TOXICOLOGY
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Objectives
1. Identify medications known to cause toxicity in overdose situations
2. Review management principles of toxic overdoses
3. Demonstrate understanding through participation in active learning activity

Figure 1. National Drug Overdose Deaths
Number Among All Ages, by Gender, 1999-2017

2017 AAPC NPDS
Age Distribution of Human Exposure Cases

2017 AAPC NPDS Top Ten Substance Categories by Age Group

Data from Table 3 of the 2017 AAPC NPDS Annual Report: Distribution of Reason for Exposure by Age, N=3,136,288
Resources

Toxidromes

Acetaminophen
- Mechanism: prostaglandin inhibitor
- Most common cause of acute hepatic failure
  - 30% incidence in patients presenting 8 hours after ingestion
- FDA maximum recommended dose: 4 grams daily

Toxic Alcohols

Calcium Channel Blockers

Beta Blockers

Acetaminophen

Toxic Alcohols

Calcium Channel Blockers

Beta Blockers
Acetaminophen Metabolism

Acetaminophen Overdose
Clinical Presentation

<table>
<thead>
<tr>
<th>Time After Ingestion (h)</th>
<th>Clinical Signs</th>
<th>Laboratory Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>Asymptomatic or mild nausea, vomiting, malaise</td>
<td>Normal or increased AST in severe cases</td>
</tr>
<tr>
<td>1-2</td>
<td>RUQ abdominal pain, nausea, vomiting, diarrhea</td>
<td>Increased AST, ALT, PT, bilirubin, and lactate acid</td>
</tr>
<tr>
<td>3-5</td>
<td>Jaundice, coagulopathy, hypoglycemia, renal dysfunction, hepatic encephalopathy, metabolic failure</td>
<td>AGA, increased serum creatinine, and ammonia</td>
</tr>
<tr>
<td>5+</td>
<td>Resolution of hepatotoxicity</td>
<td>Normalization</td>
</tr>
</tbody>
</table>

Treatment of Acetaminophen Overdose

- **N-acetylcysteine (NAC)**
  - Nearly 100% effective if administered within 8 hours of ingestion
  - Available in oral and IV formulations
  - IV form should be used in severe cases
  - Common side effects:
    - Nausea/vomiting
    - Anaphylactoid reactions

- **Activated charcoal**
  - May administer if patient has stable mental status and presents within 1 hour of ingestion

Treatment of Acetaminophen Overdose

- Administer NAC to acute APAP overdose with either possible or probable risk for hepatotoxicity (level B)
  - Ideally within 8-10 hours postingestion
- Administer NAC to patients with hepatic failure thought to be due to APAP (level B)
Treatment of Acetaminophen Overdose

<table>
<thead>
<tr>
<th>Oral</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading dose: 140 mg/kg x 1 dose</td>
<td>For treatment within 8 hours of ingestion:</td>
</tr>
<tr>
<td></td>
<td>• Initial bolus: 150 mg/kg IV over 1 hour</td>
</tr>
<tr>
<td></td>
<td>• Infusion: 50 mg/kg over 4 hours</td>
</tr>
<tr>
<td>Then: 70 mg/kg every 4 hours x 17 doses</td>
<td>• Then: 100 mg/kg over 16 hours</td>
</tr>
<tr>
<td></td>
<td>For treatment &gt; 8 hours after ingestion, chronic ingestion, or for those with hepatic failure:</td>
</tr>
<tr>
<td></td>
<td>• Infusion: 12.5 mg/kg/hr over 48 hours</td>
</tr>
</tbody>
</table>

May be discontinued once the protocol is complete if:
• Serum APAP level < 10 μg/mL.
• No signs of ongoing hepatic injury

Ethylene Glycol Clinical Presentation
- Early
  - Inebriation or altered mental status
- Late
  - Metabolic acidosis
  - Hyperventilation
  - Oxalate crystalluria
  - Renal failure
  - Clinical hypocalcemia
  - Life-threatening arrhythmias
  - Coma
  - Seizures
  - Death

Ethylene Glycol Toxicity Diagnosis
- Serum chemistry
  - Blood gases
  - Plasma EG concentration
- Osmolal gap
  - Difference between the measured osmolality and the calculated osmolality
    - Normal = < 10 mOsm/kg H₂O
- Calculated Osmolality
  - mOsm/L = 2(Na⁺) + BUN/2.8 + glucose/18

