Management of antidotes during extra-renal therapies

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Why do we use extra-renal therapies in poisonings?

• To remove toxic substances
• For symptomatic treatment of an ARF from another origin.
• Consequences of an ARF:
  – Elevation of toxic substances usually eliminated by renal filter
• Consequences of extra-renal therapies
  – Elimination of these toxic substances
  – Elimination of some useful treatments as antidotes
Different types of Renal Replacement Therapies (RRT)

• These techniques can be used alone:
  – Hemodialysis (HD)
  – Hemofiltration (HF)
  – Hemoperfusion (HP)
  – Plasma exchange (PF)

• On an intermittent or continuous mode:
  – Intermittent hemodialysis (IHD) or continuous veino-venous hemodialysis (CVVHD) or sustained low efficiency dialysis (SLED)
  – Intermittent hemofiltration (IHF) or continuous veino-venous hemofiltration (CVVHF)

• Or associated in an intermittent or continuous mode:
  – HD + HP, CVVHDF, CVVH + HP, MARS…
Hemodialysis (IHD)

Process = DIFFUSION of solutes from blood across a semipermeable membrane to an ultrafiltrate based on a concentration gradient:
- Good clearance of small MW toxins
- Rapid correction of electrolytes and acid-base disturbances, as well as excess fluid = the most often used technique of RRT in poisonings.

Concentration gradient

Best method for:
- Substances with MW < 1000 da
- Low (<80%) protein bound
- Vd < 1 L/kg
- Hydrophilic molecules
- Ionised molecules
- Clearance > 100 ml/min
<table>
<thead>
<tr>
<th>Increased by</th>
<th>Diminished by</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High blood flow</strong></td>
<td>• Filter coagulation</td>
</tr>
<tr>
<td>• High dialysate flow</td>
<td>• Dialysate saturation (= recirculation)</td>
</tr>
<tr>
<td>• High surface of the semipermeable membrane</td>
<td>• Important protein binding</td>
</tr>
<tr>
<td>• Length of the session (&gt; 4 h)</td>
<td>• Adsorption on the membrane</td>
</tr>
<tr>
<td></td>
<td>• Important renal clearance (ex: lidocaïne, metformine)</td>
</tr>
</tbody>
</table>
Hemofiltration (HF)

Process = CONVECTION of solvent and solutes from blood across a semipermeable membrane to an ultrafiltrate according to a pressure gradient:

- Good clearance of small MW toxins
- Can be used even in hemodynamic compromise

Interest of the method:
- Id than HD in term of Vd and protein binding
- But higher MW cut-off (< 40 000)
- Less hemodynamic complications
- Maintain consistent homeostasis through slow, gradual shifts in volume status and osmolality
- Less risk of rebound
Hemofiltration (HF)

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Hemofiltration efficacy

**Increased by**
- High blood flow
- High surface of the membrane
- **Length of the session**

**Diminished by**
- Filter coagulation
- Adsorption on the membrane
- Dialysate saturation (= recirculation)
- Important protein binding
- Important MW
- Pre-dilution / post-dilution
Hemoperfusion

Process = ADSORPTION of toxins on the charcoal or filter
Plasmapheresis (TPE)

Process = extracorporeal separation of plasma from the cellular components of blood, either by centrifugation or filtration.

About 3 circumstances of poisoning:
- Highly bound protein (> 80%, albumin) toxin with low Vd (< 0.2 L/kg)
- Elimination of immunotherapy in a patient with renal failure
- Support of liver device

Estimation of the volume to exchange: \((100 - \text{Hematocrit}) \times 0.7 \times \text{weight}\)

Efficacy = depends on the number of volume exchange (> 2 plasma volumes)

MARS system

- **modified hemodialysis system** with a high-flux membrane permitting passage of hydrophobic albumin-bound target substances into an albumin-enriched dialysate by means of a gradient of ligand-free sites on albumin.
- This albumin dialysate is regenerated online by passage through:
  - (i) a second dialyzer for hydrophilic or nonalbumin-bound molecules;
  - and (ii) two adsorbent columns (uncoated charcoal and anion exchange resin) for hydrophobic albumin-bound substances
What questions to ask?

