Single dose killers in Pediatrics

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Pediatric Poisoning

• Peak incidence
  – Toddlers age 1 to 3 years

• Younger children are more willing to taste dangerous substances than older children and perform hand-mouth behaviors nearly 10 times an hour

  » Rozin P, et al. the child conception of food: differentiation of categories of rejected substances in the 16 months to 5 years age range. Appetite 1986;7:141-51

Most exposure are nontoxic because the intent is exploration rather than self-harm
“One-Pill” Rule

- A single adult therapeutic dose would not be expected to produce significant toxicity in a child.
  
Nine common ingested substances known to have the potential for significant morbidity at single-pill or spoonful-sized doses.
Exception’s to the Rule

1. Calcium channel antagonists
2. Camphor
3. Clonidine and imidazolines
4. Cyclic antidepressants
5. Opioids and opiates
6. Lomotil
7. Salicylates
8. Sulfonylureas
9. Toxic alcohols
### Medications potentially fatal to 10-kg toddler

<table>
<thead>
<tr>
<th>Medication</th>
<th>Minimal fatal dose</th>
<th>Amount</th>
<th>Medication</th>
<th>Minimal fatal dose</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camphor</td>
<td>100 mpk</td>
<td>1 tsp</td>
<td>Thioridazine</td>
<td>15 mpk</td>
<td>1 tab (200 mg)</td>
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<tr>
<td>Chloroquine &amp; hydroxy</td>
<td>20 mpk</td>
<td>1 tab (500 mg)</td>
<td>DPH &amp; dimenhydrinate</td>
<td>25 mpk</td>
<td>3.5 tab</td>
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<tr>
<td>Clonidine</td>
<td>0.1 mg</td>
<td>1 tab</td>
<td>Iron</td>
<td>60 mpk</td>
<td>10 tab</td>
</tr>
<tr>
<td>Imipramine</td>
<td>20 mpk</td>
<td>1 tab (150 mg)</td>
<td>MAOI</td>
<td>25 mpk</td>
<td>15 tab</td>
</tr>
<tr>
<td>Quinine</td>
<td>80 mpk</td>
<td>1 tab (650 mg)</td>
<td>Diphenoxylate</td>
<td>30 mpk</td>
<td>15 tab</td>
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<tr>
<td>Methylsalicylate</td>
<td>200 mpk</td>
<td>1 tsp</td>
<td>Orphenadrine</td>
<td>25 mpk</td>
<td>5 tab</td>
</tr>
<tr>
<td>Thiophylline</td>
<td>8.4 mpk</td>
<td>1 tab 300</td>
<td></td>
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</tbody>
</table>
Exception's to the Rule

1. Calcium channel antagonists
2. Camphor
3. Clonidine and imidazolines
4. Cyclic antidepressants
5. Opioids and opiates
6. Lomotil
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9. Toxic alcohols
Calcium channel antagonists

- all of which act to slow the influx of calcium through L-type, voltage-sensitive channels present in a wide variety of tissue cell types, including cardiac myocytes, vascular smooth muscle, and sinoatrial and atrioventricular nodes.
- CCAs are classified into three groups:
  - The phenylalkylamines (verapamil)
  - The benzothiapirines (diltiazem), which in therapeutic doses act predominantly on cardiac tissue,
  - The dihydropyridines (eg, nifedipine), which act predominately on vascular smooth muscle.
CCA’s Clinical manifestations

- Disturbances of the cardiovascular system are the hallmark of CCA overdose.
- Classic manifestations include:
  - Hypotension
  - Bradycardia,
  - although reflex tachycardia may be seen with the dihydropyridines
- Cardiac conduction system abnormalities include second-degree and third-degree heart block.
- Extreme negative inotropy may manifest as cardiogenic shock or cardiac arrest.
CCA’s Clinical manifestations

- Although clinical effects often appear within 1 to 5 hours after ingestion of immediate-release preparations.
- Delayed in cases of sustained-release preparation ingestion.
- Hypotension may last > 24 hours.
- Cardiac conduction defects reported to last 7 days.
CCA’s Clinical manifestations

- The presence of CNS manifestations, such as
  - drowsiness,
  - confusion,
  - seizures,
- in the absence of hemodynamic collapse should suggest the presence of coingestants.
Early assessment of hemodynamic status is paramount in all cases of reported CCA ingestion.

