

## Deadly Ingestions

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Pediatric patients comprise approximately 52% of the 2.4 million toxic-exposure calls to US Poison Centers [1]. Although most of the cases are minor, the ingestion of at least seven different types of substances can lead to severe toxicity or even death. The 2003 data from the American Association of Poison Control Centers reported 34 deaths in children under the age 6 years, or 3.2% of all fatalities [1]. This was the second highest number of reported deaths in this age group during the 20 years of data collection. The availability of potentially deadly drugs is increasing because of their widespread use in various traditional and newer uses for medical and psychiatric conditions. This availability only serves to increase the likelihood of pediatric encounters and subsequent ingestion. It is therefore important that the clinician be familiar with the presenting signs and symptoms of potentially toxic ingestions and be able to initiate therapeutic and life saving interventions. This article reviews some of the deadlier ingestions to which children may be exposed.

### Sulfonylureas

Toxic exposure to oral hypoglycemic drugs continues to increase at a steady rate. Data collected from the 2003 Toxic Exposure Surveillance System (TESS) indicate that well over 10,000 oral hypoglycemic exposures were reported to participating poison control centers. Sulfonylurea agents, considered to be the cornerstone in the treatment of type 2 diabetes, comprised 4019 of the reported

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Table 1  
Sulfonylureas

	Onset (h)	Duration of action (h)	Half-life (h)
First generation			
Chlorpropamide (Diabinese, 100, 250 mg)	1	24–72	36
Tolazamide (Tolinase, 100, 250, 500 mg)	≤1 (peak 4–6)	16–24	7
Acetohexamide (Dymelor, 250, 500 mg)	1–2	12–24	1.3–1.5 (active metabolite 2–6)
Tolbutamide (Orinase, 500 mg)	1	6–12	7 (4–25)
Second generation			
Glipizide (Glucotrol, 5,10 mg; Glucotrol XL, 5,10 mg)	0.5–3	Up to 24	2–6
Glyburide (Diabeta, Micronase, 1.25, 2.5, 5 mg; Glynase, 1.5, 3, 6 mg)	0.25–1	18–24	1.4–1.8 (metabolite 5–26)
Third generation			
Glimepiride (Amaryl, 1, 2, 4 mg)	1–2	16–30	12–24

*Data from* Buse JB, Polonsky KS, Burant CS. Type 2 diabetes mellitus. In: Larsen PR, Kronenberg HM, Melmed S, et al, editors. Williams textbook of endocrinology. 10th edition. Philadelphia: WB Saunders; 2003. p. 1427–68.

exposures, with greater than one third occurring in children less than 6 years of age [1].

Table 1 lists the generations of sulfonylureas. The second-generation sulfonylureas (glimepiride, glipizide, and glyburide) exert their action by binding to specific membrane receptors within pancreatic beta islet cells, ultimately causing the inhibition of ATP-dependent potassium channels. As intracellular potassium rises, the cellular membrane depolarizes, allowing for an increase in intracellular calcium from voltage-gated channels and a subsequent release of preformed insulin into the systemic circulation [2,3]. Sulfonylureas will concurrently suppress endogenous glycogenolysis, creating a further potential for symptomatic and life-threatening hypoglycemia [2,4].

Case reports indicate that one or two tablets of a sulfonylurea compound have the potential to cause permanent neurologic disability or death [5,6]. With an increased prevalence of type 2 diabetes transcending all community, cultural, racial, and gender boundaries, the acquisition of sulfonylurea agents represents a clear and present danger to all pediatric populations.

### *Clinical presentation*

Early in the evaluation of the ill or injured child, a thoughtful consideration of toxicologic causes is always appropriate. Sulfonylurea ingestion may present with a broad spectrum of symptoms, from asymptomatic to overt coma and imminent death. Loss of appetite, weakness, dizziness, lethargy, and seizure have all been associated with significant sulfonylurea ingestion [2,4,5,7]. Behavioral changes combined with a suspicion of possible ingestion from a parent, grandparent, friend, or care provider must always prompt a high index of suspicion and

careful evaluation. The clinician must always be acutely aware of sulfonylurea ingestion with the potential to present with late symptomatic hypoglycemia. This category includes but is by no means limited to commonly prescribed agents such as chlorpropamide, glyburide, and glucotrol XL [4,5,8].

### *Management*

The management of sulfonylurea ingestion stems largely from data collected and pooled from poison control centers, retrospective reviews, and case studies found within the adult and pediatric toxicology literature [4–10]. Serious pediatric ingestion even at low doses of sulfonylureas has been documented on numerous occasions, leading to the belief that as little as one tablet carries a serious potential for lethality. Considerable controversy exists over the exact time of observation regarding the asymptomatic child who is suspected of having taken an overdose. Based on the authors' experience, a full 24-hour observation period is advocated to allow safe disposition to home with planned follow-up. However, some experts advocate an earlier disposition if the serum glucose level remains above 60 mg/dL for 8 hours [5]. Any documented hypoglycemic episodes or neurologic deteriorations obviously warrant an extension of observation time [4,5,8–10]. During the observation time period, in the absence of documented hypoglycemia or mental status deterioration, oral supplements should be encouraged.

During the initial evaluation, bedside glucose testing and a rapid primary survey of the patient's airway, breathing, and circulation are crucial. A deterioration of the patient's mental status should signal the administration of a weight-based bolus of dextrose, D25, 2 to 4 mL/kg, in children 1 to 24 months of age and D50, 1 to 2 mL/kg in children greater than 24 months, because early intervention is likely to improve mental status quickly, along with any deficiencies encountered during the primary survey.

