Bryan D. Hayes, PharmD, DABAT, FAACT, FASHP
Massachusetts General Hospital/Harvard Medical School
bryanhayes13@gmail.com
Twitter: @PharmERToxGuy

Session Title: The Antidote Anti-Hero

Physostigmine

Physostigmine gets a bad rap, in our opinion. (PharmERToxGuy blog 2017, EM Pharm Pearl 2019)

Use in TCA Overdose

Physostigmine was part of the 'coma cocktail,' until 2 patients developed asystole in the setting of TCA overdose (Pentel 1980). TCA overdose pathophysiology is complex, with more than just anticholinergic effects contributing. We overreacted and stopped using physostigmine regularly even when true anticholinergic poisoning was staring at us. The safety of physostigmine for seizures or cardiotoxicity in the setting of TCA toxicity is difficult to predict; risks/benefits should be weighed, but use for anticholineric effects is beneficial (Suchard 2003, Rasimas 2018).

Use in Anticholinergic Poisoning: Clearly beneficial

- Physostigmine controlled agitation and reversed delirium in 96% and 87% of patients, respectively, compared to 24% and 0% with benzodiazepines (Burns 2000). These findings were confirmed in a small RCT (Wang 2021).
- Benzodiazepines are used first-line more often, but intubation is more likely compared to physostigmine (Watkins 2015).
- 10-years of poison center experience concluded physostigmine had a good safety profile and often improved or resolved anticholinergic delirium with doses less than 2 mg (Arens 2018).
- Physostigmine reversed delirium in 4 out of 5 patients compared to non-antidotal therapy (36%) without increased reports of adverse events (Boley 2019).
- In 2300 patients, 18% had an adverse effect; most were minor and self-limited (nasuea, vomiting, hypersalivation). 15 had seizures and 8 had symptomatic bradycardia (Arens 2019).

Indications

Presence of peripheral or central antimuscarinic effects without significant QRS or QT prolongation

- Peripheral: dry mucosa, dry skin, flushed face, mydriasis, hyperthermia, decreased bowel sounds, urinary retention, and tachycardia
- Central: agitation, delirium, hallucinations, seizures, and coma

Adverse Effects

Have atropine available at the bedside in case you overshoot or an alternative diagnosis is underlying.

Contraindications (package insert)

Reactive airway disease, peripheral vascular disease, intestinal or bladder obstruction, intraventricular conduction defects, AV block, and in patients receiving choline esters and succinylcholine.

Dose

- 1 to 2 mg in adults and 0.02 mg/kg (max, 0.5 mg in children) IV infused over at least 5 minutes
- Onset is within minutes (Holzgrafe 1973); can be repeated after 10 to 15 minutes

My Algorithm

1. Lorazepam 2 mg IV for agitation, can be repeated
2. Physostigmine 1 mg IV over 5 minutes (mixed in 50 mL NS), can be repeated

Caveat: All physostigmine stock is now expired. Rivastigmine patches may be an alternative, though not ideal (Sandia 2017; Van Kernebeek 2021; Hughes 2021).

Toxin-Induced Cardiovascular Collapse

Expert consensus recommendations for management of calcium channel blocker poisoning in adults (St-Onge 2017)

- Majority of literature/evidence on CCB overdose is heterogenous, biased, and low-quality.
- Interventions with the strongest evidence are high-dose insulin and extracorporeal life support.
- Interventions with less evidence, but still possibly beneficial, include calcium, dopamine, norepinephrine, 4-aminopyridine (where available), and lipid emulsion therapy.
- Glucagon is no longer recommended for CCB overdose.

