Chapter e8: Clinical Toxicology

Bryan D. Hayes; Natalija M. Farrell

KEY CONCEPTS

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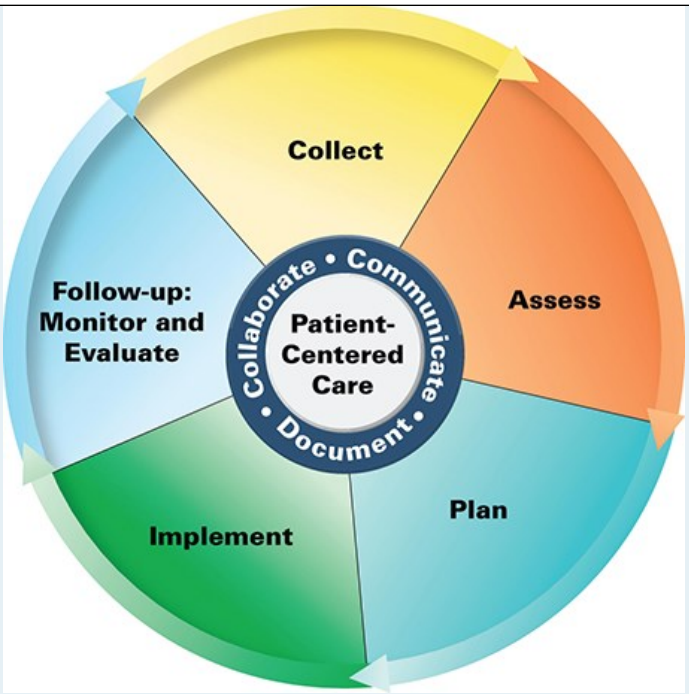
1. Poisoning can result from exposure to excessive doses of any chemical, with medicines being responsible for most childhood and adult poisonings.
2. The total number and rate of poisonings have been increasing, but preventive measures, such as child-resistant containers, have reduced mortality in young children.
3. Immediate first aid may reduce the development of serious poisoning, and consultation with a poison control center may indicate the need for further therapy.
4. The use of ipecac syrup, gastric lavage, whole bowel irrigation, and cathartics has fallen out of favor as routine therapies, whereas activated charcoal remains useful for gastric decontamination of appropriate patients.
5. Antidotes can prevent or reduce the toxicity of certain poisons, but symptomatic and supportive care is essential for all patients.
6. 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.
7. 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.
8. An overdose of calcium channel antagonists can produce severe hypotension and bradycardia and should be treated with supportive care, calcium, and insulin with supplemental dextrose.
9. Anticholinergic toxicity is characterized by dry mucous membranes, mydriasis, urinary retention, tachycardia, fever, or agitated delirium with or without hallucinations, which can be treated with physostigmine.
10. Acute opioid poisoning and overdose can produce life-threatening respiratory depression that can be treated with assisted ventilation and naloxone.
11. Chemicals can be used for mass poisonings by acts of terrorism and warfare and typically produce life-threatening effects within minutes to hours, which warrant emergency preparedness at healthcare facilities and communities.

PATIENT CARE PROCESS

Patient Care Process for Prehospital Care of Acute Poisonings



Collect (from patient, caregiver, or bystander)

- Patient symptoms (eg, none, minor, life threatening)
- Time of exposure
- Type of exposure (eg, ingestion, inhalation, injection, skin contact, eye contact)
- Substance(s) involved in the exposure
- Patient characteristics (eg, age, sex, weight)
- Circumstances of the exposure (eg, unintentional, substance abuse, self-harm)
- Patient health history (healthy, acute and chronic illnesses, pregnancy, recent hospitalization, substance use disorder)
- Prescription and nonprescription medications, dietary supplements, household products and chemicals in the vicinity
- Objective information
  - Estimate of the number of tablets or volume missing and possibly consumed
  - Exact name of the product and strength

Assess

- Presence of emergent symptoms (eg, unresponsiveness, seizures, shortness-of-breath, slowed or shallow breathing or if the exposure is likely to produce these symptoms within 1 hour)
- Presence of potential high-risk factors (eg, child-resistant container, signal words (Poison, Caution, Danger) on the product label; debilitated, elderly; suspected suicidal or homicidal intent; suspected child or elder abuse; substance abuse) (see Tables e8-1 and e8-4)
- Ability/willingness to contact a poison control center or call 9-1-1

- Ability/willingness to provide first aid (see Table e8-8) and naloxone if needed and available (see Table e8-13)

Plan*

- If emergent symptoms are present, call 9-1-1 for ambulance transport to the nearest hospital
- If unresponsive with depressed respirations and an opioid overdose is suspected, administer naloxone nasal spray or autoinjector by a trained bystander and/or call 9-1-1
- Referral to a poison control center (1-800-222-1222) to assess product toxicity, therapeutic actions, need for referral to a hospital
- If the patient does not need referral to a healthcare facility, explain self-monitoring instructions for development or resolution of symptoms

Implement*

- For hospitalized patients, assess whether the incident involves substance abuse, child or elder abuse, suicide or homicide attempt and engage appropriate healthcare professionals and law enforcement authorities
- For caregivers of children under the age of 6 years, provide poison prevention materials and instructions for contacting a poison control center
- If medications were mistakenly misused, referral to the patient's pharmacist for counseling

Follow-up: Monitor and Evaluate

- Patient's condition, response to treatment, resolution of any symptoms, and adherence to referral—typical procedures when a poison control center is involved
- Adherence to "safety proofing" a household where preschool-aged children may be present

****Collaborate with patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

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Watch the video entitled "Toxicology—The National Emergency Medicine Board Review Course" <https://www.youtube.com/watch?v=LIfermvH8YU> up to minute 21:00. Dr. William "Billy" Mallon, an emergency medicine physician, provides an overview of basic toxicology principles covered in this chapter including gastrointestinal decontamination, enhanced elimination, and antidotes. The video is useful to enhance student understanding of foundational concepts of clinical toxicology.

Poisoning is an adverse effect from a chemical that has been taken in excessive amounts. The body can tolerate and, in some cases, detoxify a certain dose of a chemical; however, toxicity ensues once a critical exposure threshold is exceeded. Poisoning can produce minor local effects that may be treated readily in the outpatient setting or systemic life-threatening effects that require intensive medical intervention. Virtually any chemical can become a poison when taken in enough quantity, but the potency of some compounds leads to serious toxicity with small quantities (Table e8-1). Poisoning by chemicals includes exposure to drugs, industrial chemicals, household products, plants, venomous animals, agrochemicals, and weapons for warfare and terrorism. This chapter describes some examples of the spectrum of toxicity, outlines means to recognize poisoning risk, and presents principles of treatment.

TABLE e8-1

Serious Toxicity in a Child Associated with Ingestion of One Mouthful or One Dosage Unit

Acids[a]	Colchicine
Anticholinesterase insecticides[a]	Cyanide[a]
Beta blockers	Diphenoxylate-atropine
Benzonatate	Hydrocarbons[a]
Calcium channel blockers	Methanol[a]
Caustics or alkalis[a]	Methyl salicylate[a]
Cationic detergents[a]	Opioids
Chloroquine	Phencyclidine or LSD
Chlorpromazine	Sulfonylureas
Clonidine	Theophylline
Cocaine	Tricyclic antidepressants

[a]Concentrated or undiluted form.

EPIDEMIOLOGY

Poisonings account for approximately 69,000 deaths, at least 2.3 million emergency department (ED) visits, and over 1.9 million nonfatal poisoning injuries each year in the United States.[1,2] Approximately 0.2% of poisoning deaths involve children younger than 5 years.[1] Of ED visits for drug-related poisoning, typically 1.1 million visits are made each year (3.5 per 100,000 population) with the highest rate observed for patients 20 to 34 years of age. One-fourth of ED visits for drug-related poisonings were hospitalized, which is twice the rate of other types of visits.[2] The age-adjusted death rates from poisonings from all circumstances have been increasing steadily, with a 297% increase from 2000 to 2016, representing 68,995 deaths representing 21.3 deaths per 100,000 population in 2016 of which 92% were drug-related poisonings. This increasing mortality trend has placed poisoning since 2008 as the leading cause of injury-related death in the United States.[1]

1 Several databases in the United States provide different levels of insight into and documentation of the poisoning problem (Table e8-2). Poisonings documented by US poison centers are compiled in the annual report of the American Association of Poison Control Centers—National Poison Data System (AAPCC-NPDS).[3] 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 2% to 3% of the annual number of deaths from poisoning tabulated in death certificates.[1,3] Despite these shortcomings, AAPCC-NPDS provides valuable insight into the characteristics and frequency of poisonings in the community at large. In the 2019 AAPCC-NPDS summary, 2,148,141 poisoning exposures were reported by 55 poison centers that served the entire United States.[3] Children younger than 6 years accounted for 43% of cases. A residence was the site of exposure in 90% of the cases, and a single substance was involved in 88% of cases. An acute exposure (ie, all at one time) accounted for 85% of cases and 77% were unintentional or accidental exposures. Fatalities accounted for 1,411 (0.06%) cases, of which 52% resulted from suicide and 0.9% 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 (49%) substances for all age groups (Table e8-3). Sixty-six percent of the poison exposures were treated at the scene. In summary, children account for most of the reported poison exposures, but a greater proportion of life-threatening poisonings are observed in adults.

TABLE e8-2

Comparison of Various Poisoning Databases

Database (Abbreviation)	Characteristics
Death certificates from state health departments compiled by the National Center for Health Statistics (NCHS) www.cdc.gov/injury/wisqars/	Compiles all death certificates whether the cause of death was by disease or external forces. Typically verified by laboratory and clinical observations.
National Electronic Injury Surveillance System—All Injury Program of US Consumer Product Safety Commission (NEISS) www.cpsc.gov/en/research--statistics/neiss-injury-data/	Surveys electronically all injuries, including poisonings, treated daily at approximately 100 emergency departments. Used to identify product-related injuries.
The American Association of Poison Control Centers—National Poison Data System (AAPCC-NPDS) www.aapcc.org	Represents largest database of poison exposures with high representation of children based on voluntary reporting to poison control centers.

TABLE e8-3

Poison Exposures by Age Group and Fatal Outcome, Ranked in Decreasing Order

Pediatric	Adult	Fatal Outcome
Cosmetics, personal care items	Medicines	Medicines
Cleaning substances	Cleaning substances	Alcohols
Medicines	Alcohols	Chemicals
Foreign bodies, toys	Pesticides	Gases, fumes
Dietary supplements	Cosmetics, personal care items	
Pesticides	Bites and envenomation	
Plants	Gases, fumes	

Data from Reference 3.

POISON PREVENTION STRATEGIES

2 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. However, the packaging was not to be difficult for normal adults to use properly.[4] Safety packaging is required for several products and product categories (Table e8-4). 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. During 2004 to 2010, ED visits for unsupervised exposures in pediatric patients increased by an average of 5.7% annually, with 75,842 in 2010. Over the next 4 years, there was an average decrease of 6.7% annually to 59,092 in 2013. Most exposures are due to opioids and benzodiazepines.[5] Additionally, improper storage of medications at home or when visiting other households, such as grandparent's homes, can contribute to accidental exposures in pediatric patients.[6,7] The "Up and Away" campaign promotes the storage of medications out of sight and out of reach of children,[8] which can help reduce unintentional pediatric medication overdoses.[7,8] Patients should be encouraged to properly dispose of medications that are outdated or no longer indicated to eliminate the risk of poisoning and drug diversion (see www.fda.gov/forconsumers/consumerupdates/ucm101653.htm).

TABLE e8-4

Examples of Products Requiring Child-Resistant Closures

Acetaminophen	Kerosene
Aspirin	Methanol
Diphenhydramine	Naproxen
Ethylene glycol	Oral prescription drugs[a]
Glue removers containing acetonitrile	Sodium hydroxide
Ibuprofen	Sulfuric acid
Iron pharmaceuticals	Turpentine

[a]With certain exceptions such as nitroglycerin and oral contraceptives.

Poison prevention requires constant vigilance. New generations of families 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. Changes in medication packaging such as unit-dose packaging or inclusion of flow restrictors for oral solutions has helped reduced pediatric overdoses involving iron and acetaminophen, respectively.[9,10] Strategies to prevent poisonings should consider the various psychosocial circumstances of poisoning (Table e8-5), prioritize risk groups and behaviors, and customize an intervention for specific situations.