After the initial evaluation, resuscitation, and stabilization is performed, primary toxicology principals should be applied. Removal of the toxin from the patient may be facilitated partially with the use of activated charcoal, 1g/kg; however, benefits exceeding 1 hour after ingestion are questionable [11]. With the potential for an extended-release preparation to cause delayed hypoglycemia, whole-bowel irrigation has been advocated as an adjunct measure to clear ingested toxin from the patient [12]. However, this measure is considered by many authorities to be lacking in evidence and may pose a significant risk of aspiration [12,13].

Significant sulfonylurea ingestion has been shown in case reports to be refractory to intravenous (IV) boluses of dextrose. In these cases, it is important to consider an IV glucose infusion to maintain a blood glucose level above 60 mg/dL to optimize ample glucose reserves. It is important to remember that continuous glucose infusion may potentiate further insulin release, thereby resulting in breakthrough hypoglycemia episodes [4]. Careful blood glucose moni-

toring every 1 to 2 hours and frequent neurologic evaluations may indicate the administration of supplemental IV dextrose boluses.

Octreotide has been studied and used as an adjunct to the treatment for sulfonylurea-induced hypoglycemia [14–17] and is recommended currently for serious sulfonylurea toxicity or recalcitrant hypoglycemia [4,5,7,14–17]. Octreotide is a somatostatin analog capable of the direct inhibition of insulin secretion. Its value has been suggested through multiple case reviews and studies; however, evaluation within the pediatric population has been limited. One case report indicates the successful management in a 5-year-old child who presented with profound hypoglycemia and status epilepticus after a glipizide overdose. Treatment included benzodiazepines, dextrose infusion, and octreotide, resulting in seizure cessation, improvement of hypoglycemia, and rapid weaning of glucose infusion [17]. Octreotide should be considered in cases of symptomatic hypoglycemia or in cases of hypoglycemia refractory to initial IV infusions or boluses of dextrose. Published dosing recommendations include 4 to 5  $\mu\text{g}/\text{kg}/\text{d}$  subcutaneous octreotide given in divided doses every 6 hours to a maximum dose of 50  $\mu\text{g}$  every 6 hours [5].

Glucagon has been used for many years as a therapeutic modality for the treatment of induced hypoglycemia. Glucagon is an endogenous catabolic hormone produced and released from pancreatic alpha cells in the islets of Langerhans. It increases circulating glucose levels by stimulating hepatic glycogenolysis and glycogen breakdown and the induction of gluconeogenesis and ketone production within the liver. When oral glucose replacement is contraindicated and peripheral IV access has proven difficult, intramuscular (IM) administration of glucagon is a viable option [18]. In children, dosing recommendations include giving 0.025 to 0.1 mg/kg, intravenously, subcutaneously, or intramuscularly. The maximum amount per dose recommended is 1 mg. Repeat dosing intervals may proceed every 20 minutes as required. The risk of vomiting and aspiration must be carefully weighed before the administration because glucagon is well known for its emetic response. The clinician must keep in mind that glucagon does not inhibit sulfonylurea-induced insulin release and that hypoglycemia may ultimately persist. Glucagon should be considered as a temporary measure in the emergent treatment of sulfonylurea-induced hypoglycemia.

### **Calcium channel antagonists**

Calcium channel antagonists are used widely in the management of a variety of medical conditions, such as hypertension, angina pectoris, supraventricular dysrhythmias, subarachnoid hemorrhage, and migraine prophylaxis. There are currently ten calcium antagonists on the market in the United States (Table 2). The widespread use and availability of these drugs increase the potential for a child to have access and accidentally ingest one or several of the pills. In 2003, there were 9650 cases of calcium antagonist exposures reported to United States

Table 2  
Calcium channel antagonists

Class	Agent	Trade name
Dihydropyridines	Amlodipine	Norvasc
	Felodipine	Plendil
	Nicardipine	Cardene, Cardene SR
	Isradipine	Dynacirc, Dynacirc CR
	Nifedipine	Adalat, Adalat CC, Procardia, Procardia XL
	Nimodipine	Nimotop
	Nisoldipine	Sular
Phenylalkylamine	Verapamil	Calan, Isoptan, Verelan
Benzothiazepine	Diltiazem	Cardizem, Cartia XT, Taztia, Tiazac

poison centers, and approximately 23% of these involved children under the age of 6 years [1].

### *Clinical presentation*

Calcium antagonists block the entry of calcium through voltage-sensitive L-type cellular membrane calcium channels. In vascular tissue, this results in arterial smooth muscle relaxation and hypotension. In cardiac cells, these agents inhibit sinoatrial and atrioventricular nodal depolarization, depress contractility, and cause bradycardia. Insulin release from pancreatic islet cells is inhibited by calcium antagonists and consequently leads to hyperglycemia [19,20]. Lactic acidosis is a common finding and is likely caused by tissue hypoperfusion.

Children can become symptomatic with exposure to as few as one or two tablets, especially in the toddler-aged group [8,19–24]. The ingestion of a single tablet may possibly cause death [24]. The onset of symptoms usually occurs within 1 to 2 hours of ingestion but may be delayed for up to 24 hours with extended-release (extended release [XL], coated tablet with fast release core [CC], controlled release [CR], sustained release [SR]) preparations. A classic presentation of calcium antagonist overdose is bradycardia with hypotension. Other dysrhythmias that may occur include junctional escape rhythms, idioventricular rhythms, atrioventricular (AV) conduction abnormalities, and complete AV block [20]. With the ingestion of dihydropyridine (nifedipine and others), the child may present with hypotension and reflex tachycardia caused by a lack of significant sinoatrial node effect. Tachycardia may occur alone after nifedipine overdose [21]. Typically, conduction abnormalities are rare with dihydropyridine agents because of absent AV node blockade [20].

