Poisoning can result from exposure to excessive doses of any chemical, with medicines being responsible for most childhood and adult poisonings.

The total number and rate of poisonings have been increasing, but preventive measures, such as child-resistant containers, have reduced mortality in young children.

Immediate first aid may reduce the development of serious poisoning, and consultation with a poison control center may indicate the need for further therapy.

The use of ipecac syrup, gastric lavage, whole bowel irrigation, and cathartics have fallen out of favor as routine therapies, whereas activated charcoal remains useful for gastric decontamination of appropriate patients.

Antidotes can prevent or reduce the toxicity of certain poisons, but symptomatic and supportive care is essential for all patients.

Acute acetaminophen poisoning produces severe liver injury and occasionally kidney failure. A determination of serum acetaminophen concentration may indicate whether there is risk of hepatotoxicity and the need for acetylcysteine therapy.

Anticholinesterase insecticides may produce life-threatening respiratory distress and paralysis by all routes of exposure and can be treated with symptomatic care, atropine, and pralidoxime.

An overdose of calcium channel antagonists will produce severe hypotension and bradycardia and can be treated with supportive care, calcium, insulin with supplemental dextrose, and glucagon.

Poisoning with iron-containing drugs produces vomiting, gross gastrointestinal bleeding, shock, metabolic acidosis, and coma and can be treated with supportive care and deferoxamine.

Acute opioid poisoning and overdose can produce life-threatening respiratory depression that can be treated with assisted ventilation and naloxone.

Overdoses of tricyclic antidepressants can cause arrhythmias, such as prolonged QRS intervals and ventricular dysrhythmias, coma, respiratory depression, and seizures, and are treated with symptomatic care and IV sodium bicarbonate.

Poisoning is an adverse effect from a chemical that has been taken in excessive amounts. The body is able to tolerate and, in some cases, detoxify a certain dose of a chemical; however, once a critical threshold is exceeded, toxicity results. Poisoning can produce minor local effects that can be treated readily in the outpatient setting or systemic life-threatening effects that require intensive medical intervention. This spectrum of toxicity is typical for many chemicals with which humans come in contact. Virtually any chemical can become a poison when taken in sufficient quantity, but the potency of some compounds leads to serious toxicity with small quantities (eTable 10-1). Poisoning by chemicals includes exposure to drugs, industrial chemicals, household products, plants, venomous animals, and agrochemicals. This chapter describes some examples of this spectrum of toxicity, outlines means to recognize poisoning risk, and presents principles of treatment.

Epidemiology

Each year poisonings account for approximately 43,000 deaths and at least 2.3 million emergency department visits in the United States.\(^1\) Males have a nearly twofold higher incidence of death than do females and 15% of adult poisoning deaths are attributed to suicide. Approximately 0.2% of poisoning deaths involve children younger than 5 years.\(^2\) Of emergency department visits for drug misuse and abuse, typically 51% involve illicit drugs, 59% involve pharmaceuticals, and 30% involve alcohol in combination with other drugs and underage drinking.\(^2\) The number and rates of poisoning deaths from all circumstances have been increasing steadily, with a twofold increase from 2000 to 2010, representing 42,917 deaths in 2010.\(^3\) This increasing mortality trend has placed poisoning as the leading cause of injury death in the United States with drugs as the most common cause.\(^3\)

Several databases in the United States provide different levels of insight into and documentation of the poisoning problem (eTable 10-2). Poisonings documented by U.S. poison centers are compiled in the annual report of the American Association of Poison Control Centers National Poison Data System (AAPCC-NPDS).\(^5\) Although it represents the largest database on poisoning, it is not complete because it relies on individuals voluntarily contacting a poison control center. The AAPCC-NPDS data set captures approximately 5% of the annual number of deaths from poisoning tabulated in death certificates.\(^5\) Despite this shortcoming, AAPCC-NPDS provides valuable insight into the characteristics and frequency of poisonings in the community at large. In the 2010 AAPCC-NPDS summary, 2,384,825 poisoning exposures were reported by 60 participating poison centers that served the entire United States.\(^5\) Children younger than 6 years accounted for 51% of cases. A residence was the site of exposure in 94% of the cases, and a single substance was involved in 90% of cases. An acute exposure accounted for 90% of cases, 82% of which were unintentional or accidental exposures. Only 15% were intentional. Fatalities accounted for 1,730 (0.07%) cases, of which 45% resulted from suicide and 3% were children younger than 6 years of age. The distribution of substances...
most frequently involved in pediatric and adult exposures differed; however, medicines were the most frequently involved (48%) substances (eTable 10-3). Seventy-one percent of the poison exposures were treated at the scene, typically a residence. In summary, children account for most of the reported poison exposures, but adults account for a greater proportion of life-threatening effects from poisoning.

POISON PREVENTION STRATEGIES

The number of poisoning deaths in children has declined dramatically over the past five decades, due, in part, to the implementation of several poison prevention approaches. These include the Poison Prevention Packaging Act (PPPA) of 1970, the evolution of regional poison control centers, the application of prompt first aid measures, improvements in overall critical care, development of less toxic product formulations, better clarity in the packaging and labeling of products, and public education on the risks and prevention of poisoning. Although all these factors play a role in minimizing poisoning dangers, particularly in children, the PPPA has perhaps had the most significant influence. The intent of the PPPA was to develop packaging that is difficult for children younger than 5 years of age to open or to obtain harmful amounts within a reasonable period of time. However, the packaging was not to be difficult for normal adults to use properly. Safety packaging is required for a number of products and product categories (eTable 10-4). Child-resistant containers are not totally childproof and may be opened by children, which can result in poisoning. Despite the success of child-resistant containers, many adults disable the hardware or simply use no safety cap, thus placing children at risk. Fatigue of the packaging materials can occur, which underscores the need for new prescription ware for refills, as required in the PPPA. After drug therapy for a condition is completed or no longer indicated, patients should be encouraged to properly dispose of medications that are outdated or unneeded to eliminate the risk of poisoning and drug diversion (see www.fda.gov/forconsumers/consumerupdates/ucm101653.htm).

Poison prevention requires constant vigilance because of new generations of families in which parents and grandparents must be educated on poisoning risks and prevention strategies. New products and changes in product formulations present different poisoning dangers and must be studied to provide optimal management. Strategies to prevent poisonings should consider the various psychosocial circumstances of poisoning (eTable 10-5), prioritize risk groups and behaviors, and customize an intervention for specific situations.

Recognition and Assessment

The clinician’s initial responsibility is to determine whether a poisoning has occurred or a potential for development of a poisoning exists. Some patients provide a clear account of an exposure that occurred with a known quantity of a specific agent. Other patients appear with an unexplained illness characterized by nonspecific signs and symptoms and no immediate history of ingestion. Exposure to folk remedies, dietary supplements, and environmental toxins also should be considered. Patients with suicide gestures can deliberately give an unclear history, and poisoning should be suspected routinely. Poisoning and drug overdoses should be suspected in any patient with a sudden, unexplained illness or with a puzzling combination of signs and symptoms, particularly in...
high-risk age groups. Nearly any symptom can be seen with poisoning, but some signs and symptoms are suggestive of a particular toxin exposure. Compounds that produce characteristic clinical pictures (toxidromes), such as organophosphate poisoning with pinpoint pupils, bradycardia, central nervous system depression, sweating, excessive salivation, and diarrhea, are most readily recognizable. The recognition of chemicals responsible for acute mass poisonings, such as acetaminophen, ethanol, iron, salicylates, and digoxin.

**Pharmacogenetic Considerations**

Pharmacogenetic factors responsible for poisoning risk among individuals have not been systematically studied, but unusual circumstances of poisoning cases have prompted the use of genotyping as a means to identify polymorphisms of drug metabolism. The following three examples demonstrate this phenomenon. Dextromethorphan, an antitussive agent, is abused to achieve euphoric effects which are not universally experienced at comparable doses. A metabolite, dextrophan, is responsible for the euphoria, dysphoria, hallucinations, and hyperactive behavior. Individuals who are extensive metabolizers via cytochrome P450 (CYP) 2D6 are more apt to experience these euphoric effects. Codeine has produced severe toxicity and death in some breast-fed infants, healthy young children, and older adults following the ingestion of typical doses. These individuals were ultrarapid CYP2D6 metabolizers of codeine, which resulted in the generation of life-threatening or fatal amounts of morphine, a metabolite of codeine.
than recommended doses over 24 hours led to the death of a young child. The postmortem blood concentration of hydrocodone was consistent with fatalities, but a major metabolite, hydromorphone, was not detected. This child was found to have a reduced capacity to metabolize hydrocodone to hydromorphone by CYP2D6. In this case presence of clarithromycin, a known CYP3A4 inhibitor, and valproic acid likely further diminished drug elimination and added to the toxicity of hydrocodone.19

The pharmacokinetic characteristics of drugs taken in overdose may differ from those observed following therapeutic doses (eTable 10-7).20,21 These differences are the result of dose-dependent changes in absorption, distribution, metabolism, or elimination; pharmacologic effects of the drug; or pathophysiologic consequences of the overdose. Dose-dependent changes may decrease the rate and extent of absorption, whereas the bioavailability of the agent may be increased because of saturation of first-pass metabolism. The distribution of a compound may be altered because of saturation of protein-binding sites. Metabolism and elimination of a compound may be retarded because of saturation of biotransformation pathways leading to nonlinear elimination kinetics. Delayed gastric emptying by anticholinergic drugs or as the result of general anesthesia from progressing to a serious intoxication is early decontamination of the poison. Basic poisoning first aid and decontamination measures (eTable 10-8) should be instituted immediately at the scene of the poisoning. If there is any question about the potential severity of the poison exposure, a poison control center should be consulted immediately (1-800-222-1222). While awaiting transport, placing the patient on the left side may afford easier clearance of the airway if emesis occurs and may slow absorption of drug from the gastrointestinal tract.25

### GENERAL APPROACH TO TREATMENT

#### Prehospital Care

#### First Aid

3 The presence of adequate airway, breathing, and circulation should be assessed and cardiopulmonary resuscitation should be started if needed. The most important step in preventing a minor exposure from progressing to a serious intoxication is early decontamination of the poison. Basic poisoning first aid and decontamination measures (eTable 10-8) should be instituted immediately at the scene of the poisoning. If there is any question about the potential severity of the poison exposure, a poison control center should be consulted immediately (1-800-222-1222). While awaiting transport, placing the patient on the left side may afford easier clearance of the airway if emesis occurs and may slow absorption of drug from the gastrointestinal tract.25

#### Ipecac Syrup

4 Ipecac syrup, a nonprescription drug, had been used in the United States since the 1950s as a means to induce vomiting for treatment of ingested poisons, but its use is now not recommended. In 1997, an expert panel of North American and European toxicologists concluded that its routine use in the emergency department should be abandoned.26 In 2003 the American Academy of Pediatrics issued a policy statement indicating that ipecac syrup was no longer to be used routinely to treat poisonings at home and that parents should discard any ipecac.27 The key reason for the policy change was that research failed to show benefits in children who were treated with ipecac syrup. In the 2010 AAPC-NPDS report, 0.02% of 2.38 million individuals still received ipecac syrup, with or without poison center direction.3

There are several contraindications to the use of ipecac syrup or any form of induced emesis, such as gagging.26 If the patient is without a gag reflex; is lethargic, comatose, or convulsing; or is expected to become unresponsive within the next 30 minutes, emesis should not be induced. If a fruitful emesis has occurred spontaneously shortly after ingestion, further emesis may not be necessary.

