Toxicology 911...Before you call the coroner

Brent W Morgan
Director, Emory/CDC/Georgia Poison Center Medical Toxicology Fellowship
Associate Professor, Department of Emergency Medicine Emory University

Disclosures
I have nothing to disclose
Like most things in the practice of Medical Toxicology the therapies I am going to discuss are not FDA approved.

Objectives
- List 3 medications that can be considered in a patient suffering drug induced cardiovascular collapse
- List the dose range of insulin when being administered to treat a calcium channel blocker overdose
- Name the highest concentration of lipid emulsion that is FDA approved for direct IV infusion
- Explain the mechanism of action of methylene blue in the hypotensive patient

Cardiovascular Drugs

Epidemiology
- Tied for #2 cause of poisoning fatalities (9.4%)
- 1.5 % of pediatric exposures, 6% of deaths
- CCBs and BAAs

CCB and BAA
- The hallmark of severe beta-adrenergic antagonist (BAA) and calcium channel blocker (CCB) toxicity is cardiogenic shock with bradycardia, vasodilation, and decreased contractility.
- This is due to direct -adrenergic receptor antagonism and calcium channel blockade.

Cardiac Energy
- The heart primarily catabolizes free fatty acids for its energy needs.
- The stressed myocardium switches preference for energy substrates to carbohydrates, as demonstrated in models of both BAA and CCB toxicity.
- The greater the degree of shock, the greater the demand for carbohydrates
Toxicodynamics
- The liver responds to stress by making more glucose available via glycogenolysis
- CCBs interfere with carbohydrate use by inhibiting pancreatic insulin release
- CCBs also inhibit pyruvate dehydrogenase, the enzyme responsible for conversion of pyruvate to acetyl-CoA.
- Metabolic derangements may occur that closely resemble diabetes with acidemia and insulin deficiency

Hyperinsulinemia Euglycemia
- Insulin used as an inotrope dates to the 1940’s
- Research of its use in CCBs/BAAs began ~ 20 years ago. First human case 18 years ago.
- In CCB & BAA induced myocardial depression the use of high-dose insulin along with sufficient glucose to maintain euglycemia can restore normal hemodynamics.

Hyperinsulinemia Euglycemia
Mechanism of Action
- Direct inotropic effect
- Increases cAMP
- Increased carbohydrate transport into cardiac myocyte
- Facilitate cardiac carbohydrate utilization during stressed states
- Increase conversion of lactate → pyruvate → acetyl-CoA

Traditional Therapies
- In studies comparing insulin to Epi and glucagon for drug-induced cardiogenic shock, insulin improved cardiac function and work efficiency.
- In contrast to catecholamines, HDI increases coronary blood flow without increasing myocardial oxygen requirements.
- Epinephrine and glucagon promoted free fatty acid utilization. As such, epinephrine and glucagon afforded limited increases in contractility at the expense of less efficient work due to increased oxygen demand

INSULIN-EUGLYCEMIA TREATMENT GUIDELINES
- Most likely going to benefit patients with cardiac drug-induced myocardial depression.
- May also be considered for those patients with hypotension due to poor vascular resistance without myocardial depression that does not respond to standard vasopressor treatment.
- The experimental evidence and human case experience is strongest for CCB toxicity.

Hyperinsulinemia Euglycemia
- Bolus 1 U/kg, then start infusion at 0.5 U/kg/hr
- Some animal evidence bolus as high as 10 U/kg
- Reluctance
- Dextrose 0.5 g/kg/hr as D_{25} or D_{50}
- Supplement K to goal 2.8 – 3.2
- Check glucose/K q30 min x 2 hours, then as necessary (usually q2)
- Attempt to wean off catecholaminevasopressors
Goals of Therapy

- Improvement in organ perfusion as demonstrated by increased BP, improved mental status, and adequate urine output.
- Other markers of effectiveness are reversal of acidemia and decreasing lactate.
- An increase in dextrose infusion to maintain euglycemia often accompanies hemodynamic and metabolic improvements.

