Deadly pediatric poisons: nine common agents that kill at low doses

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Children are exposed more frequently to potentially toxic substances than any other age group [1]. According to data compiled by the American Association of Poison Control Centers (AAPCC), more than 1.3 million exposures involving children age 12 and younger were reported to poison control centers in 2001 [2]. Of these, more than 1 million (79%) involved children 3 years old or younger.

The peak incidence for pediatric poisonings occurs in toddlers age 1 to 3 years, as does the peak incidence for hospitalization [3]. Most exposures in this age group are unintentional and reflect acquisition of developmental milestones and subsequent behaviors while exploring the environment. Children may be attracted to potentially toxic substances based on color or appearance of the agent or the container, mistakenly identifying it as a candy or beverage. Younger children are more willing to taste dangerous substances than older children and perform hand-mouth behaviors nearly 10 times an hour [4,5]. Physical environmental change plays a significant role in the epidemiology of accidental ingestion [6]. In approximately half of all accidental poisonings, the product either was in use at the time of ingestion or had been moved recently from its usual storage site.

Ingestion characteristics differ significantly in toddler exposures compared with adolescent or adult exposures [7]. Most exposures are nontoxic because the intent is exploration rather than self-harm. In 2001, cosmetics and personal care products were the leading category of agents ingested by children age 5 years or younger; this category was the eighth most common exposure in adults 20 years old or older [2]. Likewise, plant exposures

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accounted for 6.3% of preschool-age childhood exposures compared with only 2.4% of adult exposures. Amounts ingested by children are typically smaller, with the result that even ingestion of toxic substances results in nontoxic or minimally toxic outcomes.

The "one-pill" rule states that a single adult therapeutic dose would not be expected to produce significant toxicity in a child [8]. A 10-kg toddler would need to ingest approximately 10 ferrous sulfate 325-mg tablets (65 mg of elemental iron per tablet) before developing life-threatening toxicity [9]. As a result, it commonly is believed that ingestion of one or two tablets by a toddler is a benign act and not expected to produce any significant toxicity. Although this is true for most exposures, certain common agents have the potential to cause life-threatening toxicity or death despite the ingestion of only one or two tablets or sips [10–12]. This article reviews nine commonly ingested substances known to have the potential for significant morbidity at single-pill or spoonful-sized doses. Clinicians must be able to recognize the potentially catastrophic nature of these ingestions and to manage them accordingly.

Calcium channel antagonists

Overview

Since the 1990s, an increase in the number of calcium channel antagonist (CCA) exposures and the number of adverse outcomes has been seen. The AAPCC Toxic Exposure Surveillance System (TESS) database recorded 9264 CCA exposures in 2001, a 100% increase from 1990 [2,13]. Of the 9264 exposures reported in 2001, 2249 occurred in children younger than 6 years old. Pediatric-specific data from 1998 revealed 2197 exposures in children age 5 years or younger, with 88 moderate to major outcomes. No pediatric deaths were reported that year.

CCAs constitute a heterogeneous class of drugs, all of which act to slow the influx of calcium through L-type, voltage-sensitive channels present in a wide variety of tissue cell types, including cardiac myocytes, vascular smooth muscle, and sinoatrial and atrioventricular nodes [14,15]. As of June 2003, 10 calcium channel blockers were available in the United States [16]. Currently available CCAs are classified into three groups: the phenylalkylamines (verapamil) and the benzothiaprines (diltiazem), which in therapeutic doses act predominantly on cardiac tissue, and the dihydropyridines (eg, nifedipine), which act predominately on vascular smooth muscle.

Clinical manifestations

Disturbances of the cardiovascular system are the hallmark of CCA overdose [16,17]. Classic manifestations include hypotension and bradycardia, although reflex tachycardia may be seen with the dihydropyridines

because of their predominant effect on vascular smooth muscle. Cardiac conduction system abnormalities include second-degree and third-degree heart block. Extreme negative inotropy may manifest as cardiogenic shock or cardiac arrest. Although clinical effects often appear within 1 to 5 hours after ingestion of immediate-release preparations, signs and symptoms may be appreciably delayed in cases of sustained-release preparation ingestion. Hypotension may last more than 24 hours despite therapy, and cardiac conduction defects have been reported to last 7 days [18]. With the exception of nimodipine, the CCAs have poor central nervous system (CNS) penetration. The presence of CNS manifestations, such as drowsiness, confusion, or seizures, in the absence of hemodynamic collapse should suggest the presence of coingestants. Hyperglycemia noted with CCA toxicity is multifactorial, resulting from impaired insulin release and from systemic insulin resistance [19]. In contrast to β-adrenergic receptor antagonist toxicity, which is associated with hypoglycemia, hyperglycemia in the setting of bradycardia and hypotension suggests CCA ingestion.

Significant toxicity most commonly occurs with deliberate suicidal ingestion. Case reports and series have documented significant pediatric morbidity and mortality, however, despite apparently minor exposures. An 11-month-old girl developed seizures 45 minutes after ingestion of 400 mg of verapamil [20]. Although the patient survived, the hospital course was complicated by bradycardia, hypotension, decreased mental status, and respiratory arrest. Similarly, a 14-month-old girl presented pale, hypotensive (mean arterial pressure 46 mm Hg), and tachycardic (heart rate 178 beats/ min) after ingestion of a single nifedipine 10-mg tablet [21]. Despite aggressive interventions, the patient became progressively bradycardic and pulseless, dying 3 hours after presentation. A pediatric case series reported 16 symptomatic patients among 283 recorded exposures [22]. Five of the cases occurred in children after reported ingestion of a single tablet. Although two of the five cases manifested vomiting as the sole toxicity, hypotension occurred after ingestion of 5 mg of amlodipine by a 2-year-old boy, 60 mg of sustained-release nifedipine by a 20-month-old boy, and 30 mg of sustained-release nifedipine by a 16-month-old boy. Maximal elapsed time to onset of symptoms ranged from 3 hours in the case of immediate-release preparations to 14 hours in the case of sustained-release preparations.

