and of these, further information about the clinical course and outcome could be obtained from 14. In all cases, the cherimoya seeds were ingested out of ignorance of their toxicity and pureed together with the fruit pulp. Concerning the severity of symptoms, 11 had moderate and 4 minor symptoms, 6 were not well documented. The Toxindex is defined as the sum of all cases classified as lethal, severe or moderate in relation to the number of all exposure cases. This index for ingestion of crushed cherimoya seeds was high with 52%. All enquires were made between October and February.

**Conclusion:** GIZ-Nord Poisons Centre observed an increasing number of intoxications with *Annona cherimola* seeds in Northern Germany. The majority of patients had at least minor symptoms corresponding with the high gastrointestinal toxicity of the alkaloids contained in the seeds. As it is a tropical fruit, European consumers may be unfamiliar with the toxicity of cherimoya seeds. To prevent intoxications, it would be helpful if supermarkets selling the fruit put up warning signs advising consumers to avoid eating the seeds.

**275. Taxus baccata (yew) intoxication treated with sodium bicarbonate and lipid emulsion**

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**Objective:** *Taxus* (yew) is found worldwide. All the parts of the plant are toxic, except for the aril [1]. Besides paclitaxel (first extracted from *Taxus baccata* leaves), the plant contains the toxic compounds Taxine A and B. Taxine B is a negative inotropic agent, slowing A-V conduction. It is a dose-dependent sodium and calcium channel blocker, similar to class I-a antiarrhythmic drugs. We describe a case series of *Taxus baccata* intoxications treated with sodium bicarbonate and lipid emulsion.

**Case series:** Cases 1–3. A Chinese family (mother, father and one daughter) were admitted to the Emergency Department (ED) after ingestion of a tisane of *Taxus baccata* leaves, believing it had some antitumor effects. After initial gastrointestinal symptoms, the patients’ electrocardiograms (EKGs) showed tachycardia with widened QRS complexes that rapidly progressed to cardiac arrest. During cardiopulmonary resuscitation, the administration of sodium bicarbonate with a 7.45–7.55 pH target was started. Furthermore, in view of the liposolubility of the toxins, lipid emulsion was administered. EKGs quickly normalized and their vital signs stabilized (except for the mother, who experienced more than 20 cardiac arrests). Case 4. A 47-year-old man ingested *Taxus baccata* leaves with suicidal intent. He was found hypothermic and comatose (Glasgow Coma Scale [GCS] 3). He was warmed and admitted to the ED, with recovery of consciousness, but he suddenly became tachycardic (200 bpm) with widened QRS complexes. Administration of sodium bicarbonate and lipid emulsion was immediately started, and EKG normalized and remained stable. After a few hours, the patient completely recovered.

**Conclusion:** *Taxus baccata* intoxication is a life-threatening condition. Early administration of sodium bicarbonate seems protective considering the cardiotoxic mechanism, which is similar to quinidine. The early administration of lipid emulsion can reduce the toxicity of lipid soluble toxins [2]. A unified approach is still required, but the use of sodium bicarbonate and lipid emulsions seems useful and can be considered in clinical practice.

**References**


**276. Food-borne botulism, initially mistaken for plant intoxication**

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**Objective:** We present a rare case of botulism in the Netherlands, initially mistaken for plant intoxication. This demonstrates the importance of carefully assessing symptoms in patients with presumed plant intoxication, rather than focusing on specific plants in their garden.