Lipid Rescue Therapy

What is Intravenous Fat Emulsion?

- Made by Baxter® Intralipid® for TPN
- List price $658.92/500 mL
- 2 kcal/mL
- Diprivan® is propofol in 10% Intralipid vehicle

What is Intralipid®?

- 20% Soybean oil
- 1.2% egg yolk PL
- 2.25% glycerin
- Water
- Sodium Hydroxide

History of IFE

- Regional anesthesia with local anesthetics is a widespread practice
- 0.2% incidence of IV injection with axillary nerve block
- Local anesthetic lipophilicity related to analgesic potency and cardiotoxicity
- Bupivacaine > ropivacaine > mepivacaine

Local anesthetics

- Also block carnitine-dependent transport of FA across mitochondrial membrane
- ↓FA oxidation → ↓ATP
- Cardiotoxicity
- Seizure, coma, death
**Chance observation**

- 1997 - Weinberg et al.
  - Bupivacaine interferes with carnitine-dependent mitochondrial FA transport
  - Rats given lipid infusion (IFE) tolerate higher doses bupivacaine
  - Improved survival with IFE after bupivacaine-induced arrest

---

**First Human Case**

- 2006 - Rosenblatt et al describe first case of IFE used to resuscitate pt:
  - 58 yo man
  - 0.5% bupivacaine, 1.5% mepivacaine
  - Seizure and asystole
  - 100 mL 20% IFE
  - No residual neuro deficits

---

**Lipid Rescue Therapy**

**Mechanism of action**

- Improve FFA transport into and utilization by mitochondria for energy
- FFA increase intracellular Ca$^{2+}$ → indirect inotropic effect
- Lipid sink

---

**Lipid Sink**

- Creates a kind of 3rd compartment
- "Lipid compartment"
- Binds lipophilic drugs
- Keeps in vascular space
- "Sink in" from tissues

---

**Drug laden chylomicrons delivered to liver**

---

**Lipid Sink**

- Drug laden chylomicrons delivered to liver

---

**Partition constant and volume of distribution as predictors of clinical efficacy of lipid rescue for toxicological emergencies**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug class</th>
<th>Volume of Distribution (L/kg)</th>
<th>Partition constant</th>
<th>Partition lipid extraction efficiency (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>Anti-arrhythmic</td>
<td>8.0</td>
<td>0.6</td>
<td>0.30</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Anti-arrhythmic</td>
<td>6.0</td>
<td>0.5</td>
<td>0.28</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Calcium-channel blocker</td>
<td>4.5</td>
<td>0.2</td>
<td>0.18</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Calcium-channel blocker</td>
<td>3.0</td>
<td>0.1</td>
<td>0.10</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Beta-blocker</td>
<td>2.0</td>
<td>0.0</td>
<td>0.08</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>Beta-blocker</td>
<td>1.5</td>
<td>0.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Timolol</td>
<td>Beta-blocker</td>
<td>1.0</td>
<td>0.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Beta-blocker</td>
<td>0.5</td>
<td>0.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Calcium-channel blocker</td>
<td>1.0</td>
<td>0.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Calcium-channel blocker</td>
<td>0.5</td>
<td>0.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Calcium-channel blocker</td>
<td>0.1</td>
<td>0.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Anti-arrhythmic</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Anti-arrhythmic</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Calcium-channel blocker</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Calcium-channel blocker</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Beta-blocker</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>Beta-blocker</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00</td>
</tr>
<tr>
<td>Timolol</td>
<td>Beta-blocker</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Beta-blocker</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Table 2. Predicted lipid extraction efficiency calculated from the given volume of distribution and the partition constant for each drug using a linear regression model.
Lipid Rescue

- www.lipidrescue.org
- Med Literature
- CCBs, TCA’s, antipsychotics……

Case Report

- 2008 - Sirianni et al. - Annals Emerg Med
- 17 yo girl found unresponsive at home
- 5 hours after message sent to friend
- Missing pill count of bottles on scene:
  - ~ 8 g bupropion
  - ~ 4 g lamotrigine