Management

Early assessment of hemodynamic status is paramount in all cases of reported CCA ingestion. Cardiac monitoring should be instituted, and access to transcutaneous or transvenous pacing should be available. CCAs adhere well to activated charcoal, and administration should be considered for patients presenting within 1 hour of ingestion (Fig. 1) [23]. Whole-bowel irrigation with polyethylene glycol has been recommended after ingestion of
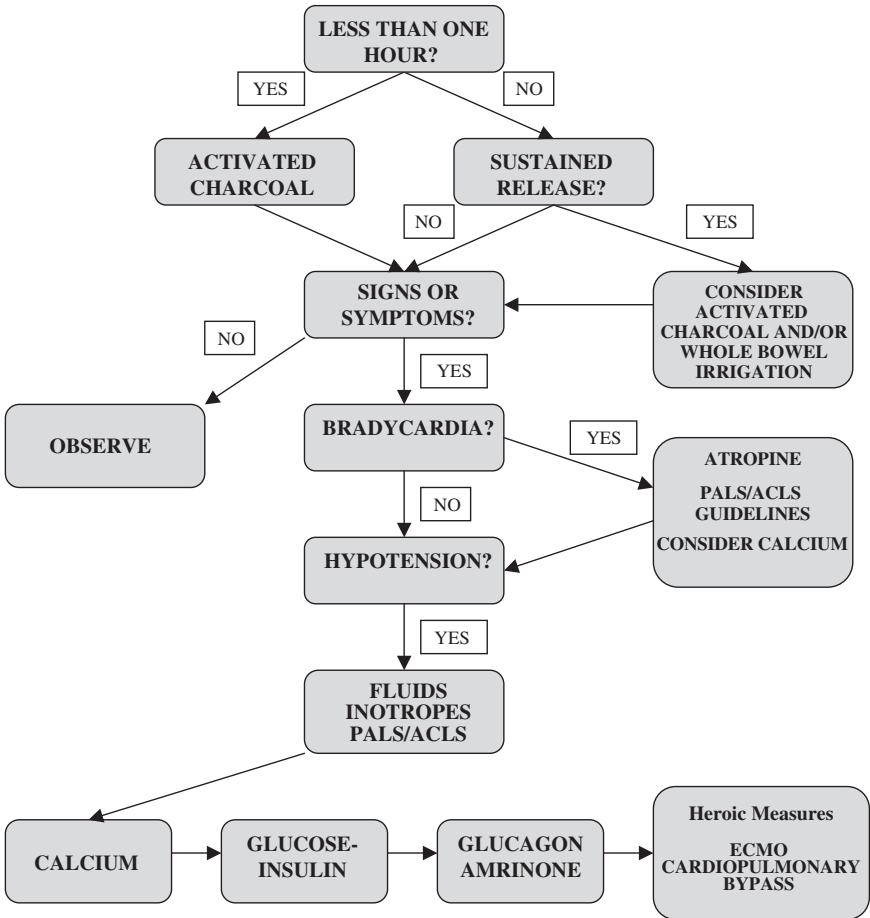
Fig. 1. Decision algorithm for calcium channel antagonist ingestion. ECMO, extracorporeal membrane oxygenation; PALS/ACLS, pediatric advanced life support/advanced cardiac life support.

sustained-release preparations [24–26]. Although the optimal dose has not been established, 500 mL/h in children 9 months to 6 years old and 1000 mL/h in children 6 to 12 years old have been recommended. Whole-bowel irrigation should be continued until clear effluent is achieved [27,28]. Hemodynamically stable patients with suspected CCA ingestions should be monitored for at least 6 to 8 hours in the case of short-acting agents and 24 hours for sustained-release preparations. Symptomatic patients require admission to an intensive care unit.

Fluid resuscitation and atropine are appropriate initial interventions for hypotension and bradycardia (Fig. 1). Hypotensive patients should be treated with normal saline boluses of 20 mL/kg, up to 60 mL/kg. Atropine is

the first-line agent in cases of drug-induced bradycardia, but has been only moderately successful in cases of CCA-induced bradycardia and may be more beneficial after calcium administration (see later) [29,30]. Other than medications used for general supportive care, optimal pharmacotherapy remains poorly defined. Rationally, calcium would seem to be the natural antidote and has been effective in correcting hypotension and bradycardia associated with CCA toxicity [17,24,26,29,30,31]. Considerable, albeit conflicting, data regarding the clinical utility of calcium exist [32–35]. It seems to be most beneficial in mild toxicity, with less efficacy in cases of significant toxicity. The current recommended dose is 10% calcium chloride, 10 to 25 mg/kg (0.10–0.25 mL/kg), or 10% calcium gluconate, 30 to 75 mg/kg (0.30–0.75 mL/kg), up to 1 g, repeated every 10 to 20 minutes, for a total of three to four doses (Table 1).

Inotropic agents, including dopamine, dobutamine, isoproterenol, epinephrine, and norepinephrine, have been used in symptomatic patients in isolated case reports. Although the optimal regimen has yet to be determined, the agent ideally should be selected to treat the specific toxicity. Vascular collapse, manifesting predominantly as hypotension, may be treated with an α-adrenergic–specific agent, such as norepinephrine or phenylephrine. For a patient with undifferentiated shock, epinephrine may be the initial pressor of choice, owing to its α-adrenergic and β-adrenergic effects [17].

In part as a result of similarities with β-adrenergic antagonist toxicity, glucagon has been recommended in cases of significant CCA toxicity [24,36–38]. Because glucagon acts by activating the intracellular second messenger cascade downstream from the β-receptor, it offers little obvious advantage beyond the use of traditional pressor agents in CCA toxicity [39]. Nonetheless, case reports have documented successful resuscitation of patients with hypotension refractory to fluids, atropine, calcium, and dopamine. Although also beneficial in some case reports, the phosphodiesterase III inhibitor amrinone has the potential for worsening hypotension. As such, current recommendations advise against its use except as second-line therapy in conjunction with an inotropic agent [40].

The successful use of high-dose glucose-insulin has been reported in some animal studies, case reports, and case series and is the current treatment of choice in refractory CCA toxicity [24,41–44]. Insulin is known to have positive inotropic effects and to reverse myocardial depression in patients with cardiogenic shock after coronary artery bypass graft surgery [45,46]. In one case series, five patients with refractory shock after CCA overdose received glucose-insulin infusions [43]. Within hours, their hemodynamic status normalized, and all five patients survived without sequelae. Although no controlled clinical trials have been published to show efficacy in CCA toxicity, the strength of animal data, coupled with the lack of other consistently effective therapeutic interventions, has led to the recommendation that glucose-insulin therapy be instituted early in the management of

Table 1
Selected pediatric antidotes

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

Lorazepam	Seizures	0.05–0.1 mg/kg IV/IO q10–15 min
	Agitation	Maximum: 4 mg
		Monitor airway status
Midazolam	Seizures	150 mg/kg IV/IO q5–15 min
	Agitation	0.2 mg/kg IM/IN q5–15 min
		Monitor airway status
Naloxone	Opioids	Age <5: 0.01–0.1 mg/kg IV/IO/IL/ET q3–5 min
	Clonidine and imidazolines	Maximum 2 mg/dose
		Age >5: 0.4–2.0 mg IV/IO/IL/ET q3–5 min
		Maximum 10 mg total dose
		Start an infusion at the response dose per hour
Octreotide	Sulfonylureas	1–2 mcg/kg IV/SC q8 h
Sodium bicarbonate	Cyclic antidepressants	1–2 mEq/kg IV bolus
	Salicylates	Infusion: Place 3 ampules sodium bicarbonate in 850 mL D_5 W and infuse at 1.5–2 times maintenance fluid requirements
	Methanol	Avoid serum pH > 7.55
	Ethylene glycol	Monitor potassium

Abbreviations: D_{10} W, D_{25} W, dextrose in water (10%, 25%); ET, endotracheal; IL, intralingual; IM, intramuscular; IN, intranasal; IV, intravenous PR, per rectum; SC, subcutaneous.