**Case report:** An 81-year-old woman was brought to the Emergency Department (ED) after eating homemade pesto from wild garlic (*Allium ursinum*) from her own garden. Upon presentation, her symptoms included nausea, vomiting, and drowsiness, soon followed by dry mouth, dysphagia, ptosis, bradycardia, orthostatic hypotension, and hypoventilation. She became increasingly respiratory insufficient and needed mechanical ventilation. The Emergency Department physician found on an Internet search that lily-of-the-valley (*Convallaria majalis*) can be mistaken for wild garlic and contacted the Poisons Information Center (DPIC) for information on possible effects and treatment. The specialist in poison information discussed the symptoms of lily-of-the-valley intoxication with the physician, who thought this intoxication could explain the symptoms. However, a neighbour said that the patient did not have lily-of-the-valley in her garden, but did have autumn crocus (*Colchicum autumnale*) growing near the wild garlic. Autumn crocus is also notorious for being mistaken for wild garlic. The patient deteriorated and developed severe muscle weakness, renal dysfunction, and paralytic ileus. Although some of her symptoms could be explained by intoxication with autumn crocus, the complete picture did not correspond well with intoxication with autumn crocus or other poisonous plants. Based on her symptoms, botulism was put forward as a possible cause of illness. Her descending paralysis and dysfunction of the autonomic nerve system matched the effects of botulinum toxin. The patient was treated with botulism antitoxin and she gradually recovered. Eleven days after presentation, she was transferred from intensive care to the neurology department. She was discharged 9 days later and transferred to a nursing home with persistent dysphagia. Feces of the patient tested positive for botulinum toxin, but the pesto tested negative. Upon inquiry, it turned out that the patient had expired foods, including salmon at home. The salmon was not kept in the refrigerator and was marked as the likely source of botulinum toxin. Unfortunately, the salmon was thrown away by a neighbour and could not be analyzed.

**Conclusion:** This case demonstrates that a reported plant ingestion by a patient does not necessarily mean that plant...
intoxication is the cause of illness. It is important to keep an open mind and assess all reasonable causes.

**277. A unique case report of a family exposed to amatoxin from foraged mushrooms including a breast-feeding mother and infant**

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**Objective:** Amatoxin poisoning can be difficult to treat with an asymptomatic incubation period and lack of a treatment modality with substantial clinical efficacy. We report a unique scenario of two cases resulting in clinical hepatotoxicity and an infant potentially exposed through breast milk.

**Case report:** A 61-year-old Chinese female visiting New York had eaten a meal consisting of foraged mushrooms. She developed nausea, vomiting, and diarrhea 11 hours post-ingestion and presented to the Emergency Department (ED) 15 hours post-ingestion with heart rate 90/min, blood pressure 153/96 mmHg, respiration 18/min, and temperature 36.6°C. Medical toxicology was consulted and she was treated with 0.9% normal saline IV, IV N-acetylcysteine, and IV penicillin G 1 million units once. Oral silimarin was considered but not available and activated charcoal was held given active vomiting. Creatinine was 85.75 μmol/L, INR 0.95, and AST 33 U/L, which increased to 773 U/L. She was transferred to a liver transplant center at 56 hours post-ingestion where treatment with normal saline and N-acetylcysteine continued. AST and INR peaked at 17,470 U/L and 2.7, respectively, without elevation in creatinine or development of encephalopathy. AST was 75 U/L and INR 1.2 upon discharge 8 days post-ingestion. Her 32-year-old daughter-in-law, who shared the meal, developed symptoms 15 hours post-ingestion and presented to the ED 29 hours post-ingestion with heart rate 85/min, blood pressure 100/87 mmHg, respiration 16/min, and temperature 36.4°C. She was provided with the same treatment. AST on presentation was 105 U/L and she was transferred to a liver transplant center where AST later peaked at 1535 U/L without elevation in creatinine, INR, or encephalopathy. AST was 187 U/L upon discharge 5 days post-ingestion. Her 4 month-old-daughter had breastfed 4 hours post-ingestion. The asymptomatic infant was evaluated 48 hours after breast-feeding and discharged from the ED with an AST of 44 U/L. Amatoxin was undetectable in the milk when later analyzed via liquid chromatography-tandem mass spectrometry (LC-MS/MS). The mushrooms were ultimately identified by a mycologist as Amanita bisporigera.

**Conclusion:** The treatments for amatoxin are quite variable with many of the most commonly implemented treatments lacking clinical efficacy. We report two cases with varying degrees of toxicity that improved primarily with IV fluids and N-acetylcysteine. There is no existing data on analytic sampling of amatoxin breast milk concentrations in current literature. We report a unique scenario of an infant potentially exposed through breast milk, that lacked detectable amatoxin when analyzed via LC-MS/MS.

