

Notes on Antidotes

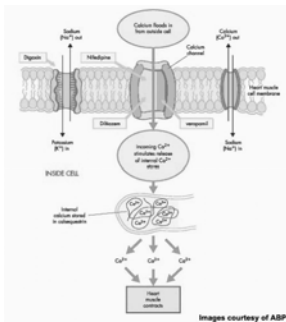
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 CSHP Spring Therapeutics Update
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Overview

- Insulin/Glucose for CCB overdose
- Hydroxocobalamin for cyanide poisoning
- Lipid rescue for local anesthetic toxicity

Insulin/Glucose



- CCB pharmacology
 - Block voltage-gated calcium channels
 - Myocardium, smooth, β -islet cells
 - Dihydropyridines
 - peripheral vasculature
 - Verapamil & diltiazem
 - cardiac + peripheral
 - \downarrow insulin from pancreas

Insulin/Glucose

- Calcium channel blockers
 - Toxic effects in overdose
 - Exaggeration of pharmacologic properties
 - Hypotension, hyperglycemia
 - Nifedipine: reflex tachycardia
 - Verapamil/diltiazem: \downarrow HR, conduction, contractility
 - Stressed heart: FFA \Rightarrow carbohydrates
 - But \downarrow insulin means poor delivery of carbs
 - Heart muscle starves

Insulin/Glucose



- Mechanism of activity
 - Insulin
 - Positive inotropy
 - Well established effect, high doses
 - Mechanism poorly understood
 - Delivers carbohydrate to stressed heart
 - Increases myocardial function without increasing work
 - Effects not immediate (30-60 minutes) \Rightarrow start early
 - Does not increase HR

Insulin/Glucose

- Evidence
 - Kline et al.
 - 4 studies in dogs
 - Verapamil infusions
 - Insulin compared to calcium chloride, epinephrine, glucagon
 - Consistent beneficial hemodynamic effects and improved survival
 - 15 human case reports
 - Verapamil, amlodipine, diltiazem, nifedipine
 - IV fluids, calcium, inotropes, glucagon
 - Insulin dose ranges: 0.1-1 U/kg/hr
 - Adjusted glucose: 10-75 g/hr (peak rate)
 - Outcomes:
 - BP improved within 60-90 min of insulin
 - ADRs: hypoglycemia, hypokalemia
 - Duration of Tx dependent on severity of condition (9-49 hours)
 - Early withdrawal \Rightarrow worsening of Sx
 - 12 survived, 1 vegetative, 3 deaths
 - Are deaths related to delay in starting insulin?

Insulin/Glucose

- Recommendations
 - O₂, IV, airway
 - Decontamination if appropriate
 - Atropine for bradycardia
 - Dopamine, other pressors
 - Calcium for hypotension
 - Insulin/glucose
 - Glucagon
 - PDE inhibitors
 - Mechanical support
- Dose
 - Insulin bolus (1 U/kg), D50W 25-50 mL
 - Insulin infusion 0.5-1.0 U/kg/hr, D10W 100 mL/hr
 - Glucometers q15-30 minutes
 - Adjust dextrose to euglycemia
 - Monitor potassium

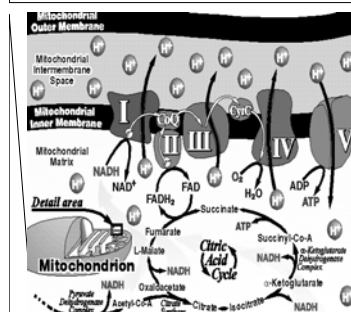
Insulin/Glucose

- Issues
 - High doses required
 - Consider relatively early
 - Close monitoring of glucose and potassium
 - Inexpensive, readily available, easy to give
 - Use in β -blocker overdose?
 - Animal studies show positive results
 - 1 human case report, amlodipine & atenolol
 - Positive inotropic effect only
 - β -blockers cause hypoglycemia
 - Glucagon still considered pressor of choice (\$\$\$)

Insulin/Glucose

- Selected References:
 - Megarbane B, et al. The role of insulin and glucose (hyperinsulinaemia/euglycaemia) therapy in acute calcium channel antagonist and β -blocker poisoning. *Toxicol Rev.* 2004;23(4):215-22.
 - DeWitt CR, et al. Pharmacology, pathophysiology and management of calcium channel blocker and β -blocker toxicity. *Toxicol Rev.* 2004;23(4):223-38.
 - Shepherd G. Treatment of poisoning caused by β -adrenergic and calcium-channel blockers. *Am J Health-Syst Pharm.* 2006;63:1828-35.
 - Yuan TH, et al. Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. *Clin Toxicol.* 1999;37(4):463-74.