CCA toxicity. The mean dose in the case series was 0.5 U/kg/h (range 0.1–1.0 U/kg/h) [43]. Supplemental glucose was provided, and frequent serum glucose measurements performed. Despite the current optimism, case reports and clinical experience still show failure of glucose-insulin as an antidotal regimen in certain cases, and even the strongest proponents are wary to describe it as the definitive antidotal therapy for CCA overdose [44,47].

In cases of hemodynamic collapse unresponsive to other therapies, heroic treatment modalities, including intra-aortic balloon counterpulsation and emergent cardiopulmonary bypass, have been attempted with mixed success. A 25-month-old toddler initially stabilized after being placed on cardiopulmonary bypass following verapamil ingestion. Levels rose again, however, after discontinuation of the procedure, and the patient subsequently died [48]. In contrast, a 41-year-old man survived to discharge without sequelae after institution of emergent bypass for intentional verapamil ingestion [49].

Camphor

Overview

Camphor is a common ingredient in a wide variety of over-the-counter topical liniments, including Vick's VapoRub, Ben-Gay, Absorbine, Tiger Balm, and Save the Baby. An aromatic terpene ketone derived from plants, camphor has a distinct odor and pungent taste. Since 1983, the US Food and Drug Administration has limited the concentration of camphor to 11% in all over-the-counter products, although higher concentrations are found elsewhere in the world [50–52]. Camphor acts as a topical rubefacient, inducing local hyperemia and warmth. Camphor is used topically as an analgesic, antipruritic, and antitussive agent, often in conjunction with other potentially toxic substances, including methyl salicylates (eg, Ben-Gay). According to the TESS database, 7805 cases of topical camphor ingestion in children younger than age 6 were reported to poison control centers in the United States in 2001, including 1287 cases of camphor/methyl salicylate coingestions [2].

Clinical manifestations

Initial signs and symptoms of toxic exposure include gastrointestinal distress and a generalized sensation of warmth. Toxic effects occur rapidly, often within 10 to 20 minutes of ingestion [53–55]. A late-onset seizure after ingestion of Vick's VapoRub was noted in a 4-year-old girl, however, who seized 9 hours after ingesting 2 oz (175 mg/kg) of the product [56]. Symptoms may progress rapidly to an initial phase of CNS hyperactivity, characterized by excitement, restlessness, delirium, and seizures, followed by a phase of CNS depression, manifesting as coma and respiratory depression

[57]. The odor of camphor is readily identifiable and an important clue to symptom etiology. Seizures may occur suddenly and without warning [58].

Death from camphor ingestion results from respiratory depression or status epilepticus [59,60]. A 3-year-old child developed seizures, coma, and respiratory depression after ingestion of 15 mL of Vicks VapoRub (700 mg of camphor) [61]. A 2-year-old developed seizures 10 minutes after ingestion of 10 mL of Campho-Phenique, followed by coma and respiratory depression lasting approximately 24 hours [57]. Ingestions of 1 to 2 g of camphor have resulted in pediatric and adult fatalities [55,62]. A 19-month-old child died after ingestion of 5 mL of 20% camphorated oil [62].

Management

No specific antidote for camphor toxicity exists, and treatment is largely supportive, involving airway management and seizure control. Asymptomatic patients should be observed for 6 to 8 hours. Aspiration and seizure precautions should be taken because of risk of spontaneous emesis and sudden CNS depression and seizures. Camphor-induced seizures should be managed initially with benzodiazepines (see Table 1). Persistent seizures may be managed with barbiturates. Hemoperfusion has been attempted, but not shown to alter clinical course and outcome [63].

Clonidine and the imidazolines

Overview

Initially developed as a topical nasal decongestant, clonidine later was marketed as a centrally acting antihypertensive and more recently in the management of attention-deficit hyperactivity disorder [64]. Other imidazolines, including naphazoline, oxymetazoline, tetrahydrozoline, and xylometazoline, are marketed as decongestants, whereas ophthalmologic brimonidine and apraclonidine are used in the treatment of glaucoma. In 2001, 1438 clonidine exposures occurred in children younger than 6 years old [2]. An additional 922 tetrahydrozoline exposures occurred in preschool-age children.

The imidazolines are central α_2-adrenergic agonists, resulting in decreased central adrenergic tone [65–67]. Additionally, these agents bind to specific imidazoline (I) receptors in the rostral ventrolateral medulla, which are distinct from α-adrenergic receptors [65,68].

Adult therapeutic doses of clonidine range from 0.2 to 2.4 mg/d delivered orally or transdermally. Currently available oral preparations contain 0.1 mg, 0.2 mg, or 0.3 mg of clonidine. Transdermal systems are designed to deliver 0.1 mg/d, 0.2 mg/d, or 0.3 mg/d with weekly replacement. These systems contain a total of 2.5 mg, 5 mg, and 7.5 mg of clonidine, all of which may be delivered over a short time if ingested [69].

Clinical manifestations

In overdose, patients may appear to have an opioid toxidrome, with decreased level of consciousness, miosis, bradycardia, hypotension, respiratory depression, and hypotonia [70]. CNS depression may range from drowsiness to coma. Although not structurally related to opioids, the α_2-adrenergic receptor targeted by clonidine and the μ receptor targeted by opioids show significant functional overlap. Both may be found on the same neuron, and both are coupled via G proteins to a common K^+ channel [71]. Binding at the α_2-adrenergic receptor seems to be responsible for the CNS and respiratory depression effects of the imidazolines, whereas binding at the I_1 receptors seems to be responsible for hypotension and bradycardia [72]. Peripheral α_1-adrenergic stimulation may result in short-lived hypertensive episodes before the onset of hypotension and bradycardia. Respiratory depression and intermittent apnea are especially common in children [70,73]. Children also seem to be most at risk of developing bradycardia [74,75]. Toxic effects typically occur within 30 to 90 minutes of ingestion, and they may persist for 1 to 3 days [76].

A retrospective study by Nichols et al [77] reviewed the cases of 80 children admitted for clonidine ingestion between 1987 and 1992. Average time to onset of symptoms was 35 minutes. The most common presenting sign or symptom was reduced level of consciousness (96%). Six children required intubation, but no deaths occurred. In this study, most of the clonidine (54%) belonged to the patients' grandmothers.

Toxic effects have been produced in children with 0.1 mg of clonidine [73, 8]. A 21-month-old girl developed bradycardia, hypotension, and coma after ingestion of a single clonidine 0.3-mg tablet [79]. A 6-year-old girl developed obtundation and bradycardia (heart rate 54 beats/min) after applying a clonidine patch that she mistook for a bandage [80]. A 9-month-old boy became lethargic 90 minutes after sucking on a discarded clonidine (Catapres-TTS-2) patch [81]. A 2-year-old child developed bradycardia and episodes of recurrent apnea after ingestion of 5 mL of apraclonidine ophthalmic drops [82].