The child may present with symptoms that include unsteady gait or dizziness, obtundation, coma, and seizure activity [20,21,23] caused by cerebral hypoperfusion. Gastrointestinal symptoms may include nausea and vomiting secondary to diminished gastric motility. Bowel hypoperfusion may cause mesenteric ischemia [21]. Ileus and small bowel obstruction have also been described and may prolong drug absorption and make decontamination efforts challenging [5]. Metabolic features include hyperglycemia and lactic acidosis. Finally, pulmonary

edema has also been reported [12,13], resulting from poor myocardial function, but noncardiogenic pulmonary edema has been described as well [14,15].

### *Management*

All children who are suspected of having ingested calcium channel blockers of any amount should be evaluated in a health care facility and monitored in an ICU setting for signs of delayed toxicity. The caretakers should be questioned carefully whenever a child presents with depressed blood pressure or heart rate to determine whether anyone in the household is taking blood pressure or heart medicine.

Treatment of severe hypotension and bradycardia should begin with intravenous fluids, atropine, and calcium chloride. Additional pressor agents may be required, and choices include epinephrine, dopamine, and norepinephrine [25,26]. Atropine is notorious for being ineffective or at least inconsistently effective. More recently, the addition of insulin and glucose, known as hyperinsulinemia euglycemic (HIE) treatment, has gained acceptance as an early intervention in the treatment of toxin-induced shock states [26]. Although the ideal starting regimen for HIE has not been established, a continuous infusion of insulin, 0.5 to 1 unit per kilogram of body weight per hour, has been used to reverse cardiovascular collapse caused by calcium channel blocker overdose. Despite the high doses of insulin administered, some patients may not require supplemental glucose [26,27]. It should be remembered that potassium levels should be checked frequently (at least every hour at the initiation of treatment) and glucose should be monitored closely [28]. It has been suggested that HIE therapy may be considered as a first-line therapy in calcium channel blocker intoxication [25]. Before this therapy can be recommended as the first-line treatment, however, more research is needed.

Glucagon has been used as an adjunct therapy to improve inotropic, chronotropic, and dromotropic effects of calcium antagonist overdose. However, a review of animal models of calcium antagonist poisoning treated with glucagon indicates that glucagon does not improve survival [29]. To date, there are no controlled human clinical trials comparing the effectiveness of glucagon therapy in calcium antagonist overdose.

### **Toxic alcohols**

Toxic alcohols, such as ethanol, isopropanol, methanol, and ethylene glycol (EG), are available in a wide array of commercial and consumer products (Table 3). Ethanol is found in varying concentrations of alcoholic beverages for adults. Because they are ubiquitous substances, these alcohols represent a clear and present danger to the pediatric population. The consequences of even a small ingestion in children carry the potential for death and permanent disability. In 2003, the TESS database reported nearly 84,000 exposures to the alcohol and

Table 3  
Toxic alcohol sources

Alcohol	Sources
Ethylene glycol	Radiator antifreeze Brake fluid (hydraulic) Cellophane softening agent Condensers and heat exchangers De-icing solutions Paints, lacquers, detergents, cosmetics Foam stabilizer Solvent
Methanol	Windshield wiper fluid Industrial solvent Gasoline additives, coolants Fuel octane booster Sterno (picnic stoves, torches) Paints and varnishes Solvent for extraction (illicit methamphetamine labs) Contaminated home-brewed beverages Duplicating chemicals
Isopropanol	Rubbing alcohol (70%–91% concentration) Industrial solvents Paints and paint thinners Inks Hair tonics

automotive product categories [1]. Ethanol accounted for more than 5600 exposures in patients under the age of 6 years. Isopropanol accounted for approximately 25,000 of the toxic alcohol exposures [1].

Although the parent alcohols can be responsible for a variable degree of central nervous system (CNS) depression, life-threatening conditions are often the result of toxic products resulting from metabolic breakdown, as shown in Table 4 [30]. Alcohols uniformly display rapid absorption profiles from the

Table 4  
Toxic alcohols metabolism

Alcohol	Enzyme	Metabolite	Enzyme/cofactor	Metabolite
Isopropyl alcohol	Alcohol dehydrogenase	Acetone <sup>b</sup>		
Methanol	Alcohol dehydrogenase <sup>a</sup>	Formaldehyde	H <sub>2</sub> O	Methanediol
	Aldehyde dehydrogenase	Formate <sup>b</sup>		
Ethylene glycol	Alcohol dehydrogenase <sup>a</sup>	Glycoaldehyde	Aldehyde dehydrogenase	Glycolate
	LDH or glycolic acid oxidase <sup>c</sup>	Glyoxylate <sup>b</sup>	B6 Thiamine, Mg <sup>2+</sup>	→Glycine →α-hydroxy-β-ketoadipate →Oxalate <sup>b</sup>
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*Abbreviations:* B6, pyridoxine; LDH, lactate dehydrogenase.

<sup>a</sup> Rate-limiting step.

<sup>b</sup> Toxic metabolite.

<sup>c</sup> Second rate-limiting step.

gastrointestinal tract, often eliciting signs of intoxication within 30 minutes of ingestion [30]. The metabolism of volatile alcohols occurs through the action of alcohol dehydrogenase (ADH). Further breakdown is achieved through other enzyme systems and pathways and is unique to each specific alcohol. Interventions focus primarily on the competitive inhibition of alcohol dehydrogenase, the enzyme serving as the rate-limiting step in alcohol breakdown [31].

Knowledge of the pharmacokinetics and metabolism of the volatile alcohol group may assist in the recognition and diagnosis of ingestion. Alcohols are of low molecular weight and display osmotically active properties when in solution. These particles are typically absent in serum concentrations and are usually not included in clinical calculations of serum osmolality. The formula for calculating osmolality is  $2(\text{Na}) + (\text{glucose [mg/dL]}) \div 18 + (\text{blood urea nitrogen [BUN] [mmol/L]}) \div 2.8$ ; or, an alternative equation is  $1.86(\text{Na}) + (\text{BUN}) + (\text{glucose}) \div 0.93$ .