### Table 10-8 First Aid for Poison Exposures

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled poison</td>
<td>Immediately get the person to fresh air. Avoid breathing fumes. Open doors and windows. If victim is not breathing, start artificial respiration.</td>
</tr>
<tr>
<td>Poison on the skin</td>
<td>Remove contaminated clothing and flood skin with water for 10 minutes. Wash gently with soap and water and rinse. Avoid further contamination of victim or first aid providers.</td>
</tr>
<tr>
<td>Poison in the eye</td>
<td>Flood the open eye with lukewarm or cool water poured from a glass 2 or 3 inches (~5–8 cm) before flushing the eye. Repeat for 10–15 continuous minutes. Remove contact lenses.</td>
</tr>
<tr>
<td>Swallowed poison</td>
<td>Unless the patient is unconscious, having convulsions, or cannot swallow, give 2–4 ounces (~60–120 mL) of water immediately and then seek further help.</td>
</tr>
</tbody>
</table>
Ingestions of caustics, corrosives, ammonia, and bleach are definite contraindications to induced emesis. Ingestion of aliphatic hydrocarbons (e.g., gasoline, kerosene, and charcoal lighter fluid) typically does not require emesis. When the agent is definitely known to be nontoxic, induction of emesis is purposeless and potentially dangerous. The rapid onset of coma or seizures or the potential to exaggerate the toxic effects of the poison may preclude further the induction of emesis. Some examples include poisonings with diphenoxylate, propoxyphene, clonidine, tricyclic antidepressants, hypoglycemic agents, nicotine, strychnine, β-blocking agents, and calcium channel blockers. Debilitated, pregnant, and elderly patients may be further compromised by induction of emesis.

**Hospital Treatment**

Supportive and symptomatic care is the mainstay of treatment of a poisoned patient. In the search for specific antidotes and methods to increase excretion of the drug, attention to vital signs and organ functions should not be neglected. Establishment of adequate oxygenation and maintenance of adequate circulation are the highest priorities. Other components of the acute supportive care plan include the management of seizures, arrhythmias, hypotension, acid-base balance, fluid status, electrolyte balance, and hypoglycemia. Placement of IV and urinary catheters is typical to ensure delivery of fluids and drugs when necessary and to monitor urine production, respectively.\(^8,9\)

**Gastric Lavage**

Gastric lavage involves the placement of an orogastric tube and washing out of the gastric contents through repetitive instillation and withdrawal of fluid. Gastric lavage may be considered only if a potentially toxic agent has been ingested within the past hour for most patients. If the patient is comatose or lacks a gag reflex, gastric lavage should be performed only after intubation with a cuffed or well-fitting endotracheal tube. The largest orogastric tube that can be passed (external diameter at least 12 mm in adults and 8 mm in children) should be used to ensure adequate evacuation, especially of undissolved tablets. Lavage should be performed with warm (37°C to 38°C) normal saline or tap water until the gastric return is clear; this usually requires 2 to 4 L or more of fluid. Relative contraindications for gastric lavage include ingestion of a corrosive or hydrocarbon agent. Complications of gastric lavage include aspiration pneumonitis, laryngospasm, mechanical injury to the esophagus and stomach, hypothermia, and fluid and electrolyte imbalance.\(^28\) Use of gastric lavage has declined in recent years as evidenced by the finding that only 0.8% of 601,197 cases treated at a healthcare facility received gastric lavage in the 2010 AAPCC-NPDS report.\(^5\)

**Single-Dose Activated Charcoal**

Reduction of toxin absorption can be achieved by administration of activated charcoal. It is a highly purified, adsorbent form of carbon that prevents gastrointestinal absorption of a drug by chemically binding (adsorbing) the drug to the charcoal surface. There are no toxin-related contraindications to its use, but it is generally ineffective for iron, lead, lithium, simple alcohols, and corrosives. It is not indicated for aliphatic hydrocarbons because of the increased risk for emesis and pulmonary aspiration. Activated charcoal is most effective when given within the first few hours after ingestion, ideally within the first hour.\(^29\) The recommended dose of activated charcoal for a child (1 to 12 years old) is 25 to 50 g; for an adolescent or adult, the recommended dose is 25 to 100 g. Children younger than 1 year can receive 1 g/kg. Activated charcoal is mixed with water to make a slurry, shaken vigorously, and administered orally or via a nasogastric tube. Activated charcoal is contraindicated when the gastrointestinal tract is not intact.

**Clinical Controversy . . .**

Activated charcoal has been promoted for use at home as a replacement for ipecac syrup, but some have contended that little evidence indicates activated charcoal can be used safely and properly in this setting.

Activated charcoal is relatively nontoxic, but two identified risks are (a) emesis following administration and (b) pulmonary aspiration of charcoal and gastric contents leading to pneumonitis in patients with an unprotected airway or absent gag reflex.\(^29\) Some activated charcoal products contain sorbitol, a cathartic that may be associated with an increased incidence of emesis following use.\(^30\) Single-dose activated charcoal use has remained relatively steady during the past decade, with 3.0% of 2.38 million cases having received it according to the 2010 AAPCC-NPDS report.\(^5\)

**Cathartics**

Cathartics, such as magnesium citrate and sorbitol, were thought to decrease the rate of absorption by increasing gastrointestinal elimination of the poison and the poison-activated charcoal complex, but their value is unproven. Poisoned patients do not routinely require a cathartic, and it is rarely, if ever, given without concurrent activated charcoal administration.\(^31\) If used, a cathartic should be administered only once and only if bowel sounds are present. Infants, the elderly, and patients with renal failure should be given saline cathartics cautiously, if at all.\(^31\)

**Whole-Bowel Irrigation**

Polyethylene glycol electrolyte solutions, such as GoLYTELY and Colyte, are used routinely as whole-bowel irrigants prior to colonoscopy and bowel surgery. These solutions also can be used to decontaminate the gastrointestinal tract of ingested toxins.\(^8,32\) Large volumes of these osmotically balanced solutions are administered continuously through a nasogastric or duodenal tube for 4 to 12 hours or more. They quickly cause gastrointestinal evacuation and are continued until the rectal discharge is relatively clear. This procedure may be indicated for certain patients in whom the ingestion occurred several hours prior to hospitalization and the drug still is suspected to be in the gastrointestinal tract, such as drug smugglers who swallow condoms filled with cocaine.\(^33\) In addition, patients who have ingested delayed-release or enteric-coated drug formulations or have ingested substances such as iron that are not well adsorbed by activated charcoal may benefit from whole-bowel irrigation.\(^32\) It should not be used in patients with a bowel perforation or obstruction, gastrointestinal hemorrhage, ileus, or intractable emesis. Emesis, abdominal cramps, and intestinal bloating have been reported with whole-bowel irrigation.\(^32\) During 2010, whole-bowel irrigation was used in 0.3% of 601,197 cases managed at a healthcare facility.\(^5\)

**Clinical Controversy . . .**

Some clinicians believe that whole-bowel irrigation should be used more routinely as a rapid means to evacuate the gastrointestinal tract. Others recognize that it does have a quick onset but point out that little proof indicates whole-bowel irrigation makes a difference in patient outcome.

**Perspectives on Gastric Decontamination**

Although there are a variety of options for gastric decontamination, two clinical toxicology groups (the American Academy of Clinical Toxicology and the European Association of Poison Centers and
Clinical Toxicologists) have concluded that no means of gastric decontamination should be used routinely for a poisoned patient without careful consideration. They indicate that therapy is most effective within the first hour and that effectiveness beyond this time cannot be supported or refuted with the available data. A clinical policy statement by the American College of Emergency Physicians concludes that although no definitive recommendation can be made on the use of ipecac syrup, gastric lavage, cathartics, or whole-bowel irrigation, activated charcoal is advocated for most patients when appropriate. The clinical policy also states that ipecac syrup is rarely of value in the emergency department and that the use of whole-bowel irrigation following ingestion of substances not well adsorbed by activated charcoal is not supported by evidence. The efficacy of activated charcoal has been demonstrated for many compounds, but a randomized, controlled clinical trial of poisoned patients indicated that charcoal therapy did not reduce length of hospital stay or positively influence patient outcomes. Although gastric lavage can reduce drug absorption if performed within 1 hour of ingestion, its use is not recommended routinely. In recent years, the use of ipecac syrup has been abandoned in part because of its apparent lower efficacy compared with activated charcoal in minimizing drug absorption. Recently, activated charcoal has been promoted for treatment of poisonings at home, but issues of safety, patient compliance, and effectiveness have not been proven in the home setting. Poison control centers may be a source of guidance on the contemporary application of gastric decontamination techniques for a specific patient.

Enhanced Elimination

Of the methods tried to increase the rate of excretion of poisons from the body, only diuresis, multiple-dose activated charcoal, and hemodialysis have demonstrated usefulness in select situations. These approaches should be considered only if the risks of the procedure are significantly outweighed by the expected benefits or if the recovery of the patient is seriously in doubt and the method has been shown to be helpful.

Diuresis

Diuresis can be used for poisons excreted predominantly by the renal route; however, most drugs and poisons are metabolized, and thus only a good urine flow (e.g., 2 to 3 mL/kg/h) needs to be maintained for most patients. Fluid and electrolyte balance should be monitored closely. Ionized diuresis by altering urinary pH may increase excretion of certain chemicals that are weak acids or bases by trapping ionized drug in the renal tubule and minimizing reabsorption. Alkalization of the urine to achieve a urine pH of 7.5 or greater for poisoning by weak acids such as salicylates or phenobarbital can be achieved by IV administration of sodium bicarbonate 1 to 2 mEq/kg (1 to 2 mmol/kg) over a 1- to 2-hour period. Complications of urinary alkalization include alkalosis, fluid and electrolyte disturbances, and inability to achieve target urinary pH values.

Acid diuresis may enhance the excretion of weak bases, such as amphetamines, but it is rarely, if ever, used because it risks worsening rhabdomyolysis commonly associated with amphetamine overdose. Generally, diuresis or ionized diuresis is rarely indicated for poisoned patients because it is ineffective relative to other methods of enhancing elimination, it is associated with a risk of unacceptable adverse effects, and renal elimination of most drugs is not enhanced dramatically.

Multiple-Dose Activated Charcoal

Multiple doses of activated charcoal can augment the body’s clearance of certain drugs by enhanced passage from the bloodstream into the gastrointestinal tract and subsequent adsorption. This process, termed charcoal intestinal dialysis or charcoal-enhanced intestinal exsorption, describes the attraction of drug molecules across the capillary bed of the intestine by activated charcoal in the intestinal lumen and subsequent adsorption of the drug to the charcoal. Furthermore, it may interrupt the enterohepatic recirculation of certain drugs. Once the drug is adsorbed to the charcoal, it is eliminated with the charcoal in the stool. Systemic clearance of several drugs has been shown to be enhanced up to several-fold. An international toxicology group’s position statement on multiple-dose activated charcoal concluded that it should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. Although a prospective, randomized study of the effects of multiple-dose activated charcoal on phenobarbital-overdosed patients demonstrated increased drug elimination, no demonstrable effect on patient outcome was observed.

This approach provides a rapid onset of action that is limited by blood flow and a maximal “ceiling effect” related to the dose of charcoal present in the intestine. The response to multiple-dose activated charcoal is greatest for drugs with the following characteristics: good affinity for adsorption by activated charcoal, low intrinsic clearance, sufficient residence time in the body (long serum half-life), long distributive phase, and nonrestrictive protein binding. A small volume of distribution is desirable, but it has a marginal influence as an isolated characteristic, particularly if multiple-dose activated charcoal is instituted during the toxin’s distributive phase. A typical dosage schedule is 15 to 25 g of activated charcoal every 2 to 6 hours until serious symptoms abate or the serum concentration of the toxin is below the toxic range. This procedure has been used in premature and full-term infants in doses of 1 g/kg every 1 to 4 hours. Serious complications, such as pulmonary aspiration, occur in less than 1% of patients. The risks of aspiration pneumonia in obtunded or uncooperative patients and of intestinal obstruction in patients prone to ileus following a period of bowel ischemia (e.g., after cardiopulmonary arrest in the elderly) may be higher. Contraindications are the same as those for single-dose charcoal.