TABLE e8-5

Psychosocial Characteristics of Poisoning Patients

Children	Adults	Elderly
Act purposefully or are poisoned by caretaker or sibling	Intentional abuse or suicidal intent is possible	Act with suicidal intent or unintentional misuse
Act with developmentally appropriate curiosity	Disregard or cannot read directions	Confuse product identity and directions for use
Attracted by product appearance	Do not recognize poisoning risk	Do not recognize poisoning risk
Ingest substances that adults find unpleasant	Reluctant to seek assistance until ill	Comorbid conditions complicate toxicity
React to stressful and disrupted household	Exaggerate or misrepresent situation	Unable or unwilling to describe situation
Imitate adult behaviors (eg, taking medicine)	Peer pressure to experiment with drugs	Multiple drugs may lead to adverse reactions

Recognition and Assessment

A 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 opioid poisoning with pinpoint pupils, central nervous system (CNS) depression, and respiratory depression, are most readily recognizable.[11] The recognition of chemicals responsible for acute mass emergencies resulting from industrial disasters, hazardous materials accidents, or acts of terrorism may be aided by evaluating characteristic signs and symptoms.[12] Some drugs may be adulterated or counterfeit products and delay appropriate recognition of a possible toxin.[13] Assessment of the patient may be aided by consultation with a poison control center. A center can provide information on product composition, typical symptoms, range of toxicity, laboratory analysis, treatment options, and bibliographic references. Furthermore, a center will have specially trained physicians, pharmacists, nurses, and toxicologists on staff or available for consultation to assist with difficult cases. Consultation with a poison control center also may identify changes in recommended therapy. A nationwide toll-free poison center access number (1-800-222-1222) routes callers to the poison control center serving the locality of the caller.

When the circumstances of a poison exposure indicate that it is minimally toxic, many poisonings can be managed successfully at the scene of the poisoning.[3,14] Poison control centers typically monitor the victim by telephone during the first 2 to 6 hours of the exposure to assess the patient's status and outcome of first aid.

Once a poisoning is suspected and confirmation of the diagnosis is needed for medical or legal purposes, appropriate biologic material should be sent to the laboratory for analysis. Gastric contents may contain the greatest concentration of drug, but they are difficult to analyze. Blood, saliva, or urine can be tested by qualitative screening to detect a drug's presence.[15,16] The results of a qualitative drug screen can be misleading because of interfering or low-level substances (Table e8-6); it rarely guides emergency therapy and thus has questionable value for nonspecific, general screening purposes.[15,16] Consultation with the laboratory technician and review of the assay package insert will help to determine the sensitivity and specificity of the assay. Quantitative determination of serum concentrations may be important for the assessment of some poisonings, such as acetaminophen,

ethanol, iron, salicylates, and digoxin.[17]

TABLE e8-6

Considerations in Evaluating the Results of Some Common Immunoassays Used for Urine Drug Screening

Drug	Detection After Stopping Use	Comments
Amphetamines	2-5 days	Many sympathomimetic amines, such as pseudoephedrine, ephedra, phenylephrine, fenfluramine, and phentermine, may cause positive results
	Up to 2 weeks with prolonged or heavy use	Other drugs, such as selegiline, chlorpromazine, trazodone, ranitidine, and amantadine, may cause false-positive results depending on the assay
Benzodiazepines	• Up to 2 weeks • Up to 6 weeks with chronic use of some drugs	Ability to detect benzodiazepines varies by drug; oxaprozin, sertraline may cause false-positive results
Cannabinoid metabolite (marijuana)	• 7-10 days • Up to 1-2 months with prolonged or heavy use	Extent and duration of use will affect detection time. Drugs such as ibuprofen and naproxen may cause false-positive results depending on the assay
Cocaine metabolite (benzoylecgonine)	• 12-72 hours • Up to 1-3 weeks with prolonged or heavy use	Cocaine is metabolized rapidly, and specific metabolites are typically the substance detected. False-positive results from “caine” anesthetics and other drugs are unlikely
Opioids	• 2-3 days • Up to 6 days with sustained-release formulations • Up to 1 week with prolonged or heavy use	Because the assay was made to detect morphine, detection of other opioids, such as codeine, oxycodone, hydrocodone, and other semisynthetic opioids, may be limited. Some synthetic opioids, such as fentanyl and meperidine, may not be detected. Drugs such as rifampin and some fluoroquinolones may cause false-positive results depending on the assay
Phencyclidine	• 2-10 days	Drugs such as ketamine, dextromethorphan, diphenhydramine, venlafaxine, ibuprofen, meperidine, and

	• 1 month or more with prolonged or heavy use	tramadol may cause false-positive results depending on the assay

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 to identify polymorphically expressed drug metabolizing enzymes. The following three examples demonstrate this phenomenon. The antitussive drug, dextromethorphan is abused to achieve euphoric effects, which are not universally experienced at comparable doses. The dextromethorphan metabolite dextrorphan is responsible for the euphoria, dysphoria, hallucinations, and hyperactive behavior. Individuals who are cytochrome P450 (CYP) 2D6 extensive metabolizers are more apt to experience these euphoric effects.[18] 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.[19,20] Lastly, hydrocodone administration at higher than recommended doses resulted in death to a child who was a CYP2D6 poor metabolizer which reduced the capacity to metabolize hydrocodone to hydromorphone.[21]

Toxicokinetic Considerations

The pharmacokinetic characteristics of drugs taken in overdose may differ from those observed following therapeutic doses (Table e8-7).[22,23] 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. Delayed gastric emptying by anticholinergic drugs or as the result of general CNS depression caused by many drugs may alter the rate and extent of absorption. Patients with a drug overdose may inherently exhibit prolonged gastric emptying and gastric hypomotility.[24] The formation of concretions or bezoars of solid dosage forms may delay the onset, prolong the duration, or complicate the therapy for an acute overdose.[25] A combination of pharmacokinetic and pharmacodynamic factors may lead to delayed onset of toxicity of several toxins, such as thyroid hormones, oral anticoagulants, acetaminophen, and drugs in sustained-release dosage forms. The distribution of a compound may be altered because of saturation of protein-binding sites. Drug-induced hypoperfusion may affect drug distribution and result in reduced hepatic or renal clearance. Changes in blood pH may alter the distribution of weak acids and bases. Metabolism and elimination of a compound may be retarded because of saturation of biotransformation pathways leading to nonlinear elimination kinetics. Drug-induced kidney or liver injury also can decrease clearance significantly. Implications of these changes for poisoning management include delayed achievement of peak concentrations with a corresponding longer period of opportunity to remove the drug from the gastrointestinal (GI) tract. The expected duration of effects may be much greater than that observed with therapeutic doses because of continued absorption and impaired clearance. The application of pharmacokinetic variables, such as percentage protein binding and volume of distribution, from therapeutic doses may not be appropriate in poisoning cases.[22,23] Data on toxicokinetics, the application of pharmacokinetic principles in the setting of overdose and toxicity, often are difficult to interpret and compare because the doses and times of ingestion are uncertain, the duration of sampling is inadequate, active metabolites may not be measured, protein binding typically is not assessed, and the severity of toxicity may vary dramatically.

TABLE e8-7

Examples of the Influence of Drug Overdosage on Pharmacokinetic and Pharmacodynamic Characteristics

Effect of Overdosage[a]	Examples
Slowed absorption due to formation of poorly soluble concretions in the gastrointestinal tract	Aspirin, lithium, phenytoin, sustained-release theophylline
Slowed absorption due to slowed gastrointestinal motility	Benztropine, nortriptyline
Slowed absorption due to toxin-induced hypoperfusion	Procainamide
Decreased serum protein binding	Lidocaine, salicylates, valproic acid
Increased volume of distribution associated with toxin-induced acidemia	Salicylates
Slowed elimination due to saturation of biotransformation pathways	Ethanol, phenytoin, salicylates, theophylline
Slowed elimination due to toxin-induced hypothermia (<35°C)	Ethanol, propranolol
Prolonged toxicity due to formation of longer-acting metabolites	Carbamazepine, dapsone, glutethimide, meperidine

[a]Compared to characteristics following therapeutic doses or resolution of toxicity.

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 initiated, 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 (Table e8-8) 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 as soon as possible (1-800-222-1222). Placing the patient on the left side while awaiting transport may afford easier clearance of the airway if emesis occurs and may slow the absorption of drug from the GI tract.[26]

TABLE e8-8

First Aid for Poison Exposures

Inhaled poison Immediately get the person to fresh air. Avoid breathing fumes. Open doors and windows. If victim is not breathing, start artificial respiration.
Poison on the skin 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.
Poison in the eye Flood the open eye with lukewarm or cool water poured from a glass 2 or 3 in. (~5-8 cm) before flushing the eye. Repeat for 10 to 15 continuous minutes. Remove contact lenses. Avoid ocular vasoconstrictor drops.
Swallowed poison Provide supportive care.

Self-Care

4 Ipecac syrup had been used in the United States since the 1960s to induce vomiting for treatment of ingested poisons, but its use is no longer recommended due to negligible benefit. 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 remaining product.[27] In 2010, ipecac syrup was no longer manufactured for use in the United States, but it still may be found in some households. Induced vomiting is not recommended via any mechanism, such as gagging, grease, salt, or hydrogen peroxide.

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, dysrhythmias, hypotension, acid-base balance, fluid status, electrolyte balance, and hypoglycemia. Placement of intravenous (IV) catheters is typical to ensure delivery of fluids and drugs when necessary.

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 is not recommended for routine use, if at all, and only by clinicians experienced in its use.[28] It may be considered for potentially life-threatening ingestions, when the ingestion occurred within 1 hour as a general guide, or when the substance is not adsorbed by activated charcoal. 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. Relative contraindications for gastric lavage include ingestion of a corrosive or hydrocarbon agent. Complications of gastric lavage include aspiration pneumonitis, laryngospasm, esophageal and gastric perforation, and fluid and electrolyte imbalance.[28] Use of gastric lavage has declined in recent years as evidenced by the finding that only 0.1% of 658,242 cases treated at a healthcare facility received gastric lavage in the 2019 AAPCC-NPDS report.[3]

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 GI 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 it should be administered within the first hour, but still can be useful up to 2 to 4 hours in some situations, for example, delayed GI transit due to food, anticholinergics, opioids, and massive overdoses with high mortality profile.[29,30] The recommended dose of activated charcoal for a child (1-12 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 GI tract is not intact or when the airway is not protected.

Activated charcoal is relatively nontoxic, but two risks include (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.[30] Some activated charcoal products contain sorbitol, a cathartic that may be associated with an increased incidence of emesis following use. 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.[27,31] Single-dose activated charcoal use has remained relatively steady during the past decade, with 5.2% of 658,242 cases in patients treated in hospitals according to the 2019 AAPCC-NPDS report.[3]

Cathartics

Cathartics, such as magnesium citrate and sorbitol, were thought to decrease the rate of absorption by increasing GI 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.[32] If used, a cathartic should be administered only once and only if bowel sounds are present. Infants, the elderly, and patients with impaired kidney function should be given saline cathartics cautiously, if at all.[32]

Whole-Bowel Irrigation

Polyethylene glycol electrolyte solutions, such as GoLYTELY and Colyte, are used routinely for whole-bowel irrigation prior to colonoscopy and bowel surgery. These solutions also can be used to decontaminate the GI tract of ingested toxins.[33] Large volumes of these osmotically balanced solutions are administered continuously through a nasogastric or duodenal tube for 4 to 12 hours or more. It quickly causes GI evacuation and is 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 GI tract, such as drug smugglers who swallow condoms filled with cocaine.[34] In addition, patients who have ingested delayed-release or enteric-coated drug formulations or have ingested substances, such as iron, lithium, and potassium, that are not well adsorbed by activated charcoal may benefit from whole-bowel irrigation.[33] It should not be used in patients with a bowel perforation or obstruction, GI hemorrhage, ileus, or intractable emesis. Emesis, abdominal cramps, and intestinal bloating have been reported with whole-bowel irrigation.[33] During 2019, whole-bowel irrigation was used in 0.2% of 658,242 cases managed at a healthcare facility.[3]

Perspectives on Gastric Decontamination

Although there are a variety of options for gastric decontamination, 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 (position statements are available at http://www.clintox.org/resources/position-statements).[28,30,32,33] Therapy is generally most effective within the first hour, and 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 activated charcoal is advocated for most patients when appropriate; however, no definitive recommendation can be made on the use of ipecac syrup, gastric lavage, cathartics, or whole-bowel irrigation.[35] The clinical policy also states that ipecac syrup is rarely of value in the ED and that the use of whole-bowel irrigation following ingestion of substances not well adsorbed by activated charcoal is not supported by evidence. In many cases treatment solely with activated charcoal or observation and supportive care should be considered. Ideally, activated charcoal should be administered within 1 to 2 hours of ingestion, but it still can be useful up to 2 to 4 hours or more in some situations (eg, delayed GI transit due to food, anticholinergics, opioids; or a massive overdose with a high likelihood of

mortality).[29] 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 (eg, 2-3 mL/kg/hr) 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.