**Reference**


**278. Amanita phalloides poisoning: effectiveness of timely administration of antidotes**

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**Objective:** In the emergency care of a patient with hepatotoxic mushroom poisoning, we must decide quickly about the administration of antidotes, when we are unable to obtain identification of the implicated mushrooms by a mycologist or do not have the ability to measure amatoxin concentrations. Our protocol is to administer silibinin with or without N-acetylcysteine depending on the start time of symptoms, the clinical condition and hepatic and renal function. We present cases of amatoxin-containing mushroom poisoning, to demonstrate the effectiveness of prompt and proper treatment with antidotes.

**Methods:** A review of patients with strong evidence of amatoxin poisoning from all Greek regions reported to us from January 2015 to December 2016. Patients were categorized into three groups. First group (n = 61, 75.3%): patients who presented vomiting, severe diarrhea, fever, tachycardia, hypotension with subsequent dehydration, without hepatic or renal impairment, 6–24 hours after ingestion of wild mushrooms. Second group (n = 12, 14.8%): patients who presented 24–48 hours after ingestion, reported gastrointestinal symptoms which had resolved, and had liver impairment, with or without renal impairment, which was deteriorating. Third group (n = 8, 9.9%): patients who presented 3–5 days after ingestion. They had liver failure, seizures with hepatic encephalopathy and coagulopathy and some also had renal failure. Administration of antidotes: First group: silibinin. Second and third group: silibinin in combination with N-acetylcysteine as antioxidant/hepatoprotective agent. Doses were as follows: silibinin 20 mg/kg/day in 4 divided doses as a 2 hour IV infusion for 2–3, and 3 and 8 days in group 1, 2 and 3, respectively, and acetylcysteine 150 mg/kg IV infusion over 1 hour, then 50 mg/kg over 4 hours and thereafter 6.25 mg/kg/h continuous infusion. In addition, hemoperfusion was needed in 5.6% of patients (group 3).

**Results:** There were 81 patients with strong evidence of amatoxin poisoning. There was no testing of amatoxins or identification of mushrooms in any case. In group 1, 13 of the 61 patients developed transient liver dysfunction. The outcome was good for all patients. Patients recovered fully in 3–6, 5–7 and 10–15 days, in group 1, 2 and 3, respectively. No patient required liver transplantation.

**Conclusion:** Generally, it seems that timely and proper antidote treatment, as well as general supportive care, leads to complete recovery of these patients. Our long-term experience (over 20 years) in the treatment of hepatotoxic amanitins, has proved that direct therapy with antidotes, even if the patient presents 3–4 days after ingestion, inhibits hepatic injury and progressively aids hepatic regeneration.

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Objective: There are approximately 25 known cyanogenic glycosides present in an estimated 11% of cultivated plants [1]. When these plants are chewed and ingested, the gastric juices may hydrolyse the cyanogenic glycosides, releasing hydrogen cyanide. This is a highly toxic agent, which at chronic low doses can cause neurological impairment and in high doses can be fatal. We report the incidence of enquiries to the NPIS concerning ingestions of plant material containing cyanogenic glycosides.

Methods: Records of telephone enquiries to the NPIS between 1 January 2008 and 31 December 2016 involving ingestions of cyanogenic glycoside-containing plants were reviewed to determine incidence and clinical features.

Results: The NPIS received 1101 relevant enquiries during this period. The plants involved were cherries (16%), cotoneaster (14%), hydrangea (8%), cherry laurel (7%), apricot (7%), elderberry (7%), plum (6%), aquilegia (5%), cassava (4%), and apple (3%). Other categories were 2% or less. The majority of enquiries concerned patients who were asymptomatic (n = 855, 78%). One patient had severe features, which corresponded to a maximum Poisoning Severity Score of 3. Other symptoms reported at the time of inquiry were minor and included vomiting (n = 58), abdominal pain (n = 38), nausea (n = 38), diarrhea (n = 33), dizziness (n = 20), headache (n = 16), and somnolence (n = 9). The majority of enquiries concerned ingestion; 1027 were accidental, 23 were intentional, 22 were recorded in association with some sort of medicinal intent, 15 were listed as other or general information, and 12 were of unknown circumstance. Apricot kernels were most commonly ingested with intent for self-harm and also caused the most severe features. One patient received a cyanide antidote. Eighty-eight percent of enquiries followed exposure in a home or domestic setting, 7% at school, 2% in a public area, 0.7% in a nursing home, 0.6% in work, and 0.8% at an unspecified location. There were 581 enquiries involving children less than five years old (53%).

