Terrible Toxins
Prashant Joshi, MD
Western NY Poison Center

Goals
- to discuss the demographics of childhood poisoning and death from poisoning
- to explore the toxic agents involved in childhood fatalities
- to make the audience aware of potentially highly lethal agents

Poison Prevention Week
March 15 - 21, 2009

2007 U.S. Statistics
- 1,271,595 calls to U.S. Poison Centers concerning children under 6 years of age
- 35 deaths in this age group
- only represent less than 3% of all fatalities

2007 WNY Statistics
- 7,376 calls to the Western NY Poison Center concerning children under 6 years of age
- NO deaths

Why do youngsters die?
- carbon monoxide poisoning
- smoke inhalation
- opioids
  - fentanyl patch
  - meperidine
  - hydrocodone
- aluminum phosphide
Carbon Monoxide

- largest single cause of poisoning death in children
- associated with household fires, faulty heating appliances, misuse of appliances
- largely PREVENTABLE
- spike seen in exposures during power failures
  - e.g. October 2006 ice storm

<table>
<thead>
<tr>
<th>CO level in air (ppm)</th>
<th>Carboxyhemoglobin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>120</td>
<td>20</td>
</tr>
<tr>
<td>220</td>
<td>30</td>
</tr>
<tr>
<td>350 - 520</td>
<td>40 - 50</td>
</tr>
<tr>
<td>800 - 1220</td>
<td>60 - 70</td>
</tr>
<tr>
<td>1950</td>
<td>80</td>
</tr>
</tbody>
</table>

Carbon monoxide

- multiple sites of action
- impairs ability to transport oxygen
- causes NO release
- leads to lipid peroxidation in CNS
- survivors of severe poisoning can experience long-term neuro/cognitive deficits

- symptoms and signs
  - headache, fatigue, nausea, weakness, drowsiness, seizures, coma
  - transcutaneous oxygen saturation will read NORMAL
  - red skin is seen in moribund or dead individuals

Carbon monoxide

- Assessment
  - ABC’s
  - carboxyhemoglobin level
  - for confirmation—does not correlate with clinical effects

Masimo RAD-57
Carbon monoxide
Treatment is OXYGEN!!!

Hyperbaric oxygen is controversial

Opioids

- Among the most commonly prescribed medications
- Available in tablets, lollipops, liquids, patches, nasal spray

Opioid toxicity

- CNS depression
- Respiratory depression
- Miosis

Opioid poisoning
May not be recognized in children--not suspected!
Fentanyl patch

- controlled-release dermal patches for pain control in non-naive patients
- often used for cancer pain
- release 12, 25, 50, 75, or 100 mcg/h
- must be changed every 72 hours

A completely used patched still contains 2 days worth of drug

Fentanyl is 100X as potent as morphine

Even a used 12 mcg patch contains enough drug to kill a toddler

Aluminum phosphide

- AlP is a restricted use rodenticide, insecticide, fumigant
- Reacts with water or acid to form phosphine gas
- phosphine gas blocks cytochrome C oxidase
Aluminum phosphide
- Lethal dose is less than 0.5 g
- Causes widespread failure of energy production
- Early signs include vomiting, chest/abdo pain, profuse sweating
- Shock and multiorgan system failure follow
- Care is supportive; mortality is very high

One pill to kill

Are there medications that might be predicted to be more dangerous based on their toxic dose and available forms?

Are there medications that could potentially be lethal with the ingestion of one tablet or 5 mL?

The following review will not address idiosyncratic reactions or drug interactions

Cyclic antidepressants
Cyclic antidepressants
- imipramine, desipramine, clomipramine, trimipramine
- amitriptyline, nortriptyline, protriptyline
- maprotiline
- doxepin

Cyclic antidepressants
- Quinidine-like (Type Ia) effects: fast sodium channel blockade and potassium channel blockade lead to arrhythmias
- alpha blockade: hypotension
- antimuscarinic: mydriasis, tachycardia, warm dry flushed skin, quiet abdomen
- CNS effects: seizures and coma

Cyclic antidepressants
- different compounds have very similar toxic doses
- ingestions over 5 mg/kg are referred to ED
- > 10 mg/kg considered potentially serious
- > 15 mg/kg associated with fatalities

Cyclic antidepressants
- largest dose unit is 150 mg
- represents 15 mg/kg in a 10 mg toddler

Oil of wintergreen
- used as a rub, or in minute quantities as a flavoring agent
- contains 98-99% methylsalicylate
- sports creams may contain smaller concentrations of methylsalicylate
Methylsalicylate

- Like aspirin (acetylsalicylate), it is metabolized to salicylate.
- Like aspirin, toxicity occurs primarily after oral ingestion.
- Deaths from excessive topical use have been described.

Salicylates

- Cause an early primary respiratory alkalosis.
- Are weak acids → metabolic acidosis.
- Interfere with Krebs cycle.
- Dyscouple oxidative phosphorylation → metabolic acidosis, heat generation.
- Increase FA metabolism → ketoacidosis.

