Beyond Standard Anticholinergics: The Use of Physostigmine for Reversal of Somnolence and Delirium in a Cohort of Overdose Patients

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Physostigmine first used in poisoning in 1864

In 1864, in Prague, severe atropine intoxications occurred. Five prisoners in the jail of Prague drank a bottle of spirit atropine solution while cleaning the jail ambulatory. Profound unconsciousness followed, which could not be alleviated by common treatment used in those days, and the victims were considered lost. However, the young medical doctor Ludwig Kleinwächter discussed the atropine cases with his colleague, who was an ophthalmologist. A suggestion was made to try an anti-atropine drug, extraction of Calabar bean. Kleinwächter, who was the jail medical doctor, administered the extraction per os, with a surprising result: all five comatose prisoners were saved. Shortly after, Kleinwächter’s report was printed on the front page of *Berl. Klin. Wochenschr.* [4]. Kleinwächter concluded that the success of the Calabar bean extract against atropine poisoning was based on specific antagonism.

Physostigmine: short history and its impact on anaesthesiology of present days

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For every delirium there is an Antilirium!

- 1960’s-70’s use increased for TCA’s
- Non-specific ‘analeptic’ use became prevalent in 70’s – for barbiturates, other sedative-hypnotics.

Physostigmine Therapy in Acute Tricyclic Antidepressant Poisoning*

Thomas L. Slovis, M.D.; John E. Ott, M.D.; Daniel T. Teitelbaum, M.D.; and William Lipscomb, M.D.
Asystole Complicating Physostigmine Treatment of Tricyclic Antidepressant Overdose

Paul Pentel, MD
Charles D. Peterson, PharmD
Minneapolis, Minnesota

Physostigmine is a commonly used therapy for the anticholinergic manifestations of tricyclic antidepressant (TCA) overdose. We describe two patients with TCA toxicity who developed asystole following the administration of physostigmine to treat seizures. Pentel P, Peterson CD: Asystole complicating physostigmine treatment of tricyclic antidepressant overdose. Ann Emerg Med 9:588-590, November 1980.

asystole, complication of physostigmine use; overdose, tricyclic antidepressant, treatment with physostigmine, physostigmine, for tricyclic antidepressant overdose, asystole complicating; tricyclic antidepressant overdose, treatment with physostigmine, asystole complicating
Reevaluation in the 1990’s – current.

- Physostigmine more effective than benzodiazepines in diphenhydramine overdose.
- Increasing critical reviews of physostigmine

Pharmacology in Emergency Medicine

ASSESSING PHYSOSTIGMINE’S CONTRAINDICATION IN CYCLIC ANTIDEPRESSANT INGESTIONS

Jeffrey R. Suchard, MD
Caveats...the swinging pendulum...

Gamma-Hydroxybutyrate Overdose and Physostigmine: Teaching New Tricks to an Old Drug?

Physostigmine? Doesn’t that cause asystole?

Medline® Abstract for Reference 29 of ‘Tricyclic antidepressant poisoning’

29 PubMed
TI Asystole complicating physostigmine treatment of tricyclic antidepressant overdose.
AU Pentel P, Peterson CD

Physostigmine is a commonly used therapy for the anticholinergic manifestations of tricyclic antidepressant (TCA) overdose. We describe two patients with TCA toxicity who developed asystole following the administration of physostigmine to treat seizures.
Effective, rational, underutilized – for the right overdose.

- Reports of physostigmine use in quetiapine, cyclobenzaprine and olanzapine overdose.

**Brief Report**

**Reversal of quetiapine-induced altered mental status with physostigmine: a case series**

Jon B. Cole MD\(^a,b,\)*, Samuel J. Stellpflug MD\(^a,b\), Heather Ellsworth MD\(^a,b\), Carson R. Harris MD\(^a,b\)

\(^a\)Hennepin Regional Poison Center, Mail Code: RL, Minneapolis, MN 55415, USA
\(^b\)Regions Hospital, Department of Emergency Medicine, Saint Paul, MN 55101, USA
Methods

- Retrospective review of Toxicology Consult Service cases from a single site, tertiary care, hospital in the US from 1/1/2011 – 11/15/2011
- ACMT ToxIC Case Registry site entries followed by chart review
- Descriptive review including:
  - Patient information (age/gender)
  - Agents ingested (primary and co-ingestants)
  - Primary toxicity treated by physostigmine
  - Response to physostigmine
  - Adverse effects directly due to physostigmine
Results

- 482 unique patient encounters over 11 ½ months.
  - Physostigmine administered in 16/482 encounters a total of 20 times (including one infusion/drip).

