Pediatric Poisonings

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LEARNING OBJECTIVES

1. Distinguish between toxidrome presentations in a pediatric patient.
2. Assess the role of decontamination strategies in the initial management of a toxic ingestion.
3. Evaluate the role of naloxone in the management of methadone and buprenorphine exposures.
4. Develop a treatment and monitoring plan for a tricyclic antidepressant ingestion.
5. Distinguish laboratory abnormalities associated with toxic alcohol ingestions.
6. Analyze nonpharmacologic management strategies for common household ingestions.

ABBREVIATIONS IN THIS CHAPTER

PCC	Poison control center
TCA	Tricyclic antidepressant

Table of other common abbreviations.

INTRODUCTION

Epidemiology

Pre-Pandemic

The number of prescription medications used by both adult and pediatric patients continues to increase significantly in the United States. Prescription and illicit drugs as well as nonpharmaceutical products kept in the household (e.g., cleaning products, cosmetics, and pesticides) can pose a risk for pediatric patients, leading to unintentional and unsupervised exposures (i.e., ingestions, chewing tablets/films, inhalations, contact with skin or eyes, and injections). Pediatric patients, specifically toddlers, are also at risk of exposures because of their mouthing behaviors and tendency to mimic adult actions. Medication dosing errors in the home and clinical settings may also lead to therapeutic errors, resulting in adverse effects or need for additional monitoring. Weight-based prescription and age-based OTC medication dosing strategies used in the pediatric population can lead to many inadvertent errors, which are often reported to poison control centers (PCCs) (Schillie 2009). These types of errors include wrong medication dose taken/administered; dose given twice or too close together; incorrect route, formulation, or concentration administered; and dispensing cup errors (e.g., wrong unit of measure, administering dose equivalent to entire cup size). In addition, adolescents may misuse medications (e.g., dextromethorphan) for euphoric effects (Schwartz 2005), experience unintentional toxicity secondary to participating in misguided challenges posted on social media (e.g., "cinnamon challenge") (Grant-Alfieri 2013), or intentionally use medications as a form of self-harm (Gilley 2020).

According to the 2020 National Poison Data System report, children younger than 5 years accounted for around 42% of all human-reported exposures, with children, adolescents, and adults

younger than 20 years representing 55% of total exposures. In over 924,000 substance exposures reported to PCCs in 2020 for pediatric patients younger than 5 years, the most common included cosmetics/personal care products (11.82%), cleaning substances (11.3%), analgesics (7.57%), foreign bodies/toys/miscellaneous (6.71%), and dietary supplements/herbals/homeopathic (6.44%). The substance categories most commonly reported by the National Poison Data System in 74 pediatric (younger than 5 years) deaths were analgesics (18.92%), fumes/gases/vapors (17.57%), cardiovascular drugs (10.81%), and batteries (6.76%). These results do not include the exposures reported as "unknown child" or "unknown age" and are limited by the cases reported to PCCs (Gumin 2021). Finally, since 2010, adolescent intentional overdoses have increased (Gilley 2020).

COVID-19–Related Inflection Points

Although some poisonings may safely be monitored at home with minimal anticipated adverse effects or toxicity, ingestions are a common reason for ED presentation. In March 2020, the COVID-19 pandemic changed caregivers' responsibilities as well as children's daily environments because of school and child care center closures. Health care systems' priority in medical care was shifted from nonemergency and elective/preventive care to greater efforts on limiting virus transmission and treating patients with COVID-19 across the country. Pediatric ED visits decreased by 45.7% in 27 U.S. children's hospitals during the pandemic period (March 15, 2020, to August 31, 2020) compared with previous years (March 15, 2017, to August 31, 2019), though visits related to substance use disorders and poisoning appeared to be less affected by the pandemic (DeLaroche 2021; Lelak 2021). Overall, PCC calls related to disinfectant exposures (hand sanitizers and nonalcohol disinfectants) in the first 3 months of 2020 were notably higher than in the first 3 months of 2019 (45,550 calls and 37,822 calls, respectively) (Kuehn 2020), with a 43% increase in hand-sanitizer exposures noted specifically in patients younger than 20 years (Lelak 2021). One tertiary care children's hospital also noted a significant trend toward a higher rate of foreign body ingestions, such as coins and button batteries, during the COVID-19 pandemic than during a similar pre-pandemic period. These trends were attributed to increased home exposures because of school closures and local "shelter-in-place" orders (Klein 2022).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of toxicokinetics: absorption, distribution, metabolism, and excretion
- General knowledge of available antidotes
- Basic recognition of toxidromes

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American Association of Poison Control Centers: www.poisonhelp.org/
- American Academy of Clinical Toxicology: www.clintox.org
- American College of Medical Toxicology: https://www.acmt.net/
- Extracorporeal Treatments in Poisonings Workgroup (EXTRIP): https://www.extrip-workgroup.org/
- LipidRescue Resuscitation: www.lipidrescue.org

Common and Life-threatening Pediatric Ingestions

"One Pill Can Kill"

The intent of an ingestion in the toddler or preschool age groups usually differs from that in an adolescent or adult, given that the exposure is a result of environmental "exploration" through developmental milestones rather than self-harm (Michael 2004). Many scenarios involve unwitnessed or unmeasured exposures, further complicating the situation. Although most incidents are benign and nontoxic, some medications (prescription and OTC) as well as household products can cause severe toxicity or death in young children. Clinicians and pharmacists should be aware of common medications and medication classes that can potentially be lethal to children (weight less than 10 kg) with the ingestion of a single tablet/capsule or teaspoonful (Matteucci 2005) (Box 1). A teaspoonful serves as a surrogate for the volume of liquid associated with a sip or swallow, which has been difficult to define precisely, despite several study attempts (Ratnapalan 2003; Jones 1961). Patients with known or one-pill-can-kill ingestions should promptly be evaluated in the ED.

Household Items (Button Batteries and Laundry Detergent Pods)

Nonpharmaceutical-related ingestions account for many reported pediatric exposures. Foreign body ingestions by pediatric patients can also cause serious health complications and adverse effects and may require emergency interventions for removal. Most recently, the many button batteries used in several household devices, introduction of laundry detergent pods to the U.S. market in 2010, and high-powered magnets in the home have introduced a new group of reported exposures. Ingestion of button batteries and laundry pod products can lead to permanent and severe caustic GI injuries despite standard management. Laundry

Box 1. Notable One-Pill-Can-Kill Medications/Classes

- α_2-Adrenergic agonists
- β-Receptor antagonists
- Benzonatate
- Bupropion
- Button batteries
- Calcium channel antagonists
- Camphor
- Caustics
- Chloroquine/hydroxychloroquine
- Chlorpromazine
- Clozapine
- Diphenoxylate/atropine
- Hydrocarbons
- Laundry pods
- Methyl salicylate
- Nicotine
- Olanzapine
- Opioids
- Salicylates
- Sulfonylureas
- Theophylline
- Thiazolidinediones
- Toxic alcohols
- Tricyclic antidepressants

Information from: Madden MA. Pediatric toxicology: emerging trends. J Pediatr Intensive Care 2015;4:103-10; Michael JB, Sztajnkrycer MD. Deadly pediatric poisons: nine common agents that kill at low doses. Emerg Med Clin North Am 2004;22:1019-50.

pod ingestions can also cause respiratory distress and pulmonary edema (O'Donnell 2017). Although clinicians continue to develop protocols and recommendations for treating these ingestions in the emergency setting, exposure prevention should be the focus for caregivers.

Evaluation of Patient

Classic Toxidromes

Evaluation of a pediatric patient with a toxicology emergency should include a detailed history to determine the route of exposure. For pharmaceutical products, clinicians should try to identify and characterize the xenobiotic, dose, dosage form (e.g., tablet, capsule, patch, liquid), release mechanism (immediate release or extended release), and quantity of pills or volume of liquid ingested (Toce 2017a). For nonpharmaceutical product exposures, packaging or ingredient lists can help determine potentially toxic substances. When possible, photographs of plants or mushrooms that may have been consumed can be shared with the PCC or other experts (e.g., botanists, mycologists) for identification. Medical personnel or household members can help by providing pill bottles or containers at the scene or medication lists of household members to account for all potential exposures. Pharmacists can help acquire the medication history and identify the tablets or capsules found on the patient or at the scene.

Route of exposure (e.g., oral, buccal, dermal, inhalation) is important to clarify, given potential differences in response to a xenobiotic between pediatric and adult patients because of physiologic differences. Young children have a higher respiratory rate and minute ventilation, thereby increasing the amount of an inhaled drug exposure. In addition, a large body surface area/weight ratio may increase total dermal exposure in a child with a higher risk of insensible losses (Calello 2014).

Time of exposure is critical in assessing and treating the patient with poisoning. Some GI decontamination strategies and antidotes are only effective if administered within a specific time window after ingestion. After a topical exposure, dermal decontamination may be needed to remove the substance. In addition, a clinician may determine an appropriate observation period for a patient on the basis of time of exposure and toxicokinetic properties of the xenobiotic.

