Antidotes for Poisoning: Pearls and Pitfalls

Craig Smollin MD
Associate Medical Director,
California Poison Control Center, SF Division
Assistant Professor of Emergency Medicine
University of California, San Francisco
Disclosures

No financial relationship to any commercial products discussed in this talk
What are the most common interventions performed in acute poisoning?
Interventions in poisoning AAPCC 2008

No. Cases
Interventions in poisoning AAPCC 2008

No. Cases
First and foremost, poisoned patients need good supportive care!
Be prepared!
Antidotes are Sexy
John Travolta injects Uma Thurman with “adrenaline”
Success.

- Recognition
- Rapid Response
- Know Treatment Options
Case 1

Massive Overdose: “But looks good…”
Case 1

45 year-old female with history of hypertension ingests 70 tablets of amlodipine (10mg) 1.5 hours prior to arrival in your emergency department. She is awake and conversant. Physical exam reveals cool dry skin but is otherwise unremarkable.

VS: BP 110/60, HR 60, RR 18, FSG 240

“She looks pretty good”
Case 1

A short time later the patient is vomiting. Repeat vital signs: BP 83/50 mm Hg, Pulse 65 bpm
## Pitfall

Not all calcium channel blockers are equal!

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Release</td>
<td>6 hours</td>
</tr>
<tr>
<td>Modified-release (Non Verapamil)</td>
<td>18 hours</td>
</tr>
<tr>
<td>Modified-release Verapamil</td>
<td>24 hours</td>
</tr>
</tbody>
</table>
A normal heart rate in the setting of hypotension is not normal.

BP 83/50 HR 65 bpm
Calcium Channel Blockers

Heart

↓ ionotropy
↓ chronotropy
Calcium Channel Blockers

Heart
  ↓ ionotropy
  ↓ chronotropy

Peripheral Vasculature
  ↓ vascular resistance
Calcium Channel Blockers

Heart
- ↓ ionotropy
- ↓ chronotropy
  Ex. Verapamil

Peripheral Vasculature
- ↓ vascular resistance
  Ex. Amlodipine, Nifedipine, Nimodipine
Hypotension
Acidosis
Shock
Clues to the diagnosis

- Bradycardia
- Hypotension
- Conduction abnormalities
Hyperglycemia predicts poor outcomes

Table 2. Median blood glucose values and vital sign variables for those who did and did not meet composite end points

<table>
<thead>
<tr>
<th></th>
<th>No Composite End Point</th>
<th>Composite End Point</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, ( n )</td>
<td>( 28 )</td>
<td>( 12 )</td>
<td></td>
</tr>
<tr>
<td>Initial blood glucose, mg/dL(^a)</td>
<td>129 (98.5–156.5)</td>
<td>188 (143.5–270.5)</td>
<td>.0058</td>
</tr>
<tr>
<td>Peak blood glucose, mg/dL(^a)</td>
<td>145 (107.5–160.5)</td>
<td>364 (267.5–408.5)</td>
<td>.0001</td>
</tr>
<tr>
<td>Initial heart rate, beats/( \text{min} )(^a)</td>
<td>60 (45–87)</td>
<td>50.5 (40–67.5)</td>
<td>.18</td>
</tr>
<tr>
<td>Minimal heart rate, beats/( \text{min} )(^a, b)</td>
<td>58 (40–68)</td>
<td>40 (39–45)</td>
<td>.0589</td>
</tr>
<tr>
<td>Initial systolic blood pressure, mm Hg(^a)</td>
<td>129 (100–144)</td>
<td>89 (60–113)</td>
<td>.0091</td>
</tr>
<tr>
<td>Lowest systolic blood pressure, mm Hg(^a, b)</td>
<td>110.5 (94–130)</td>
<td>72 (60–84)</td>
<td>.0004</td>
</tr>
</tbody>
</table>

\(^a\)Median (interquartile range); \(^b\)lowest value during the first 24 hrs of admission.

Composite Endpoints = Death, need for pacemaker, vasoactive agents
Pay attention to the glucose early on in a possible CCB overdose.
Clues to the diagnosis

- Bradycardia
- Hypotension
- Conduction abnormalities
Conduction abnormalities

Clues to the diagnosis

Bradycardia
Hypotension
Conduction abnormalities
Hyperglycemia
Shotgun Approach

- Intravenous fluids
- Calcium
- Atropine
- Glucagon
- Pressors
- Cardiac Pacing
New therapies?

