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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. 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.

Objectives

- In the setting of a smoke inhalation victim, interpret laboratory results and and create a treatment plan.
- Describe how calcium gluconate works just as quickly as calcium chloride to raise serum calcium levels.
- Identify the role of insulin and lipid emulsion therapy for treating non-local anesthetic toxicity.
- Given a patient with toxin-induced shock, devise a treatment plan including calcium, vasopressors, insulin, and fat emulsion.

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, pCO2 19, HCO3 9, SaO2 - SvO2 = 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?

New 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).

- 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.
- Glucagon is no longer recommended for CCB overdose.

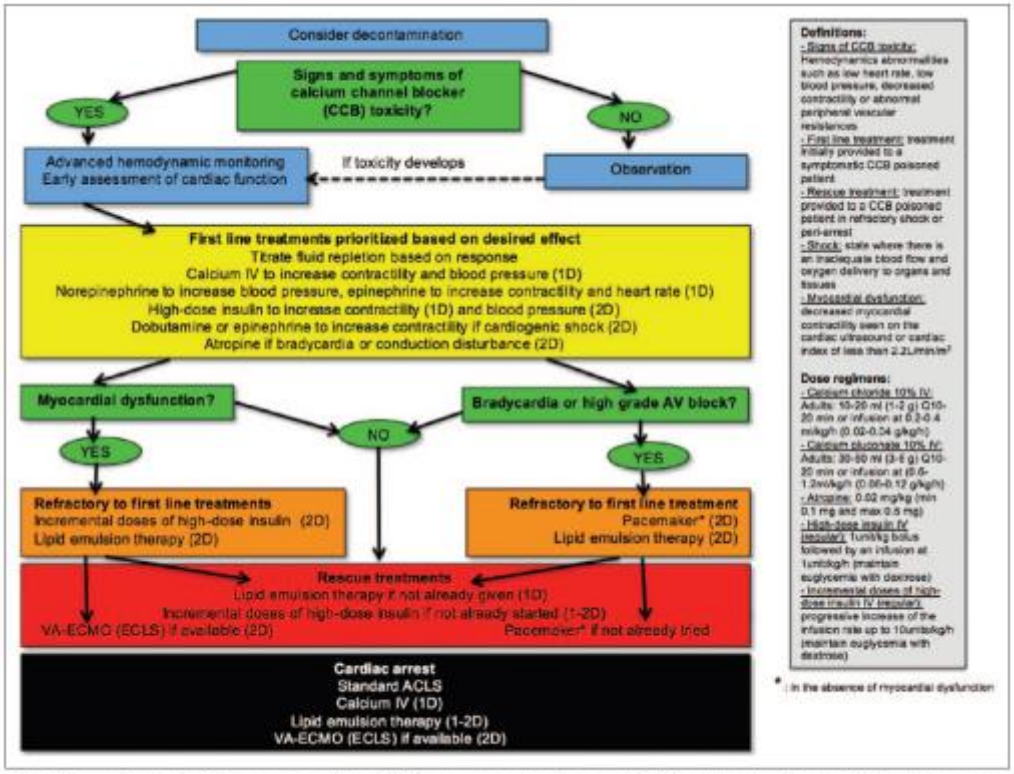

Figure 3. Progression of care for key recommendations. ACLS = advanced cardiac life-support, CCB = calcium channel blocker, ECLS = Extracorporeal Life Support, VA-ECMO = venoarterial extracorporeal membrane oxygenation.

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 no longer be recommended for calcium channel blocker overdoses.
    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 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 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.
    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;32(1):79-102, Engebretsen KM, et al. *Clin Toxicol* 2011;49(4):277-83)
    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 supports that insulin's positive inotropic effects occur because of metabolic support of the heart during hypodynamic shock. (Goldfrank's Toxicologic Emergencies, 10th 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.

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. The working theory on how this works is thinking of it like a shuttle (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. The chief pharmacokinetic effect of ILE is accelerated redistribution from targets to reservoir organs.
    d. Lipid effects last for 30-60 minutes. Fat emulsion undergoes lipolysis to free fatty acids which are utilized by mononuclear phagocyte system (reticuloendothelial cells).
    e. Consider lipid emulsion for CCB, BB, TCA, local anesthetics, bupropion, chloroquine and other lipid soluble, cardiotoxic agents (French D, et al. *Clin Toxicol* 2011;49:801-9).
    f. Evidence-based recommendations (Gosselin S, et al. Clin Toxicol 2016;54:899-923):
        i. For the management of cardiac arrest, we recommend using ILE with bupivacaine toxicity, while our recommendations are neutral regarding its use for all other toxins.
        ii. For the management of life-threatening toxicity, (1) as first line therapy, we suggest not to use ILE with toxicity from amitriptyline, non-lipid soluble beta receptor antagonists, bupropion, calcium channel blockers, cocaine, diphenhydramine, lamotrigine, malathion but are neutral for other toxins, (2) as part of treatment modalities, we suggest using ILE in bupivacaine toxicity if other therapies fail, but are neutral for other toxins, (3) 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.
        iii. In the treatment of non-life-threatening toxicity, recommendations are variable according to the balance of expected risks and benefits for each toxin.
    g. '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;66(2):185-8)
    h. Possible adverse effects include ALI, pancreatitis, allergic reaction, fat emboli, and DVT (Hayes BD, et al. Clin Toxicol 2016;54:365-404).

i. Also beware of laboratory interference (Grunbaum AM, et al. *Clin Toxicol* 2012;50:812-7) 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.