However, in many cases, the xenobiotic ingestion may be unknown. Children may be exposed to substances without supervision, or the patient may not be willing to disclose this information to the clinician. This can make decisions about treatment more challenging because the clinician must rely on objective data from physical examination findings, vital sign abnormalities, and laboratory data. Toxidromes are a collection of symptoms associated with certain classes of xenobiotics (Erickson 2007). Clinicians can use toxidromes to help identify a potential single-drug exposure and anticipate possible changes in the clinical course. In patients presenting after a multisubstance exposure, toxidromes may help eliminate certain suspected ingestions on the basis of the absence of physical examination findings; however, xenobiotics may also show overlapping features (Holstedge 2012).

The most commonly encountered classic toxidromes are sympathomimetic, opioid, sedative/hypnotic, anticholinergic, and cholinergic. Each toxidrome is characterized by anticipated changes in vital signs and physical examination findings associated with exposure to a xenobiotic within each toxidrome class (Table 1). Clinicians who do not routinely care for the pediatric population should carefully consider age-specific vital sign abnormalities to prevent delays in recognizing potential evolving complications from ingestions (Toce 2017a).

Current/Emerging Toxidromes

In addition to the classic toxidromes, increasing use of recreational drugs among adolescents has led to more ED visits associated with use of nicotine-containing e-cigarettes, marijuana, synthetic cannabinoids, and dextromethorphan (Assaf 2021). Patients who have ingested the nicotine liquid used in vaping devices can present with GI effects (nausea, vomiting,

Table 1. Common Pediatric Toxidromes

	Vital Signs					
	Heart Rate	Blood Pressure	Respiratory Rate	Temp	Key Physical Examination Findings	Examples
Sympathomimetic	↑	↑	↑	↑	Agitation, delirium, diaphoresis, tremor, myoclonus, fussiness, decreased sleep, crying	Cocaine, amphetamines, cathinones, pseudoephedrine
Opioid	↓	↓	↓	↓	Sedation, miosis, hyporeflexia, decreased bowel sounds, sleeping more than usual, poor eating	Morphine, oxycodone, fentanyl, heroin, methadone, buprenorphine
Sedative/hypnotic	↓	↓	–/↓	–/↓	Decreased level of consciousness, agitation, hyporeflexia, sleeping more than usual, poor eating, respiratory depression, particularly with high doses or combination with other respiratory depressants (e.g., opioids)	Benzodiazepines, nonbenzodiazepine soporifics (e.g., Z-drugs such as eszopiclone, zaleplon, zolpidem)
Anticholinergic	↑	↑[a]	–	↑	Delirium/hallucinations, flushed, dry mucous membranes, mydriasis, increased urinary retention, fussiness, decreased sleep, crying	Antihistamines, antipsychotics, tricyclic antidepressants, atropine, scopolamine
Cholinergic	↑/↓	–	–	–	Diarrhea, diaphoresis, seizures, involuntary urination, emesis, lacrimation, salivation, decreased sleep	Organophosphates, nerve agents

[a]TCAs may reduce blood pressure and cause dysrhythmias.

Information from: Calello DP, Henretig FM. Pediatric toxicology: specialized approach to the poisoned child. Emerg Med Clin North Am 2014;32:29-52; Holstedge CP, Borek HA. Toxidromes. Crit Care Clin 2012;28:479-98; Nelson LS, Howland M, Lewin NA, et al. Initial evaluation of the patient: vital signs and toxic syndromes. In: Nelson LS, Howland M, Lewin NA, et al., eds. Goldfrank's Toxicologic Emergencies, 11th ed. McGraw-Hill, 2019.

abdominal pain), increased salivation, and respiratory effects (bronchorrhea and wheezing). Lung injury can occur as a result of vaping, known as e-cigarette or vaping product use-associated lung injury, which may progress to respiratory failure (Assaf 2021). Acute cannabis toxicity is common in EDs because of various forms of the *Cannabis sativa* plant and its wide availability through smoking, inhaling, and ingestion. Tetrahydrocannabinol and cannabidiol have historically been two of the most popular cannabinoids used for euphoric, hallucination, and sedative effects. Synthetic analogs of tetrahydrocannabinol, known as synthetic cannabinoids, have gained popularity because of higher CNS receptor affinity and greater euphoric effects, with limited ability to detect use on drug tests. Signs and symptoms of marijuana exposure may include anxiety, tachycardia, and dysphoria in adolescents, as well as intractable nausea, vomiting, and abdominal pain, now classified as cannabis-induced hyperemesis syndrome. Young children are more commonly exposed to tetrahydrocannabinol in high concentrations in food products, leading to altered mental status and, in more severe cases, may present with decreased muscle coordination and seizures (Wong 2019). Despite age-restriction laws to limit those younger than 18 years from purchasing dextromethorphan, its use in dozens of OTC cold and cough products allows easy accessibility. Dextromethorphan, a semisynthetic codeine analog lacking mu-receptor activity, can produce euphoric and dissociative effects because of metabolite activity at *N*-methyl-D-aspartate receptors. Patients consuming dextromethorphan can present with a variety of dose-dependent symptoms and physical examination findings such as restlessness, mydriasis, nystagmus, ataxia, and disassociation (Wong 2019).

GENERAL MANAGEMENT STRATEGIES

Poison Control Centers

In the United States, local PCCs are easily accessible for both health care providers and the general public by internet (poison.org) or telephone (1-800-222-1222) to provide consultation services regarding the management of an ingestion. General management strategies should be considered, when appropriate, for all patients with an exposure to a potentially toxic substance or those with signs of a toxicologic emergency. Some patients will require supportive care measures, depending on specific symptoms. Decontamination strategies can be used for some ingestions, depending on the agent and time of presentation after the ingestion. Finally, antidote administration or targeted therapies when an antidote does not exist or the patient does not meet the criteria for its use may be appropriate for some patients, depending on the type of ingestion and severity.

Poison control centers were introduced in the United States in the early 1950s as a resource for the medical community regarding poison information. Services were quickly expanded to provide poison information to the general public, and a national organization was developed (formerly the American Association of Poison Control Centers; now America's Poison Centers) to streamline and provide free, open access, specialized care. Poison control centers are staffed by trained nurses, pharmacists, advanced practice providers, and board-certified toxicologists to provide consulting services for health care professionals. Staff members are also trained to help assess and triage the level of care needed (home monitoring, follow-up with primary care, or referral to hospital setting) for various types of ingestions related to drugs, plants, and chemicals. Poison control centers play an essential role as part of the medical team by performing assessments and providing monitoring recommendations in hospitalized patients with poisoning. The role of PCCs also includes reducing health care costs through decreasing ED visits and hospital lengths of stay related to poisoning (Spiller 2009; Zaloshnja 2006).

Supportive Care

Supportive care is the cornerstone in treating the patient with poisoning. Initial efforts both prehospital and in the ED should focus on basic life support measures, including maintaining a patent airway with adequate oxygenation and normalization of vital signs. Young children are at higher risk of respiratory decline because of a higher metabolic rate and decreased respiratory reserve with prolonged use of abdominal accessory muscles (Calello 2014). Pediatric patients with poisoning may also rapidly progress from an altered mental status to an obtunded/deep coma. This rapid decompensation increases the risk of airway obstruction from increased secretion production and depressed airway reflexes. Patients may need supplemental oxygen or invasive ventilation, depending on the severity of respiratory depression, declining mental status, and ability to protect their airway. Those presenting with signs and symptoms of poor circulation or shock as reflected as hypotension or tachycardia may require volume resuscitation with intravenous crystalloids, followed by vasopressors or inotropic therapy. Additional supportive care measures may include rapid assessment of a point-of-care blood glucose to indicate need for supplemental dextrose administration. Clinicians should also consider early administration of naloxone in patients presenting with depressed mental status and respiratory rate, given the wide use of opioid prescription products as well as fentanyl and heroin in the United States (Vivolo-Kantor 2020). Finally, xenobiotic-induced seizures should be treated with benzodiazepines after correction of blood glucose, if applicable (Calello 2014; Erickson 2007). The Resuscitation chapter in this book provides more detailed information on supportive care treatment strategies.

Decontamination

The American Academy of Clinical Toxicology and European Association of Poisons Centers and Clinical Toxicologists have published a series of position statements regarding the use of GI decontamination strategies in the treatment of patients with poisoning. Gastrointestinal decontamination, used to prevent absorption of an ingested substance, is not routinely indicated in most pediatric patients. In specific cases, however, GI decontamination can be considered (Table 2). Use of cathartics (e.g., stimulant laxatives) and syrup of ipecac is no longer recommended for prehospital or hospital management of ingestions because of lack of benefit in clinical outcomes and risk of severe electrolyte abnormalities and dehydration through GI losses (Höjer 2013; Position Statement 2004a, 2004b). Although syrup of ipecac is no longer manufactured in the United States, some families have not removed it from the home despite calls for its disposal (AAP 2003).

The taste and texture of activated charcoal often pose a challenge for timely administration to prevent further xenobiotic ingestion. Mixing the dose in a 1:1 ratio with chocolate milk or cola may improve palatability for patients, though ease of swallowing may not be affected with improved taste (Cheng 2007). Sorbitol formulations of activated charcoal should be avoided in children because of the risk of severe dehydration and electrolyte imbalances. If activated charcoal containing sorbitol is given, it should be limited to a one-time dose.