Hemodialysis

Hemodialysis may be necessary for certain severe cases of poisoning. Dialysis should be considered when the duration of symptoms is expected to be prolonged, normal pathways of excretion are compromised, clinical deterioration is present, the drug is dialyzable, and appropriate personnel and equipment are available. Drugs that are hemodialyzable usually have a low molecular weight, are not highly or tightly protein bound, and are not highly distributed to tissues. The principles of hemodialysis for acutely ill individuals are described in Chapter 30. Hemodialysis and charcoal hemoperfusion are efficient methods of dialysis, but both pose serious risks related to anticoagulation, blood transfusions, loss of blood elements, fluid and electrolyte disturbances, and infection. Hemodialysis may be lifesaving for methanol and ethylene glycol poisoning and effective for other poisons, such as lithium, salicylates, ethanol, and theophylline. Continuous veno-venous hemofiltration transports drugs across a semipermeable membrane by convection in response to hydrostatic pressure gradients. (See Chap. 28 for a detailed description of the procedure.) Limited experience is reported with the use of hemofiltration for poisonings, but it may be attractive for the hemodynamically unstable patient who cannot tolerate hemodialysis.

Antidotes

The search for and use of an antidote should never replace good supportive care. Specific systemic antidotes are available for many common poisonings. Inadequate availability of antidotes at acute care hospitals has been noted throughout the United States and can complicate the care of a poisoned patient.
An evidence-based consensus of experts has recommended minimum stocking requirements for 24 antidotes for acute care hospitals and that 12 should be available for immediate administration on patient arrival. These recommendations may act as antidotes to reverse acute toxicity, such as activated charcoal adsorption, but they do not mimic physiologic conditions sufficiently to allow direct clinical application of the findings. Despite their limitations, these data compose the basis for the therapy of poisoned patients and are tempered with the considerations of nonpoisoning-related factors such as a patient’s underlying medical condition, age, and need for concurrent supportive measures.

### CLINICAL SPECTRUM OF POISONING

Poisoning and drug overdose with acetaminophen, anticholinesterase insecticides, calcium channel blockers, iron, opioids, and tricyclic antidepressants are the focus of the remainder of this chapter because they represent commonly encountered poisonings for which pharmacotherapy is indicated. These agents also were chosen because they represent common examples with different mechanisms of toxicity, and they illustrate the application of general treatment approaches as well as some agent-specific interventions.

### Acetaminophen

#### Clinical Presentation

Acute acetaminophen poisoning characteristically results in hepatotoxicity and is a leading cause of acute liver failure in the United States. Clinical presentation (see the Clinical Presentation of Acute Acetaminophen Poisoning) is dependent on the time since ingestion, presence of risk factors, and the ingestion of other drugs. During the first 12 to 24 hours after ingestion, nausea, vomiting, anorexia, and diaphoresis may be observed; however, many patients are asymptomatic. During the next 1 to 3 days, which is a latent phase of lessened symptoms, patients often have an asymptomatic rise in liver enzymes and bilirubin. Signs and symptoms of hepatic encephalopathy. Prolongation of the international normalized ratio (INR) worsens as hepatic necrosis progresses and may lead to disseminated intravascular coagulopathy. Patients with severe hepatic damage may develop hepatic coma and hepatorenal syndrome, and death can occur. Survivors of severe hepatotoxicity usually exhibit no residual functional or histologic abnormalities of the liver within 1 to 6 months of the incident.

#### Mechanism of Toxicity

Acetaminophen is metabolized in the liver primarily to glucuronide or sulfate conjugates, which are excreted into the urine with small amounts (less than 5%) of unchanged drug. Approximately 5% of a therapeutic dose is metabolized by the CYP mixed-function
CLINICAL PRESENTATION

Acute Acetaminophen Poisoning

**General**
- No or mild nonspecific symptoms within 6 hours of ingestion

**Symptoms**
- Nausea, vomiting, and abdominal discomfort within 1 to 12 hours after ingestion
- Right upper abdominal quadrant tenderness, typically within 1 to 2 days

**Signs**
- Typically no signs present within first day
- Jaundice, scleral icterus, bleeding within 3 to 10 days
- Oliguria occasionally within 2 to 7 days

- With severe poisoning, hepatic encephalopathy (delirium, depressed reflexes, coma) within 5 to 10 days

**Laboratory Tests**
- Toxic serum acetaminophen concentration no earlier than 4 hours after ingestion by comparison with nomogram
- Elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum bilirubin, and international normalized ratio (INR); hypoglycemia within 1 to 3 days
- Elevated serum creatinine and blood urea nitrogen (BUN) within 2 to 7 days

Acetaminophen, also known as paracetamol, is available widely without prescription as an analgesic and antipyretic. It is available in various oral dosage forms, including extended-release preparations. Acetaminophen may be combined with other drugs, such as antihistamines or opioid analgesics, and marketed in cough and cold preparations, menstrual remedies, and allergy products. Some patients may not recognize that they are consuming several products containing acetaminophen, which can increase the total daily dose taken and the subsequent risk of hepatotoxicity.

### Incidence
Acetaminophen is one of the drugs most commonly ingested by small children and is used commonly in suicide attempts by adolescents and adults. Each year acetaminophen accounts for approximately 78,000 emergency department visits with 78% related to acts of self-harm. The 2010 AAPCC-NPDS report documented 55,753 nonfatal single-drug product exposures and 60 deaths from acetaminophen alone, with 60% of the exposures in children younger than 6 years.

In children younger than 9 to 12 years, acetaminophen undergoes more sulfation and less glucuronidation. The reduced fraction available for metabolism by the cytochrome system may explain the rare development of serious toxicity in young children who take large overdoses. Earlier treatment intervention and spontaneous emesis also may reduce the risk of toxicity in children.

### Risk Assessment
There is a risk of developing hepatotoxicity when patients 6 years or older acutely ingest at least 10 g or 200 mg/kg, whichever is less, of acetaminophen or when children younger than 6 years acutely ingest 200 mg/kg or more. Patients have survived much larger doses, particularly with early treatment. Initial symptoms, if present, do not predict how serious the toxicity eventually may become.

Chronic exposure to drugs that induce the cytochrome oxidase system—specifically isoenzyme CYP2E1, which is responsible for most of the formation of NAPQI—may increase the risk of acetaminophen hepatotoxicity. Poorer outcomes have been noted in patients who chronically ingest alcohol and those receiving anticonvulsants, both known to induce CYP2E1. Patients with chronic alcoholism have a 3.5 greater odds of mortality with acute acetaminophen poisoning. Concurrent acute ingestion of alcohol and acetaminophen may decrease the risk of acetaminophen-induced hepatotoxicity by ethanol acting as a competitive substrate for CYP2E1, thus reducing

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**eFIGURE 10-1** Pathway of acetaminophen metabolism and basis for hepatotoxicity. (NAPQI, N-acetyl-p-benzoquinoneimine, a reactive acetaminophen metabolite.)

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NAPQI formation. Ethanol coingestion is not advocated as a preventive measure, and it is difficult to account for its specific impact on care.

Repeated ingestion of supratherapeutic doses of acetaminophen (defined for patients < 5 years: ≥200 mg/kg over 8 to 24 hours, ≥ 150 mg/kg/day for 2 days, ≥ 100 mg/kg/day for 3 days or longer; for patients ≥ 6 years: ≥ 10 g or 200 mg/kg [whichever is less] over a single 24-hour period, ≥ 6 g or 150 mg/kg [whichever is less] per 24-hour period for ≥ 48 hours) has been associated with hepatotoxicity. Patients who are fasting or have ingested alcohol in the preceding 5 days appear to be at greater risk. Young children who receive repetitive supratherapeutic doses of acetaminophen have a higher risk of developing hepatotoxicity, particularly when they have been acutely fasting as the result of a febrile illness or gastroenteritis. Patients with suspected risk factors, such as alcoholism, isoniazid therapy, or prolonged fasting, should be referred for medical evaluation if there is evidence that the ingestion exceeded 4 g/day or 100 mg/kg/day, whichever is less.

The risk of developing hepatotoxicity may be predicted (eFig. 10-2) based on the acetaminophen serum concentration and time after ingestion. Treatment should be started if the person’s serum concentration is above the line on the nomogram that starts at 150 mcg/mL (1.000 μmol/L) at 4 hours. The other lines on the nomogram indicate differing levels of risk for hepatotoxicity based on a multicenter study of 11,195 patients. If the plasma concentration plotted on the nomogram falls above the nomogram treatment line, indicating that hepatic damage is possible, a full course of treatment with acetylcysteine is indicated. When the results of the acetaminophen determination will be available later than 8 hours after the ingestion, acetylcysteine therapy should be initiated based on the history and later discontinued if the results indicate nontoxic concentrations.

The nomogram is not useful for assessing chronic or supratherapeutic exposures to acetaminophen. Some have advocated that patients with chronic alcoholism should be treated with acetylcysteine regardless of the risk estimation. Assessment and management of IV administered acetaminophen (introduced in the United States in 2011) is similar to the acute oral overdose.

Management of Toxicity

Therapy of an acute acetaminophen overdose depends on the amount ingested, time after ingestion, and serum concentration of acetaminophen. When excessive amounts are ingested, the history is unclear, or an intentional ingestion is suspected, the patient should be evaluated at an emergency department and acetaminophen serum concentrations obtained. Prehospital care generally is not indicated. If the patient presents to the emergency department within 4 hours of the ingestion or ingestion of other drugs is suspected, one dose of activated charcoal can be administered.

Acetylcysteine (also known as N-acetylcysteine), a sulfhydryl-containing compound, replenishes the hepatic stores of glutathione by serving as a glutathione surrogate that combines directly with reactive metabolites or by serving as a source of sulfate, thus preventing hepatic damage. It should be started within 10 hours of the ingestion to be most effective. Initiation of therapy 24 to 36 hours after the ingestion may be of value in some patients, particularly those with measurable serum acetaminophen concentrations. Patients with fulminant hepatic failure may benefit through other mechanisms by the administration or initiation of acetylcysteine several days after ingestion.

Therapy should be initiated with acetylcysteine within 10 hours of ingestion when indicated. The oral liquid was the only approved form of acetylcysteine in the United States until 2004, when the Food and Drug Administration (FDA) approved an IV formulation. A systematic review of the literature indicated that acetylcysteine is superior to supportive care, but there is no clear evidence of which regimen is better. There are several notable differences between the oral and IV forms of acetylcysteine (eTable 10-10). Most notable is the occurrence (approximately 10% of cases) of anaphylactoid reactions (see eChap. 22) following the IV infusion. Twice as many patients were treated with IV acetylcysteine compared to the oral form as reported in the 2010 AAPCC-NPDS. When acetaminophen plasma concentrations are below the nomogram treatment line, there is little risk of toxicity, protective therapy with acetylcysteine is not necessary, and medical therapy likely is unnecessary. The acetaminophen blood sample should be drawn no sooner than 4 hours after the ingestion to ensure that peak acetaminophen concentrations have been reached. If a concentration is obtained less than 4 hours after ingestion, it is not interpretable, and a second determination should be done at least 4 hours after ingestion. Serial determinations of a serum concentration, 4 to 6 hours apart, typically are unnecessary unless there is some evidence of slowed gastrointestinal motility as the result of the ingestion of certain drugs (e.g., opioids, antihistamines, or anticholinergics) or unless an extended-release product is involved. In these circumstances, therapy with acetylcysteine is continued if any concentration is above the treatment line of the nomogram, and provisional therapy is discontinued when both concentrations are below the treatment line.

Clinical Controversy...

The 72-hour oral acetylcysteine and the 21-hour IV regimen are satisfactory for most patients, but some state that the 72-hour regimen is too long while others believe the 21-hour regimen is too short. Individualized therapy based on clinical end points, for example, absence of acetaminophen in the blood at the end of a regimen, presence of hepatic encephalopathy or ALT approaching normal range, has been proposed as an alternative to strict adherence to the duration in the package insert. Accepted and validated criteria are lacking at present.
Although young children have an inherently lower risk of acetaminophen-induced hepatotoxicity, these patients should be managed in the same manner as adults. When acetaminophen serum concentrations predict that toxicity is probable, young children should receive acetylcysteine in the dosing regimen described previously. 61

If fulminant hepatic failure develops, the approaches described in Chapter 24 should be considered. In patients unresponsive to acetylcysteine, liver transplantation is a lifesaving option. 53

**Anticholinesterase Insecticides**

**Clinical Presentation**

The clinical manifestations of anticholinesterase insecticide poisoning include any or all of the following: pinpoint pupils, excessive lacrimation, excessive salivation, bronchorrhea, bronchospasm, and abdominal cramps. The severity of these symptoms can range from mild to life-threatening, depending on the extent of exposure.