Conclusion: The most common exposure type was accidental, occurring at home in children under five years old. Apricot kernels were most commonly ingested with intent for self-harm and also caused the most severe features. Only one patient required antidote treatment, suggesting the likelihood of severe cyanide poisoning from ingestion of plants is very rare.

Reference

280. Acute hepatitis following valerian root ingestion

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Objective: Valerian root-induced hepatitis is unfamiliar to many providers. No formal studies have described it in the medical literature and all evidence is limited to case reports. The goal of this report is to present an unusual case of valerian-induced hepatic injury to heighten clinical suspicion.

Case report: A 56-year-old female presented with visual hallucinations for two days. She endorsed recent anorexia, but denied vomiting or abdominal pain. Exam was notable for absence of abdominal tenderness, hepatosplenomegaly, scleral icterus, or other stigmata of chronic liver disease. Laboratory testing revealed an elevated aspartate aminotransferase (AST) 160 U/L (range 12–39), alanine aminotransferase (ALT) 109 U/L (range 7–52), direct bilirubin 0.7 mg/dL (range 0.0–0.3), and total bilirubin 1.5 mg/dL (range 0.3–1.4). Review of her chart from six months prior demonstrated all transaminases within normal reference range. Upon further history, she admitted to ingesting an over-the-counter xenobiotic containing 75 mg valerian root, chamomile, and melatonin due to insomnia and anxiety after stopping clonazepam. She reported taking roughly 4 pills per day for 4 consecutive days, with the last ingestion 3 days prior to her presentation to the hospital. In addition, she reported a chronic history of 1–2 drinks of ethanol per day with her last ethanol intake 48 hours prior. Her visual hallucinations resolved after restarting her clonazepam. Three days after admission, hepatic markers improved to AST 100 U/L and ALT 78 U/L. Follow-up testing two weeks later demonstrated consistent improvement (AST 51 U/L and ALT 64 U/L).

Conclusion: Valerian root has anxiolytic properties and components act through binding to the beta subunit of the γ-aminobutyric acid (GABA) ion channel. The patient’s hallucinations were likely from withdrawal from her multiple xenobiotics that modulated GABA-A channel, as hallucinations resolved with resumption of clonazepam. Valerian root has been shown to cause cellular free radical damage and hepatocyte cellular death in experimental in vitro studies. Valerian root toxicity has been reported as mild to moderate transaminitis, as in our case, to rare reports of hepatic encephalopathy. As valerian root usage may not be reported to providers, the true prevalence of its toxicity is not well elucidated. While ethanol hepatitis was initially considered in our case due to her daily ingestion, she had previously had normal hepatic markers, despite daily ethanol ingestion. Clinicians should continue to inquire about herbal products and supplements, and valerian root should be considered in the differential diagnosis for acute hepatic injury.

281. Neurotoxic shellfish poisoning from the consumption of contaminated conch

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**Objective:** The consumption of brevetoxin-contaminated shellfish can cause Neurotoxic Shellfish Poisoning [1]. Brevetoxin stimulates voltage-sensitive sodium channels initiating sodium influx; the resulting membrane depolarization causes nausea, vomiting, abdominal pain, dizziness, ataxia, paresthesias, slurred speech, and muscle weakness. Symptoms develop within 3 hours and may last for up to 72 hours [2]. Molluscan shellfish are filter feeders and can accumulate brevetoxin from *Karenia brevis*, a dinoflagellate found in the Gulf of Mexico. Large blooms of *K. brevis* change the color of the ocean to a reddish/brown hue. These “red tides” occur along the Florida coast during the months of September to April. Harmful algae blooms (HABs) are responsible for large fish kills and other animal species that feed on them [3]. Aside from ingestion of contaminated shellfish, wave action may aerosolize brevetoxin causing ocular, nasal, and pulmonary irritation. We report two cases of neuromuscular paralysis from consuming brevetoxin-contaminated conch.