Antidotes

Antidote therapy may play a role in the treatment of pediatric patients with poisoning, depending on the type of xenobiotic ingestion, availability of the antidote, and timing of antidote administration in consideration of time of exposure. When used appropriately and administered in a timely manner,

Table 2. GI Decontamination Strategies

	Dosing	Role in Therapy	Contraindications/Warnings
Single-dose activated charcoal (adsorption)	Dosing of 0.5–1 g/kg recommended by some sources Infants < 1 yr Oral, NG: 10–25 g Children 1–12 yr Oral, NG: 25–50 g Adolescents Oral, NG: 25–100 g Palatability may be increased by mixing in cola or chocolate milk or adding cherry flavoring	Within ~1 hr of xenobiotic ingestion Multidose activated charcoal may be considered for initial GI decontamination and enhanced elimination in life-threatening ingestions of carbamazepine, dapsone, phenobarbital, quinine, or theophylline	GI discontinuity/perforation Anticipated need for endoscopic visualization Risk of aspiration in altered mental status/airway compromise *Formulations containing sorbitol are not recommended because of risk of severe dehydration and electrolyte imbalances. Activated charcoal containing sorbitol should be limited to a one-time dose, if used*
Whole bowel irrigation (flush out the GI tract)	Polyethylene glycol + electrolyte solution Children Oral, NG: 500 mL/hr or 25 mL/kg/hr Adolescents Oral, NG: 1–2 L/hr Continued for 4–6 hr or until clear rectal effluent	Not routinely recommended Consider in potentially toxic ingestions of sustained-release products, bezoars, or extended-release products; xenobiotic not adsorbed by activated charcoal (e.g., iron, lithium); passage of illicit drugs in body "stuffers/packers" or other foreign bodies	Nausea/vomiting GI discontinuity/perforation Hemodynamic instability
Gastric lavage (gastric irrigation)	*Not routinely recommended; see "Position Paper Update: Gastric Lavage for GI decontamination" for additional information*	Not routinely recommended because of its association with life-threatening complications (e.g., aspiration pneumonitis/pneumonia, esophageal or gastric perforation, fluid/electrolyte imbalances)	Craniofacial abnormalities; concomitant head trauma GI discontinuity/perforation Risk of aspiration in altered mental status/airway compromise

NG = nasogastric(ally).

Information from: Benson BE, Hoppu K, Troutman WG, et al. Position paper update: gastric lavage for gastrointestinal decontamination. Clin Toxicol 2013;51:140-6; Position paper: single-dose activated charcoal. Clin Toxicol 2005;43:61-87; Position paper: whole bowel irrigation. Clin Toxicol 2004;42:843-54.

specific antidotes improve outcomes and decrease morbidity and mortality (Wang 2012); however, pediatric patients are often excluded from or represent only a small fraction of the study population (Calello 2014). Although supportive care is usually appropriate and sufficient, several xenobiotics have preferred antidotes (Table 3) to be considered when appropriate in certain cases. The rest of this chapter focuses on managing common one-pill-can-kill ingestions and the pathophysiology of toxicity associated with these agents/classes.

OPIOIDS – METHADONE AND BUPRENORPHINE

Opioid toxicity among pediatric patients has increased, especially in overdose-related fatalities in adolescents (Lim 2021). Before the COVID-19 pandemic, there was an increase in pediatric exposures to methadone and buprenorphine (Darracq 2021; Farnaghi 2021; Rege 2020). The regulatory changes during the COVID-19 pandemic have increased methadone and buprenorphine availability in the home (Goldsamt 2021), which may further increase exposures to these agents. Their respective liquid and sublingual formulations may also increase the amount the patient is exposed to after an accidental ingestion.

Methadone is a full agonist, and buprenorphine is a partial agonist at the mu-opioid receptor, which is the receptor responsible for much of the toxicity. The opioid toxidrome develops quickly about 1 hour after ingestion and consists of the triad of CNS depression, respiratory depression, and miosis (Boyer 2010). When the patient is exposed to lower concentrations, the toxidrome may develop over several

Table 3. Xenobiotics with Preferred Antidotes

Toxic Agent	Selected Pediatric Antidotes and Targeted Therapies[a]
Acetaminophen	Acetylcysteine (IV, PO)
Anticholinergics	Physostigmine (IV)
Anticoagulants	
• Heparin, low-molecular-weight heparins	• Protamine (IV)
• Warfarin, vitamin K antagonists	• Phytonadione (IV, PO), prothrombin complex concentrates (IV), fresh frozen plasma (IV)
• Dabigatran	• Idarucizumab (IV)
• Direct-acting anticoagulants (rivaroxaban, apixaban)	• Inactivated coagulation factor Xa [recombinant] (IV), prothrombin complex concentrates (IV)
Benzodiazepines	Flumazenil (IV)
β-Blockers	Glucagon (IV), calcium (IV), insulin (IV), vasopressors (IV)
Botulinum toxin (secondary to botulism)	Botulinum antitoxin (IV), botulism immune globulin (IV)
Calcium channel blockers	Calcium (IV), insulin (IV), vasopressors (IV)
Cholinergics	Atropine (IV), pralidoxime chloride (IV, IM), and diazepam (IV, IM, PO) in organophosphate toxicity
Cyanide	Sodium nitrate (IV) and sodium thiosulfate (IV); hydroxocobalamin (IV)
Digoxin	Digoxin fab antibodies (IV)
Iron	Deferoxamine (IV)
Isoniazid	Pyridoxine (IV)
Lead	Calcium disodium EDTA (ethylenediaminetetraacetic acid) (IV), dimercaprol (IM), succimer (PO)
Local anesthetics, lipophilic xenobiotics	Lipid emulsion (20%) (IV)
Methemoglobinemia	Methylene blue (IV)
Methotrexate	Glucarpidase (IV), leucovorin (IV)
Opioids	Naloxone (IV, IM, intranasal, intraosseous, SC)
Sulfonylureas	Dextrose (PO, IV), octreotide (SC, IV)
Toxic alcohols (ethylene glycol and methanol)	Fomepizole (IV), ethanol (IV, PO)
Tricyclic antidepressants	Sodium bicarbonate (IV)
Valproic acid	Levocarnitine (IV, PO)

[a]Supportive care measures should be used in the management of all exposures and may include evaluation for further management with renal replacement therapy and/or extracorporeal membrane oxygenation in severe cases.

IM = intramuscular(ly); IV = intravenous(ly); PO = oral(ly); SC = subcutaneous(ly).

Information from: Dart RC, Goldfrank LR, Erstad BL, et al. Expert consensus guidelines for stocking of antidotes in hospitals that provide emergency care. Ann Emerg Med 2017;71:314-25; Madden MA. Pediatric toxicology: emerging trends. J Pediatr Intensive Care 2015;4:103-10.

hours. Compared with methadone, buprenorphine has higher rates of loss of consciousness but fewer complications, such as apnea, during hospitalization (Farnaghi 2021). Pediatric patients, unlike adults, may be more susceptible to buprenorphine's respiratory depressant effects. Methadone also inhibits the potassium channels in the myocardium, which can lead to QTc prolongation and dysrhythmias (Boyer 2010). Although methadone-induced cardiotoxicity is rare after an acute overdose in pediatric patients, providers should be aware of and monitor for it (Riasi 2021; Boyer 2010). Methadone has also been implicated in serotonin syndrome (Baldo 2018). In a matched observational study comparing

buprenorphine and methadone toxicity in pediatric patients, more patients with methadone toxicity had clinical effects classified as major, suggesting that methadone is more toxic than buprenorphine (Farnaghi 2021; Rege 2020). Although the agents' duration of effect is usually less than 8 hours (Hayes 2008; Sachdeva 2005), most pediatric exposures to methadone or buprenorphine result in hospital admission (Toce 2017b; Pedapati 2011; Hayes 2008; Geib 2006).

The triad of respiratory depression, CNS depression, and miosis with relatively acute onset should strongly suggest opioid toxicity and warrant a therapeutic trial of antidotal naloxone therapy together with ventilatory support. Therapy should not be delayed pending laboratory confirmation of an opioid in a routine urine drug test. The recommended naloxone dose is 0.1 mg/kg, but lower doses may be considered to prevent naloxone-induced opioid withdrawal in patients chronically receiving opioids. Naloxone can be administered by various routes, including intravenous, intraosseous, endotracheal, intranasal, intramuscular, and subcutaneous. Intravenous administration has the fastest onset within 5 minutes; however, intravenous access is often not established in the prehospital setting. If intravenous access has not already been established, naloxone should be administered by other routes in order not to delay the time to lifesaving therapy (Boyer 2010). Over 50% of patients have at least a partial response to naloxone (Toce 2017b; Hayes 2008). Patients who are discharged too early before opioid clearance and without an adequate trial off naloxone may be re-sedated after leaving. If several naloxone doses are needed to sustain respiratory drive, a naloxone infusion should be initiated at one-half the total hourly requirement in milligrams per hour (e.g., initiate a naloxone infusion at 1 mg/hour if the patient received a total of 2 mg). The half-life of opioid agonists exceeds that of naloxone, so patients often receive a naloxone infusion for 8–24 hours until their respiratory drive recovers (Lewis 1984). Some patients may require intubation to maintain appropriate oxygenation-ventilation. Activated charcoal may be considered for unintentional ingestions before significant absorption occurs (typically within the first hour after ingestion), after weighing the risks of pulmonary aspiration. In addition, patients should have a point-of-care glucose checked because hypoglycemia can mimic some of the opioid toxidrome findings (Bond 2012). For an unknown opioid overdose or polysubstance toxicity, the patient should have an acetaminophen concentration sent because of the prevalence of opioids containing acetaminophen (Bond 2012; Boyer 2010).

