

## Session Title: Killer Poisoning Cases

### Session overview

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 utilize a case-based approach to provide practical pearls for managing complex overdose patients with toxin-induced shock. In addition, physostigmine and flumazenil get a bad rap, but should they? We will explore why we rarely use these antidotes to evaluate whether a change in practice is needed.

### Objectives

- In the setting of a smoke inhalation victim, interpret laboratory results and create a treatment plan.
- Describe how calcium gluconate works as quickly as calcium chloride to raise serum calcium.
- Given a patient with toxin-induced shock, devise a treatment plan including calcium, vasopressors, insulin, and fat emulsion.
- Develop a treatment plan for sodium channel blocker toxicity when sodium bicarbonate is on shortage.
- In a patient with benzodiazepine poisoning, determine when it is appropriate to administer flumazenil.
- In a patient with anticholinergic poisoning, determine when it is appropriate to administer physostigmine.

### Cyanide Poisoning

Since cyanide levels are not readily available, surrogate labs must be utilized in the appropriate clinical setting to rule in/out cyanide. In an unresponsive patient with a history including the potential for cyanide exposure (eg, smoke inhalation, chemical plant), an elevated lactate and lack of oxygen utilization can be very helpful. Measure an arterial and venous blood gas and calculate the difference between the arterial and venous oxygen saturations.

Though cyanide antidote kits (amyl nitrate, sodium nitrate, sodium thiosulfate) were used for many years, hydroxocobalamin is now the standard for cyanide poisoning.

- It can be used in combination with the cyanide antidote kit or by itself.
- Hydroxocobalamin combines with cyanide to form cyanocobalamin (vitamin B12) which is then excreted in the urine. ([Gerth K, et al. Clin Toxicol 2006](#))
- Administration: Add 200 mL NS to the vial; Adults: 5 g over 15 min, Pediatrics: 70 mg/kg. May repeat dose if not improving.
- Because hydroxocobalamin is red, it interferes with certain lab values
  - Cooximetry hemoglobin measurements
  - Colorimetric laboratory tests including: Aspartate aminotransferase, Bilirubin, Creatinine, Magnesium ([Lee, Ann Emerg Med 2007](#); [Curry, Ann Emerg Med 1994](#))
- Causes red skin and urine which can last for up to a week. ([Uhl W, et al. Clin Toxicol 2006](#))

## Toxin-Induced Cardiovascular Collapse

Expert consensus expert recommendations for the management of calcium channel blocker poisoning in adults were published in 2016 ([St-Onge M, et al. Crit Care Med 2016](#)).

- 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. Glucagon should be administered for beta blocker overdoses at a dose of 3-5 mg IV/IO. Beware of vomiting when administering a high dose. If successful, a glucagon infusion may be administered at a rate of 5-15 mg/hr.
  - a. Available in 1 mg vials (powder), each needs reconstitution with sterile water. This takes a few minutes to prepare, even if glucagon is stocked in your unit-based cabinets.
3. Calcium – give it, optimal dose unclear. Start with at least 1 gm CaCl<sub>2</sub> or 2 gm calcium gluconate.
  - a. Does calcium gluconate act slower than CaCl<sub>2</sub> because it needs hepatic activation? **No!**
    - i. Serum ionized calcium levels were measured in 15 hypocalcemic patients during the anhepatic stage of liver transplantation. Half received CaCl<sub>2</sub> 10 mg/kg, the other half received calcium gluconate 30 mg/kg. Equally rapid increases in calcium concentration were observed, suggesting that calcium gluconate does not require hepatic metabolism for the release of calcium in the absence of hepatic function. ([Martin TJ, et al. Anesthesiology 1990;73:62-5](#))
    - ii. A randomized prospective study in both children and dogs compared ionization of CaCl<sub>2</sub> and calcium gluconate ([Cote CJ, et al. Anesthesiology 1987](#)). Equal elemental calcium doses of calcium gluconate (10%) and CaCl<sub>2</sub> (10%):
      1. Are equivalent in their ability to raise calcium concentration
      2. The changes in calcium concentration are short-lived (minutes)
      3. The rapidity of ionization seems to exclude hepatic metabolism as an important factor in the dissociation of calcium gluconate
    - iii. In ferrets and in vitro human blood, equimolar quantities of CaCl<sub>2</sub> and calcium gluconate produced similar changes in plasma ionized calcium concentration. This does not support the common suggestion that CaCl<sub>2</sub> is preferable to calcium gluconate because of its greater ionization. ([Heining MP, et al. Anaesthesia 1984;39:1079-82](#))
4. Vasopressors should be instituted early on. Though no one vasopressor is preferred, epinephrine or norepinephrine both seem to be a good starting choice considering the  $\beta_1$  and  $\alpha_1$  agonist properties of each.