**Case report:** In August 2017, the Florida Poison Center in Tampa was contacted regarding 2 pediatric patients that had consumed conch gathered off the coast of Sarasota, Florida. All 8 people that ate the conch developed dizziness, but the 2 children progressed to significant neurological symptoms. The dizziness reported by the adults resolved after taking diphenhydramine. The children presented 3 hours after consumption with symptoms of nausea, diaphoresis, slurred speech, ataxia, paresthesias, ophthalmoplegia and myasthenia which progressed to an inability to move their extremities. Onset of symptoms of the younger female patient developed within an hour, the older male sibling’s onset was 45 minutes later. After 21 hours of supportive care, both children did well and were discharged.

**Conclusion:** Brevetoxin toxicity should be placed on the top of the differential diagnosis when patients present with gastrointestinal and neurological symptoms after consuming a seafood meal. The harvesting and consumption of shellfish should be limited to months of the year when there is a low risk of HABs, and close attention paid to public notices of shellfish harvesting restrictions.

**References**


**283. Amatoxin poisoning: a 30-year retrospective analysis and evaluation of 153 patients**

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**Objective:** Fatalities due to mushroom intoxication occur worldwide, with more than 90% of deaths resulting from ingestion of amatoxin-containing species. Limited information is available about epidemiology and management of these types of intoxications.

**Methods:** A retrospective evaluation of the history and clinical outcome of the patients treated from 1982 to 2016 in the Toxicology Unit-CAV of Azienda Ospedaliero-Universitaria Careggi, Florence, Italy, is reported. Clinical information was retrieved from the hospital database, as well as the biological parameters monitored, therapeutic, and antidotal protocol used and outpatient follow-up evaluation.

**Results:** The clinical data of 153 patients and their biological parameters were evaluated every 12–24 hours until discharge.
Five patients died, all of them were admitted to the hospital more than 28 hours after consuming the mushroom meal. Of all the hematological parameters examined, prothrombin activity and transaminases are the most indicative of prognosis, according to our Poisoning Severity Score [1]. The patients were treated with high-dose penicillin G, glutathione or acetylcysteine and dexamethasone as part of their treatment regimen. Penicillin G is an antidote that antagonizes hepatic amatoxin toxicity, inhibiting organic anion transporting polypeptide (OATP)-3. Our follow-up evaluation showed that all the survivors had a complete recovery. Our experience indicates that our therapeutic protocol is effective for amatoxin poisoning, especially if patients are treated within 36 hours of mushroom ingestion.

**Conclusion:** Our experience indicates that our therapeutic protocol is effective for amatoxin poisoning, especially if patients are treated within 36 hours of mushroom ingestion.

**Reference**


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**284. A significant portion of moderate to severe courses after ingestion of mushrooms is caused by inadequately stored or prepared edible mushrooms**

**Uwe Stedtler and Maren Hermanns-Clausen**  
Poisons Centre, Center for Pediatrics, Medical Center – University of Freiburg, Freiburg, Germany

**Objective:** Mushroom exposures are considered dangerous if more than minor amounts are consumed. This induces strong efforts to identify the mushrooms involved and very often aggressive treatment. We analysed the poison center (PC) database for moderate, severe or fatal mushroom poisonings.