1. Is the continuation of the antidote necessary during the technique of RRT?
2. Is the antidote eliminated totally or in part during RRT?
3. If needed what are the adjustments of the dosage of the antidote during RRT?
N-acetylcysteine (NAC)

- Data are lacking on pharmacokinetics of NAC during Renal Replacement Therapies (RRT)
- NAC is extracted by RRT:
  - Small molecule (MW=163.2), not bound to proteins, low VD (0.3 – 0.5 L/kg)

A study was conducted on 6 patients presenting a fulminant hepatic failure associated with renal failure linked to a severe APAP poisoning.
- All patients received a **continuous infusion of 6.25 mg/kg/h of NAC**
- Samples from urine, plasma (pre- and post-filter), dialysate and/or UF
- **Method:** NAC kinetics were determined in up to 3 stages:
  - In the absence of RRT
  - During RRT
  - After discontinuation of NAC

Results

• In the absence of RRT:
  – Mean blood [NAC] = 31.8 mg/L

• During RRT:
  – Continuous Veno-Venous Hemofiltration (CVVH):
    • High intra and interindividually variability
  – Total NAC:
    – Mean extraction ratio = 0.08 (0.03 – 0.15)
    – Mean fractional clearance = 9% (3-14%)
    – Removal of 33.2 mg total NAC/h (15.1 – 48.9)
  – Free NAC:
    – Mean extraction ratio = 0.13 (0.02 – 0.44)
    – Mean fractional clearance = 0.2% (0-0.6%)
    – Removal of 1.21 mg free NAC/h (0.15 – 0.34)

Results

- During RRT:
  - Hemodialysis (HD):
    - High intra and interindividual variability
  - Total NAC:
    - Mean extraction ratio = 0.26 (0.15 – 0.34)
    - Mean fractional clearance = 50% (5-85%)
    - Removal of 233 mg total NAC/h (25 – 395)
  - Free NAC:
    - Mean extraction ratio = 0.29 (0.03 – 0.56)
    - Mean fractional clearance = 5% (1 - 12%)
    - Removal of 18 mg free NAC/h (5 – 43)

- Conclusions:
  - CVVH clearance is minimal: no need to adjust NAC dosing
  - HD clearance is significant and an adjustment of NAC dosing is mandatory
NAC: case report

- Woman aged 18, ingestion of 100 g of APAP
- Symptoms: decreased mental status, lactic acidosis
- NAC = 150 mg/kg on 1h then continuous infusion of 12.5 mg/kg/h (before and during HD).
- H+7: Intermittent HD for 7 h (blood flow rate = 400 ml/min, dialysate flow rate = 1000 mL/min)
- Concerning NAC:
  - Fluctuations of blood [NAC] during HD: between 162.7 and 364.9 mcmol/L
  - HD clearance = 190.3 mL/min
  - Extraction ratio = 69%
  - Removal of 17.9 g of NAC during the 7 h HD = 2557.1 mg NAC/h
  - T1/2 = 1.9 h during HD (5.2 h prior and 4.6 h after RRT).
- After HD discontinuation NAC was continued at a rate of 6.25 mg/kg/h during 28.5 h. [NAC] = 335.7 mcmol/L.
- Conclusion: doubling NAC regimen is necessary during HD to maintain a [NAC] similar to those seen post-HD.

NAC: study on HD

• 3 patients presenting severe APAP poisoning (> 1000 mg/kg) with lactic acidosis were dialysed.

• **NAC protocol:**
  – After a loading dose of 150 mg/kg NAC between 10 and 18h > ingestion
  – Additional empirical doses during HD were given on the hypothesis that NAC was also dialysed.