**Laboratory Tests**

- Markedly depressed serum pseudocholinesterase activity
- Altered arterial blood gases (acidosis), serum electrolytes, BUN, and serum creatinine in response to respiratory distress and shock within 1 to 6 hours

**Other Diagnostic Tests**

- Chest radiographs for progression of pulmonary edema or hydrocarbon pneumonitis in symptomatic patients
- Electrocardiogram (ECG) with continuous monitoring and pulse oximetry for complications from toxicity and hypoxia

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**TABLE 10-10 Comparison of IV and Oral Regimens for Acetylcysteine in the Treatment of Acute Acetaminophen Poisoning**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IV</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>150 mg/kg in 200 mL D,W infused over 1 hour, then 50 mg/kg in 500 mL D,W over 4 hours, followed by 100 mg/kg in 1,000 mL D,W over 16 hours</td>
<td>140 mg/kg, followed 4 hours later by 70 mg/kg every 4 hours for 17 doses diluted to 5% with juice or soft drinks</td>
</tr>
<tr>
<td>Total dose (mg/kg)</td>
<td>300</td>
<td>1,330</td>
</tr>
<tr>
<td>Duration (h)</td>
<td>21</td>
<td>72</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Anaphylactoid reactions (rash, hypotension, wheezing, dyspnea); acute flushing and erythema in first hour of the infusion that typically resolves spontaneously</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Ancillary therapy, if needed</td>
<td>Antihistamines and epinephrine for severe anaphylactic reactions</td>
<td>Antiemetics</td>
</tr>
<tr>
<td>Trade name</td>
<td>Acetadote</td>
<td>Mucomyst</td>
</tr>
<tr>
<td>Available strength</td>
<td>20%</td>
<td>10%, 20%</td>
</tr>
</tbody>
</table>

D,W, 5% dextrose in water for injection.

*For patients <40 kg and those requiring fluid restriction, the total volume for dilution should be reduced as directed in the package insert.*
Organophosphate insecticide effects after exposure

- Neuromuscular paralysis
- Bronchorrhea
- CNS depression
- Cardiovascular effects, e.g., bradycardia, hypotension
- Respiratory failure
- Hypoxia
- Acidosis
- Myocardial dysfunction

*Generally muscarinic effects predominate, but nicotinic effects can be observed.*

**Mechanism of Toxicity**

Anticholinesterase insecticides phosphorylate the active site of cholinesterase in all parts of the body. Inhibition of this enzyme leads to accumulation of acetylcholine at affected receptors and results in widespread toxicity. Acetylcholine is the neurotransmitter responsible for physiologic transmission of nerve impulses from preganglionic and postganglionic neurons of the cholinergic (parasympathetic) nervous system, preganglionic adrenergic (sympathetic) neurons, neuromuscular junction in skeletal muscles, and CNS receptors (mixed type). Symptoms of anticholinesterase poisoning and their response to antidotal therapy depend on the action of excessive acetylcholinesterase at different receptor types (Table 10-11).

The time of onset and severity of symptoms depend on the route of exposure, potency of the agent, and total dose received (see the Clinical Presentation of Anticholinesterase Insecticide Poisoning box). Toxic signs and symptoms develop most rapidly after inhalation or IV injection and slowest after skin contact. Anticholinesterase insecticides are absorbed through the skin, lungs, conjunctivae, and gastrointestinal tract. Severe symptoms can occur from absorption by any route. Most patients are symptomatic within 6 hours, and death may occur within 24 hours without treatment. Death typically is caused by respiratory failure resulting from the combination of pulmonary and cardiovascular effects (eFig. 10-3). Poisoning may be complicated by aspiration pneumonia, urinary tract infections, and sepsis.

Organophosphate poisoning has been associated with several residual effects, such as intermediate syndrome, extrapyramidal symptoms, neuropsychiatric effects, and delayed chronic neuropathy. Intermediate syndrome becomes manifest in some patients approximately 1 to 3 days after exposure and generally resolves within weeks of onset without further treatment. It is characterized by muscle weakness of proximal limbs, cranial nerve innervated muscles, and muscles of respiration. The inability of the patient to raise his or her head is often an initial sign. Extrapyramidal symptoms, which may develop 1 to 7 days after exposure, usually resolve spontaneously within a few days of onset. Neuropsychiatric effects, such as confusion, lethargy, memory impairment, headache, and depression, typically begin weeks to months after exposure and may last for years. Chronic neuropathy often presents as cramping muscle pain in the legs (upper extremities are sometimes involved), followed by rapidly progressive weakness and paralysis and develops 1 to 5 weeks after recovery from the acute poisoning exposure. Paresthesia and pain may be present. It is unresponsive to further atropine or pralidoxime therapy. Improvement may be delayed for months to years, and in some cases the patient develops permanent disability. It is not associated with all organophosphates.

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muscles, and multiple nerve endings in the central nervous system (eFig. 10-4).

Causative Agents

Anticholinesterase insecticides include organophosphate and carbamate insecticides. These insecticides are currently in widespread use throughout the world for eradication of insects in dwellings and crops. Carbamates typically are less potent and inactivate cholinesterase in a more reversible fashion through carbamylation compared with organophosphates. The prototype anticholinesterase agent is the organophosphate, which is the focus of this discussion. A large number of organophosphates are used as pesticides (e.g., dichlorvos, disulfoton, malathion, mevinphos, phosphet), and several were specifically developed for use as potent chemical warfare agents (see eChap. 12). The chemical warfare agents act like organophosphate insecticides, but they are highly potent, are quickly absorbed, and can be deadly to humans within minutes. An anticholinesterase insecticide typically is stored in a garage, chemical storage area, or living area. Anticholinesterase agents also can be found in occupational (e.g., pest exterminators) or agricultural (e.g., crop dusters or farm workers) settings. These agents also have been used as a means for suicide or homicide.

Incidence

Anticholinesterase insecticides are among the most poisonous substances commonly used for pest control and are a frequent source of serious poisoning in children and adults in rural and urban settings. The 2010 AAPCC-NPDS report documented 5,743 nonfatal single-product exposures and eight deaths from anticholinesterase insecticides. The 2010 AAPCC-NPDS report documented 5,743 nonfatal single-product exposures and eight deaths from anticholinesterase insecticides alone or in combination with other pesticides, with 30% of exposures in children younger than 6 years.

Risk Assessment

The triad of miosis, bronchial secretions, and muscle fasciculations should suggest the possibility of anticholinesterase insecticide poisoning and warrants a therapeutic trial of the antidote atropine. In cases of low-level exposure, failure to develop signs within 6 hours indicates a low likelihood of subsequent toxicity. Ruling out other chemical exposures may be guided initially by symptoms at presentation.

Although the lethal dose for parathion is approximately 4 mg/kg, as little as 10 to 20 mg can be lethal to an adult and 2 mg (0.1 mg/kg) to a child. Small children may be more susceptible to toxicity because less pesticide is required per body weight to produce toxicity. Estimation of an exact dose is impossible in most cases of acute poisoning; thus, tabulated “toxic” doses generally are not helpful in assessing risk of toxicity. Generally, ingestion of a small mouthful (approximately 5 mL in adults) of the concentrated forms of an organophosphate intended to be diluted for commercial or agricultural use will produce serious, life-threatening toxicity, whereas a mouthful of an already diluted household product, such as an aerosol insecticide for household use, typically does not produce serious toxic effects.

Measurement of acetylcholinesterase activity at the neuronal synapse is not feasible clinically. Cholinesterase activity can be measured in the blood as the pseudocholinesterase (butyrylcholinesterase) activity of the plasma and acetylcholinesterase activity in the erythrocyte. Both cholinesterases will be depressed with anticholinesterase insecticide poisoning. Severity can be estimated roughly by the extent of depressed activity in relation to the low end of normal values. Because there are several methods to measure and report cholinesterase activity, each particular laboratory’s normal range must be considered. Clinical toxicity usually is seen only after a 50% reduction in enzyme activity, and severe toxicity typically is observed at levels 20% or less of the normal range. The intrinsic activity of acetylcholinesterase may be depressed in some individuals, but the absence of any manifestations in most people does not permit recognition of the relative deficiency in the general population. Therapy should not be delayed pending laboratory confirmation when insecticide poisoning is clinically suspected.

Management of Toxicity

People handling the patient should wear gloves and aprons to protect themselves against contaminated clothing, skin, or gastric fluid of the patient. Because many insecticides are dissolved in a hydrocarbon vehicle, there is an additional risk of pulmonary aspiration of the hydrocarbon leading to pneumonitis. The risks and benefits of gastric decontamination (e.g., gastric lavage, activated charcoal) should be considered carefully and should involve consultation with a poison control center or clinical toxicologist. Symptomatic cases of anticholinesterase insecticide exposure typically are referred to an emergency department for evaluation and treatment.

If the poison has been ingested within 1 hour, gastric lavage should be considered and followed by the administration of activated charcoal. For the patient with skin contamination, contaminated clothing should be removed and the patient washed with copious amounts of soap and water before he or she is admitted to the emergency department or other patient care area. An alcohol wash may be useful for removing residual insecticide because of its lipophilic nature. A surgical scrub kit for the hands, feet, and nails may be useful for exposure to those areas. Supportive therapy should include maintenance of an airway (including bronchotracheal suctioning), provision of adequate ventilation, and establishment of an IV line. Based on a history of an exposure and presence of typical symptoms, the anticholinesterase syndrome should be recognized without difficulty.

Pharmacologic management of organophosphate intoxication relies on the administration of atropine and pralidoxime. Atropine has no effect on inhibited cholinesterase, but it competitively blocks the actions of acetylcholine on cholinergic and some central nervous system receptors. It thereby alleviates bronchospasm and reduces bronchial secretions. Although atropine has little effect on the flaccid muscle paralysis or the central respiratory failure of severe poisoning, it is indicated in all symptomatic patients and can be used as a diagnostic aid. It should be given IV and in larger than conventional doses of 0.05 to 0.1 mg/kg in children younger
than 12 years and 2 to 5 mg in adolescents and young adults. It should be repeated at 5- to 10-minute intervals until bronchial secretions and pulmonary rales resolve. Therapy may require large doses over a period of several days until all absorbed organophosphate is metabolized, and acetylcholinesterase activity is restored.

**Clinical Controversy...**

Gastric lavage for organophosphate ingestions is performed routinely by some clinicians within 1 hour of ingestion. Evidence for the use of gastric lavage for organophosphates is based on reports of the lavage fluid having the odor of the insecticide. Others argue that excessive bronchial secretions and decreased mental status introduces substantial risk of pulmonary aspiration during gastric lavage.

Restoration of enzyme activity is necessary for severe poisoning, characterized by a reduction of cholinesterase activity to less than 20% of normal, profound weakness, and respiratory distress. Pralidoxime (Protopam), also called 2-PAM or 2-pyridine aldoximemethiodide, breaks the covalent bond between the cholinesterase and organophosphate and regenerates enzyme activity. Organophosphate-cholinesterase binding is reversible initially, but it gradually becomes irreversible. Therefore, therapy with pralidoxime should be initiated as soon as possible, preferably within 36 to 72 hours of exposure. The drug should be given at a dose of 25 to 50 mg/kg up to 1 g IV over 5 to 20 minutes. If muscle weakness persists or recurs, the dose can be repeated after 1 hour and again if needed. A continuous infusion of pralidoxime has been shown to be effective in adults when administered at 2 to 4 mg/kg/h preceded by a loading dose of 4 to 5 mg/kg and in children at 10 to 20 mg/kg/h with a loading dose of 15 to 50 mg/kg. Both atropine and pralidoxime should be given together because they have complementary actions (eTable 10-12). Systematic reviews of the literature indicate that the effectiveness of pralidoxime and similar oxime compounds in the treatment of organophosphate poisoning is inconclusive because of problems with study design.