Hydroxocobalamin



- Cyanide poisoning
 - CN binds to iron in mitochondrial cytochrome a3 complex
 - Inhibits cellular oxygen utilization
 - Cellular anoxia \Rightarrow accumulation of hydrogen ions \Rightarrow acidemia
 - Shift to anaerobic metabolism \Rightarrow \uparrow lactate \Rightarrow AG acidosis
 - Organs with high demand for O₂ most susceptible
 - Heart and brain

Hydroxocobalamin

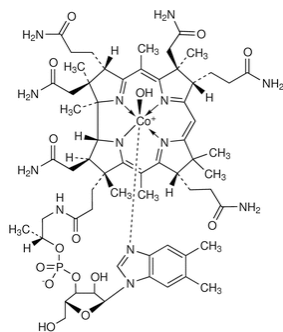


- Signs & symptoms
 - House fires, common source
 - Sx < 1 min after inhalation, rapid death
 - Altered mental status, seizures, coma
 - Tachypnea (early)
 - Hypertension
 - Vomiting
 - Cardiovascular collapse
 - AG lactic acidosis

Hydroxocobalamin

- Treatment
 - Nitrites
 - Induce MeHg (goal is 15-20%)
 - CN prefers MeHg over cytochrome a3
 - Displaces CN from cyt a3 \Rightarrow cyanoMeHg \Rightarrow restores aerobic metabolism
 - Advantage: Fast onset
 - Adverse effects: vasodilation, hypotension, \downarrow O₂ carry capacity
 - Caution: pregnancy, infants, smoke inhalation, shock
 - Contraindicated in CO exposure
 - Sodium thiosulfate
 - Sulfur donor: Pulls CN from cyanoMeHg \Rightarrow thiocyanate \Rightarrow excreted in urine
 - Reversible reaction catalyzed by rhodanese
 - Disadvantage: slow onset, small VD
 - ADR: hypersensitivity, hypotension, thiocyanate accumulation

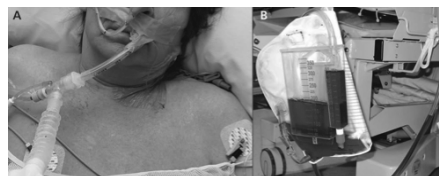
Hydroxocobalamin



- Treatment (cont'd)
 - Hydroxocobalamin
 - Unique mechanism
 - CN binds to Co moiety
 - Equimolar
 - > affinity than cytochrome a3
 - Forms cyanocobalamin
 - Excreted in urine
 - Half-life
 - Cyanocobalamin: 9 hrs
 - Hydroxocobalamin: 3-20 hrs
 - Dose
 - Adult: 5 g over 15 min
 - Children: 70 mg/kg
 - 5 g effective for ~ 40 µmol/L
 - Additional doses
 - Synergism with Na thiosulfate?

Hydroxocobalamin

- Adverse reactions
 - Reddening of the skin, urine, mucous membranes
 - May last for days
 - Rare: allergic reactions, transient hypertension
 - Interaction: forms inactive complex with Na thiosulfate
 - Labs: Red colour interferes with certain lab tests
 - AST, bilirubin, SCr, Mg, Iron, Hg, COHg, MeHg
- Photo source: CMAJ 2009;180(2):251



Hydroxocobalamin



- Availability
 - Health Canada SAP
 - Cyanokit®
 - Merck Sante in France
 - 2 vials x 2.5 G
 - Infusion kit
 - Cost: ~400 plus shipping
 - Expiry: 30 months
 - No refunds for expired stock
- US: FDA approved Dec/06
 - Distributed by Dey

Hydroxocobalamin

- Place in therapy
 - Rapid onset, well tolerated, effective
 - Improved safety over nitrites
 - Consider as first line therapy for acute cyanide intoxication
 - Effective for reducing nitroprusside-induced cyanide accumulation
- Issues
 - No comparison with nitrite/thiosulfate
 - Rarely used, urgently needed
 - Cost = double nitrite/thiosulfate
 - Should it be used in combination with Na thiosulfate?