Alkalinization 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 (mmol/kg) bolus followed by an infusion of 100 to 150 mEq (mmol) in 1 L of dextrose 5% in water at 1.5 to 2 times the rate of maintenance fluid administration. Complications of urinary alkalinization include alkalemia, hypokalemia, alkalotic tetany, and inability to achieve target urinary pH values.[36] Acid diuresis may enhance the excretion of weak bases, such as amphetamines, but it should not be used because it risks worsening amphetamine-related rhabdomyolysis with corresponding acute kidney injury. Generally, diuresis or ionized diuresis is rarely indicated for poisoned patients because it is inefficient 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 GI 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 severalfold.[37] 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.[37] 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.[38]

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 low or nonrestrictive protein binding. A small volume of distribution is desirable, but it has a marginal influence as an isolated characteristic,[39] particularly if multiple-dose activated charcoal is instituted during the toxin's distributive phase. A typical dosage schedule is 12.5 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. Activated charcoal formulations without sorbitol should be used for multiple-dose activated charcoal regimens, because repeated doses of activated charcoal formulations with sorbitol increase the risk of adverse effects including dehydration, hypotension, and electrolyte derangements.[32,37] Serious complications, such as pulmonary aspiration, occur in less than 1% of patients.[40] The risks of aspiration pneumonitis in obtunded or uncooperative patients and of intestinal obstruction in patients prone to ileus following a period of bowel ischemia (eg, after cardiopulmonary arrest in the elderly) may be higher.[40] Contraindications are the same as those for single-dose charcoal.[30,37]

Hemodialysis

Intermittent hemodialysis or other extracorporeal dialytic therapies including continuous renal replacement therapies (eg, continuous veno-venous hemofiltration [CVVH]) 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 (ie, cleared by dialysis hemofilters), and appropriate personnel and equipment are available. Drugs that are dialyzable typically exhibit similar physiochemical and pharmacokinetic properties that collectively render them amenable to extracorporeal clearance. For example, drugs exhibiting a low molecular mass (<1,000 daltons), low protein binding (<80%), and a small to modest volume of distribution (<1 L/kg) are generally dialyzable.[41,42] The principles of renal replacement therapy for acutely ill individuals and patients with chronic kidney disease are described in Chapters 61 and 64, respectively. Although hemodialysis can provide an efficient means of enhanced elimination, it can 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 many ethylene glycol poisonings and effective for other poisons, such as lithium, salicylates, and theophylline. Another dialysis technique is CVVH that transports drugs across a semipermeable membrane primarily by convection in response to hydrostatic pressure gradients (described in Chapter 61).[41,42] 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. The Extracorporeal Treatments in Poisoning Workgroup (EXTRIP) has published several evidence-based guidelines on the use of extracorporeal methods on specific poisons (http://www.extrip-workgroup.org/).

Antidotes

5 The search for and use of an antidote should not replace good supportive care. Specific systemic antidotes are available for many common poisonings (Table e8-9).[43] Inadequate stocking, maintenance of supplies, and corresponding shortages of antidotes at acute care hospitals have been noted throughout the United States and can complicate the care of a poisoned patient.[43,44] 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.[45] These recommendations may provide guidance to pharmacy and therapeutics committees in establishing a hospital's antidote needs. Drugs used conventionally for non-poisoning situations may act as antidotes to reverse acute toxicity, such as insulin-dextrose for β-adrenergic blocker or calcium channel antagonist overdose, glucagon for β-adrenergic blocker overdose, and octreotide for sulfonylurea-induced hypoglycemia.[43,46] Commercially available IV lipid emulsion has been used to reduce cardiac and CNS toxicity from several lipid-soluble drugs, such as local anesthetics, and is sometimes used as a "rescue" for patients with non-local anesthetic poisoning.[47] IV lipid emulsion is thought to work through several mechanisms, including redistribution away from critical organs (lipid shuttle) and non-scavenging effects such as acting as an energy substrate for affected organs.[48] There are several dosing schemes that involve single or multiple boluses followed by a continuous infusion, but none are well studied. The literature seems to support the use of IV lipid emulsion therapy for local anesthetic toxicity. Some human case studies report IV lipid emulsion therapy producing dramatic improvements in clinical status for non-local anesthetic overdose (eg, amlodipine). Others report no effect, or even worsening clinical status. Evidenced-based recommendations were only possible for a few types of poisoning based on low quality evidence available at the time of publication. Dose-finding and controlled studies in human poisoning are needed to further elucidate its role. Lastly, the use of toxin-specific antibodies (eg, fragment antigen binding [Fab] antibody fragments for digoxin or North American crotaline snake venom) has offered a new approach to treatment of poisoning victims.[43]

TABLE e8-9

Systemic Antidotes Available in the United States

Toxic Agent	Antidote
Acetaminophen	Acetylcysteine
Anticholinesterase insecticides	Atropine
Anticholinergics	Physostigmine
Benzodiazepines	Flumazenil

Botulism	Botulism antitoxin
Carbon monoxide	Oxygen
Cyanide	Sodium nitrate and sodium thiosulfate
Cyanide	Hydroxocobalamin
Dabigatran	Idarucizumab
Digoxin	Digoxin immune Fab
Ethylene glycol, methanol	Ethanol
Ethylene glycol, methanol	Fomepizole
Factor Xa inhibitor (apixaban, rivaroxaban)	Coagulation factor Xa [recombinant], inactivated-zhzo
Heavy metals (copper, lead)	Dimercaprol
Heavy metals (copper, lead)	Penicillamine
Iron	Deferoxamine
Isoniazid	Pyridoxine
Lead	Edetate calcium disodium
Lead	Succimer
Methemoglobinemia	Methylene blue
Opioids	Naloxone
Organophosphate insecticides	Pralidoxime
Radioactive americium, curium, plutonium	Diethylenetriaminepentaacetate
Radioactive iodine	Potassium iodide
Scorpion	*Centruroides* immune Fab
Snake, coral	*Micrurus fulvius* antivenin
Snakes (rattlesnakes, cottonmouth, copperhead)	*Crotalidae* polyvalent immune Fab
Snakes (rattlesnakes, cottonmouth, copperhead)	*Crotalidae immune F(ab') 2 (equine)*
Spider, black widow	*Lactrodectus mactans* antivenin
Thallium or cesium	Prussian blue

Tubocurarine	Neostigmine
Warfarin	Phytonadione and Prothrombin Complex Concentrate

Fab, fragment antigen binding.

Assessing the Effectiveness of Therapies

Case reports, clinical studies, human volunteer studies, animal investigations, and in vitro tests yield findings with limited generalizability to the care of humans who have been poisoned. Case reports are difficult to assess because they are uncontrolled, the histories are uncertain, and multiple therapies frequently are used. Although clinical studies may describe tens to hundreds of patients, they can exhibit serious shortcomings, such as weak randomization procedures, no laboratory confirmation or correlation with history, insufficient number of severe cases, no control group, and no quantitative measure of outcome. Extrapolation of data from human volunteer studies to patients who overdose is difficult because of potential or unknown variations in pharmacokinetics (eg, differing dissolution, gastric emptying, and absorption rates) seen with toxic as opposed to therapeutic doses,[22,23] differences in time to institute therapy in the emergency setting, and differences in absorption in fasted human volunteers compared with the full stomach of some patients who overdose. However, these studies provide the most controlled and objective measures of the efficacy of a treatment. Experiences from animal studies cannot be applied directly to humans because of interspecies differences in toxicity and metabolism. In vitro tests serve to screen the efficacy of some approaches, 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 evidence base for the therapy of poisoned patients and are tempered with the consideration 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, anticholinergics, opioids, and weapons of mass chemical poisoning are the focus of the remainder of this chapter. These agents were chosen because they provide examples of different mechanisms of toxicity and the application of general treatment approaches, as well as some agent-specific pharmacotherapeutic interventions.

Acetaminophen

Clinical Presentation

6 Acute acetaminophen poisoning characteristically results in hepatotoxicity and is a leading cause of acute liver failure in the United States.[49] Clinical presentation 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 injury become manifest 3 to 5 days after ingestion and include right upper quadrant abdominal tenderness, jaundice, hypoglycemia, and 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 encephalopathy (coma) and hepatorenal syndrome, and death can occur.[49,50] Survivors of severe hepatotoxicity usually exhibit no residual functional or histologic abnormalities of the liver within 1 to 6 months of the incident.[51]

Mechanism of Toxicity

Acetaminophen is metabolized in the liver primarily to glucuronide or sulfate conjugates, which are excreted into the urine with small amounts (<5%) of unchanged drug. Approximately 5% of a therapeutic dose is metabolized by CYPs, primarily CYP2E1, to the reactive metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI). Normally, NAPQI is subsequently conjugated with glutathione, a sulfhydryl-containing compound, in the hepatocyte and excreted in the urine as a non-toxic mercapturate conjugate (Fig. e8-1).[49]

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

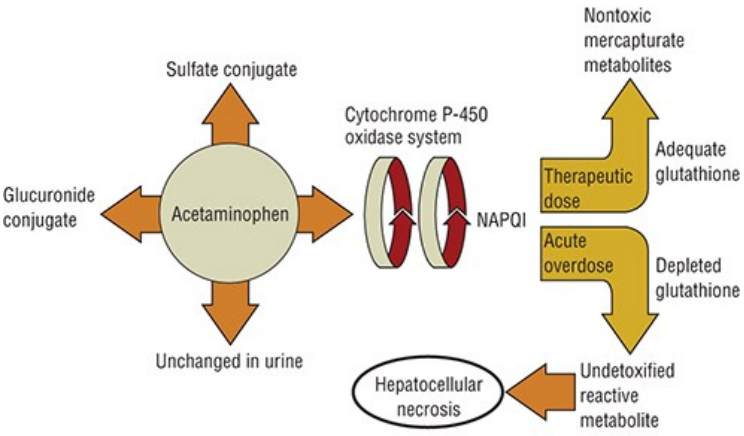
- Typically, no signs present within first day.
- Jaundice, scleral icterus, and bleeding within 3 to 10 days.
- Oliguria occasionally within 2 to 7 days.
- With severe poisoning, hepatic encephalopathy (delirium, depressed reflexes, and coma) within 5 to 10 days.

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 INR; hypoglycemia within 1 to 3 days.
- Elevated serum creatinine and blood urea nitrogen (BUN) within 2 to 7 days.

FIGURE e8-1

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



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Sulfate stores are depleted in an acute overdose situation. This leads to increased acetaminophen metabolism via CYP2E1 and eventual depletion of the available glutathione used to detoxify NAPQI, which then reacts with other hepatocellular sulfhydryl compounds. This results in centrilobular hepatic necrosis.[49] Several other mechanisms, such as cytokine release and oxidative stress, also may be initiated by the initial cellular injury.[49]

In many cases of severe hepatotoxicity, impaired kidney function also is present and may range from oliguria to acute kidney injury. The etiology of the impaired kidney function may be a direct effect of NAPQI, generated by renal cytochrome oxidase, or a consequence of hepatic injury resulting in hepatorenal syndrome.[50]

Causative Agents

Acetaminophen, also known as paracetamol, is available widely without prescription as an analgesic and antipyretic. It is available in various dosage forms, including oral extended-release preparations, rectal suppositories, and an IV formulation. 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 dose, systemic exposure, and the subsequent risk of hepatotoxicity.

Incidence

Acetaminophen is commonly ingested by small children and is used frequently in suicide attempts by adolescents and adults.[3] Each year acetaminophen accounts for approximately 78,000 ED visits with 78% related to acts of self-harm.[52] The 2019 AAPCC-NPDS report documented 53,295 nonfatal single-drug product exposures and 127 deaths from acetaminophen alone, with 39% of the exposures in children younger than 6 years. Another 16,285 exposures were from combination drug products containing acetaminophen.[3]

Age-based differences in the metabolism of acetaminophen are responsible for major differences in the incidence of serious toxicity. Despite the common ingestion of acetaminophen by young children, few develop hepatotoxicity from acute overdosage.[3] In children younger than 9 to 12 years, acetaminophen undergoes more sulfation and less glucuronidation. The reduced fraction available for metabolism by CYPs 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

Acute, single-ingestion of at least 10 g or 200 mg/kg, whichever is less, of acetaminophen by patients 6 years or older is associated with development of hepatotoxicity (200 mg/kg or more of acetaminophen in children younger than 6 years).[53] Patients have survived much larger doses, particularly with early treatment. Initial symptoms, if present, do not predict the severity of the toxicity that eventually occurs.

Repeated ingestion of supratherapeutic doses of acetaminophen has been associated with hepatotoxicity in adults and children.[53-56] Patients who are fasting or have ingested alcohol in the preceding 5 days are at greater risk.[57] Young children have a higher risk when they have been acutely fasting as the result of a febrile illness or gastroenteritis.[56] Patients 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 for 2 or more days.[53]

Chronic exposure to drugs that induce CYPs—specifically 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.[51] Patients with chronic alcoholism have 3.5 greater odds of mortality with acute acetaminophen poisoning.[55]

The risk of developing hepatotoxicity with acute ingestion of acetaminophen may be predicted with a commonly used nomogram that is based on the acetaminophen serum concentration and time after ingestion.[57] The nomogram used in the United States is readily available in the United States Food and Drug Administration (FDA) approved package insert for acetylcysteine (available at: http://dailymed.nlm.nih.gov/) and in several electronic information databases (eg, Micromedex, UpToDate). Treatment should be started if the patient's serum concentration is above the line on the nomogram that starts at 150 mcg/mL (1,000 µmol/L) at 4 hours. If the plasma concentration plotted on the nomogram falls above the nomogram treatment line, indicating that hepatic damage is possible, a 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.[57] Outside of the United States, other countries have adopted a lower threshold on the nomogram for the treatment of acetaminophen toxicity.[58,59]

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.[55,60] Assessment and management of IV administered acetaminophen is presently similar to the acute oral overdose.[61]

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 ED and acetaminophen serum concentrations obtained. Prehospital care generally is not indicated.[53] If the patient presents to the ED 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.[62] It should be started within 10 hours of the ingestion to be most effective.[57] Initiation of therapy 24 to 36 hours after the ingestion may be of value in some patients, particularly those with measurable serum acetaminophen concentrations.[62,63] Patients with fulminant hepatic failure may benefit through other mechanisms by the administration or initiation of acetylcysteine several days after ingestion.[62,63]

Oral and IV formulations of acetylcysteine are available for clinical use. While there is no clear evidence favoring one formulation over the other,[64] there are several notable differences between them (Table e8-10).[62,64,65] Most notable is the occurrence (approximately 10% of cases) of anaphylactoid reactions (see Chapter e108) following the IV infusion. Acetylcysteine IV was used 10 times more frequently than the oral form as reported in the 2019 AAPCC-NPDS.[3] 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.[57,62] 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 GI motility as the result of the ingestion of certain drugs (eg, opioids, or anticholinergics), when an extended-release product is involved or if chronic or supratherapeutic overdoses are suspected. 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. Several alternative dosing regimens for acetylcysteine with different duration, administration technique, and clinical endpoints have been proposed.[65,66] The 72-hour oral acetylcysteine and the 21-hour (“three—bag”) 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. Several alternative, higher acetylcysteine dosing regimens have been described in the literature for massive acetaminophen overdoses,[67] but the number of patients in the studies has been relatively small and the findings are not generalizable. Similarly, “two-bag” acetylcysteine IV regimens have been described in literature and suggest reduced adverse effects and delays in treatment compared to the traditional, “three-bag” method.[68-72] For both the higher dose regimen and “two-bag” method, accepted and validated criteria are lacking at present.