- Indications for use included:
  - Reversal of CNS depression or coma
  - Reversal of Central anticholinergic toxicity *(agitation/delirium and hallucinations)*
  - Reversal of bothersome peripheral anticholinergic symptoms (i.e. urinary retention) usually as part of constellation of both peripheral/central anticholinergic features.
Use of physostigmine was at the discretion of the consultant Toxicologist – *not used in severe TCA, with conduction block/signs Na-channel blockade, bradycardia or without some signs anticholinergic effects on exam.*

Physostigmine was administered in 2.0 mg increments diluted in 10 mL of saline given IV over 5-10 minutes.

Repeat administration occurred at discretion of Toxicologist (or primary team) after 30 minutes without adequate response.

In one patient a drip started (2 mg/hr/6.5 hrs) after 2 doses showed benefit yet rapid recurrence of toxicity.
# | Age | Gender | Primary Agent(s) | Co-ingestant | Toxicity | Outcome | Adjunctive Therapies | Adverse Effects | Dose |
--- | ---- | ------ | --------------- | ----------- | -------- | ------- | ------------------- | --------------- | ----- |
1 | 22  | Female | Diphenhydramine 2.25 grams* | None | Central (Agitation Delirium) Peripheral | Positive Sustained | BZDs Prior to physo | None | 2 mg |
2 | 45  | Female | Diphenhydramine 600 mg* Cyclobenzaprine 300 mg* | Both primary | Coma Central Peripheral | Positive transient | BZDs Prior to physo | None | 2 mg X 2 doses |
3 | 54  | Female | Diphenhydramine Several days – 400 mg/day* | None -Opioid w/d | Central Peripheral | Positive Sustained | BZDs Prior to physo | None | 2 mg |
4 | 13  | Female | Diphenhydramine 600-900 mg* Bupropion 3.5 g* Citalopram 400 mg* acetaminophen | Central Peripheral | Positive Sustained | BZDs Phenobarbital concomitant | None | 2 mg + infusion 2 mg/hr/6.5 hrs |
5 | 14  | Female | Diphenhydramine 1.2 grams* | None | Central Peripheral | Positive Sustained | BZDs Haloperidol (prior to physo) | None | 2 mg |
<table>
<thead>
<tr>
<th>#</th>
<th>Age</th>
<th>Gender</th>
<th>Primary Agent(s)</th>
<th>Co-ingestant</th>
<th>Toxicity</th>
<th>Outcome</th>
<th>Adjunctive therapies</th>
<th>Adverse Effects</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>54</td>
<td>Female</td>
<td>Hydroxazine “empty bottle”</td>
<td>Venlafaxine 4-6 tabs* Cocaine Binge</td>
<td>Agitation Delirium Peripheral</td>
<td>Positive Sustained</td>
<td>BZDs Concomitant</td>
<td>None</td>
<td>2 mg</td>
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<tr>
<td>7</td>
<td>38</td>
<td>Female</td>
<td>Promethazine “50-60” dose unknown</td>
<td>Gabapentin Clonazepam</td>
<td>Coma Peripheral Central</td>
<td>Positive</td>
<td>BZDs After physo – w/d treatment</td>
<td>None</td>
<td>2 mg</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>Male</td>
<td>Donnatol “2 weeks” – accidental--hyoscyamine -scopolamine-atropine -phenobarbital</td>
<td>None -PB in Donnatol</td>
<td>Central – persistent x 48 hours</td>
<td>Positive Sustained</td>
<td>BZDs After physo</td>
<td>Panic on emergenc e Attenuate d w/ BZD’s</td>
<td>2 mg</td>
</tr>
</tbody>
</table>
### Results C. Atypical antipsychotics