- a. One inpatient toxicology service reported good success with high-dose vasopressors for CCB toxicity over a 25-year period ([Levine M, et al. Ann Emerg Med 2013](#)).
  - b. Vasopressors should generally be used in conjunction with high-dose insulin therapy.
  - 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 CA, et al. Clin Toxicol 2017](#))
5. Insulin ([Jang DH, et al. Emerg Med Clin N Am 2014](#), [Engebretsen KM, et al. Clin Toxicol 2011](#))
- a. High-dose insulin (bolus + infusion) can be safe in refractory CCB/BB overdose.
  - 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.
  - c. CCB overdose patients typically present with hyperglycemia, in part due to the CCB blocking L-type calcium channels on the pancreas that lead to secretion of insulin ([Levine M, et al. Crit Care Med 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<sub>25</sub>W or D<sub>50</sub>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
    - i. High dose is not familiar to physicians, nurses, and pharmacists.
    - ii. Much education is required to get everyone on board (education is recommended to be recurrent and prior to your first massive CCB/BB overdose)
    - iii. Be clear with all team members (including pharmacists) what the plan is and the purpose of the high dose.
    - iv. Requires special mixing from pharmacy as normal size bags run out quickly.
6. IV Lipid Emulsion
- a. Yes, we are talking about giving the same fat we put in TPN to a crashing tox patient.
  - b. Mechanism: think of it like a shuttle that accelerates removal of drug from cardiac tissue within the first several minutes of administration ([Fettiplace, J Control Release 2015](#); [Fettiplace, Reg Anesth Pain Med 2018](#)). It also exerts nonscavenging effects that include postconditioning along with cardiostimulant and vasoconstrictive benefits.
  - c. Lipid effects last for 30-60 minutes. Fat emulsion undergoes lipolysis to free fatty acids which are utilized by mononuclear phagocyte system (reticuloendothelial cells).
  - d. Consider lipid emulsion for local anesthetics, CCB, BB, TCA, bupropion, chloroquine, and other lipid soluble, cardio-/neurotoxic agents ([French D, et al. Clin Toxicol 2011](#)).
  - e. Evidence-based recommendations ([Gosselin S, et al. Clin Toxicol 2016;54:899-923](#)):
    - i. In cardiac arrest, we recommend using ILE with bupivacaine toxicity, while our recommendations are neutral regarding its use for all other toxins.

- ii. In life-threatening toxicity:
  1. as part of treatment modalities, we suggest using ILE in bupivacaine toxicity if other therapies fail, but are neutral for other toxins
  2. if other therapies fail, we recommend ILE for bupivacaine toxicity and we suggest using ILE for toxicity due to other LAs, amitriptyline, and bupropion, but our recommendations are neutral for all other toxins.
- f. '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 MR, et al. Ann Emerg Med 2015](#))
- g. Possible adverse effects include ALI, pancreatitis, allergic reaction, fat emboli, and DVT ([Hayes BD, et al. Clin Toxicol 2016;54:365-404](#)).
- h. Also beware of laboratory interference ([Grunbaum AM, et al. Clin Toxicol 2012](#)) and incompatibility with other resuscitation medications ([Cocchio C, et al. SOJ Pharm PharmSci 2014;1\(1\):3](#)). Labs should be drawn before lipid is given, if possible, and it should be administered in its own line.
- i. Lipid can interfere with extracorporeal treatments

### **Tricyclic Antidepressant Poisoning** (during a sodium bicarbonate shortage)

- ASHP has a great resource center for drug shortages: <http://www.ashp.org/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 if needed ([Ann Emerg Med 2003](#), [Ann Emerg Med 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.

### **Flumazenil**

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 ([Acad Emerg Med 1997](#)). On one hand, flumazenil can reverse CNS depression. However, resedation, 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 ([Br Dent J 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, ([Eur J Anaesthesiol 2001](#)). Higher benzodiazepine dosing can also overcome the problem ([Pharmacotherapy 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 ([J Toxicol Clin Toxicol 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 ([Acta Med Scand 1998](#)).

In a retrospective study, overdosed comatose patients were assigned to either a low-risk or non-low-risk group ([Ann Emerg Med 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 ([Med Toxicol Adverse Drug Exp 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 ([Crit Care Med 2000](#)). Flumazenil also may cause a large increase in intracranial pressure in patients receiving midazolam for head injury.

### *Attempts to Prove Safety*

Three relatively recent 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 ([J Emerg Med 2012](#)). A 2nd study specific to pediatric patients reported 83 patients with no seizures and no deaths ([Pediatr Emerg Care 2012](#)). A 3rd study found 1 seizure and 0 deaths in 80 patients ([Emerg Med J 2012](#)). A small, retrospective ED study of 23 patients found that 15 woke up (at least partially) with no seizures, even in the 7 pts with reported proconvulsant coingestants ([Am J Emerg Med 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 ([Basic Clin Pharmacol Toxicol 2016](#))." Cases in which to consider flumazenil are pediatric patients and reversal of procedural sedation if needed.

## Physostigmine

### Use in TCA Overdose

Physostigmine used to be part of some 'coma cocktail' formulas until two patients developed asystole in the setting of TCA overdose ([Ann Emerg Med 1980](#)). TCA overdose pathophysiology is complex, certainly much more than just anticholinergic effects are 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 ([J Emerg Med 2003](#)).

### Use in Anticholinergic Poisoning

Clearly beneficial: Physostigmine controlled agitation and reversed delirium in 96% and 87% of patients, respectively ([Ann Emerg Med 2000](#)). Benzodiazepines controlled agitation in 24% of patients but were ineffective in reversing delirium.

### 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, and AV block and in patients receiving therapeutic doses of choline esters and succinylcholine.

### Dose

- 1 to 2 mg IV in adults and 0.02 mg/kg (max 0.5 mg) in children infused over at least 5 minutes
- Onset is within minutes ([Anesth Analg 1973](#))
- Can be repeated after 10 to 15 minutes

My Algorithm - Stock in medication cabinets in appropriate areas.

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