**Methods:** Retrospective search of the PC database for exposures to mushrooms (except mold) in the years 2001 to 2016.

**Results:** We retrieved 3830 documented exposures to mushrooms (13.3% of all cases). In 1125 of these cases (29.4%), follow-up information for more than 24 hours post-ingestion was available. Symptoms were rated moderate in 172 cases, severe in 35 cases and two patients died. In 192 patients, the exposure was unintentional, 8 patients consumed mushrooms to trigger central nervous effects, one case was suicidal and in one case, the patient used a poisonous mushroom as a remedy. In 7 cases, the circumstances of exposure remained unclear. One 18-month-old child vomited 4 times after eating an unknown amount of a mushroom she found while playing. All other patients ingested at least one bigger or several small specimens (10 patients), most of them a larger amount as a meal (188 patients). In 10 patients, the amount ingested remained completely unclear. The 19 moderate and 7 severe cases were probably caused by amanitin-containing mushrooms. In 14 moderate and 3 severe cases, this was analytically confirmed. One moderate and 6 severe cases were related to orellanine, which was analytically confirmed in one severe case. Four moderate courses and one severe course were caused by muscarine-containing mushrooms. Edible mushrooms were involved in 38 moderate to severe cases and 3 severe cases. In 15 of these moderate to severe cases, the mushrooms were obtained from commercial sources and in 9 of these cases, the mushrooms were grown in culture. Most likely, the mushrooms were inadequately stored or prepared. Six further cases were caused by mushrooms, which are usually considered edible but known to cause adverse symptoms in some people. In 75 cases, the causative agent remained unclear. In two fatal cases, the causative agent remained unknown, though the symptoms (liver and renal failure) were suggestive of amanitin.

**Conclusion:** In many moderate to severe mushroom intoxica-tions, it is difficult to identify the causative agent. In this study, a significant proportion (22.5%) of moderate or severe mushroom intoxications were caused by edible mushrooms. Children rarely developed more than minor symptoms after accidental ingestion of mushroom.

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**285. Regional ileitis as a non-specific symptom of Boletus species poisoning**

Ruben Goncalves\(^{a}\), Françoise Giraud\(^{b}\), Laurie Cordier\(^{b}\), Olivier Ely\(^{c}\) and Magali Labadie\(^{a}\)

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\(^{b}\)University Hospital, Poison Control Center, Toulouse, France;  
\(^{c}\)Emergency Department, Périgueux, France

**Objective:** In France, mushroom poisoning occurs frequently and several new syndromes in mushroom poisoning have been described [1]. There are many reports on the toxicity of Boletus species but none describe regional ileitis.

**Case report:** A 28-year-old man without previous medical history was admitted at the Emergency Department due to severe gastrointestinal symptoms, six hours after eating a single self-prepared meal with Boletus mushrooms. Symptoms, such as abdominal pain, repeated vomiting, and profuse watery diarrhea occurred three hours after the meal. On admission, all blood tests were normal and the patient was afebrile and physical examination was unremarkable except for abdominal sensitivity. Hyperthermia occurs six hours after admission (38.6 °C) and repeat blood tests showed hyperkalemia (6.1 mmol/L), raised C-reactive protein (CRP) (34.3 mg/L), and procalcitonin (PCT) (53.4 ng/mL) with negative hemocultures; liver function tests were normal at the 12th hour. Regional ileitis was identified by computed tomography showing gastrointestinal parietal thickening of the proximal ileum and sub-occlusive syndrome without obstructive pathology. He was given an antibiotic and the fever, hyperkalemia, and digestive symptoms gradually decreased during the day after ingestion, whereas the CRP and PCT began to decline after 24 hours. He was discharged after three days of hospitalization and all biological parameters were normal one week after leaving hospital. One year later, the patient has had no recurrence of ileitis.

**Conclusion:** There was no formal identification of the mushroom by a mycologist but from a description, it was probably *Boletus satanas*. This species is well known to cause an early gastrointestinal syndrome with vomiting, abdominal pain, and intense and profuse diarrhea [2] and it also causes hyperprocalcitoninemia [3,4]. In our case, no other etiology could explain the occurrence of this patient’s febrile ileitis and poisoning with *Boletus satanas* may be the direct cause.

**References**


286. Accidental fatal poisoning with *Colchicum autumnale* due to mistaken identification: a case report

Ruth Kastanje and Aet Variksoo
Poison Information Centre, Tallinn, Estonia

**Objective:** Until the mid-20th century use of wild edible plants was common in Estonia [1]. More recently, knowledge of plants has been decreased but with healthy nutrition trends, wild plants are gathering popularity again. “Fashion plants” are recommended on social media as “super foods”, and used by people with limited botanical knowledge. A popular plant recently has been *Allium ursinum* (wild garlic). There are case reports from throughout Europe about poisonous plants mistaken for *Allium ursinum* including *Colchicum autumnale* and *Veratrum album* [2,3]. We present a case report of fatal poisoning due to *Colchicum autumnale* mistaken for *Allium ursinum*.