Management

Management of imidazoline toxicity is largely supportive with treatment measures guided by signs and symptoms of exposure. Because of the risk of bradycardia and atrioventricular nodal blockade, all patients with suspected exposure should undergo continuous cardiac monitoring, and 12-lead electrocardiogram (ECG) should be performed as required. Continuous assessment and management of the airway are crucial. Symptomatic patients may respond variably to naloxone [83]. The typical naloxone dose is 0.1 mg/kg, up to a total of 10 mg (see Table 1). In a retrospective review of pediatric clonidine exposures, 39 of 80 patients (49%) received naloxone, and a positive response, defined by increased level of consciousness or

improved vital sign parameters, occurred in only 4 patients (16%) [77]. Symptomatic bradycardia should be treated initially with atropine [69,83]. Hypotension unresponsive to fluid resuscitation or complicated by persistent bradycardia may require dopamine [81,84,85].

Cyclic antidepressants

Cyclic antidepressants were the leading cause of poisoning fatality in the United States until 1993, and antidepressants remain the second most common class of agents ingested in fatalities reported to the AAPCC [2]. During 2001, 1586 cyclic antidepressant exposures were reported in children younger than age 6. Although not entirely elucidated, therapeutically these agents seem to act in part by interfering with reuptake of biogenic amines at nerve terminals [86,87]. All of these compounds are potent inhibitors of norepinephrine reuptake. Presence of a tertiary-amine side chain on some of these agents results in additional inhibition of serotonin reuptake. In addition to effects on norepinephrine and serotonin, tricyclic antidepressants (TCAs) exert effects on diverse central and peripheral receptor systems, including inhibition of histamine H_1 receptors, dopamine D_2 receptors, muscarinic cholinergic M_1 receptors, and sympathetic α_1 receptors [86]. Blockade of fast voltage-gated sodium channels in cardiac myocytes results in the typical finding of QRS interval prolongation noted on ECGs of TCA-intoxicated patients [88,89]. Inhibition of the chloride ionophore on the γ-aminobutyric acid channel complex provides a partial explanation for seizures observed in overdose [90].

Clinical manifestations

Cyclic antidepressant toxicity reflects effects on the CNS, including CNS depression and seizures, and the cardiovascular system, including conduction abnormalities, dysrhythmias, and hypotension. Seizure activity is greatest in antidepressants showing dopamine and norepinephrine reuptake inhibition, such as amoxapine, bupropion, and venlafaxine [91]. Additional evidence of cyclic antidepressant intoxication includes an anticholinergic toxidrome, such as mydriasis, flushing, dry mucous membranes, tachycardia, and hyperthermia, and CNS findings, such as delirium, hallucinations, seizures and coma. Signs of significant toxicity can be expected to present within 6 hours of ingestion.

Mortality associated with TCA ingestion is secondary to cardiotoxicity and CNS toxicity. Hypotension seen with TCA intoxication may be due to arrhythmia-induced cardiogenic shock and reduced peripheral vascular resistance secondary to α-adrenergic blockade and sympathomimetic amine depletion. Seizures associated with cyclic antidepressant toxicity typically are self-limited and generalized tonic-clonic in nature, although status epilepticus has been reported [92]. Rapid cardiovascular deterioration has

been observed during or shortly after seizures [93,94]. Amoxapine is associated with a higher incidence of seizures and a lower incidence of cardiotoxicity than first-generation TCAs. Seizures can occur in the absence of antecedent ECG abnormalities [95,96].

Ingestions of 10 to 20 mg/kg of most TCAs is likely to result in significant CNS and cardiovascular symptoms. A dose of 15 to 20 mg/kg is believed to represent a lethal exposure [97]. A 3-year-old girl developed seizures and cardiac dysrhythmias after ingestion of 100 mg of desipramine [98]. Ingestions of 250 mg of imipramine and amoxapine have resulted in fatalities in children [96,99].

Management

Management of cyclic antidepressant toxicity consists of aggressive supportive care, including airway management. Rapid deterioration in mental status should be anticipated, as should abrupt onset of seizure activity [94,100–102]. A prospective study of acute first-generation cyclic antidepressant ingestions showed the utility of the ECG in predicting cardiac dysrhythmias and seizures [103]. QRS complex duration greater than 100 ms has been shown to be a marker for toxicity, with an increased incidence of serious toxicity, including coma, hypotension, and need for intubation. One third of patients with a QRS complex duration greater than 100 ms developed seizures, and 14% developed ventricular dysrhythmias. Fifty percent of patients with a QRS complex duration greater than 160 ms developed ventricular dysrhythmias. Although useful in adult poisonings, rightward deviation of the terminal 40-ms QRS axis (T40-ms axis >130) has not been predictive of toxicity in pediatric intoxications [104–106]. Serum drug levels may be used to confirm exposure but otherwise have little value in acute intoxication [103]. Asymptomatic patients with normal vitals signs, normal ECG findings, and no other signs of toxic exposure may be discharged after a 6-hour observation period.

Sodium bicarbonate is the mainstay of treatment for reversing the cardiotoxic effects of TCA ingestion. Serum alkalinization and the administration of sodium reduce the incidence of ventricular arrhythmias [107]. Although acidemia can aggravate TCA toxicity, sodium bicarbonate has been found to be beneficial with even normal arterial pH [108]. The optimal dosing strategy and means of administration (intermittent intravenous bolus versus continuous infusion) remain to be determined. An initial bolus of sodium bicarbonate, 1 to 2 mEq/kg, may be administered to patients with evidence of cyclic antidepressant toxicity and a QRS duration greater than 100 ms (see Table 1). Care should be taken not to allow serum pH to exceed 7.55. Hypertonic saline has been used successfully in a patient with severe alkalemia and pH 7.5 [109]. Sodium bicarbonate is the first-line agent for cyclic antidepressant–induced ventricular dysrhythmias [110]. Use of class IA and class IC antidysrhythmics (eg, quinidine, procainamide) is

contraindicated because of their effects on sodium channels [111]. Seizures may be treated with benzodiazepines as a first-line agent. Phenytoin is not recommended in the management of cyclic antidepressant–induced seizures because some animal studies have indicated that it may potentiate ventricular dysrhythmias [112].

Opioids and opiates

Overview

According to the TESS database, there were 5914 reported ingestions of products containing opiates or opioids by children younger than 6 years old in 2001 [2]. The most common ingestions were hydrocodone in combination with acetaminophen, followed by codeine with acetaminophen, propoxyphene with acetaminophen, and oxycodone with acetaminophen. For these ingestions, acetaminophen toxicity should be considered accordingly, although single-pill ingestions would not be expected to cause toxicity.

Actions of opiates (derived from opium, the dried extract of the poppy plant *Papaver somniferum*) and opioids (synthetic derivatives with opiate-like effects) are mediated through three specific receptor classes, μ, κ, and δ [113]. Activation of the μ receptor is responsible for supraspinal analgesia and the respiratory depression noted with excess opioid administration [114].