Salicylates

- Early presenters have respiratory alkalosis.
- Next stage is mixed respiratory alk/metabolic acidosis.
- CNS depression eventually leads to combined respiratory and metabolic acidosis.

Salicylates

- Toxic dose is > 100 mg/kg.
- Potentially lethal dose is > 500 mg/kg.

One teaspoon (5 mL) of Oil of Wintergreen contains the equivalent of 7 grams of aspirin!
Morphine

- widely prescribed opiate
- found in a variety of oral and parenteral forms
- major concern is respiratory depression

1 mg/kg parenterally in an opiate-naive patient can cause apnea. Allowing for a 6:1 oral:parenteral ratio, this equates to 6 mg/kg oral morphine.

Morphine controlled-release formulations are available in doses up to 200 mg. When a controlled release tablet is chewed, it becomes immediate-release.

In a 10 kg toddler, this represents a dose of 20 mg/kg of morphine. Even a 100 mg tablet could kill a small child.

Other opioids

- Opana ER (oxymorphone) 40 mg tablet equivalent to 120 mg morphine
- Oxycontin 80 mg and 160 mg (twice as potent as oral morphine)

Sulfonylureas

- Act on pancreatic β cells to stimulate insulin release
- Usual feedback mechanisms are overcome
- Insulin secretion continues in the face of hypoglycemia
- Newer agents last 18 - 24 hours
- Manifestations of hypoglycemia are well known
**Sulfonylureas**

- examples include glyburide, glipizide and glimepride

**Sulfonylureas**

- 2.5 mg has produced marked, prolonged hypoglycemia in toddlers
- largest dose size is 5 mg
- ingestion unlikely to be fatal however unless child has a prolonged fast following intoxication

**Calcium channel blockers**

- indications:
  - hypertension
  - dysrhythmias
  - CHF
  - cardiomyopathy

**Calcium channel blockers**

- examples:
  - verapamil
  - diltiazem
  - dihydropyridines
    - nifedipine
    - amlodipine

**Calcium channel blockers**

- bind to calcium channels in the heart, vascular smooth muscle, and pancreas
- result in vasodilation, negative chronotropy, negative inotropy, impaired insulin release
- overdose leads to shock
Verapamil
- typical maximum pediatric dose is 2 mg/kg (8 mg/kg/day)
- adult deaths reported with approximately 1 gram
- largest available dose = 360 mg
  - 36 mg/kg in a 10 kg toddler

Diltiazem
- typical maximum daily dose is 3.5 mg/kg
- doses up to 6 mg/kg/day have been used investigationally
- deaths in adults reported with ingested doses between 1 and 3 grams (15 - 40 mg/kg)
- largest available dose is 420 mg
  - 42 mg/kg in a 10 kg toddler!

Dihydropyridines
- considerably less toxic than the other calcium channel antagonists
- based on currently available dosage forms, a minimum of 2-3 tablets would be required to deliver a potentially lethal dose based on case reports

Chloroquine
- antimicrobial drug used for chemoprophylaxis and treatment of malaria
- also used in the treatment of rheumatologic diseases
- Has Type Ia-like antidysrhythmic activity

Chloroquine
- CNS Effects - depressed CNS, blurred vision, excitation with seizures
- CVS effects - decreased contractility, prolonged QT, widened QRS, VT, VF, hypotension
- metabolic - severe hypokalemia from redistribution
- Rapid onset - death within 12 hours

Chloroquine
- 2 case reports in the literature document death in toddlers ingesting 300 mg
- currently available adult tablet is 500 mg chloroquine phosphate (equivalent to 300 mg chloroquine base)
Podophyllin
- naturally-occurring substance comes from May Apple
- used topically for treatment of venereal warts
- derivatives include etoposide and teniposide

Podophyllin
- mechanism of action similar to colchicine
- causes mitotic arrest in metaphase

Podophyllin
- earliest sign is vomiting following by coma and peripheral neuropathy
- fever and leukocytosis are common
- progress to multi-organ system failure
- survivors manifest bone marrow depression

Podophyllin
- 350 mg is the minimum fatal dose reported in the literature
- available as a 25% solution for use in a physician office
- 350 mg represents 1.4 mL of the preparation

So what about iron?
- iron frequently cited in textbooks as a leading cause of childhood death from poisoning
- a vanishingly-rare cause of death in the past decade
- no deaths in children from iron poisoning in at least 15 years in Western NY

Iron
- children’s multivitamins contain at most 18 mg of elemental iron
- adult iron tablets and prenatal vitamins contain approximately 60 mg
Iron

- < 10 mg/kg unlikely to produce significant symptoms
- > 20 mg/kg likely to produce significant GI toxicity
- > 60 mg/kg required for systemic toxicity
- Lethal range is >> 100 mg/kg

Using 60 mg/kg as the cutoff, a 10 kg toddler would have to consume at least 10 adult iron tablets, or at least 33 children’s multivitamins

Summary

- All medications should be considered to be potentially harmful to children
- A subset of medications have a high risk of causing severe harm
- Pediatricians should continue to incorporate drug safety/poisoning prevention as part of their routine