TABLE e8-10

Comparison of the FDA Approved IV and Oral Regimens for Acetylcysteine in the Treatment of Acute Acetaminophen Poisoning

Characteristic	IV	Oral
Regimen	150 mg/kg in 200 mL D_5W infused over 1 hour, then 50 mg/kg in 500 mL D_5W over 4 hours, followed by 100 mg/kg in 1,000 mL D_5W over 16 hours[a]	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
Total dose (mg/kg)	300	1,330
Duration (hr)	21	72
Adverse effects	Nausea, vomiting; anaphylactoid reactions (rash, hypotension, wheezing, dyspnea); acute flushing and erythema in first hour of the infusion that typically resolves spontaneously	Nausea, vomiting
Ancillary therapy, if needed	Antihistamines and epinephrine for severe anaphylactic reactions	Antiemetics
Trade name	Acetadote	Mucomyst
Available strength	20%	10%, 20%

FDA, Food and Drug Administration; D_5W, 5% dextrose in water for injection.

[a]For patients <40 kg and those requiring fluid restriction, the total volume for dilution should be reduced as directed in the package insert.

Although young children have an inherently lower risk of acetaminophen-induced hepatotoxicity, these patients are 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.[66]

Hemodialysis may be considered in rare cases when serum acetaminophen concentrations are exceedingly high (>700-1,000 mcg/mL [>4,600-6,600 µmol/L]) with the early development of altered mental status and severe metabolic acidosis prior to the onset of hepatic failure.[73] If fulminant hepatic failure develops, the approaches described in Chapter e56 should be considered. In patients unresponsive to acetylcysteine, liver transplantation is a lifesaving option.[51]

Monitoring and Prevention

Baseline liver function tests (AST, ALT, bilirubin, INR), and serum creatinine concentration should be obtained on admission and repeated at 24-hour intervals until at least 96 hours have elapsed for patients at risk. Most patients with liver injury develop elevated transaminase concentrations within 24 hours of ingestion. Serum concentrations of AST or ALT greater than 1,000 international units per liter (IU/L) (16.7 µkat/L) commonly are associated with other signs of liver dysfunction and have been used as the threshold concentration in outcome studies to define severe liver toxicity.[57] The extent of transaminase elevation is not correlated directly with the severity of hepatic injury, with nonfatal cases demonstrating peak concentrations as high as 30,000 IU/L (500 µkat/L) between 48 and 72 hours after ingestion.[51] The King's College Criteria for acetaminophen toxicity (arterial pH <7.30, INR >6.5 or PT >100 s, creatinine ≥3.4 mg/dL [300 µmol/L], or Grade III-IV hepatic encephalopathy) is used to determine patients with acetaminophen toxicity

that may benefit from a liver transplant and thus require transportation to a liver transplant center.[74,75]

Prevention of acetaminophen poisoning is based on recognition of the maximum daily therapeutic doses (4 g in adults), observance of general poison prevention practices, and early intervention in cases of suspected overdose. The frequent involvement of acetaminophen in poisonings and overdoses, whether declared by the patient, has led to the routine determination of acetaminophen concentrations in patients admitted to EDs for any overdose.[60]

Anticholinesterase Insecticides

Clinical Presentation

7 The clinical manifestations of anticholinesterase insecticide poisoning include any or all of the following: pinpoint pupils, excessive lacrimation, excessive salivation, bronchorrhea, bronchospasm, and expiratory wheezes, hyperperistalsis producing abdominal cramps and diarrhea, bradycardia, excessive sweating, fasciculations and weakness of skeletal muscles, paralysis of skeletal muscles (particularly those involved with respiration), convulsions, and coma.[76] Helpful mnemonics include DUMBELLS (diarrhea, urination, miosis, bradycardia/bronchospasm/bronchorrhea, emesis, lacrimation, lethargy, salivation) and SLUDGE + the Killer Bs (salivation, lacrimation, urination, defecation, GI symptoms, emesis + bradycardia/bronchospasm/bronchorrhea). Importantly, the life-threatening problems are bronchorrhea, bronchospasm, and bradycardia, hence the "Killer Bs" terminology. Symptoms of anticholinesterase poisoning and their response to antidotal therapy depend on the action of excessive acetylcholinesterase at different receptor types (Table e8-11).

TABLE e8-11

Effects of Acetylcholinesterase Inhibition at Muscarinic, Nicotinic, and CNS Receptors

Muscarinic Receptors	**Nicotinic-Sympathetic Neurons**
Diarrhea	Increased blood pressure
Urination	Sweating and piloerection
Miosis[a]	Mydriasis[a]
Bronchorrhea	Hyperglycemia
Bradycardia[a]	Tachycardia[a]
Emesis	Priapism
Lacrimation	**Nicotinic-neuromuscular neurons**
Salivation	Muscular weakness
CNS receptors (mixed type)	Cramps
Coma	Fasciculations
Seizures	Muscular paralysis

[a]Generally muscarinic effects predominate, but nicotinic effects can be observed.

CLINICAL PRESENTATION: Anticholinesterase Insecticide Poisoning

General

- Mild symptoms may resolve spontaneously; life-threatening toxicity may develop with 1 to 6 hours of exposure.

Symptoms

- Diarrhea, diaphoresis, excessive urination, miosis, blurred vision, pulmonary congestion, dyspnea, vomiting, lacrimation, salivation, and shortness of breath within 1 hour.
- Headache, confusion, coma, and seizures possible within 1 to 6 hours.

Signs

- Increased bronchial secretions, tachypnea, rales, and cyanosis within 1 to 6 hours.
- Muscle weakness, fasciculations, and respiratory paralysis within 1 to 6 hours.
- Bradycardia, atrial fibrillation, atrioventricular block, and hypotension within 1 to 6 hours.

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.

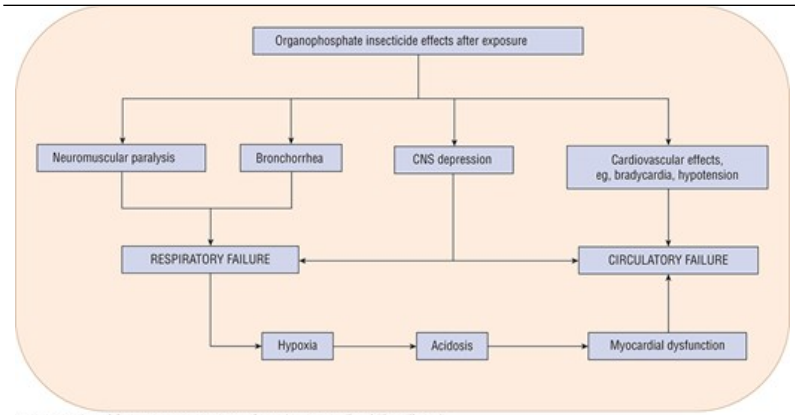
Other Diagnostic Tests

- 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.

The time of onset and severity of symptoms depend on the route of exposure, potency of the agent, and total dose received. 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 GI 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 (Fig. e8-2).[76] Poisoning may be complicated by aspiration pneumonia, urinary tract infections, and sepsis.[76,77]

FIGURE e8-2

Pathogenesis of life-threatening effects of organophosphate poisoning.



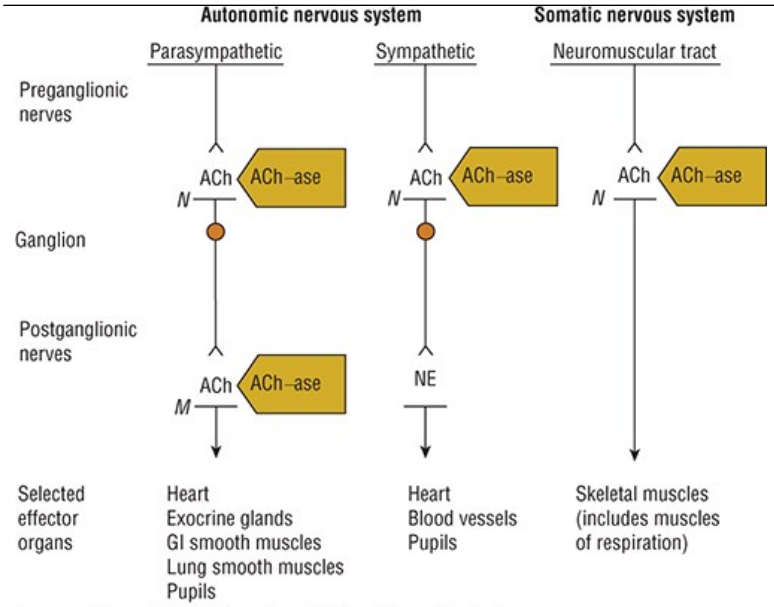
Organophosphate poisoning has been associated with several residual effects, such as intermediate syndrome, extrapyramidal symptoms, neuropsychiatric effects, and delayed chronic neuropathy. Intermediate syndrome becomes manifest in some patients approximately 1 to 3 days after exposure and generally 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 persist and are unresponsive to further atropine or pralidoxime therapy. Improvement may be delayed for months to years, and in some cases the patient develops permanent disability. Chronic neuropathy is not associated with all organophosphates.[76]

Mechanism of Toxicity

Anticholinesterase insecticides phosphorylate the active site of cholinesterase in all parts of the body.[76] 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 multiple nerve endings in the CNS (Fig. e8-3).

FIGURE e8-3

Organization of neurotransmitters of the peripheral nervous system and site of acetylcholinesterase action. (ACh, acetylcholine; ACh-ase, acetylcholinesterase; M, muscarinic receptor; N, nicotinic receptor; NE, norepinephrine.)



Causative Agents

Anticholinesterase insecticides include organophosphate and carbamate insecticides. These insecticides are 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.[76] The prototype anticholinesterase agent is the organophosphate, which is the focus of this discussion. Many organophosphates are used as pesticides (eg, dichlorovos, disulfoton, malathion, parathion, mevinphos, and phosmet), and several were specifically developed for use as potent chemical warfare agents and adapted as terrorist chemical weapons (see the section later in this chapter).[12,76] An anticholinesterase insecticide typically is stored in a garage, chemical storage area, or living area. Anticholinesterase agents also can be found in occupational (eg, pest exterminators) or agricultural (eg, 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 2019 AAPCC-NPDS report documented 3,258 nonfatal single-product exposures and 1 death and 28 severe cases from anticholinesterase insecticides alone or in combination with other pesticides, with 28% of exposures in children younger than 6 years.[3]

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.[76] Ruling out other chemical exposures may be guided initially by symptoms at presentation.[11,12]

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.[76] 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 small mouthful of an already diluted household product, such as an aerosol

insecticide for household use, typically does not produce serious toxic effects.[78]

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.[76,78] 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 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.[77] 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. Based on a history of an exposure and presence of typical symptoms, anticholinesterase toxicity should be readily recognized.[11]

Management of Toxicity

At the scene of the incident, move the patient away from area containing the organophosphate and decontaminate affected body surfaces with conventional first aid measures (see Table e8-8). Remove all contaminated clothing. People handling the patient should wear gloves and aprons to protect themselves against contaminated clothing, skin, or gastric fluid of the patient.[76,78] Because many insecticides are dissolved in a hydrocarbon vehicle, there is an additional risk of pulmonary aspiration of the hydrocarbon leading to pneumonitis when ingested. The risks and benefits of gastric decontamination (eg, activated charcoal) should be considered carefully and should involve consultation with a poison control center or clinical/medical toxicologist. Symptomatic cases of anticholinesterase insecticide exposure typically are referred to an ED for evaluation and treatment.

If the poison has been ingested within 1 hour, gastric lavage may be considered and followed by the administration of activated charcoal. For the patient with large-surface skin contamination, contaminated clothing should be removed, and the patient washed with copious amounts of soap and water before he or she is transported and admitted to the ED 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.

