

## Session Title: Killer Poisoning Cases

### Session overview

In a typical emergency department, serious toxicology cases are just rare enough to present a challenge for the treating practitioner. This session will utilize a case-based approach to provide practical pearls for managing complex overdose patients. We will also explore antidote choices in the setting of drug shortages and adverse drug reactions to monitor for when administering treatment.

### Objectives

- In the setting of a smoke inhalation victim, interpret laboratory results and create a treatment plan.
- Identify the role of insulin and lipid emulsion therapy for treating non-local anesthetic toxicity.
- Develop a treatment plan for sodium channel blocker toxicity when sodium bicarbonate is on shortage.

### Cyanide Poisoning

Peddy SB, et al. *Pediatr Crit Care Med* 2006;7:79-82. Case from Maryland in which one friend poisoned another with cyanide. The patient presented unresponsive with the following vitals and labs:

BP 89/48 mm Hg, HR 79 bpm, RR 4 rpm, pupils fixed and dilated, GCS 3, weak peripheral pulses, lactate 20.3 mmol/L, AG 38, pH 7.25, pCO<sub>2</sub> 19, HCO<sub>3</sub> 9, SaO<sub>2</sub> - SvO<sub>2</sub> = 0.

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 the 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;44:S29-S36.)
- Administration: Dilute each vial in 100 cc NS, 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 J, et al. *Ann Emerg Med* 2007;49:802-5.
- Curry SC, et al. *Ann Emerg Med* 1994; 24:65–67.
- It also causes red skin and urine which can last for up to a week. (Uhl W, et al. *Clin Toxicol* 2006;44:S17-S28.)

### Toxin-Induced Cardiovascular Collapse

A 47-year old female presents with amlodipine overdose. Upon arrival, she quickly develops hypotension and is administered IV fluids and calcium (Meany CJ, et al. *Hosp Pharm* 2013;48(10):848-54).

What do you do next?

In a precursor to a forthcoming international guideline on the management of calcium channel blocker poisoning, a recent systematic review has been published assessing the available evidence (St-Onge M, et al. *Clin Toxicol* 2014;52(9):926-44).

A few findings from the systematic review:

- The majority of literature on calcium channel blocker overdose management is heterogenous, biased, and low-quality evidence.
- 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.

Stay tuned for the international guideline coming out soon. One treatment recommendation from the new guideline, reported at the 8th European Congress on Emergency Medicine September 2014, is not to use glucagon.

### Treatments for Toxin-Induced Shock

1. Initial assessment and treatment of toxin-induced shock (particularly beta blockers and calcium channel blockers) should include charcoal (if indicated), atropine (if bradycardia), calcium, and crystalloid fluids. The goals of treatment in poison-induced shock are to 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. Glucagon will no longer be recommended for calcium channel blocker overdoses with the new international guideline.
  - b. Glucagon is available in 1 mg vials (powder). Each vial must be reconstituted with sterile water. This takes a few minutes to prepare, even if glucagon is stocked in your ED's 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 calcium chloride 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 10 mg/kg, the other half received calcium gluconate 30 mg/kg. Serum concentrations of ionized calcium were determined before and up to 10 min after calcium therapy. Equally rapid increases in calcium concentration after administration of CaCl and gluconate were observed, suggesting that calcium gluconate does not require hepatic metabolism for the release of calcium and is as effective as CaCl in treating ionic hypocalcemia in the absence of hepatic function. (Martin TJ, et al. *Anesthesiology* 1990;73:62-5)
    - ii. A weird randomized prospective study in both children and dogs compared ionization of CaCl and calcium gluconate. The authors conclude that equal elemental calcium doses of calcium gluconate (10%) and CaCl (10%) (approximately 3:1), injected over the same period of time:
      1. Are equivalent in their ability to raise calcium concentration during normocalcemic states in children and dogs
      2. The changes in calcium concentration following calcium administration are short-lived (minutes)
      3. The rapidity of ionization seems to exclude hepatic metabolism as an important factor in the dissociation of calcium gluconate (Cote CJ, et al. *Anesthesiology* 1987;66:465-70)
    - iii. In ferrets and in vitro human blood, equimolar quantities of CaCl and calcium gluconate produced similar changes in plasma ionised calcium concentration when injected IV into anaesthetised ferrets or when added to human blood in vitro. In vivo changes were followed with a calcium electrode positioned in the animal's aorta, and this showed that the ionisation of calcium gluconate on its first pass through the circulation is as great as that of CaCl. This does not support the common suggestion that CaCl is preferable to calcium gluconate because of its greater ionisation. (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;62(3):252-8).
  - b. Vasopressors should generally be used in conjunction with high-dose insulin therapy.
5. Insulin
- a. High-dose boluses and infusions of insulin can be safe in the treatment of refractory calcium channel blocker/beta-blocker overdose. This therapeutic approach is associated with a low incidence of clinically significant hypoglycemia and hypokalemia.
  - b. In the nonstressed state, the heart primarily catabolizes free fatty acids for its energy needs. On the other hand, the stressed myocardium switches preference for energy substrates to carbohydrates. The preponderant evidence demonstrates that insulin's positive inotropic effects occur because of metabolic support of the heart during hypodynamic shock. (Goldfrank's Toxicologic Emergencies, 9<sup>th</sup> ed)
  - c. Calcium channel blocker 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. This may be one way to differentiate CCB overdose from beta blocker (may present with hypoglycemia or normoglycemia).
  - d. The recommended dose for regular insulin is 1 unit/kg IV bolus. **Yes 1 unit/kg!** An infusion of 0.5 to 1 unit/kg/hour should follow.
    - 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. It will require a special mixing from the pharmacy as the normal size bag will run out very quickly.
  - f. Further reading
    - i. Jang DH, et al. *Emerg Med Clin N Am* 2014;32(1):79-102.
    - ii. Engebretsen KM, et al. *Clin Toxicol* 2011;49(4):277-83.
6. IV Lipid Emulsion
- a. First case of non-local-anesthetic toxicity use was a 17 year old female with refractory cardiac arrest after bupropion/lamotrigine overdose (Sirianni A, et al. *Ann Emerg Med* 2008;51(4):412-5).