Cardiac monitoring should be instituted, and access to transcutaneous or transvenous pacing should be available.

Activated charcoal administration should be considered for patients presenting within 1 hour of ingestion.

Whole-bowel irrigation with polyethylene glycol has been recommended after ingestion of sustained-release preparations.
<table>
<thead>
<tr>
<th>Antidote</th>
<th>Indication/toxin</th>
<th>Pediatric dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>Clonidine and imidazolines</td>
<td>0.02 mg/kg IV/IO/ET q2–5 min</td>
</tr>
<tr>
<td></td>
<td>Calcium channel antagonists</td>
<td>Minimum dose: 0.1 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximum dose (child): 0.5 mg</td>
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<tr>
<td></td>
<td></td>
<td>Maximum dose (adolescent): 1 mg</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>Calcium channel antagonists</td>
<td>10–25 mg/kg 10% Calcium chloride IV q10–20 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximum dose: 1 g</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>Calcium channel antagonists</td>
<td>30–75 mg/kg 10% Calcium gluconate IV q10–20 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximum dose: 1 g</td>
</tr>
<tr>
<td>Dextrose</td>
<td>Hypoglycemia</td>
<td>Neonates: 2 mL/kg D_{10} W, repeat as needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children: 2-4 mL/kg D_{25} W, repeat as needed</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Seizures</td>
<td>0.2–0.5 mg/kg IV/ET/PR q2–5 min</td>
</tr>
<tr>
<td></td>
<td>Agitation</td>
<td>Maximum dose: 10 mg</td>
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<tr>
<td></td>
<td></td>
<td>Monitor airway status</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Methanol</td>
<td>1 mL/kg 10% ethanol IV over 1 h, then 0.15 mL/kg/h</td>
</tr>
<tr>
<td></td>
<td>Ethylene glycol</td>
<td>Titrate to blood ethanol level 100–150 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor glucose, airway status</td>
</tr>
<tr>
<td>Fomepizole (4-MP)</td>
<td>Methanol</td>
<td>Initial dose: 15 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Ethylene glycol</td>
<td>Subsequent 4 doses: 10 mg/kg</td>
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<tr>
<td></td>
<td></td>
<td>Subsequent doses: 15 mg/kg</td>
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<tr>
<td></td>
<td></td>
<td>Administer q12 h unless on hemodialysis, in which case dosing frequency is</td>
</tr>
<tr>
<td></td>
<td></td>
<td>increased to q4 h</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Calcium channel antagonists</td>
<td>50 µg/kg IV initial bolus, double and triple</td>
</tr>
<tr>
<td></td>
<td></td>
<td>subsequent bolus if no effect</td>
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<tr>
<td></td>
<td></td>
<td>Start infusion at response dose per hour</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resuspend in normal saline rather than supplied diluent</td>
</tr>
<tr>
<td>Glucose-insulin</td>
<td>Calcium channel antagonists</td>
<td>0.5 U/kg regular insulin IV bolus, followed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>by 0.1–1.0 U/kg/h, titrate to hemodynamic effect</td>
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<tr>
<td></td>
<td></td>
<td>D_{10} W infusion, titrate to euglycemia</td>
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<td></td>
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<td>Monitor potassium</td>
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</table>
Camphor
Camphor

- Over-the-counter topical liniments, including Vick’s VapoRub, Ben-Gay, Absorbine, Tiger Balm, and Save the Baby.
- An aromatic terpene ketone derived from plants.
- A distinct odor and pungent taste.
- Is used topically as an analgesic, antipruritic, and antitussive agent, often in conjunction with other potentially toxic substances, including methyl salicylates (eg, Ben-Gay).
Camphor - Clinical manifestations