High dose insulin euglycemia therapy
High dose insulin outperforms epinephrine and glucagon…

… In dogs
High dose insulin outperforms epinephrine and glucagon in dogs

Kline et al, Insulin a superior antidote for cardiovascular toxicity induced by verapamil in the canine.
Evidence - Human Studies

- No randomized controlled trials
- Many case reports demonstrating both beneficial and no effect
- Case reports with no effect often used HIET as last resort
Start high dose insulin euglycemia therapy early in suspected severe calcium channel blocker overdose.
High dose insulin euglycemia therapy

IV regular insulin bolus 1U/kg
IV infusion of regular insulin at 0.5-1 U/kg/hr
Choose your poison

A

B
Choose your poison

A
Aspirin free night time pain relief

B
Sweet and sour candies
Choose your poison

A

B
Choose your poison

A

Bret Michaels of glam band “Poison”

B

Jeff Tabas - course director HREM
Case 2

When animals attack...
Case 2

- 28 y/o man bitten near right upper lip by pet rattlesnake.
- Previously bitten 14 times.
- Now what?
- Patient placed on the ground close to a car.
- Lead wire from one of the car’s spark plugs attached to the patient’s lip.
- Neighbor started car and revved engine to 3000 rpm for 5 minutes.
Hypothesis Driven Science

- Null Hypothesis
- Observational study Design
Snakebite Severity Index (SSI)
Rattlesnake Bite 2 Days and 1 Week
Rattlesnake Bite - Proximal Progression
Rattlesnake Bite - Systemic Toxicity

- Cardiovascular
- Neurologic
- Hematologic
## Antivenom

<table>
<thead>
<tr>
<th><strong>Antivenom Polyvalent (Wyeth)</strong></th>
<th><strong>Crotalidae Polyvalent Immune Fab</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Horse Derived</td>
<td>• Sheep Derived</td>
</tr>
<tr>
<td>• Unpurified</td>
<td>• Purified</td>
</tr>
<tr>
<td>• Complications:</td>
<td>• Complications:</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Delayed</td>
</tr>
<tr>
<td>Serum Sickness</td>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>
Pitfall: Delayed Thrombocytopenia

Recurrence of Hemorrhage

- Significant bleeding associated with delayed thrombocytopenia reported
  - Fazelat et al. Recurrent hemorrhage after western diamondback rattlesnake envenomation treated with crotalidae polyvalent immune fab(ovine) Clin Tox (Phila) 2008;46(9):823-6
“No NAC, I’ll be back...”
Case 3

23 year-old female intentionally overdosed on an unknown number of ibuprofen tablets 7 hours prior to arrival in your emergency department. She complains of mild nausea and vomiting. Vital signs are normal and physical exam is unremarkable.
Case 3

The patient receives activated charcoal and is observed for 6 hours and remains asymptomatic and is discharged to psychiatry.
Case 3

The patient is referred back to the emergency department 24 hours later with nausea, vomiting and jaundice. AST, ALT and total Bili are elevated and a Tylenol level is 40 ug/ml
Clues to the diagnosis
<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Patients (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen level &gt;1 µg/mL</td>
<td>175 (9.6%)</td>
</tr>
<tr>
<td>Acetaminophen History Positive</td>
<td>120 (6.5%)</td>
</tr>
<tr>
<td>Acetaminophen History Negative</td>
<td>55 (3.0%)</td>
</tr>
<tr>
<td>Acetaminophen level &gt;50 µg/mL and History Negative</td>
<td>5 (0.3%)</td>
</tr>
</tbody>
</table>
Pearl: check APAP level on all overdose patients

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Patients (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen level &gt;1 µg/mL</td>
<td>175 (9.6%)</td>
</tr>
<tr>
<td>Acetaminophen History Positive</td>
<td>120 (6.5%)</td>
</tr>
<tr>
<td>Acetaminophen History Negative</td>
<td>55 (3.0%)</td>
</tr>
<tr>
<td><strong>Acetaminophen level &gt;50 µg/mL and History Negative</strong></td>
<td><strong>5 (0.3%)</strong></td>
</tr>
</tbody>
</table>

**TABLE 1. Acetaminophen Serum Levels in 1,820 Patients With Suicidal Ingestion or AMS**
APAP Induced Liver Damage

APAP $\xrightarrow{P450}$ NAPQI
APAP Induced Liver Damage

APAP $\xrightarrow{P450}$ NAPQI $\xrightarrow{\text{glutathione}}$ Nontoxic metabolites
APAP Induced Liver Damage