- b. Yes, we are talking about giving the same fat we put in TPN to a crashing tox patient.
- c. There are numerous successful cases, case series, animal trials, and meeting abstracts in both adult and pediatric patients and for local anesthetic and non-local-anesthetic toxicity (Cave G, et al. *Emerg Med Australas* 2011;23(2):123-41 & Presley JD, et al. *Ann Pharmacother* 2013;47:735-43).
- d. The most commonly cited mechanism is the 'lipid sink' in which lipid soluble drugs are sequestered within the lipid globules and are therefore not available for binding to receptors (Weinberg GL. *Anesthesiology* 2012;117(1):180-7).
- e. A newer theory, which makes a lot of sense, has been published recently: Fettiplace MR, et al. *J Control Release* 2015;198:62-70.
  - i. Lipid Resuscitation Therapy accelerated removal of drug from cardiac tissue within the first several minutes of administration.
  - ii. Once the concentration of drug in cardiac tissue was reduced below a certain threshold, lipid emulsion provided a direct inotropic effect.
  - iii. A shift in the bupivacaine blood:organ partition coefficient. This was a key point since it offers a clear demonstration of partitioning. So showing a definitive change in partitioning with ILE is important. The chief PK effect of ILE is accelerated redistribution from targets to reservoir organs.
- f. Lipid effects last for 30-60 minutes. Fat emulsion undergoes lipolysis to free fatty acids which are utilized by mononuclear phagocyte system (reticuloendothelial cells).
- g. Consider lipid emulsion for CCB, BB, TCA, local anesthetics, bupropion, chloroquine and other lipid soluble, cardiotoxic agents. A good reference for which medications are lipid soluble is French D, et al. *Clin Toxicol* 2011;49:801-9.
- h. Current guidance from the experts:
  - i. American College of Medical Toxicology: "Given the uncertainty of its beneficial effect in human poisonings, it is the opinion of the ACMT that there are no standard of care requirements to use, or to choose not to use, LRT. However, in circumstances where there is serious hemodynamic, or other, instability from a xenobiotic with a high degree of lipid solubility, LRT is viewed as a reasonable consideration for therapy, even if the patient is not in cardiac arrest." (*J Med Toxicol* 2011;7:81-2)
  - ii. American Heart Association: "...It **may be reasonable** to administer ILE, concomitant with standard resuscitative care, to patients with local anesthetic systemic toxicity and particularly to patients who have premonitory neurotoxicity or cardiac arrest due to bupivacaine toxicity (Class IIb, LOE C-EO). It **may be reasonable** to administer ILE to patients with other forms of drug toxicity who are failing standard resuscitative measures (Class IIb, LOE C-EO)." (Lavonas EJ, et al. *Circulation* 2015;132:S501-18)
  - iii. American Society of Regional Anesthesia also has a guideline specifically for local anesthetic toxicity (Neal JM, et al. *Reg Anesth Pain Med* 2010;35(2):152-61).

- i. Possible adverse effects include ALLI, pancreatitis, allergic reaction, fat emboli, and DVT (Levine M, et al. *J Med Toxicol* 2014;10:10-4 & Abdelmalek D, et al. *Am J Ther* 2014;21(6):542-4 & Shenoy U, et al. *Paediatr Anaesth* 2014;24(3):332-4).
- j. Also beware of laboratory interference (Grunbaum AM, et al. *Clin Toxicol* 2012;50(9):812-7) 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.
- k. An international group is publishing 6 papers as part of an evidence-based review and recommendations for the use of lipid in toxicology. Two papers have been published to date:
  - i. Gosselin S, et al. *Clin Toxicol* 2015;53:557-64.
  - ii. Grunbaum AM, et al. *Clin Toxicol*. 2015 Dec 1. [Epub ahead of print]

#### Tricyclic Antidepressant Poisoning - what to do if sodium bicarbonate is on shortage or unavailable

- The American Society of Health-System Pharmacists (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
  - McKinney PE, et al. *Ann Emerg Med* 2003;42:20-4.
  - McCabe JL, et al. *Ann Emerg Med* 1998;32:329-33.
- 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 required if giving > 3% hypertonic saline.