- Initial symptoms of toxic exposure include gastrointestinal distress and a generalized sensation of warmth.
- Toxic effects occur within 10 to 20 minutes of ingestion.
- Symptoms may progress rapidly to an initial phase of CNS hyperactivity, characterized by excitement, restlessness, delirium, and seizures, followed by a phase of CNS depression, manifesting as coma and respiratory depression.
- Death from camphor ingestion results from respiratory depression or status epilepticus.
Management

- No specific antidote for camphor toxicity exists, and treatment is largely supportive, involving airway management and seizure control.
- Asymptomatic patients should be observed for 6 to 8 hours.
- Camphor-induced seizures should be managed initially with benzodiazepines.
- Persistent seizures may be managed with barbiturates. Hemoperfusion has been attempted, but not shown to alter clinical course and outcome.
Clonidine and the imidazolines
Clonidine and the imidazolines

- Initially developed as a topical nasal decongestant, Clonidine later was marketed as a centrally acting antihypertensive and more recently in the management of attention-deficit hyperactivity disorder.

- The imidazolines are central a2-adrenergic agonists, resulting in decreased central adrenergic tone.
Dosage

- Adult therapeutic doses of Clonidine range from 0.2 to 2.4 mg/d delivered orally or transdermally.
- Currently available oral preparations contain 0.1 mg, 0.2 mg, or 0.3 mg of Clonidine.
In overdose, patients may appear to have an Opioids toxidrome, with decreased level of consciousness, miosis, bradycardia, hypotension, respiratory depression, and hypotonia.

CNS depression may range from drowsiness to coma. Although not structurally related to Opioids, the $\alpha_2$-adrenergic receptor targeted by Clonidine and the $\mu$ receptor targeted by Opioids show significant functional overlap.
Clonidine—Clinical manifestations

- Peripheral \( \alpha_1 \)-adrenergic stimulation may result in short-lived hypertensive episodes before the onset of hypotension and bradycardia.
- Respiratory depression and intermittent apnea are especially common in children.
- Children also seem to be most at risk of developing bradycardia.
- Toxic effects typically occur within 30 to 90 minutes of ingestion, and they may persist for 1 to 3 days.
A retrospective study by Nichols et al reviewed the cases of 80 children admitted for clonidine ingestion between 1987 and 1992.

- Average time to onset of symptoms was 35 minutes.
- The most common presenting sign or symptom was reduced level of consciousness (96%).
- Six children required intubation, but no deaths occurred.
- In this study, most of the clonidine (54%) belonged to the patients’ grandmothers.

• Toxic effects have been produced in children with 0.1 mg of clonidine

Management

- Supportive guided by signs and symptoms of exposure.
- All patients should undergo continuous cardiac monitoring, and 12-lead ECG performed as required.
- Continuous assessment of the airway are crucial.
- Symptomatic patients may respond variably to naloxone.
- The typical naloxone dose is 0.1 mg/kg, up to a total of 10 mg.
  - In a retrospective review of pediatric clonidine exposures, 39 of 80 patients (49%) received naloxone, and a positive response, defined by increased level of consciousness or improved vital sign parameters, occurred in only 4 patients (16%).
- Symptomatic bradycardia treated initially with atropine.
- Hypotension unresponsive to fluid resuscitation or complicated by persistent bradycardia may require dopamine.
Cyclic antidepressants
All of these compounds are:

- Inhibitors of norepinephrine reuptake.
- Inhibition of serotonin reuptake.
- Inhibition of histamine H1 receptors.
- Inhibition of Dopamine D2 receptors.
- Inhibition of Muscarinic cholinergic M1 receptors.
- Inhibition of Sympathetic α1 receptors.