• **Results during HD (length: 3 – 4 h):**
  – Mean extraction ratio across the circuit = 73 – 87%
  – Dialysance = 3 – 5.3 ml/kg/min

• **Conclusion:** **HD doubles the clearance of NAC**

NAC: conclusions

- NAC is dialysed by most of the RRT, mostly by IHD
- Extraction ratio > 50% of the dose necessitating a compensation of removal during IHD
- It is mandatory to double the dose of NAC during IHD
- It seems not useful to modify dose regimen during CVVH
- In case of CVVHDF a compensation is probably necessary as for HD.

EXTRIP workgroup recommendatons on extracorporeal treatment for acetaminophen poisoning:
- NAC should be continued during RRT at an increase rate, especially during HD.

Ethanol

- Formula = C2H5OH
- Molecular weight = 46.07
- Volume of distribution (Vd) = 0.64 L/kg in women and 0.72 L/kg in men
- Elimination rate = from 12.4 mg/dL/h (2.6 ± 0.9 mmol/L/h) in nondrinkers to 30 ± 9 mg/dL/h (6.4 ± 2 mmol/L/h) in alcoholics
- Therapeutic blood level > 100 mg/dL (21.7 mmol/L)
- Low protein binding
- Dialyzance = 120 mL/min (= 7200 ml/h) for a 70 kg patient

Fomepizole

- **Formula** = C4H6N2
- **Molecular weight** = 82.1 or 118.6 (hydrochloride form)
- **Volume of distribution** (Vd) = 0.7 L/kg.
- Low protein binding
- Total urinary excretion = 3% of the dose
- Mainly eliminated by metabolism (oxidation to 4-OHMP then to 4-carboxypyrazole = 70% of the dose excreted in the urine).
- Elimination after IV is saturable
- Dialyzance = 52 – 80 mL/min and **20% of the dose is removed during a 4-hour hemodialysis**

FOMEPIZOLE during RRT in case of methanol poisoning

• Very few studies have been published on this antidote during RRT.

• Methanol and formic acid are easily dialyzable and efficiently removed by RRT:

<table>
<thead>
<tr>
<th>Type of Extracorporeal Treatment</th>
<th>Methanol Clearance (mL/min)</th>
<th>Methanol $T_{1/2}$ (hr)</th>
<th>Formate $T_{1/2}$ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>Range</td>
<td>$n$</td>
</tr>
<tr>
<td>Intermittent hemodialysis</td>
<td>208</td>
<td>77–400</td>
<td>38</td>
</tr>
<tr>
<td>Sorbent hemoperfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>37</td>
<td>5–70</td>
<td>2</td>
</tr>
<tr>
<td>Continuous renal replacement therapy</td>
<td>36.7</td>
<td>17–48</td>
<td>3</td>
</tr>
</tbody>
</table>

$T_{1/2}$ = half-life.

*Patients who had more than one ECTR may appear at more than one place.

*Data obtained in the initial search. A subsequent publication reported median half-lives: methanol 3.7 hr by intermittent hemodialysis ($n = 11$) and 8.1 hr by continuous venovenous hemodialysis (filtration) ($n = 13$), and formate 1.6 and 3.6 hr, respectively; both $p < 0.001$ (47).

Methanol poisoning outbreak, Czech Republic, 2012-2013

• 25 patients, mean age 50
• Severe methanol poisoning hospitalized between september 2012 and july 2013
• Indications for RRT:
  – Serum methanol > 50 mg/L (15.6 mmol/L)
  – Metabolic acidosis with pH < 7.30
  – Visual toxicity
• Techniques of RRT used:
  – IHD: 13 patients
  – CVVHD / HDF: 11 patients

Methanol poisoning outbreak, 2012-2013

• Antidote treatment during RRT:
  – Fomepizole: Initial bolus of 15 mg/kg, then 10 mg/kg / 4h during RRT and / 12 h before or after RRT (and > the 5th dose: 15 mg/kg / 12 h).
  – Ethanol: in order to provide an [ethanol] > 1 g/L – hard to maintain (44% < 1 g/L during observation time).