CARDIOVASCULAR DRUGS

Cardiovascular medications can pose a significant risk in the setting of pediatric ingestions. Calcium channel and β-adrenergic antagonists can lead to a wide spectrum of toxicities, depending on the class of medication and specific drug properties. Pharmacists should be aware of the difference in characteristics between various calcium channel blockers and β-blockers to understand the potential complications associated with each agent in an overdose case. Non-dihydropyridine calcium channel blockers (e.g., verapamil and diltiazem) produce greater effects within the cardiac myocytes to decrease cardiac contractility and inhibit conduction through the sinoatrial and atrioventricular nodes, inducing early bradycardia and hypotension. Dihydropyridines (e.g., amlodipine and nifedipine) produce greater effects in peripheral smooth muscle relaxation, leading to systemic vasodilation and hypotension (Shephard 2006; Michael 2004). However, selectivity is often lost in overdose cases, and effects of both classes can be observed concomitantly. In amlodipine toxicity, clinicians should be prepared for a decrease in chronotropy and inotropy leading to a profound peripheral vasodilation and bradycardia (Shephard 2006; Michael 2004).

Those who ingest nonselective β-blockers with α_1-antagonist activity are most likely to experience peripheral vasodilation and hypotension. The lipophilic properties of propranolol may induce CNS toxicities such as altered mental status and seizures. Seizures are most often observed in β-blocker toxicities involving propranolol. Propranolol also causes sodium channel blockade that results in the widening of the QRS interval on ECGs. Sotalol, a nonselective β-blocker with more prominent potassium channel blockade properties, may induce a prolonged QTc leading to torsades de pointes (Shephard 2006).

Patients presenting after a calcium channel blocker or β-blocker overdose should be monitored for signs and symptoms of cardiac toxicity through ECGs, vital sign assessments, and bedside ECGs. Serum glucose concentrations should be monitored because both calcium channel blockers and β-blockers can affect glucose. Calcium channel blockers may inhibit insulin secretion, which can cause hyperglycemia in more severe cases of toxicity. In contrast, hypoglycemia may be observed with β-blocker toxicity because β-blockers inhibit glycogenolysis and gluconeogenesis.

Management of calcium channel blocker/β-blocker overdose highly depends on the patient's signs and symptoms. Asymptomatic patients may require only vital sign and cardiac monitoring. First-line therapy for hypotension includes intravenous fluid resuscitation and vasopressors. Glucagon administration may be considered in β-blocker toxicity to treat bradycardia because glucagon bypasses β-receptors to facilitate normal adenosine triphosphate use by the cardiac myocyte. Initial glucagon bolus doses are 0.05 mg/kg intravenously, with a typical dosing range of 3–10 mg. Glucagon can also be administered as a continuous infusion at a rate (mg/hour or mg/kg/hour) equal to the effective bolus dose. Pharmacists should note the reconstitution process of glucagon (1 mg of glucagon diluted with 1 mL of sterile water) and time required for preparation of larger bolus doses and infusions. In addition, many institutions may not have large

quantities of glucagon available on-site to support long durations of therapy. Antiemetics may be needed because glucagon commonly causes nausea and vomiting. Calcium gluconate boluses (60 mg/kg) can be considered in calcium channel blocker overdose to overcome drug antagonist activity at calcium channel receptors in the cardiac myocyte. Both glucagon and calcium therapy may provide benefit in heart rate management. Glucagon is more effective for β-blocker toxicity than for calcium channel blocker toxicity. Atropine (0.02 mg/kg intravenously) is commonly used as part of the initial management of symptomatic bradycardia; however, it is not typically effective in the setting of β-blocker and calcium channel blocker–induced bradycardia (Bartlett 2019; Shephard 2006; Michael 2004).

For patients with signs of diminished cardiac output, high-dose insulin euglycemic therapy can improve cardiac contractility. Regular insulin is administered at a bolus dose of 1 unit/kg, followed by a continuous infusion of 0.5–1 units/kg/hour, with dose titrations up to a maximum of 10 units/kg/hour depending on patient response and improvements in cardiac output, heart rate, and mean arterial pressure (Krenz 2018; St-Onge 2017). Potassium and glucose concentrations should be monitored closely, with more frequent monitoring (e.g., glucose checks every 15 minutes, potassium checks every 60 minutes) during insulin infusion titrations. Blood glucose concentrations should be maintained at 150–200 mg/dL, with supplemental dextrose infusions titrated on the basis of insulin dose changes and response. The clinician should be cautious with potassium repletion, with general acceptance of permissive hypokalemia (e.g., K greater than 2.8 mEq/L) to prevent large shifts in serum and intracellular potassium when the insulin infusion is discontinued. Patients may require more concentrated insulin and dextrose infusions to prevent volume overload throughout the acute treatment phase (Krenz 2018; St-Onge 2017).

Patients with significant signs of cardiovascular compromise should be evaluated for extracorporeal membrane oxygenation. For cardiac arrest from presumed calcium channel blocker or β-blocker toxicity, lipid emulsion therapy may also be considered. A bolus of lipid emulsion 20% 1.5 mL/kg (according to lean body weight) can be administered, followed by an infusion of 0.25 mL/kg/minute for 30–60 minutes. The maximum total lipid emulsion dose is 12.5 mL/kg (St-Onge 2017). Pharmacists should be aware of the effects of lipids on other medications, such as decreasing the effectiveness of vasopressor therapy as well as interfering with laboratory samples.

SULFONYLUREAS

Sulfonylureas are a commonly prescribed class of oral hypoglycemic agents used in the management of type 2 diabetes. The second- and third-generation sulfonylureas (e.g., glipizide, glyburide, and glimepiride) are the most commonly used agents in practice and cause blood glucose reduction through release of insulin from pancreatic beta cells. Sulfonylureas have a narrow therapeutic index and can cause hypoglycemia as quickly as 30 minutes to 2 hours of ingestion, but the onset of hypoglycemia can be delayed up to 24 hours. Extended-release formulations are more likely to cause a delayed hypoglycemic event. The duration of hypoglycemia is prolonged and typically lasts around 24 hours (Toce 2017a). Ingestion of a single sulfonylurea tablet by a young child can induce fatal hypoglycemia; therefore, patients usually require monitoring to ensure age-appropriate mental status, adequate oral intake, and normal blood glucose concentrations without additional oral or intravenous dextrose supplementation (Little 2005). Pediatric patients are at higher risk of hypoglycemia because of increased glucose use at baseline and with impaired glucose production as a result of low total body muscle mass and possibly reduced glycogen storage (Toce 2017a).

Hypoglycemia after sulfonylurea ingestion usually occurs within 8 hours but can occur up to 24 hours after the ingestion (Little 2005). Thus, patients are typically monitored for at least 24 hours after a sulfonylurea exposure. Patients with blood glucose concentrations below 60 mg/dL or presence of symptoms should receive oral or intravenous dextrose. Intravenous dextrose boluses may be followed by a continuous infusion of dextrose (typically 5%–20%), depending on blood glucose trends, volume status, and intravenous access site (peripheral or central) (Little 2005; Michael 2004). Intramuscular glucagon is not typically recommended once intravenous access has been established because of the delayed onset of action. Patients should be monitored for rebound hypoglycemia because exposure to continuous dextrose infusions may stimulate increased insulin secretion. Blood glucose concentrations should be monitored hourly in asymptomatic patients and more frequently, as needed, in those with symptomatic hypoglycemia (Dougherty 2010).

Octreotide has also been used in the management of refractory hypoglycemia as a result of sulfonylurea toxicity. Octreotide is a somatostatin analog that binds to the voltage-gated calcium channels in the pancreatic beta cells to prevent downstream insulin secretion through a decrease in the influx of calcium (Dougherty 2010). Octreotide doses of 1–2 mcg/kg up to a maximum of 50 mcg can be administered subcutaneously (preferred because of longer duration of action) or intravenously every 6–12 hours. In rare situations refractory to standard treatment, the patient may be initiated on an octreotide continuous infusion. Octreotide may cause adverse effects like injection site pain, nausea, abdominal pain, and hyperglycemia. Bradycardia and hypotension have also been noted with octreotide use in other indications; therefore, patients should be monitored closely when receiving treatment (Dougherty 2010). The octreotide long-acting depot injectable is not recommended for this indication because of its delayed onset of action.