One of the pitfalls of therapy is the delay in administering sufficient doses of atropine or pralidoxime. The adverse effects of atropine and pralidoxime, predictable extensions of their anticholinergic actions, are minimally important compared with the life-threatening effects of severe anticholinesterase poisoning and can be minimized easily by decreasing the dose.

### Calcium Channel Blockers

#### Clinical Presentation

Overdose with calcium channel blockers typically results in bradycardia and hypotension (eFig. 10-5). Many patients become lethargic and may develop agitation and coma. If the degree of hypotension becomes severe or is prolonged, the secondary effects of seizures, coma, and metabolic acidosis usually develop. Pulmonary edema, nausea, and vomiting, and hyperglycemia are frequent complications of calcium channel blocker overdoses. Paralytic ileus, mesenteric ischemia, and colonic infarction have been observed in patients with severe hypotension. Many symptoms become manifest within 1 to 2 hours of ingestion (see the Presentation of Calcium Channel Blocker Poisoning box). If a sustained-release formulation is involved, the onset of overt toxicity may be delayed by 6 to 18 hours from the time of ingestion. Severe poisoning can result in refractory shock and cardiac arrest. Death can occur within 3 to 4 hours of ingestion.

#### Mechanism of Toxicity

Most toxic effects of calcium channel blockers are produced by three basic actions on the cardiovascular system: vasodilation through relaxation of smooth muscles, decreased contractility by action on cardiac tissue, and decreased automaticity and conduction velocity through slow recovery of calcium channels. Calcium channel blockers interfere with calcium entry by inhibiting one or more of the several types of calcium channels and binding at one or more cellular binding sites. Selectivity of these actions varies with the calcium channel blocker and provides some therapeutic distinctions, but these differences are less clear with overdose. Calcium channel blockers also inhibit insulin secretion, which results in hyperglycemia and changes in fatty acid oxidation in the myocardium that alter myocardial calcium flow and reduce contractility. Current experiences suggest that the signs and symptoms of calcium channel blocker toxicity are similar among the drugs in this class.

#### Causative Agents

Approximately 10 calcium channel antagonists are marketed in the United States for treatment of hypertension, certain dysrhythmias, and some forms of angina. The calcium channel blockers are classified by their chemical structure as phenylalkylamines (e.g., verapamil), benzothiapiines (e.g., diltiazem), and dihydropyridines (e.g.,amlodipine, felodipine, nicardipine, and nifedipine). Several of
Clinical Presentation: Calcium Channel Blocker Poisoning

### General
- Life-threatening cardiac toxicity (bradycardia, depressed contractility, dysrhythmias) within 1 to 3 hours of ingestion, delayed by 12 to 18 hours if a sustained-release product is involved

### Symptoms
- Nausea and vomiting within 1 hour
- Dizziness, lethargy, coma, and seizures within 1 to 3 hours

### Signs
- Hypotension and bradycardia within 1 to 6 hours
- Unresponsiveness and depressed reflexes within 1 to 6 hours
- Atrioventricular block, intraventricular conduction defects, and ventricular dysrhythmias on ECG

### Laboratory Tests
- Significant hyperglycemia (greater than 250 mg/dL [13.9 mmol/L]) may indicate severe toxicity and consideration for aggressive therapy
- Altered arterial blood gases (metabolic acidosis), serum electrolytes, BUN, and serum creatinine in response to shock within 1 to 6 hours

### Other Diagnostic Tests
- ECG with continuous monitoring and pulse oximetry to monitor for toxicity and shock
- Monitor for complications of pulmonary aspiration such as hypoxia and pneumonia by physical findings and chest radiographs

### Incidence
In 2010, the AAPCC-NPDS report documented 4,945 single-product toxic exposures to a calcium channel blocker; 65 patients exhibited and survived major toxic effects, and 13 died.

### Risk Assessment
Ingestion of doses near or in excess of 1 g of diltiazem, nifedipine, or verapamil may result in life-threatening symptoms or death in an adult. Ingestion of an amount that exceeds the usual maximum single therapeutic dose or a dose equal to or greater than the lowest reported toxic dose (whichever is less) warrants referral to a poison control center and/or an emergency department. The threshold doses of several agents and dosage forms vary (e.g., diltiazem: adults, >120 mg for immediate release and chewed sustained release,

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**eFIGURE 10-5** Pathophysiologic changes associated with calcium channel blocker poisoning.
>360 mg for sustained release, >540 mg for extended release; children younger than 6 years: >1 mg/kg.44 Patients on chronic therapy with these agents who acutely ingest an overdose may have a greater risk of serious toxicity. Elderly patients and those with underlying cardiac disease may not tolerate mild hypotension or bradycardia. Concurrent ingestion of β-adrenergic blocking drugs, digoxis, class I antiarrhythmics, and other vasodilators may worsen the cardiovascular effects of calcium channel blockers.10,82,84 The presence of persistent and significant hyperglycemia (greater than 250 mg/dL [13.9 mmol/L]) has been suggested as a sign of grossly disturbed cardiac metabolism and physiology that merits attention and aggressive intervention.85

Management of Toxicity
There is no accepted specific prehospital care for calcium channel blocker poisoning, except to summon an ambulance for symptomatic patients. The therapeutic options for management of calcium channel blocker poisoning include supportive care, gastric decontamination, and adjunctive therapy for the cardiovascular and metabolic effects. Supportive care consists of airway protection, ventilatory support, IV hydration to maintain adequate urine flow, and maintenance of electrolyte and acid–base balance. Maintaining vital organ perfusion is critical for successful therapy in order to allow time for calcium channel blocker toxicity to resolve.81,82

Gastric lavage and a single dose of activated charcoal should be administered if instituted within 1 to 2 hours of ingestion. Besides exhibiting a slower onset of symptoms, sustained-release formulations can form concretions in the intestine.81,82 Whole-bowel irrigation with polyethylene glycol electrolyte solution may accelerate rectal elimination of the sustained-release tablets and should be considered for ingestions of sustained-release calcium channel blocker formulations.32

Adjunctive therapy is focused on treating hypotension, bradycardia, and resulting shock. Hypotension is treated primarily by correction of coexisting dysrythmias (e.g., bradycardia, heart block) and implementation of conventional measures to treat decreased blood pressure. Infusion of normal saline and placement of the patient in the Trendelenburg position are initial therapies. Further fluid therapy should be guided by central venous pressure monitoring. Dopamine and epinephrine in conventional doses for cardiogenic shock should be considered next. If hypotension persists, dysrhythmias are present, or other signs of serious toxicity are present, calcium should be administered IV.79,82

A calcium chloride bolus test dose (10 to 20 mg/kg up to 1 to 3 g) is the preferred therapy for patients with serious toxicity. In adults, calcium chloride 10% can be diluted in 100 mL normal saline and infused over 5 minutes through a central venous line. If a positive cardiovascular response is achieved with this test dose, a continuous infusion of calcium chloride (20 to 50 mg/kg/h) should be started. Calcium gluconate is less desirable to use because it contains less elemental calcium per milligram of final dosage form. Calcium salts IV can produce vomiting and tissue necrosis on extravasation.48,82 Atropine also may be considered for treatment of bradycardia, but it is seldom sufficient as a sole therapy.81

Clinical Controversy...

Some clinicians believe that hyperinsulinemia /euglycemia or glucagon therapy for calcium channel blocker poisoning should be used early in the course of therapy. Others reserve it for life-threatening symptoms not responsive to other therapy. More safety and effectiveness data are needed to define the place of these two agents in therapy.

For severe cases of calcium channel blocker toxicity refractory to conventional therapy, an infusion of high-dose insulin with supplemental dextrose and potassium to produce a state of hyperinsulinemia and euglycemia should be considered.49,79–83 Case reports suggest that an IV bolus of regular insulin (0.5 to 1 U/kg) with 50 mL dextrose 50% (0.25 mg/kg for children) followed by a continuous infusion of regular insulin (0.5 to 1 U/kg/h) may improve myocardial contractility. The effect of insulin is presently unclear, but it may improve myocardial metabolism that is adversely affected by calcium channel blocker overdoses, such as decreased cellular uptake of glucose and free fatty acids and a shift from fatty acid oxidation to carbohydrate metabolism.79,81,83 This insulin regimen is titrated to improvement in systolic blood pressure over 100 mm Hg and heart rate over 50 beats/min. Serum glucose concentrations should be monitored closely to maintain euglycemia. Patients with serum potassium concentrations less than 2.5 mEq/L (2.5 mmol/L) may need supplemental potassium (see Chap. 36). The insulin infusion rate can be reduced gradually as signs of toxicity resolve. IV sodium bicarbonate may be also necessary to establish acid–base balance and correct the metabolic acidosis that is common with serious calcium channel blocker overdoses.

If the bradycardia and hypotension are refractory to the foregoing therapy, a bolus infusion of glucagon (0.05 to 0.20 mg/kg, initial adult dose is 3 to 5 mg over 1 to 2 min) should be considered. Benefit typically is observed within 5 minutes of administration and can be sustained with a continuous IV infusion (0.05 to 0.1 mg/kg/h) titrated to clinical response.49,51 Glucagon possesses chronotropic and inotropic effects in part by stimulating adenylatecyclase and increasing cyclic adenosine monophosphate, which may promote intracellular entry of calcium through calcium channels. It thereby may improve hypotension and bradycardia.49 Vomiting is not uncommon with these large doses of glucagon, and the airway should be protected to prevent pulmonary aspiration. Hyperglycemia may occur or be exacerbated in those patients receiving glucagon therapy.

Therapies with glucagon and insulin are based on animal studies and case reports; clinical trials demonstrating effectiveness have not been performed to date.49,79–83

Several lifesaving options may be warranted for patients with cardiogenic shock that is refractory to conventional therapy, such as electrical cardiac pacing, intraaortic balloon counterpulsation or cardiopulmonary bypass. Animal studies and case reports suggest that the emergent infusion of lipid emulsion, for example, Intralipid, can dramatically “rescue” patients with severe cardiac toxicity from lipid soluble drugs such as calcium channel blockers.50,51 Some current hypotheses on the actions responsible for this effect include serving as a “lipid sink” for lipophilic drugs and as an energy substrate for the myocardium. There are several dosing schemes that involve single or multiple boluses followed by a continuous infusion, but none are well studied. Further evidence is needed to define its place in therapy.