Hydroxocobalamin

- Selected References:
 - Hall AH, Rumack BH. Hydroxocobalamin/sodium thiosulfate as a cyanide antidote. J Emerg Med. 1987;5:115-21.
 - Clin Tox. 2006;44(Suppl 1):1-47.
 - Ann Emerg Med. 2007;49(6):794-816.
 - Shepherd G, et al. Role of hydroxocobalamin in acute cyanide poisoning. Ann Pharmacother. 2008;42:661-9.

Lipid Rescue

- Local anesthetic toxicity
 - Intravascular injection of LA
 - Absorption of large dose from a tissue depot
 - Regional anesthesia, pain control
 - Neurological effects
 - CNS excitation, seizures, coma
 - CVS effects
 - Arrhythmias, hypotension, CV collapse
 - Resistant to treatment
 - Mechanism
 - Blockage of cardiac sodium channels
 - Uncoupling of oxidative phosphorylation
 - Interferes with mitochondrial transport of fatty acids

Lipid Rescue

- Bupivacaine
 - Advantage: Lipophilicity⇒ long duration of action
 - Disadvantage: More toxic than other LAs
- Experimental evidence
 - Dogs 10 mg/kg bupivacaine bolus with or without 20% lipid emulsion
 - Hypotension & bradycardia
 - Lipid⇒ normalized ECG & BP
 - No lipid⇒ asystole and death

Lipid Rescue

- Human case reports
 - Rosenblatt, et al 2006
 - 58 y/o male
 - 100 mg bupivacaine + 300 mg mepivacaine interscalene block
 - Rapidly developed seizures and asystole
 - No response to ACLS
 - After 20 minutes⇒ 100 mL 20% lipid (1.2 mL/kg)⇒ rapid improvement
 - Lipid infusion of 0.5 mL/kg/min over next 2 hours
 - Patient remained in sinus rhythm and recovered
 - Numerous other reports showing dramatic response
- Other drugs
 - Verapamil
 - β-blockers
 - Quetiapine/sertraline
 - Bupropion/lamotrigine
 - TCAs?

Lipid Rescue



- Dose (70 kg)
 - 20% lipid emulsion
 - 100 mL IV over 1 min
 - 17.5 mL/min infusion
 - Continue chest compressions
 - Repeat bolus, ↑ infusion rate
 - Rec max dose: 560 mL
- TPN dose
 - 20%, 250 mL over 12 hrs

Lipid Rescue

- Possible mechanisms
 - Fat sink, "gift of the glob"
 - Provides FFA to myocardial cells
 - FFA activation of calcium channels
 - Lipid sink theory likely most plausible
- Issues
 - Experimental data impressive
 - Inexpensive
 - Human cases anecdotal, biased reporting
 - Endorsed by anesthetists and hospitals for LA-induced CA
 - No consensus on use in other lipophilic or cardiotoxic agents
 - Optimal dose?
 - Lack of safety data
 - High doses
 - Fat emboli?
 - Interactions with other antidotes?

Lipid Rescue



Evolution



not

Revolution

Lipid Rescue

- Selected References:
 - www.lipidrescue.org
 - Weinberg G, et al. Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity. Reg Anesth Pain Med. 2003;28(3):198-202.
 - Rosenblatt MA, et al. Successful use of a 20% lipid emulsion to resuscitate a patient after presumed bupivacaine-related cardiac arrest. Anesthesiology. 2006;105:217-18.
 - Felice KL, et al. Intravenous lipid emulsion for local anesthetic toxicity: A review of the literature. J Med Toxicol. 2008;4(3):184-91.
 - Sirinani AJ, et al. Use of lipid emulsion in the resuscitation of a patient with prolonged cardiovascular collapse after overdose with bupropion and lamotrigine. Ann Emerg Med. 2008;51:412-5.
 - Finn SDH, et al. Early treatment of a quetiapine and sertraline overdose with Intralipid®. Anaesthesia. 2009;64:191-4.
 - Brent J. Poisoned patients are different - Sometimes fat is a good thing. Crit Care Med. 2009;37(3):1157-8.