Even if asymptomatic, patients are typically admitted for 24 hours to monitor for hypoglycemia. After stabilization of blood glucose and discontinuation of octreotide or supplemental dextrose, patients should be monitored for 4–6 hours before discharge. Patients should not be symptomatic at the time of discharge. This is done to minimize the risk of rebound hypoglycemia because supplemental dextrose and octreotide have a shorter duration of effect than the toxin (Dougherty 2010; Little 2005; Michael 2004).

ANTIDEPRESSANTS – SSRIS, SNRIS, BUPROPION, AND TRICYCLIC ANTIDEPRESSANTS

Antidepressants are in the top 25 substance categories most often involved in the adult or pediatric exposures reported to the National Poison Data System (Gummin 2021).

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are among the most common classes of antidepressants prescribed and among the most common agents involved in adolescent suicide attempts (Gilley 2020). The therapeutic index of SSRIs is fairly high, with no more than mild toxicity expected with ingestions up to 5 times the initial adult therapeutic dose (Nelson 2007). Selective serotonin reuptake inhibitors are typically well tolerated in overdose (Isbister 2004), with typical symptoms including, but not limited to, GI effects, somnolence, anxiety, tremor, hypertension, and bradycardia. However, there are a few notable exceptions. Seizures and cardiac effects like QTc prolongation are more common with citalopram (Klein-Schwartz 2012; Hayes 2010; Yilmaz 2010). Although less toxic than citalopram, cardiac effects may also be observed with escitalopram toxicity (Klein-Schwartz 2012; Hayes 2010; Van Gorp 2009). Compared with tricyclic antidepressant (TCA) overdoses, SSRI overdoses are less likely to cause coma, require ICU admission, or prolong the QRS interval; however, they are more likely to cause serotonin syndrome (Whyte 2003). Around 25% of venlafaxine overdoses result in seizures, which may be delayed 7–24 hours after ingestion (Vo 2020). Compared with TCAs, venlafaxine overdoses are less likely to cause coma but more likely to cause serotonin syndrome (Whyte 2003). Although rare, serotonin syndrome is most likely after an overdose of antidepressants, particularly SSRIs (Hutchison 2021). Polypharmacy can contribute to the development of serotonin syndrome (Davis 2020).

Cardiotoxicity is the hallmark of TCA toxicity (Ruben Thanacoody 2005). Fortunately, most unintentional pediatric exposures to TCAs are asymptomatic (McFee 2001a). Minor toxic effects may occur with TCA ingestions greater than 5 mg/kg, except for greater than 2.5 mg/kg for desipramine, nortriptyline, and trimipramine (Woolf 2007; McFee 2001b). Moderate to severe toxicity is most likely with ingestions greater than 10–20 mg/kg (Rosenbaum 2005). Electrocardiographic manifestations of QRS greater than 100 milliseconds in lead aVR can be considered diagnostic when there are suspicions for and clinical symptoms suggestive of TCA toxicity (Ruben Thanacoody 2005; Groleau 1990). Cardiac effects include hypotension, tachycardia, QRS prolongation, PR prolongation, QTc prolongation, and dysrhythmias (Ruben Thanacoody 2005; Pentel 1986). Seizures, agitation, coma, and anticholinergic effects (e.g., dry mouth, mydriasis, urinary retention) may also occur (Ruben Thanacoody 2005; McFee 2001a).

Bupropion is a unicyclic antidepressant that is a selective neuronal reuptake inhibitor of dopamine, norepinephrine, and serotonin with some peripheral α_1-adrenergic agonism and possibly sodium channel blockade or gap junction inhibition (Caillier 2012; Spiller 2010). Patients who ingest bupropion less than 10 mg/kg are unlikely to develop significant symptoms (Spiller 2010). Most symptomatic pediatric patients have ingested a mean dose of 18.6 mg/kg (±13.4 mg/kg) (Spiller 2010), and a mean bupropion dose of 38.8 mg/kg (±44.0 mg/kg) has been observed in moderate to major outcome cases (Beuhler 2010). Overdoses can result in sinus tachycardia, nausea, vomiting, hyperactivity, agitation, hallucinations, seizures (single, multiple, or status epilepticus), hypertension, QRS prolongation, QTc prolongation, and dysrhythmias, including cardiac arrest (Overberg 2019; Beuhler 2010; Spiller 2010; Belson 2002). Age 13–18 years, QTc greater than 500 milliseconds, and tachycardia with heart rate greater than 140 beats/minute have been associated with seizure development after a bupropion overdose (Rianprakaisang 2021). Average time to seizure is 4 hours with a maximum of 14 hours, which could suggest ingestions of delayed- or extended-release formulations (Beuhler 2010). Bupropion overdoses are significantly more likely than SSRI overdoses to result in seizures, hallucinations, major outcomes (symptoms as a result of the exposure that were life threatening or resulted in significant residual disability or disfigurement), and fatalities. As such, patients with bupropion overdose have more need for cardiopulmonary resuscitation, intubation, vasopressors, and benzodiazepines (Overberg 2019). Compared with TCA overdoses, bupropion overdoses are more likely to cause seizures, admissions, and major outcomes. Bupropion overdoses are less likely to result in hypotension and intubations than TCA overdoses (Sheridan 2018).

Initial monitoring after an antidepressant overdose consists of an ECG, a basic metabolic panel, and vital signs. As symptoms develop, more frequent ECGs (e.g., every 2 hours) and continuous telemetry may be needed. Pharmacists should consult with the physicians to determine whether the patient's ECG has manifestations of sodium channel blockade, including QRS greater than 100 milliseconds in lead aVR, terminal 40-ms frontal plane axis greater than 120 degrees, and Brugada pattern (Ruben Thanacoody 2005; Groleau 1990), which may influence the patient's treatment. Qualitative urine drug tests for TCAs generate many false positives (Brahm 2010). In general, a 6-hour observation

time is needed (Woolf 2007); however, the observation time may be extended to 24 hours in the setting of bupropion extended-release formulations and venlafaxine exposures (Vo 2020; Overberg 2019).

Treatment of SSRI, SNRI, and bupropion overdoses consists of supportive care. Activated charcoal can be administered within 1–2 hours of ingestion in patients who are alert and oriented. Antiemetics can be used to manage nausea and vomiting. QTc-prolonging agents should be avoided and electrolytes optimized in the setting of QTc prolongation (Bradberry 2005). Intravenous fluids can be used to treat hypotension and sinus tachycardia. Particularly with TCA overdoses, vasopressors may also be needed to manage the hypotension (Knudsen 1997). Benzodiazepines can be used to manage agitation, tremors, and seizures (Woolf 2007). Sodium bicarbonate is the antidote for patients with TCA overdoses experiencing cardiotoxicity, as evidenced by a QRS greater than 100 milliseconds in lead aVR. Sodium bicarbonate is given intravenously as a bolus (1–2 mEq/kg), followed by an infusion (around 1.5 times the maintenance fluid rate for the patient's weight). Sodium bicarbonate is titrated to maintain a pH of 7.45–7.55 (Woolf 2007; Bradberry 2005). Sodium bicarbonate in combination with direct-acting vasopressors such as epinephrine and norepinephrine may be most effective for treating TCA toxicity (Knudsen 1997). Some toxicologists may also recommend sodium bicarbonate for bupropion or citalopram toxicity cases with a QRS greater than 100 milliseconds in lead aVR (Bruccoleri 2016). In a sodium bicarbonate shortage, sodium acetate can replace sodium bicarbonate on an equimolar basis; however, patients should receive sodium acetate as a continuous infusion instead of as a bolus (Neavyn 2013). Hypertonic saline 3% intravenous boluses (2–4 mL/kg not to exceed 100 mL) may be considered in the absence of sodium bicarbonate or sodium acetate (ACMT 2017). An ECG and venous blood gas with potassium should be obtained at least every 6 hours in addition to placing the patient on continuous telemetry while receiving sodium bicarbonate therapy (Ruben Thanacoody 2005). Lidocaine 1 mg/kg intravenously can be used as an adjunct to sodium bicarbonate to treat dysrhythmias associated with TCA toxicity (Foianini 2010; Bradberry 2005; Pentel 1986). Intubation may be needed to maintain oxygenation and ventilation (Overberg 2019). Lipid emulsion therapy has been used in the management of treatment-refractory TCA and bupropion overdoses during peri-arrest or cardiac arrest situations (Gosselin 2016; Presley 2013).

Most admissions for bupropion or TCA toxicity are for 1 or 2 days (Overberg 2019; McFee 2001a). In patients with home antidepressant overdoses, bupropion and TCAs may safely be resumed when the signs and symptoms of toxicity have resolved and 1 additional elimination half-life has passed (Tay 2019). Serotonin syndrome is a diagnosis of exclusion and may be diagnosed using decision rules such as the Hunter Serotonin Toxicity Criteria (i.e., spontaneous clonus, inducible clonus and agitation or diaphoresis, ocular clonus and agitation or diaphoresis, tremor and hyperreflexia, or hypertonic and temperature greater than 38°C and ocular or inducible clonus) (Dunkley 2003). Management of serotonin syndrome consists of discontinuing the serotonergic agent and administering benzodiazepines with or without cyproheptadine (e.g., 0.25 mg/kg/day divided every 6 hours to a maximum of 12 mg/day) (Hutchison 2021).