Pharmacologic management of organophosphate intoxication relies on the administration of atropine and pralidoxime.[76,78] Atropine has no effect on inhibited cholinesterase, but it competitively blocks the actions of acetylcholine on cholinergic and some CNS 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.[78] It should be repeated at 5- to 10-minute intervals until bronchial secretions and pulmonary rales resolve. Some recommend aggressive escalation of doses (eg, doubling of each successive dose) in cases with severe toxicity.[79] Therapy may require large doses over a period of several days until all absorbed organophosphate is metabolized, and acetylcholinesterase activity is restored.

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 in a process referred to as "aging." Therefore, therapy with pralidoxime should be initiated as soon as possible, preferably within 36 to 72 hours of exposure.[78] The drug should be given at a dose of 25 to 50 mg/kg up to 1 to 2 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 is effective in adults when administered at 2 to 4 mg/kg/hr preceded by a loading dose of 4 to 5 mg/kg[80] and in children at 10 to 20 mg/kg/hr with a loading dose of 15 to 50 mg/kg.[81] Both atropine and pralidoxime should be given together because they have complementary actions (Table e8-12). Carbamate insecticide poisonings typically do not require the administration of pralidoxime.

TABLE e8-12

Comparative Characteristics of Atropine and Pralidoxime for Anticholinesterase Poisoning

Characteristic	Atropine	Pralidoxime
Interaction	Synergy with pralidoxime	Reduces atropine dose requirement
Indication	Any anticholinesterase agent	Typically needed for organophosphates
Primary sites of action	Muscarinic, CNS	Nicotinic > muscarinic > CNS
Adverse effects	Coma, hallucinations, tachycardia	Dizziness, diplopia, tachycardia, headache
Daily dose[a]	2-1,600 mg	1-12 g
Total dose[a]	2-11,422 mg	1-92 g

[a]Range of reported cases; higher doses may be required in rare cases.

One of the pitfalls of therapy is the delay in administering sufficient doses of atropine or pralidoxime.[76,79] The adverse effects of atropine and pralidoxime, which can be minimized by decreasing the dose, are predictable extensions of their anticholinergic actions and are minimally important compared with the life-threatening effects of severe anticholinesterase poisoning.

Monitoring and Prevention

Poisoned patients may require monitoring of vital signs, measurement of ventilatory adequacy such as blood gases and pulse oximetry, leukocyte count with differential to assess development of pneumonia, and chest radiographs to assess the degree of pulmonary edema or development of hydrocarbon pneumonitis. Workers involved in the formulation and application of pesticides should be monitored by periodic measurement of cholinesterase activity in their bloodstream. Untreated, acetylcholinesterase activity returns to normal values in approximately 120 days. Long-term follow-up for severe cases of poisoning may be necessary to detect the presence of delayed or persistent neuropsychiatric effects.

Many anticholinesterase insecticide poisonings are unintentional as a consequence of misuse, improper storage, failure to follow instructions for mixing or application, or inability to read directions for use. Training and vigilant adherence to directions may minimize some poisonings. Storing pesticides in original or labeled containers can minimize the risk of unintentional ingestion. Keeping pesticides out of children's reach may decrease the risk of childhood poisoning.[82]

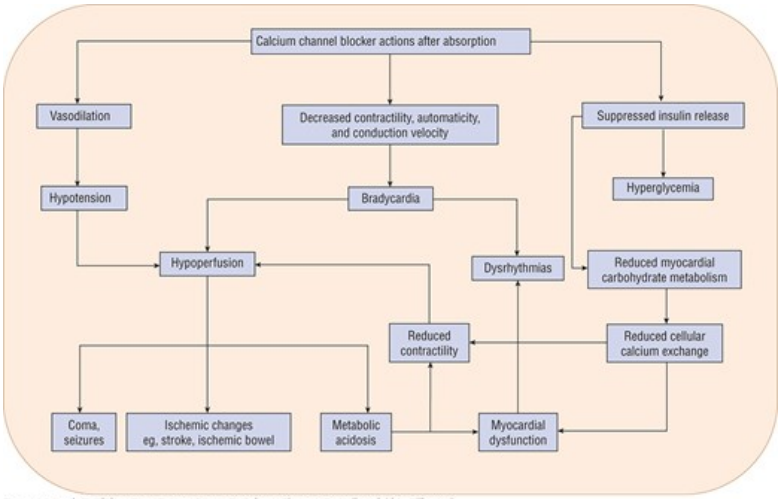
Calcium Channel Blockers

Clinical Presentation

Overdosage with calcium channel blockers typically results in bradycardia and hypotension (Fig. e8-4). Some patients become lethargic and may develop agitation and coma, but interestingly, in many cases mental status is preserved until patients are very ill. 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 manifest within 1 to 2 hours of ingestion, but 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.[83-86]

FIGURE e8-4

Pathophysiologic changes associated with calcium channel blocker poisoning.



Mechanism of Toxicity

Most toxic effects of calcium channel blockers result from 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 overdosage.[86] Although verapamil is most specific to the myocardial receptors (followed by diltiazem and then the dihydropyridines), signs and symptoms of overdose are similar among all drugs in this class due to the loss of selectivity.[87] 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.[88] In fact, the degree of hyperglycemica may correlate with severity of toxicity.

CLINICAL PRESENTATION Calcium Channel Blocker Poisoning

General

- Life-threatening cardiac toxicity (bradycardia, depressed contractility, and 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, and coma within 1 to 3 hours (mental status may be preserved in absence of significant hypotension).

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 blood gases (metabolic acidosis), serum electrolytes, lactic acid, 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.

Causative Agents

Several calcium channel blockers 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 (eg, verapamil), benzothiazepines (eg, diltiazem), and dihydropyridines (eg, amlodipine, clevidipine, felodipine, isradipine, nicardipine, nifedipine, and nimodipine). Several of these drugs, including diltiazem, nifedipine, and verapamil, are formulated as sustained-release oral dosage forms or have a slow onset of action and longer half-life (eg, amlodipine), allowing once-daily administration.

Incidence

In 2019, the AAPCC-NPDS report documented 6,020 nonfatal single-product toxic exposures to a calcium channel blocker; 111 patients exhibited and survived major toxic effects, and 31 died.[3]

Risk Assessment

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 ED. The threshold doses of several agents and dosage forms vary (eg, diltiazem: adults, greater than 120 mg for immediate release and chewed sustained release, greater than 360 mg for sustained release, greater than 540 mg for extended release; children younger than 6 years: >1 mg/kg).[89] 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, digoxin, class I antidysrhythmics, and other vasodilators may worsen the cardiovascular effects of calcium channel blockers.[84,86,89] The presence of persistent and significant hyperglycemia (>250 mg/dL [13.9 mmol/L]) may be a sign of grossly disturbed cardiac metabolism and physiology that merits attention and aggressive intervention.[88]

Management of Toxicity

There is no accepted specific prehospital care for calcium channel blocker poisoning, except to summon an ambulance for symptomatic patients.[90] 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 output, and maintenance of electrolyte and acid-base balance. Maintaining vital organ perfusion is critical for successful therapy to allow time for calcium channel blocker toxicity to resolve.[85,86]

A single dose of activated charcoal should be considered if instituted generally within 1 to 2 hours after ingestion. Besides exhibiting a slower onset of symptoms, sustained-release formulations can form concretions in the intestine.[85,86] Whole-bowel irrigation with polyethylene glycol electrolyte solution may accelerate intestinal elimination of the sustained-release tablets and should be considered for ingestions of sustained-release calcium channel blocker formulations. However, it should be used with caution if hemodynamic instability is present.[33] Adjunctive therapy is focused on treating hypotension, bradycardia, and resulting shock. Hypotension is treated primarily by correction of coexisting dysrhythmias (eg, bradycardia, heart block) and implementation of conventional measures to treat decreased blood pressure. Infusion of IV fluids and placement of central and arterial catheters are initial therapies for resuscitation and intensive monitoring. Further fluid therapy should be guided by bedside cardiac ultrasound as the poisoned heart may not be able to handle an excessive volume.[91] If hypotension persists, dysrhythmias are present, or other signs of serious toxicity are present, more specific therapy is indicated.[47,48,83] First-line therapies include IV calcium, norepinephrine and/or epinephrine, and high-dose insulin. Dobutamine, atropine, and lipid emulsion therapy may be considered. Interventions with the strongest level of evidence are high-dose insulin and extracorporeal life support.[83] Glucagon is no longer recommended for calcium channel blocker overdose but may still be helpful in beta blocker poisoning.[83]

Calcium IV is usually given first (or concomitant with early fluid resuscitation), in part because it is quick to administer and readily available with little preparation. Either calcium chloride or calcium gluconate is acceptable, if an equivalent amount of elemental calcium is provided (calcium chloride 1 g = calcium gluconate 3 g). In adults, calcium gluconate 2 g can be diluted in 100 mL normal saline and infused over 5 minutes through a peripheral line. If a positive cardiovascular response is achieved, the dose may be repeated every 30 minutes or a continuous infusion may be initiated. If multiple doses or a continuous infusion of calcium are administered, frequent laboratory monitoring is necessary to avoid clinically significant hypercalcemia. If calcium chloride is used, institutions vary on how dilute it should be to administer in a peripheral vein. One advantage of calcium gluconate is that it is less irritating and can be given peripherally. Central access is sometimes challenging in emergency scenarios and may take 10 to 15 minutes to secure. Calcium gluconate can infuse while central access is obtained. Atropine also may be considered for treatment of bradycardia, but it is seldom enough as a sole therapy.[83] Norepinephrine is the first vasopressor to initiate, with epinephrine, and/or dobutamine as additional options.[83] Higher than usual doses may be needed.[90]

For severe cases of calcium channel blocker toxicity refractory to fluids, calcium, and initial vasopressor doses, an infusion of high-dose insulin to produce a state of hyperinsulinemia and euglycemia should be initiated.[43,92] In the nonstressed state, the heart primarily catabolizes free fatty acids for its energy needs, while the stressed myocardium switches preference to carbohydrates. Insulin's positive inotropic effects seem to occur because of metabolic support of the heart during hypodynamic shock.[93] An IV bolus of regular insulin (0.5-1 units/kg) with 50 mL dextrose 50% (0.25 mg/kg for children) followed by a continuous infusion of regular insulin (0.5-1 units/kg/hr) may improve myocardial contractility.[94] 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. Supplemental glucose will be necessary in most patients but recall that hyperglycemia is a consequence of the poisoning. So, the amount needed will vary. Patients with serum potassium concentrations less than 3.5 mEq/L (mmol/L) will need supplemental potassium IV (see Chapter 70). The insulin infusion rate can be reduced gradually as signs of toxicity resolve. Glucose supplementation may be needed up to 24 hours after discontinuation of the insulin infusion.

Initiation of high-dose insulin therapy presents unique challenges. In an individual institution, it may be rare to encounter this therapy, meaning it

might not be familiar to physicians, nurses, pharmacists, and other clinicians. There is often resistance because the dose is 10 to 100 times higher than what is used for other indications (eg, diabetic ketoacidosis). Recurrent education is important to inform all team members of the plan and purpose. Protocols and electronic order sets may facilitate safe and efficient administration. In addition, a standard insulin infusion is 1 unit/mL. A 70-kg patient receiving 5 units/kg/hr will use 350 mL/hr. This much fluid may be harmful in some patients and IV bags would need frequent preparation, straining resources. However, insulin is a high-risk medication in terms of safety, so simply having a more concentrated infusion for this one indication may also cause problems. Some centers use alternative concentrations such as 10 or 16 units/mL specifically for this indication.[95] Having the unique concentrations built into smart pump libraries also reduces the risk of error.

Intravenous lipid emulsion has the potential to rapidly reverse the severe cardiac toxicity of calcium channel blockers, though it has not been consistently demonstrated.[42,43,96] It can be considered in refractory cases. A reasonable dose for oral poisonings is 20% lipid emulsion as a 1.5 mL/kg bolus, followed by 0.25 mL/kg/min for 3 min, followed by 0.025 mL/kg/min up to 6.5 h.[78,97] Possible adverse effects include acute lung injury, pancreatitis, allergic reaction, fat emboli, and deep vein thrombosis.[79,98] Laboratory interference and incompatibility with other resuscitation medications are important logistical factors.[99-101] Blood specimens for labs should be drawn before lipid is given, if possible, and it should be administered in its own IV line. Lipid can also interfere with extracorporeal treatments.[82,102]

Several lifesaving options may be warranted for patients with cardiogenic shock that is refractory to conventional therapy, such as electrical cardiac pacing, intra-aortic balloon counterpulsation, or cardiopulmonary bypass. Measures to enhance elimination from the bloodstream by hemodialysis or multiple-dose activated charcoal are not effective and are not indicated for calcium channel blocker poisoning.[32,37,69,71,84,86] Venoarterial extracorporeal membrane oxygenation (ECMO) is available at some centers and is sometimes utilized in poisoned patients.[83,103,104] The circuit pumps blood from the venous side to the arterial side, while essentially removing the sick heart from the equation. Gas exchange and hemodynamic support are provided via ECMO until the heart recovers.[83]

Monitoring and Prevention

Regular monitoring of vital signs and ECG is essential in suspected calcium channel blocker poisoning. Determinations of serum electrolytes and lactic acid, serum glucose, blood gases (venous sampling is sufficient in most clinical scenarios), urine output, and kidney 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.[73,89] 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 and delayed up to 12 to 18 hours after ingestion.[68,73,83,89] Serum concentrations of these drugs in overdose patients do not correlate well with the ingested dose, degree of toxicity, or outcome.