Case Report

- ED GCS = 6
- ECG: ST, wide QRS, R wave in aVR
- Admit to ICU

Case Report

- ICU: Tonic-clonic seizure → cardiac arrest
- Code #1: 11 shocks, 6 rounds epi, 2 bicarb
- Code #2: 12 rounds epi, NE/E gtt, pacing

Case Report

- 52 minutes into 2nd code
- 100 mL 20% intravenous fat emulsion given
- 1 minute later sustained pulse palpated

Case Report

- PICU recovery = 24 days
- On discharge:
  - Conversant and talkative
  - Slight tremor
  - Mild memory deficits
  - Fine motor incoordination
Fat Emulsion Dosing
- There is no one proven dosing regimen
- Published reports have used: 20% lipid emulsion
  - 1-1.5 ml/kg over 1 minute
  - May repeat every 3-5 minutes with a max of 3 ml/kg
  - 0.25-0.5 ml/kg/hr
- Most case reports use a 100 ml bolus; few reports of using an infusion
- Optimal end-point is unknown

Fat Emulsion Adverse Effects
- Adverse effects are extrapolated from complications of total parenteral nutrition:
  - Fat emboli
  - Anaphylaxis
  - Seizures
  - Increased susceptibility to infection
  - Thrombophlebitis
  - Pancreatitis, cholestasis

More problems
- Hypersensitivity rxn, phlebitis
- Potential interaction with other meds used to treat intoxication
- Difficult lab analysis of lipemic blood
- Theoretical risk of IFE enhancing GI drug absorption (reverse gut dialysis)

Indications for Fat Emulsion Therapy?
- Availability in your ED?
- Not standard of care
- Local anesthetic overdose
  - Best supported in the anesthesia literature
- Life threatening overdoses not responsive to standard of care therapy
  - Patient circling the drain
  - "Any objections to calling the code"

Take Home Points
1. Clearly something to IFE
2. Lipid sink mechanism
3. IFE 20%, 1.5 mL/kg bolus, 0.25-0.5 mL/kg/min
4. Lots of research opportunities
5. Precise role/indication currently unclear

Vasoplegic Syndrome (VS)
- A state of endothelial dysregulation resulting in persistent hypotension despite adequate fluid resuscitation and vasopressor therapy
- Found in sepsis, anaphylaxis, cardiac surgery, renal failure, liver failure, ? Drug overdose
- Low SVR, MAP, hypoperfusion
- VS: dysregulation of Nitric Oxide synthesis/release & vascular smooth muscle cell guanylate cyclase activation = increased cGMP and hypotension
What is Methylene Blue?

- Heterocyclic aromatic compound
- C16H18N3SCI
- Solid dark green powder
- Characteristic blue color when dissolved in water

Medical Uses

- Medicine
  - Methemoglobin Therapy
  - Used to synthesize chlorpromazine and other antipsychotics
  - Malaria treatment prior to WW II
    - Discontinued because of side effects; but making a comeback
      - Green urine
      - Blue sclera
      - MAO Inhibitor

Vasoplegia

- Methylene blue
  - Inhibits guanylate cyclase
    - decreases cGMP
  - May be helpful for treatment of refractory vasodilatory shock in
    - Cardiac bypass
    - Sepsis
    - Anaphylaxis

Published uses in Hypotension

- Cardiopulmonary Bypass
- Anaphylaxis
- Septic Shock
- Hepatorenal hypotension

Nitric Oxide

- Beneficial effects of nitric oxide
  - Increased oxygen delivery to ischemic tissue
  - Amplified macrophage activity
  - Reduced platelet aggregation
  - Augmented free radical scavenger capabilities
- Nonspecific blockade of NOS may therefore have deleterious effects
  - One study of a nonspecific NOS inhibitor
    - associated with increased mortality in septic shock

Methylene Blue

- Methylene Blue targets downstream pathway responsible for vasodilatation
  - Inhibits guanylate cyclase
    - Decreases cGMP
    - Prevents smooth muscle relaxation in vessel walls
### Systematic Review
- **2010 Systematic Review**
- Searched various databases
  - MEDLINE (1966-6/2009)
- **Key words**
  - Methylene Blue, Nitric Oxide Inhibitor, Nitric Oxide and Sepsis, Nitric Oxide Synthase Inhibition