BENZONATATE

Benzonatate is a commonly prescribed short-acting antitussive agent (McLawhorn 2013) and may have been prescribed more often as a result of the COVID-19 pandemic (O'Keefe 2021). Benzonatate is not recommended for use in patients younger than 10 years (McLawhorn 2013). Benzonatate is structurally related to tetracaine and results in both local anesthetic effects on respiratory stretch receptors and sodium channel blockade. Intentional overdoses of benzonatate increase the risk of significant toxicity; however, as little as 200 mg can result in severe toxicity, including cardiac arrest, in children younger than 6 years (Winter 2010). Cardiotoxicity and neurotoxicity resembling that of TCA or local anesthetic toxicity are the hallmark symptoms of benzonatate overdose. These symptoms develop rapidly over the course of minutes and include QRS prolongation, QTc prolongation, dysrhythmias including cardiac arrest, hypotension, tachycardia, respiratory depression, agitation, seizures, and coma (Minhaj 2021; Billington 2020; McLawhorn 2013; Winter 2010; Crouch 1998). Most cases that develop cardiac arrest with return of spontaneous circulation do not develop neurologic deficits (Minhaj 2021). Because of benzonatate's short half-life, asymptomatic patients should be observed for at least 4 hours after an exposure. Management consists of supportive care such as a sodium bicarbonate 1- to 2-mEq/kg intravenous bolus for QRS prolongation and dysrhythmias, intravenous fluids with or without vasopressors for hypotension, magnesium for torsades de pointes, antidysrhythmics for dysrhythmias, intubation for respiratory depression, and lipid emulsion therapy with lipid emulsion 20% 1.5 mL/kg intravenously, then 0.25 mL/kg/minute for 30 minutes for cardiac arrest (Minhaj 2021; Billington 2020; McLawhorn 2013; Winter 2010; Crouch 1998).

CHLOROQUINE AND HYDROXYCHLOROQUINE

Chloroquine and hydroxychloroquine are traditionally used as antimalarials or anti-inflammatory agents in the treatment of rheumatoid arthritis or lupus (Doyno 2021); however, they were also temporarily considered for use off-label for the treatment of COVID-19 (Stolbach 2020). This practice has since been rejected. Chloroquine is more potent than hydroxychloroquine, but they produce similar toxicologic effects (Doyno 2021; Della Porta 2020; Smith 2005). Severe

Patient Care Scenario

K.L. is a 17-year-old female adolescent (weight 61 kg) who was admitted to the pediatric ICU for monitoring after an intentional ingestion of her mother's amlodipine 10-mg tablets. The patient arrived at the ED within 30 minutes of ingestion and received 25 g of activated charcoal orally. Her initial vital signs were stable with no significant findings on ECG or bedside echocardiography. However, about 5 hours after ingestion, her blood pressure has decreased to 78/44 mm Hg, and her heart rate is now 50 beats/minute. What initial therapies should be initiated for this patient? What therapies should be initiated for refractory cases?

ANSWER

Initial blood pressure management in the setting of calcium channel blocker toxicity includes intravenous crystalloid fluid administration. For persistent hypotension after adequate fluid resuscitation, vasopressor therapy such as a norepinephrine or epinephrine infusion should be initiated to increase mean arterial pressure and blood pressure. K.L. should be placed on continuous cardiac monitoring, with serial bedside ultrasounds/echocardiograms performed to access cardiac output. For poor response to vasopressor therapy or poor contractility, hyperinsulinemia euglycemia therapy should be initiated, with cautious glucose and potassium monitoring during initiation of insulin bolus/infusion and during any rate adjustments.

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toxicity can develop rapidly over 1–2 hours, and patients should be observed for at least 4–6 hours after an exposure. As few as 1 or 2 tablets of chloroquine (greater than 10 mg/kg) can be toxic in pediatric patients (Smith 2005). Providers should obtain a CBC, comprehensive metabolic panel, and ECG at least every 4 hours. Depending on symptoms, patients should also be placed on continuous telemetry. Mild toxicity consists of GI effects, headache, visual disturbances (e.g., diplopia, tunnel vision, mydriasis, loss of visual acuity), and hearing disturbances (e.g., tinnitus, decreased hearing acuity). Moderate to severe toxicity consists of quinidine-like sodium channel blockade causing cardiotoxicity (e.g., QRS prolongation, QTc prolongation, dysrhythmias, hypotension); hypokalemia secondary to intracellular shifts; hypoglycemia from a mechanism similar to that of sulfonylureas; seizures, coma, hypoxia, myopathy, and weakness; and bone marrow suppression. Acute severe toxicity is associated with a mortality rate as high as 30% (Della Porta 2020). Management consists of supportive care. Activated charcoal 1 g/kg orally, nasogastrically, or orogastrically may be considered in patients who present within 1–2 hours of the ingestion and have no contraindications to therapy. Antiemetics can be used to manage GI symptoms; however, they can prolong QTc intervals. Hypotension is managed with intravenous fluids with or without vasopressors. Patients may require high doses of vasopressors. Patients with severe overdoses may also benefit from diazepam 2 mg/kg intravenously over 30 minutes, followed by 1–2 mg/kg/day, because diazepam's peripheral benzodiazepine receptor agonist effects are cardioprotective (Doyno 2021; Della Porta 2020). A sodium bicarbonate 1- to 2-mEq/kg intravenous bolus followed by a continuous infusion to maintain a pH of 7.45–7.55 can be used to manage cardiotoxicity with QRS prolongation. Clinicians should be cautious with potassium supplementation because hyperkalemia may develop 12–24 hours after the ingestion once the potassium shifts extracellularly. Dextrose supplementation should be used as needed to manage hypoglycemia. Benzodiazepines may also be used to treat seizures. Class IA, IC, and III antidysrhythmics should be avoided (Doyno 2021; Della Porta 2020). Lipid emulsion therapy and extracorporeal membrane oxygenation have also been reported in the management of severe toxicity (Della Porta 2020).

TOXIC ALCOHOLS

The term *toxic alcohols* typically refers to ethanol, methanol, ethylene glycol, and isopropanol. Toxic alcohols are water soluble, rapidly absorbed, and renally eliminated. In this chapter, ethanol toxicity is not discussed. Given their similar presentations and treatment strategies (Ross 2022), methanol and ethylene glycol are discussed together.

Ethylene glycol exposures from antifreeze ingestions are more common than methanol exposures from windshield wiper fluid, solid cooking fuel for camping, model airplane fuel, and gasoline antifreeze (Ross 2022; Hoyte 2021). Beginning in the 1990s, bittering agents were added to some ethylene glycol–containing antifreeze products as a deterrent, but this has not reduced pediatric exposures (White 2009; Mullins 2004). Methanol is metabolized by alcohol dehydrogenase to formaldehyde, which undergoes further metabolism through aldehyde dehydrogenase to formic acid. Ethylene glycol is metabolized by alcohol dehydrogenase to glycolaldehyde, which then undergoes metabolism through aldehyde

dehydrogenase to glycolic acid. Glycolic acid undergoes further metabolism through lactate dehydrogenase or glycolic acid oxidase to form glyoxylic acid, which is further metabolized to α-hydroxy-β-ketoadipic acid, oxalic acid, glycine, and hippuric acid. The high toxicity of both methanol and ethylene glycol is a result of their toxic metabolites (Ross 2022). Signs and symptoms of toxicity include CNS depression through inhibition of γ-aminobutyric acid and *N*-methyl-D-aspartate glutamate receptors (parent alcohol primarily), initial osmol gap reflective of the accumulation of the parent alcohol, and later anion gap metabolic acidosis as a result of the accumulation of toxic organic acids. Elevated osmol gaps [measured osmolality minus calculated osmolarity defined as [[sodium × 2] + [glucose/18] + [BUN/2.8]] and anion gaps (sodium − [chloride + bicarbonate]) are not exclusive to toxic alcohols. Methanol can also cause visual impairments ranging from blurred vision to total blindness, which can occur 12–24 hours after initial ingestion. Ethylene glycol can cause acute kidney injuries secondary to damage from the calcium oxalate crystals and can also cause hypocalcemia (Ross 2022). Toxic alcohol concentrations should be obtained when there is suspicion for a toxic alcohol ingestion, though it can take upward of 24–48 hours to result at most institutions. Thus, treatment is empirically initiated when there is suspicion for a toxic alcohol exposure on the basis of an osmol gap greater than 10 mOsm/L [measured serum osmolality − calculated osmolality] (early presenters), anion gap metabolic acidosis (late presenters), or symptoms that correlate with exposure (e.g., visual changes with methanol, acute kidney injury with ethylene glycol). Oxalate crystalluria and urine fluorescence (from fluorescein additive in antifreeze) may not be observed in all ethylene glycol toxicity cases (Parsa 2005; Casavant 2001). Gastrointestinal decontamination is rarely indicated because toxic alcohols are rapidly absorbed and have limited binding to activated charcoal (Ross 2022). Patients should be initiated on empiric therapy with fomepizole or ethanol when fomepizole is not available (Ross 2022; Caravati 2005).