The difference between the laboratory measurement of osmolality and the calculated osmolality provides the osmolal gap, or  $\text{osmolal gap} = \text{osm measured} - \text{osm calculated}$ . A discrepancy of greater than 10 to 15 mosm/kg H<sub>2</sub>O may support the ingestion of a volatile alcohol [31,32]. It cannot be overemphasized, however, that the absence of an osmolar gap does not exclude volatile alcohol ingestion [30,31]. Another useful characteristic of methanol and ethylene glycol ingestion is their potential to cause an anion gap acidosis through the formation of organic acids. In all patients presenting with increased anion gap metabolic acidosis, ethylene glycol or methanol poisoning should be considered, especially in the absence of shock. Isopropanol is converted to nonacidic metabolites and thus does not cause acidosis in the absence of co-ingestions. This characteristic distinguishes isopropanol from ethylene glycol or methanol ingestion and may further assist in the evaluation and diagnosis [30,31]. Volatile alcohol measurements, if available, can rapidly expedite a diagnosis, but awaiting results should never delay treatment.

### *Clinical presentation*

#### *Isopropanol*

Isopropanol causes two to three times the intoxicating effect of ethanol at similar serum concentrations. It crosses the blood-brain barrier with particular ease, leading to variable CNS depression, based on the amount of ingestion. The isopropanol metabolite acetone was believed to be the cause of CNS effects, but that remains controversial [33,34]. Respiratory depression, coma, and hypotension are common symptoms with ingestions measuring  $\geq 400$  mg/dL [35,36]. A child may present with hemorrhagic gastritis and hematemesis if a significant amount has been ingested.

#### *Methanol*

Symptoms of methanol ingestion may be delayed for up to 72 hours in some cases [32]. Methanol is well absorbed by inhalation, ingestion, or dermal ex-



posure. It is oxidized in the liver to formaldehyde and then to formic acid, which contributes to the profound metabolic acidosis occurring in acute methanol poisoning. The metabolic products of methanol can produce a syndrome of delayed-onset acidosis, obtundation, visual disturbance, and death. An observed triad of symptoms includes abdominal pain, visual changes, and acidosis. CNS depression and agitation can occur. The metabolite formic acid is extremely lethal, and death has been reported with as little as 15 to 30 mL (1 to 2 tablespoons) of ingested methanol [8,37,38]. Recently, this claim of lethal low-volume ingestion has come under question after a critical review of the literature [39]. Patients may describe visual loss or snowfield vision that occurs typically late in ingestion. Although visual acuity assessment in the toddler may be difficult, attempts should be made to evaluate the fundi as well as vision. Blindness is usually permanent but can be avoided in cases of early presentation, diagnosis, and intervention.

### *Ethylene glycol*

The ingestion of as little as 3 mL of a product containing 95% ethylene glycol carries the potential for lethality in toddler-aged children [8]. Ethylene glycol toxicity often manifests in three different clinical phases. The first phase, occurring up to 12 hours after ingestion, displays altered CNS findings, including decreased mental status, slurred speech, ataxia, hallucinations, coma, and seizures. Cardiopulmonary effects dominate during the second phase and occur 12 to 24 hours after ingestion. Tachycardia, tachypnea, hypertension, congestive heart failure, acute respiratory distress syndrome, and circulatory collapse are encountered commonly at this time. The third and final clinical phase occurs 24 to 72 hours after ingestion and manifests primarily as toxic metabolite-mediated nephrotoxicity [3]. Additionally, the precipitation of calcium into calcium oxalate crystals may cause hypocalcemia, presenting as tetany and prolongation of the QT interval on EKG [40]. Oxalate crystals, which may be found in the child's urine, are more typically the monohydrate type (needle shaped) than the dihydrate (envelope shaped) crystals. Because some ethylene glycol-containing products contain fluorescein, the urine may fluoresce, although this is not a definitive test and cannot be relied on to confirm or refute the diagnosis of ingestion.

### *Management*

Initial laboratory and ancillary tests should include obtaining levels of electrolytes, BUN, creatinine, glucose, lactate, and ionized calcium and an electrocardiogram. In addition, methanol and ethylene glycol levels should be determined, and a urinalysis and arterial blood gas analysis should be performed. A chest radiograph is indicated if there is suspicion that the child may have aspirated or has pulmonary edema. In methanol poisoning, the degree of acidosis and magnitude of the anion gap elevation tend to correlate with blood formate concentrations [30]. In ethylene glycol poisoning, an increased anion gap acidosis correlates with glycolate levels [41]. Seizures may be an indication of

hypocalcemia and should be treated with benzodiazepines. For hypoglycemia, give glucose, 50% or 25%, 2 mL/kg body weight in children. Thiamine and pyridoxine are adjunct therapies in EG poisoning, as are folic acid or folinic acid in methanol poisoning (1 mg/kg, or up to 50 mg). Symptomatic hypocalcemia should be treated using calcium gluconate. Calcium should not be given for hypocalcemia alone because it may increase the formation of calcium oxalate crystals [37].

### *Isopropanol*

Airway protection is paramount, and the clinician should maintain a low threshold for intubation and mechanical ventilation. Hypotension will usually respond to a fluid bolus. Hemodialysis, although rarely indicated, may greatly enhance serum elimination and is considered definitive management in cases of prolonged coma and hypotension [36].

### *Methanol and ethylene glycol*

The cornerstone of management includes the correction of acidosis, competitive inhibition of ADH, and hemodialysis-assisted elimination. The antidote fomepizole acts through the binding of ADH 500 to 1000 times more effectively than methanol, essentially eliminating the formation of toxic metabolites. For methanol poisoning, this antidote is indicated with symptomatic toxicity, methanol levels  $\geq 20$  mg/dL or pH level  $\leq 7.20$  [37–40,42]. A loading dose of 15 mg/kg is given initially, followed by 10 mg/kg every 12 hours for 48 hours and then 15 mg/kg until the methanol level is below 20 mg/dL [43,44].