Blockade of fast voltage-gated sodium channels in cardiac myocytes results in the typical finding of QRS interval prolongation noted on ECGs of TCA-intoxicated patients.
Cyclic antidepressants—Clinical manifestations

- CNS
  - CNS depression
  - Seizures – TCA’s with dopamine and norepinephrine reuptake inhibition.
- Cardiovascular system
  - Conduction abnormalities
  - Dysrhythmias
  - Hypotension.
- Anticholinergic toxidrome
  - Mydriasis
  - Flushing
  - dry mucous membranes
  - Tachycardia
  - Hyperthermia
  - CNS findings, such as delirium, hallucinations, seizures and coma.
- Signs of significant toxicity can be expected to present within 6 hours of ingestion.

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• Mortality is secondary to cardiac and CNS toxicity.
• Hypotension may be due to arrhythmia-induced cardiogenic shock and reduced peripheral vascular resistance.
• Seizures are self-limited and status epilepticus has been reported.
• Ingestions of 10 to 20 mg/kg of most TCAs is likely to result in significant CNS and cardiovascular symptoms.
• Ingestions of 250 mg of imipramine and amoxapine have resulted in fatalities in children.
Management

- Aggressive supportive care, including airway management.
- Rapid deterioration in mental status should be anticipated, as should abrupt onset of seizure activity.
- QRS complex duration greater than 100 ms has been shown to be a marker for toxicity, with an increased incidence of serious toxicity, including coma, hypotension, and need for intubation.
- 50% of patients with a QRS complex duration $> 160$ ms developed ventricular dysrhythmias.
Management

- Serum drug levels may be used to confirm exposure but otherwise have little value in acute intoxication.
- Asymptomatic patients may be discharged after a 6-hour observation period.
Management

- Sodium bicarbonate is the mainstay of treatment for reversing the cardiotoxic effects of TCA ingestion.
- An initial bolus of sodium bicarbonate, 1 to 2 mEq/kg, to patients with evidence of cyclic antidepressant toxicity and a QRS duration greater than 100 ms.
- Seizures may be treated with benzodiazepines as a first-line agent.
- Phenytoin is not recommended because some animal studies have indicated that it may potentiate ventricular dysrhythmias.
Opioids and opiates
The most common ingestions were hydrocodone in combination with acetaminophen, followed by codeine with acetaminophen, propoxyphene with acetaminophen, and oxycodone with acetaminophen.

Actions of opiates are mediated through three specific receptor classes, μ, κ, and δ.

Activation of the μ receptor is responsible for supraspinal analgesia and the respiratory depression noted with excess Opioids administration.
Clinical manifestations

- Classically manifests as a toxidrome of CNS depression, respiratory depression, and miosis.
- Infants and children are more susceptible to the toxic effects than adults.
- Most deaths are secondary to respiratory depression and subsequent hypoxia.
- 50% of children exposed to > 1 mg/kg of codeine developed evidence of toxicity, often within 1 hour of ingestion.
- In infants, 2.5 mg of hydrocodone has been lethal.
Management

- The time to peak effect for most oral preparations is less than 1 hour, and duration of action is 3 to 6 hours.
- Immediate release preparations should be observed for at least 6 hours.
- Whole-bowel irrigation may be considered.
- Naloxone should be instituted whenever significant signs or symptoms of opioid intoxication are present.
Management

- Naloxone is a pure competitive antagonist that inhibits the binding of opiates and opioids at receptor sites.
- It rapidly reverses induced respiratory and CNS depression.
- Onset of action is < 2 minutes, its duration of action is 20 to 90 minutes, and its elimination half-life is 60 to 90 minutes in adults, less than that of many opiates and opioids.
- Repeat dosing or continuous infusions are often necessary.
- For non–life-threatening cases, the recommended initial dose for naloxone in children younger than 5 years old is 0.01 mg/kg intravenously.
- Life-threatening cases in these children should be treated initially with 0.1 mg/kg up to 2 mg intravenously, titrated to effect every 3 to 5 minutes to a maximum dose of 10 mg.
- Children 5 years old and older should receive 0.4 mg intravenously.
- Other causes of intoxication should be investigated if complete reversal of respiratory and CNS depression is not seen after 10 mg.
Lomotil