Measures to enhance elimination from the bloodstream by hemodialysis or multiple-dose activated charcoal have not been shown to be effective and are not indicated for calcium channel blocker poisoning.50,80,82,86

Monitoring and Prevention
Regular monitoring of vital signs and ECG is essential in suspected calcium channel blocker poisoning. Determinations of serum electrolytes, serum glucose, arterial blood gases, urine output, and renal function are indicated to assess and monitor symptomatic patients. If serious toxicity is likely to develop, overt symptoms will manifest within 6 hours of ingestion.84 For ingestions of sustained-release products in toxic doses, observation for 24 hours in a critical care unit may be prudent because the onset of symptoms may be slow.
**General**
- Gastrointestinal symptoms shortly after ingestion with possible rapid progression to shock and coma

**Symptoms**
- Vomiting, abdominal pain, and diarrhea within 1 to 6 hours
- Lethargy, coma, seizures, bloody vomiting, bloody diarrhea, and shock within 6 to 24 hours

**Signs**
- Hypotension and tachycardia within 6 to 24 hours
- Liver dysfunction and failure possible in 2 to 5 days

**Laboratory Tests**
- Toxic serum iron concentrations greater than 500 mcg/dL (90 μmol/L)
- Altered arterial blood gases and serum electrolytes associated with a high anion gap metabolic acidosis within 3 to 24 hours
- Elevated BUN, serum creatinine, AST, ALT, and INR within 1 to 2 days

**Other Diagnostic Tests**
- Guaiac test of stools for the presence of blood
- Abdominal radiograph to detect solid iron tablets in gastrointestinal tract

**Iron**

**Clinical Presentation**

9 In the first few hours after ingestion of toxic amounts of iron, symptoms of gastrointestinal irritation (e.g., nausea, vomiting, and diarrhea) are common (see the Clinical Presentation of Acute Iron Poisoning box). In certain severe cases, acidosis and shock can become manifest within 6 hours of ingestion. Some have observed a quiescent phase between 6 and 48 hours after ingestion when symptoms improve or abate, but this phenomenon is poorly characterized.97 Continued gastrointestinal symptoms, poor perfusion, and oliguria should suggest the development of severe toxicity, with other effects still to become manifest. Generally, within 24 to 36 hours of the ingestion, central nervous system involvement with coma and seizures; hepatic injury characterized by jaundice, increased INR, increased bilirubin, and hypoglycemia; cardiovascular shock; and acidosis also develop.97,98 Adult respiratory distress syndrome (ARDS) may develop in patients with severe cardiovascular shock and further compromise recovery.99 Coagulopathy with decreased thrombin formation is one of the early direct effects of excessive iron concentrations, and later disturbances of coagulation (after 24 to 48 hours of ingestion) are a consequence of hepatotoxicity.90 Mucosal injury, an iron-rich circulation, or deferroxamine therapy may promote sepsis with *Yersinia enterocolitica* during iron overdose; other bacteria or viruses also may cause sepsis.97 Two to 4 weeks after the exposure, a small percentage of patients experience persistent vomiting from gastric outlet obstruction as the result of pyloric and duodenal stenosis from the earlier gastric mucosal injury. Autopsy findings in children indicate prominent iron deposition in intestinal mucosa and portal necrosis of the liver that correlate with the primary symptoms of serious iron poisoning.91

**Mechanism of Toxicity**

The toxicity of acute iron poisoning includes local effects on the gastrointestinal mucosa and systemic effects induced by excessive iron in the body.97,99 Iron is irritating to the gastric and duodenal mucosa, which may result in hemorrhage and occasional perforations. Once absorbed, iron is taken up by tissues, particularly the liver, and acts as a mitochondrial poison. It occasionally causes hepatic injury. Iron may inhibit aerobic glycolysis and perturb the electron transport system. Further, iron may shunt electrons away from the electron transport system, thereby reducing the efficiency of oxidative phosphorylation. These biochemical factors, along with the cardiovascular effects of iron, lead to metabolic acidosis. The pathogenesis of shock is not well understood but may include the development of hypovolemia and lactic acidosis, release of endogenous vasodilators, and the direct vasodepressant effects of iron and ferritin on the circulation (eFig. 10-6).

**Causative Agents**

Iron poisoning results from the ingestion and absorption of excessive amounts of iron from iron tablets, multiple vitamins with iron, and prenatal vitamins. Different iron salts and formulations contain varying amounts of elemental iron (see Chaps. 29 and 80). Generally, children’s chewable vitamins are less likely to produce systemic iron poisoning in part because of their lower iron content.92

**Incidence**

Acute iron poisoning can produce death in children and adults.91,92 The 2010 AAPCC-NPDS report documented 3,931 single-agent iron ingestions, with 3.0% of the exposures exhibiting moderate to severe toxicity. Children younger than 6 years accounted for 58% of the exposures. Multiple vitamins with iron were involved in 16,309 cases, with 0.3% exhibiting moderate-severe toxicity. One death was associated with an iron product during this year.3

**Risk Assessment**

A patient who exhibits lethargy, paleness, persistent or bloody emesis, or diarrhea should be immediately referred to an emergency department.92 Ingestion of 10 to 20 mg/kg elemental iron usually elicits mild gastrointestinal symptoms. Ingestion of 20 to 40 mg/kg is not likely to produce systemic toxicity, and typically these patients can be conservatively managed at home. Ingestions of 40 mg/kg or more of elemental iron are often associated with serious
iron-binding capacity is unreliable, insensitive, and has little relationship to acute toxicity. Management of Toxicity

Many patients vomit spontaneously, and no iron-specific prehospital care is indicated. At the emergency department, gastric lavage with normal saline can be considered. Lavage with normal saline may remove iron tablet fragments and dissolved iron, but because the lumen of the tube is often smaller than some whole tablets, effective removal is unlikely. Activated charcoal administration is not warranted routinely because it adsorbs iron poorly. If abdominal radiographs reveal a large number of iron tablets, whole-bowel irrigation with polyethylene glycol electrolyte solution typically is necessary. Although removal by gastrostomy has been used in a few cases, early and aggressive decontamination and evacuation of the gastrointestinal tract usually will be adequate to minimize iron absorption and thereby reduce the risk of systemic toxicity. Lavage solutions of phosphate or deferoxamine have been proposed previously as a means to render iron insoluble, but they were found ineffective and dangerous.

Deferoxamine is a highly selective chelator of iron that theoretically binds ferric (Fe$^{3+}$) iron in a 1:1 molar ratio (100 mg deferoxamine to 8.5 mg ferric iron) that is more stable than the binding of iron to transferrin. Deferoxamine removes excess iron from the circulation and some iron from transferrin by chelating ferric complexes in equilibrium with transferrin. The resulting iron—deferoxamine complex, ferrioxamine, is then excreted in the urine. Its action on intracellular iron is unclear, but it may have a protective intracellular effect or may chelate extramitochondrial iron. The presence of discolored urine as a therapeutic end point has been challenged because it is not sensitive and is difficult to detect.

Psychiatric as well as medical intervention is indicated for adults and adolescents who intentionally ingest iron as a suicide gesture. An abdominal radiograph may help to confirm the ingestion of iron tablets and indicate the need for aggressive gastrointestinal evacuation with whole-bowel irrigation. An abdominal radiograph is most useful within 2 hours of ingestion. The visualization of radiopaque iron tablets is confounded by the presence of other hard-coated tablets and some extended-release tablets that also are radiopaque. Furthermore, the radiopacity of iron tablets diminishes as the tablets disintegrate, and chewable and liquid formulations typically are not radiopaque.

Iron poisoning causes vomiting and diarrhea, but these symptoms are poor indicators of later serious toxicity. The presence of a combination of findings such as coma, radiopacities, leukocytosis, and increased anion gap, however, is associated with dangerously high serum concentrations greater than 500 mcg/dL (90 μmol/L). The presence of single signs and symptoms, such as vomiting, leukocytosis, or hyperglycemia, is not a reliable indicator of the severity of iron poisoning in adults or children.

Once iron is absorbed, it is eliminated only as the result of blood loss or sloughing of the intestinal and epidermal cells. Thus, iron kinetics essentially represent a closed system with multiple compartments. The serum iron concentration represents a small fraction of the total-body content of iron and is at its greatest concentration in the postabsorptive and distributive phases, typically 2 to 10 hours after ingestion. Serum iron concentrations greater than 500 mcg/dL (90 μmol/L) have been associated with severe toxicity, whereas concentrations less than 350 mcg/dL (62.7 μmol/L) typically are not associated with severe toxicity; however, exceptions have been reported for both thresholds.

Serious toxicity is best determined by assessing the development of gross gastrointestinal bleeding, metabolic acidosis, shock, and coma regardless of the serum iron concentration. The serum iron concentration serves as a guide for further assessment and treatment options. The ratio of the serum iron concentration to the total iron-binding capacity is unreliable, insensitive, and has little relationship to acute toxicity.

Management of Toxicity

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Patients with systemic symptoms (e.g., shock, coma, or gross gastrointestinal bleeding or metabolic acidosis) should receive parenteral deferoxamine as soon as possible. If the serum iron concentration is greater than 500 mcg/dL (90 μmol/L), deferoxamine is also indicated because serious systemic toxicity is likely. Its use is less clear in patients with serum iron concentrations in the range from 350 to 500 mcg/dL (62.7 to 90 μmol/L) because many of these patients do not develop systemic symptoms.

Clinical Controversy...

There is little evidence on how much deferoxamine should be given for iron poisoning or for how long it should be administered. The dosage regimen should balance the benefits of increased iron removal in patients with exceedingly high serum iron concentrations versus the risk of developing ARDS when therapy lasts for more than 1 to 3 days.

An initial IV infusion of 15 mg/kg/h generally is indicated, although some have used up to 30 mg/kg/h for life-threatening cases. In these situations, the dose must be titrated carefully to minimize deferoxamine-induced hypotension. The rapid IV infusion of deferoxamine (greater than 15 mg/kg/h) has been associated with tachycardia, hypotension, shock, generalized erythema, and urticaria. Anaphylaxis has been reported rarely. The use of deferoxamine for more than 24 hours at doses used for treatment of acute poisoning has been associated with exacerbation or development of ARDS. Although the manufacturer states that the total dose in 24 hours should not exceed 6 g, the basis for this recommendation is unclear, and daily doses as high as 37.1 g have been administered without incident. Good hydration and urine output may moderate some of the secondary physiologic effects of iron toxicity and ensure urinary elimination of ferrioxamine. In the patient who develops renal failure, hemodialysis or hemofiltration does not remove excess iron but will remove ferrioxamine.

The desired end point for deferoxamine therapy is not clear. Some have suggested that deferoxamine therapy should cease when the serum iron concentration falls below 150 mcg/dL (26.9 μmol/L). The decline of serum iron concentrations, however, may not account for the potential cellular action of deferoxamine irrespective of its effect on iron elimination. The cessation of orange-red urine production that is indicative of ferrioxamine excretion is not a reliable sign because many individuals cannot distinguish its presence in the urine. Considering these shortcomings, deferoxamine therapy should be continued for 12 hours after the patient is asymptomatic and the urine returns to normal color or until the serum iron concentration falls below 350 mcg/dL (62.7 μmol/L) and approaches 150 mcg/dL (26.9 μmol/L).

Monitoring and Prevention

Once a poisoning has occurred, acid–base balance (anion gap and arterial blood gases), fluid and electrolyte balance, and perfusion should be monitored. Other indicators of organ toxicity, such as ALT, AST, bilirubin, INR, serum glucose and creatinine concentrations, as well as markers of physiologic stress or infection such as leukocytosis, also should be monitored.

Iron poisoning often is not recognized as a potentially serious problem by parents or victims until symptoms develop; thus, valuable time to institute treatment is lost. Parents should be made aware of the potential risks and asked to observe basic poison prevention measures. Some hard-coated iron tablets resemble candy-coated chocolates and are confused easily by children. Iron tablets are typically packaged in child-resistant containers, often in blister packs.

Opioids

Clinical Presentation

Acute opioid poisoning can produce life-threatening effects that typically include respiratory depression and coma that can lead to death. Virtually all opioids produce these symptoms and some agents have additional toxic effects (see the Clinical Presentation of Acute Opioid Poisoning box). The time of onset and severity of symptoms depend on the route of exposure, potency of the agent, and total dose received, concurrent drugs, coexisting conditions and pharmacogenetic characteristics. Toxic signs and symptoms develop most rapidly after IV injection (within minutes) or inhalation of fumes (heroin), followed by inhalation from snorting particles, powder, or solutions. Immediate-release tablets typically have an onset of toxicity within 1 to 4 hours, followed by sustained-release tablets and skin absorption from dermal patches that have the slowest onset. Severe symptoms can occur from absorption by any route. Death typically is caused by respiratory failure, the metabolic consequences of hypoxia, noncardiogenic pulmonary edema and, in some cases, pulmonary aspiration of gastric contents after vomiting. Opioid poisoning may be complicated by hypothermia, rhabdomyolysis, and resultant acute renal failure. Seizures, arrhythmias, concurrent exposure to and toxicity from other medications and illicit drugs, and the presence of adulterants and contaminants may complicate the person’s presentation. Finally, hepatotoxicity from the conjugation of acetaminophen-containing medications, and infectious diseases from IV drug use may occur.

Mechanism of Toxicity

Action at the μ receptor is primarily responsible for many of the life-threatening effects of opioids, such as respiratory depression and sedation, and all opioid analgesics appear to have some activity at this receptor. Meperidine’s metabolite, normeperidine, produces CNS excitation that leads to delirium, tremor, and seizures. Meperidine also blocks the reuptake of serotonin and may produce serotonin syndrome particularly in patients taking monoamine oxidase inhibitors. Methadone acts on the myocardium to block potassium efflux leading to arrhythmias, syncope, and sudden death. Tapentadol and tramadol block reuptake of norepinephrine and serotonin, respectively, and are associated with seizures at high doses.