Historically, a 10% ethanol solution has been used to elicit competitive inhibition of toxic metabolites. When fomepizole is not available, oral or IV ethanol is the antidote of choice, along with other adjunctive care. Serum ethanol concentrations should be maintained between 100 and 150 mg/dL. Dosing schedules are variable, and the clinician must be aware of the potential risk for aspiration and further CNS decline [37]. Most authorities ascribe an overall cost savings with the use of fomepizole; however, ethanol still exists as a viable option [40].

Hemodialysis is considered a definitive treatment modality and should be considered early in cases suspected of having methanol or ethylene glycol ingestion. Indications include visual impairment, profound acidosis, renal failure, and methanol or ethylene glycol values greater than 50 mg/dL (Table 5) [40,43]. In methanol poisoning, folate should be given at a dose of 1 mg/kg intravenously in 100 mL D5W over 30 to 60 minutes, up to 50 mg every 4 hours for six doses [45]. This treatment serves as an enzyme cofactor in the conversion of formate to CO<sub>2</sub> and water [37,45]. Most authorities suggest ICU admission for close observation during the early stages of therapy. In cases of EG poisoning, pyridoxine and thiamine should be given daily because they will help shunt the toxic metabolite glyoxalate through nontoxic pathways. Cardiac monitoring in the

Table 5  
Indications for hemodialysis in toxic alcohol poisoning

Treatment	Dose	Indication
Fomepizole	15 mg/kg loading dose, followed by 10 mg/kg q12 h for 48 h, then 15 mg/kg q12 h until toxic alcohol level $\leq$ 20 mg/dL	Ingestion of multiple substances with depressed level of consciousness Altered consciousness Inability to provide intensive care staffing or monitor ethanol administration Relative contraindication to ethanol Critically ill patient with an anion gap metabolic acidosis of unknown cause and potential exposure to ethylene glycol or methanol Patients with active hepatic disease
Ethanol (10%)	600–800 mg/kg (0.6–0.8 g/kg or 6–8 mL/kg) loading dose, then 0.83 mL/kg/h maintenance; monitor serum ethanol level q1–2 h to maintain level 100–150 mg/dL	Unable to give fomepizole Able to provide adequate intensive care staffing and obtain ethanol levels in timely manner Strong clinical suspicion of toxic alcohol ingestion and metabolic acidosis with osmolal gap $\geq$ 10 mosm/kg H <sub>2</sub> O
Hemodialysis		Severe metabolic acidosis (pH 7.25–7.3) unresponsive to therapy Renal failure (Cr $\geq$ 3.0) EG or methanol level $\geq$ 50 mg/dL unless fomepizole is being administered and patient is asymptomatic with normal arterial pH

*Data from Casavant MJ. Fomepizole in the treatment of poisoning. Pediatrics 2001;107(1):170–1.*

pediatric ICU is always appropriate because of the potential for cardiopulmonary decline.

## Clonidine

Clonidine is a commonly prescribed, centrally acting antihypertensive, which recently has enjoyed an expanded therapeutic role in the treatment of pediatric attention deficit hyperactivity disorder and Tourette's syndrome. Clonidine is a central  $\alpha$ -adrenoreceptor agonist that allows inhibition of sympathetic outflow. Because of its widespread use in all age populations, clonidine remains a common substance of pediatric ingestion. In 2002, the TESS reported over 1600 (31%) ingestions in children under the age of 6 years [46]; and in 2003, 5402 clonidine exposures occurred, with 1736 (32%) exposures in children under the age of 6 years [1]. Lethality is attributed largely to toxic effects on the CNS and cardiovascular systems and may be seen with doses as small as 10  $\mu$ g/kg. The typical exposure scenario is the child who ingests the drug while visiting

grandparents, where tablets have been left out on the nightstand or in a loosely capped pill container, which allow easy access for the child.

### *Clinical presentation*

Because of a functional overlap in the  $\alpha_2$  receptors targeted by clonidine and the  $\mu$  receptors targeted by opioids, the constellation of symptoms that have been described with clonidine toxicity largely resemble an opioid toxidrome [47,48]. Symptoms include altered mental status, somnolence, respiratory depression, miosis, bradycardia, and hypotension. Dose-related responses have been documented, with cardiovascular effects seen with ingestions between 0.01 and 0.02 mg/kg and respiratory depression occurring with ingestions greater than 20  $\mu$ g/kg [47,49]. Apnea and respiratory depression are common when the dose exceeds 0.02 mg/kg [49]. Most children will have signs or symptoms of toxicity within 30 to 90 minutes after ingestion [47]. The toddler may respond somewhat differently than older children, presenting in a deeply comatose state, with apnea and bradycardia. However when stimulated, the toddler may respond with increased respiration and pulse, with an improved level of consciousness. If the child is not stimulated, she may quickly return to the previous state or even slip into cardiopulmonary arrest [47]. Although they are rare, seizures can occur with significant overdoses.

### *Management*

The management of suspected clonidine overdose remains largely supportive. Careful attention must be focused on the establishment and maintenance of a patent airway. Because of the risks of bradycardia, heart block, and hypotension, continuous cardiac monitoring and a 12-lead EKG should be used. Activated charcoal should be administered if the patient presents within 1 hour of ingestion. The rapid absorption profile of clonidine precludes recommendations for multiple dosing of charcoal [47].

Naloxone has been used with variable success in treating severe clonidine overdose. It has been shown to reverse both cardiovascular and respiratory depression in up to 50% of case reports [47,50–54]. This is likely caused by opioid receptor overlap, as described above. Suggested naloxone dosing is 0.1 mg, up to a maximum of 10 mg [47,52,54]. Refractory cases of bradycardia will usually respond to atropine. Hypotension should be managed with aggressive fluid resuscitation. Dopamine is recommended by most authorities as the vasopressor of choice, starting at 5  $\mu$ g/kg/min and increasing in 5- $\mu$ g/kg/min increments as needed. Norepinephrine should be added if more than 20  $\mu$ g/kg/min of dopamine is needed. At moderate doses, dopamine may provide sufficient blood pressure support, while its chronotropic properties may mitigate clonidine-induced bradycardia [47].