- An antidiarrheal agent containing 2.5 mg of the opioid diphenoxylate and 0.025 mg of the antimuscarinic agent atropine.
- Catastrophic outcomes have been reported after ingestion of this agent by children.
- Absorbed rapidly by GI, although absorption may be delayed in overdose secondary to inhibitory effects on smooth muscle motility.
- Diphenoxylate subsequently is metabolized to difenoxin, which is five times more active than the parent compound and has an elimination half-life of 12 to 14 hours.
Clinical manifestations

• In one study of pediatric ingestions, only 4 of 36 patients developed early anticholinergic symptoms, whereas 15 of 36 patients developed evidence of opioid toxicity only

• Little correlation exists between reported ingested dose and clinical outcome.

• Toxicity in the pediatric population has been reported after ingestion of one-half tablet
Management

- Similar to that of other opioids.
- Initial symptoms, including potentially fatal coma and respiratory depression, may be delayed.
- Symptoms have recurred 24 hours after initial resolution of opioid symptoms.
- The current recommendation is that children with Lomotil exposures should be admitted to a monitored environment for no less than 24 hours observation.
Salicylates
Salicylates

- Numerous over-the-counter products, including aspirin (acetylsalicylic acid), oil of wintergreen (methyl salicylate), and Pepto-Bismol (bismuth subsalicylate).
- The minimal potentially toxic ingested dose in children is 150 mg/kg.
- One teaspoon of 98% methyl salicylate contains 7000 mg of salicylate, the equivalent of nearly 90 baby aspirin, and more than four times the potentially toxic dose for a 10-kg child.
- Signs and symptoms of toxicity may occur at levels > 30 mg/dL.
- Levels > 100 mg/dL are potentially life-threatening.
- The half-life of salicylates increases from 2 to 4 hours at therapeutic levels to 15 to 29 hours at toxic doses in children.
Clinical manifestations

- Signs and symptoms of salicylate intoxication (referred to as salicylism) include nausea; vomiting; diaphoresis; tinnitus; and nonspecific neurologic findings including agitation, delirium, hallucinations, and lethargy.
- Salicylates directly stimulate the brainstem respiratory center, resulting in hyperventilation and hyperpnea.
- Severe intoxications may cause noncardiogenic pulmonary edema, cerebral edema, coma, and death.
- Hyperthermia, reflects severe intoxication and is often a preterminal finding.
- In children, the respiratory alkalosis may be transient, such that the predominant acid-base derangement is a metabolic acidosis.
- The presence of a respiratory acidosis is a grave finding and suggests the presence of pulmonary edema, respiratory muscle fatigue from prolonged hyperventilation, or a mixed ingestion.
Clinical manifestations

- Additional laboratory findings include hyperglycemia or hypoglycemia and ketonuria, reflecting impaired glucose metabolism.
- Oil of wintergreen poses a particular hazard to children because of its pleasant aroma and its high salicylate content (typically contains 98–100% methyl salicylate).
- A 21-month-old girl developed significant poisoning, with a peak serum salicylate concentration of 81 mg/dL, after ingesting 4 mL of oil of wintergreen.
- Less than one teaspoon of oil of wintergreen has been fatal in a child.
Management

- Rapid determination of serum salicylate concentrations.
- Although the Done nomogram has been used in salicylate toxicity, caution should be exercised because of its limited applicability. It indicates severity of toxicity based on a 6-hour level of non-enteric-coated aspirin rather than need for antidotal therapy.
- Individuals have died in less than 6 hours after methyl salicylate ingestion.
- Serum salicylate concentrations should be reassessed every 2 hours until the patient is clinically improving and has a nontoxic serum salicylate level (<30 mg/dL) with normal or alkalemic blood pH.
- A declining serum salicylate level in the setting of acidemia may reflect increased CNS distribution rather than increased clearance and would be expected to mirror a deteriorating clinical picture.
Management

- The current American Academy of Clinical Toxicology/European Association of Poison Control Centers and Toxicologists position statement has concluded that insufficient evidence exists to recommend multiple-dose activated charcoal.
- Whole-bowel irrigation also has been advocated, especially after ingestion of enteric-coated formulations, although outcome-based evidence is lacking.
In addition to aggressive supportive care and appropriate gastric decontamination, enhanced elimination through either urinary alkalinization (“ion trapping”) or hemodialysis.