APAP $\xrightarrow{\text{P450}}$ NAPQI $\xrightarrow{\text{glutathione}}$ Nontoxic metabolites

Liver damage
APAP Induced Liver Damage

CENTRILOBULAR NECROSIS

NORMAL LIVER
Acute ingestion clinical course

0 h → Asymptomatic → 24 h
Acute ingestion clinical course

24 h  

Asymptomatic  AST/ALT  36 h
Acute ingestion clinical course

(1) Liver Failure
36 h (2) Recovery

Asymptomatic  AST/ALT
Acute ingestion treatment timeline

- Asymptomatic
- AST/ALT
Acute ingestion treatment timeline

Asymptomatic

0 h 8 h

AST/ALT
Nomogram

Acetaminophen Plasma Concentration (µg/mL)

Hours After Ingestion

Possible Hepatic Toxicity

Probable Hepatic Toxicity

No Hepatic Toxicity

25%
APAP Induced Liver Damage

APAP $\xrightarrow{P450}$ NAPQI $\xrightarrow{\text{glutathione}}$ Nontoxic metabolites

Liver damage
Pitfall Late administration of NAC
Acute ingestion treatment timeline

Asymptomatic

0 h  8 h

AST/ALT
Acute ingestion treatment timeline

Asymptomatic

AST/ALT

0 h

8 h

Start SCN

20 hour Protocol
Acute ingestion treatment timeline

- Asymptomatic
- AST/ALT

0 h
8 h

Start SCN

nl AST/ALT
APAP < 10
Stop Therapy

20 hour Protocol
Premature discontinuation of NAC
Acute ingestion treatment timeline

0 h
Start SCN

Asymptomatic

8 h

nl AST/ALT
APAP < 10
Stop Therapy

20 hour Protocol

AST/ALT
Acute ingestion treatment timeline

- **Asymptomatic**
- **AST/ALT**

- **0 h**
- **8 h**

Extend NAC Therapy until APAP = 0 and AST/ALT trending down
APAP Induced Liver Damage

APAP $\xrightarrow{P450}$ NAPQI

Nontoxic metabolites

Liver damage

glutathione
APAP Induced Liver Damage

APAP $\xrightarrow{\text{P450}}$ NAPQI $\xrightarrow{\text{glutathione}}$ Nontoxic metabolites

Liver damage

NAC
Oral vs Intravenous NAC

No. Cases
Oral and intravenous NAC are equally efficacious.
Question:

True or false:

Intravenous and oral NAC cost the same

False
<table>
<thead>
<tr>
<th>Oral</th>
<th>Intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>$50 for 72 hour course</td>
<td>$470 for 20 hour course</td>
</tr>
</tbody>
</table>
Question:

True or false:

Intravenous NAC is associated with anaphylactoid reactions

True
Pitfall: Anaphylactoid Reactions

Mild

GI Symptoms

Flushing

Pruritis

Mild Dyspnea

SPECTRUM

Severe

Chest pain

Hypotension

Respiratory Distress
Who is at risk?

- History of asthma
- Previous allergy (atopic or drug allergy)
- Low acetaminophen concentrations
If possible, avoid the use of intravenous NAC in patients with asthma, or those with low acetaminophen concentrations.
Choose your poison

A

B
Choose your poison

A
D-con rat poison

B
Mini sweet and sour candies
Case 4

“Burning down the house”
Case 4

40-year old male pulled from an enclosed fire. He is confused and agitated. He arrives in your emergency department disoriented and in moderate distress, coughing up soot and complaining of difficulty breathing.

VS: BP 90/60, HR 120, RR 30, O2 sat 95%
Recognition
Case 4

Laboratory Data:
VBG: pH 6.8, pO2 = 75,
Lactate = 16 mmol/L
COHgb = 20%
CXR negative
Head CT negative

Diagnosis is CO poisoning right?
Consider this…

• HCN produced in combustion of:

  - Paper
  - Silk
  - Wool
  - Plastic
  - Cotton

• Probability of HCN production/exposure is high
% of Patients

> 3 mg/L CN

> 50 % HbCO

Dupont Plaza

Happy Land

Manchester Aircraft
Correlation between cyanide levels and mortality

Baud F et al, Elevated blood cyanide concentrations in victims of smoke inhalation, NEJM 1991
Clues to the Diagnosis