Admission to the pediatric ICU is always appropriate in patients who manifest altered mental status, respiratory depression, or cardiac abnormality. Patients who

do not show signs of toxicity within 6 to 8 hours after ingestion are usually safe for discharge after a 6- to 8-hour observation period [50,55–57].

### **Tricyclic antidepressants**

Antidepressant medications are responsible for a large number of ingestion-related deaths each year. According to the 2003 TESS report, tricyclic antidepressants (TCA) are the third leading cause of death after analgesics and sedative-hypnotics and antipsychotics categories [1]. There were over 12,700 reported exposures to tricyclic antidepressants, and over 1500 exposures occurred in children under the age of 6 years. Amitriptyline, imipramine, and nortriptyline comprise the majority of tricyclic ingestions in children less than 6 years of age, accounting for 13% of all prescribed cyclic antidepressants within the last 10 years, in light of the fact that this group of agents is considered a second- and third-line therapy for depression [58]. The acquisition of this medication class is further enhanced because of its expanded therapeutic value. Currently, tricyclic antidepressants are used to treat numerous medical and psychiatric conditions in both adult and pediatric populations [59].

A growing body of evidence suggests that tricyclic antidepressants exert their therapeutic effects through the centrally mediated inhibition of biogenic amines (serotonin and norepinephrine), thereby correcting a theoretical “imbalance” that may manifest initially as psychiatric illness [58,60]. Clinically important peripheral manifestations of TCA use and toxicity include the inhibition of histamine H<sub>1</sub> and muscarinic cholinergic M<sub>1</sub> receptors, the clinical findings of which are discussed below. The hallmark of TCA toxicity is the dangerous blockade of fast voltage-gated sodium channels found on cardiac myocytes. The altered sodium influx effectively slows phase-zero depolarization, manifesting as a widened QRS complex on the EKG; this is an ominous sign in light of a known or suspected TCA ingestion [8,58,60–63].

#### *Clinical presentation*

Most authorities agree that TCA doses as low as 15 mg/kg can be lethal among toddler-aged children [61]. Exposures of 5 mg/kg or less are generally well tolerated and may follow an asymptomatic course [58,60,61]. Although the deleterious effects of TCA toxicity are primarily associated with the cardiovascular and central nervous systems, early toxicity may present with signs and symptoms consistent with an anticholinergic toxidrome. Effects on the CNS and peripheral cholinergic receptors may manifest as confusion, delirium, dilated pupils, dry mouth, urinary incontinence, diminished bowel activity, and tachycardia [8,58,60,61]. Mortality, however, is attributed to overt cardiovascular collapse and CNS toxicity, to include seizure and coma.

In the pediatric population, EKG findings can be suggestive and aid in the conformation of TCA toxicity. However, the EKG is unable to provide any

prognostic information regarding the severity or outcome of a TCA overdose. EKG findings include sinus tachycardia, ventricular dysrhythmias, heart block, widening QRS and QTc intervals, and an R wave greater than 3 mm in lead aV<sub>R</sub> [8,58,60–63].

### *Management*

The management of TCA overdose requires the rapid suspicion or recognition of the offending agent along with aggressive airway and hemodynamic support. Neurologic deterioration and cardiovascular collapse must be anticipated, and aggressive supportive care must be provided. The child may show a sudden change in sensorium, such as sudden seizure or coma. Continuous cardiac monitors, ample IV access, and supplemental oxygen should be employed immediately. Because of its anticholinergic properties, TCA ingestion may cause delayed gastric emptying [8,58,61]. It is therefore essential that activated charcoal be administered as soon as possible in an attempt to minimize further absorption [64].

Neurologic decline occurs quickly with life-threatening amounts of TCA ingestion. Should this occur or appear imminent, intubation and mechanical ventilation is strongly suggested. Seizures are usually responsive to benzodiazepines [8,58]. Barbiturates should be avoided for the risk of potentiating hypotension [8,60]. Phenytoin has been shown to induce ventricular dysrhythmias in animal models, and its use is not recommended to achieve seizure control [58].

Sodium bicarbonate has long been the primary treatment of TCA-induced cardiotoxicity. Some controversy exists over the exact mechanism through which sodium bicarbonate exerts its therapeutic effect. Some animal studies suggest that sodium bicarbonate mitigates toxicity through an increase in serum pH level, whereas others site an increase in serum sodium level [60]. Regardless of the mechanism, sodium bicarbonate is indicated in the event of severe clinical toxicity, widening of the QRS complex  $\geq 100$  ms, ventricular dysrhythmias, and hypotension [58–63,65,66]. Although drip- versus bolus-dosing strategies remain controversial, a starting IV bolus of 1 to 2 mEq/kg in children is appropriate [8,58,60]. A serum pH level of greater than 7.5 should not be exceeded. The patient must be monitored for the development of hypokalemia, and IV supplementation may be required.

The use of classes IA and IC antidysrhythmics should be strictly avoided based on their potential to exacerbate TCA-induced cardiotoxicity [58,60]. Dopamine and norepinephrine have been used to overcome alpha blockade-induced hypotension. There is no clear evidence to suggest one over the other at this time [60]. The use of physostigmine should be avoided because it may lead to seizures and fatal cardiac dysrhythmias [60].

In cases of accidental ingestion in a child who is asymptomatic, she may be observed in the emergency department (ED) for 6 hours after ingestion. If no evidence of toxicity occurs, the child may be safely discharged in the care of responsible adults. If symptoms do occur during the period of observation in the

ED, appropriate treatment should be initiated, and the child should be admitted to a monitored inpatient setting.