Ethylene Glycol Mechanism of Toxicity
Treatment of Ethylene Glycol Toxicity

Criteria for Fomepizole

Documented recent history of ingestion of a toxic amount of toxic alcohol and osmolal gap > 10 mOsm/L

Documented plasma concentration ≥ 20 mg/dL

Suspected ingestion with at least 3 of the following criteria:
- Arterial pH < 7.3
- Serum bicarbonate concentration < 20 mmol/L
- Osmolal gap > 10 mOsm/L
- Oxalate crystalluria

Fomepizole Dosing

- Loading dose: 15 mg/kg IV infused over 30 minutes
- Followed by 10 mg/kg IV q12h x 4 doses
- Then 15 mg/kg q12h until ethylene glycol concentration < 20 mg/dL and pH is normalized

Dose adjustment
- If patient requires concomitant hemodialysis (HD)

Fomepizole

- Adverse reactions
  - Headache
  - Nausea
  - Dizziness
  - Drowsiness
  - Metallic taste

- Food interactions
  - Ethanol decreases the rate of fomepizole elimination by ~ 50%
  - Fomepizole decreases rate of elimination of ethanol by ~ 40%

Hemodialysis Indications

- Arterial pH < 7.0
- Drop in arterial pH > 0.05 resulting in an abnormal pH despite bicarbonate infusion
- Inability to maintain arterial pH > 7.3 despite bicarbonate therapy
- Decrease in bicarbonate concentration > 5 mEq/L despite bicarbonate therapy
- Renal failure
- Deteriorating vital signs despite intensive supportive care
Other Treatment Principles for Ethylene Glycol Toxicity

- Gastric lavage, activated charcoal, or ipecac syrup are not recommended
- Asymptomatic inhalation exposures can be managed out-of-hospital
- Unintentional, asymptomatic ingestions > 24h since exposure without alcohol co-ingestion do not require medical treatment
- Sodium bicarbonate should be administered if pH < 7.3
- Calcium is only recommended if hypocalcemia significantly contributes to symptoms
- Pyrithione and thiamine

Alternative Treatments??

Treatment of Ethylene Glycol Toxicity

- Fomepizole
  - Advantages: Higher affinity for ADH, minimal adverse effects, monitoring not necessary
  - Disadvantages: Expensive, certain patients may not need dialysis
- Ethanol
  - Advantages: Inexpensive, available in most medical centers, traditional antidote
  - Disadvantages: Significant adverse effects, requires ICU, intensive monitoring

CCB/B-blocker Overdose
Calcium Channel Blockers (CCBs): Pharmacology

- **Dihydropyridines**: antagonism of L-type calcium channels in the peripheral vasculature
  - Produce potent vasodilation, have minimal effect on cardiac contractility
  - Ex: Amlodipine, nicardipine, nimodipine

- **Non-dihydropyridines**: antagonism of L-type calcium channels in the myocardium
  - Produce a reduction in cardiac contractility, heart rate
  - Ex: diltiazem, verapamil

Beta Blockers: Pharmacology

- **Antagonism of beta-1 and beta-2 receptors**
  - Beta-1: primarily located in cardiac tissue, increased inotropy/chronotropy
  - Beta-2: most prominent in vascular smooth muscle and bronchioles, leads to vasodilation and bronchodilation

Beta Blocker Overdose: Clinical Presentation

- **Cardiovascular**
  - Hypotension
  - Bradycardia
    - Most commonly with non-dihydropyridine overdoses
  - Tachycardia
    - Most commonly with dihydropyridine overdoses
  - Signs of heart failure
    - Pulmonary edema
    - Jugular venous distention

- **Endocrine**
  - Hyperglycemia

Overdose Treatment

- Calcium
- Glucagon
- Catecholamines

- May potentiate seizures, delirium, coma

Lipophilic beta blockers
- Propranolol
- Nebivolol
- Carvedilol

Calcium Preparations

<table>
<thead>
<tr>
<th>Calcium gluconate</th>
<th>Calcium chloride</th>
</tr>
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<tbody>
<tr>
<td>10 mL of 10% solution</td>
<td>10 mL of 10%</td>
</tr>
<tr>
<td>4.5 mEq of Ca$^{2+}$</td>
<td>13.6 mEq of Ca$^{2+}$</td>
</tr>
</tbody>
</table>

- Must be administered via central venous access
- Adjust infusion based on ionized calcium
- Calcium is contraindicated in concurrent digoxin toxicity