**Case report:** A 69-year-old man and a 66-year-old woman were hospitalised after eating homemade wild garlic pesto the previous evening. Some hours later, both developed severe gastrointestinal symptoms but did not seek medical help. The next day, an ambulance was called and they were admitted to the hospital. The wife felt better and was later discharged. Discussing the plant eaten, both were sure it was not wild garlic. Both *Convallaria majalis* and *Colchicum autumnale*, which have leaves similar to *Allium ursinum* grew in the same garden. The signs and description of the plant fit *Colchicum autumnale*. The husband deteriorated, and developed signs of hepatic failure and cytolysis. The Poison Information Centre was contacted. He was admitted to the intensive care unit (ICU) and then transferred to an internal medicine ward the next day. He was delirious, agitated, and pyrexic (38 °C). On day 5, he developed pancytopenia and on day 7, returned to ICU with hypotonia, hypoxia, deteriorating mental status, and multi-organ failure. Despite aggressive treatment with mechanical ventilation, dialysis, and vasopressors, he died on day 9.

**Conclusion:** After the fatal accident, several articles and blog posts were published by the Estonian Poison Information Centre and botanists to raise awareness about dangerously similar looking plants and the toxicity of *Colchicum autumnale*. Considering the gaps in general botanical knowledge, it would be more useful in the future for the Poison Information Centre to follow wild plant trends on social media and identify and introduce to the public the potential mistaken identification dangers of popular plants.

**References**


288. Rhabdomyolysis associated with mushroom poisoning: clinical characteristics and outcomes

Satariya Trakulsrichai,a,b, Peerawich Jeeratheepatanonta, Sunun Wongvisavakornb, Charuwan Sriaphac, Achara Tongpob, Umaporn Udomsubpayakula and Winai Wananukub,d

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**Objective:** To describe and analyze the clinical characteristics and outcomes of cases of rhabdomyolysis after mushroom ingestion in Thailand.

**Methods:** We performed a retrospective cohort study of cases of rhabdomyolysis associated with mushroom poisoning from the Ramathibodi Poison Center Toxic Exposure Surveillance System, during a 5-year period (2012–2016).

**Results:** There were 24 consultations totally of 41 poisoning cases. The mean age was 48 years. Most patients were male (53.7%) and from the north-east region (53.7%). The median onset of gastrointestinal symptoms after taking mushrooms was 2 hours (range 0.17–24 hours). The common presenting symptoms were nausea or vomiting (85.4%), abdominal pain (63.4%) and myalgia (46.3%). Rhabdomyolysis, elevated liver enzymes, acute kidney injury (AKI), and hyperkalemia were reported in 80.5%, 78%, 45.7%, and 31.3% of the patients, respectively. The median maximum serum creatine phosphokinase (CPK) value was 47,861 (range 8,616–330,000) U/L. Seventeen patients were investigated for serum troponin I or T, and 15 (88.2%) had elevated troponin concentrations. In 4 patients who had an echocardiogram, 3 patients showed abnormal findings as low ejection fraction. Most patients (95.1%) were admitted to the hospital and the median hospital stay was 5 days. Most patients received treatment including intravenous fluids (81.6%), urine alkalization (48.8%), hemodialysis (12.2%), and peritoneal dialysis (4.9%). The mortality rate was 26.8%. In one incident of poisoning (3 cases), the relatives brought the mushrooms to the hospital and photographs were identified by an experienced mycologist as *Russula* species. We performed an analysis between the non-surviving and surviving patients and found that age (0.018), AKI (<0.001), initial and maximum serum potassium (0.038, <0.001), initial and maximum serum creatinine (0.045, 0.001) and maximum CPK (0.029) were statistically significantly different between the 2 groups.

**Conclusion:** Rhabdomyolysis associated with mushroom poisoning caused high fatality. Some patients developed cardiac toxicity and elevated liver enzymes. Age, AKI, serum potassium, serum creatinine, and serum CPK were the factors associated with death.
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