## Salicylates

Data from the American Association of Poison Control Centers' annual report for 2003 [1] list the most common classes of substances involved in fatalities as the analgesics, stimulants, street drugs, antidepressants, cardiovascular agents, and sedative-hypnotics-antipsychotics. During this reporting period, an analgesic was believed to be the primary responsible agent in 375 fatalities. Of these, 23 fatalities involved aspirin alone. Over 50% of these patients had salicylate concentrations less than 100 mg/dL. Of the 916 nonaspirin salicylate exposures, 456 involved children less than 6 years of age.

Salicylates can be found in high concentration in several products commonly used in the home and accessible to children; most notably, oil of wintergreen (methyl salicylate), which is contained in liniments or analgesic balms. This product is deceptively toxic, and 1 mL of a 98% concentration is equivalent to 1400 mg of salicylate. Because the toxic dose of salicylate is 200 mg/kg, it is obvious that exposure to less than 1 teaspoonful can be lethal to a toddler. The liquid preparations undergo rapid absorption, typically within 1 hour, and are converted quickly to salicylate [67]. It should be remembered that Chinese herbal medications or Chinese medicated oils may also contain salicylates [68–70]. At toxic doses in children, the elimination half-life of salicylates increases from 2 to 4 hours at therapeutic levels to 15 to 29 hours [71].

Salicylates have several pathophysiologic mechanisms leading to toxicity. Stimulation of the respiratory center in the brainstem causes hyperventilation, with increases in the depth and rate of breathing. The uncoupling of oxidative phosphorylation results in increased oxygen consumption, further respiratory stimulation, metabolic acidosis, and a compensatory response by the kidney to excrete bicarbonate, potassium, and sodium. An increase in pulmonary vascular permeability and an increase in leukotrienes can lead to pulmonary edema [67]. Salicylates toxicity increases glucose consumption, inhibits gluconeogenesis, and enhances insulin secretion [67,72]. These toxic actions can lead to significant hypoglycemia, particularly in children [72] compared with adults.

### *Clinical presentation*

Children under the age of 2 years have a tendency to present with metabolic acidosis, compared with adolescents and adults, who may present with respiratory alkalosis [73]. The child may present with the odor of oil of wintergreen on her breath, lethargy, diaphoresis, and an increase in all vital signs. Severe toxicity may cause coma, seizures, and cardiovascular collapse. Table 6 shows the clinical manifestations of salicylate toxicity. Dehydration is a common presentation secondary to vomiting and the inability to tolerate oral fluids as well



Table 6  
Clinical presentation of salicylate toxicity

System	Clinical findings
CNS	Disorientation, combative or agitated Hallucinations (auditory) Coma, convulsions due to cerebral edema or low cerebrospinal fluid glucose
Gastrointestinal	Nausea, vomiting, and epigastric discomfort
Cardiovascular	Sinus tachycardia, hypotension, ventricular dysrhythmias, shock, asystole
Respiratory	Pulmonary edema, hyperpnea
Renal/acid-base	Renal failure, respiratory alkalosis, mixed respiratory alkalosis, increased anion gap metabolic acidosis
Electrolytes	Dehydration, hypokalemia, hyponatremia or hypernatremia Hypoglycemia/hyperglycemia, hypocalcemia/hypercalcemia
Miscellaneous	Tinnitus and deafness, sweating, hyperpyrexia, leukocytosis, hypoprothrombinemia, rhabdomyolysis

as tachypnea, diaphoresis, and early diuresis. Potassium losses from gastrointestinal and urinary losses, as well as an obligatory intracellular shift of potassium in exchange for hydrogen ions, lead to severe hypokalemia. Of note, clinical deterioration can be rapid, and aggressive management of the sick child is warranted.

### *Management*

Laboratory testing should include a salicylate level, but this level should not be relied on to predict prognosis. The Done nomogram is no longer recommended to assist in predicting the severity of toxicity [74]. The child's clinical presentation coupled with metabolic status should weigh heavily in the treatment and monitoring plan. Arterial blood gases, electrolytes, and serum glucose levels should be carefully monitored and managed appropriately. In the euglycemic patient who has depressed level of consciousness, the management includes monitoring calcium levels because both hypocalcemia and hypercalcemia have been reported in severe salicylate toxicity [75,76].

The administration of oral activated charcoal should be given early after ingestion. Because one of the primary symptoms of this deadly ingestion is vomiting and altered mentation, the child is at risk of aspiration, and appropriate precautions must be instituted. The child may easily present with severe dehydration and require aggressive rehydration. The child's fluid status must be monitored closely in order not to overload the cardiopulmonary system. This should be done in the pediatric ICU setting. Maintaining a urine output of 2 to 3 mL/kg/h is recommended.

After rehydration, another important management goal is to alkalinize the urine to a pH level of 7.5 to 8.5 to enhance the elimination of the salicylate ion. Equally important is to alkalinize the blood to a pH level of 7.5 to 7.55 [72]. One approach to achieving urinary alkalization is to add 150 mL of sodium bicarbonate to 850 mL of D5W and infuse at a rate of 1.5 to 2 times the main-



tenance calculated for the child [67]. Alternatively, in a child, sodium bicarbonate may be administered, 25 to 50 mmol (25 mL of an 8.4% solution), intravenously over 1 hour and give additional boluses intravenously to maintain the urine pH level in the range of 7.5 to 8.5. The endpoint of alkalinization is when the salicylate level is less than 25 mg/dL [77].