Calcium channel blocker poisoning may be the result of an intentional suicide or unintentional ingestion by young children. Prevention of calcium channel blocker poisonings in children rests with the education of patients receiving these agents, particularly individuals who have children visit their homes infrequently, of their dangers on overdosage. Safe storage and use of child-resistant closures may reduce the opportunities for unintentional poisonings by children.

Anticholinergics

Clinical Presentation

Anticholinergic toxicity may present with peripheral and/or central findings. Peripheral anticholinergic effects include elevated body temperature, dry mucous membranes, flushed appearance, mydriasis that is minimally responsive to light, blurred vision, photophobia, tachycardia, urinary retention, and decreased bowel sounds.[11] Central findings include delirium, agitation, confusion, restlessness, visual or auditory hallucinations, seizures, or picking at imaginary objects.[11,105] CNS findings may persist longer than the peripheral findings; however, it is uncommon for patients to only experience central anticholinergic toxic effects.[106] Severe toxicity can manifest as seizures, cardiac conduction abnormalities (eg, QRS widening or increased QTc interval) with or without dysrhythmias, hypotension, or rhabdomyolysis.[107-109] The mnemonic “hot as a hare” (fever), “red as a beet” (flushed skin), “blind as a bat” (mydriasis), “dry as a bone” (dry mouth, decreased sweating), “mad as a hatter” (delirium), and “full as a flask” (urinary retention) can be helpful for remembering the anticholinergic toxidrome.

Mechanism of Toxicity

Anticholinergic agents are competitive antagonists of acetylcholine at the muscarinic receptors.[11,110] There are at least five muscarinic receptors (M1-M5), and the location of these receptors influences the clinical features of the anticholinergic toxidrome.[105,110] Competitive antagonism at the muscarinic receptor sites found in the smooth muscles, secretory glands, sweat glands, and eye ciliary leads to the peripheral anticholinergic effects, while the antagonism of acetylcholine at the central muscarinic receptors results in the CNS effects.[110] Pharmacologic agents commonly have other mechanisms of action and toxicity in addition to their anticholinergic properties,[111] which leads to the anticholinergic effects serving as either the primary (eg, diphenhydramine, dimenhydrinate, cetirizine) or secondary (eg, tricyclic antidepressants) source of toxicity.[112,113]

CLINICAL PRESENTATION Acute Anticholinergic Poisoning

General

- Multiple medications and plant species have anticholinergic properties, which can result in toxicity due to overdose as well as drug interactions

Symptoms

- Dry mouth, blurred vision, photophobia, or dry skin may occur within 6 to 8 hours of ingestion
- Delirium with or without hallucinations, confusion, agitation, or seizures may occur within 6 to 8 hours of ingestion

Signs

- Tachycardia, elevated body temperature, absent or decreased bowel sounds, dilated pupils minimally responsive to light Hemodynamic instability is less likely to occur, but may be seen with medications that have anticholinergic properties in addition to other mechanisms of action (eg, tricyclic antidepressants, quetiapine)

Laboratory Tests

- Due to combination products containing both acetaminophen and anticholinergic agents, obtain a toxic serum acetaminophen concentration no earlier than 4 hours after ingestion by comparison with nomogram
- Creatine kinase, serum electrolytes, and serum creatinine to assess for rhabdomyolysis and acute kidney injury

Other Diagnostic Tests

- ECG with continuous monitoring and pulse oximetry to monitor for toxicity
- Bladder scan for detection of urinary retention

Causative Agents

More than 600 unique pharmaceutical and herbal compounds can cause anticholinergic effects through their ability to inhibit the binding of acetylcholine to the muscarinic acetylcholine receptors.[111] The majority of these agents are ingested orally, though there are reports of anticholinergic toxicity due to adulterated drugs of abuse such as cocaine or heroin, which may be administered via injection, insufflation, or inhalation.[114,115]

Medications classes with anticholinergic properties include tricyclic antidepressants (eg, amitriptyline, nortriptyline, doxepin), selective serotonin reuptake inhibitors (eg, paroxetine, fluoxetine, citalopram), antihistamines (eg, diphenhydramine, doxylamine, cetirizine, loratadine, hydroxyzine), antiparkinson drugs (eg, benztropine, trihexyphenidyl), antipsychotics (eg, haloperidol, quetiapine, olanzapine), antispasmodics (eg, oxybutynin, tolterodine), antitussives (eg, dextromethorphan), belladonna alkaloids (eg, scopolamine, hyoscyamine), inhaled bronchodilators (eg, ipratropium, tiotropium), mydriatics (eg, atropine, cyclopentolate), and antiepileptics (eg, carbamazepine, oxcarbazepine) among others. The anticholinergic

activity may be exerted through the medication's primary or secondary pharmacologic activity. Even in the therapeutic setting, co-ingestion of multiple medications with anticholinergic effects can have a synergistic effect on toxicity, which is particularly important in the elderly.[116] Antihistamines and decongestants are increasingly misused by adolescents and young adults seeking euphoric effects through "legal highs."[117]

Plants such as jimson weed (*Datura stramonium*), angel's trumpet (*Brugmansia*), and nightshade (*Atropa belladonna*) contain potent alkaloids including atropine, hyoscyamine, and scopolamine.[118-120] There are reports of anticholinergic toxicity following recreational use of jimson weed and Angel's trumpet in pursuit of their hallucinogenic properties.[119,120] Teas brewed from anticholinergic plants are also associated with causing toxicity.[121]

Incidence

Anticholinergic toxicity commonly occurs due to drug interactions, intentional ingestions, accidental ingestions, and misuse of medications or plants in the pursuit of a "legal high."[3,117] According to the 2019 AAPCC-NPDS annual report, there were over 200,000 calls to poison control centers about exposures to pharmaceutical classes of medications with anticholinergic properties (eg, 137,881 calls for antidepressant exposures; 112,819 calls for antihistamine exposures). Over the last decade, the 2019 AAPCC-NPDS determined that antihistamines had the second for greatest rate of exposure increase. Anticholinergic medication classes also occupied several of the spots in the top 25 categories with the largest number of fatalities reported to AAPCC-NPDS in 2019.[3] Up to 20% of hospital admissions may be caused by anticholinergic delirium.[122]

Risk Assessment

Anticholinergic toxicity is a clinical diagnosis and should be suspected when patients present with symptoms consistent with the anticholinergic toxidrome.[111] Multiple individual medications with anticholinergic properties have established thresholds for toxicity.[112,113,123,124] Sedating, first-generation antihistamines have greater potential for toxicity than non-sedating, second-generation antihistamines.[112,124] Thus exposures to less than 7.5 mg/kg of diphenhydramine or 300 mg of dimenhydrinate, which are both first-generation antihistamines, are unlikely to cause significant toxicity. This allows for asymptomatic pediatric patients with accidental exposures to be monitored at home.[112] Patient age and routine, home medications influence the toxic potential of atypical antipsychotic medications. Specifically, patients that are less than 12 years old and naïve to atypical antipsychotics may experience moderate toxicity following an ingestion of 4 or more times the initial atypical antipsychotic starting dose in an adult (ie, aripiprazole 15 mg, clozapine 50 mg, olanzapine 10 mg), whereas patients age 12 years and older that are naïve to atypical antipsychotic medications may experience moderate toxicity following an ingestion of 5 or more times the initial atypical antipsychotic starting dose in an adult. Those chronically on atypical antipsychotics are unlikely to experience significant toxicity following an acute ingestion of less than five times their current single dose.[123] TCAs have a narrow therapeutic index and their sodium channel blocking effects can cause profound cardiac toxicity in addition to anticholinergic effects. In children less than 2 years old, an exposure to as little as one pill can result in significant morbidity ("one pill can kill" medication).[125,126] In older patients, an accidental ingestion of greater than 5 mg/kg of amitriptyline or 2.5 mg/kg of nortriptyline would necessitate an evaluation in the ED.[113] Unless a patient was exposed to a sustained release product, significant toxicity will manifest within 6 to 8 hours of the exposure if it is to occur at all.[105,112,113,123]

Management of Toxicity

The treatment strategies differ depending on the severity of anticholinergic toxicity and agent(s) involved. Supportive care with an emphasis on maintaining the patient's airway, breathing, and circulation is part of standard care for patients with mild to severe anticholinergic toxicity. IV fluid resuscitation is utilized to correct the state of dehydration, provide hemodynamic support, and treat rhabdomyolysis. Benzodiazepines may be utilized for the treatment of seizures or agitation. Sodium bicarbonate boluses of 1 to 2 mEq/kg (mmol/kg) IV followed by continuous infusions run at 1.5 to 2 times the maintenance fluid rate can be used to reverse wide complex dysrhythmias.[127,128] Antidysrhythmic agents like lidocaine and vasopressors may be utilized to treat dysrhythmias and hypotension unresponsive to IV fluids, respectively. At least one IV access should be obtained. Following the obtainment of a baseline ECG, the clinical condition of the patient will drive the need for continuous cardiac monitoring, continuous pulse oximetry, and supplemental oxygen. GI decontamination with activated charcoal may be considered in patients who are not at risk of aspiration and present within 1 to 2 hours of ingestion.[30,129,130]

Physostigmine is a carbamate acetylcholinesterase inhibitor which can reverse both the central and peripheral manifestations of anticholinergic toxicity. Toxicologists have variable practices for when they recommend its use,[131] but it is typically reserved for the management of moderate-to-severe anticholinergic toxicity.[106,122,131-134] Physostigmine is more effective than benzodiazepines in controlling agitation and reversing delirium associated with anticholinergic toxicity, which leads to a shorter time to recovery.[106,122,133,135] When compared to patients receiving benzodiazepines, those receiving physostigmine have had lower rates of complications related to anticholinergic toxicity including sedation, aspiration, and intubation.[106]

Historically, physostigmine was associated with severe adverse effects, which have limited its widespread use. Specifically, there are three case reports of cardiac arrest following physostigmine administration in patients with tricyclic antidepressant overdoses experiencing severe cardiotoxicity including hypotension and wide complex dysrhythmias.[136,137] These cases occurred before sodium bicarbonate therapy was widely incorporated as the antidote for tricyclic antidepressant overdoses, so the lack of sodium bicarbonate antidote administration could have also contributed to the cardiac arrests.[113,128,136-138] More recent studies suggest that physostigmine rarely causes the significant adverse effects of bradycardia, bradydysrhythmias, or seizures.[106,122,133-135,139]

Due to its potential for serious adverse, patients are carefully assessed to determine if benefits of physostigmine administration outweigh the risks.[106,122,135] As a result, it is typically reserved for the treatment of moderate-to-severe anticholinergic toxicity and avoided in patients known or suspected to have a tricyclic antidepressant toxicity.[131,139] Before physostigmine administration, an ECG should be obtained to assess for widened QRS intervals greater than 100 to 120 ms,[122] which could suggest tricyclic antidepressant involvement.[140] At the time of physostigmine administration, patients should be placed on continuous cardiac monitoring and have atropine readily available to reverse physostigmine-induced cholinergic effects of bradycardia or bronchorrhea. The recommended physostigmine dose for adult patients is 0.5 to 2 mg IV over at least 5 minutes.[106,122] Pediatric patients receive a weight based dose of 0.02 mg/kg IV over at least 5 minutes with a maximum dose of 0.5 mg.[122] Slow IV administration helps reduce the risk of rate-dependent adverse effects like bradycardia and seizures. Additional doses may be repeated every 10 to 15 minutes for inadequate response or recurrence of moderate-to-severe anticholinergic toxicity.[122] Physostigmine's 45 to 60 minute duration of action is often shorter than that of the offending agent, which necessitates repeat doses of physostigmine in approximately one third of patients.[132]

Monitoring and Prevention

Anticholinergic poisoning may be a result of intentional suicide, unintentional ingestions, or drug-drug interactions due to coadministration of multiple agents with anticholinergic properties. In patients presenting with features of the anticholinergic toxidrome, clinicians should physically examine patients for transdermal patches like scopolamine and remove them from the patient's body. Concealment of scopolamine transdermal patches by clothing can continue to exacerbate toxicity in addition to delay the recognition, identification, and management of anticholinergic toxicity.[141] Regular monitoring of vital signs and ECG is essential in suspected anticholinergic overdoses. Severe toxicity can manifest cardiotoxic effects such as dysrhythmias. Serum electrolytes, serum glucose, kidney function, CPK, and urine output aid in the assessment and monitoring of symptomatic patients. Bladder scans are beneficial to assess for urinary retention, which can exacerbate agitation. If serious toxicity is likely to develop, patients will exhibit peripheral or central anticholinergic effects within 6 hours of ingestion. Exposure to a sustained release product with anticholinergic properties may delay the development of symptoms by approximately 12 to 24 hours.