Clinical manifestations

Opioid toxicity classically manifests as a toxidrome of CNS depression, respiratory depression, and miosis. Infants and children may be more susceptible to the toxic effects of opiates and opioids compared with adults [115]. Most deaths are secondary to respiratory depression and subsequent hypoxia, although aspiration pneumonitis and pulmonary edema are additional concerns. Half of children exposed to more than 1 mg/kg of codeine developed evidence of toxicity, often within 1 hour of ingestion [116]. In infants, 2.5 mg of hydrocodone has been lethal [117].

Management

The time to peak effect for most oral preparations is less than 1 hour, and duration of action is 3 to 6 hours [115]. Patients exposed to immediate-release preparations should be observed for at least 6 hours. Sustained-release preparations containing morphine and oxycodone exist and require longer observation periods. Whole-bowel irrigation for these preparations may be considered. Care must be taken in the interpretation of urine drug screens because opioid agents are not identified consistently by these opiate-specific tests [118].

In addition to supportive management, reversal of the offending agent with naloxone should be instituted whenever significant signs or symptoms

of opioid intoxication are present (see Table 1). Naloxone, a congener of oxymorphone, is a pure competitive antagonist that inhibits the binding of opiates and opioids at receptor sites. It rapidly reverses opiate-induced and opioid-induced respiratory and CNS depression. Although naloxone's onset of action is less than 2 minutes, its duration of action is 20 to 90 minutes, and its elimination half-life is 60 to 90 minutes in adults, less than that of many opiates and opioids [119–121]. For this reason, repeat dosing or continuous infusions are often necessary.

For non–life-threatening cases, the recommended initial dose for naloxone in children younger than 5 years old is 0.01 mg/kg intravenously. Life-threatening cases in these children should be treated initially with 0.1 mg/kg up to 2 mg intravenously, titrated to effect every 3 to 5 minutes to a maximum dose of 10 mg [122]. Children 5 years old and older should receive 0.4 mg intravenously. Life-threatening cases are treated with 2 mg intravenously repeated every 3 to 5 minutes until adequate reversal has been achieved. If complete reversal of respiratory and CNS depression is not seen after 10 mg, other causes of intoxication should be investigated.

Lomotil

Overview

Lomotil, an antidiarrheal agent containing 2.5 mg of the opioid diphenoxylate and 0.025 mg of the antimuscarinic agent atropine, is a unique opioid agent that warrants special attention. Catastrophic outcomes have been reported after ingestion of this agent by children [123,124]. During 2001, 153 cases of Lomotil ingestion by children younger than 6 years old were reported [2].

Both agents are absorbed rapidly by the gastrointestinal tract in therapeutic doses, although absorption may be delayed in overdose secondary to inhibitory effects on smooth muscle motility. Diphenoxylate subsequently is metabolized to difenoxin, which is five times more active than the parent compound and has an elimination half-life of 12 to 14 hours [125].

Clinical manifestations

Although Lomotil toxicity classically is described as biphasic, with initial antimuscarinic symptoms manifesting 2 to 3 hours after ingestion followed by delayed opioid symptoms, more recent studies have shown this progression to occur in only a few cases [126]. In one study of pediatric ingestions, only 4 of 36 patients developed early anticholinergic symptoms, whereas 15 of 36 patients developed evidence of opioid toxicity only [126]. Little correlation exists between reported ingested dose and clinical outcome. Toxicity in the pediatric population has been reported after ingestion of one-half tablet [123].

Management

Management of Lomotil ingestions is similar to that of other opioids. Initial symptoms, including potentially fatal coma and respiratory depression, may be delayed [126]. Symptoms have recurred 24 hours after initial resolution of opioid symptoms. This recurrence has been attributed either to the presence of the difenoxin metabolite or to return of gastric function with subsequent reabsorption of the agent. The current recommendation is that children with Lomotil exposures should be admitted to a monitored environment for no less than 24 hours observation [127].

Salicylates

Overview

Salicylates are present in numerous over-the-counter products, including aspirin (acetylsalicylic acid), oil of wintergreen (methyl salicylate), and Pepto-Bismol (bismuth subsalicylate). Because it is not widely known that these products contain salicylates, many cases of significant toxicity may not be recognized initially as salicylate ingestion. The minimal potentially toxic ingested dose in children is 150 mg/kg. Placed in perspective, one teaspoon of 98% methyl salicylate contains 7000 mg of salicylate, the equivalent of nearly 90 baby aspirin, and more than four times the potentially toxic dose for a 10-kg child. Therapeutic serum acetylsalicylic acid concentrations for analgesic effects are 15 to 30 mg/dL (150–300 mg/L). Signs and symptoms of toxicity may occur at levels greater than 30 mg/dL. Levels greater than 100 mg/dL are potentially life-threatening [128]. At higher doses, levels of free salicylates increase exponentially as serum protein binding becomes saturated [129]. The half-life of salicylates increases from 2 to 4 hours at therapeutic levels to 15 to 29 hours at toxic doses in children [130,131].

Clinical manifestations

Signs and symptoms of salicylate intoxication (referred to as *salicylism*) include nausea; vomiting; diaphoresis; tinnitus; and nonspecific neurologic findings including agitation, delirium, hallucinations, and lethargy. Salicylates directly stimulate the brainstem respiratory center, resulting in hyperventilation and hyperpnea [132]. Severe intoxications may cause noncardiogenic pulmonary edema, cerebral edema, coma, and death. Hyperthermia, resulting from the uncoupling of oxidative phosphorylation, reflects severe intoxication and is often a preterminal finding [133]. Laboratory findings in salicylate toxicity classically include a mixed acid-base disturbance, with a combined anion gap metabolic acidosis and respiratory alkalosis [133,134]. In children, the respiratory alkalosis may be transient, such that the predominant acid-base derangement is a metabolic acidosis [133]. The presence of a respiratory acidosis is a grave finding

and suggests the presence of pulmonary edema, respiratory muscle fatigue from prolonged hyperventilation, or a mixed ingestion [128]. Additional laboratory findings include hyperglycemia or hypoglycemia and ketonuria, reflecting impaired glucose metabolism.

Oil of wintergreen poses a particular hazard to children because of its pleasant aroma and its high salicylate content (typically contains 98–100% methyl salicylate). A 21-month-old girl developed significant poisoning, with a peak serum salicylate concentration of 81 mg/dL, after ingesting 4 mL of oil of wintergreen [135]. Less than one teaspoon of oil of wintergreen has been fatal in a child [136].

Management

Management of salicylate-exposed patients includes rapid determination of serum salicylate concentrations. Although the Done nomogram has been used in salicylate toxicity, caution should be exercised because of its limited applicability. In contrast to the Rumack-Mathew nomogram, the Done nomogram indicates severity of toxicity based on a 6-hour level of non–enteric-coated aspirin rather than need for antidotal therapy. Individuals have died in less than 6 hours after methyl salicylate ingestion [128]. Serum salicylate concentrations should be reassessed every 2 hours until the patient is clinically improving and has a nontoxic serum salicylate level (<30 mg/dL) with normal or alkalemic blood pH. Peak salicylate levels may not occur for 12 or more hours after ingestion of enteric-coated products. Interpretation of serum salicylate levels always should be based on the clinical condition of the patient. A declining serum salicylate level in the setting of acidemia may reflect increased CNS distribution rather than increased clearance and would be expected to mirror a deteriorating clinical picture. Care also must be taken when evaluating serum salicylate concentrations to note the reported units. Some laboratories report salicylate levels in terms of mg/L rather than mg/dL, a 10-fold difference in values.

Considerable controversy exists regarding methods of gastric decontamination in acute salicylate toxicity. Multiple-dose activated charcoal seems to increase the elimination of salicylates compared with single-dose activated charcoal, although animal and human data have been conflicting [138–141]. The current American Academy of Clinical Toxicology/European Association of Poison Control Centers and Toxicologists position statement has concluded that insufficient evidence exists to recommend multiple-dose activated charcoal [141]. Whole-bowel irrigation also has been advocated, especially after ingestion of enteric-coated formulations, although outcome-based evidence is lacking [27].

In addition to aggressive supportive care and appropriate gastric decontamination, treatment of salicylate poisoning is directed toward enhanced elimination through either urinary alkalinization ("ion trapping")

or hemodialysis. By increasing the urine pH, the relative fraction of salicylate present in the anionic form increases, reducing reabsorption in the distal tubules. The goal of alkalinization is a urine pH of 7.5 or greater, through administration of intravenous sodium bicarbonate [128]. An initial bolus of 1 to 2 mEq/kg is followed by a continuous sodium bicarbonate infusion at a rate equivalent to 1.5 to 2 times the calculated maintenance fluid requirements (see Table 1). Three sodium bicarbonate ampules (44 mEq in 50 mL total volume) placed in 850 mL of 5% dextrose in water provides an osmolality roughly equivalent to normal saline. An additional benefit of intravenous sodium bicarbonate administration is serum alkalinization, mitigating acidemia-mediated salicylate shifts into the CNS. As with cyclic antidepressant toxicity, care should be taken to avoid serum pH greater than 7.55. Careful monitoring of serum potassium concentration is essential. In the setting of acidemia and hypokalemia, the distal tubule preferentially excretes protons in exchange for sodium, resulting in an inability to alkalinize the urine.

Extracorporeal elimination is indicated for critically ill patients or patients in whom the sodium load necessary for urinary alkalinization is contraindicated (Box 1) [128]. Hemodialysis traditionally has been the method of choice because it can correct electrolyte and acid-base abnormalities rapidly in addition to increasing drug clearance.

Sulfonylureas

Overview

Diabetes mellitus is the most common endocrine disorder in Western society, with type 2 diabetes mellitus accounting for 86% of cases [142]. The oral hypoglycemic agents, which include the sulfonylureas and biguanides, are the mainstay of pharmacologic treatment for type 2 diabetes mellitus.

Box 1. Indications for hemodialysis in salicylate toxicity

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

Adapted from Done AK. Salicylate intoxication: significance of measurements of salicylate in cases of acute ingestion. Pediatrics 1960;26:800–7.

Commensurate with the rising prevalence of diabetes, there has been a marked increase in pediatric exposures to oral hypoglycemic agents. The TESS database reported a total of 2652 cases of unintended oral hypoglycemic exposures in children younger than age 6 in 2001, nearly three times the number reported in 1990 [2]. Sulfonylureas accounted for 56% of these exposures.

The sulfonylureas modulate a reduction in serum glucose concentration by direct inhibition of an adenosine triphosphate–dependent potassium channel located in the membrane of the pancreatic beta cells [143,144]. The subsequent increase in intracellular potassium results in membrane de-polarization and insulin release independent of circulating glucose concentrations with the potential for subsequent hypoglycemia. Sulfonylureas also potentiate the action of insulin on target tissues [145]. In addition, elevated insulin levels lead to suppression of compensatory glycogenolysis. In contrast, the biguanides are not expected to produce hypoglycemia in nondiabetic patients [144]. Sulfonylureas are classified as first-generation, second-generation, and third-generation agents with later generations generally exhibiting greater binding specificity, shorter times to peak effect and lower risk for hypoglycemia at therapeutic doses [145].

Glyburide and glipizide are second-generation agents, introduced in the early 1980s. In 2001, glyburide was the most widely prescribed sulfonylurea agent in the United States and the second most widely prescribed hypoglycemic agent after metformin [146]. Among the second-generation and third-generation agents, glyburide and long-acting glipizide have been associated with the greatest risk for hypoglycemia at therapeutic doses [147,148].

Clinical manifestations

Clinically, the principal manifestation of sulfonylurea intoxication is hypoglycemia. Clinical findings of hypoglycemia may include lethargy, confusion, headache, irritability, and seizure. Secondary sequelae of hypoglycemia include permanent neurologic impairment and death [149].

A 2-year-old child presented to a local emergency department within 40 minutes of ingestion of a single glipizide 5-mg tablet. Despite gastric decontamination and supplemental dextrose-containing intravenous fluids, the patient developed hypoglycemia (glucose 49 mg/dL) 11 hours after ingestion [150]. A 20-month-old child presented with decreased level of consciousness and seizures 21 hours after ingestion of 15 mg of glyburide [151]. A retrospective pediatric case series reported three cases of hypoglycemia after ingestion of a single chlorpropamide (a first-generation sulfonylurea) 250-mg tablet, a glipizide 5-mg tablet, and a glyburide 2.5-mg tablet [152]. In a prospective study of 185 cases of reported sulfonylurea exposure in children, 30% developed hypoglycemia, 5 of whom ingested no more than a single tablet of glipizide or glyburide [153].

Management

Management of suspected sulfonylurea ingestions should be directed toward rapid detection and treatment of hypoglycemia (Fig. 2). Activated charcoal may be considered for patients presenting within 1 hour of ingestion. For extended-release preparations, whole-bowel irrigation may be helpful beyond 1 hour. A retrospective review of pediatric sulfonylurea ingestions showed delayed hypoglycemia in 4 of 25 patients, including 1 patient who reportedly manifested hypoglycemia 16 hours after ingestion [152]. Based on these findings, the current recommendation is that all children suspected or known to have ingested sulfonylurea be admitted for a minimal 24-hour observation, even if not initially hypoglycemic [154]. Currently, data are insufficient to determine length of observation for extended-release preparations.

While under observation, asymptomatic patients may be allowed to eat, but should not receive supplemental intravenous dextrose for fear of masking hypoglycemia, with subsequent development on cessation of treatment. Serial neurologic examinations and serum glucose measurements are essential. Asymptomatic patients initially should have serum glucose measured at least hourly.

Patients with signs or symptoms of hypoglycemia should receive a bolus of intravenous dextrose [154]. This bolus may be followed by continuous infusion of a 5% to 20% dextrose solution to maintain serum glucose levels greater than 100 mg/dL, the rate and duration of which should be dictated by clinical severity and the plasma half-life of the ingested agent. Dextrose therapy may stimulate exaggerated insulin release further in the setting of sulfonylurea toxicity, with subsequent rebound hypoglycemia and need for additional dextrose.

In the 1990s, investigations were conducted on the use of diazoxide and octreotide for the treatment of sulfonylurea-induced hypoglycemia. Diazoxide acts to inhibit release of insulin, mitigating toxicity [145,155]. Its use is limited, however, by its potent vasodilator properties, with potential for hypotension. Diazoxide was removed from the US pharmaceutical market in 2003, although it is available elsewhere in the world. Octreotide, a somatostatin analogue, inhibits secretion of several hormones, including glucagon and insulin (see Table 1) [156–158]. A retrospective review of nine patients treated with dextrose and octreotide found that the total number of ampules of 50% dextrose administered before and after administration of octreotide declined from 2.9 to 0.2, and the number of hypoglycemic events recorded declined from 3.2 to 0.2 [156]. A prospective study by Boyle et al [157] examined eight normal subjects given glipizide, 1.45 mg/kg, to induce hypoglycemia (<50 mg/dL) on three separate occasions, treated with octreotide, diazoxide, or dextrose alone. Dextrose was given as needed in all three cases to maintain euglycemia. The study found that octreotide eliminated the need for dextrose rescue in four of the eight subjects and
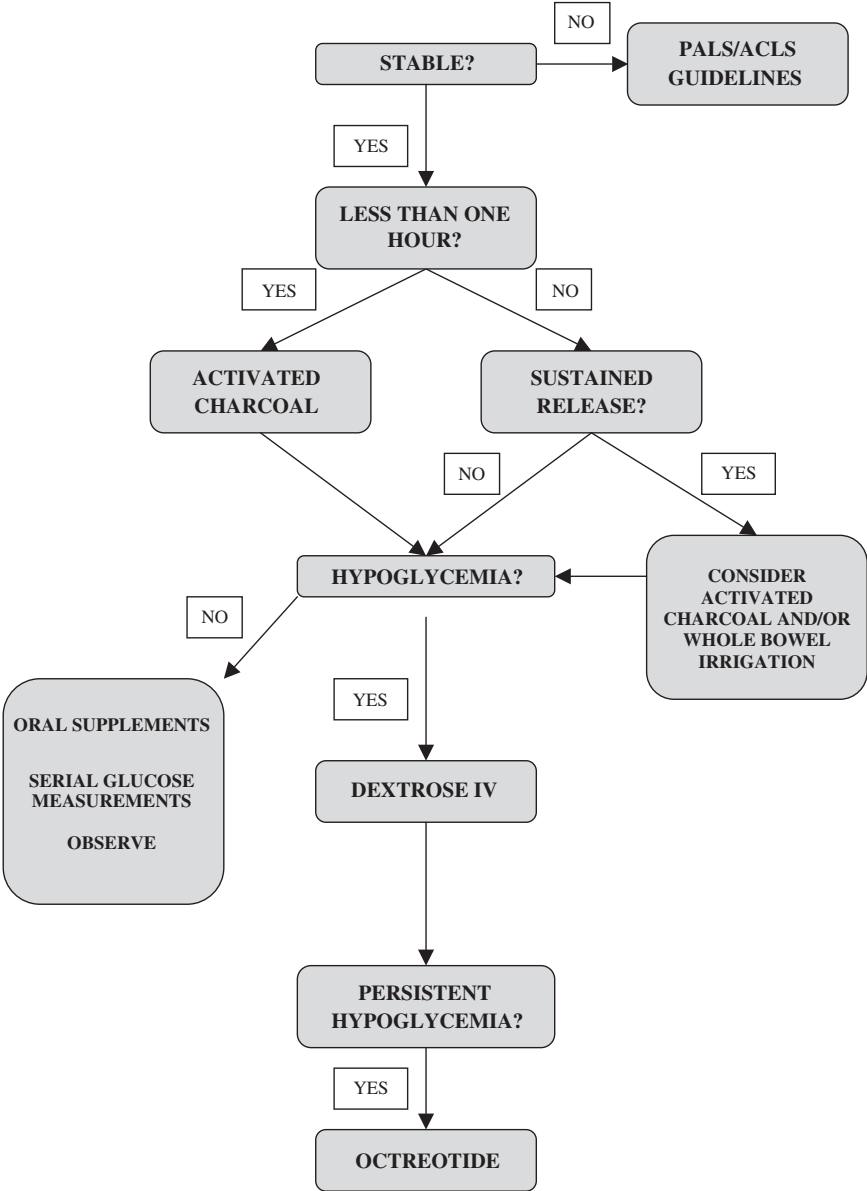
Fig. 2. Decision algorithm for sulfonylurea ingestion. PALS/ACLS, pediatric advanced life support/advanced cardiac life support.

reduced the supplemental glucose requirements of the remaining four with no adverse outcomes.

Toxic alcohols

Overview

The toxic alcohols include methanol, ethylene glycol, and isopropanol [159]. All are potentially unsuspected killers, in part because they are readily available household items, small amounts are sufficient to cause significant injury, and their presentation may be attributed initially to ethanol inebriation. The parent alcohols are responsible for early signs of toxicity, primarily CNS depression. Each alcohol subsequently is metabolized through a sequential two-step process, involving the enzymes alcohol dehydrogenase and aldehyde dehydrogenase. The first enzyme, alcohol dehydrogenase, is the rate-limiting step and the target for therapeutic intervention. According to the TESS database, 19,643 cases of toxic alcohol ingestions in children younger than age 6 were reported in 2001 [2]. Isopropanol, the most common ingredient in household rubbing alcohols, accounted for more than 90% of these ingestions. Serious adverse outcomes with isopropanol ingestions are rare, however. In the case of methanol and ethylene glycol, metabolites are responsible for the end-organ toxicity and acidosis. Metabolism of isopropanol leads to generation of acetone rather than an organic acid.

Methanol is found in numerous household products, including deicing solutions, windshield washer fluid, and carburetor cleaners, and concentrations may be 95%. Methanol-containing windshield washer fluid is often brightly colored and may be mistaken for sweetened drinks with similar appearance [160]. Despite its unpleasant taste, toxic exposures in children can occur because of the potential toxicity of even small quantities. Ingestion of 4 mL of 95% methanol by a 10-kg toddler may result in a serum methanol concentration of 50 mg/dL. Methanol is absorbed rapidly after ingestion, and peak levels often occur within 1 hour [161]. Ethylene glycol is a common component of antifreeze, with concentrations of 95%. It is additionally used in some fire extinguishers, inks, and adhesives. Ingestion of 2.9 mL of 95% ethylene glycol by a 10-kg toddler may result in a serum concentration of 50 mg/dL. Peak levels after ingestion are reached within 1 to 4 hours. The presence of glycol groups imparts a sweet taste, attractive to children and to animals.

Clinical manifestations

After methanol ingestion, development of symptoms may be delayed 8 to 24 hours [161]. Methanol is metabolized by alcohol dehydrogenase to formaldehyde, which is metabolized rapidly by aldehyde dehydrogenase to

its terminal and most toxic product, formic acid [162,163]. Symptoms include CNS depression, ranging from mild inebriation to coma. Hyperpnea may reflect the development of an underlying metabolic acidosis. Visual symptoms include blurred, double, or hazy vision, described as a "snowstorm." Pupils may be dilated, with constricted visual fields. Funduscopic examination may reveal an edematous retina and hyperemic optic disks. Formic acid is responsible for the anion gap metabolic acidosis and the retinal toxicity associated with methanol ingestion [163,164].

Ethylene glycol manifests a four-phase toxicity [159]. The first stage, attributable to the inebriating effects of the parent alcohol, often appears within 4 to 8 hours of ingestion. The second phase is primarily metabolic and reflects metabolism of the parent alcohol to toxic metabolites, including glycolic acid, glyoxylic acid, and oxalic acid. During this phase, the osmolar gap decreases as osmotically active parent alcohol is metabolized to organic acids, with development of profound anion gap metabolic acidosis. Glycolic acid seems to be most responsible for the profound metabolic acidosis [165]. The third phase reflects the renal toxicity of the excreted calcium oxalate crystals, with acute tubular necrosis occurring 12 to 48 hours after ingestion [166]. Profound hypocalcemia with ECG changes and tetany also may occur during this phase [166,167]. A fourth phase, manifesting as cranial nerve deficits, including ophthalmoplegia, pupillary deficits, facial weakness, hearing loss, dysarthria, and dysphagia, may occur and persist weeks to months [168].

Management

Initial management of a potentially toxic alcohol exposure consists of supportive care and rapid determination of toxic alcohol levels [159,169]. Although serum methanol and ethylene glycol levels do not correlate well with eventual outcome, they provide confirmation of exposure and need for subsequent definitive treatment. In the case of methanol, adverse outcomes are associated with a 10-hour or greater delay in recognition of toxic symptoms and elevated serum formate levels [170].

Because of delays in obtaining toxic alcohol levels, adjunctive diagnostic strategies have been developed to detect the presence of toxic alcohols. Osmolality refers to the number of particles dissolved per kilogram of solution. Calculation of serum osmolality is based on summation of the known osmotically active particles in solution, typically sodium, glucose, blood urea nitrogen, and ethanol if present. The osmol gap refers to the difference between measured and calculated osmolality. Presence of an elevated osmol gap has been used as evidence for the presence of an uncounted osmotically active toxic alcohol. Care must be taken when using this approach, however. The normal osmol gap may range from 8 to 15 mOsm [171]. Although an elevated osmol gap may suggest the presence of a toxic alcohol, a normal osmol gap should not be used to disprove the

presence of a significant toxic alcohol ingestion. A "normal" osmol gap of 10 may hide a serum methanol concentration of 32 mg/dL or a serum ethylene glycol concentration of 62 mg/dL.

Additional indirect laboratory findings include the development of an anion gap metabolic acidosis in the case of methanol and ethylene glycol toxicity and presence of urinary dihydrate calcium oxalate crystals in ethylene glycol poisoning [159,172]. Fluorescein is added to some brands of antifreeze to aid in the identification of radiator leaks and can cause urine to fluoresce after ethylene glycol ingestion [173–175]. These findings may be considered supportive evidence but lack adequate sensitivity and specificity to determine definitively whether ingestion has occurred. In one study, three physicians examining urine from normal children considered at least 75% of the specimens fluorescent [173].

In addition to supportive measures, several specific therapies should be considered for methanol and ethylene glycol ingestions. The toxicity of these agents stems from the metabolites rather than the parent compound. As a result, inhibition of the rate-limiting enzyme, alcohol dehydrogenase, has been employed to mitigate development of toxicity. Ethanol is a preferential substrate for the enzyme (see Table 1). At serum concentrations of 100 to 150 mg/dL, ethanol effectively inhibits metabolism of the toxic alcohol, which is eliminated unmetabolized by the body [159,172]. Maintaining a consistently therapeutic serum ethanol concentration may be difficult, however, and requires frequent blood ethanol concentration measurements. Additionally, the potential for ethanol-induced airway compromise and hypoglycemia often mandates admission to an intensive care unit.

Fomepizole (4-methylpyrazole) has been approved as a competitive inhibitor of alcohol dehydrogenase in cases of methanol and ethylene glycol intoxication (see Table 1). The current dosing regimen provides consistent inhibition of alcohol dehydrogenase without the significant adverse effects of ethanol. Fomepizole has been found to be safe and effective for the treatment of suspected toxic alcohol ingestions [169,176–180]. Although concerns exist regarding the expense of fomepizole, cost-benefit analysis comparing ethanol infusion versus fomepizole has shown an overall cost savings [181].

Before the development of fomepizole, ethylene glycol or methanol levels greater than 50 mg/dL had been recommended as absolute indications for hemodialysis [159,172,182,183]. Many toxicologists advocated 25 mg/dL as the action level for hemodialysis [159]. In a product containing a toxic alcohol concentration of 95%, ingestion of 4 mL of methanol or 2.9 mL of ethylene glycol by a 10-kg toddler might be expected to result in a serum level of 50 mg/dL. Additional indications for hemodialysis include significant metabolic acidosis, especially unresponsive to sodium bicarbonate, and impaired renal function. With the development of consistently effective alcohol dehydrogenase inhibition, elevated serum toxic alcohol concentration

in the absence of acidosis or end-organ effects no longer may serve as an indication for hemodialysis [184].

Additional therapeutic interventions include the administration of sodium bicarbonate to correct acidosis, to prevent access of formic acid to the retina by ion trapping, and to increase the renal elimination of glycolic acid. Intravenous folate has been shown to accelerate the conversion of formic acid to carbon dioxide and water [159,183]. Thiamine and pyridoxine have been used in cases of ethylene glycol toxicity to divert metabolism of glyoxalic acid away from the nephrotoxic oxalic acid and toward less toxic metabolites [159,185].

Summary

More than 97% of pediatric exposures reported to the AAPCC in 2001 had either no effect or mild clinical effects [2]. Despite the large number of exposures, only 26 of the 1074 reported fatalities occurred in children younger than age 6. These findings reflect the fact that, in contrast to adolescent or adult ingestions, pediatric ingestions are unintentional events secondary to development of exploration behaviors and the tendency to place objects in the mouth [7]. Ingested substances typically are nontoxic or ingested in such small quantities that toxicity would not be expected.

As a result, it commonly is believed that ingestion of one or two tablets by a toddler is a benign act and not expected to produce any consequential toxicity [8]. Select agents have the potential to produce profound toxicity and death, however, despite the ingestion of only one or two tablets or sips. Although proven antidotes are a valuable resource, their value is diminished if risk after ingestion is not adequately appreciated and assessed. Future research into low-dose, high-risk exposures should be directed toward further clarification of risk, improvements in overall management strategies, and, perhaps most importantly, prevention of toxic exposure through parental education and appropriate safety legislation.

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