Most fatal cases of salicylate poisoning are those that fail to receive hemodialysis in a timely manner, which suggests that more aggressive and earlier use of dialysis may be indicated in the treatment of highly concentrated salicylate ingestions. Children who present with or develop significant neurologic presentations (agitation, lethargy, coma, and convulsions), cardiac instability, and renal failure or have significantly elevated or increasing salicylate levels are candidates for hemodialysis. Specific levels should not dictate whether the patient receives hemodialysis, but rather clinical symptoms in conjunction with the level should be considered. Traditionally, levels of 80 to 100 mg/dL were cause for mandatory dialysis. Hemodialysis can also correct the acid-base abnormalities.

Some of the pitfalls in the management of methyl salicylate poisoning are underestimating the toxicity of small amounts, attempting to use the Done nomogram, focusing on urine alkalinization rather than considering blood pH level, hypoventilating the intubated child, which allows the blood pH level to decrease, failing to monitor the patient for hypoglycemia, and failing to initiate hemodialysis when it is clinically indicated [72].

## Opioids

Opioids are a popular analgesic for moderate to severe pain. They are also used as adjuncts to anesthesia, cough suppressants, and antidiarrheals. Methadone, a long-acting synthetic narcotic analgesic used in the detoxification treatment of opiate dependence and for maintenance in heroin and narcotic addiction, may also be prescribed for the relief of moderate to severe pain. Opioids can be used recreationally and abused for their sedative and analgesic effects. Because of their widespread use, either legally or illicitly, their availability is high, and children may have easy access to these dangerous agents in the home. The 2003 TESS database reported 34 deaths of children under the age of 6 years. Nine of these fatalities were unintentional general, with six deaths involving prescription medications. Three of the prescription medications were opioids. Overall, of the 375 fatalities implicating analgesic drugs as the primary causative agent of death, 100 involved an acetaminophen-combined product, usually containing an opioid [1].

Although the number of deaths related to methadone or oxycodone compared with 2002 data has decreased, these agents continue to be incriminated to a significant degree in major toxicity. Although the minimal lethal pediatric dose is unknown, a small child who ingests even residual amounts of a methadone suspension left in a bottle can progress from drowsiness to coma within 30 minutes [78]. The increasing use of methadone in the treatment of heroin addiction

has created a situation in which the drug may be readily available to children and other family members of maintenance patients, causing serious consequences. Because of their increased mobility after infancy, curiosity, and oral fixation, toddlers may be especially susceptible to getting into illicit narcotics, such as powdered heroin and fentanyl patches, left unattended by the adult. Fentanyl transmucosal lozenges have been reported as the cause of an unintentional death in an 11-year-old child [1].

Opioids interact with three main receptors ( $\mu$ ,  $\kappa$ , and  $\delta$ ) located throughout the CNS and peripheral nervous systems and in the gastrointestinal tract. Activation of these receptors by the opioids results in a variety of life-threatening complications [79].

### *Clinical presentation*

The classic triad of miosis, CNS depression, and respiratory depression should alert the clinician to probable opioid toxicity. Other signs and symptoms of opioid toxicity include dizziness, euphoria or dysphoria, depressed reflexes, altered sensory perception, lethargy, and coma. The child may also display analgesia to painful stimuli, dry mucous membranes, facial flushing, diaphoresis or clammy skin, nausea and vomiting, muscle flaccidity, bronchospasm, and bradycardia [79,80]. Apnea, noncardiogenic pulmonary edema, circulatory collapse, coma, cardiac arrest, and possible death can occur in significant ingestions that go unrecognized or when the child is found too late for effective treatment. It is important to question the adult caretaker regarding the possibility of access to either short- or long-acting narcotics when the child presents with a narcotic syndrome.

### *Management*

The mainstay of treatment for opioid toxicity is the administration of naloxone. The usual initial dose of naloxone for patients with CNS depression without respiratory depression is 0.1 to 0.4 mg intravenously for both adults and children. If there is partial or absent response, then naloxone, 2 mg, should be administered as an intravenous bolus and repeated every 3 minutes up to a total dose of 10 to 20 mg. When there is respiratory depression, initial higher doses of naloxone should be given, starting with 1 to 2 mg. The effective dose may need to be repeated every 20 to 60 minutes, depending on the half-life of the opioid ingested and the patient's response. A continuous infusion is titrated to the patient's respiratory status and level of consciousness if long-acting narcotics such as methadone are ingested [79,81]. The infusion rate may be started at two thirds the amount needed to reverse the child's respiratory depression per hour [80].

If an IV is not available, naloxone can be given through almost any route, including intranasally and by nebulizer [82,83]. Although the intranasal route is not as effective as the intramuscular route, it is still effective in reversing opiate-induced respiratory depression [82].

The long-acting narcotic antagonist nalmefene is an option in children who are nonopioid-dependent and not at risk of withdrawal. Although there is limited literature on this treatment in children, it appears to be safe and effective in treating opioid toxicity [84]. If the child presents within 1 hour of ingesting a delayed-absorption product such as diphenoxylate-atropine (Lomotil) or sustained release morphine or oxycodone, activated charcoal should be administered, paying close attention to the mental status and respiratory depression [64]. Activated charcoal should be given at a dose of 1 g/kg, orally or by naso- or orogastric tube.

The decision to discharge, observe in the ED, or admit the patient is still controversial. Children with recurrent respiratory depression after initial treatment with naloxone, who have evidence of pulmonary edema or who have ingested long-acting or delayed absorption opioids, should be admitted. Long-acting opioids such as methadone have a tendency to cause a significant recurrence of symptoms, typically within 2 hours of presentation [85]. Also, consideration of the home environment and safety of the child must be weighed in the decision to release or admit the child.

## Summary

The mantra of toxicology is that “the dose makes the poison,” and in the case of pediatric ingestions, this is very true. There are scores of products and agents that can be deadly if the appropriate “dose” is ingested. This article presents only a few of the potentially deadly ingestions this patient population might encounter, but the clinician is cautioned to use sound judgment in managing children presenting with a history of being found with pills in their possession. In addition, social issues surrounding the ingestion should be considered when making a disposition.

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