<table>
<thead>
<tr>
<th>#</th>
<th>Age</th>
<th>Gender</th>
<th>Primary Agent(s)</th>
<th>Co-ingestant</th>
<th>Toxicity</th>
<th>Outcome</th>
<th>Adjunctive therapies</th>
<th>Adverse Effects</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>33</td>
<td>Male</td>
<td>Quetiapine (300-600 mg)</td>
<td>Lorazepam 2-3 mg**</td>
<td>Somnolent Mild periph. Urinary retention*</td>
<td>Partial Unchanged course</td>
<td>Antiemetic</td>
<td>Vomiting X 1</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>10</td>
<td>45</td>
<td>Female</td>
<td>Quetiapine 6 – 9 grams* Cyclobenzaprine 300 mg*</td>
<td>Both as Primary</td>
<td>Coma Peripheral</td>
<td>Positive Sustained</td>
<td>None</td>
<td>None</td>
<td>2 mg</td>
</tr>
<tr>
<td>11</td>
<td>63</td>
<td>Male</td>
<td>Quetiapine “bottle” unknown dose*</td>
<td>None</td>
<td>Coma Peripheral (miosis)</td>
<td>Intubation avoided</td>
<td>None</td>
<td>None</td>
<td>2 mg</td>
</tr>
<tr>
<td>12</td>
<td>18</td>
<td>Male</td>
<td>Olanzapine 400 mg*</td>
<td>None</td>
<td>Coma Miosis Subtle periph.</td>
<td>Intubation Avoided</td>
<td>None</td>
<td>None</td>
<td>2 mg X 2 doses</td>
</tr>
<tr>
<td>13</td>
<td>23</td>
<td>Male</td>
<td>Olanzapine Missing bottle</td>
<td>Ethanol Trazadone Cocaine</td>
<td>Coma Peripheral Tachycardia HR 180’s</td>
<td>Transient arousal – ultimately intubated</td>
<td>Intubation Propofol Supportive cares</td>
<td>None</td>
<td>2 mg X 2</td>
</tr>
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</table>
### Results D.) *Primarily cyclobenzaprine*

<table>
<thead>
<tr>
<th>#</th>
<th>Age</th>
<th>Gender</th>
<th>Primary Agent(s)</th>
<th>Co-ingestant</th>
<th>Toxicity</th>
<th>Outcome</th>
<th>Adjunctive therapies</th>
<th>Adverse Effects</th>
<th>Dose</th>
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<tbody>
<tr>
<td>14</td>
<td>43</td>
<td>Male</td>
<td>Cyclobenzaprine 300 mg*</td>
<td>None</td>
<td>Coma Peripheral</td>
<td>Intubation Avoided</td>
<td>None</td>
<td>None</td>
<td>2 mg</td>
</tr>
<tr>
<td>15</td>
<td>41</td>
<td>Female</td>
<td>Cyclobenzaprine &quot;unknown&quot; Aripiprazole* &quot;unknown&quot;</td>
<td>Under primary</td>
<td>Coma Peripheral <strong>Tachy</strong></td>
<td>Coma reversed - Tachycardia remained</td>
<td>None</td>
<td>None</td>
<td>2 mg</td>
</tr>
<tr>
<td>16</td>
<td>44</td>
<td>Female</td>
<td>Cyclobenzaprine &quot;empty bottle&quot;*</td>
<td>None</td>
<td>Coma Peripheral</td>
<td>Somnolence Reversed</td>
<td>None</td>
<td>None</td>
<td>2 mg</td>
</tr>
</tbody>
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In diphenhydramine overdose agitation/delirium was the primary indication for physostigmine -- restraints were removed in 4 patients after administration.

In atypical antipsychotic overdose (quetiapine and olanzapine) coma or sedation was the primary toxicity treated – intubation avoided in 3 patients.

Physostigmine was effective in reversing coma, central and peripheral anticholinergic toxicity in cyclobenzaprine overdose.
In one patient a physostigmine drip (along with aggressive use of GABAergic agents including BZDs/barbs) helped attenuate severe anticholinergic toxicity with hyperthermia.

Adverse effects occurred in 2/16 and included a single episode of vomiting and a panic/anxiety reaction after emergence from delirium.

No episodes of bradycardia or seizure occurred.

No episodes of other cardiac arrhythmia.
Thanks to:
Rachel Gorodetsky, PharmD
Nicole Acquisto, PharmD