Treatments for Toxin-Induced Shock

1. Initial assessment and treatment should include charcoal (if indicated), atropine (if bradycardia), calcium, and crystalloid fluids. Goals: preserve organ perfusion and increase survival
2. Calcium – give it, optimal dose unclear. Start with at least 1 gm $CaCl_2$ or 2 gm calcium gluconate.
    a. Does calcium gluconate act slower than $CaCl_2$ because it needs hepatic activation? No! Serum ionized calcium levels increase to the same degree and within the same timeframe irrespective of the salt used (Martin 1990, Cote 1987, Heining 1984). Further reading: ALiEM blog 2013.
3. Vasopressors should be instituted early on. Though no one vasopressor is preferred, epinephrine or norepinephrine both are good starting choices with β_1 and α_1 agonist properties.
    a. One inpatient toxicology service reported good success with high-dose vasopressors for CCB toxicity over a 25-year period (Levine 2013)
    b. Vasopressors should generally be used in conjunction with high-dose insulin therapy (Rietjens 2023)
    c. Human cases suggest that even though vasopressors are not often effective, they don't seem to be harmful (unlike in the animal data) (Skoog 2017)
4. Insulin (Jang 2014; Engebretsen 2011)
    a. High-dose insulin (bolus + infusion) safe in refractory CCB/BB overdose (Cole 2018)
    b. In the nonstressed state, the heart primarily catabolizes free fatty acids for its energy needs, while the stressed myocardium switches preference to carbohydrates. Insulin's positive inotropic effects seem to occur because of metabolic support of the heart during hypodynamic shock. Insulin impairs the Na-Ca antiporter resulting in increased intracellular Ca.

c. CCB overdose patients typically present with hyperglycemia, in part due to blocking of L-type calcium channels on the pancreas that lead to insulin secretion (Levine 2007). This may be one way to differentiate CCB overdose from BB (may present with hypoglycemia or normoglycemia).
d. Dose: regular insulin bolus 1 unit/kg IV, then infusion 0.5-1 unit/kg/hour
    i. Monitor potassium
    ii. Monitor glucose
        1. A recommended starting dose of dextrose is 0.5 g/kg/hr delivered as $D_{25}W$ or $D_{50}W$ (by central venous access).
        2. Insulin receptors are saturable, meaning that the hypoglycemia is limited at a certain point. You may end up needing less dextrose than you think, but still proceed with caution.
e. Challenges of starting high dose insulin (Schult 2022)
    i. High dose is not familiar to physicians, nurses, and pharmacists
        1. Education is required to get everyone on board (education is recommended to be recurrent and prior to your first massive CCB/BB overdose)
        2. Be clear with all team members (including pharmacists) what the plan is and the purpose of the high dose
    ii. Requires special mixing from pharmacy as normal-size bags run out quickly

5. IV Lipid Emulsion (Thurgur 2023)
    a. Seems to work like a shuttle to accelerate redistribution from targets to reservoir organs (Fettiplace 2015, Fettiplace 2018)
    b. Lipid effects last for 30-60 minutes. Fat emulsion undergoes lipolysis to free fatty acids which are utilized by mononuclear phagocyte system (reticuloendothelial cells).
    c. Consider lipid emulsion for local anesthetics, and other lipid-soluble, cardio-/neurotoxic agents after standard therapies fail (Fettiplace 2023, Graudins 2023, French 2011).
    d. Evidence-based recommendations: Gosselin 2016
    e. 'Best' dose for oral poisonings: 20% lipid emulsion - 1.5 mL/kg bolus, 0.25 mL/kg/min X 3 min, 0.025 mL/kg/min up to 6.5 hrs (Fettiplace 2015)
    f. Possible adverse effects include ALI, pancreatitis, allergic reaction, fat emboli, and DVT (Hayes 2016).
    g. Beware of laboratory interference (Grunbaum 2016, Petersen 2018) and incompatibility with other resuscitation medications (Cocchio 2014, Ross 2020). Labs should be drawn before lipid is given, if possible, and it should be administered in its own line.
    h. Lipid may interfere with extracorporeal treatments

Tricyclic Antidepressant Poisoning (during a sodium bicarbonate shortage)

- ASHP has a great resource center for drug shortages
- If sodium bicarbonate is not available, it may actually be the sodium that is the most important factor in reversing ECG findings from TCA poisoning, as opposed to pH manipulation. Consider administering hypertonic saline (McKinney 2003; McCabe 1998); also has been used in other poisoning (Mahan 2021; Omraninava 2022).

- One amp/syringe (50 mL) of 8.4% sodium bicarbonate contains the same amount of sodium as 97 mL of 3% sodium chloride or 38 mL of 7.5% sodium chloride
- A central line is suggested if giving > 3% hypertonic saline

Extracorporeal Treatments

- Guidance on when to use hemodialysis and other extracorporeal removal of poisons (EXTRiP Workgroup)
- ECMO can be considered for poisoned patients (in consultation with critical care experts) (Cole 2020; Upchurch 2021; Weiner 2020; Lewis 2019; Maier 2023)
    - Survival is reported in up to 61%