

## Session Title: Antidote Updates for the Acute Care Setting

### Session overview

In a typical emergency department, serious toxicology cases are just rare enough to present a challenge for the treating practitioner. Standard ACLS therapies are usually not effective in toxicological-induced cardiac arrest. This session will discuss four uncommon, but important antidotes to and present an approach for safe utilization in the poisoned patient.

### Objectives

- Recommend appropriate use of physostigmine and flumazenil
- Identify barriers to use of high-dose insulin and hypertonic saline in the poisoned patient

### **Flumazenil**

I like to think of flumazenil as the naloxone of benzodiazepines. Flumazenil is an antagonist at the benzodiazepine receptor, has a similar onset (1-2 min) and duration (45-60 min) to naloxone, and also has similar dosing 0.5-1 mg.

Just a year after flumazenil came to market, Dr. Lewis Goldfrank penned an editorial questioning the need for it ([Goldfrank 1997](#)). On one hand, flumazenil can reverse CNS depression. On the other hand, re sedation, seizure/withdrawal, inconsistent reversal of respiratory depression, and proconvulsant coingestions are all problematic, potentially swinging the pendulum more in favor of risk than benefit.

### Reversing Procedural Sedation

When a benzodiazepine is used for procedural sedation, flumazenil seems safe and effective for reversing over-sedation ([Girdler 2002](#)). Resedation can occur after flumazenil wears off so continued monitoring is needed.

### Reversing Paradoxical Reactions

Flumazenil seems safe and effective for paradoxical reaction to benzodiazepines, ([Weinbroum 2001](#)). Higher benzodiazepine dosing can also overcome the problem ([Mancuso 2004](#)).

### Reversing Overdose in Pediatric Patients

In pediatric overdose patients not chronically on benzodiazepines, flumazenil is reasonable to consider, either for diagnostic or therapeutic purposes ([Wiley 1998](#)).

### Reversing Overdose in Adult Patients

Overall complication rate with benzodiazepine overdose is low: Of 702 patients who had taken benzodiazepines alone or in combination with ethanol or other drugs, 0.7% died and 9.8% had complications ([Hojer 1988](#)).

In a retrospective study, overdosed comatose patients were assigned to either a low-risk or non-low-risk group ([Gueye 1996](#)). Low-risk patients had CNS depression with normal vital signs, no other neurologic

findings, no evidence of ingestion of a tricyclic antidepressant, no seizure history, and absence of an available history of chronic benzodiazepine use. Of 35 consecutive patients, 4 were assigned to the low-risk group. In the low-risk group, 3 patients had complete awakening and the 4th had partial awakening, with no adverse events. In the non-low-risk group, 4 patients had complete awakening and 5 had partial awakenings. Seizures occurred in 5 patients. Therefore, although flumazenil use probably was safe and effective in the low-risk group, few patients could be considered low risk. Risk of seizures appears significant in non-low-risk patients.

14 of 1700 patients developed adverse drug reactions, half were related to abrupt arousal ([Amrein 1987](#)). Flumazenil was given to 12 patients on midazolam infusions. Serum norepinephrine and epinephrine concentrations rose within 10 minutes and correlated with increased heart rate, blood pressure, and myocardial oxygen consumption ([Kamijo 2000](#)). Flumazenil also may cause a large increase in intracranial pressure in patients receiving midazolam for head injury.

### Attempts to Prove Safety

Three poison center studies have attempted to demonstrate the safety of flumazenil in this setting. In the first study there were 904 adult patients with 13 reported seizures and 1 death ([Kreshak 2012](#)). A second study specific to pediatric patients reported 83 patients with no seizures and no deaths ([Kreshak 2012](#)). A third study found 80 patients with 1 seizure and 0 deaths ([Veirajah 2012](#)). A fourth small retrospective study 23 ED patients found that 15 woke up (at least partially) and there were no seizures even in the 7 patients with reported proconvulsant coingestants ([Nguyen 2015](#)).

On the surface, it may appear that flumazenil is safe to give. But, retrospective poison center studies from voluntary reporting cannot be used to prove a drug's safety. The true denominator is unknown. In the pediatric study, we wouldn't expect children to experience withdrawal since they aren't on chronic benzodiazepine therapy. So, it's no surprise there weren't any seizures or deaths.

### Bottom Line

A 2016 systematic review and meta-analysis of randomized trials summed it up perfectly: "Flumazenil should not be used routinely, and the harms and benefits should be considered carefully in every patient ([Peninga 2016](#), [Sivilotti 2016](#))." Cases in which to consider flumazenil are pediatric patients and reversal of procedural sedation if needed.

## **Physostigmine**

Physostigmine gets a bad rap, in my opinion. ([PharmERToxGuy blog 2017](#))

### Use in TCA Overdose

Physostigmine used to be 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. Unfortunately, we somewhat overreacted and stopped using physostigmine regularly even when true anticholinergic poisoning was staring at us. The safety of

physostigmine use for seizures or cardiotoxicity in the setting of TCA toxicity is difficult to predict and thus not recommended ([Suchard 2003](#)).

### Use in Anticholinergic Poisoning

Clearly beneficial:

- Physostigmine controlled agitation and reversed delirium in 96% and 87% of patients, respectively. ([Burns 2000](#)) Benzodiazepines controlled agitation in 24% of patients but were ineffective in reversing delirium.
- One group published 10-years of poison center experience with physostigmine and concluded that it had a good safety profile and often improved or resolved anticholinergic delirium when administered in doses less than 2 mg. ([Arens 2018](#))
- Another poison center group confirmed that physostigmine reversed delirium in four out of 5 patients compared to non-antidotal therapy (36%) without increased reports of adverse events. ([Boley 2018](#))

### 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 of 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

Stock it in your ED.

### **High-Dose Insulin**

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

#### High-Dose Insulin ([Jang 2014](#); [Engebretsen 2011](#))

- High-dose insulin (bolus + infusion) safe in refractory CCB/BB overdose ([Cole 2018](#))
- 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.
- 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).
- Dose: regular insulin bolus 1 unit/kg IV, then infusion 0.5-1 unit/kg/hour
  - Monitor potassium
  - Monitor glucose
    - i. A recommended starting dose of dextrose is 0.5 g/kg/hr delivered as D<sub>25</sub>W or D<sub>50</sub>W (by central venous access).
    - ii. 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.
    - iii. Dextrose may be required up to 24 hours after insulin is discontinued
- Challenges of starting high dose insulin
  - High dose is not familiar to physicians, nurses, and pharmacists
  - Education is required to get everyone on board (education is recommended to be recurrent and prior to your first massive CCB/BB overdose)
  - Be clear with all team members (including pharmacists) what the plan is and the purpose of the high dose
  - Requires special mixing from pharmacy as normal size bags run out quickly

#### 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](#))
- 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 recommended if giving > 3% hypertonic saline.