Cardiovascular Collapse

Lactate > 10 mmol/L

Elevated venous pO2
Failure to consider CN exposure
Cyanide Antidote Kit
Cyanide Antidote Kit
Cyanide Antidote Kit
Pitfall

Administration of nitrites to patients with both HCN and CO poisoning
Cyanide Antidote Kit
Cyanide Antidote Kit
Cyanide Antidote Kit
Hydroxocobalamin

Hydroxocobalamin + CN $\rightarrow$ Vitamin B12 (cyanocobalamin)
Animal Evidence

- Efficacy studies in multiple animal models
- Beagle Dogs treated with intravenous KCN followed by saline vs hydroxocobalamin (75 and 150)
Animal Evidence
Human Evidence

- One retrospective review
- One Prospective observational case series
- No controlled trials in humans comparing hydroxycobalamin and sodium thiosulfate
Human Evidence

• Total of 69 smoke inhalation victims treated
  – 67 % survival rate
  – 51% without any neuropsychiatric sequelae
  – Plasma lactate >10 umol/L relatively sensitive and specific marker for cyanide poisoning
  – No serious side effects
In the undifferentiated smoke inhalation victim, hydroxocobalamin may be the best antidote.
Case 5

“Back from the dead…”
Case 5

- 58 yr-old male undergoing interscalene block with bupivacaine.
- Patient injected with 40 ml total (0.5% bupivacaine).
- 30 seconds later tonic-clonic seizure terminated with propofol.
- 90 seconds later repeat seizure and full cardiac arrest.
- Vtach --> Vfib --> Asystole
Case 5

• Treatment:
  – Intubation
  – ACLS
  – 3 mg epinephrine
  – 2 mg atropine
  – 300 mg amiodarone
  – 40 U vasopressin
  – Monophasic defibrillation (200, 300, 360 x 2)
Case 5

• 20 minutes post code: 100ml of 20% intralipid through peripheral IV followed by additional chest compression and one defibrillation
• 15 seconds later, sinus rhythm at 90 beats/second with palpable pulse.
• 2.5 hours later patient extubated without any neurologic sequelae.
Intralipid
Intralipid as a lipid sink?

Tissues

- Fat
- Bone
- Liver
- Heart
- Brain

Blood

Drug
Intralipid as a lipid sink?
Intralipid as a lipid sink?

Tissues
- Fat
- Bone
- Liver
- Heart
- Brain

Blood
Intralipid as a lipid sink?

- Fat
- Bone
- Liver
- Heart
- Brain
Intralipid as a lipid sink?

- Tissues: Fat, Bone, Liver, Heart, Brain
- Blood:
Intralipid as a lipid sink?

Tissues

Blood

Fat
Bone
Liver
Heart
Brain
Intralipid as a lipid sink?
Intralipid as a lipid sink?

Tissues → Blood

- Fat
- Bone
- Liver
- Heart
- Brain
Intralipid as a lipid sink?
Intralipid as a lipid sink?

- Tissues: Fat, Bone, Liver, Heart, Brain
- Blood
Animal Studies

• Intralipid prolongs survival in a rat model of verapamil toxicity
• The role of fat emulsion therapy in a rodent model of propranolol toxicity: a preliminary study
• And many others…
Successful human case Reports

Bupivicaïne
Ropivicaïne
Lidocaïne
Verapamil
Quetiapine
Buproprionaïne
Lamotrigine
Think about intralipid in the patient crashing with local anesthetic toxicity or lipophillic drug ingestions.
Take home points
• First and foremost, poisoned patients need good supportive care
Case 1 - underappreciated CCB overdose

- The type and formulation matter
- Look for hypotension and relative bradycardia
- Hyperglycemia is an early indicator of toxicity
- Think high dose insulin euglycemia therapy early
Case 2 - Rattlesnake envenomation

• Dosing is dependent on the progression of symptoms
• Delayed thrombocytopenia and bleeding
Case 3 - unrecognized Tylenol overdose

- Think about Tylenol in every overdose patient
- Intravenous and oral NAC are equally efficacious
- Pitfalls include late administration and premature termination of NAC
- Intravenous NAC can cause anaphylactoid reactions
Case 4 - unrecognized cyanide exposure

- CN toxicity is under-diagnosed
- Lactate > 10 mmol/L think CN
- Avoid nitrites in the smoke inhalation patient with possible CO and CN exposure
- Hydroxocobalamin may be the best antidote.
Case 5- bupivacaine overdose

- Think about Intralipid for anesthetic overdoses for lipophilic drug ingestions.
Questions?