An initial bolus of 1 to 2 mEq/kg is followed by a continuous sodium bicarbonate infusion at a rate equivalent to 1.5 to 2 times the calculated maintenance fluid requirements.

Hemodialysis traditionally has been the method of choice because it can correct electrolyte and acid-base abnormalities rapidly in addition to increasing drug clearance.
Hemodialysis in salicylate toxicity

- Pulmonary edema
- Altered mental status/cerebral edema
- Renal failure
- Lack of response to standard therapy
- Concomitant life-threatening acid-base or electrolyte abnormalities
- Salicylate level: 100 mg/dL in acute intoxication; 60 mg/dL in chronic intoxication
Sulfonylureas
Sulfonylureas

- The oral hypoglycemic agents, are the mainstay of pharmacologic treatment for type 2 diabetes mellitus.
- The sulfonylureas modulate a reduction in serum glucose concentration by direct inhibition of an adenosine triphosphate–dependent potassium channel located in the membrane of the pancreatic beta cells.
- Sulfonylureas also potentiate the action of insulin on target tissues.
Sulfonylureas are classified as first-generation, second-generation, and third-generation agents with later generations generally exhibiting greater binding specificity, shorter times to peak effect and lower risk for hypoglycemia at therapeutic doses.

Among the second-generation and third-generation agents, glyburide and long-acting glipizide associated with the greatest risk for hypoglycemia at therapeutic doses.
Clinical manifestations

- Clinically, the principal manifestation of sulfonylurea intoxication is **hypoglycemia**.
- Clinical findings of hypoglycemia may include lethargy, confusion, headache, irritability, and seizure.
- Secondary sequelae of hypoglycemia include permanent neurologic impairment and death.
- A retrospective pediatric case series reported three cases of hypoglycemia after ingestion of a single chlorpropamide (a first-generation sulfonylurea) 250-mg tablet, a glipizide 5-mg tablet, and a glyburide 2.5-mg tablet.


- In a prospective study of 185 cases of reported sulfonylurea exposure in children, 30% developed hypoglycemia, 5 of whom ingested no more than a single tablet of glipizide or glyburide [153].

Management

• Rapid detection and treatment of hypoglycemia.
• Activated charcoal for patients presenting within 1 hour of ingestion.
• For extended-release preparations, whole-bowel irrigation may be helpful beyond 1 hour.
• The current recommendation is that all children suspected or known to have ingested sulfonylurea be admitted for a minimal 24-hour observation, even if not initially hypoglycemic.

Management

- Asymptomatic patients may be allowed to eat, but should not receive supplemental intravenous dextrose for fear of masking hypoglycemia.
- Asymptomatic patients initially should have serum glucose measured at least hourly.
- Patients with signs or symptoms of hypoglycemia should receive a bolus of intravenous dextrose.
- This bolus may be followed by continuous infusion of a 5% to 20% dextrose solution to maintain serum glucose levels greater than 100 mg/dL, the rate and duration of which should be dictated by clinical severity and the plasma half-life of the ingested agent.
Management

• In the 1990s, investigations were conducted on the use of diazoxide and octreotide for the treatment of sulfonylurea-induced hypoglycemia.

• Diazoxide acts to inhibit release of insulin, mitigating toxicity
• Its use is limited, however, by its potent vasodilator properties, with potential for hypotension.