Although there are two treatment options (fomepizole or ethanol) for methanol or ethylene glycol toxicity, fomepizole is the antidote of choice. Both fomepizole and ethanol reduce the production of the toxic metabolites through direct inhibition of alcohol dehydrogenase (fomepizole) or act as a competitive substrate for alcohol dehydrogenase (ethanol). Fomepizole is preferred because it is associated with fewer medication errors, fewer adverse effects, easier dosing strategies, and more predictable treatment effect than ethanol (Lepik 2011, 2009; Brent 2010; Caravati 2005). Pediatric patients may be particularly vulnerable to ethanol's toxic effects, such as CNS depression, respiratory depression, and hypoglycemia. Fomepizole's cost may limit its availability at some institutions (Ross 2022; Caravati 2005). Fomepizole is dosed at 15 mg/kg intravenously, followed by 10 mg/kg intravenously every 12 hours until the ethylene glycol or methanol concentrations are less than 20 mg/dL (Ross 2022). Dialysis may also be used depending on the toxic alcohol concentration, symptoms, response to antidotal therapy, and evidence of renal impairment (Ross 2022; Roberts 2015). In patients receiving dialysis or more than four doses, fomepizole dose or frequency adjustments are needed (Ross 2022).

Isopropanol is a clear, colorless liquid with a fruity odor and bitter taste that is commonly found in rubbing alcohols, cleaners, disinfectants, solvents, inks, and pharmaceuticals. Isopropanol is metabolized by alcohol dehydrogenase to acetone. Unlike methanol and ethylene glycol, isopropanol is the parent alcohol, not the metabolites, that is responsible for toxicity (Slaughter 2014; Stremski 2000). Isopropanol ingestions greater than 30 mL can cause toxicity in pediatric patients (Stremski 2000). Isopropanol causes a profound CNS depression. Additional signs of toxicity include nausea, vomiting, hemorrhagic gastritis, ataxia, elevated osmol gap without anion gap, ketonemia, ketonuria, fruity odor on the breath, and respiratory depression. Severe toxicity with circulatory collapse is rare. Toxicity typically develops within 30 minutes to 2 hours of ingestion. Management consists of supportive care. Dialysis may be indicated for the rare management of refractory cases with hypotension, CNS depression, and respiratory depression (isopropanol concentration greater than 200 mg/dL) (Slaughter 2014; Stremski 2000).

LAUNDRY PODS

Use of laundry detergent pods, also known as laundry detergent packs or liquitabs, in households across the United States has increased in popularity during the past decade. Laundry detergent pods contain highly concentrated detergent within a water-soluble polyvinyl alcohol membrane. Young children are drawn to these household products because of their bright colors, good smell, smooth texture, and resemblance to candy (O'Donnell 2017). Social media challenges encouraging intentional ingestion of the pods have also led to exposures in older children (CPSC 2022). Although companies have tried to improve safe storage of pods through safety messages and additional locking features on the containers, many consumers have opted to remove the products from their households (O'Donnell 2017; Beuhler 2013). Although most reported exposures to laundry pods have not led to significant health complications, clinicians should be aware of the various routes of toxicities associated with pods because some fatalities have been linked with laundry pod exposures (Reynolds 2021; Rocka 2021). Fortunately, the incidence of morbidity and mortality has decreased since the implementation of product safety changes (Reynolds 2021).

The mechanism of toxicity of laundry detergent pods is thought to be linked to the high concentrations of both nonionic surfactants (ethoxylated alcohols) and anionic surfactants (ethanol and propylene glycol) in the detergent's membrane packaging. Contact with mucous membranes or

wet surfaces potentiates disintegration of the membrane, leading to contact with both the polyvinyl alcohol pod membrane and the pod contents. The most common route of exposure to the liquid detergent is through ingestion, though ocular and dermal exposures have also been reported. The most common symptoms after ingestions include vomiting and salivation. Other less common symptoms of toxicity include coughing, choking, lethargy, seizures, gastric burns, and respiratory arrest (Rocka 2021).

Management of laundry pod exposure is mainly targeted supportive care, depending on the route of exposure. Patients presenting after a laundry pod ingestion should be evaluated for GI, CNS, and respiratory-related effects.

E-CIGARETTES

Electronic cigarettes (e-cigarettes), or vaping products, have become popular among adolescents and young adults, making pediatric patients more vulnerable to toxicity from accidental ingestions of these highly concentrated, flavored products (Gordon 2022; Overbeek 2020). E-cigarettes use liquids ("e-liquids" or "e-juice," "vape juice") supplied from bottles or prefilled cartridges. These typically have colorful packaging and vary in size (10–120 mL) and nicotine concentration (3–36 mg/mL), which contribute to the unintentional ingestion and the associated toxicity. Compared with nicotine exposures from traditional cigarettes, children exposed to nicotine in e-cigarettes are 5.2 times more likely to be admitted to a health care facility and have 2.6 times the risk of a severe outcome (Kamboj 2016). Nicotine toxicity results in overstimulation of the nicotinic acetylcholine receptors, leading to GI effects, dizziness, headache, tremors, diaphoresis, tachycardia, hypertension, pallor, and seizures (Overbeek 2020). The most common symptoms after ingestion of e-cigarette liquids include tachycardia, agitation or lethargy, and vomiting (Maessen 2020). Significant toxicity can occur with ingestions of greater than 3 mg/kg. The pediatric lethal dose is considered 6–13 mg/kg (Mayer 2014), which may be as little as 5 mL in a child younger than 2 years. The onset of significant toxicity normally occurs within a few hours. Supportive care is the treatment mainstay. Benzodiazepines are the primary adjunct used to reduce the autonomic nervous system stimulation (Overbeek 2020; Kim 2015). In addition, e-cigarettes can contain many additives (e.g., diethylene glycol, acrolein, formaldehyde) and drugs other than nicotine (e.g., tetrahydrocannabinol). The chronic health hazards from vaping are unknown. One emerging health hazard is e-cigarette or vaping product use-associated lung injury, which causes respiratory, GI, and constitutional symptoms together with bilateral ground-glass opacifications on chest radiography. Most patients with e-cigarette or vaping product use-associated lung injury are hospitalized and receive supportive care, including corticosteroids (no standardized regimen) (Cao 2020; Siegel 2019).

Practice Points

- **Contact Poison Control by telephone (1-800-222-1222) to reach the PCC to consult with a specialist in poison information or the toxicologist for assistance in managing a pediatric exposure.**
- **The approach to the undifferentiated pediatric patients with poisoning should involve a thorough physical examination and history while also incorporating patient age, demographics, and developmental stages when assessing for likely toxins and signs of common toxidromes.**
- **Supportive care interventions can be considered for all ingestions and are not limited to specific exposures or toxins.**
- **Targeted therapies and antidotes may be considered in ingestions having the potential for significant harm, with attention to timing of administration in relation to ingestion, variations in dosing depending on patient weight, and monitoring.**
- **Clinicians should be familiar with one-pill-can-kill medications to facilitate rapid evaluation and treatment.**
- **Laundry pods, electronic nicotine delivery systems, and button batteries have become common household items ingested by pediatric patients; however, treatments are currently largely limited to supportive care.**

BUTTON BATTERIES

Button batteries are common in household products, including electronic devices used by children. Ingestions of button batteries cause injury because of a combination of local pressure necrosis, corrosive damage from leakage of battery content, heavy metal toxicity, and electric injury (Mubarak 2021). Ingestion of button batteries by pediatric patients is linked to a high rate and wide spectrum of morbidity and mortality ranging from no effect to death, with an increased risk in patients younger than 4 years (Litovitz 2010). Clinicians should recognize the immediate challenges of button battery ingestion injuries and characteristics of high-risk ingestions, such as batteries with large diameters (greater than 20 mm) that are likely to cause impaction in the esophagus, as well as button batteries containing lithium, because of an increase in voltage delivery compared with other ions (Kramer 2015). Mucosal damage can occur within 2 hours of button battery lodgment, but severe complications may take longer to develop. Signs and symptoms associated with battery ingestion include drooling, emesis/hematemesis, stridor, abdominal pain, and respiratory distress. Perforations rarely develop in the first 12 hours and are usually diagnosed within the first 2 days (Mubarak 2021). Radiography is commonly used to assess the location of the battery and help determine the next course of action. The narrowest side of the button battery contains the negative battery pole and is responsible for most of the damage caused by the exposure (NCPC 2018). Button batteries in the esophagus require immediate removal because of the risk of developing caustic injuries and progression to perforation (O'Donnell 2017), whereas smaller

button batteries in the stomach may be monitored with serial imaging. Patients with hematemesis or signs of hemodynamic instability may require battery removal in the operating room with advanced imaging to detect more invasive injuries (Leinwand 2016; Kramer 2015). Honey (10 mL every 10 minutes up to six doses in children older than 12 months and ingestion less than 12 hours prior) in the prehospital setting and sucralfate (1 g/10 mL every 10 minutes up to three doses) before endoscopy can be considered as acid-neutralizing therapies to coat the battery surface with a nonpolar substance and delay tissue burns related to battery contact until the battery can be removed (Mubarak 2021; NCPC 2018). After removal, patients will likely require outpatient follow-up with gastroenterology because complications like fistulas and esophageal strictures can take weeks to months to develop (Mubarak 2021). Although medication therapy may be limited in the management of button battery ingestions, pharmacists should be aware of the severe consequences of the ingestion and recognize the urgent need for gastroenterology consultation and evaluation.