• Results:
  – IHD > CVVHD/HDF in terms of methanol and formate elimination

<table>
<thead>
<tr>
<th></th>
<th>Methanol</th>
<th>Formate</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD</td>
<td>3.7±1.4 h</td>
<td>1.6±0.4 h</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CVVHD/HDF</td>
<td>8.1±1.2 h</td>
<td>3.6±1.0 h</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

– Favorising factors: high blood flow rate, high dialysate rate, high dialyzer surface.

– No result on extraction of fomepizole or ethanol during the procedures.

FOMEPIZOLE:
- Loading dose = 15mg/kg
- Then 1 – 1.5 mg/kg/h infusion
- Or repeat loading dose / 4 h

ETHANOL:
- Dose to maintain blood ethanol > 1g/L
- Dose X 2 or 3 during ECTR with regular blood tests
Case report on methanol poisoning

- 39 old man: intoxication with methanol on a period of 2 days (dose ingested = unknown)
- On admission: only visual blurring, mild tachycardia (101/min) and polypnea (18/min) – pH = 7.2 with annion gap of 24.
- Initial blood methanol level = 117 mg/dL
- Loading dose of fomepizole was administrated
- HD was performed for 10 hours without maintenance dose of fomepizole:
  - No clinical deterioration

4.4 Methylpyrazole monitoring during haemodialysis of ethylene glycol

- Study of fomepizole (4-methylpyrazole) kinetics during intermittent hemodialysis in 2 anuric patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient 1 (Mean (SD))</th>
<th>Patient 2 (Mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>0.776 (0.037)</td>
<td>0.705 (0.080)</td>
</tr>
<tr>
<td>Range</td>
<td>0.711 – 0.801</td>
<td>0.574 – 0.782</td>
</tr>
<tr>
<td>(\text{CL_D}) (ml/min)</td>
<td>137 (6.6)</td>
<td>117 (13.3)</td>
</tr>
<tr>
<td>Range</td>
<td>126 – 142</td>
<td>95.5 – 130</td>
</tr>
<tr>
<td>dose of 4-MP administered (mg/kg)</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>AUC ((0 \rightarrow t)) artery (mg \cdot h \cdot l^{-1})</td>
<td>49.9</td>
<td>40.4</td>
</tr>
<tr>
<td>AUC ((0 \rightarrow t)) vein (mg \cdot h \cdot l^{-1})</td>
<td>19.7</td>
<td>11.5</td>
</tr>
<tr>
<td>lost AUC ((0 \rightarrow t)) (mg \cdot h \cdot l^{-1})</td>
<td>30</td>
<td>28.9</td>
</tr>
<tr>
<td>% loss</td>
<td>60.4</td>
<td>71.5</td>
</tr>
<tr>
<td>(A_D(0 \rightarrow t)) (mg)</td>
<td>248</td>
<td>204</td>
</tr>
<tr>
<td>loss (mg \cdot h^{-1})</td>
<td>83</td>
<td>51</td>
</tr>
</tbody>
</table>

Fomepizole during IHD and CVVHD for EG poisoning: case report

- 42 yo patient with EG and isopropanol poisoning: coma, metabolic acidosis, moderate renal failure
- Blood ethylene glycol: 192 mmol/L.
- Antidote: Fomepizole every 4 hours during IHD and /8 h during CVVHD
- Consecutive IHD (blood flow: 200 ml/min) for 4 hours then CVVHD (blood flow: 150 ml/t) for 18 hours.
- Sampling (/4 h during IHD and /8h during CVVHD): pre- and post-filter and in the dialysate
- Results (recommended therapeutic blood [fomepizole] = 10μ mol/L):
  - End of IHD: lowest blood [fomepizole] = 77 μ mol/L
  - Dialysance IHD = 95 ml/min
  - During CVVHD: lowest blood [fomepizole] = 116 μ mol/L
  - Dialysance CVVHD = 14 ml/min