Causative Agents

Many drugs that are naturally found in opium (morphine, codeine, tincture of opium, i.e., opiates), synthetically synthesized (e.g., fentanyl, methadone, meperidine) as well as semisynthetic derivatives of opiates (e.g., hydromorphone, hydrocodone, oxycodone) are available in the United States for the management of moderate to severe pain (see Chap. 44). Heroin, a schedule I controlled substance and illicit drug, produces a greater degree of euphoria than many other opioids and also produces the same life-threatening effects with added complications of adulterants and infections from IV drug use. Chemical analogs of legitimate opioids such as fentanyl are produced by clandestine laboratories. Illicit analogs often have much greater potency unbeknownst to the user and thus increase the risk of a lethal overdose.

Incidence

Acute poisoning and overdose from opioid analgesics have become one of the most frequent causes of drug-related death in the United States with annual rates exceeding those for cocaine and heroin combined. Methadone accounts for one-third of deaths from opioid analgesics. The number of fatal poisonings involving opioid analgesics more than tripled from 4,000 to 13,800 deaths from 1999 to 2006 based on death certificates. Opioid analgesics were involved in almost 40% of all poisoning deaths. Poisoning from opioids occurs in all age groups from neonates through intrauterine exposure.
Acute Opioid Poisoning

General
- Life-threatening respiratory depression (12 or less breaths per minute) within minutes to hours of use depending upon the drug, route of administration, product formulation and coexisting conditions; often delayed by 8 or more hours with ingestion of a sustained-release product or in preschool-aged children

Symptoms
- Lethargy progressing to coma
- Flaccid extremities
- Seizures associated with meperidine and tramadol
- Acute muscular rigidity with rapid injection of fentanyl
- Deafness with some overdoses

Signs
- Depressed respiratory depth and rate leading to apnea
- Pinpoint pupils (uncommon with meperidine, tramadol, severe hypoxia)
- Unresponsiveness and depressed reflexes
- Mild hypotension and bradycardia, worsening with increasing hypoxia
- Absent bowel sounds, gastrointestinal hypomotility
- Hypothermia if exposed to cold conditions
- Frothy pink sputum, end-inspiratory crackles on auscultation, and shortness of breath

Laboratory Tests
- Altered arterial blood gases (acidosis) and serum electrolytes in response to hypoxia
- Serum glucose concentration
- Determine serum acetaminophen concentration no earlier than 4 hours after ingestion and alanine aminotransferase (ALT) in case an opioid-acetaminophen combination product ingested

Other Diagnostic Tests
- Pulse oximetry and ECG with continuous monitoring
- Monitor for complications of rhabdomyolysis (creatinine, electrolytes) and subsequent acute renal failure (blood urea nitrogen [BUN], creatinine) if patient has been lying immobile for several hours
- Evaluate for infectious diseases if IV drug use, and local- or systemic-infection suspected

Risk Assessment
A patient’s symptoms, presence of drugs at the scene, and availability of opioids can be helpful indicators of risk. The triad of depressed respirations (12 or less breaths per minute), coma, and pinpoint pupils (miosis) with relatively acute onset should strongly suggest opioid poisoning and warrants a therapeutic trial of the antidote naloxone. Measurement of opioid serum concentrations are not available in clinical laboratories and are not necessary to guide appropriate therapy. Therapy should not be delayed pending laboratory confirmation of an opioid in a drug screen because many opioids are not detected by routine drug screens (see eTable 10-6) and critical time will be lost awaiting results that will not guide therapy.

Management of Toxicity
The foundation of treatment of opioid poisoning is adequate respiratory support, and the administration of the opioid antagonist, naloxone. Symptomatic cases of opioid overdoses should be transported to an emergency department for evaluation and treatment. There is no conventional prehospital care except for cardiopulmonary resuscitation; however, naloxone can be administered at the scene by trained personnel. If the opioid has been ingested within 1 hour, the administration of activated charcoal should be considered. Based on a history of an exposure, presence of typical symptoms and the response to naloxone, an acute opioid poisoning should be recognizable in most cases. If a patient presents with coma of unknown origin, a combination of naloxone, dextrose, and thiamine should be considered to rule out opioids, hypoglycemia, and Wernicke encephalopathy associated with alcoholism. Whole bowel irrigation should be considered for ingestions of extended-release formulations, packets of drugs such as heroin intended for smuggling, and fentanyl dermal patches once the patient is stabilized.

Naloxone is a competitive opioid receptor antagonist that acts on known opioid receptors to reverse the toxic effects of opioids and can be life-saving. The goal of therapy is to restore adequate spontaneous respirations. It is typically administered by rapid IV injection, acts within 2 minutes and has a short duration of 20 to 90 minutes. Intramuscular, intraosseous, intralingual injection and intranasal and intratracheal instillation are also effective if the IV route is not immediately available, but oral administration is ineffective. Naloxone for injection is available in...
concentrations of 0.02, 0.4, and 1.0 mg/mL. The effect of naloxone may not be evident in several circumstances (see eTable 10-13) and the initial dose may not be sufficient.

Clinical Controversy...

The initial dose of naloxone for opioid overdose varies. When naloxone was first introduced the initial dose was 0.4 mg, but observations of inadequate response in some patients led to the dose being changed to 0.4 to 2.0 mg. Currently, initial doses of 0.04 to 0.05 mg are proposed by some clinicians to minimize the risks of abrupt withdrawal associated with adverse effects.

The dosing of naloxone should consider a balance of reversing toxic effects without causing abrupt withdrawal symptoms, which can produce agitation, hypertension, tachycardia, emesis with the risk of aspiration, and harm to the patient and caregivers from disorientation.102 Dosage regimens have evolved from clinical experience and differ from the recommended starting dose of 0.4 to 2.0 mg in the package insert. A typical approach involves administering 0.04 to 0.05 mg (0.01 mg/kg in a young child) as the first dose. If there is no improvement in respirations within 2 minutes, 0.5 mg is administered to adults and children. At 2-minute intervals the dose can be increased to 2, 4, 10, and 15 mg until adequate respirations are achieved.49,103 If there is no response at the 10 to 15 mg dose, confounding or other causes of the patient’s condition should be considered. Other regimens with similar progressive increases in dose have been proposed. Overdoses with buprenorphine, fentanyl, and methadone often require doses in the upper range for a response.102 The duration of naloxone’s effect is generally shorter than many opioids, particularly for methadone and extended-release formulations, and requires close monitoring and repeated administration. If repeated doses of naloxone are required for maintenance of adequate respiration, a continuous infusion should be considered that is approximately two-thirds of the single-dose, that produces a response given at an hourly rate.49,102

The adverse effects of large doses of naloxone are rare, minimal and insignificant and it can be given safely to persons with acute poisonings of any cause. Rare isolated reports of hypertension, hyperventilation, and tachycardia in opioid-dependent patients may be related to the release of catecholamines and other mediators in response to stress from abrupt withdrawal.8,102 The progressive escalation of naloxone doses to prevent abrupt withdrawal is partially based on its potential association with acute lung injury that may produce or exacerbate pulmonary edema.49,100

Spontaneous or naloxone-induced withdrawal in neonates born with opioid dependence requires special considerations.108 The management of chronic opioid abuse as a substance abuse disorder is discussed in Chapter 48.

Monitoring and Prevention

Poisoned patients may require monitoring of vital signs, measurement of ventilatory adequacy such as blood gases and pulse oximetry, and chest radiographs to assess the degree of pulmonary edema or development of aspiration pneumonitis. Patients should also be monitored for the potential development of complications such as rhabdomyolysis, acute renal failure, or seizures. Determination of a serum acetaminophen concentration is warranted to rule out the coincidental ingestion of acetaminophen with an opioid-acetaminophen combination product such as Vicodin, Percocet, or Lortab.101–103

The rising number of deaths from prescription opioid analgesics has been categorized as an epidemic by the Centers for Disease Control and Prevention. Multiple strategies have been implemented and proposed to prevent opioid-related deaths.105 A prescription monitoring database has been implemented in nearly every state in order to identify individuals using frequent prescriptions of controlled substances from multiple prescribers (“doctor shopping”) or fraudulent prescriptions.111 Enforcement and implementation of laws on “doctor shopping,” indiscriminately prescribing of controlled substances without a medical evaluation by “pill mills,” and efforts to improve medical practice through educational programs and guidelines for the treatment of chronic pain are underway. The FDA has developed a Risk Evaluation and Mitigation Strategy for long-acting and extended-release opioids that involves prescriber training on appropriate prescribing practices.122 “Drug take-back” events to dispose of unneeded medications have been conducted in communities nationwide.7 Reducing the availability of medications, particularly opioids, in the home reduces the opportunity for stealing and diverting medications that can lead to overdoses and drug abuse. Several cities are providing naloxone for administration by trained bystanders in the community to opioid-dependent individuals and heroin abusers at risk for life-threatening overdose in order to prevent death before an ambulance arrives.113 Education of the general public on the risks of opioid poisoning and appropriate use and storage of opioid analgesics should be a routine practice in the prescribing and dispensing of opioid analgesics.

**Tricyclic Antidepressants**

**Clinical Presentation**

Patients may deteriorate rapidly and progress from no symptoms to life-threatening cardiotoxicity or seizures within 1 hour.114,115 Major symptoms of tricyclic antidepressant overdose typically are manifest within 6 hours of ingestion.114 The principal effects of tricyclic antidepressant poisoning involve the cardiovascular system and the central nervous system and can result in arrhythmias, hypotension, coma, and seizures (see the Clinical Presentation of Tricyclic Antidepressant Poisoning box).

Prolongation of the QRS complex on ECG indicating nonspecific intraventricular conduction delay or bundle-branch block is the most distinctive feature of tricyclic antidepressant overdose.116 Sinus tachycardia with rates typically less than 160 beats/min is common and does not cause serious hemodynamic changes in most patients. Ventricular tachycardia is a common ventricular arrhythmia, but it may be difficult to distinguish from sinus tachycardia in the presence of QRS complex prolongation and the apparent absence of P waves. It often occurs in patients with marked QRS complex prolongation or hypotension and may be precipitated by seizures.115,116 High rates of mortality are associated with ventricular tachycardia; ventricular fibrillation is the terminal rhythm. Torsade de points is observed infrequently with tricyclic antidepressant poisoning. With massive
tricyclic antidepressant overdose, slow ventricular rhythms may be observed. Hypotension is a significant factor in most cases of tricyclic antidepressant poisoning. Refractory hypotension leading to death is due to vasodilatation and impaired cardiac contractility. Other factors, such as extreme heart rates, intravascular volume depletion, hypoxia, hyperthermia, seizures, and acidosis, may contribute to refractory hypotension.

Coma usually is present in patients with tricyclic antidepressant poisoning and may or may not be associated with QRS complex prolongation. In severe cases, coma is sufficient to depress respirations. Delirium, manifest as agitation or disorientation, may occur early in the course of severe poisoning or with poisoning of moderate severity. Seizures occur often within 2 hours of ingestion and usually are generalized, single, and brief. Seizures may result in acidosis, hyperthermia, or rhabdomyolysis, and 10% to 20% of patients may abruptly develop cardiovascular deterioration. Myoclonus also may be observed with tricyclic antidepressant overdose. Hyperthermia often results from seizures and myoclonic activity in the presence of decreased sweating and is associated with a high incidence of neurologic sequelae and mortality. Anticholinergic symptoms, such as urinary retention, ileus, and dry mucous membranes, often are observed with tricyclic antidepressant overdose. Pupil size is variable.