### Clinical Study Data N=9
- In all studies, methylene blue started late in the course of septic shock
- Unknown impact if started early
- Studies show improvement in hemodynamic variables but no benefits in clinical outcomes
- Limitations of studies included
  - Small sample sizes
  - Poor methodological quality
  - Lack of placebo-controlled trials

### Case Report
- **Ann Emerg Med Dec. 2011**

#### Methylene Blue in the Treatment of Refractory Shock From an Amlodipine Overdose
- **Dihydropyridine amloidipine**
  - Vasodilatory effect > direct cardiac tissue effect
  - 30-60 hour half-life can delay onset of action
  - Toxicity S/S mimic vasodilatory shock of sepsis/anaphylaxis
    - Can be refractory to conventional therapies

#### Case Report
- **25 yo, 60kg female ingested 40 tabs of 10mg amlodipine one hour PTA**
  - Initially everything normal except for sinus tachycardia (110)
  - Given 1g/kg activated charcoal
  - 2-3hrs post-ingestion time
    - BP 75/40
    - HR 120
  - 3L IV NS given during first 3 hours
  - 40mL 10% calcium gluconate IV
  - 10mg glucagon
  - No improvement

<table>
<thead>
<tr>
<th>7 hours post-ingestion, started:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine 5µg/kg/min</td>
</tr>
<tr>
<td>Norepinephrine 1µg/min</td>
</tr>
<tr>
<td>BP and HR unchanged</td>
</tr>
<tr>
<td>Mental status preserved</td>
</tr>
<tr>
<td>EKG unchanged</td>
</tr>
<tr>
<td>8 hours post-ingestion</td>
</tr>
<tr>
<td>Consulted poison center</td>
</tr>
</tbody>
</table>

| 30mL 10% calcium gluconate       |
| High dose insulin-euglycemia therapy |
  - 1 unit/kg bolus, then infusion of 0.5-1 unit/kg/hr
  - 1 hr later
    - BP 75/40
    - HR 110
- Patient became confused and lethargic
  - Intubated
  - Sent to ICU (lactate 4.1)
- Transthoracic echo
  - Hyperdynamic LV
  - No effusions
  - Normal IVC
- Right-sided heart cath
  - PCWP 16 (2-10)
  - CI 5.1 (2.5-4.2)
  - SVR 400 (700-1600)

- Failed to improve more than 14 hours post-ingestion despite additional
  - Insulin
  - Dopamine
  - Norepinephrine
- 16 hours post-ingestion
  - Methylene blue 2mg/kg over 20 minutes, then 1mg/kg/hr infusion
  - 1 hour later, BP 90/75 and HR 90

- Eventually weaned off pressors and insulin
- Methylene blue stopped
- Discharged from hospital 6 days later
- Serum concentration of amlodipine on admission was 36µg/mL (3-10 therapeutic)

Role
- Further research is needed to better understand methylene blue’s role in treatment of drug-induced hypotension
- Could be considered after more traditional therapies for drug overdoses with low SVR have failed

Common Adverse Effects
- Blue discoloration of skin and urine
  - Reversible and harmless
- Falsely lowers O2-saturation readings on pulse oximetry
  - Methylene blue absorbs light
    - Interpreted as reduced circulating Hgb
- At high doses (>4mg/kg) can induce methemoglobinemia by acting as an oxidizing agent
- Risk of inducing hemolytic anemia in G6PD deficient patients
Dosing recommendations

- Most studies used the methemoglobinemia treatment dose (1-2mg/kg)
- Larger bolus doses associated with more pronounced detrimental effects on pulmonary gas exchange (Safety with ALI)
- Single bolus of methylene blue would likely increase BP for 2-3 hours
- Continuous infusions (0.25mg/kg/hr) allow for titration based on response
  - Allows for lower doses