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Case report on methanol and ethylene-glycol poisoning

- 73 old man: intoxication with a de-icer fluid containing methanol and ethylene glycol (dose ingested = unknown)
- On admission (H + 1): normal exam, no metabolic acidosis
- Initial blood methanol level = 305 mg/dL and EG = 64 mg/dL
- Loading dose of fomepizole was administrated
- HD was performed for 14 hours **without maintenance dose of fomepizole:**
  - No clinical deterioration and no visual disturbance
  - No anion gap appeared

Fomepizole: conclusions

- Methanol and its main metabolite formate are removed by RRT especially IHD
- Ethylene-glycol and its main metabolite glycolate are removed by RRT especially IHD
- Ethanol and fomepizole are removed by IHD and need an adjustment to maintain therapeutic blood concentrations.
- Some case reports suggest that fomepizole maintenance during IHD is not clinically relevant.
- **Question:** is it mandatory to maintain fomepizole or ethanol during IHD in all cases?
Digoxin Fab

- MW = 50 000 d
- Vd = 0.40 L/kg and t1/2 = 16 to 20 hours.
- Elimination: 50% renal
- Fab may reside in the serum of anephric patients for 2 to 3 weeks after administration.
- Free digoxin concentrations fall rapidly after Fab administration and then rebound upwards within 12 to 130 hours in patients with renal dysfunction and end-stage renal disease.
- **RRT techniques fail to remove significant amount of digoxin** (less than 4% according to the technique used: HD, CAVH, PD).
Plasmapheresis for Fab-digoxin

- 46 old man, with congestive heart failure and chronic renal failure
- Intoxication with 12.5 to 15 mg of digoxin
- On admission: 3rd degree atrio-ventricular block.
- Serum digoxin: 21 ng/mL, serum creatinine: 5.7 mg/dL
- Antidote (H+1): digoxin-Fab (14 vials, 560 mg)
- PE was started 26 h > antidote treatment: 4 liters
- 2nd dose of Fab about 24 h > first PE: 440 mg
- Then: 2nd PE performed (5 L) 2.5 h > the 2nd dose of Fab.

Total digoxin measurement in the PE1 ultrafiltrate = 8.1 ng/mL
Total digoxin measurement in the PE2 ultrafiltrate = 19.9 ng/mL

Total amount of digoxin removed by PE1 = 0.032 mg
Total amount of digoxin removed by PE2 = 0.100 mg

Conclusion of the study: PE is more efficient with a short delay after Fab administration (< 3h)
**BAL (dimercaprol)**

- Formula = C3H8OS2 - Molecular weight = 124.2
- Volume of distribution (Vd) =
- Elimination rate =
- Therapeutic blood level > 100 mg/dL (21.7 mmol/L)
- Low protein binding
- Dialyzance = NO CLEAR DATA
  - BAL – mercury complex = 5 ml/min
  - BAL – arsenic complex = unknown but 2 studies showed that there was no modification of As clearance before or after BAL injection.

Calcium edetate (EDTA)

- Formula = C10H10CaNa2O8 - Molecular weight = 374.27
- Volume of distribution (Vd) = 0.19 L/kg
- Elimination (IV administration) = unchanged in urine through glomerular excretion: 75% in 2.5 h and 100% in 24h
- Elimination T1/2 = 20-60 min
- Clearance = 76 ml/min // creatinine clearance if > 100ml/min
- Clearance EDTA is lowered to 26 ml/min if creatinine clearance < 70 ml/min
- Main elimination of the complexes metal-EDTA is renal and lowered in case of ARF.

Succimer (DMSA)

- Formula = C4H6O4S2 - Molecular weight = 182.2
- Volume of distribution (Vd) = 0.19 L/kg
- Elimination = excreted mainly in urine (80 – 90% as mixed disulfides) greater in healthy patients than in lead poisoned patients (77 vs 24.7 ml/min/m²).
- 92 to 95% protein bound (mainly albumin)
- Dialyzance = NO DATA
  - unknown but DMSA don’t seem to increase the HD clearance of toxic metals in anuric patients.
  - One study suggests that DMSA-arsenic complexes do not pass through the dialyzer membrane, with a risk of accumulation and secondary dissociation of the chelate.