Tricyclic antidepressant overdose can be staged based on the patient’s symptoms and recovery time. In stage 1, patients are responsive to pain, have sinus tachycardia, and recover within 24 hours. In stage 2, seizures, coma, and cardiac conduction problems are evident; respiratory support typically is needed. Patients recover within 24 to 48 hours of ingestion. Stage 3 is characterized by the features of stage 2 with the addition of respiratory arrest, hypotension, ventricular dysrhythmias, and asystole, which may occur within 1 to 24 hours of ingestion. Typically symptoms appear within 2 hours, and more serious effects usually are not seen until 6 hours post-ingestion; rarely rapid clinical deterioration is observed within 1 to 2 hours.

Amoxapine, bupropion, and maprotiline are atypical antidepressants associated with a higher incidence of seizures on overdose; amoxapine produces minimal cardiotoxicity, but venlafaxine has been associated with greater mortality. The selective serotonin reuptake inhibitors (SSRIs) generally produce a common toxicity profile on overdose despite their structural and pharmacologic distinctions. The SSRIs inhibit presynaptic neuronal uptake of serotonin, resulting in increased synaptic serotonin levels. When ingested in excess, SSRIs typically produce nausea, vomiting, diarrhea, tremor, and decreased level of consciousness. Tachycardia, seizures, and death are infrequent. Serotonin syndrome is a condition in which certain drugs (e.g., meperidine, nonselective monoamine oxidase inhibitors, dextromethorphan, linezolid, tricyclic antidepressants, SSRIs) acutely increase serotonin levels. This syndrome develops within minutes to hours (typically within 6 hours) after starting a medication, increasing the dose of a medication, or overdosing. It is characterized by a collection of neurobehavioral (e.g., confusion, agitation, coma, seizures), autonomic (e.g., hyperthermia, diaphoresis, tachycardia, hypertension), and neuromuscular (e.g., myoclonus, rigidity, tremor, ataxia, shivering, nystagmus) signs and symptoms. Most cases are mild and resolve spontaneously within 24 to 72 hours. Cardiac arrest, coma, and multiorgan system failure have been reported as consequences of serotonin syndrome. Recognition of the syndrome is based on a high index of suspicion and identification of risk factors.

**Mechanism of Toxicity**

Many of the toxic effects of tricyclic antidepressants are associated with an exaggeration of their pharmacologic action. The tricyclic antidepressants, such as type 1a antiarrhythmic drugs, inhibit the fast sodium channel so that phase 0 depolarization of the myocardium is slowed. This action leads to QRS complex prolongation, atrioventricular block, ventricular tachycardia, and decreased myocardial contractility. Tricyclic antidepressants also block vascular \(\alpha\)-adrenergic receptors, resulting in vasodilatation, which contributes to hypotension. Sinus tachycardia is related to the inhibition of norepinephrine reuptake and anticholinergic effects. Other anticholinergic effects include urinary retention, ileus, dry mucous membranes, and impaired sweating. Inhibition of norepinephrine reuptake also may account for the early, transient, and self-limiting elevation of
blood pressure observed in some patients. The central nervous system toxicity of tricyclic antidepressants is not well understood.

Causative Agents

Tricyclic antidepressants and SSRIs are used to treat a variety of behavioral conditions (see Chaps. 51 to 54). The tricyclic antidepressants include drugs such as amitriptyline, desipramine, doxepin, imipramine, and nortriptyline. Atypical agents include amoxapine, bupropion, maprotiline, nefazodone, trazodone, and venlafaxine. The SSRIs include fluoxetine, paroxetine, and sertraline. The tricyclic antidepressants are generally highly protein bound, exhibit a large volume of distribution, and possess elimination half-lives of 8 to 24 hours or more. Virtually none of the drug is eliminated unchanged in the urine. Metabolism of the parent drug produces active metabolites in most cases (e.g., amitriptyline to nortriptyline) that may contribute to toxicity after the first 12 to 24 hours. Genetic polymorphism at CYP2D6 may lead to slower recovery in patients who are slow hydroxylators.

Incidence

The 2010 AAPCC-NPDS report documented 5,429 patients with single-agent exposures to tricyclic antidepressants; 47% of these cases were considered to be intentional overdoses. A total of 349 people experienced a major effect, and 21 people died.9 The SSRIs accounted for 19,562 nonfatal single-agent exposures with 97 people exhibiting severe toxicity and six deaths were reported this year.

Risk Assessment

Referral to an emergency department is warranted for ingestions less than 5 mg/kg of amitriptyline, clomipramine, doxepin, and imipramine; less than 2.5 mg/kg of desipramine, nortriptyline, and trimipramine; and less than 1 mg/kg of protriptyline.110 Patients who exhibit weakness, drowsiness, dizziness, tremulousness, and palpitations after an ingestion of a tricyclic antidepressant and patients suspected of a suicide gesture or those who are suspected victims of malicious poisoning should be promptly referred to an emergency department. A QRS complex greater than 160 milliseconds or progressive prolongation of the QRS complex is an indicator of toxicity such as seizures or ventricular arrhythmias and often precedes the onset of serious symptoms.114,116,117 The QRS complex duration should not be used as the sole indicator of risk for tricyclic antidepressant poisoning.113 A drug screen for tricyclic antidepressants can only confirm the presence of the drug and not the potential risk for the development of toxicity.

Patients with coexisting cardiovascular and pulmonary conditions (e.g., ARDS, pulmonary infection, pulmonary aspiration) may be more susceptible to the toxic effects or complications of tricyclic antidepressant poisoning.11 Tricyclic antidepressants interact with other central nervous system depressant drugs, which together may lead to increased central nervous system and respiratory depression.

Consult a poison control center for current recommendations for doses of SSRIs that would warrant referral to an emergency department.114 The risk of serotonin syndrome may be increased shortly after dosage increases of SSRIs or when drug interactions increase serotonin activity.106 Concomitant or proximal use of SSRIs, tricyclic antidepressants, or nonselective monoamine oxidase inhibitors may cause serotonin syndrome. Furthermore, the addition of certain drugs, such as trypotphan, dextromethorphan, cocaine, or sympathomimetics, to SSRI therapy may increase the risk of developing serotonin syndrome.

Management of Toxicity

Once the ingestion of an overdose of tricyclic antidepressant is suspected or for any intentional ingestions, medical evaluation and treatment should be sought promptly. If the patient is symptomatic, it may be prudent to call for an ambulance because of the rapid progression of some cases. At the emergency department, the patient should be monitored carefully, have vital signs assessed regularly, and have an IV line started. Supportive and symptomatic care includes oxygen, IV fluids, and other treatments as indicated. Prompt administration of activated charcoal may decrease the absorption of any remaining tricyclic antidepressant. It also may be useful beyond the first hour of ingestion because of decreased gastrointestinal motility from the anticholinergic action of tricyclic antidepressants. Gastric lavage may be considered if the time of the ingestion is unknown or if ingestion occurred within the past 1 to 2 hours. Some practitioners avoid gastric lavage altogether.119 Multiple-dose activated charcoal has been shown to increase the elimination of some tricyclic antidepressants in human volunteers19 and has been used in poisoned patients.115,116 It may be most useful during the first 12 hours of ingestion while the drug is distributing to tissue compartments. Because the tricyclic antidepressants possess a large volume of distribution, little of the drug is present in the bloodstream; thus hemodialysis is not useful for the extracorporeal removal of tricyclic antidepressants.

Sodium bicarbonate IV is part of the first-line treatment of QRS complex prolongation, ventricular arrhythmias, and hypotension caused by tricyclic antidepressant overdose.48,115,125 Typically 1 to 2 mEq/kg (1 to 2 mmol/kg) sodium bicarbonate (1 mEq/mL [1 mmol/mL]) is administered as a bolus infusion (usually a 50-mEq [50-mmol] ampule in an adult) and repeated as necessary to achieve an arterial blood pH of 7.50 to 7.55 or abatement of toxicity.114,115 A therapeutic effect usually is observed within minutes. Excessive use of sodium bicarbonate may produce dangerous alkalemia, which by itself is associated with ventricular arrhythmias.115 The mechanism of action of sodium bicarbonate is unclear. Although some practitioners have proposed that sodium bicarbonate increases protein binding of tricyclic antidepressants, this theory has been discounted. Sodium may play an important role by stabilizing tricyclic antidepressant—induced changes to the sodium gradient of the myocardium.115,126 Regardless of its action, it is effective and generally safe.

Hyperventilation to produce a mild state of respiratory alkalosis has been used to treat some dysrhythmias, but it is used less widely than sodium bicarbonate.114,115

Clinical Controversy...

Because IV sodium bicarbonate is used as therapy for certain arrhythmias and hypotension caused by tricyclic antidepressant poisoning, some practitioners have advocated its prophylactic use. Little evidence indicates which patients would benefit from prophylactic use. The risks of potentially producing alkalosis in a patient who is not seriously toxic should be considered.

Treatment of the complications of tricyclic antidepressant poisoning is outlined in eTable 10-14 and includes pharmacologic and nonpharmacologic approaches.114,115 Several agents generally should be avoided in the treatment of tricyclic antidepressant poisoning. Other drugs that inhibit the fast sodium channel, such as procainamide and quinidine, are contraindicated. Phenytoin has limited usefulness in treating tricyclic antidepressant seizures and has questionable efficacy in managing cardio toxicity.114 Physostigmine was used in the past as a treatment of tricyclic antidepressant-induced cardiotoxicity and seizures because it antagonizes anticholinergic actions. However, physostigmine has been associated with bradycardia and asystole115,127 and has been avoided in the contemporary treatment of tricyclic antidepressant cardiovascular or central nervous system toxicity. Flumazenil is used to antagonize the effects...
Treatment Options for Acute Tricyclic Antidepressant Toxicity

**Toxicity** | **Treatment**
---|---
**Cardiovascular**
QRS prolongation, if progressive or greater than 0.16 s | IV sodium bicarbonate to a blood pH of 7.5 even in the absence of acidosis; generally avoid other antiarrhythmic drugs
Hypotension | Intravascular fluids; IV sodium bicarbonate; consider norepinephrine or dopamine
Ventricular tachycardia | IV sodium bicarbonate; lidocaine, overdrive pacing
Ventricular bradycardia | Epinephrine drip; cardiac pacemaker
Atrialventricular block type II, second or third degree | Cardiac pacemaker
Cardiac arrest | Advanced cardiac life support, prolonged resuscitation may be needed
**Neurologic**
Seizures, agitation | Benzodiazepines; neuromuscular blockade may be needed if hyperthermia or acidosis is present
Coma | Endotracheal intubation; mechanical ventilation if needed
**Homeostatic**
Hyperthermia | Treat seizures and agitation; consider cooling blanket, ice water lavage, and cool water mist of body
Acidosis | IV sodium bicarbonate

Monitoring and Prevention

Measurement of vital signs, electrolytes, and blood urea nitrogen (BUN) and a urinalysis are indicated for initial assessment. Patients should be monitored continuously by ECG, and a 12-lead ECG should be obtained if QRS complex prolongation is noted. If patients start to show signs of cardiotoxicity, arterial blood gases should be determined. Patients who show no signs of toxicity during 6 hours of observation and have received activated charcoal promptly require no further medical monitoring. Psychiatric evaluation is indicated for adolescents and adults. When signs of tricyclic antidepressant toxicity are present in a patient, cardiac monitoring generally is recommended for at least 24 hours after the patient is without findings.

Prevention of tricyclic antidepressant poisoning poses unique challenges. Many of the dosage forms are small in size, and adults and children can consume large numbers easily. In the course of treating depression, several antidepressant agents may be tried to achieve results. By not discarding unused medicines, a storehouse of potentially deadly drugs may be available for children to discover or for the despondent patient to use to attempt suicide. Although patients take tricyclic antidepressants for therapeutic relief of depression, they are also a group likely to contemplate suicide with tricyclic antidepressants. Strategies that would limit the amount of tricyclic antidepressant prescribed at one time also potentially would impair adherence to a dosage regimen and thereby compromise the therapeutic potential of these agents. Patients with a history of suicidal gestures may be candidates for the atypical antidepressants or SSRIs, which possess less cardiotoxicity. General poison prevention measures may limit childhood poisonings; and monitoring depressed patients for suicidal ideation may identify patients at risk.

**REFERENCES**