Polypharmacy is common in elderly patients.[142] Pharmacists can help prevent anticholinergic toxicity in this patient population through the review of patient home medications for opportunities to deprescribe anticholinergic medications.[116]

Opioids

Clinical Presentation

10 Acute opioid poisoning can produce life-threatening effects that typically include respiratory depression and coma that may lead to death.[143] Virtually all opioids produce these symptoms and some agents have additional toxic effects. The time of onset and severity of symptoms depend on the route of exposure, formulation of the drug product, potency of the opioid 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 dermal patches on the skin, which exhibit 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 kidney injury. Seizures, dysrhythmias, 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 co-ingestion of acetaminophen-containing medications, and infectious diseases from IV drug use may occur.[143]

Mechanism of Toxicity

Action at the μ-opioid receptor is primarily responsible for many of the life-threatening effects of opioids, such as respiratory depression and sedation, and all opioid analgesics 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.[144] Methadone acts on the myocardium to block potassium efflux leading to dysrhythmias such as Torsades de pointes, syncope, and sudden death.[145] Tapentadol and tramadol block reuptake of norepinephrine and serotonin, respectively, and are associated with seizures.[143]

Causative Agents

Many opioid drugs are available in the United States for the management of moderate-to-severe pain (see Chapter 79). These include drugs that are naturally found in opium (ie, opiates such as morphine and codeine), synthetic opioids (eg, fentanyl, methadone, and meperidine), and semisynthetic opiate derivatives (eg, hydromorphone, hydrocodone, and oxycodone). Heroin is a schedule I controlled substance and illicit drug. It produces more euphoria than many other opioids and 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. Illicitly manufactured analogs often have much greater potency unbeknownst to the user and thus increase the risk of a lethal overdose.[146]

Incidence

Based on provisional estimates for 2017 approximately 49,000 Americans died from opioid overdoses, including analgesics, heroin and illicit synthetic opioids, which represents a 4.1-fold increase compared to 2002. Deaths related to fentanyl and fentanyl analogs accounted for the sharpest increase with nearly 30,000 deaths—a 22-fold increase compared to 2002. During this same period heroin-related deaths increased 7.6-fold with approximately 16,000 deaths in 2017. Prescription opioid pain relievers accounted for 17,087 deaths in 2016 which was a 2.6-fold increase compared to 2002.[147] Poisoning from opioids occurs in all age groups, from neonates through intrauterine exposure to the elderly, and in rural and urban areas. Poisoning can occur from a variety of circumstances such as the unintentional ingestion of medicines by young children. Inadvertent overdoses can occur in adolescents or adults from taking single or multiple "therapeutic" doses of opioids with several sedating drugs (particularly benzodiazepines). Using opioids to produce self-harm can end in suicide and abusing opioids as part of a substance use disorder may also lead to death. The 2019 AAPCC-NPDS report documented 21,211 nonfatal single-product exposures that were voluntarily reported to poison centers, 4,311 with severe symptoms, and 284 deaths from opioids alone; 55% of the cases were associated with intentional use and 14% of exposures occurred in children younger than 6 years of age.[3]

CLINICAL PRESENTATION: 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.

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, and severe hypoxia).
- Unresponsiveness and depressed reflexes.
- Mild hypotension and bradycardia, worsening with increasing hypoxia.
- Absent bowel sounds, GI hypomotility.
- Hypothermia if exposed to cold conditions.
- Frothy pink sputum, end-inspiratory crackles on auscultation, and shortness of breath several hours after exposure consistent with pulmonary edema.
- QT-interval prolongation leading to Torsades de pointes on ECG with methadone.
- One or more opioid-containing drug patches (eg, fentanyl) on the skin.
- “Needle tracks” or skin infections if IV drug user.

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 ALT in case an opioid-acetaminophen combination product ingested.

Other Diagnostic Tests

- Pulse oximetry and ECG with continuous monitoring.
- Monitor for complications of pulmonary aspiration such as hypoxia and pneumonitis by physical findings and chest radiographs.
- Monitor for complications of rhabdomyolysis (creatine kinase, electrolytes) and subsequent acute kidney injury (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 or substance abuse paraphernalia 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.[11,43,143] Clonidine and certain atypical antipsychotics (eg, olanzapine) may present similarly. 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 routine drug screen because many opioids are not detected (see Table e8-6) 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.[143] Symptomatic cases of opioid overdoses should be transported to an ED for evaluation and treatment. Naloxone is the primary treatment in the prehospital setting. In the current opioid epidemic, naloxone availability has increased and there is a focus on preparing family members, friends, and bystanders to respond to overdoses. The number of naloxone training programs has increased, and many states have made naloxone available without a prescription. The intranasal route is safest for bystanders and prehospital providers, and newer formulations of naloxone have made administration by this route even easier.

Activated charcoal is generally not administered to adult patients with suspected opioid overdose. However, for unintentional ingestions (eg, children), charcoal may be considered after weighing the risks of pulmonary aspiration (ie, if vomiting occurs in a patient with altered or worsening mental status), if the opioid has been ingested within 1 hour.[30,143] 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. Whole bowel irrigation can 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.[33,34,143]

Naloxone is a competitive opioid receptor antagonist that acts on known opioid receptors to reverse the toxic effects of opioids (Table e8-13) 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 action of 20 to 90 minutes.[43] Intramuscular, intraosseous, intralingual injection, intranasal, and intratracheal instillation are also effective if the IV route is not immediately available. Oral administration is ineffective for reversing CNS opioid intoxication due to its low bioavailability but can be used for opioid-induced ileus. Naloxone for injection is available in concentrations of 0.02, 0.4, and 1 mg/mL. The effect of naloxone may not be evident in several circumstances (see Table e8-13) and the initial dose may not be sufficient.

TABLE e8-13

Responses to Naloxone in Opioid Poisoning

Therapeutic Reversal of Toxicity	Factors for Poor or No Response
Respiratory depression	Polydrug overdose (eg, benzodiazepines, sedatives, muscle relaxants, ethanol)
CNS depression	Inadequate dose of naloxone
Miosis	Concurrent head injury
Cardiovascular depression	Hypoglycemia
Gastrointestinal hypomotility	Hypoxic state (CNS, acid/base disorders)
Euphoria	Postictal state
Dependence leading to withdrawal	No opioid involved

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.[148] Intravenous

dosage regimens have evolved from clinical experience and differ from the recommended starting dose of 0.4 to 2 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 IV 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.[43,148] 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 and methadone often require doses in the upper range for a response.[148] The duration of naloxone's effect is generally shorter than many opioids (usually 45-60 minutes), 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.[43] The IM autoinjector delivers naloxone 2 mg per injection and the intranasal spray delivers 4 mg per use and are typically used for children and adults by first-responders and trained bystanders.

In patients with no opioid present, 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. In opioid-dependent patients, however, hypertension, hyperventilation, and tachycardia can occur and may be related to the release of catecholamines and other mediators in response to stress from abrupt withdrawal.[148] Agitation, confusion, and vomiting are possible additional effects following naloxone administration. 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.[43,149]

Monitoring and Prevention

Poisoned patients may require monitoring of vital signs, ventilatory adequacy (ie, 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 kidney injury, or seizures. Determination of a serum acetaminophen concentration is warranted to rule out the coincidental ingestion of acetaminophen with an opioid-acetaminophen combination product.[143]

The rising number of deaths from prescription opioid analgesics has been categorized as an epidemic by the Centers for Disease Control and Prevention (CDC). Multiple strategies have been implemented and proposed to prevent opioid-related deaths.[150] A controlled substances monitoring database (also called a prescription drug monitoring program) 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.[151] Enforcement and implementation of laws on "doctor shopping," indiscriminate 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 implemented a Risk Evaluation and Mitigation Strategy for oral opioids that involve prescriber training on appropriate prescribing practices. "Drug take-back" events to dispose of unneeded medications have been conducted in communities nationwide. 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. Most states have enacted laws to allow intranasal or intramuscular administration of naloxone by trained bystanders and law enforcement officers 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.[152] 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.

Weapons of Mass Chemical Poisoning

Clinical Presentation

11 Most chemicals used in warfare or terrorist attacks act immediately upon contact with the skin, mucous membranes, or respiratory tract. The variety of potential agents has been generally categorized by the type of toxic action or target organ system (Table e8-14) that also reflects the anticipated signs and symptoms of poisoning. Typically, clusters of victims have similar presentation, but the extent and onset of injury depends upon the person's level of exposure, which is related to their proximity to the source of the chemical, the method of deployment (eg, vapor, liquid, gas, and aerosol explosive device) and the mechanism of toxicity of the chemical. Inhalational exposures to nerve agents or cyanide will produce symptoms and sometimes death within minutes of exposure, whereas slower absorption with dermal contact will delay the onset. Agents such as sulfur mustard and phosgene may take 4 to 6 hours for onset of toxicity.[12] Some toxins of biologic origin, such as ricin, often require days to weeks for characteristic

symptoms to develop due to the mechanism of action. Nerve agents are highly potent anticholinesterases that have the same pathogenesis of toxicity (see Fig. e8-2) and produce the full spectrum of signs and symptoms of organophosphate insecticides (see Table e8-14).[12,153] One of the several major differences between nerve agents and organophosphate insecticides is the hyperacute onset of life-threatening symptoms, such as fulminant respiratory failure within seconds to minutes with nerve agents.[12] Another difference is the extreme oculogyric torsion with nerve agents that may require administration of tropicamide ophthalmic drops to relieve eye pain. Moderate-to-severe poisonings from chemical warfare or terrorist agents will typically require care in an intensive care unit.[154]

TABLE e8-14

Categories of Chemicals of Mass Poisoning

Category and General Effects	Examples*
Biotoxins *(variety of toxicities from plant or animal origin)*	Ricin
Blister Agents/Vesicants *(severely blister the eyes, respiratory tract, and skin on contact)*	Mustards, sulfur mustard gas (H), lewisites (L), chloroarsine agents, phosgene oxime (CX)
Blood Agents *(interfere with the delivery and use of oxygen)*	Arsine (SA), carbon monoxide, cyanides, sodium monofluoroacetate
Choking/Lung/Pulmonary Agents *(cause severe irritation or swelling of the respiratory tract)*	Ammonia, chlorine, hydrogen chloride, methyl isocyanate, phosgene (CG), phosphine
Corrosives (Caustics, Acids) *(burn or corrode skin, eyes, and mucus membranes on contact)*	Hydrofluoric acid, hydrogen chloride, sulfuric acid
Incapacitating Agents *(cause an altered state of cognition and consciousness or unconsciousness)*	Fentanyl analogs and other opioids, "QNB" 3-quinuclidinyl benzilate (BZ)
Metals *(heavy metals that disrupt cellular function)*	Arsenic, mercury, thallium
Nerve Agents *(anticholinesterases that affect normal functioning of peripheral and central nervous systems)*	Novichok agents, Sarin (GB), soman (GD), tabun (GA), VX
Riot Control Agents/Tear Gas *(cause significant irritation of the eyes, skin, and airway)*	Bromobenzylcyanide (CA), chloroacetophenone (CN), chlorobenzylidenemalononitrile (CS), chloropicrin (PS), dibenzoxazepine (CR)
Vomiting Agents *(cause severe nausea and vomiting)*	Adamsite (DM)

*North Atlantic Treaty Organization (NATO) code in parentheses.

Data from Emergency Preparedness and Response: Chemical Emergencies.

Centers for Disease Control and Prevention. Atlanta, GA. November 25, 2014. http://emergency.cdc.gov/chemical/index.asp.

Mechanism of Toxicity

There is no single unifying mechanism of toxicity of the chemicals used for warfare or terrorism because of the variety of different agents involved (see Table e8-14). The mechanism for nerve agents is well characterized by its anticholinesterase action (see earlier section on Anticholinesterase Insecticides).[76,153] Some agents act by an extreme exaggeration of their pharmacologic actions such as BZ producing extreme anticholinergic CNS

effects and fentanyl analogs producing extreme opioid toxicity (see **CLINICAL PRESENTATION BOX** for acute opioid poisoning). Vesicants, such as sulfur mustard, irreversibly alkylate deoxyribonucleic acid (DNA), RNA and proteins and produce burns, blisters, and tissue destruction.[153] Blood agents act in several ways, but ultimately interfere with the transport or utilization of oxygen by cells. Cyanide, for example, is a potent competitive inhibitor of cytochrome oxidase and other enzymes and stops cellular respiration throughout the body.[12,153] Pulmonary agents, such as chlorine or phosgene, both react with water to produce hydrochloric acid, which produces severe irritation and destruction to mucosal tissue, ocular surfaces, the airway and lungs.[153]

Causative Agents

Many different chemicals have been used or have been recognized for their potential for terrorism or warfare (see Table e8-14). Adaptation of other commercial chemicals, synthesis of analogs of existing toxins, or creation of novel chemicals may introduce additional hazards in the future.