Calcium Guidelines

20 mg/kg Ca$^{2+}$
Bolus
(0.2 ml/kg CaCl$_2$)

Favorable hemodynamic response

20-50 mg/kg/hr Ca$^{2+}$
Continuous infusion (0.2-0.5 ml/kg/hr CaCl$_2$)

No hemodynamic changes

Alternate therapy

Optimum Calcium Dosing

- Failure of human cases are probably under resuscitated
- Animal models suggest need for high doses

<table>
<thead>
<tr>
<th>Bolus</th>
<th>Infusion</th>
<th>Endpoint</th>
</tr>
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<tr>
<td>• 8-20 mg/kg (0.4-1 mEq/kg)</td>
<td>• 36-300 mg/kg/hr (1.8-15 mEq/kg/hr)</td>
<td>• 1.5-2 x [Ca$^{2+}$] associated with improved cardiodynamics</td>
</tr>
</tbody>
</table>

Calcium Adverse Effects

- Hypokalemia
- Hypotension
- Bradycardia
- Dysrhythmia
- Tissue extravasation

Glucagon

- Evidence
  - Highest level in beta-blocker overdose
  - Successes and failures in calcium channel blockers
- Indications
  - Hypotension
  - Bradycardia
- Dose
  - Bolus: 2-5 mg IV
  - Infusion: 1-10 mg/hr
Glucagon Limitations

- **Cost**
  - Glucagon 1 mg = $205.92

- **Availability**
  - Survey of 47 hospitals in Washington DC
    - 30 mg in 26%
    - 50 mg in 15%

- **Nausea and vomiting**

- **Transient response**

High Dose Insulin and Glucose Infusion

- **Rationale**
  - Promotes carbohydrate metabolism in stressed myocardium
    - Positive inotropy and chronotropy

- **Administration**
  - Initial insulin bolus: 0.5-1 unit/kg IV
  - 0.5-1 unit/kg IV infusion, titrated to mean arterial pressure (MAP)
  - Dextrose infusion: 0.5 gm/kg/hr to maintain serum glucose levels
  - Aggressive potassium replacement

Vasopressor Therapy

- Norepinephrine is typically first choice
  - High doses and multiple agents may be necessary
  - Dobutamine may be added for confirmed cardiogenic shock

- **Avoid**
  - Dopamine
  - Vasopressin as monotherapy

Methylene Blue

- **Mechanism**
  - Inhibitor of guanylate cyclase
  - Decreased levels of cGMP
  - Scavenger of NO
  - Reduces vasodilation, counteracts calcium channel blocker mechanism of action

Intravenous Lipid Emulsion (ILE) Therapy

- Infusion of parenteral nutrition lipid formulation as a therapy for overdoses
  - Initially studied in local anesthetic overdoses
  - Now studied in wide range of overdoses

- **Mechanism theories**
  - “Lipid sink”
  - Free fatty acid source of energy for myocardium

- **Administration**
  - 1 to 1.5 ml/kg IV boluses of 20% solution over 1 minute
  - Repeat up to 3 times
  - 0.25 to 0.5 ml/kg/min infusion until hemodynamic stability occurs

Intravenous Lipid Emulsion Therapy Adverse Effects

- **Hypertriglyceridemia**
- **Fat embolism**
- **Infection**
- **Hypersensitivity reactions**
- **Venous thromboembolism**
- **Acute kidney injury**
- **Pancreatitis**

- **Lipid dose of a 70 kg patient**
  - Bolus dose: 14-21 gm
  - Continuous infusion: 3.5-7 gm/min
BB Lipophilicity and ILE Efficacy

- Lipid sink mechanism of action for ILE may limit usefulness in non-lipophilic drugs
  - Less partitioning of the drug molecules into the infused lipid reservoir from tissues

<table>
<thead>
<tr>
<th>Beta Blocker</th>
<th>Lipid Solubility Coefficient (log P)</th>
<th>Relative Lipid Solubility</th>
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<tbody>
<tr>
<td>Carvedilol</td>
<td>3.29</td>
<td>High</td>
</tr>
<tr>
<td>Propranolol</td>
<td>2.8</td>
<td>High</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1.35</td>
<td>Low to moderate</td>
</tr>
<tr>
<td>Alpenolol</td>
<td>0.56</td>
<td>Low</td>
</tr>
</tbody>
</table>
