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Session Title: Pearls for the Critically Ill Poisoned Patient

Session overview

Managing the critically ill poisoned patient is challenging, particularly toxin-induced shock. Standard ACLS therapies are usually not effective in toxicological-induced cardiac arrest. This session will outline an approach to treating toxin-induced shock with a focus on calcium, vasopressors, insulin, and fat emulsion.

Objectives

- Given a patient with toxin-induced shock, devise a treatment plan including calcium, vasopressors, insulin, and fat emulsion.
- Describe how calcium gluconate works just as quickly as calcium chloride to raise serum calcium levels.
- Provide dosing recommendations for high-dose insulin therapy in the management of poisoning cases.
- Describe the proposed mechanism(s) of action of lipid emulsion's beneficial effects and list 3 potential adverse drug effects that have been reported with the use of lipid emulsion therapy in poisoning cases.

Introduction

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.

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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 $CaCl_2$ 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 β1 and α1 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, 9th 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 $D_{25}W$ 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
        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. Other mechanisms include increased fatty acid uptake by the mitochondria, decreased sodium channel binding, and increased calcium channel entry. Lipid emulsion exerts rapid, positive inotropic and positive lusitropic effects in both intact animal and isolated heart models. We hypothesize that this inotropy and the resulting increase in tissue blood flow contribute to the phenomenon of lipid reversal of cardiac toxicity caused by drug overdose. (Fettiplace MR, et al. *Crit Care Med* 2013;41:e156-62 & Harvey M, et al. *Br J Anaesth* 2014;112(4):622-5).
   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 consider 1.5 mL/kg of 20% long-chain fatty acid emulsion as an initial bolus, repeated every 5 minutes until cardiovascular stability is restored. After the patient is stabilized, **some**

papers suggest a maintenance infusion of 0.25 mL/kg per minute for at least 30 to 60 minutes. A maximum cumulative dose of 12 mL/kg has been **proposed**." (Vanden Hoek TL, et al. *Circulation* 2010;122(suppl 3):S829-61)

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 ALI, 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.