CONCLUSION

The pharmacist's role in managing pediatric toxicologic emergencies encompasses both clinical and operational aspects. Pharmacists can help other health providers understand signs and symptoms of common toxidromes and quickly identify exposure to one-pill-can-kill medications. Early recognition of ingestions and exposures can prevent delays in important pharmacotherapy interventions or monitoring strategies, depending on the xenobiotic or presumed toxidrome. Pharmacists should advocate for consulting the PCC in the management of all pediatric toxicology cases. The bedside pharmacist can serve as a liaison between the clinical team and the PCC by providing information to the toxicologist as requested and can help facilitate recommendations for supportive care or administration of antidotes. Finally, pharmacists can provide recommendations for dosing strategies, monitoring values, and adverse effects of supportive and antidote therapies. From an operational perspective, pharmacists can play an essential role in the development of an antidote stocking guide (Dart 2017) and procurement to ensure the availability and/or process to obtain antidotes in a timely manner in future toxicology cases.

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Self-Assessment Questions

1. An 18-month-old boy (weight 9.8 kg) is referred to the ED by his pediatrician after his grandmother discovers the child eating tablets from her weekly pill organizer. Her medication list includes aspirin enteric coated 81 mg daily, levothyroxine 88 mcg every morning before breakfast, metformin 500 mg twice daily, atorvastatin 10 mg nightly, lisinopril 10 mg daily, glipizide extended release 10 mg daily, and melatonin 3 mg nightly. Which one of the following medications most likely prompted the referral for emergency evaluation?

   A. Aspirin
   B. Lisinopril
   C. Levothyroxine
   D. Glipizide extended release

Questions 2–4 pertain to the following case.

S.R. is a 10-year-old boy (weight 34 kg) with no significant medical history seen by emergency medical services after his brother reported changes in his behavior. His blood pressure is 88/54 mm Hg, heart rate is 45 beats/minute, and respiratory rate is 8 breaths/minute. S.R. is minimally arousable.

2. Which one of the following toxidromes most likely explains S.R.'s presentation?

   A. Opioid or sedative/hypnotic
   B. Cholinergic or sympathomimetic
   C. Anticholinergic or opioid
   D. Sedative/hypnotic or sympathomimetic

3. Which one of the following pertinent physical examination findings most likely provides additional information to clarify S.R.'s presenting toxidrome?

   A. Hyporeflexia
   B. Miosis
   C. Diaphoresis
   D. Hyperthermia

4. Which one of the following is the most appropriate prehospital opioid reversal strategy to use in S.R.?

   A. Naloxone 0.1 mg/kg intranasally
   B. Naltrexone 0.01 mg/kg intramuscularly
   C. Naloxone 4 mg intravenously
   D. Naltrexone 4 mg intravenously

5. A 2-year-old girl (weight 12.3 kg) is brought to the ED by her parents after she was observed ingesting 1 glimepiride 4-mg tablet about 45 minutes before arrival. The patient is alert and interacting appropriately with her parents. Which one of the following doses of activated charcoal is best to recommend for this patient?

   A. 12.5 mg of activated charcoal
   B. 12.5 g of activated charcoal
   C. 25 g of activated charcoal with sorbitol
   D. Activated charcoal not indicated, given patient's age

Questions 6 and 7 pertain to the following case.

R.T. is a 4-year-old boy (weight 16 kg) brought to the ED after a witnessed ingestion. His parents report several prescription medications in the household, including many medications prescribed to grandparents and stored in bottles. Medications were found scattered by family; however, the family states that both grandparents have a history of atrial fibrillation and that the mother takes medications to prevent and treat migraines. The patient interacts with staff appropriately on arrival, but his vital signs are significant for hypotension and bradycardia. His blood glucose is 65 mg/dL.

6. Which one of the following medications is best to recommend for the initial management of R.T.'s bradycardia?

   A. Calcium gluconate 200-mg/kg intravenous bolus
   B. Regular insulin infusion, starting at 1 unit/kg/hour
   C. Glucagon 50 mcg/kg intravenously × 1
   D. Atropine 1 mg intravenously × 1

7. Two hours after ED arrival, R.T. has become lethargic, and the team reports witnessed seizure-like activity. R.T. is treated with benzodiazepines and ultimately requires intubation because of persistent altered mental status. A repeat ECG reveals a prolonged QRS interval. Overdose of which one of the following medications most likely explains R.T.'s presentation?

   A. Nifedipine
   B. Metoprolol
   C. Verapamil
   D. Propranolol

8. Which one of the following patients is most likely to be discharged safely from the hospital after a sulfonylurea ingestion?

   A. 2-year-old with altered mental status requiring a continuous dextrose infusion for the past 3 hours
   B. 18-month-old who has been admitted for 26 hours and has tolerated oral intake with no supplemental oral or intravenous dextrose for 12 hours
   C. 3-year-old with blood glucose readings greater than 60 mg/dL for the first 6 hours of their ED length of stay
   D. 1-year-old who has been in the ED for 12 hours and received two intravenous dextrose boluses, with the last dose 3 hours ago

9. A 2-year-old girl is found crying, pale, shaking, and diaphoretic after being left alone in her 16-year-old brother's room for around 30 minutes. She is taken to the ED after attempts to calm her fail. In the ED, her vital signs are heart rate 180 beats/minute, blood pressure 120/70 mm Hg, and respiratory rate 38 breaths/minute. Which one of the following substances was she most likely exposed to?

    A. Laundry pod
    B. Isopropanol
    C. Fentanyl
    D. Nicotine

10. Which one of the following scenarios best describes the role of fomepizole and ethanol in the treatment of isopropanol toxicity?

    A. Fomepizole is easier to dose and better tolerated than ethanol.
    B. Fomepizole is less expensive than ethanol.
    C. Fomepizole reduces the need for dialysis compared with ethanol.
    D. Fomepizole and ethanol are not indicated.

11. A 6-year-old girl accidentally ingested up to 10 capsules of benzonatate belonging to her older sibling. On ED arrival, she has agitation before becoming increasingly somnolent, and the rhythm on the monitor reveals a wide-complex ventricular dysrhythmia. The preferred treatment is on shortage. Which one of the following is best to recommend for this patient?

    A. Hemodialysis
    B. Sodium acetate
    C. Diazepam
    D. Naloxone

12. When comparing antidepressant toxicities, which one of the following scenarios is most likely to result in seizures?

    A. Bupropion greater than tricyclic antidepressants (TCAs) greater than SSRIs.
    B. TCAs greater than bupropion greater than SSRIs.
    C. SSRIs greater than TCAs greater than bupropion.
    D. SNRIs greater than TCAs greater than bupropion.

13. A 16-year-old male adolescent with a medical history of depression while taking nortriptyline presents to the ED with hypotension in the setting of a recently reported nortriptyline overdose. He is taken to the resuscitation room, and while providers are establishing intravenous access, he becomes unresponsive and is found to be in cardiac arrest. High-quality cardiopulmonary resuscitation is initiated together with intubation and establishment of intraosseous access. Which one of the following is best to recommend for this patient?

    A. Lipid emulsion 20% 1.5 mL/kg intravenously followed by 0.25 mL/kg/minute over 30 minutes
    B. Lidocaine 1.5-mg/kg intravenous bolus
    C. Epinephrine 10 mg intravenously
    D. Sodium bicarbonate 2 mEq/kg intravenously

14. A 7-year-old girl presents from home 1 hour after her father found her in the garage drinking from a container that may have stored antifreeze. She reports the liquid tasted "sweet." A toxic alcohol concentration was sent but is not expected to result for at least 24 hours. Her laboratory results are as follows: Na 135 mEq/L, K 4.4 mEq/L, Cl 100 mEq/L, HCO_3 26 mEq/L, BUN 12 mg/dL, SCr 0.7 mg/dL, glucose 120 mg/dL, and serum osmolality 303 mOsm/kg. Her urine sample did not fluoresce under black light, and no calcium oxalate crystals were seen. Which one of the following findings best supports the differential diagnosis of toxic alcohols in this patient?

    A. Anion gap 9 mEq/L
    B. Anion gap 22 mEq/L
    C. Osmol gap 9 mOsm/L
    D. Osmol gap 22 mOsm/L

15. A 3-year-old boy presents from home after a witnessed button battery ingestion from a car keyless entry fob. The patient is immediately triaged to an examination room in the ED for physician evaluation. On a review of systems, the patient is noted to be drooling and has had one reported episode of emesis. One team member has been tasked with determining which type of battery the child may have ingested. Ingestion of which one of the following button batteries is most likely to cause a poor outcome in this patient?

    A. 1.5-V alkaline button battery
    B. 25-mm-diameter lithium button battery
    C. 18-mm-diameter zinc button battery
    D. 12-mm-diameter lithium button battery

Learner Chapter Evaluation: Pediatric Poisonings

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.
12. The activity met the stated learning objectives.
13. If any objectives were not met, please list them here.

OTHER COMMENTS

14. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
15. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter: