

chapter 18

Toxicology

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Objectives

- 1 Explain the general management principles for ingestions and toxic exposures.
- 2 Identify methods used to minimize drug absorption.
- 3 Describe the specific therapies, including antidotes, for common poisonings.
- 4 Identify the available resources for consultation for treating the child with poisoning or toxin exposure.
- 5 Describe recreational drugs of abuse and misuse in adolescent patients.
- 6 Describe the ways smoke exposure can be toxic.
- 7 Discuss the clinical progression of inhalation toxicity.
- 8 Describe the steps in evaluation and treatment of the patient exposed to smoke and who might have carbon monoxide poisoning.

Chapter Outline

General Evaluation and Management of Ingestions

Specific Ingestions

Acetaminophen (paracetamol)

Alcohol

Toxic Alcohols, Methanol, and Ethylene Glycol

Amphetamines

Anticholinergic Agents

β -Blockers and Calcium Channel Blockers

Caffeine

Caustics

Clonidine

Cocaine

Cyanide

Cyclic Antidepressants

Digitalis

Gamma Hydroxybutyrate

Hydrocarbons and Inhalants

Hypoglycemics

Isoniazid

Iron

Ketamine

Lead

Mercury

Methemoglobinemia

Neuroleptics and Antipsychotics

Nonsteroidal Antiinflammatory Drugs

Opioids

Organophosphates

Rodenticides

Salicylates

Sedative Hypnotics

Selective Serotonin Reuptake Inhibitors

Theophylline

Overall Management Issues

Toxins Lethal in Small Doses

Additional Routes of Exposure

Ophthalmic and Cutaneous Exposure

Smoke Inhalation



CASE SCENARIO 1

A 2-year-old boy presents to the emergency department (ED) with his frantic parents, who had found him unresponsive in the bathroom with pills and empty bottles “scattered all over the floor.” The child is normally healthy but now is lethargic with no response to stimuli and shallow and slow respirations but no cyanosis. Vital signs include a respiratory rate of 8/min, a pulse of 70/min, blood pressure of 80/40 mm Hg, and temperature of 35.6°C (96°F). Focused physical examination reveals pupils that are 4 mm each and reactive to light, a supple neck, clear lungs, nontender abdomen with no masses, normoactive bowel sounds, extremities with good pulses, and no focal neurologic deficits. There is no evidence of trauma.

1. What are the initial management priorities in this child?
2. What antidotes should be administered?
3. What further history is important in this case?

General Evaluation and Management of Ingestions

Poisoning continues to be a preventable cause of morbidity and mortality in children and adolescents. It is imperative that pediatricians, family physicians, emergency physicians, and pediatric emergency physicians be familiar with the general approach to the poisoned child and the latest treatment methods available.

Poisoning can occur from ingestion, dermal absorption, or inhalation of toxins, with ingestions being the most common exposure (**Figure 18.1**). Although many pediatric patients present

with a history of a specific toxic exposure, others present with unexplained signs or symptoms and no history of poisoning.

Epidemiology

Since the early 1960s, there has been a 95% decrease in the number of pediatric poisoning deaths. Child-resistant product packaging, increased public awareness of potential household toxins, a national toll-free poison control telephone number, and advances in emergency and critical care medicine have all helped to reduce morbidity and mortality.^{1,2} More than 60% of

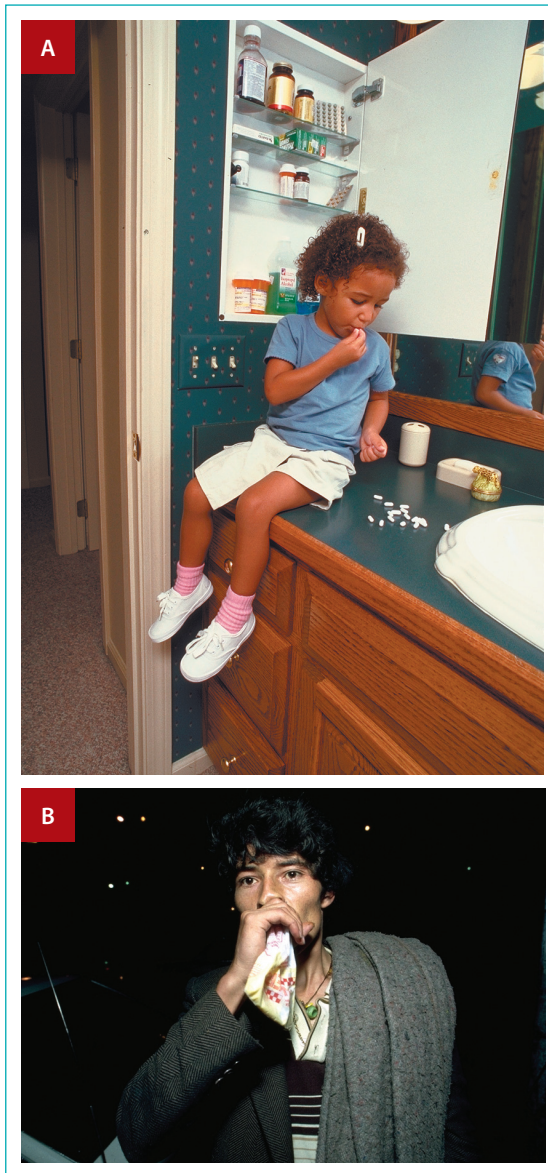


Figure 18.1 A. Ingestion. B. Inhalation of toxins.

calls received by regional poison centers in the United States involve children younger than 17 years. Most exposures in this group are unintentional and result in minimal toxic effects. The highest morbidity and mortality rates occur in adolescent and adult patients, but younger children also can be severely affected.^{3,4}

Clinical Features

Toxins cause damage to the body by a variety of mechanisms. Poisons can act at a cellular level (eg, cyanide) or affect a specific organ system, such as the brain (eg, opioids, hypnotic sedatives, and major tranquilizers), autonomic ner-

vous system (eg, organophosphates), lung (eg, hydrocarbons and paraquat), gastrointestinal tract (eg, caustics and corrosives), liver (eg, acetaminophen [paracetamol] and cyclopeptide mushrooms), or blood (eg, heavy metals). The range of pathologic processes that can be caused by noxious agents is great.

If possible, the specific poison should be identified. A detailed history should be obtained from the patient, family members, friends, rescuers, or bystanders. It is important to identify the ingested substance or substances, the amount and time of ingestion, presence of allergies or underlying diseases, and any first aid treatment that has already been administered. Family, friends, or police might need to search the home for the toxin. Examine clothing and personal effects for ingestants and MedicAlert identification. In addition, a detailed environmental and social history should be obtained.^{4,5}

A brief physical examination should be performed, concentrating on neurologic and cardiopulmonary status. Distinct toxic syndromes should be identified if present (Table 18-1).

The physical examination and vital signs can help identify particular groups of toxins (Table 18-2). Hypertension suggests a sympathomimetic overdose, such as cocaine, amphetamines, or phencyclidine; hypotension suggests β -blocker, calcium channel blocker (CCB), digitalis, or antihypertensive agents, such as clonidine. Tachycardia can be present in ingestions of the same sympathomimetic drugs that cause hypertension, as well as methylxanthines such as theophylline; bradycardia can be associated with digitalis, β -blockers, calcium channel antagonists, or clonidine. Hypothermia is associated with hypoglycemia, ethanol, and opioids. Fever can be produced by salicylates, anticholinergics, or withdrawal from alcohol or narcotics. Respirations are depressed with sedative-hypnotics and opioids but increased in cases of pulmonary aspiration (hydrocarbons), pulmonary edema (narcotics and salicylates), metabolic acidosis (ethylene glycol, methanol, and salicylates), chemical pneumonitis, and smoke inhalation. Pupil size (Table 18-3), skin signs (Table 18-4), and specific odors (Table 18-5) also can help identify the class of ingested agent.^{1,2,6}

TABLE 18-1 Common Toxidromes

<p>Cholinergic Examples: organophosphates, carbamates, pilocarpine</p> <p>DUMBELLS Diarrhea, diaphoresis Urination Miosis Bradycardia, bronchosecretions Emesis Lacrimation Lethargic Salivation</p> <p>Nicotinic M-Mydriasis T-Tachycardia W-Weakness T-Tremors F-Fasciculations S-Seizures S-Somnolent</p>	<p>Opioid Examples: heroin, morphine, codeine, methadone, fentanyl, oxycodone, hydrocodone</p> <p>Miosis Bradycardia Hypotension Hypoventilation Coma</p>
<p>Anticholinergic Examples: antihistamines, cyclic antidepressants, atropine, bupropion, phenothiazines, scopolamine</p> <p>Hyperthermia (HOT as a hare) Flushed (RED as a beet) Dry skin (DRY as a bone)</p> <p>Dilated pupils (BLIND as a bat) Delirium, hallucinations (MAD as a hatter) Tachycardia Urinary urgency and retention</p>	<p>Withdrawal Diarrhea Mydriasis Goose flesh Tachycardia Lacrimation Hypertension Yawning Cramps Hallucinations Seizures (with alcohol and benzodiazepine withdrawal)</p>
<p>Sympathomimetic Examples: cocaine, amphetamines, ephedrine, phencyclidine, pseudoephedrine</p> <p>Mydriasis Tachycardia Hypertension Hyperthermia Seizures</p>	

With an assessment of mental status based on the Glasgow Coma Scale or AVPU (alert, responds to verbal stimuli, responds to painful stimuli, unresponsive) system, the level of consciousness should be quantified. Always

consider other causes of altered mental status, such as infection, metabolic imbalance, or trauma, and rule these out through appropriate diagnostic evaluation (Table 18-6).⁷

TABLE 18-2 Diagnosing Toxicity From Vital Signs

<p>Bradycardia (PACED) Propranolol (β-blockers), poppies (opiates), propoxyphene, physostigmine Anticholinesterase drugs, antiarrhythmics Clonidine, calcium channel blockers Ethanol or other alcohols Digoxin, digitalis</p>	<p>Hypotension (CRASH) Clonidine, calcium channel blockers Rodenticides (containing arsenic and cyanide) Antidepressants, aminophylline, antihypertensives Sedative-hypnotics Heroin or other opiates</p>
<p>Tachycardia (FAST) Free base or other forms of cocaine, Freon Anticholinergics, antihistamines, antipsychotics, amphetamines, alcohol withdrawal Sympathomimetics (cocaine, caffeine, amphetamines, phencyclidine), solvent abuse, strychnine Theophylline, tricyclic antidepressants, thyroid hormones</p>	<p>Hypertension (CT SCAN) Cocaine Thyroid supplements Sympathomimetics Caffeine Anticholinergics, amphetamines Nicotine</p>
<p>Hypothermia (COOLS) Carbon monoxide Opioids Oral hypoglycemics, insulin Liquor (alcohols) Sedative-hypnotics</p>	<p>Rapid respiration (PANT) Phencyclidine, paraquat, pneumonitis (chemical), phosgene Acetylsalicylic acid and other salicylates Noncardiogenic pulmonary edema, nerve agents Toxin-induced metabolic acidosis</p>
<p>Hyperthermia (NASA) Neuroleptic malignant syndrome, nicotine Antihistamines, alcohol withdrawal Salicylates, sympathomimetics, serotonin syndrome Anticholinergics, antidepressants, antipsychotics</p>	<p>Slow respiration (SLOW) Sedative-hypnotics (barbiturates, benzodiazepines) Liquor (alcohols) Opioids Weed (marijuana)</p>

Diagnostic Studies

Patients with central nervous system (CNS) or cardiopulmonary compromise require cardiac monitoring. If cardiac rhythm disturbances are present or the patient is known to have ingested a cardiotoxic poison (eg, tricyclic antidepressant [TCA], CCB, or digitalis), a 12-lead electrocardiogram (ECG) should be performed and the blood pressure closely monitored.^{2,4}

If the level of consciousness is altered or respiratory problems are present, a chest radiograph should be performed. Aspiration pneumonia, noncardiogenic pulmonary edema, or acute lung injury can be present. Certain medications, such as iron, other heavy metals, and illicit drug packets, might be seen on abdominal radiographs (Table 18-7).

Serum electrolyte and arterial blood gas determinations can provide valuable information about possible toxic or metabolic processes. If the arterial blood gas analysis reveals a metabol-

TABLE 18-3 Agents That Affect Pupil Size

<p>Miosis (COPS) Cholinergics, clonidine, carbamates Opiates, organophosphates Phenthiazines (antipsychotics), pilocarpine, pontine hemorrhage Sedative-hypnotics</p>
<p>Mydriasis (SAW) Sympathomimetics Anticholinergics Withdrawal</p>

ic acidosis, calculation of the anion gap ($\text{Na}^+ - [\text{Cl}^- + \text{CO}_2]$) can provide valuable information. A normal anion gap of 8 to 12 mEq/L can result from loss of bicarbonate (diarrhea) or the addition of chloride. An increased anion gap greater than 12 mEq/L is suggestive of the presence of organically active acids, which can occur with several toxins (salicylates, iron, isoniazid, methanol, ethylene glycol, toluene, and cyanide) or metabolic problems (diabetic ketoacidosis and lactic acidosis) (Table 18-8).^{1,2}

An osmolar gap (measured osmoles minus calculated osmoles) of greater than 10 will be present in patients who have ingested ethanol, methanol, isopropanol, or ethylene glycol. Calculated osmoles are derived from the formula $2 \times \text{Na}^+ + \text{glucose}/18 + \text{blood urea nitrogen (BUN)}/2.8 + \text{ethanol}/4.6$ (Table 18-9).^{1,2}

Toxicology screening of blood and urine rarely contributes to the short-term treatment. There might be academic or forensic indications for performing these studies, in which case they can be performed on a routine turnaround time.

A negative toxicology screen result does not rule out the possibility of a toxin. If a particular drug or class of drugs is suspected, this should be communicated to the laboratory. Serum levels of specific drugs might be available to guide management or predict prognosis. Examples include acetaminophen (paracetamol), acetylsalicylic acid, digoxin, ethanol, ethylene glycol, methanol, iron, lead, lithium, and theophylline.

Management

Management is based on the following general principles:

- Pediatric assessment triangle (PAT)
- ABCs (airway, breathing, circulation)
- Provision of supportive care
- Prevention or reduction of absorption
- Enhancement of excretion
- Administration of antidotes

Primary Assessment

In the primary assessment, the physician must determine rapidly whether a child is in respiratory failure or shock.

TABLE 18-4 Agents That Cause Skin Signs

<p>Diaphoretic skin (SOAP) Sympathomimetics Organophosphates Acetylsalicylic acid or other salicylates Phencyclidine</p>	<p>Flushed or red appearance Anticholinergics, niacin Boric acid Carbon monoxide (rare) Cyanide (rare)</p>
<p>Dry Skin Antihistamines, anticholinergics</p>	<p>Cyanosis Ergotamine Nitrates Nitrites Aniline dyes Phenazopyridine Dapsone</p> <p>Any agent causing hypoxemia, hypotension, or methemoglobinemia</p>
<p>Bullae Barbiturates and other sedative-hypnotics Bites: snakes and spiders</p>	
<p>Acneiform rash Bromides Chlorinated aromatic hydrocarbons</p>	

TABLE 18-5 Odors That Suggest the Diagnosis

Odor	Possible Source
Bitter Almonds	Cyanide
Carrots	Cicutoxin (water hemlock)
Fruity	Diabetic ketoacidosis, isopropanol
Garlic	Organophosphates, arsenic, dimethyl sulfoxide, selenium
Gasoline	Petroleum distillates
Mothballs	Naphthalene, camphor
Pears	Chloral hydrate
Pungent aromatic	Ethchlorvynol
Oil of wintergreen	Methylsalicylate
Rotten eggs	Sulfur dioxide, hydrogen sulfide
Freshly mowed hay	Phosgene

The patient, not the poison, should be treated. Attention to the standard ABCs of resuscitation is always the first priority. The PAT should be performed: evaluate the appearance, work of breathing, and circulation to the skin. Derangements should be treated with oxygen, support of ventilation, specific therapy, and fluid resuscitation as indicated. The PAT is followed by the ABCDEs (airway, breathing, circulation, disability, exposure). The glucose level should be assessed using a bedside glucose oxidase reagent strip and glucose administered (0.5-1 g/kg as 2-4 mL/kg of 25% dextrose in water or, for older children, as 1-2 mL/kg of 50% dextrose in water) by intravenous (IV) push if indicated. Naloxone can be used for any child in a coma at a dose of 0.1 mg/kg; it is also acceptable to administer 2 mg for a child older than 5 years. If an adolescent is opioid habituated, small incremental doses are recommended.²

Prevention or Reduction of Absorption

Syrup of ipecac-induced emesis is no longer advocated in the health care setting for the treatment of the acutely poisoned patient.^{4,8-12} Gastric lavage is indicated only if the patient arrives in the ED less than 1 hour after ingestion of a potentially life-threatening toxin, if the patient has ingested massive amounts of the toxin, or for those substances that do not bind to charcoal.¹³

TABLE 18-6 Agents That Cause Coma or Seizures⁷

COMA (LETHARGIC)

L-Lead, lithium
 E-Ethanol, ethylene glycol, ethchlorvynol
 T-Tricyclic antidepressants, thallium, toluene
 H-Heroin, hemlock, hepatic encephalopathy, heavy metals, hydrogen sulfide, hypoglycemics
 A-Arsenic, antidepressants, anticonvulsants, antipsychotics, antihistamines
 R-Rohypnol (sedative hypnotics), risperidone
 G-Gamma hydroxybutyrate
 I-Isoniazid, insulin
 C-Carbon monoxide, cyanide, clonidine

SEIZURES (OTIS CAMPBELL*)

Organophosphates, oral hypoglycemics
 Tricyclic antidepressants
 Isoniazid, insulin
 Sympathomimetics, strychnine, salicylates

 Camphor, cocaine, carbon monoxide, cyanide, chlorinated hydrocarbons
 Amphetamines, anticholinergics
 Methylxanthines (theophylline, caffeine), methanol
 Phencyclidine, propranolol
 Benzodiazepine withdrawal, botanicals (water hemlock, nicotine), bupropion, gamma hydroxybutyrate
 Ethanol withdrawal, ethylene glycol
 Lithium, lidocaine (lignocaine)
 Lead, lindane

*Famous television "town drunk" on *The Andy Griffith Show*.

Standard-sized nasogastric tubes have too small a lumen to make a significant difference in a child after an ingestion of pills. If indicated, a larger oral gastric tube would be necessary in an older or adolescent patient.¹

First-line treatment for significant ingestions consists of a single dose of activated charcoal in water.¹⁴⁻¹⁹ Mixing the charcoal in soda or juice makes it more palatable for children. The dose is 1 to 2 g/kg in children younger than 6 years and 50 to 100 g in adolescents or adults. If the dose of the agent ingested is known, a 10:1 ratio of activated charcoal to drug is

TABLE 18-7 Agents Visible on Abdominal Radiographs (COINS)

Chloral hydrate, cocaine packets, calcium
Opium packets
Iron, other heavy metals, such as lead, arsenic,
mercury
Neuroleptic agents
Sustained-released or enteric coated agents

TABLE 18-8 Agents Causing Metabolic Acidosis and Elevated Anion Gap (METAL ACID GAP)

Methanol, metformin, massive overdoses
Ethylene glycol
Toluene
Alcoholic ketoacidosis
Lactic acidosis

Acetaminophen (paracetamol, large ingestions)
Cyanide, carbon monoxide, colchicine
Isoniazid, iron, ibuprofen (large ingestions)
Diabetic ketoacidosis

Generalized seizure-producing toxins
Acetylsalicylic acid or other salicylates
Paraldehyde, phenformin

TABLE 18-9 Agents Increasing the Osmolar Gap (ME DIE)

Methanol
Ethylene glycol

Diuretics (mannitol), diabetic ketoacidosis
(acetone)
Isopropyl alcohol
Ethanol

preferred.² A nasogastric tube might be required for complete administration. There are few contraindications for its use, although overzealous administration should be avoided in children with altered mental status, combative behavior, or airway compromise due to concerns of potential aspiration.¹⁸ Although highly effective for most agents, activated charcoal is ineffective for a small group of substances (Table 18-10).

Hyperosmolar adjunctive cathartics (eg, sorbitol and magnesium citrate) are contraindicated in young children because of the potential risk of fluid and electrolyte imbalance.²⁰ In young children, it is recommended that activated charcoal be administered with water only, without any cathartic agent.² Of note, the efficacy of cathartic use in reducing the absorption or increasing the elimination of toxins has not been established.²⁰ There are no published data demonstrating an improved outcome with cathartic use alone or combined with activated charcoal.

TABLE 18-10 Substances Not Adsorbable by Activated Charcoal (PHAILS)

Pesticides, potassium
Hydrocarbons
Acids, alkali, alcohols
Iron, insecticides
Lithium
Solvents

Whole bowel irrigation can be accomplished through the administration of polyethylene glycol electrolyte lavage solution (Colyte, GoLYTELY) via nasogastric tube.²¹ Unlike standard cathartics, this solution is osmotically safe and does not result in dehydration and electrolyte imbalance. It irrigates out the contents of the gastrointestinal tract and is indicated for the ingestion of significant amounts of iron, leaded paint chips, delayed-release pharmaceuticals, or illicit drug packets. The rate of administration is 500 mL/h for preschoolers and 1 to 2 L/h for teenagers and adults. The end point is a clear rectal effluent that might take several hours. This procedure is contraindicated in patients with hemodynamic instability, ileus, obstruction, perforation, or significant gastrointestinal hemorrhage.

Enhancement of Excretion

Several techniques aimed at enhancing excretion can be used, and each is indicated in only a few situations.

Ion Trapping

In theory, acidification and alkalization of the urine enhance the excretion of weak bases and weak acids. The former should be avoided

because of the risks of acidemia and exacerbation of rhabdomyolysis. Urinary alkalinization should be considered for significant salicylate and phenobarbital poisonings.

Neutral Diuresis

Urine flow can be increased through the administration of excess (twice maintenance) IV crystalloid and should be considered for significant lithium or bromide poisonings. Pulmonary edema, cerebral edema, and renal failure are contraindications for this technique. Forced diuresis with diuretics is no longer indicated.

Multiple-Dose Charcoal

Multiple-dose charcoal might be indicated for drugs that undergo enterohepatic or enteroenteric recirculation (eg, phenobarbital, theophylline, and carbamazepine).¹⁴ In theory, this technique enhances the excretion of toxins by using the gastrointestinal epithelium as a dialysis membrane (gastrointestinal dialysis) (Table 18-11). Other indications for multiple dosing of charcoal include large ingestions not adequately adsorbed by a single standard dose of activated charcoal (eg, large aspirin overdoses). In smaller children, overzealous administration should be avoided to prevent iatrogenic complications, such as charcoal aspiration and bowel obstruction.^{16,18}

As noted above, repeated doses of any cathartic agent when administering multiple doses of activated charcoal are contraindicated.

Hemodialysis

This technique is indicated for methanol, ethylene glycol, significant salicylate, phenobarbital, theophylline, and lithium poisonings (Table 18-12A and B).

Charcoal Hemoperfusion

This technique involves placement of a charcoal cartridge within the dialysate tubing. It is rarely indicated but efficacious with significant theophylline poisoning.

Administration of Antidotes

Antidotes and antagonists are available for only a small number of poisonings and are not

TABLE 18-11 Agents Responsive to Multiple Doses of Activated Charcoal (ABCD)

Antimalarials (quinine), aminophylline (theophylline)
 Barbiturates (phenobarbital)
 Carbamazepine
 Dapsone

TABLE 18-12A Toxins Accessible to Hemodialysis (UNSTABLE)

Uremia
 No response to conventional therapy
 Salicylates
 Theophylline
 Alcohols (isopropanol, methanol)
 Boric acid, barbiturates (phenobarbital)
 Lithium
 Ethylene glycol

TABLE 18-12B Enhanced Elimination by Charcoal Hemoperfusion

Theophylline
 Barbiturates
 Carbamazepine
 Paraquat
 Glutethimide

intended for indiscriminate use. Antidotes should be used carefully, particularly in the pediatric patient with an unknown overdose, because overuse can complicate an initial presentation by producing other forms of poisoning. In weighing the benefits and risks of administering a specific antidote, the patient's clinical status, appropriate laboratory values, expected pharmaceutical action of the toxin, and possible adverse reactions associated with the antidote should be considered.²²⁻²⁴ Specific antidotes are listed in Table 18-13.

TABLE 18-13 Antidotes and Their Indications

Antidote	Indication (agent)
N-acetylcysteine	Acetaminophen (paracetamol)
Ethanol and fomepizole (4-MP)	Methanol and ethylene glycol
Oxygen and hyperbarics	Carbon monoxide
Naloxone and nalmefene	Opioids
Physostigmine	Anticholinergics
Atropine and pralidoxime (2-PAM)	Organophosphates
Methylene blue	Methemoglobinemia
Nitrites and hydroxycobalamin	Cyanide
Deferoxamine	Iron
Dimercaprol (BAL)	Lead, arsenic
Succimer (DMSA)	Lead, mercury
CaEDTA	Lead
Fab fragments	Digoxin, crotalids, colchicine
Glucagon	β -Blockers, calcium channel blockers
Sodium bicarbonate	Tricyclic antidepressants
Calcium, insulin, and dextrose	Calcium channel antagonists
Dextrose, glucagons, and octreotide	Oral hypoglycemic agents
Lipid emulsion therapy	Local anesthetics, antipsychotics

Abbreviations: 4-MP, 4-methylpyrazone; EDTA, calcium EDTA; BAL, British antilewisite; DMSA, dimercaptosuccinic acid; 2-PAM, 2-pralidoxime.

CASE SCENARIO 2

A 16-year-old girl presents to the ED 3 hours after ingesting two handfuls of extrastrength acetaminophen (paracetamol). She experiences nausea and vomiting. She has no significant medical history. The patient is alert but has a depressed affect and makes poor eye contact. She has no increased work of breathing, and her skin color is normal. Vital signs include a respiratory rate of 20/min, pulse of 110/min, blood pressure of 130/60 mm Hg, and temperature of 37.3°C (99°F). Focused examination reveals that her pupils are 3 mm bilaterally reactive to light; she has a supple neck, no heart murmurs, and clear lungs. Her abdomen is tender to touch in the epigastric region, but there is no guarding and no peritoneal signs. She has good symmetrical pulses and no focal neurologic deficits.

1. What is the primary target organ of acetaminophen (paracetamol) poisoning?
2. What diagnostic laboratory data should be obtained?
3. Does this patient meet the criteria for antidote therapy?

Specific Ingestions

Acetaminophen (Paracetamol)

Clinical Features

Acetaminophen (paracetamol) is the most commonly used drug for analgesia and antipyresis in children. Ingestions most often are seen in children younger than 6 years, but overdose also can be associated with suicide attempts in adolescents. Significant toxic effects are unlikely in children younger than 6 years because they usually ingest smaller quantities. Ingestions in older children and multiple dosing in younger children by well-meaning parents are potentially serious and can result in long-term toxic effects. In this setting, careful assessment and management are necessary to ensure a good outcome.²⁵

Acetaminophen (paracetamol) is absorbed rapidly after ingestion, with peak plasma levels at less than 1 hour. The drug is metabolized in the liver, with 2% excreted unchanged in the urine. In older children, 94% is metabolized to the glucuronide and sulfate conjugates, and 4% is metabolized through the cytochrome oxidase P-450 system (which produces the reactive metabolite NAPQI). When the glutathione stores are less than 30% of normal, the highly reactive metabolite binds to hepatic macromolecules, and hepatic damage ensues.²⁵

The clinical course has been divided into four stages as follows²⁵⁻²⁷:

- Stage 1. This stage consists of the first 24 hours after ingestion. Young children might vomit; older children can have nausea, vomiting, generalized malaise, and diaphoresis. The mean onset of symptoms is 6 hours after the ingestion, with 60% of patients symptomatic by 14 hours. In this stage, liver enzyme levels and prothrombin times (PTs) are normal.
- Stage 2. Patients are less asymptomatic during the second 24 hours (known as the quiescent phase). Liver enzyme levels can become elevated in larger overdoses.
- Stage 3. In serious overdoses, the peak of symptoms and abnormalities is seen 48 to 96 hours after the ingestion. Serum aspartate transaminase concentrations

can be as high as 20,000 to 30,000 IU/L. An elevated PT is considered the most accurate prognostic laboratory guide to the severity of hepatic encephalopathy. Death can occur in this stage from hepatorenal failure, encephalopathy, or profound coagulopathy.

- Stage 4. Approximately 7 to 8 days after ingestion, hepatic abnormalities are almost resolved in survivors. Recovery is complete, and permanent hepatic sequelae are not expected.

Diagnostic Studies

Draw blood samples to determine acetaminophen (paracetamol) levels from patients with potentially serious overdoses. After a single immediate ingestion, blood is drawn up to 4 hours after ingestion to determine acetaminophen (paracetamol) level. If more than 4 hours have passed, blood should be drawn immediately. Once the plasma level has been determined, it should be plotted on the Rumack-Matthew nomogram to determine whether the level is potentially hepatotoxic in relation to time (**Figure 18.2**).^{25,28} If the level cannot be determined within 8 hours of ingestion, treatment with *N*-acetyl-L-cysteine should be initiated after consultation with a regional poison center. If the time and amount of ingestion are unknown, determination of acetaminophen (paracetamol) level is still recommended with subsequent blood drawn at 4-hour intervals to determine the half-life of the drug. A prolonged elimination half-life of more than 3 hours is indicative of hepatic damage or delayed absorption. It is also important to follow laboratory parameters in a case of serious poisoning; these parameters include PT, aspartate transaminase, alanine aminotransferase, and bilirubin, as well as electrolytes, BUN, and creatinine.²⁵

Differential Diagnosis

Patients with acetaminophen (paracetamol) poisoning usually do not present with altered mental status within the first 24 hours after ingestion. The possibility that patients presenting with CNS depression have a multiple-drug overdose, such as acetaminophen (paracetamol) with codeine, hydrocodone, or diphenhydramine, should be considered. Histories should be interpreted with

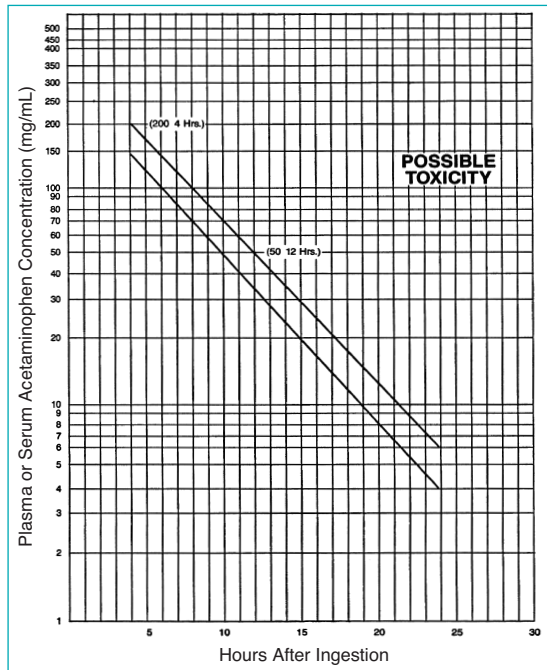


Figure 18.2 Rumack-Matthew nomogram for estimating severity of acute acetaminophen (paracetamol) poisoning. The time coordinate refers to time of ingestion. Serum levels drawn before 4 hours might not represent peak levels.

Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. *Pediatrics*. 1975;55:871-876. Adapted with permission.

caution, particularly in the adolescent. It often is difficult to distinguish between toxic and non-toxic overdoses by history alone. With any potential acetaminophen (paracetamol) ingestion, any other over-the-counter medications and pain relievers, such as salicylates (aspirin) and non-steroidal anti-inflammatory agents (e.g. NSAIDs such as ibuprofen), should be considered in the differential diagnosis.

Management

After a brief assessment, activated charcoal in water should be administered if less than 4 hours have elapsed since the ingestion. Activated charcoal binds well to acetaminophen (paracetamol) and can lessen a potentially hepatotoxic ingestion. In the older child, a relatively large dose, such as 100 g, might be required because of the large amount of acetaminophen (paracetamol) typically ingested. In practice, the concern of charcoal absorbing orally administered *N*-acetyl-l-cysteine and diminishing its bioavailability has been overstated. Routine doses of both agents can be administered if indicated.

Oral *N*-acetyl-l-cysteine is available as a 20% concentrate. It has a strong smell of sulfur, which is generally unacceptable to children. Dilute the concentrate to a 5% concentration (ie, if starting with a 20% concentrate, dilute 3:1). The taste might be improved by mixing it with orange juice or carbonated beverages. Use a cup with a cap and hole for a straw to avoid the smell. The initial dose of *N*-acetyl-l-cysteine is 140 mg/kg, with subsequent doses of 70 mg/kg at 4-hour intervals for 17 doses. The length of treatment may be shortened by following a patient-tailored acetylcysteine protocol based on specific clinical endpoints.²⁹

Intravenous *N*-acetyl-l-cysteine is licensed in the United States, Europe, and Canada. Currently, there are two IV protocols: 21 hours and 48 hours. In the 21-hour protocol, the drug is given as three separate infusions: 150 mg/kg in the first 60 minutes, 50 mg/kg in the next 4 hours, and 100 mg/kg in the next 16 hours.^{23,25,28,30} Administration of the first infusion in 60 instead of 15 minutes decreases the risk for adverse reactions, such as flushing, itching, and hives. The advantages of IV therapy are a shorter protocol, no concern that vomiting or charcoal will decrease the bioavailability of the antidote, and ease of administration. It is not uncommon for patients receiving IV *N*-acetyl-l-cysteine to develop hives, requiring treatment with antihistamines. Most patients with acetaminophen (paracetamol) poisoning (99%) recover within 1 week if treated appropriately.³¹ Patients requiring careful monitoring might be treated best in a pediatric tertiary care center.

Alcohol

Ethanol poisoning is more likely to occur in an older child; however, it can also occur in a toddler. In addition to alcohol-containing beverages, such as beer, wine, and hard liquor, children have access to cologne and perfume (40%-60% ethanol), mouthwash (containing up to 75% ethanol), and numerous over-the-counter and prescription medications containing ethanol.^{32,33} (Figure 18.3) Characteristic breath odor and serum levels confirm the diagnosis. Mixed drug-ethanol toxicity frequently confounds the clinical picture. A blood ethanol level of

100 mg/dL is considered sufficient to cause intoxication. Levels approaching 500 mg/dL can be lethal, particularly in an alcohol-naive patient or novice drinker. In general, treatment is supportive and sometimes includes assisted ventilation. Due to low hepatic glycogen stores, small children are extremely prone to hypoglycemia when intoxicated with ethanol. Intoxication in combination with hypoglycemia can markedly impair mental status.



Figure 18.3 Common sources of ethanol.

Toxic Alcohols, Methanol, and Ethylene Glycol

Clinical Features

Very small volumes of methanol or ethylene glycol are potentially life-threatening. These toxic alcohols are commonly found in windshield washer fluid and antifreeze products and other widely available commercial and household products that are brightly colored and highly attractive to young children.³⁴ (Figure 18.4)



Figure 18.4 The bright colors make toxins highly attractive to children.

Both methanol and ethylene glycol produce an altered mental status with inebriation and CNS depression. Both induce an osmolar gap and severe anion gap metabolic acidosis. Methanol can eventually lead to blindness, and ethylene glycol can cause acute renal failure. Both act through the production of toxic metabolites (formic acid with methanol, and glycolic acid and oxalate in ethylene glycol), which can be blocked by ethanol or fomepizole through a competitive inhibition of the alcohol dehydrogenase enzyme.³⁴

Diagnostic Studies

The following laboratory studies should be performed: complete blood cell (CBC), measurement of serum electrolytes and glucose, renal function tests (BUN/creatinine), arterial blood gas analysis, serum osmolality, and measurement of serum ethanol, ethylene glycol, methanol, and isopropanol levels.³⁴

Differential Diagnosis

When considering the possibility of methanol poisoning, the physician should also consider ethylene glycol poisoning. In addition, isopropanol and ethanol poisoning should be included in the differential diagnosis because each can create an osmolar gap; however, they do not generally produce a profound metabolic acidosis. The metabolite produced by isopropanol is acetone.

Management

Treatment of methanol and ethylene glycol poisoning has been recently revolutionized by the introduction of the antidote 4-methylpyrazole or fomepizole, which competitively inhibits the alcohol dehydrogenase enzyme. Unlike ethanol therapy, 4-methylpyrazole does not potentiate sedation or induce profound hypoglycemia, and it can be safely administered in children. A fomepizole loading dose of 15 mg/kg should be administered, followed by 10 mg/kg every 12 hours for four doses or until the methanol or ethylene glycol levels are below 10 mg/dL.³⁵⁻³⁸

If 4-methylpyrazole is unavailable, in addition to acid/base, fluid, and electrolyte monitoring, an alternative treatment consists of ethanol therapy to produce a serum concentration of 100 mg/dL. The usual dose is 0.6 g/kg infused during 30 to 40 minutes. Oral ethanol can be used if IV

ethanol is not readily available. During the infusion of an ethanol drip, the child's glucose levels should be monitored to avoid hypoglycemia.^{34,39}

In patients with significant metabolic acidosis or peak serum methanol and ethylene glycol levels of greater than 50 mg/dL, nephrology consultation for extracorporeal intervention with hemodialysis is indicated.³⁷ Folate (up to 50 mg every 4 hours) is a therapeutic cofactor for methanol, and thiamine (up to 100 mg) serves a similar function for ethylene glycol.

Amphetamines

Clinical Features

Ecstasy (3,4-methylenedioxymethamphetamine) is a designer amphetamine that has become one of the most widely abused drugs in the adolescent patient population.⁴⁰ (Figure 18.5) The pharmacologic effects are a blend of sympathomimetic amphetamine stimulation with the hallucinogenic effects of mescaline. The drug is extremely popular at “rave” parties and at dance clubs.^{41,42}



Figure 18.5 Ecstasy.

After ingestion, the onset of action is 30 to 90 minutes; plateau effects are achieved in 2 to 3 hours. The drug is abused because (in therapeutic doses) it induces extreme euphoria, increased energy, feelings of belonging, heightened sensations, empathy, music appreciation, fear dissolution, and bright, intense visual perceptions.^{41,43}

Negative toxic effects of ecstasy include bruxism, trismus, short-term memory loss, confusion, headaches, vertigo, ataxia, vomiting, depression, and psychological addiction. Major complications include profound hyperthermia, hypertension, seizures, dehydration, hyperna-

tremia and hyponatremia, hepatic and renal failure, rhabdomyolysis, myocardial infarction, and intracranial hemorrhage.^{42,44}

Pure methamphetamines, such as crystal methamphetamine, are highly addictive, resulting in sympathomimetic effects with acute toxic effects. Epidemics have been well documented in rural communities of the United States. Long-term abuse can result in profound malnutrition and weight loss because users direct all their efforts toward feeding their drug addiction. A common clinical feature is “meth mouth,” which results from direct chemical effects and poor dental hygiene and bruxism.^{43,45} Methamphetamine users have various skin conditions, ranging from scabs and rashes to large abscesses from picking at their skin or “skin popping” the drug when IV access is limited. Methamphetamines are equally dangerous to manufacture, often resulting in highly combustible reactions and explosions that produce traumatic burns and injuries.

Differential Diagnosis

The drugs that could be confused with ecstasy ingestion include other amphetamines, lysergide (LSD), and phencyclidine (PCP).

Management

The treatment of symptomatic patients is supportive care, airway management, and rapid cooling, along with liberal doses of benzodiazepines for tachycardia, hypertension, and agitation.^{43,44} For gastric decontamination of recent ingestions, activated charcoal is recommended. The results of toxicology urine screens that are marketed to detect amphetamines can be negative after ecstasy and designer amphetamine use.

YOUR FIRST CLUE

Signs and Symptoms of Anticholinergic Poisoning

- “Red as a beet” (flushing)
- “Blind as a bat” (pupillary mydriasis)
- “Dry as a bone” (dry skin, decreased oral secretions)
- “Hot as a hare” (febrile)
- “Mad as a hatter” (delirium)

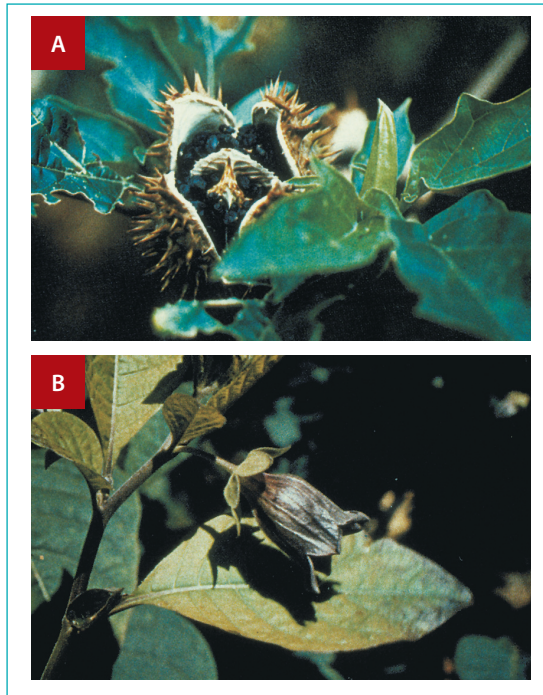


Figure 18.6 A. Jimsonweed. B. Deadly nightshade.

Anticholinergic Agents

Clinical Features

Anticholinergic poisoning can be caused by jimsonweed, deadly nightshade, potato leaves, and a number of medications, including antihistamines, benzotropine, atropine, phenothiazines, and TCAs (Figure 18.6). Most overdoses involving drugs with anticholinergic actions do not result in a pure anticholinergic syndrome; this is especially so for cyclic antidepressants because the life-threatening toxic effects are due to more direct myocardial depression at the sodium channels.

Diagnostic Studies

Routine laboratory studies should include measurement of CBCs, serum electrolytes, BUN, creatinine, and glucose. If the patient demonstrates seizures or hyperthermia, creatinine phosphokinase and urine myoglobin should be measured to rule out rhabdomyolysis. With any moderate to severe overdose, a 12-lead ECG is indicated. Routine toxicology screens usually do not include detection of antihistamines.

Differential Diagnosis

If the child is hyperthermic, bacteremia or sepsis should be considered. Other drugs that can cause hyperthermia include nicotine, an-

tidepressants, sympathomimetics, and antihistamines (mnemonic NASA). With delirium or acute mental status changes, consider other drug ingestions, metabolic causes, or head trauma. If the patient is tachycardic, other drugs, such as the sympathomimetic agents (cocaine, amphetamines, and PCP), should be ruled out.

Management

Treatment is mainly supportive with administration of oral activated charcoal. With the exception of TCAs, in severe pure anticholinergic poisoning, the antidote physostigmine can be considered. Indications include severe agitation, profound hyperthermia, hallucinations, or uncontrollable seizures refractory to standard benzodiazepine therapy. Intravenous physostigmine is administered in a dose of 0.5 mg to a young child and 1 to 2 mg to an adolescent for 2 to 3 minutes. An alternative frontline therapy would be IV administration of a benzodiazepine, such as diazepam, in a similar clinical scenario.⁴⁶

β -Blockers and Calcium Channel Blockers

Clinical Features

Cardiovascular manifestations of β -blocker toxicity include hypotension, bradycardia, heart block, and congestive heart failure. Due to the rapid absorption of many β -blockers, the onset of symptoms can be as rapid as 30 minutes after ingestion, but it most commonly occurs within 1 to 2 hours.^{47,48} The cardiovascular manifestations include hypotension, bradycardia, heart block, and congestive heart failure.⁴⁹ Respiratory toxic effects includes noncardiogenic pulmonary edema, pulmonary edema, exacerbation of asthma, and decreased respiratory drive. Patients can also present with CNS depression or seizures.⁴⁸

Different pharmacologic profiles of CCBs will cause various presentations, but in all cases, the cardiovascular effects predominate. Verapamil and diltiazem typically cause bradycardia and hypotension. Hypotension can be due to sinoatrial node depression, atrioventricular (AV) node depression leading to AV blocks, negative inotropic effects, or decreased peripheral vascular resistance. Neurologic and respiratory findings are usually secondary to cardiovascular toxic effects and shock. Respiratory effects include decreased respiratory drive, pulmonary

edema, and acute respiratory distress syndrome. Neurologic sequelae include depressed sensorium, cerebral infarction, and seizures.⁵⁰

Differential Diagnosis

Other agents causing hypotension and bradycardia should be considered, such as digitalis, clonidine, sedative hypnotics, and opioids.

Diagnostic Studies

In any patients with a β -blocker or CCB overdose, ECG should be immediately performed. In addition to AV block, ECG manifestations of β -blocker and CCB overdose include prolongation of the PR interval, QRS complex, and QT interval, as well as bundle branch block.^{48,49} Laboratory tests for blood levels of β -blockers or CCBs are available from reference laboratories. These tests are time-consuming and helpful only in confirming the exposure and are rarely clinically useful. In CCB overdose, electrolyte abnormalities can occur and decreased insulin release can lead to hyperglycemia. Hypoperfusion can lead to profound lactic acidosis. Hypocalcemia is the most frequent electrolyte abnormality. Hypokalemia and hyperkalemia have also been reported.

Management

Absorption of β -blockers can be decreased by gastric lavage and administration of activated charcoal. If the ingestion occurred less than 1 hour before presentation, gastric lavage should be considered. In patients with symptomatic bradycardia and hypotension from β -blocker toxicity, glucagon is often used as the first-line agent to reverse the toxic effects. Glucagon is a positive inotrope that works by increasing cyclic adenosine monophosphate. In adults and older adolescents, an initial bolus of IV glucagon is administered at a dose of 3 to 5 mg for 1 minute. If symptoms recur, an additional bolus is given. If symptoms persist, an infusion can be started at 1 to 5 mg per hour. Pediatric doses of 0.05 to 0.1 mg/kg of IV glucagon are administered, followed by a continuous infusion at 0.07 mg/kg per hour.⁴⁸ Patients who do not respond to glucagon are treated with aggressive fluid resuscitation and adrenergic agonists. Epinephrine (adrenaline) is the adrenergic agonist of choice.⁵¹

In CCB overdose with hypotension, fluid administration, calcium salts, atropine, gluca-

gon, and therapy with adrenergic agonists are indicated.⁴⁸ High-dose insulin has been recently used in the management of CCB overdose in those patients refractory to calcium and glucagon therapy.⁵² Insulin improves myocardial contractility by improving myocardial carbohydrate use. Insulin can be administered as a bolus of regular insulin, 1.0 U/kg, along with 0.5 to 1 g/kg of dextrose. This treatment is followed by an infusion of 0.2 to 0.5 U/kg per hour. Serum glucose must be monitored at least hourly during the infusion and dextrose administered to maintain euglycemia. Glucose infusion can be initiated at 0.5 g/kg per hour and adjusted based on the results of blood glucose levels.^{52,53} A decrease in serum potassium level is anticipated due to an intracellular shift of potassium. Serum potassium should be monitored and replaced to maintain serum potassium levels of 2.8 to 3.2 mEq/L.

Caffeine

Clinical Features

In children, short-term oral doses of 80 to 100 mg/kg of caffeine have produced severe symptoms. Stimulation of the myocardium causing tachycardia, dysrhythmias, and extrasystoles can occur. Hypertension secondary to vasoconstriction is common. Patients can appear agitated and anxious, with increased psychomotor activity. A hyperadrenergic state is seen in most children with acute caffeine toxic effects; manifestations include excitement, insomnia, flushed face, gastrointestinal symptoms, rambling thoughts and speech, periods of inexhaustibility, and psychomotor agitation. Seizures can occur in significant overdoses. Hyperglycemia can result from catecholamine-induced increase in gluconeogenesis, lipolysis, and glycogenolysis. Potassium can be shifted intracellularly through a catecholamine-induced mechanism, leading to hypokalemia. Rhabdomyolysis has been reported after caffeine overdose.⁵⁴

Other manifestations of caffeine use or abuse fall into several typical presentations.

The “anxiety presentation” in children and adolescents mimics hyperactivity. Symptoms include diuresis, restlessness, tremulousness, hyperactivity, irritability, dry mouth, dysesthesias,

tinnitus, ocular dyskinesias, and scotomata. In a “hypochondriasis-like presentation” the patient has vague, nonspecific symptoms, such as generalized discomfort, tremor, and myalgias. The “insomnia and/or headache presentation” is characterized by difficulty sleeping or increased motility during sleep. Withdrawal headaches with nausea and vomiting can occur in moderate or sporadic users of caffeine products. Other withdrawal symptoms include nausea, yawning, drowsiness or lethargy, rhinorrhea, irritability, nervousness, and poor attention in school. The “depressive presentation” is seen in heavy users of caffeine products (>750 mg daily). Patients generally present with a depressed mood and affect.⁵⁴

Diagnostic Studies

The diagnosis of caffeine toxicity is made on a detailed history and exclusion of other organic causes. A comprehensive urine toxicology screen can detect caffeine. In selected cases evaluation of serum electrolytes might be indicated to assess serum potassium. An ECG is indicated in patients with severe toxic effects and associated tachycardia or dysrhythmias.

Management

In most cases, caffeine overuse in children is due to beverages, and activated charcoal has no value. If, however, the child has ingested a significant amount of a caffeine-containing medication and presents to the ED within 1 hour, activated charcoal can be administered at a dose of 1 g/kg. Supraventricular tachydysrhythmias can be treated with esmolol, 500 mcg/kg for 2 minutes, then a 200-mcg/kg per minute infusion. Ventricular dysrhythmias should be managed according to standard protocol. Seizures can be treated with benzodiazepines or phenobarbital.^{54,55}

Caustics

Clinical Features

Caustics are chemicals that cause tissue injury on contact (Figure 18.7). These agents account for approximately 5% of all unintentional toxic exposures, with small children most frequently affected. Agents such as drain cleaners, lye, Clinitest tablets, oven cleaners, automatic dishwasher detergents, toilet bowl cleaners, hair relaxers, and button batteries are examples of caustic substanc-

es. Alkali burns cause liquefaction necrosis and injury that penetrates deep into the tissues, predominantly in the esophagus. Acid burns cause coagulation necrosis, primarily in the stomach, with severe injury to superficial gastric mucosa. The exposed child might present with excessive crying, refusal to eat or drink, drooling, oropharyngeal burns, stridor, vomiting, and abdominal pain. If severe, the patient might have acute respiratory distress, airway edema, and shock.



Figure 18.7 Caustics cause tissue injury on contact.

Diagnostic Studies

Laboratory studies should include a CBC count, serum electrolyte level, renal function tests, coagulation profile, and glucose level. Pulse oximetry and a chest radiograph are indicated in any child with respiratory symptoms. Patients with abdominal pain should undergo abdominal radiography to assess for gastrointestinal perforation and diagnostic free air. Endoscopy will determine the extent of the injury, guide management, and determine prognosis.

Differential Diagnosis

Identification of the specific caustic agent, whether acid or alkali, its volume, concentration, and pH is critical in determining an agent's potential toxicity. As with any child in respiratory or upper airway distress, infections such as epiglottitis, pharyngeal abscess, and tracheitis must be considered. In addition, foreign-body aspiration must be ruled out.

Management

Initial treatment might include immediate dilution with small aliquots of water or milk. A regional poison center should be contacted for instructions regarding proper dilution in the home. Often, well-meaning caregivers give too

large a volume of milk or water, causing gastric distention and vomiting. Children with oral burns or a definite history of significant ingestion should be considered for esophagoscopy within 12 hours of the injury.^{56,57} After ingestion of liquid drain cleaners, esophageal burns can occur without the presence of oropharyngeal burns.⁵⁶ Gastric evacuation is contraindicated, and charcoal provides no benefit. Depending on the stages of second-degree esophageal burns, corticosteroids and antibiotics might be indicated.

Clonidine

Clinical Features

Clonidine is a centrally acting antihypertensive agent. It stimulates α_2 -adrenergic receptors in the brain, which makes it effective in lowering blood pressure. It primarily is prescribed for patients with chronic hypertension and patients in narcotic detoxification programs. It is packaged in small tablets (0.1 mg, 0.2 mg, and 0.3 mg) that can be hard for the elderly to see and easy for a child to swallow (Figure 18.8). Clonidine also is available in patch form, which can still contain the drug after use. A child can obtain a toxic dose simply by sucking on the patch.⁵⁸⁻⁶⁰



Figure 18.8 In tablet form, clonidine can be difficult to see and easy for children to swallow.

Symptoms of ingestion mimic opioid overdose, including low blood pressure, altered mental status, miosis, and respiratory depression.⁶¹ Children present with respiratory rates, blood pressure, and pulse rates less than 50% of normal for their age groups. The child who ingests massive quantities of clonidine can present with initial hypertension, usually lasting less than 1 hour.⁶⁰ As the brain perceives the hypertension, the central sympatholytic downregulating effects begin to

dominate and the patient becomes hypotensive. Antihypertensive drugs should not be used because of the transient nature of the hypertension.

Diagnostic Studies

If the child is manifesting signs and symptoms of toxicity, such as CNS depression, laboratory studies should include measurement of CBC, serum electrolytes, renal function, and glucose. Pulse oximetry and chest radiography are indicated in any child with respiratory symptoms. If the child is demonstrating cardiovascular toxicity marked by hypotension and bradycardia, an ECG should be performed and the child should receive continuous cardiac monitoring.

Differential Diagnosis

Children with clonidine overdose resemble those with opioid poisoning, with symptoms including miotic pupils, CNS depression, bradycardia, and hypotension. Other medications that can cause bradycardia include β -blockers, anticholinesterase drugs, CCBs, ethanol, and digoxin (mnemonic PACED).

Management

Treatment is straightforward and supportive. Stimulation of a child with altered mental status often will increase heart and respiratory rates. Oxygen should be applied by face mask. If hypotensive, the child should be placed in a Trendelenburg position. Intravenous access should be obtained and a 20-mL/kg bolus of lactated Ringer or normal saline should be administered. Inotropic drugs seldom are required but, if necessary, are generally effective. If the respiratory rate does not improve, begin bag mask ventilation. A few children will require

WHAT ELSE?

Differential Diagnosis for Toxicologic Causes of Bradycardia and Hypotension

- Opioids
- Antihypertension medications (clonidine)
- β -Blockers
- CCBs
- Digoxin
- Cardiac glycosides

intubation and mechanical ventilation until the drug effects wear off, usually within 24 hours.

Because children with clonidine overdose resemble those with opioid poisoning, including small pupils, naloxone has been used. In the patient with known clonidine ingestion, naloxone is of little use because it is not necessary in milder cases, it will not correct the severe cases and might sufficiently lighten them so that hypertension is aggravated, and it is of no help in the hypotensive stage. Although naloxone can transiently increase the respiratory rate, it rarely obviates the need for ventilatory support in more severe overdoses. The symptomatic child will have to be observed in the hospital for 12 to 36 hours.

Cocaine

Clinical Features

Cocaine abuse and toxicity continue to be pervasive problems. Adolescents and adults predominantly use cocaine as a recreational drug. Children usually experience toxic effects when exposed to cocaine being used by others. In overdose, cocaine toxicity will cause a sympathomimetic toxidrome manifested by agitation, mydriasis, diaphoresis, hypertension, tachycardia, and hyperthermia. Cardiotoxicity manifesting as acute coronary syndromes and myocardial infarctions, as well as cerebral vascular accidents and intracranial bleeds, have been well documented in patients with cocaine toxicity.^{62,63}

Seizures have been reported in children who unintentionally ingest cocaine, and toxic effects have occurred in toddlers who inhale cocaine being “free-based” by nearby adults.^{64,65}

Differential Diagnosis

Other types of sympathomimetics, such as amphetamines and PCP, should also be considered. Methylxanthines, such as theophylline and caffeine, are also in the differential diagnosis. Patients with anticholinergic toxicity will also present with similar symptoms, except that cocaine typically causes diaphoresis, whereas anticholinergics produce dry skin.

Diagnostic Studies

Baseline laboratory studies, including a urine toxicology screen for cocaine metabolites (benzoylecgonine), should be performed. If the

patient has chest pain or tachycardia, an ECG is recommended to rule out signs of cardiotoxicity. In addition, a chest radiograph is useful to exclude pneumothorax, pneumomediastinum, or infiltrate. For patients with severe headache or neurologic deficits, a computed tomography scan of the brain is indicated to rule out the possibility of a cocaine-induced cerebrovascular accident or bleed.

Management

Benzodiazepines are the first-line agents for reversing mild to moderate cocaine-induced sympathetic symptoms, including agitation and seizures. Active cooling measures are critical in patients with profound hyperthermia.⁶⁶ Activated charcoal and whole bowel irrigation might be indicated for orally ingested cocaine, as in cases of body packing and stuffing.^{63,67}

Cyanide

Clinical Features

Poisoning with cyanide can occur through inhalation in the industrial setting, dermal exposures, or ingestion of silver polish, jewelry cleaners, photographic processing chemicals, laetrile, certain insecticides, specific masticated fruit seeds, and acetonitrile-containing nail cosmetics (nail glue removers). Pulmonary exposure appears frequently in home fires (ie, cyanide gas released from burning synthetic materials); such exposure should be suspected in smoke inhalation patients.⁶⁸ Death in this scenario can occur within 1 to 15 minutes. Survivors who reach the ED can manifest seizures, profound acidosis, shock, or coma. Flushing often is a unique sign, and cyanosis is a relatively late finding. The characteristic smell of bitter almonds is detected in some cases, but its absence does not rule out cyanide exposure.

Diagnostic Studies

Cyanide blood levels can be obtained, but the results are never available emergently and therefore have little clinical applicability. Measurement of arterial blood gases, serum electrolytes, and serum lactic acid can be helpful in the acute care setting because cyanide induces a profound elevated anion gap metabolic acidosis.⁶⁸ If the traditional cyanide antidote kit has been administered, serial methemoglobin levels should be

monitored. If the patient was involved in a fire, a carbon monoxide level should be obtained.

Differential Diagnosis

If the child has been in a fire, carbon monoxide poisoning should be ruled out. Other toxic causes of elevated anion gap acidosis include aspirin, iron, ethylene glycol, isoniazid, and methanol poisoning. In addition, diabetic ketoacidosis and sepsis should be considered.

Management

Rapid treatment with 100% oxygen, ventilatory assistance, and administration of the cyanide antidote kit (amyl nitrite, sodium nitrite, followed by thiosulfate) should be started. The ampule of sodium nitrite in the older commercially available cyanide antidote kits is an adult dose; therefore, if that dose is rapidly given to a child, it could cause profound hypotension, severe methemoglobinemia, and death. The dose of sodium nitrite for a child is 10 mg/kg or 0.33 mL of 3% solution of sodium nitrite per kilogram of body weight. A slower rate of infusion will also help prevent hypotension. Sodium thiosulfate is administered in a 25% solution at a pediatric IV dose of 1.6 mL/kg (400 mg/kg) up to 50 mL (12.5 g) for 10 minutes.⁶⁸

Hydroxycobalamin, a precursor to vitamin B₁₂, detoxifies cyanide by binding it to form cyanocobalamin, a nontoxic compound excreted in the urine. This antidote was approved for use in the United States in 2007 and is now found in some cyanide treatment kits, replacing sodium nitrite and sodium thiosulfate. Hydroxycobalamin is not associated with the complications of hypotension or excessive methemoglobinemia as seen with nitrite therapy. Red discoloration of the skin seems to be the primary adverse effect. Doses of 70 mg/kg are generally recommended for pediatric patients.^{69,70}

Cyclic Antidepressants

Clinical Features

Mechanisms of cyclic antidepressant toxicity include direct myocardial (quinidine-like) depression, inhibition of norepinephrine (noradrenaline) uptake, and anticholinergic activity. Ingestion can produce significant CNS and life-threatening cardiovascular toxic effects. Find-

ings include combativeness, delirium, coma, seizures, hypotension, and dysrhythmia.⁷¹ A clinical hallmark of cyclic antidepressant poisoning is that the child might appear clinically stable soon after ingestion, only to rapidly deteriorate within the first 2 hours of presentation.⁷² Seizures are a poor prognostic sign because seizures induce metabolic acidosis, exacerbating the cardiotoxic effects of the cyclic antidepressant. After an unintentional TCA ingestion, children are often initially asymptomatic.

Diagnostic Studies

In all suspected cases of TCA toxicity, an ECG should be performed immediately. A QRS duration of greater than 100 milliseconds is a risk factor for dysrhythmia.⁷³ Specific serum levels for cyclic antidepressants have little clinical applicability guiding management but might help document the presence of the drug in a child with an unknown ingestion. Also, some of the newer urine toxicology tests can more rapidly qualitatively screen for the presence of cyclic antidepressants. Serial arterial blood gas analysis should be performed to guide clinical management of the patient's acid-base status.

Differential Diagnosis

The physician should also consider other anticholinergic drugs, such as diphenhydramine, and other antipsychotic agents, such as phenothiazines, newer atypical antipsychotics, selective serotonin reuptake inhibitors (SSRIs), and lithium.⁷⁴ The differential diagnosis can include other cardiotoxic drugs, such as cocaine, digitalis, carbamazepine, and calcium channel antagonists.

Management

Hypotension should be treated with a crystalloid challenge of 20 mL/kg of normal saline; if unsuccessful, pressors should be used. The drug of choice for the patient with a dysrhythmia is IV sodium bicarbonate. A wide QRS interval is an early indication for its use.⁷³ Alkalinization via hyperventilation also is efficacious. The goal is blood pH 7.45 to 7.55. Physostigmine has no role in cyclic antidepressant overdose, despite the anticholinergic properties; the other potent cardiotoxic properties of cyclic antidepressants contraindicate its use. Neurotoxicity manifested as seizure activity is best managed with benzodiazepines and phenobarbital.⁷¹

Symptomatic patients require an intensive care unit setting; however, long periods of monitoring of asymptomatic patients are not required. For patients with a normal level of consciousness, vital signs, and normal ECG from the outset, a 6-hour period of continuing normality of these parameters is sufficient. Those with an abnormality in any of these three require at least a 24-hour observation period in a monitored setting.

Digitalis

Clinical Features

The early signs and symptoms of digitalis can be subtle. Anorexia, nausea, vomiting, and diarrhea are clues to digoxin toxicity. Other symptoms that might be present in children include visual disturbances, such as photophobia and altered red-green color perception. Other symptoms consistent with digoxin toxicity are fatigue, malaise, weakness, headache, rashes, altered mental status, and paraesthesias. Bradycardia, hyperkalemia, and vomiting are the most predictive symptoms in patients with acute digoxin intoxication.⁴⁸

Cardiovascular toxic effects are clearly the most important factor in determining morbidity and mortality. Symptoms reflecting cardiovascular toxic effects include palpitations and dizziness usually secondary to hypotension. There are a myriad of abnormal rhythms that can be seen with digoxin toxicity. There is no pathognomonic rhythm. Dysrhythmias can be supraventricular, nodal, and ventricular in nature. Commonly occurring rhythms include ventricular premature

beats, junctional escape beats and rhythms (especially accelerated junctional rhythms), paroxysmal atrial tachycardia with block, and AV block of varying degrees. The most common ECG manifestation of digitalis toxicity is the presence of ventricular premature beats. Sinus bradycardia or first-degree AV block are also commonly noted in pediatric patients.^{48,75}

Differential Diagnosis

Other agents that induce hypotension and bradycardia, such as β -blockers, CCBs, and clonidine, should be considered. Also, cardioglycoside plants, such as foxglove, oleander, and lily of the valley, contain digitalis-like toxins.

Diagnostic Studies

Laboratory studies for digoxin toxicity include a CBC count; measurement of serum electrolytes, magnesium, calcium, BUN, and creatinine; and ECG. If the condition is severe, arterial blood gas analysis will reveal metabolic acidosis from hypoperfusion. If the ingestant is unknown, it is appropriate to obtain acetaminophen (paracetamol) and salicylate levels and to perform a urine toxicology screen.

A digoxin level should be measured whenever there is clinical suspicion for digoxin toxicity. Therapeutic digoxin levels are usually considered to be 0.8 to 1.8 ng/mL. Levels are obtained on admission and again at 6 hours after ingestion to account for full distribution of the drug.⁴⁸ Serum digoxin concentrations measured 6 to 12 hours after ingestion correlate well with the clinical course of intoxication.

The distinction between the immediate and gradual ingestion is important. In the immediate ingestion setting, the patient will have more noticeable clinical and laboratory findings than in the gradual ingestion setting. In the immediate ingestion group, the onset of symptoms will be more abrupt, with severe nausea and vomiting. In the gradual ingestion group, there might be only mild nausea and vomiting. Serum levels will be higher in the immediate ingestion setting. The patients in the gradual ingestion group will be symptomatic and sicker, with lower digoxin serum levels.

Management

It is essential for children with possible digoxin toxicity to be treated aggressively. This is justified

KEY POINTS

Management of Antidepressant Ingestion

- Fluid resuscitation at 20 mL/kg
- Sodium bicarbonate for wide QRS interval
- Physostigmine *contraindicated*
- Benzodiazepines for seizures
- 24-hour monitoring for alteration in mental status, vital signs, or ECG abnormalities

by the high potential for morbidity. All patients should receive IV access, frequent vital sign assessment, and continuous cardiac monitoring.

Activated charcoal can be administered as a single dose.⁴⁸ Digoxin immune Fab fragments are specific antidigoxin antibodies. The use of the Fab fragments is indicated in cases of severe digitalis intoxication that is suspected by history, a high level of digoxin, or a child manifesting significant signs and symptoms of toxicity. A digoxin level higher than 5 ng/mL after immediate ingestion of digoxin is an indication for administration. The presence of a life-threatening dysrhythmia or conduction delay would be another indication.⁷⁶ Again, this might be seen at lower digoxin levels in the case of chronic toxicity. Dosage of Fab fragments is based on either the amount ingested or the serum level. Guidelines are available in the package insert. Each vial of Fab fragments contains 40 mg of drug, which will bind approximately 0.6 mg of digoxin.^{48,76} Subsequent monitoring of digoxin levels will be falsely elevated after the administration of Fab fragments, and this will take several days to correct. Radioimmunoassay measures all digoxin not just the free digoxin, therefore giving a falsely elevated result.

Because hyperkalemia can potentiate digoxin toxicity, a potassium level greater than 5.5 mEq/L (hyperkalemia) is another indication for the use of Fab fragments. Standard modalities to treat hyperkalemia can also be used (glucose, insulin, and bicarbonate), with the exception of calcium salts. It is believed that the administration of calcium in the face of digoxin toxicity can exacerbate the development of dysrhythmias.⁴⁸

Gamma Hydroxybutyrate

Gamma hydroxybutyrate (GHB) was synthesized in 1960 and first used as an anesthetic agent for the treatment of sleep disorders because it induces rapid eye movement sleep. However, its use was halted when the drug was found to induce seizure activity. An erroneous study in the 1970s reported that GHB might stimulate growth hormone production; therefore, the drug became popular in the body-building community. In addition, because of its euphoric and mind-altering effects, it has become a popular drug of abuse

with adolescents in the party scene.⁷⁷ The Drug Enforcement Administration has classified GHB as a federally controlled Schedule I substance. It has also been used in date rape because of its rapid onset and amnesic properties. A form of it is used to treat the symptom of cataplexy (sudden loss of muscle tone) in those with narcolepsy.⁷⁷

Gamma hydroxybutyrate is a colorless, odorless liquid or gel (Figure 18.9). As a powder, it has a salty taste. Its onset of action is rapid, and it is obtainable on the street and over the Internet and can be easily produced in the home. One of the precursors of GHB, gamma butyrolactone, has also gained recent popularity.



Figure 18.9 Gamma butyrolactone.

Clinical Features

Ingestion of GHB results in drowsiness, dizziness, and disorientation within 15 to 30 minutes. High doses can result in a depressed respiratory drive, bradycardia, and anesthesia. The hallmark of GHB toxicity is marked agitation with stimulation despite apnea and hypoxia.⁷⁷⁻⁷⁹

Differential Diagnosis

Included in the differential for a GHB overdose are opiates; sedative-hypnotics, including barbiturates, benzodiazepines, and chloral hydrate (the original “Mickey Finn”); CCBs; clonidine; and ethanol.

Management

Treatment involves airway protection if necessary (often, patients will suddenly awaken in 4-6 hours and extubate themselves). Atropine can be used for profound bradycardia. Activated

charcoal can be administered after recent ingestions or mixed ingestions for gastric decontamination; however, caution is advised in patients with respiratory distress or failure. There is no proven antidote for GHB toxicity, although some anecdotal reports claim that physostigmine can reverse the effects of GHB toxicity. Currently, this practice is not widely supported in the literature and is not recommended.^{77,80}

Hydrocarbons and Inhalants

Clinical Features

Hydrocarbons are found as solvents, fuels, and additives in household cleaners and polishes. The major toxic effect of such compounds stems from their low surface tension and vapor pressure, which allow them to spread over large surface areas, such as in the lungs, leading to a chemical pneumonitis.⁸¹ Young children usually ingest hydrocarbons unintentionally, whereas adolescents often abuse hydrocarbons as volatile inhalants (model glue) and paint solvents (toluene).⁸²

Patients who ingest hydrocarbons might choke, cough, and gag as the product is swallowed and vomit soon afterward. Aspiration of the product at the time of the initial swallowing can cause aspiration pneumonitis.⁸¹ It has been shown that the mere presence of the substance in the hypopharynx can cause chemical pneumonitis by spreading to contiguous surfaces in the airway. In addition to the pulmonary findings, there can be transient associated CNS symptoms secondary to systemic absorption of some of the hydrocarbons. Rarely, hepatic, renal, or myocardial injury occurs.

The amount of a hydrocarbon that has been ingested by a child often is difficult to quantify. Less than 1 mL of some compounds, such as mineral seal oil, when aspirated directly into the trachea, can produce severe pneumonitis and eventual death. Other compounds are difficult to aspirate and are not well absorbed from the gastrointestinal tract. Generally, compounds such as asphalt or tar, lubricants (eg, motor oil, household oil, and heavy greases), and liquid petroleum are not toxic when ingested.

Adolescents who abuse hydrocarbons can immediately experience CNS toxic effects, such as euphoria, disinhibition, disorientation, and

hallucinations. These patients are also at risk for chemical pneumonitis and life-threatening cardiotoxic effects via catecholamine sensitization. Tragically, inhalant abuse is on the rise, as is mortality from its use. It is now one of the leading causes of toxic death in adolescents.⁸²⁻⁸⁴ Long-term abuse can result in renal complications and lasting neurocognitive impairment.

Diagnostic Studies

After hydrocarbon ingestion, pulse oximetry and serial chest radiographs are indicated for the child demonstrating respiratory symptoms to rule out hypoxia and aspiration pneumonitis. In an adolescent abusing a volatile substance, ECG and continuous cardiac monitoring should be performed. In addition, serum electrolyte levels, renal function, and the patient's acid-base status should be determined.

Differential Diagnosis

In any child with a history of hydrocarbon ingestion, it is important to identify the agent because this can have implications for management and prognosis. In a child with respiratory symptoms, pneumonia, reactive airway disease, and foreign-body ingestion should be ruled out. Other chemicals causing respiratory compromise, such as insecticides (organophosphates), herbicides (paraquat), and pulmonary irritants (chlorine gas), should be considered. In an adolescent abusing volatile substances, the chance concomitant use of other illicit drugs, such as cocaine, amphetamines, opioids, hallucinogens, and marijuana, should be addressed.

Management

Asymptomatic children with a normal physical examination should be observed for 4 to 6 hours in the ED. If they remain well, they can be discharged with appropriate instructions to return if fever, tachypnea, or cough develops.

Treatment of hydrocarbon pneumonitis consists of supportive care. Antibiotics should not be used prophylactically. The use of corticosteroids in the treatment of aspiration from hydrocarbons has been associated with increased morbidity and is not recommended.⁸¹

Inducement of emesis with syrup of ipecac and decontamination with gastric lavage are contraindicated. Charcoal administration is not indicated unless the ingested compound contains

a dangerous additive that has the potential for systemic toxic effects. Other hydrocarbon compounds, including gasoline, kerosene, charcoal lighter fluid, and mineral spirits, are unlikely to produce systemic symptoms after ingestion.

Treatment for adolescents under the influence of volatile hydrocarbons includes supportive care measures and standard cardiac life support measures as indicated. Because of the cardiac sensitization of the volatiles, some experts caution against the overuse of cardiac stimulants, such as epinephrine (adrenaline), and advocate the use of β -blockers for ventricular tachydysrhythmias. However, this theory is underreported and requires further study.⁸¹

Hypoglycemics

The brain's reliance almost exclusively on glucose for fuel makes it the most sensitive organ to hypoglycemia. Any CNS abnormality, including agitation, psychosis, ataxia, seizures, focal neurological deficits, and coma, should prompt physicians to rule out hypoglycemia. Other symptoms are caused by hypoglycemia-triggered catecholamine release and include tremor, pallor, diaphoresis, tachycardia, anxiety, dry mouth, mydriasis, and hypertension. Hypoglycemic patients can also be hypothermic, particularly if there has been exposure to a cool environment.

Differential Diagnosis

Agents that lower serum glucose levels in children include oral hypoglycemic sulfonylureas; biguanide class medications, such as metformin; ultra-, short-, and long-acting insulin preparations; ethanol; β -blockers; and unripened akee fruit (which contains the toxin hypoglycin).

Diagnostic Studies

Glucose monitoring is the mainstay of diagnostic testing. Such monitoring can be done at the bedside using reagent strips or a glucometer or in the hospital laboratory. Reagent strips are usually not as accurate as laboratory testing. It also must be remembered that the blood glucose levels at which patients show clinical signs of hypoglycemia are variable and are often higher in diabetic than in nondiabetic patients.

Plasma C-peptide levels can be determined if there is a question of endogenous vs exogenous insulin as the cause of hypoglycemia.

When insulin is administered to a patient, the C-peptide level is low because commercially available forms of insulin contain only the active insulin. When patients are hypoglycemic due to endogenous insulin production, such as insulinoma or sulfonylurea ingestion, the C-peptide level will be high.⁸⁵ Other useful studies include electrolytes, BUN, creatinine, ethanol, and liver function tests.

Management

Initial resuscitation of a hypoglycemic patient from any cause includes administration of glucose. Glucose is given at an IV dose of 0.5 to 1 g/kg as 50% dextrose in water in older children, 25% dextrose in water in younger children, and 10% dextrose in water in neonates. Patients who are alert should be given oral glucose in the form of food or juice because an IV glucose bolus can produce only transient euglycemia. Glucagon should be administered only if IV access is unavailable. Glucagon is given at an intramuscular/subcutaneous dose of 0.3 mg/kg in neonates or 0.025 to 0.1 mg/kg in children, with a maximum dose of 1 mg.⁸⁶ Glucagon increases glucose levels by mobilizing glycogen stores, which might be inadequate in children. Mental status should be monitored closely and subsequent blood glucose measurements should be obtained every 1 to 2 hours. Glucose infusion might be required to maintain euglycemia and given as either 5% dextrose in water or 10% dextrose in water, titrated as necessary. Patients must maintain euglycemia without glucose infusions before they can be considered medically clear.^{86,87}

Octreotide, a somatostatin analog, can be helpful in the management of hypoglycemia due to sulfonylurea or meglitinide ingestion. Octreotide acts by decreasing insulin secreted by the delta cells of the pancreas. Recommended doses are 4 to 5 mcg/kg per day, up to 50 mcg/kg, divided every 6 hours. Patients should be monitored for 24 hours after discontinuation of octreotide therapy.⁸⁵

Isoniazid

Clinical Features

Isoniazid is still considered the first-line treatment for active tuberculosis worldwide. The classic clinical triad of severe acute isoniazid

toxicity consists of refractory seizures, profound anion gap metabolic acidosis (pH 6.8–6.9), and coma. Nausea, vomiting, dizziness, hyperpyrexia, and hypotension are other abnormalities seen with acute isoniazid toxicity.⁸⁸ Patients are usually symptomatic within 30 to 45 minutes of ingestion; however, symptoms can be delayed for up to 2 hours after ingestion, when peak serum levels are reached.^{89,90}

Diagnostic Studies

Serum isoniazid concentrations are not commonly available and therefore are not included among routine toxicology screening tests. Serum concentrations, however, are not necessary for treatment of the immediately poisoned patient, and one should initiate specific therapy if clinical suspicion of isoniazid ingestion is high. Other laboratory studies include electrolytes, glucose, BUN, and creatinine measurement; liver function tests; and blood gas analysis. A patient who presents with seizures after an unknown ingestion might require a chest radiograph if there is concern for aspiration.⁹¹ Radiographic abnormalities suggestive of tuberculosis indicate a potential role of isoniazid in the etiology of seizures.

Differential Diagnosis

The differential diagnosis includes other agents that induced seizures and metabolic acidosis, including: cyanide, carbon monoxide, methanol, ethylene glycol, salicylates, and false morel (*gyromitrin*) mushrooms.

Management

Aggressive airway management and seizure treatment are the cornerstones of therapy. The airway should be maintained and ventilatory assistance provided if necessary. Gastric decontamination of these patients has a limited role, given that isoniazid is absorbed rapidly from the small intestine. Although activated charcoal adsorbs isoniazid well, the risk of early seizures must be considered in the decision because the risk of aspiration increases tremendously in a convulsing patient.⁸⁹

Commonly used anticonvulsants, such as benzodiazepines, phenytoin, and phenobarbital, are generally not effective in controlling isoniazid-induced refractory seizures. Pyridoxine (vitamin B₆), a specific antidote that augments and

replaces γ -aminobutyric acid, usually terminates benzodiazepines-resistant seizures and should be given as soon as possible. The dose of pyridoxine is equivalent to the amount of isoniazid ingested; the pediatric dose of 70 mg/kg, up to 5 g, should be administered if the amount of isoniazid is unknown. Pyridoxine can be repeated if the seizures continue or recur. Pyridoxine can also hasten the resolution of metabolic acidosis. If acidosis is not responsive to pyridoxine and seizure-control, IV sodium bicarbonate should be given. If IV pyridoxine is not available, the oral preparation can be crushed and administered via a standard nasogastric tube.⁸⁹

Iron

Clinical Features

Fortunately, during the past decade the pediatric mortality rate associated with iron poisoning has decreased with heightened public awareness and improved childproof packaging enforced by the Food and Drug Administration (Figure 18.10).



Figure 18.10 Adult multivitamins are a potential cause of iron poisoning.

The lethal dose of elemental iron is 200 to 250 mg/kg, although gastrointestinal symptoms can be seen at doses of 15 to 30 mg/kg. When calculating the ingested dose, remember that the elemental iron per unit dose is only a fraction of the total milligram weight of the tablet. Ferrous sulfate, the most commonly ingested product, is 20% elemental iron; ferrous fumarate has 32% elemental iron, and ferrous gluconate has only 10%. The toxic dose is not absolute, and fatal reactions have been reported with ingestions of

only 75 mg/kg. Therefore, all ingestions should be considered potentially dangerous. Significant toxicity, however, is uncommon at amounts less than 60 mg/kg. Universally, patients who have ingested potentially significant amounts of iron develop gastrointestinal symptoms within 6 hours.⁹²

For iron-poisoned patients, the pathophysiologic findings and clinical picture have been classified into four stages, as follows⁹²:

- **Gastrointestinal Stage.** The first signs of iron toxicity are gastrointestinal; early symptoms include vomiting, rapid onset of diarrhea, colicky abdominal pain, and gastrointestinal hemorrhage. Iron directly damages the gastrointestinal mucosa and can lead to massive fluid loss and hemorrhage. The gastrointestinal effects can contribute to systemic hypovolemia by the third spacing of the fluid in the small bowel.
- **Relative Stability (Quiescent) Stage.** The gastrointestinal signs and symptoms might ameliorate before the onset of overt shock. In such instances, there is a stage of relative stability. This does not last longer than 6 to 12 hours, and patients are not really symptom free during this time. Careful assessment will yield evidence of decreased perfusion and acidosis.
- **Shock Stage.** The third stage is characterized by circulatory failure, profound shock, and acidosis. Shock, the most common cause of fatality in iron poisoning, has a complex etiology that includes hypovolemic, distributive, and cardiac depressant factors. The chief causes of the acidosis are the hydrated unbound circulating iron and lactic acidosis secondary to shock.
- **Hepatotoxicity Stage.** Hepatotoxicity occurs within the first 48 hours. Earlier onsets correlate with increased severity. This is the second most common cause of mortality.

Gastrointestinal scarring is a late manifestation of iron poisoning, occurring 2 to 6 weeks after ingestion. Typically, it presents as gastric outlet obstruction, but any portion of the small intestine can be involved.

Diagnostic Studies

Prompt clinical assessment coupled with early abdominal radiographs and timely serum iron levels are the mainstay of the treatment of the iron-poisoned patient (Table 18-14). A negative radiograph in a symptomatic patient does not exclude iron ingestion. Reasons for a negative radiography result can be that the iron was not ingested, the ingested iron has dissolved or was absorbed, a liquid iron preparation was ingested, or a pediatric multivitamin-plus-iron pharmaceutical agent with a small amount of iron per tablet was ingested. The multivitamin-plus-iron pharmaceutical agent is associated with only mild symptoms. Serum iron levels, if obtained promptly, often correlate with the likelihood of developing symptoms. Usually, iron levels of less than 350 mcg/dL, when samples are drawn 2 to 6 hours after ingestion, predict a benign course. Patients with levels in the range of 350 to 500 mcg/dL often show mild stage I symptoms but rarely develop serious complications. Levels higher than 500 mcg/dL suggest significant risk for stage III manifestations. However, serum iron determination is not always available on an emergent basis.⁹²

TABLE 18-14 Treatment of the Iron-Poisoned Patient

- Assess stability of patient's condition and stabilize if required.
- History: How much? When? Type of iron salt? Enteric coated? Symptoms?
- Determine serum iron level.
- Perform abdominal radiography to corroborate ingestion. Consider gastrotomy for the presence of concretions, gastric wall adherence, or a potentially fatal amount of iron in the stomach.
- If the radiograph suggests a significant iron ingestion, begin whole bowel irrigation with polyethylene glycol electrolyte lavage solution. Patients with negative radiography results do not require gastrointestinal decontamination. If asymptomatic, they will remain so; if symptomatic, it is too late for it to be clinically beneficial.
- Chelate the symptomatic patient with deferoxamine.
- Admit the patient to the intensive care unit for shock or decreased level of consciousness.

A CBC count, serum electrolytes, BUN, creatinine, and glucose measurement and liver function tests should also be performed. An arterial blood gas analysis can be helpful because an elevated anion gap acidosis can occur.

Differential Diagnosis

Other toxins that cause gastrointestinal irritation and vomiting should be considered, such as salicylates, theophylline, lead, and colchicine. Other hepatotoxins, such as acetaminophen (paracetamol), arsenic, carbon tetrachloride, and *Amanita phalloides* mushrooms, should be added to the differential list of potential poisons. Other medications besides iron that are visible (radiopaque) on radiograms include choral hydrate, heavy metals (mercury), drug packets, enteric-coated pills (salicylates), and sustained-release medications. The mnemonic COINS can be used for an easy memory tip.

Management

The amount of iron ingested is often hard to quantify, and minimal safe levels are not well established. Gastric lavage has little benefit more than 1 hour after ingestion. In addition, the diameter of the gastric evacuation tube used in a child often is too small to allow removal of significant pill fragments and concretions. Iron is not adsorbed to charcoal. Whole bowel irrigation is considered the technique of choice with large ingestions.⁹² Gastrotomies have been performed in cases of massive overdoses. Intragastic complexing with bicarbonate, phosphate, or deferoxamine should be avoided because these approaches are ineffective and can cause adverse effects.

Patients with severe early symptoms of iron toxicity, including vomiting, diarrhea, gastrointestinal bleeding, depressed sensorium, or circulatory compromise require, urgent, intensive treatment. The first priority is obtaining venous access. Simultaneously, blood should be drawn for CBC count; blood glucose, electrolytes, BUN, serum iron measurement; liver function tests; and typing and cross-matching. The total iron-binding capacity level often is inaccurate in patients with iron poisoning and not useful in the management of an immediate overdose. Patients in shock should be supported with normal saline solution and blood transfusions if indicated.

These patients often are acidotic and require large amounts of sodium bicarbonate. Specific chelation therapy with IV deferoxamine should be started immediately in all severely poisoned patients. Careful attention should be paid to hydration states because fluid-depleted patients treated with deferoxamine are at risk for hypotension, anaphylaxis, and acute renal failure.

Chelation therapy with parenteral deferoxamine enhances the excretion of iron. Indications for chelation are the presence of symptoms or a serum iron concentration higher than 350 mcg/dL. The IV dose of deferoxamine is 15 mg/kg per hour up to a maximum of 6 g per day.^{93,94} Indications for cessation of chelation are the absence of symptoms and resolution of acidosis or when the maximal dose has been given. The classic “vin rose” urine color change will result if iron-binding stores are saturated and free iron is complexed with deferoxamine. Although this finding can be helpful in diagnosing toxicity, its results often are subtle; therefore, an absent color change does not rule out significant iron poisoning.

Further problems can include hypotension, profound metabolic acidosis, hypoglycemia or hyperglycemia, anemia and colloid loss due to gastrointestinal hemorrhage (after equilibration), renal shutdown due to shock, and hepatic failure with an associated bleeding diathesis. The maintenance of an adequate urine output is critical to prevent renal failure and promote excretion of the iron-deferoxamine complex. If renal failure occurs, chelation can be continued with concurrent extracorporeal removal, such as charcoal hemoperfusion or hemodialysis for removal of the iron-deferoxamine complex.

Ketamine

Clinical Features

Ketamine is often used for the induction of anesthesia, especially in status asthmaticus. Conscious sedation with ketamine is often used for elective procedures in children. The onset of action is rapid. Clinically, the patient's eyes will glaze over in a dissociative state and can be seen within seconds to a minute.^{95,96} The muscular tone can become increased, and purposeless movements of the extremities will often occur. Pharyngeal and laryngeal reflexes remain intact, depression of the

cough reflex can occur, and increased salivary secretions or drooling often develops. The increase in secretions can be minimized by concurrent administration of an anticholinergic agent, such as glycopyrrolate or atropine.

It is also abused recreationally and has nicknames such as “Special K,” “K,” “KitKat,” and “Vitamin K.” Ketamine is used regularly at all night raves and nightclubs because of its “hallucinatory effects” and “out-of-body/near-death” experiences. The drug is fairly inexpensive and has a duration of action of approximately 15 to 45 minutes.

Differential Diagnosis

Ketamine’s toxicity is similar to PCP, but it is far less potent. Unlike PCP, ketamine is not typically manufactured illegally. It is obtained from diverted veterinary, dental, and medical sources. Other agents with similar clinical effects include exotic hallucinogens, such as mescaline, psilocybin, LSD, or tetrahydrocannabinol.

Management

Most patients presenting with ketamine intoxication require supportive care addressing their airway, circulation, and thermoregulation. Ketamine toxicity induced iatrogenically should be managed conservatively. Airway compromise from increased salivation and tracheobronchial secretions, or laryngospasm, might rarely require intubation. Other adverse reactions include emergence reactions, agitation, and persistent incoherence. Benzodiazepines can be used for the agitation and dysphoria that are associated with emergence.⁹⁵

Lead

Lead poisoning affects people of all ages and classes, but the prevalence of lead poisoning remains highest in inner-city, underprivileged children.^{97,98} Ingestion of leaded paint is the most common and clinically relevant source of lead poisoning in children. Most homes built before 1978 were painted with lead-based paint. A small paint chip containing 50% lead can produce acute lead poisoning in a toddler.⁹⁹ Lead poisoning has traditionally been a problem in children living in poorly maintained, inner-city buildings. However, renovation of old homes in the last decade and poorly controlled lead abatement has been identified as a significant risk for

lead poisoning through inhalation and ingestion of contaminated dust and soil. Lead exposure can also occur through ingestion of drinking water contaminated by lead in plumbing. Other potential sources of toxicity include secondary exposure to lead brought home from workplaces, drinking from improperly fired lead-glazed pottery, some folk remedies, and retained bullets lodged in joint spaces. The phase-out of leaded gasoline has had a major impact in reducing exposure to lead.⁹⁹

Clinical Features

Symptoms and signs of lead toxicity can be subtle and nonspecific.⁹⁷ Because the effects of detrimental lead levels are often clinically silent, emphasis should be placed on periodic screening in preschool children.¹⁰⁰ Symptomatic lead poisoning is characterized by one or more of the following: decrease in play activity, irritability, drowsiness, anorexia, sporadic vomiting, intermittent abdominal pain, constipation, regression of newly acquired skills (particularly speech), sensorineural hearing loss, clumsiness, and slight attenuation of growth.⁹⁹ It is not uncommon for some children to be seen by a health care practitioner several times with these nonspecific symptoms before lead poisoning is even considered. Peripheral neuropathy consists mainly of motor weakness in the upper and lower limbs. In the upper limbs, weakness can result in “wrist drop.” Lead encephalopathy can ensue after days or weeks of symptoms; can be accompanied by ataxia, forceful vomiting, lethargy, or stupor; and can progress to coma and seizures. Permanent brain damage can result in children with lead encephalopathy, even with optimal treatment.⁹⁹

Diagnostic Studies

Lead toxicity is grossly correlated with a blood lead level (BLL) but is more pronounced in young children and in those with prolonged exposure to lead. Lead encephalopathy can occur with a BLL of 70 mcg/dL but is generally associated with BLLs in excess of 100 mcg/dL. Mild elevation in levels of liver transaminases can occur. Iron deficiency microcytic anemia frequently coexists with lead poisoning. Elevation in the BLL is followed by an increase in the free erythrocyte protoporphyrin or zinc protoporphyrin levels.

Radiographic evidence of lead poisoning consists of bands of increased density at the metaphyses of long bones that are best seen in radiographs of the distal femur and proximal tibia and fibula. The common term “lead lines” is a misnomer because the increased radiopacity is caused by abnormal calcification from the disrupted metabolism of bone matrix rather than actual deposition of lead in the metaphysis. Radiopaque foreign material seen in the intestine by a flat abdominal radiogram suggests a recent ingestion of lead-containing paint chips.⁹⁹

Differential Diagnosis

Because lead poisoning is so frequent and can be accompanied by a variety of signs and symptoms, a high index of suspicion is required to make the diagnosis. The differential diagnosis of lead poisoning includes iron deficiency, mercury poisoning, behavior and emotional disorders, abdominal colic and constipation, intellectual disability, and idiopathic seizures.

Management

The principles of management in lead poisoning include identification and removal of the lead source, chelation therapy, supportive therapy, and long-term follow-up.¹⁰¹ For patients with lead levels between 10 and 20 mcg/dL, treatment consists of environmental management, nutritional evaluation, and repeated screening. In many cases, this involves removing the child from the home until the source of lead exposure is identified and removed. If there is evidence of recent ingestion of lead paint on an abdominal radiogram, whole bowel irrigation with a polyethylene glycol/electrolyte solution should be considered. Whole bowel irrigation at a rate of 500 mL to 2 L per hour should be performed until rectal effluent is clear and repeat radiograms are normal.

For patients with BLLs between 20 and 44 mcg/dL, pharmacologic intervention might be indicated and is accomplished on an outpatient basis if the child is asymptomatic. Oral dimercaptosuccinic acid (DMSA) (succimer) is currently the only treatment approved for oral chelation of childhood lead poisoning. Chemically, DMSA is similar to British antilewisite and produces a lead diuresis comparable to that produced by calcium EDTA (CaEDTA) without

depletion of other metals. It is given at a dosage of 30 mg/kg per day in three divided doses for the first 5 days, then 20 mg/kg per day in two divided doses for 14 more days.

Children with asymptomatic lead poisoning and BLLs of 45 to 69 mcg/dL are admitted to the hospital for chelation therapy with either CaEDTA or DMSA.^{98,99} Children with symptomatic lead poisoning and all patients with BLLs greater than 70 mcg/dL should be treated with British antilewisite at a dose of 25 mg/kg per day in six divided doses given by deep intramuscular injection. Once the first dose is given and adequate urine flow is established, CaEDTA is added as a continuous IV infusion at 50 mg/kg per day in dextrose or saline.⁹⁹

Mercury

Clinical Features

Elemental Mercury

Ingestion: The gastrointestinal absorption of elemental mercury is of negligible clinical significance and is considered essentially nontoxic. Thus, caregivers should be reassured that the concern of a broken mercury thermometer in the mouth is the potential for injury from glass.¹⁰²

Inhalation: Inhalation of large amounts of mercury vapor results in an acute, severe illness that can include respiratory distress and non-cardiac pulmonary edema. Erosive dermatitis and a characteristic neurologic syndrome called erethism can follow should the patient recover from the acute inhalational effects. Patients with erethism often experience mood swings and social withdrawal.^{102,103}

Inorganic Mercury

The immediate ingestion of mercury salts is rare but is seen on occasion after unintentional or suicidal ingestion of pesticides containing mercuric chloride. The patient presents with vomiting, abdominal cramps, and diarrhea; volume loss and third spacing lead to cardiovascular collapse. Acute tubular necrosis ensues. Immune-mediated glomerulonephritis has also been reported.^{103,104}

Organic Mercury

Symptoms after immediate exposures to organic mercurials are often delayed several days.

Personality changes, visual field constriction, cerebellar dysfunction, and coma characterize the progressive neurologic deterioration.^{102,103}

Diagnostic Studies

In general, a timed 24-hour urine collection is the most reliable method for determining body burden of elemental or inorganic mercury and will generally reflect exposures during the previous month. Spot blood and urine analyses can be useful as screening tests or at the initiation of therapy in a clinically poisoned patient. Whole blood mercury measurements are more reliable as a measurement of body burden of organic mercury because this compound is relatively concentrated in the red blood cells. Normal blood mercury levels rarely exceed 1.5 mcg/dL, although this level can be elevated several days after consuming certain types of seafood.

Management

Elemental Mercury Exposure

Ingestion: It is reasonable to perform abdominal radiography after a large ingestion and follow urinary excretion if there is residual retained mercury.

Inhalation: Significant symptoms from household or occupational exposure to elemental mercury can occur. The importance of minimizing vaporization after a spill should therefore be emphasized. Detailed protocols for spill management exist and should be followed. Assistance should be sought from the state Department of Environmental Protection and the regional poison control center for spills larger than a household clinical thermometer.¹⁰⁵ In the rare circumstance after a significant exposure to elemental mercury when elevated urinary concentrations are documented, chelation therapy might become necessary once the patient is removed from the source of exposure. Dimercaprol (British antilewisite) was the mercury chelator of choice for years. Currently, it is reserved for severe mercury poisoning but is not recommended for organic mercury toxicity because of the potential of increasing CNS mercury concentrations secondary to postchelation redistribution. Mild-moderate mercury toxicity can be treated with oral DMSA (succimer). The dosing of succimer is 10 mg/kg per dose three times a day for 5 days and then twice a day for

14 days. A 2-week hiatus or drug holiday is recommended for repeat cycles of therapy. The end point of therapy is guided by clinical symptoms and decreasing mercury levels in the urine.^{102,105}

Methemoglobinemia

Clinical Features

Cyanosis unresponsive to oxygen, despite normal arterial oxygen tension, is the hallmark of methemoglobinemia. Such cyanosis is typically most notable in the skin, lips, and nail beds. Neonates and infants often present with nonspecific clinical findings, such as tachycardia, poor feeding, vomiting, irritability, excessive crying, or excessive sleeping, so the detection of methemoglobinemia in these patients requires a high index of suspicion.^{106,107} Agents responsible for inducing methemoglobinemia include nitrates, nitrites, benzocaine, dapsone, and phenazopyridine (Pyridium).^{106,107}

Differential Diagnosis

Cyanosis, in conjunction with the above clinical signs and symptoms, can be easily misinterpreted as a sign of structural heart disease. Also, children with congenital forms of methemoglobinemia appear well yet exhibit lifelong cyanosis. Finally, an illness-associated methemoglobinemia of infancy often associated with diarrhea, dehydration, and metabolic acidosis is another consideration.^{106,107}

Diagnostic Studies

The arterial blood of children with methemoglobinemia is classically described as “chocolate brown,” although comparison of suspect blood to control blood on a white paper towel or filter paper highlights this distinction. In contrast to deoxygenated blood from patients with cardiopulmonary disease, methemoglobin-darkened blood does not redden on exposure to room air.^{106,107}

Pulse-oximetry assessment of the oxygen saturation of hemoglobin is inaccurate for diagnosing methemoglobinemia. Typically, pulse-oximetry underestimates oxygen saturation at low methemoglobin levels and overestimates oxygen saturation at high levels. Multiple-wavelength co-oximetry is the laboratory method of choice for confirming and quantifying methemoglobinemia.

Management

In all cases of acquired methemoglobinemia, careful attention should be given to the status of the patient's ABCs and neurologic function. Supplemental oxygen should be administered. Supportive care is sufficient therapy for most identified cases of methemoglobinemia.

Antidotal therapy with IV methylene blue should be considered for patients with overt signs of tissue hypoxia, CNS depression, or cardiovascular instability. If no contraindications exist (such as in glucose-6-phosphate dehydrogenase deficiency), methylene blue therapy is otherwise generally recommended for methemoglobin levels in excess of 30% or when comorbid conditions limit a patient's tolerance for decreases in oxygen delivery. Methylene blue is administered for 5 minutes at a dose of 1 to 2 mg/kg (0.1-0.2 mL/kg) of a 1% solution. Persistent or recurrent methemoglobinemia might require additional doses, but caution is recommended when the total approaches 4 to 7 mg/kg because methylene blue itself might become a source of oxidant stress. The kidneys comprise the primary route of elimination for methylene blue, and the urine will develop a blue-green discoloration after therapy.^{106,107}

Neuroleptics and Antipsychotics

Clinical Features

Depending on chemical class, neuroleptics cause varying degrees of CNS depression, anticholinergic symptoms, cardiac toxicity, and movement abnormalities. Movement disturbances, known as extrapyramidal symptoms, include acute dystonic reactions, dyskinesias, akathisia, and tardive dyskinesia. Cardiac conduction disturbances, most notably a prolonged QT interval, are significant complications associated with piperidine phenothiazines, such as thioridazine, and butyrophenones, such as haloperidol. Neuroleptic malignant syndrome (NMS) is a life-threatening condition associated with long-term medication therapy and immediate drug overdose characterized by hyperthermia, skeletal muscle rigidity, and altered mental status.¹⁰⁸ Newer "atypical neuroleptics" offer therapeutic advantages of lowered incidences of extrapyramidal symptoms and NMS.

Toxic effects from these agents can include blood dyscrasias (clozapine), CNS and respiratory depression (clozapine and olanzapine), and hypotension and reflex tachycardia (quetiapine and ziprasidone).^{109,110} Atypical antipsychotics are described in [Table 18-15](#).¹¹¹⁻¹¹⁴

Differential Diagnosis

Like the TCAs, poisoning from neuroleptics can result in altered mental status, coma, orthostatic hypotension, and cardiac dysrhythmias. Other differential diagnoses include atypical antipsychotic agents, lithium, SSRIs, and opioid toxicity.

Diagnostic Studies

Although serum phenothiazine levels can be obtained to confirm ingestion, levels correlate poorly with clinical effects, making their utility negligible. Baseline laboratory tests include CBC count, measurement of electrolytes, renal function tests, and glucose measurement. Urine should be collected for myoglobin testing, particularly if the patient is hyperthermic.¹¹⁰ Because of potential neuroleptic-induced cardiotoxicity, an ECG is indicated.¹¹⁵

Management

If a child exhibits signs of acute muscular dystonia, IV diphenhydramine (2 mg/kg up to 50 mg for several minutes) is rapidly administered. Alternatively, the patient can be given benztropine intramuscularly in a dose of 0.05 to 0.1 mg/kg (up to 2 mg). Improvement usually occurs within 15 minutes.¹¹⁰ Doses exceeding 8 mg during a 24-hour period can result in severe anticholinergic symptoms.¹¹⁰

After an immediate overdose of neuroleptics, mild CNS depression is common, usually occurring within 1 to 2 hours of the ingestion. Children are more susceptible to these sedative effects than adults. In cases of overdose, respiratory depression can occur but rarely requires aggressive airway management. Phenothiazines tend to lower a patient's seizure threshold, although the actual incidence of seizures in immediate overdose patients is low.

Initial management of an immediate neuroleptic overdose includes stabilizing the airway and circulation. If the patient remains hypotensive despite adequate amounts of IV fluid, a vasopressor with α -agonist activity, such as norepinephrine (noradrenaline), can be consid-

TABLE 18-15 Atypical Antipsychotics^{111,112}

Clozapine (Clozaril)

Clozapine can cause salivation, CNS depression, agitation, seizures, and rarely cardiac disturbances. It is known for its potential to precipitate clinically significant agranulocytosis during long-term therapy and after immediate overdose.¹¹³

Olanzapine (Zyprexa)

In overdose patients, olanzapine can cause CNS depression, which can be prolonged and require airway protection, miosis, QT interval prolongation, and ketosis.

Quetiapine (Seroquel)

Quetiapine toxicity results in agitation, combativeness, depressed sensorium, hypotension, tachycardia, and QT interval prolongation as has been reported in large overdoses.¹¹⁴

Risperidone (Risperdal)

Central nervous system depression, described as transient lethargy, hypotension, and tachycardia, has been reported in adolescent overdose patients.

Ziprasidone (Geodon)

Overdose of ziprasidone can cause sedation and QT interval prolongation. Serious neurologic or cardiovascular complications are uncommon, but morbidity and mortality have been reported with mixed ingestions.

Aripiprazole (Abilify)

Overdose can cause sedation in children for several hours, drooling, flaccid facial muscles, mild hypotension, ataxia, tremor, and vomiting. Toxicity is generally not associated with QT interval prolongation, dysrhythmias, or seizures.

ered. Because of the potential cardiotoxicity of phenothiazines, patients require close cardiac monitoring.^{110,115} Activated charcoal can be administered after a recent ingestion. No specific antidote exists for immediate neuroleptic poisoning and hemodialysis is not efficacious. Most children presenting after acute neuroleptic toxicity do well with supportive care alone.

The NMS results in a high mortality rate and is treated aggressively with rapid cooling and administration of IV dantrolene at 0.8 to 3.0 mg/kg every 6 hours, up to 10 mg/kg per day. Dantrolene acts peripherally by treating skeletal muscle rigidity. Oral bromocriptine

(a direct dopamine agonist) has been successfully used alone and in conjunction with dantrolene to successfully treat adult patients with NMS.¹¹⁰

Nonsteroidal Anti-inflammatory Drugs

Clinical Features

Generally, NSAIDs do not cause serious toxic effects. Patients who overdose on NSAIDs commonly exhibit gastrointestinal symptoms. Central nervous system toxic effects, including sedation, coma, and metabolic acidosis, can occur with large or massive ingestions.¹¹⁶⁻¹¹⁸ Prolonged NSAID use is associated with renal toxic effects. In severe overdose patients, NSAID toxicity has infrequently been associated with anion gap metabolic acidosis.

Differential Diagnosis

The differential diagnosis includes other over-the-counter pain relievers, such as aspirin and acetaminophen (paracetamol).

Diagnostic Studies

Laboratory data include a CBC count, measurement of electrolytes, assessment of renal function, and salicylate and acetaminophen (paracetamol) measurement. An arterial blood gas analysis for acid-base assessment in large immediate overdose patients might be indicated. Measurement of serum levels for NSAIDs is possible but is time-consuming and has little clinical efficacy.¹¹⁹

Management

Treatment consists of supportive care, hydration, IV hydration, assessment for gastrointestinal bleeding, and gastric decontamination with activated charcoal for larger immediate overdose patients.

Opioids

Clinical Features

Opioid agents include heroin, codeine, morphine, meperidine, propoxyphene, methadone, and diphenoxylate-atropine (Lomotil). The classic triad of opioid overdose is decreased level of consciousness, depressed respirations, and pinpoint pupils (**Figure 18.11**). In massive overdoses, noncardiogenic pulmonary edema can occur. Overdoses with meperidine can cause seizures, whereas overdoses with propoxyphene

and methadone can cause respiratory depression and cardiotoxicity.^{120,121} Unintentional overdoses with methadone in younger children (particularly toddlers) have been increasing, resulting in increased fatalities.¹²²⁻¹²⁵



Figure 18.11 Pinpoint pupils are part of the classic triad of opioid overdose.

National Institute on Chemical Dependency (<http://www.nicd.us/signsandsymptomsofuse.html>).

Diagnostic Studies

In a pediatric patient presenting with a suspected opioid overdose, a CBC count, serum electrolytes level, and glucose level should be measured. The patient should receive continuous cardiac monitoring with pulse oximetry measured. If the patient is in respiratory distress, chest radiography should be performed to rule out aspiration pneumonitis, noncardiogenic pulmonary edema, or acute lung injury.

YOUR FIRST CLUE

Signs of Opioid Ingestion

- Decreased level of consciousness
- Decreased respirations
- Pinpoint pupils

WHAT ELSE?

Differential Diagnosis for Opioids

- Sedative-hypnotics, phenothiazines
- Ethanol or toxic alcohols, clonidine

A standard urine toxicology screen will qualitatively detect most opioids such as heroin but do not routinely screen for methadone or fentanyl. Ingestions of propoxyphene and methadone can result in cardiotoxicity due to prolongation of the QRS complex and QT interval, respectively. As a result, a screening ECG is indicated in overdoses or exposure to these opioids.¹²⁶

Differential Diagnosis

The differential diagnosis of a child presenting with respiratory and CNS depression should include sedative-hypnotic agents (benzodiazepines and barbiturates), ethanol, and any of the other toxic alcohols. A patient with pinpoint pupils might have also been exposed to clonidine, phenothiazines, or organophosphate insecticides or could be experiencing a pontine hemorrhage. If an adolescent patient is under the influence of heroin, other illicit drugs should be considered.

Management

The primary treatment of opioid ingestion includes airway stabilization and the administration of the pure opioid antagonist naloxone.¹²⁶ If given rapidly, intubation can generally be avoided. Any patient with suspected opioid toxicity or any patient with altered mental status of unknown cause should receive a trial of an IV bolus of naloxone (0.1 mg/kg or 2 mg for children >5 years of age).¹²⁶ If needed, IV naloxone can be continued via continuous infusion. In addition, the antidote can be administered via the tracheal tube, subcutaneously, or intralingually with a comparable onset of action.¹²⁷ Lomotil, propoxyphene, methadone, and fentanyl overdoses might require larger doses of naloxone and prolonged therapy due to their long duration of action and high potency.¹²⁶ Some sources recommend the IV administration of a longer-acting opioid antagonist, such

as nalmefene, for those narcotic agents with a longer pharmacologic half-life in nonhabituated pediatric patients.¹²⁶

Organophosphates

Clinical Features

Organophosphates permanently inactivate acetylcholinesterase, leading to an accumulation of acetylcholine at the neuromuscular junction.

Vomiting usually is the initial symptom. Other associated symptoms, such as pinpoint pupils, muscle fasciculation, and wheezing, also can be present.¹²⁸ Toxicity can mimic gastroenteritis, asthma, seizures, or heat exhaustion. These symptoms usually are seen clinically as a result of toxic exposures to organophosphate and carbamate insecticides.^{129,130} The most serious symptoms for these patients are overwhelming bronchorrhea and respiratory failure.¹³¹

Diagnostic Studies

Laboratory studies in symptomatic patients include electrolytes for patients with vomiting and diarrhea, along with a chest radiograph and arterial blood gas analysis for any child with severe respiratory distress. Organophosphates will cause depression of the red blood cell (true) cholinesterase and plasma (pseudo) cholinesterase activity. Levels can be obtained, but the long turnaround time (particularly for the true cholinesterase level) usually makes this test obsolete in the emergent care of the critically ill child.¹²⁸

Differential Diagnosis

The differential diagnosis for a child with suspected organophosphate poisoning includes carbamate insecticide toxicity, herbicide poisoning (paraquat), hydrocarbon ingestion, and aspiration, as well as nerve or chemical warfare agent poisoning. Nontoxic causes of respiratory distress, such as pneumonia, reactive airway disease, and foreign-body aspiration, should be ruled out.

Management

In moderate to severe poisoning, the treatment priority is maintenance of the airway, accomplished through intubation. Atropine can be injected at 0.5- to 1-mg IV doses or more until the airway has become sufficiently dry with resolution of bronchosecretions that ventilation

YOUR FIRST CLUE

Signs of Organophosphate Ingestion (massive cholinergic overdrive)

DUMBELLS:

D-Diarrhea

U-Urination

M-Miosis

B-Bradycardia, bronchosecretions

E-Emesis

L-Lacrimation

L-Lethargic

S-Salivation

is no longer impaired. Large doses (≥ 10 mg) of atropine might be required for satisfactory clinical response.¹²⁸ With a significant organophosphate insecticide poisoning, a cholinesterase regenerator such as pralidoxime chloride (2-pralidoxime [Protopam]) will be required. The dosing includes a 25 mg/kg IV loading dose for 5 to 30 minutes, then 10 mg/kg per hour or repeat loading every 1 to 2 hours per dose for 1 to 2 doses until muscle weakness is relieved, then at 10- to 12-hour intervals if cholinergic signs recur.¹²⁸ This drug is not indicated in carbamate insecticide poisoning. When treating these patients, skin decontamination is essential, as is protection of the staff from dermal absorption (ie, gloves and protective clothing must be worn).

KEY POINTS

Management of Organophosphate Poisoning

- Staff protection
- Airway maintenance
- Atropine
- 2-Pralidoxime

Rodenticides

Clinical Features

Most commercially available rodenticides contain warfarin. Bleeding issues after unintentional ingestion of anticoagulant warfarin-containing rodenticides by pediatric patients is unlikely, although mild PT prolongation has been noted. Clinical evidence of bleeding can occur, however, after immediate intentional ingestions of large amounts or repeated ingestions as in the case of pica, child abuse, or Münchausen syndrome by proxy.¹³²

Signs and symptoms in patients experiencing toxic effects range from minor to life-threatening bleeding. These symptoms include epistaxis, easy bruising, gingival bleeding, petechiae, hematuria, hematemesis, melena, hemoptysis, extremity pain associated with compartment syndrome, vaginal bleeding, and intracerebral hemorrhage.¹³²

Clinical recovery after immediate warfarin ingestion occurs in less than 1 week. Because of longer duration of action, second-generation “super warfarins” pose a more significant risk of coagulopathy, which can persist for weeks to months.

Diagnostic Studies

Coagulation studies or other laboratory testing is not indicated in the asymptomatic pediatric patient after a single unintentional ingestion of a small amount of an anticoagulant rodenticide.¹³² In the asymptomatic patient presenting soon after a single large intentional ingestion of an anticoagulant product, the PT, partial thromboplastin time (PTT), and international normalized ratio (INR) should be immediately measured; the patient should be reevaluated at 24 and 48 hours. If an abnormal PT/PTT or INR is found in a clinically asymptomatic child, the physician should consider repeating the test to rule out a falsely elevated value from incomplete filling of the citrated blue-top tube.¹³²

In symptomatic patients or those demonstrating abnormal coagulation profiles, the physician should consider obtaining a PT/PTT or INR every 6 to 12 hours until the patient is stabilized and a CBC count to follow hemoglobin levels, hematocrit, and platelet counts. Also, a urinalysis should be performed to assess for

hematuria and a stool hemocult test to assess for the presence of blood. A type and screen or a type and cross-match should be performed if significant bleeding is present. Physicians should consider performing liver function tests to rule out hepatotoxicity as a cause of coagulopathy. Finally, if mental status changes are present, an immediate computed tomographic scan of the brain is necessary to rule out intracranial hemorrhage.¹³²

Differential Diagnosis

It is important that efforts be made to identify the product involved in a rodenticide poisoning. The brand name, active ingredients, and concentration should be documented.

Formulations of proprietary products periodically change. A child presenting soon after a rodenticide exposure with rapid onset of gastrointestinal, neurologic, or cardiovascular symptoms should raise the suspicion of an old, illicitly sold, or highly toxic pesticide, such as sodium monofluoroacetate, thallium, strychnine, arsenic, cyanide, or phosphorous-containing rodenticides.

Management

In general, no gastrointestinal decontamination procedures are necessary after unintentional trivial ingestions of these products.¹³³ For patients presenting soon after intentional ingestions of large amounts, one dose of activated charcoal without a cathartic should be administered. Gastric lavage should not be performed or vomiting induced in any patient actively bleeding or demonstrating an elevated PT or INR.¹³²

For clinically significant active bleeding, fresh frozen plasma is essential to replenish all clotting factors (except platelets). The pediatric fresh frozen plasma dose is 10 to 25 mL/kg. The adolescent dose is 2 to 4 U. This dose can be repeated as needed. Packed red cells, which do not supply clotting factors, can be given to correct severe anemia secondary to hemorrhage.¹³²

Vitamin K₁ is a specific antidote because it is a necessary cofactor that competes with warfarin and the long-acting anticoagulants to initiate formation of depleted clotting factors II, VII, IX, and X. Vitamin K₁ therapy is indicated for any patient experiencing active bleeding or demonstrating elevated PT or INR.^{132,134} Prophylactic therapy

is not indicated in asymptomatic patients with normal coagulation studies.¹³⁵ Vitamin K₁ administration would merely provide a false sense of security for the prescribing physician and only serve to delay the onset of anticoagulant effects of the rodenticide due to its much longer duration of action. It is crucial to note that the only effective form of vitamin K is K₁ phytonadione (Mephyton), which is the active form of the vitamin. Other forms of vitamin K (eg, vitamin K₃ and menadione [Synkayvite]) are ineffective and should not be used.¹³²

Oral vitamin K₁ is the safest method of administration. It can be given with or without food. It has an onset of effect ranging from 6 to 12 hours. Vitamin K₁ is usually administered three to four times daily because it has a short therapeutic half-life.¹³⁴ Vitamin K₁ (phytonadione) can also be given parenterally via the intramuscular, subcutaneous, or IV routes. Intramuscular administration poses the risk of hematoma; therefore, the subcutaneous route might be a safer alternative. Intravenous phytonadione offers the fastest onset of action (as little as 1-2 hours).¹³² Because of the potential for significant adverse effects, such as anaphylactoid reactions, IV administration is reserved

for bleeding in which rapid correction of clotting is mandatory. Untoward reactions, which can occur even at correct dosages and rates, include flushing, hypotension, cyanosis, dizziness, diaphoresis, dyspnea, cardiac, and/or respiratory arrest. Physicians should be prepared to resuscitate with epinephrine (adrenaline), antihistamines, and corticosteroids.¹³²

Salicylates

Clinical Features

The usual signs and symptoms of immediate salicylate ingestion are nausea, vomiting, hyperventilation, hyperpyrexia, tinnitus, oliguria, disorientation, coma, convulsions, and hyperglycemia (hypoglycemia in the young child). Less common manifestations include respiratory depression, pulmonary edema, acute tubular necrosis, hepatotoxicity, and syndrome of inappropriate secretion of antidiuretic hormone.

Diagnostic Studies

In any child with a suspected aspirin overdose, arterial blood gases should be measured. Although the classic interpretation of blood gas tests in acute salicylism is a mixed respiratory alkalosis and metabolic acidosis, children with salicylate poisoning can rapidly develop metabolic acidosis not preceded by respiratory alkalosis. Serum electrolytes, BUN, creatinine, serum glucose, serum ketones, and acetaminophen (paracetamol) levels should also be determined.

In immediate ingestions, serum salicylate levels are prognostic and are usually measured approximately 6 hours after ingestion. They have less use in chronic salicylism. The Done nomogram (**Figure 18.12**), although historically known to determine the severity of a salicylate overdose, has limited use clinically. This nomogram is only used in patients with a single immediate overdose. It was originally designed as a prognostic tool not as a guide for therapy (as with the acetaminophen [paracetamol] nomogram). Serum levels in patients with chronic toxic effects or ingestions of enteric-coated preparations should not be plotted. The ultimate decision to treat should be predicated on serial serum levels, symptoms, and acid-base status rather than the Done nomogram result.

YOUR FIRST CLUE

Signs and Symptoms of Salicylate Poisoning

- Nausea and vomiting
- Hyperventilation
- Hyperpyrexia
- Tinnitus
- Oliguria
- Disorientation or coma
- Seizures
- Hyperglycemia
- Pulmonary edema
- Acute tubular necrosis
- Syndrome of inappropriate secretion of antidiuretic hormone
- Liver failure

Because of the potential for delayed salicylate toxicity and formation of gastric concretions, more than one salicylate level is recommended to ensure a declining trend.^{136,137} Generally, ingestions of less than 150 mg/kg are mild, 150 to 300 mg/kg are moderate, 300 to 500 mg/kg are serious, and more than 500 mg/kg are severe.

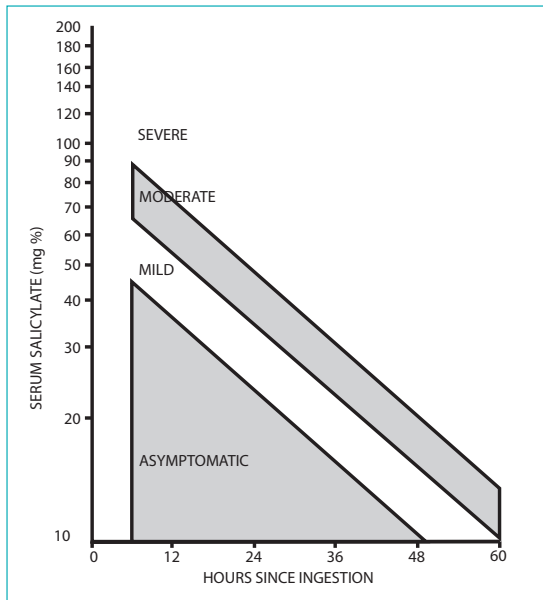


Figure 18.12 Done nomogram for salicylate poisoning. The Done nomogram has limited clinical application and should be used with the following cautions: the patient has immediately ingested salicylate and is not experiencing chronic toxicity and has not ingested a delayed-release aspirin preparation; the blood level to be plotted on the nomogram was from a sample drawn more than 6 hours after ingestion.

Done AK. Salicylate intoxication: significance of measurements of salicylate in blood in cases of acute ingestion. *Pediatrics*. 1960;26:800. Adapted with permission.

Differential Diagnosis

In any pediatric patient with suspected aspirin toxicity, poisoning with other pain relievers, such as acetaminophen (paracetamol) and NSAIDs, should be considered.

In addition, because salicylate poisoning impairs glucose metabolism and results in ketosis, diabetic ketoacidosis should be ruled out. Other pharmaceutical agents that cause elevated anion gap metabolic acidosis (iron and isoniazid) should also be considered.

Management

Management includes the general principles for all ingestions. Potassium levels should be

monitored carefully because they are typically diminished. For moderate and severe ingestions, an IV catheter should be inserted, and 5% dextrose in water with 50 mEq/L of sodium bicarbonate given at a rate of 10 to 15 mEq/kg for 1 to 2 hours. The goal of alkalinization is to maintain urine pH at greater than 7.0; however, this will not be accomplished without adequate potassium supplementation.¹³⁸ Arterial blood gas analysis helps determine the degree of acidosis. If the pH is less than 7.15, an additional 1 to 2 mEq/kg of bicarbonate can be given for 1 to 2 hours.¹³⁸ Rapid bicarbonate administration should be avoided because it can lead to relative CNS acidosis and seizures. Severe, persistent acidosis might require 1 to 2 mEq/kg of bicarbonate every 2 hours. Hemodialysis or hemoperfusion might be necessary in unresponsive acidosis (pH <7.1), renal failure, noncardiogenic pulmonary edema, seizures, or progressive deterioration despite standard therapy measures. The salicylate level is not useful as the only criterion for dialysis unless it is higher than 80 mg/dL in an immediate ingestion. The threshold for dialysis is lower for gradually poisoned patients (50–60 mg/dL) because the toxic effects are more severe and, generally, serum levels are less impressive than in the immediate overdose patient.¹³⁸

KEY POINTS

Management of Salicylate Ingestions

- IV fluid resuscitation and sodium bicarbonate administration
- Monitoring and replacement of potassium as needed
- Hemodialysis or hemoperfusion for salicylate level >80 mg/dL, renal failure, severe metabolic acidosis, pulmonary edema, or seizures

Sedative Hypnotics

Clinical Features

Classic sedative hypnotic agents include benzodiazepines, barbiturate, and chloral hydrate.

In an overdose setting, sedative hypnotics typically produce CNS and respiratory depression. Benzodiazepines are among the most commonly prescribed drugs in the world, and they constitute most sedative hypnotic overdoses.¹³⁹ They are used for their anxiolytic, muscle relaxant, and anticonvulsant properties. In the setting of benzodiazepine overdose, the most important therapeutic intervention is airway management. Flunitrazepam (Rohypnol) is a potent benzodiazepine that has been popularized as a street drug of abuse.¹⁴⁰ Benzodiazepines tend to produce less CNS and respiratory depression than barbiturates. The barbiturates are classified as either ultrashort acting (thiopental), short acting (pentobarbital), or long acting (phenobarbital). In the overdose setting, the pediatric patient will present with CNS depression, often accompanied by respiratory depression. Vital signs can reveal hypotension, bradycardia, and hypothermia. Chloral hydrate overdose is unique in that it can result in CNS depression and cardiotoxicity.¹⁴¹

Diagnostic Studies

Quantitative benzodiazepine concentrations correlate poorly with pharmacologic or toxicologic effects and are poor predictors of clinical outcome. However, qualitative screening for benzodiazepines in the serum or urine can be useful in diagnosing patients as having coma of unknown origin. Many standard urine toxicology screens are insufficiently sensitive to detect low levels of flunitrazepam.

In addition to baseline laboratory studies, a quantitative serum phenobarbital level is obtained to document the toxicity but is not mandatory for definitive management. Therapeutic concentrations of phenobarbital range from 15 to 40 mg/L. Patients with levels greater than 50 mg/L will exhibit mild toxic effects, whereas those with levels greater than 100 mg/L are typically unresponsive to pain and experience respiratory and cardiac depression. An ECG should be obtained in patients presenting with symptomatic chloral hydrate toxicity. In large overdoses, chloral hydrate can depress myocardial contractility and will sensitize the myocardium to catecholamines, resulting in dysrhythmias.

Management

The most critical management intervention is stabilization of the patient's airway and respiratory status. Activated charcoal is recommended in significant overdoses.

Flumazenil can reverse the somnolence caused by benzodiazepine toxicity in healthy children with isolated benzodiazepine overdose. Flumazenil is an antidotal agent that reduces or terminates benzodiazepine effects by competitive inhibition at the CNS γ -aminobutyric acid sites. In comatose children, initial IV doses of 0.01 mg/kg have been recommended. If no response is elicited, this dose can be repeated.^{142,143} The duration of flumazenil is less than 1 hour; thus, repeat doses or continuous infusions might be necessary. Contraindications to flumazenil administration include seizure disorders, long-term benzodiazepine use, and coingestion of proconvulsant agents, such as TCAs, cocaine, or isoniazid. Therefore, flumazenil should not be administered to children with coma of unknown cause. Administration of flumazenil is safe in healthy children with altered mental status caused by immediate benzodiazepine overdose. If a coingestion is suspected, a urine drug screen and ECG should be performed to rule out concomitant cyclic antidepressant toxicity before flumazenil is administered.^{142,143}

Multiple dosing of activated charcoal will significantly reduce the serum half-life of certain barbiturates, such as phenobarbital, which undergoes enterohepatic circulation.^{144,145} Urinary alkalization with sodium bicarbonate to a pH of 7.5 to 8.0 can hasten the renal excretion of phenobarbital, which is a weak acid and primarily renally excreted. Alkalinization can be accomplished with an initial sodium bicarbonate bolus of 1 mEq/kg, followed by a continuous infusion. This infusion is made by adding 100 to 150 mEq of sodium bicarbonate to 850 mL of 5% dextrose in water and titrating it to maintain a urine pH greater than 7.5 with an arterial pH less than 7.5. The rate must be assessed hourly to avoid excessive administration of fluid or bicarbonate amounts, which can cause pulmonary or cerebral edema or electrolyte imbalance.¹⁴⁴

In unstable patients not responsive to standard therapeutic measures or in those with renal

failure, hemodialysis is indicated for long-acting barbiturates. Fortunately, extracorporeal elimination is rarely indicated because most barbiturate overdose patients do well with supportive care alone. Charcoal hemoperfusion seems more efficacious for shorter-acting agents, which possess greater fat and protein binding.

Selective Serotonin Reuptake Inhibitors

Clinical Features

Selective serotonin reuptake inhibitors, such as fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), and herbal St. John's wort, are popular antidepressants currently available and widely prescribed. In therapeutic doses, SSRIs are relatively safe and were originally designed in response to the high incidence of adverse effects and deaths attributed to cyclic antidepressants. However, in large overdoses or in combination with other medications, SSRIs can cause significant morbidity and mortality in pediatric patients.¹⁴⁶⁻¹⁴⁸

Immediate oral overdose can be associated with nausea and vomiting, dizziness, tremors, lethargy, and CNS depression.⁷² Seizure activity and death have been reported with doses more than 100 times the recommended therapeutic dose. Most side effects are associated with co-ingestions or secondary to hyperthermia by a drug-drug interaction known as the serotonin syndrome. This syndrome is similar in presentation to the NMS but milder in presentation with less associated mortality. Pharmacologically, it results from serotonin excess as opposed to dopamine depletion, as is the case with NMS.

Differential Diagnosis

The differential diagnosis of SSRI ingestion should be cyclic antidepressants, phenothiazines, and newer atypical antipsychotic agents. If hyperthermia develops, anticholinergics and antihistamines should be added to the list of possibilities.

Management

Most unintentional pediatric SSRI overdoses result in only mild toxic effects. Treatment of SSRI toxicity includes supportive care, airway management, and gastric decontamination with activated charcoal. If the serotonin syndrome is diagnosed or suspected, cooling measures and

benzodiazepines usually suffice. In moderately symptomatic patients, the antihistamine cycloheptidine has been recently recommended as adjunctive therapy.⁷²

Theophylline

Clinical Features

The primary clinical manifestations of acute aminophylline or theophylline toxicity are in the gastrointestinal, cardiovascular, and neurologic systems.¹⁴⁹ Disturbances in serum electrolytes (potassium, bicarbonate, and glucose) have been observed as well.¹⁵⁰

Gastrointestinal findings include nausea, severe and refractory vomiting, and gastrointestinal bleeding. Nausea and vomiting are nonspecific and can occur with therapeutic use. Cardiovascular findings include tachyarrhythmias, hypotension, and cardiac arrest. Sinus and supraventricular tachycardias are the most common presentations of theophylline toxicity, regardless of cause. Peripheral β_2 -receptor-stimulated vasodilation is responsible for the hypotension that is unique to acute theophylline overdoses.¹⁴⁹ Neurologic manifestations include mental status changes, tremor, seizures, and coma. Seizures, typically generalized tonic-clonic, are a grave sign. Status epilepticus can occur and is associated with greater morbidity and mortality than other causes of status epilepticus in children.¹⁵⁰

Differential Diagnosis

Sympathomimetic agents, such as cocaine, amphetamines, and PCP, should also be considered. Other methylxanthines, such as caffeine, have similar properties to theophylline when taken in overdose. Other agents that can induce hypotension, such as CCBs, β -blockers, and digitalis, should be included in the differential diagnosis.

Diagnostic Studies

The most important laboratory evaluation for suspected theophylline toxicity is a serum theophylline concentration. The adult reference range is 10 to 20 mg/L, and the toxic range is greater than 20 mg/L. Significant toxic effects are likely with concentrations higher than 100

mg/L for immediate overdoses. Increased mortality is associated with an age younger than 2 years or a serum theophylline concentration higher than 100 mg/L in immediate pediatric overdoses. It is critical, especially in known sustained-release overdoses, that serial concentrations be measured every 1 to 2 hours, until two consecutive theophylline concentrations establish a decreasing trend.^{149,151} Serum concentration monitoring should continue until theophylline is undetectable. Additional initial laboratory testing includes bedside glucose measurement, serum electrolytes measurement, arterial blood gas analysis, and 12-lead ECG. Electrolyte disturbances, fairly typical in the immediately intoxicated patient, include hypokalemia, hypophosphatemia, and hypercalcemia. These concentration-dependent changes reflect transient cellular shifts associated with β_2 -adrenergic stimulation and are not associated with any significant if theophylline alone is the cause.

Management

Patients presenting with acute theophylline toxicity are treated with conventional supportive care and individualized treatment of specific complications. There is no specific antidote for theophylline toxicity. Activated charcoal is the gastric decontamination treatment of choice. The ideal decontamination dose should be calculated to deliver 10 g of charcoal for every gram of ingested theophylline. With unknown amounts, the initial dose of activated charcoal should be 50 to 100 g of charcoal in adolescents and 15 to 25 g in children. Multiple dosing of activated charcoal results in elimination enhancement (gastrointestinal dialysis) in theophylline toxicity.¹⁵²

For any significant ingestion, 12.5 to 25 g of oral activated charcoal every 1 to 2 hours should be initiated and continued until concentrations are less than 20 mg.

Hemodialysis and charcoal hemoperfusion are indicated prophylactically in patients with theophylline concentrations greater than 100 mg/L or when charcoal therapy is contraindicated or poorly tolerated. Withholding these modalities until toxic effects occur is undesirable because severe toxic effects can cause hypotension, seizures, and tachyarrhythmias, which can preclude initiation of these procedures. Hemoperfusion was once preferred to

hemodialysis because it achieves higher clearances rates; newer hemodialysis machines achieve clearances comparable to those of hemoperfusion.¹⁴⁹

The treatment of choice for seizures is benzodiazepine administration. Barbiturates should be second-line therapy. Phenytoin is contraindicated in the absence of any known prior indications: in vitro studies show that it lowers seizure threshold in theophylline intoxication and is not clinically effective. Arrhythmias are treated with β -receptor or calcium channel blockade. Short-acting β -receptor antagonists, such as esmolol, are preferred; verapamil should be avoided because it can inhibit theophylline metabolism. Ventricular arrhythmias and cardiac arrests should be managed conventionally. Hypotension that is refractory to conventional support can be β_2 -receptor mediated and therefore might respond to β -receptor blockade. Electrolyte disturbances that are the result of immediate theophylline overdose do not require immediate correction and often resolve spontaneously. The cellular shifts of electrolytes are transient, resolving within 2 to 3 hours, and are generally nonpathologic.¹⁴⁹

Overall Management Issues

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Consultation with a local or regional poison center can often provide helpful input in making the decision regarding disposition. After being observed for 4 to 6 hours, some patients who have ingested potentially toxic substances and are asymptomatic or minimally affected can be discharged with appropriate instructions for return if necessary. In this setting, a stable social environment and adequate caretaker supervision should be ensured. Because repeat ingestions occur in up to 50% of children, all discharged patients and their families should be given instructions about poison prevention techniques.

Toxins Lethal in Small Doses

Children with significant toxic ingestions or potential intoxication with substances that have delayed effects (sustained-release products) require admission to the hospital.¹⁵³ The specific ingestion and degree of physiologic alteration

determine whether treatment in a pediatric intensive care unit is warranted. A conservative approach is also recommended for toxins that can cause potential mortality in small doses (eg, camphor, benzocaine, diphenoxylate and atropine, chloroquine, methyl salicylates, imidazole decongestants and eye drops, lindane, and hydrofluoric acid).¹⁵³⁻¹⁵⁸ Patients with intentional overdoses should undergo psychiatric assessment for possible admission and extended observation.

Additional Routes of Exposure

Hazardous chemical exposure includes direct contact with the skin or eye or inhalation of nox-

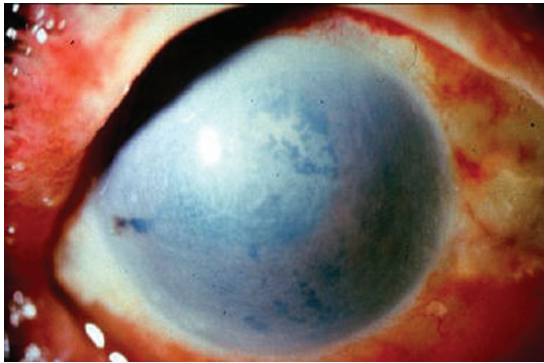


Figure 18.13 Injury caused to the eye by hazardous chemical exposure.

ious gases (**Figure 18.13**). The risk of skin exposure is chiefly from acid or alkali burns due to direct contact. However, systemic toxicity is possible in situations involving lipophilic substances. Eye exposure is a local injury concern not systemic toxic effects. Inhalation exposures are discussed in detail in Online Chapter 21, Preparedness for Acts of Nuclear, Biological, and Chemical Terrorism. Health care workers must be careful to avoid personal exposure to toxic chemicals. Appropriate protective clothing is indicated.

Ophthalmic and Cutaneous Exposure

Assessment consists of direct inspection of the body part for evidence of caustic or corrosive damage. Copious irrigation of exposed areas with water or saline solution should be initiated immediately, preferably at the scene. Chemical burns are managed as thermal burns. Irrigation of caustic eye injuries should be copious and started as early as possible. Adequacy of irrigation can be judged by checking pH of the tears when acidic or basic compounds have resulted in eye injury. Follow-up management of eye exposures is dependent on the results of the fluorescein examination after irrigation. A negative result requires no interventions; ophthalmologic consultation should be considered for any positive finding.¹⁶³

CASE SCENARIO 3

A 5-year-old boy was in an apartment fire but escaped with burns to his feet. In the ED he is frightened but able to speak in full sentences. His respiratory rate is 30/min, heart rate is 120/min, blood pressure is 100/70 mm Hg, and temperature is 37.6°C (99.7°F). Physical examination reveals no carbonaceous sputum and no stridor or wheezing. He has partial-thickness burns to the soles of his feet, with good distal pulses and color.

1. What is the most significant physical examination finding in this child?
2. What is the most important therapy for this patient?

Smoke Inhalation

Background

Smoke inhalation is a leading cause of morbidity and mortality in burn patients. Exposure to noxious substances in the atmosphere can directly injure the respiratory apparatus or can indirectly produce systemic intoxication (Figure 18.14). The nature of the resulting illness depends on the source, intensity, and duration of exposure. Offending agents range from single, well-defined chemicals, such as hydrogen cyanide, which produces severe systemic toxic effects when inhaled, to the airborne products of a residential fire, a complex matrix of organic and inorganic chemicals, heated atmospheric gases, and the gaseous products of incomplete combustion.

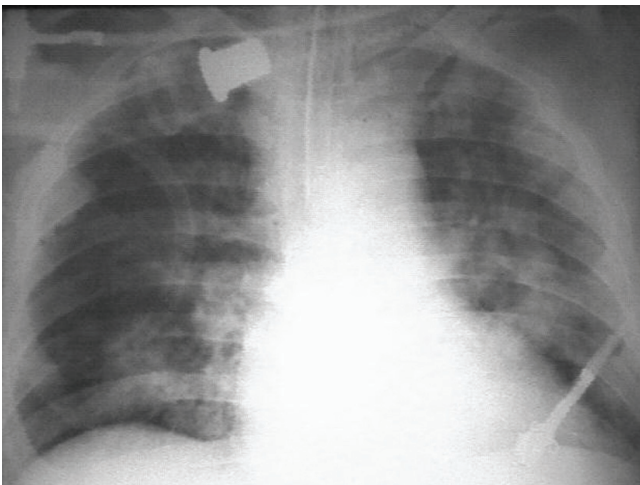


Figure 18.14 Exposure to noxious substances in the atmosphere can directly injure the airway, bronchi, and lungs.

Smoke contains four categories of environmental threat: heat, asphyxiants (chiefly carbon monoxide and hydrogen cyanide), particulate matter, and pulmonary irritants.

Heat

Upper airway burns are often encountered in patients of closed-space fire and can occur whenever the temperature of inhaled gas exceeds 150°C (302°F). However, thermal injury distal to the vocal cords is unusual because the temperature of inhaled smoke decreases rapidly as it passes down the respiratory tree; thus, direct thermal injury to the lung is uncommon. However, significant burns of the supraglottic region or vocal cords frequently produce edema sufficiently severe to result in upper airway obstruction. In contrast, the latent heat of steam is sufficiently high that burns of the distal airway and lung occur with this toxic inhalation.

Asphyxiants

Asphyxiants include carbon monoxide, which is produced by the incomplete combustion of hydrocarbons such as wood and paper, and hydrogen cyanide, a byproduct of combustion of nitrogen-containing polymers such as wool or silk. Hydrogen sulfide is a physical asphyxiant that produces hypoxemia through displacement of oxygen from the atmosphere. The characteristic odor of cyanide is that of burned or bitter almonds, whereas that of sulfides is rotten eggs.

Carbon monoxide is the most frequently encountered asphyxiant.¹⁵⁹ This colorless, odorless compound has an affinity for hemoglobin approximately 240 times greater than that of

oxygen. Binding of carbon monoxide to hemoglobin diminishes the oxygen-carrying capacity of blood by a proportion equal to the percentage of carboxyhemoglobin and shifts the oxyhemoglobin dissociation curve to the left. In addition, there is evidence that carbon monoxide interferes with cellular oxygen metabolism at the mitochondrial level. Dissolved oxygen is not affected by carbon monoxide; therefore, the measured PaO_2 can be normal even when the oxygen saturation (percentage of hemoglobin bound to oxygen) is profoundly depressed.¹⁵⁹

Venous carbon monoxide concentrations up to 5% are found in healthy individuals. Concentrations of 20% often produce significant neurologic symptoms, but a single level might not correlate with clinical manifestations. Concentrations of greater than 60% can be associated with death or neurologic morbidity. In a particular patient, however, specific carboxyhemoglobin levels are less important in management than the history of exposure and condition of the patient.¹⁵⁹

In addition to household fires, children can be exposed to many other sources of carbon monoxide, including poorly repaired motor vehicles and those left running while parked, riding in the back of pickup trucks, swimming around or under houseboats, indoor grilling, and malfunctioning household heaters. In rare instances, children are exposed to other asphyxiants, such as hydrogen cyanide or hydrogen sulfide, after environmental catastrophes or while playing in an industrial area.

Particulate Matter

Particulate matter consists mainly of carbon. Large particles (ie, >5 μm) are deposited in the trachea or bronchi, and those smaller than 1 μm reach the pulmonary alveoli. Although carbon per se is physiologically inert, it can be coated with toxic chemical products of combustion, such as acrolein, hydrochloric acid, or aromatic hydrocarbons. In addition, inhalation of carbon dust has been shown to produce airway hyper-reactivity.

Pulmonary Irritants

Pulmonary irritants are a heterogeneous group of compounds, including ammonia, sulfur oxides, nitrogen oxides, halogen acids (eg, hydro-

chloride), chlorine gas, aldehydes (eg, acrolein), ketones, and phosgene. These chemicals present both as gases or bound to the surface of small particles and can incite delayed pulmonary edema and mucosal injury.

Clinical Features

Inhalation injury should be considered in any child who is exposed to fire or presents with a burn injury (other than scald). History of exposure in an enclosed space or physical features, such as facial burns, singed nasal hairs, carbonaceous deposits in the pharynx, stridor, or hoarseness, suggest the possibility of upper airway injury. Although respirations might be unlabored initially, laryngeal edema is progressive in the smoke inhalation patient and is not at its peak until 2 to 8 hours after injury.

The presentation of pulmonary injury ranges in severity from mild wheezing, rales, and rhonchi to frank respiratory failure with cyanosis. After a patient's exposure to fire, an altered sensorium, particularly with loss of consciousness, should be assumed to indicate carbon monoxide poisoning and CNS hypoxia. Concurrent traumatic closed-head injury should remain in the differential diagnosis until excluded.

Non-fire-related toxic inhalation also chiefly involves carbon monoxide. Carbon monoxide poisoning should be considered in any child with nausea, vomiting, or headache, with or without altered sensorium, when there is no other obvious cause. Typical presentations include a child who is found unconscious in a home in which a charcoal grill is used for heating, a child who begins to vomit and becomes somnolent while riding in the back seat of an automobile in poor repair, or a child living in a kerosene-heated home. Not infrequently, the child with occult carbon monoxide toxicity presents with a nonfebrile flulike illness and improves considerably while under care in the ED. The symptoms subside after removal of the child from exposure to a faulty car exhaust or a toxic home environment. Multiple patients from the same locale suggest carbon monoxide poisoning as well. Even when all individuals are exposed to similar amounts of carbon monoxide, children are often more severely affected.¹⁵⁹

A high index of suspicion for carbon monoxide toxicity must be maintained to prevent recurrent toxicity or even death.

Diagnostic Studies

The diagnostic evaluation of the child after inhalation injury focuses on assessment of airway patency, baseline pulmonary function, and determination of carbon monoxide poisoning. Children who present with a history consistent with exposure to fire or carbon monoxide intoxication require determination of carbon monoxide level (usually expressed as percent carboxyhemoglobin). In most hospitals, this determination is performed with co-oximetry, which also indicates the percentage of methemoglobin. This can be run on a venous or arterial sample. Although pulse oximetry is useful in the evaluation of oxygen saturation, this technique does not detect the presence of carboxyhemoglobin or other abnormal hemoglobin levels and should never be depended on for this purpose. In fact, the oxygen saturation is falsely elevated with carbon monoxide poisoning.¹⁵⁹

In room air, the half-life of carboxyhemoglobin is approximately 4 hours. It decreases to 60 to 90 minutes when the child receives an F_{IO_2} of 1.0 and 15 to 30 minutes under hyperbaric conditions (three atmospheres). Because burn patients are generally treated with oxygen (F_{IO_2} of 1.0) at the scene of the fire and en route to

the hospital, significant toxic effects can occur even when carboxyhemoglobin levels are low at the time of presentation. A normal carboxyhemoglobin level at the time of admission does not exclude carbon monoxide poisoning if the history or physical findings suggest that condition to be present.

The chest radiograph is an essential baseline diagnostic study, particularly when exposure occurs in a fire. It initially can be normal but eventually will reveal bilateral patchy and confluent areas of opacification. Other appropriate laboratory studies include a CBC count; urinalysis; measurement of serum electrolytes, BUN, and creatinine; and liver function tests. An ECG should be performed to establish a baseline and to detect the presence of myocardial ischemia or infarction.

Management

Care of the child with inhalation injury follows the usual ABC emergency sequence. In addition to administration of oxygen (F_{IO_2} of 1.0) and routine measures to assess and secure the airway, after stabilization, children at risk of upper airway thermal injury (facial, oral, or pharyngeal burns, hoarseness, or stridor) require urgent bronchoscopy to evaluate for life-threatening airway obstruction. When airway edema appears to be evolving or signs of obstruction are severe, immediate intubation is required and can prevent catastrophic loss of airway patency.

Aggressive fluid administration, consistent with appropriate burn resuscitation parameters, does not increase the risk of pulmonary edema in the patient with combined burn and inhalation injury. Fluids should not be restricted in an effort to limit the progression of airway and pulmonary compromise.

Diagnostic and management algorithms are presented in **Figures 18.15** and **18.16**. Oxygen is the initial treatment of choice for most other sequelae of toxic inhalation. As noted previously, oxygen reduces the half-life of carboxyhemoglobin, thereby accelerating the rate at which levels decrease. Oxygen (F_{IO_2} of 1.0) is administered until the carboxyhemoglobin concentration is less than 5% and the patient has fully regained normal neurologic function.¹⁵⁹

YOUR FIRST CLUE

Signs and Symptoms of:

Smoke Inhalation

- Facial burns
- Carbonaceous sputum
- Stridor

Carbon Monoxide Poisoning

- Nausea
- Vomiting
- Headache
- Decreased level of consciousness
- Multiple patients with similar symptoms

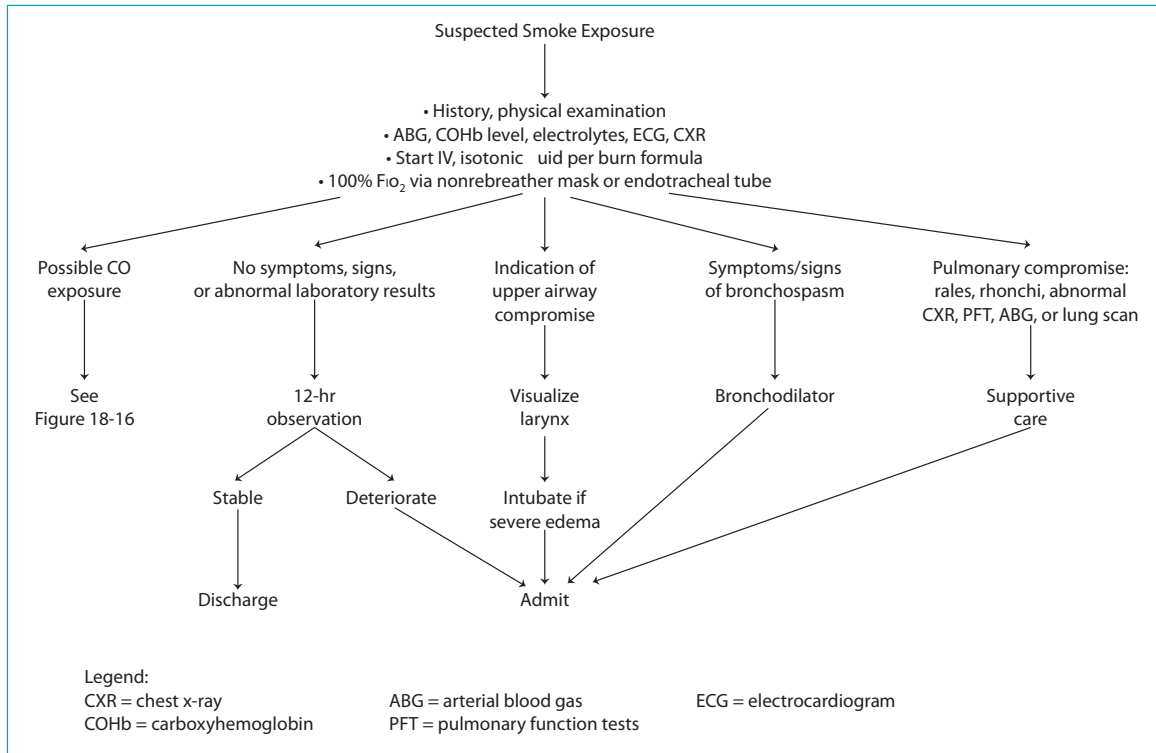


Figure 18.15 General guide for treatment of children exposed to smoke.

Thom SR. Smoke inhalation. *Emerg Med Clin North Am.* 1989;7(2):371-387. Adapted with permission.

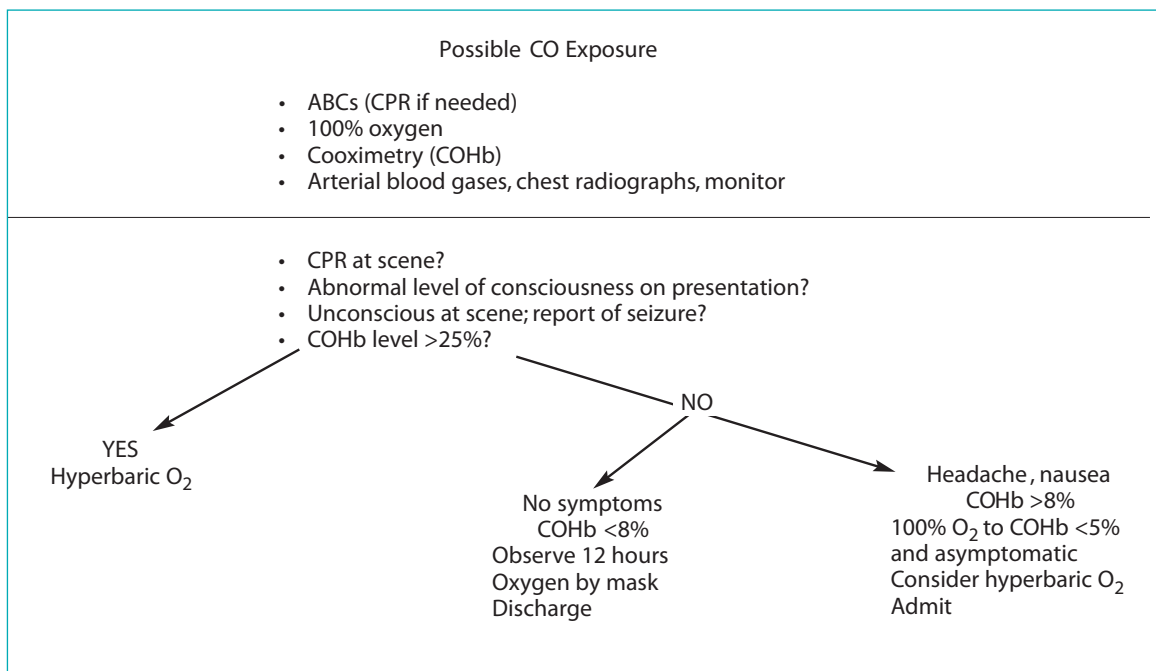


Figure 18.16 Guide for known or suspected carbon monoxide poisoning.

Thom SR. Smoke inhalation. *Emerg Med Clin North Am.* 1989;7(2):371-387. Adapted with permission.

In cases of carbon monoxide poisoning, there is a significant residual tissue burden of carbon monoxide that remains bound to cellular cytochrome systems and myoglobin even when the blood carboxyhemoglobin concentration has returned to normal. Treatment with 100% oxygen under hyperbaric conditions (eg, two to three atmospheres) can accelerate the rate of tissue decontamination.¹⁶⁰ Therefore, when the history suggests exposure to carbon monoxide, children who are found unconscious at the scene of the exposure and those with neurologic dysfunction at the time of presentation should be referred to a hyperbaric facility even if the blood carboxyhemoglobin concentration has returned to normal. When profound neurologic dysfunction exists at the fire scene, there is a strong probability that carbon monoxide intoxication is implicated (perhaps in concert with hypoxemia). In this context, direct referral to a cooperating hyperbaric facility from the fire scene might be appropriate before determination of carboxyhemoglobin concentration. There are studies suggesting that early application of hyperbaric oxygen can be lifesaving or reduce the possibility of severe neurologic injury.^{161,162} Most sources would agree that ex-

posed children, even if neurologically intact, with a measured carboxyhemoglobin level of higher than 25% and all pregnant women with levels higher than 15% should be referred to a hyperbaric facility.

The decision to refer the patient to a hyperbaric facility will depend on locally available facilities and the stability of the patient. In many communities, hyperbaric chambers capable of permitting critical care during hyperbaric conditions are available. After the initial resuscitation and stabilization, assisted ventilation and hemodynamic support need not prevent hyperbaric treatment. Every ED should develop referral agreements and protocols with local and regional hyperbaric centers. Some recent sources question the overall efficacy of hyperbaric oxygen therapy in the setting of carbon monoxide poisoning and argue that 100% normobaric oxygen administration is a more practical and equally efficacious with fewer adverse effects.

Suspected exposure to hydrogen cyanide is treated as described earlier for cyanide. The treatment for hydrogen sulfide toxicity is the same except that thiosulfate is not needed. Management of other sequelae of inhalation injury follows standard principles of care. Respiratory failure is treated with assisted ventilation, including positive end-expiratory pressure, as indicated. A bronchodilator might be of value, but empiric use of antibiotics or a corticosteroid is discouraged.

KEY POINTS

Management of Carbon Monoxide Poisoning

- Assess and treat abnormalities in ABCs.
- Provide 100% oxygen.
- Determine carboxyhemoglobin level.
- Provide hyperbaric oxygen treatment for neurologic symptoms, carboxyhemoglobin level higher than 25%,^a and pregnant women with levels higher than 15%.

^aCarbon monoxide level recommendations can vary in different regions the country and with various hyperbaric center protocols.

THE BOTTOM LINE

- Toxins should be considered as a cause for sudden changes in mental status or other physiologic features.
- Management focuses on the assessment and treatment of abnormalities in ABCs, identification of the toxin, and administration of an antidote.

CHAPTER REVIEW

Check Your Knowledge

- Activated charcoal will adsorb all of the following medications except:
 - ferrous sulfate.
 - phenobarbital.
 - salicylates.
 - theophylline.
 - verapamil.
- A high anion gap metabolic acidosis would be anticipated in each of the following toxic ingestions except:
 - ethylene glycol.
 - iron.
 - isopropanol.
 - methanol.
 - salicylates.
- A comatose adolescent patient with an immediate exposure to an unknown toxin should receive all of the following therapeutic interventions except:
 - dextrose or rapid glucose measurement.
 - flumazenil.
 - intravenous normal saline solution.
 - naloxone.
 - oxygen.
- A mother brings her 2-month-old daughter to be checked for carbon monoxide poisoning because their detector had sounded 1 hour earlier that evening. The infant has stable vital signs and a normal pulse oximetry but is noted to be lethargic. The mother is experiencing a headache. While waiting for the blood gas results, you place both the mother and infant on 100% oxygen. The carbon monoxide levels return for both the mother and child at 20%. Which of the following is an indication for treatment with hyperbaric oxygen therapy?
 - The mother's presenting symptom of headache
 - The child's mental status
 - The carbon monoxide level of 20%
 - The child's age
 - Too much time has elapsed from the exposure to make hyperbaric oxygen therapy advantageous

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CHAPTER REVIEW

CASE SUMMARY 1

A 2-year-old boy presents to the emergency department (ED) with his frantic parents, who had found him unresponsive in the bathroom with pills and empty bottles “scattered all over the floor.” The child is normally healthy but now is lethargic with no response to stimuli and shallow and slow respirations but no cyanosis. Vital signs include a respiratory rate of 8/min, a pulse of 70/min, blood pressure of 80/40 mm Hg, and temperature of 35.6°C (96°F). Focused physical examination reveals pupils that are 4 mm each and reactive to light, a supple neck, clear lungs, nontender abdomen with no masses, normoactive bowel sounds, extremities with good pulses, and no focal neurologic deficits. There is no evidence of trauma.

1. *What are the initial management priorities in this child?*
2. *What antidotes should be administered?*
3. *What further history is important in this case?*

On initial presentation, the greatest concern should be the status of the child’s airway. Bag mask ventilation was begun and vascular access obtained. The rapid glucose assessment demonstrated a reading of 20 mg/dL. The child’s mental status and respiratory drive significantly improved with intravenous dextrose administration, obviating the need for further assisted ventilation and intubation. The child was given activated charcoal by nasogastric tube because the specific toxin ingested was unknown. Baseline laboratory test results were all within normal limits. The results of serum acetaminophen (paracetamol), salicylate, and iron tests were negative. The results of a urine toxicology screen for the standard drugs of abuse were also negative. Further history from the parents revealed the child had no history of diabetes mellitus or glucose disturbances. Among the many toxins available in the bathroom, it was determined that the child had most likely drunk from a previously full bottle of mouthwash, which contained ethanol and mint flavoring. The child’s ethanol level returned with a serum level of 180 mg/dL. After close observation in the pediatric intensive care unit, with fluid and glucose supplementation, the child recovered uneventfully and was discharged home 48 hours after initial presentation.

CASE SUMMARY 2

A 16-year-old girl presents to the ED 3 hours after ingesting two handfuls of extrastrength acetaminophen (paracetamol). She experiences nausea and vomiting. She has no significant medical history. The patient is alert but has a depressed affect and makes poor eye contact. She has no increased work of breathing, and her skin color is normal. Vital signs include a respiratory rate of 20/min, pulse of 110/min, blood pressure of 130/60 mm Hg, and temperature of 37.3°C (99°F). Focused examination reveals that her pupils are 3 mm bilaterally reactive to light; she has a supple neck, no heart murmurs, and clear lungs. Her abdomen is tender to touch in the epigastric region, but there is no guarding and no peritoneal signs. She has good symmetrical pulses and no focal neurologic deficits.

1. What is the primary target organ of acetaminophen (paracetamol) poisoning?
2. What diagnostic laboratory data should be obtained?
3. Does this patient meet the criteria for antidote therapy?

The patient's 4-hour acetaminophen (paracetamol) level was measured at 300 mcg/mL, which is consistent with potential hepatotoxicity on the nomogram. As a result, oral N-acetyl-L-cysteine was administered, which the patient promptly vomited. Antiemetic agents were administered and intravenous N-acetyl-L-cysteine therapy was initiated. Laboratory tests produced normal liver function test and coagulation study results and a positive urine pregnancy test result. The patient admitted she overdosed on acetaminophen (paracetamol) when she learned of her untimely pregnancy. Despite the positive pregnancy test result, the intravenous N-acetyl-L-cysteine therapy was continued for the standard 21-hour regimen because the minimal risk of fetal toxic effects from the antidote is greatly outweighed by the benefits of properly treating the mother's acetaminophen (paracetamol)-induced hepatotoxicity. The patient recovered medically but was transferred to a psychiatric ward, with an obstetric consultation for initiation of prenatal care. Seven months later, the patient delivered a healthy full-term infant.

A 5-year-old boy was in an apartment fire but escaped with burns to his feet. In the ED he is frightened but able to speak in full sentences. His respiratory rate is 30/min, heart rate is 120/min, blood pressure is 100/70 mm Hg, and his temperature is 37.6°C (99.7°F). Physical examination reveals no carbonaceous sputum and no stridor or wheezing. He has partial-thickness burns to the soles of his feet, with good distal pulses and color.

1. What is the most significant physical examination finding in this child?
2. What is the most important therapy for this patient?

Although the child's burns could have caused severe pain, the priority remained his airway. The lack of respiratory distress, stridor, or wheezing was important but did not diminish concerns of delayed pulmonary injury. The child required 100% oxygen by face mask, carboxyhemoglobin measurement, arterial blood gas analysis, and a chest radiograph. Careful monitoring of his respiratory status continued while he received initial burn care.

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