• Octreotide, a somatostatin analogue, inhibits secretion of several hormones, including glucagon and insulin
Management

- A retrospective review of nine patients treated with dextrose and octreotide found that the total number of ampules of 50% dextrose administered before and after administration of octreotide declined from 2.9 to 0.2, and the number of hypoglycemic events recorded declined from 3.2 to 0.2

- A prospective study examined eight normal subjects given glipizide, 1.45 mg/kg, to induce hypoglycemia (<50 mg/dL) on three separate occasions, treated with octreotide, diazoxide, or dextrose alone. Dextrose was given as needed in all three cases to maintain euglycemia.

- The study found that octreotide eliminated the need for dextrose rescue in four of the eight subjects and reduced the supplemental glucose requirements of the remaining four with no adverse outcomes.
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- **Stable?**
  - **Yes**
    - **Less than one hour?**
      - **Yes**
        - Activated charcoal
      - **No**
        - Sustained release?
          - **No**
            - Hypoglycemia?
              - **No**
                - Oral supplements
                  - Serial glucose measurements
                  - Observe
              - **Yes**
                - Dextrose IV
                  - Persistent hypoglycemia?
                    - **Yes**
                      - Octreotide
                    - **No**
                      - PALS/ACLS guidelines
          - **Yes**
            - Consider activated charcoal and/or whole bowel irrigation

- **No**
It's Time I think Am Late
Toxic alcohols
The toxic alcohols include methanol, ethylene glycol, and isopropanol.

All are potentially unsuspected killers, in part because they are readily available household items, small amounts are sufficient to cause significant injury.

The parent alcohols are responsible for early signs of toxicity, primarily CNS depression.

Each alcohol subsequently is metabolized through a sequential two-step process, involving the enzymes alcohol dehydrogenase and aldehyde dehydrogenase.

Isopropanol, the most common ingredient in household rubbing alcohols, accounted for more than 90% of these ingestions.

Serious adverse outcomes with isopropanol ingestions are rare.
Toxic alcohols

- Methanol is found in numerous products, including windshield washer fluid, and carburetor cleaners, and concentrations may be 95%.
- Ingestion of 4 mL of 95% methanol by a 10-kg toddler may result in a serum methanol concentration of 50 mg/dL.
- Ethylene glycol is a common component of antifreeze, used in some fire extinguishers, inks, and adhesives.
- Ingestion of 2.9 mL of 95% ethylene glycol by a 10-kg toddler may result in a serum concentration of 50 mg/dL.
- Peak levels after ingestion are reached within 1 to 4 hours.
Clinical manifestations

- After methanol ingestion, development of symptoms may be delayed 8 to 24 hours.
- Methanol is metabolized by alcohol dehydrogenase to formaldehyde, which is metabolized rapidly by aldehyde dehydrogenase to its terminal and most toxic product, *formic acid*.
- Symptoms include CNS depression, ranging from mild inebriation to coma.
- Hyperpnea may reflect the development of an underlying metabolic acidosis.
- Visual symptoms include blurred, double, or hazy vision, described as a “snowstorm.” Pupils may be dilated, with constricted visual fields.
- Funduscopic examination may reveal an edematous retina and hyperemic optic disks.
- Formic acid is responsible for the anion gap metabolic acidosis and the retinal toxicity associated with methanol ingestion.
Clinical manifestations

- Ethylene glycol manifests a four-phase toxicity
  - **The first stage**, attributable to the inebriating effects of the parent alcohol, often appears within 4 to 8 hours of ingestion.
  - **The second phase** is primarily metabolic and reflects metabolism of the parent alcohol to toxic metabolites, including glycolic acid, glyoxylic acid, and oxalic acid. During this phase, the osmolar gap decreases as osmotically active parent alcohol is metabolized to organic acids, with development of profound anion gap metabolic acidosis.
    - Glycolic acid seems to be most responsible for the profound metabolic acidosis
  - **The third phase** reflects the renal toxicity of the excreted calcium oxalate crystals, with acute tubular necrosis occurring 12 to 48 hours after ingestion
    - Profound hypocalcemia with ECG changes and tetany also may occur during this phase
  - **A fourth phase**, manifesting as cranial nerve deficits, including ophthalmoplegia, pupillary deficits, facial weakness, hearing loss, dysarthria, and dysphagia, may occur and persist weeks to months
Management

- Initial management of a potentially toxic alcohol exposure consists of supportive care and rapid determination of toxic alcohol levels.