Chelators: what do we do?

- Chelators (BAL, DMSA, DMPS, desferoxamine) are not measured and dosed in case of renal failure (ARF)
- Indirect measures are made with toxic substances in blood and/or dialysate
- But what is measured:
  - Free toxic substance?
  - Metal – chelator complexes?
- In these cases the best endpoints were the evolution of the clinical condition of the patients.

Oximes

- **Pralidoxime Chloride** (2-PAM, USA, Canada):
  - Formula: C₇H₉ClN₂O - MW = 172.6
  - Vd steady state = 0.6 – 0.8 L/kg

- **Pralidoxime Mesylate** (P2S, UK):
  - Formula: C₈H₁₂N₂O₄S - MW = 232.3
  - Vd steady state = 0.78 L/kg

- **Pralidoxime Methylsulfate** (France):
  - Formula: C₈H₁₂N₂O₅S - MW = 248.3
  - Vd steady state = 2.7 L/kg

- **Obidoxime Chloride** (Germany, Australia, Sweden…):
  - Formula: C₁₄H₁₆Cl₂N₄O₃ - MW = 359.2
  - Vd steady state = 0.17 L/kg
Oximes: considerations for EER

- Pralidoxime and Obidoxime are eliminated in fater excretion by tubules.
- Pralidoxime is better excreted in acidic urine and alcalinisation slows elimination.
- Studies have shown that exercise and heat modify pralidoxime distribution and renal elimination with an increase of central and peripheral compartment and elimination half-life.

Thanks to Pr Horst Thiermann
Patient with parathion poisoning and acute renal failure at d 8. Obidoxime: 250 mg IV than 750 mg / 24 h continously. Goal: to maintain a [10 – 20 mM]

Blood Obidoxime: T1/2 from 90 min (intact renal function) to 3 h under and after UF = accumulation.

Hydroxocobalamine

- Very few data on what happens to hydroxocobalamine during RRT.
- Highly protein bound to transcobalamin I and II
- Despite high BP a study has shown that hydroxocobalamine is partially (anecdotal) lost in high-flux membrane HD in end-stage renal failure.
- Clearance was estimated to 9.1 ml/min
- 45 mcg found in dialysate of a 4-h HD.

Blood leak alarm interference by hydroxocobalamin is hemodialysis machine dependent

<table>
<thead>
<tr>
<th>Dialysis machine</th>
<th>Manufacturer</th>
<th>Is Pseudo-blood leak likely to happen with hydroxocobalamin use?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Althin</td>
<td>Baxter</td>
<td>No</td>
</tr>
<tr>
<td>C3</td>
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<tr>
<td>DBB 06</td>
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<td>DCS-6</td>
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<td>Dialog Plus</td>
<td>B-Braun</td>
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<tr>
<td>Prismaflex</td>
<td>Gambro</td>
<td>No</td>
</tr>
</tbody>
</table>

Sutter ME. Clin Tox 2012
Avila J. Clin Nephrol 2012
Conclusions

• Studies are still too rare on antidotes during RRT.
• Correct sampling is essential whatever the number of filters involved.
• Always make sampling simultaneously:
  – Pre and post each filter
  – At the beginning of the technique (before the first filter) and at the end of the technique
  – If there is a dialysate or ultrafiltrate: sampling
  – If urine remains: urine samples
• At the same time collect data on the blood flow, dialysate flow
• Then make calculations: clearance, extraction ratio…
• And note the evolution of the patient’s clinical conditions:
  – Improvement of conscience or other parameters,
  – Saving therapies stopped during the procedure
• And… find a laboratory which can dose the antidote: good luck!