- Presence of an elevated osmol gap has been used as evidence for the presence of an uncounted osmotically active toxic alcohol.

- A normal osmol gap should not be used to disprove the presence of a significant toxic alcohol ingestion.
  - A “normal” osmol gap of 10 may hide a serum methanol concentration of 32 mg/dL or a serum ethylene glycol concentration of 62 mg/dL.
• Additional indirect laboratory findings include the development of an anion gap metabolic acidosis in the case of methanol and ethylene glycol toxicity and presence of urinary dihydrate calcium oxalate crystals in ethylene glycol poisoning

• Fluorescein is added to some brands of antifreeze to aid in the identification of radiator leaks and can cause urine to fluoresce after ethylene glycol ingestion

• In one study, three physicians examining urine from normal children considered at least 75% of the specimens fluorescent.

Management

- In addition to supportive measures
- Inhibition of the rate-limiting enzyme, alcohol dehydrogenase, has been employed to mitigate development of toxicity.
- Ethanol is a preferential substrate for the enzyme.
- At serum concentrations of 100 to 150 mg/dL, ethanol effectively inhibits metabolism of the toxic alcohol, which is eliminated unmetabolized by the body.
- The potential for ethanol-induced airway compromise and hypoglycemia often mandates admission to an intensive care unit.
Management

• Fomepizole (4-methylpyrazole) has been approved as a competitive inhibitor of alcohol dehydrogenase in cases of methanol and ethylene glycol intoxication.
• Fomepizole has been found to be safe and effective for the treatment of suspected toxic alcohol ingestions.
• Although concerns exist regarding the expense of fomepizole, cost-benefit analysis comparing ethanol infusion versus fomepizole has shown an overall cost savings.
Management

- Before the development of fomepizole, ethylene glycol or methanol levels greater than 50 mg/dL had been recommended as absolute indications for hemodialysis.
- Many toxicologists advocated 25 mg/dL as the action level for hemodialysis.
- In a product containing a toxic alcohol concentration of 95%, ingestion of 4 mL of methanol or 2.9 mL of ethylene glycol by a 10-kg toddler might be expected to result in a serum level of 50 mg/dL.
- Additional indications for hemodialysis include significant metabolic acidosis, especially unresponsive to sodium bicarbonate, and impaired renal function.
- With the development of consistently effective alcohol dehydrogenase inhibition, elevated serum toxic alcohol concentration in the absence of acidosis or end-organ effects no longer may serve as an indication for hemodialysis.
Management

- Additional therapeutic interventions include the administration of sodium bicarbonate to correct acidosis, to prevent access of formic acid to the retina by ion trapping, and to increase the renal elimination of glycolic acid.
- Intravenous folate has been shown to accelerate the conversion of formic acid to carbon dioxide and water.
- Thiamine and pyridoxine have been used in cases of ethylene glycol toxicity to divert metabolism of glyoxallic acid away from the nephrotoxic oxalic acid and toward less toxic metabolites.
Summary

• Pediatric ingestions are unintentional events secondary to development of exploration behaviors and the tendency to place objects in the mouth.
• Ingested substances typically are nontoxic or ingested in such small quantities that toxicity would not be expected.
• As a result, it commonly is believed that ingestion of one or two tablets by a toddler is a benign act and not expected to produce any consequential toxicity.
Summary

- Some agents have the potential to produce profound toxicity and death, however, despite the ingestion of only one or two tablets or sips.
- Although proven antidotes are a valuable resource, their value is diminished if risk after ingestion is not adequately appreciated and assessed.
- Future directions toward prevention of toxic exposure through parental education and appropriate safety legislation is paramount.
Call in the Consultants!