Incidence

The use of chemical weapons during the past century has been documented in numerous warfare and terrorism settings that produced mass casualties. For example, during World War I, 100,000 deaths and 1.2 million casualties were attributed to attacks with chlorine, phosgene or mustard.[155] In 1995, terrorists released sarin in the Tokyo subway system, leading to 11 deaths and 5,510 people seeking medical attention including many first-responders.[156,157] More recently, in the United Kingdom, a Novichok anticholinesterase agent was implicated in a 2018 assassination attempt of a former Russian spy and his adult daughter.[158]

Risk Assessment

Assessment of injuries at the scene, triage stations, and healthcare facilities should identify victims at greatest risk and priority for treatment. The acute onset of serious symptoms in many victims without signs of trauma suggests a mass chemical exposure. Patients with typical clusters of symptoms, such as those associated with anticholinesterase agents, may provide clues to the type of chemical and guide treatment.[12,159]

Management of Toxicity

High priorities for managing exposures to chemical warfare or terrorism agents are to evacuate victims from the contaminated area, decontaminate any exposed surfaces with first aid measures (see Table e8-8), and removal of contaminated clothing.[159] First-responders should guard against being poisoned by wearing personal protective equipment, such as body suits, gloves, boots, and air supply, as appropriate for the situation. Supportive and symptomatic care with attention to airway, breathing and circulation are critical for all types of exposures and may be the extent of treatment options useful for a toxin.[12,154,159,160] Most chemicals associated with mass poisoning exposures do not have a specific therapy or antidote. Several toxins, such as nerve agents, opioids, and cyanides, do have specific antidotes that may be life-saving (see Table e8-9). The sooner therapy can be instituted in the field, as in carrying atropine, pralidoxime, and diazepam autoinjectors in an area where a nerve agent attack is anticipated, generally the better the outcome will be. Depending upon the conditions, additional decontamination before a victim enters a healthcare facility may be necessary to avoid contaminating healthcare workers and other patients in the treatment area. Guidance on treatment for a specific chemical exposure is available at several Websites of the Centers for Disease Control and Prevention (CDC) (http://emergency.cdc.gov/chemical/index.asp; www.cdc.gov/NIOSH/ershdb/default.html; www.atsdr.cdc.gov).

Monitoring and Prevention

Survivors of a chemical attack may develop long-term effects or life-long disabilities.[161] For example, vesicants have been associated with cancer, severe burns, and scars; pulmonary agents may produce permanent respiratory conditions; and nerve agents may lead to short- and long-term neuromuscular disabilities. Victims of any mass poisoning are at risk for developing psychological distress after the attack and warrant follow-up once the acute medical condition is stabilized.

Prevention of chemical attacks is beyond the scope of healthcare professionals' standard responsibilities; however, preparation for mass chemical emergencies is a vital element of mass casualty preparedness. Working with local health department representatives, safety officials and other healthcare professionals to develop a community plan is important because no single site can likely provide the necessary resources to treat the

number of victims. The CDC has resources that provide guidance on medical management of chemical hazards (http://emergency.cdc.gov/agent/agentlistchem.asp), healthcare preparedness and response (https://www.cdc.gov/phpr/readiness/healthcare/index.htm), and access to the Strategic National Stockpile (http://www.cdc.gov/phpr/stockpile/stockpile.htm) among other areas of interest.

ABBREVIATIONS

AAPCC-NPDS	American Association of Poison Control Centers—National Poison Data System
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
BZ	3-quinuclidinyl benzilate
CDC	Centers for Disease Control and Prevention
CNS	central nervous system
CVVH	continuous veno-venous hemofiltration
CYP	cytochrome P450
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ED	emergency department
ECMO	extracorporeal membrane oxygenation
Fab	fragment antigen binding
FDA	Food and Drug Administration
GI	gastrointestinal
IV	intravenous
INR	international normalized ratio
NAPQI	*N*-acetyl-*p*-benzoquinoneimine
PPPA	Poison Prevention Packaging Act of 1970
RNA	ribonucleic acid

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SELF-ASSESSMENT QUESTIONS

1. Which of the following statements are true characterizations of poisonings in children and adults?

   A. Medicines are the most common cause of poisoning in adults and children.

   B. More children die from poisonings than adults.

   C. Only adults may act purposefully or with obvious intent to ingest a substance that may be poisonous.

   D. Only children may not recognize a product's risk for poisoning.

2. Which one of these examples of first aid for poisoning is correct?

   A. Immediately rinse the eye with sterile water when a chemical is splashed on it.

   B. For an ingested poison, 2-4 ounces (60-120 mL) of water can be given unless the person is unconscious, having convulsions, or cannot swallow.

   C. Contact a poison control center after symptoms develop.

   D. Inhaled poisons typically cannot penetrate a handkerchief over the nostrils so that it can be used to protect against fumes in order to rescue someone.

3. In which of the following circumstances should the particular form of gastric decontamination be used for a person who swallowed something that could be poisonous?

   A. Gastric lavage should be used routinely for those who have ingested a liquid or small tablet.

   B. Single-dose activated charcoal should be considered for most ingestions if contraindications are not present.

   C. Whole bowel irrigation should be started for any ingestion of a plant, foreign body, or large tablet.

   D. A cathartic such as magnesium citrate should be administered for all ingestions.

4. A 24-year-old woman who has acutely ingested immediate-release acetaminophen tablets 10 hours ago has a serum acetaminophen concentration of 100 µg/mL (660 µmol/L). Her only complaint is nausea and she has vomited several times in the past 2 hours. No other drugs are suspected. Which of the following would be appropriate?

   A. Repeat the serum concentration and wait 2 hours for the results

   B. Administer activated charcoal orally

   C. Begin therapy with intravenous acetylcysteine

   D. Begin therapy with oral acetylcysteine

5. Which of the following is a potential advantage of the intravenous formulation of acetylcysteine compared to the oral formulation?

   A. Medication administration errors are infrequent with the intravenous formulation.

   B. The duration of therapy is shorter with the intravenous formulation.

   C. The total dose of acetylcysteine is greater with the intravenous formulation.

   D. The systemic adverse effects are no different than those with the oral formulation.

6. What is the preferred treatment for a 55-year-old farmer who is exhibiting excessive bronchial and oronasal secretions following exposure to an organophosphate insecticide and is otherwise healthy?

A. Atropine intravenously

B. Diphenhydramine orally

C. Physostigmine intramuscularly

D. Pralidoxime intramuscularly

7. Which of the following is true regarding the treatment of an organophosphate insecticide poisoning?

A. Doses of atropine necessary to treat organophosphate poisoning are similar to those normally used to treat simple bradycardia in patients not poisoned with organophosphates.

B. An endpoint of therapy with atropine is an acceptable heart rate.

C. Excessive drying of bronchial secretions may contribute to death.

D. An endpoint of therapy with pralidoxime is an improved and acceptable respiratory effort.

8. Which of the following is true regarding calcium channel antagonist overdose?

A. The drugs in the chemical classes of calcium channel antagonists differ in their predominant toxicity upon overdose.

B. Hypoglycemia occurs due to excess insulin release.

C. Concurrent ingestion of beta adrenergic blockers or digoxin may worsen the cardiovascular toxicity.

D. The onset of toxicity of immediate-release formulations is often delayed by 6 to 18 hours.

9. Beyond standard supportive care, what drug, given intravenously, is preferred as the first choice for bradycardia and hypotension from a calcium channel antagonist overdose?

A. Calcium chloride

B. Norepinephrine

C. Atropine

D. Lipid intravenous emulsion

10. Which of the following is true regarding the clinical presentation of anticholinergic toxicity?

A. Coma, respiratory depression, miosis

B. Hypotension, bradycardia, altered mental status, hypoglycemia

C. Dry mucous membranes, urinary retention, mydriasis, tachycardia, delirium

D. Diarrhea, urination, miosis, bronchospasm, bronchorrhea, bradycardia, emesis, lethargy, lacrimation, salivation

11. What is the treatment of choice for a 30-year-old male who overdosed on diphenhydramine and is now experiencing signs of severe anticholinergic toxicity including sinus tachycardia with ECG demonstrating a QRS of 80 ms, bladder scan demonstrating 500 mL of retained urine, and agitation?

A. Pralidoxime intravenously

B. Atropine intravenously

C. Lorazepam intravenously

D. Physostigmine intravenously

12. Which collection of sign and symptoms would suggest an acute overdose of an opioid?

A. Depressed respirations, miosis, and unresponsiveness

B. Hypotension, bradycardia, and hyperglycemia

C. Muscle fasciculations, miosis, and shortness of breath

D. Vomiting, diarrhea, and hypotension

13. Which of the following can be a factor in poor reversal of opioid toxicity by naloxone?

A. Gastrointestinal hypomotility

B. Hyperglycemia

C. Opioid dependence

D. Overdose with other drugs that have sedating effects

14. Dermal exposure to which of the following chemical weapons is most likely to produce seizures and increased body secretions?

A. Chlorine

B. Hydrogen cyanide

C. Lewisite

D. Sarin

15. The pharmacologic mechanism of action of a nerve agent is most similar to which of the following drug categories?

A. Anticholinergics

B. Anticholinesterases

C. Calcium channel blockers

D. Opioids

SELF-ASSESSMENT QUESTIONS-ANSWERS

1. **A.** Medicines were the most frequently involved (49%) substances for all age groups. While children account for most reported exposures to poison control centers, fatal poisonings are more common in adults. Intentional poisonings are most common in adults; however, approximately 23% of pediatric exposures reported to the National Poison Data System in 2020 were intentional. Both children and adults may not recognize a product's risk of toxicity.

2. **B.** In patients that are not at risk of aspiration, drinking 2 to 4 ounces (60 - 120 mL) of water promotes dilution which may reduce the absorption of the ingested poison or minimize the poison clinical effects related to gastric irritation. Following ocular chemical exposures, the open eye should be flooded with lukewarm or cool water poured from a glass 2 to 3 in. (5-8 cm) before flushing the eye. Afterwards, the eyes should be flushed for 10 to 15 continuous minutes. Poison Control Centers should be contacted as soon as possible regardless of symptom development. Inhaled poisonings have varying particle sizes and can be small enough to pass through a handkerchief leading to toxicity.

3. **B.** Activated charcoal is the most common method of gastric decontamination due to its effectiveness and safety profile when administered early

following the ingestion of an oral agent in patients who are not at risk of aspiration. Gastric lavage and whole bowel irritation are only administered in certain poisonings in which activated charcoal cannot be used. Gastric lavage is not routinely recommended due to it being a more invasive procedure that only experienced clinicians should perform due to its complications. Whole bowel irrigation is used for specific ingestions, such as delayed-release or enteric coated drug formulations, iron, lithium, and potassium. Cathartics are rarely if ever given without concurrent activated charcoal administration. Cathartics should only be given once and only if bowel sounds are present.

4. **C.** A 10-hour serum acetaminophen concentration of 100 µg/mL (660 µmol/L) crosses the Rumack-Matthew nomogram line indicating the need for treatment with acetylcysteine. Acetylcysteine is most effective when administered within 10 hours of the ingestion. Intravenous acetylcysteine would be preferred in this situation, because the unpalatable taste and high incidence of vomiting after oral acetylcysteine can lead to delays or interruptions in antidote therapy which puts the patient at an increased risk of developing hepatotoxicity. Activated charcoal would not be appropriate for this patient, since the ingestion occurred more than 2 hours ago and the patient is actively vomiting, which would put them at risk of aspirating the activated charcoal. Serum acetaminophen concentrations are reliable after 4 hours from the time of ingestion, so there is no need to repeat the drug level to determine if antidote therapy is indicated.

5. **B.** The standard acetylcysteine treatment course is 21 hours with the intravenous formulation and 72 hours with the oral formulation, respectively. Medication administration errors, including delays in treatment related preparation, administration of the “three-bag” acetylcysteine in the incorrect order, and administration of the “three-bag” acetylcysteine over the incorrect time frame, have been reported with the intravenous formulation of acetylcysteine. Oral acetylcysteine has a total dose of 1440 mg/kg which is greater than the total dose of 300 mg/kg with the intravenous formulation. Oral acetylcysteine is associated with more adverse effects related to nausea and vomiting while the intravenous acetylcysteine has been associated with more anaphylactoid reactions.

6. **A.** Atropine is the preferred antidote for a cholinergic toxidrome. Diphenhydramine would not reduce the excessive secretions and oral administration would be challenging in patients already having difficulty managing their secretions. Physostigmine is the antidote for symptomatic patients experiencing an anticholinergic toxidrome. Pralidoxime can be administered for organophosphate toxicity; however, it would be administered in conjunction with atropine and the intravenous administration of pralidoxime would be preferred over intramuscular administration.

7. **D.** Bronchorrhea and bronchospasms are often responsible for fatal organophosphate insecticide poisonings. Pralidoxime helps to treat the respiratory muscle weakness, and improved respirator rates and efforts are appropriate endpoints of therapy. The amount of atropine needed to treat organophosphate insecticide poisoning often exceeds the doses used to treat bradycardia in non-poisoned patients. Tachycardia is tolerated with atropine treatment in order to reverse the cholinergic toxidrome-related bradycardia, bronchorrhea, and bronchospasms. The intended effect of our treatments for organophosphate insecticide poisoning is to dry the excessive secretions to prevent the patient from drowning in their own secretions.

8. **C.** Calcium channel blockers, beta adrenergic blockers, and digoxin are all cardiac toxins. Coingestion of these agents can lead to additive or synergistic toxicity resulting in hypotension, bradycardia, and dysrhythmias. Nondihydropyridine calcium channel antagonists are more commonly reported in severe calcium channel blocker overdoses; however, both dihydropyridine and nondihydropyridine calcium channel antagonists result in similar toxicities. Calcium channel antagonist overdoses most often result in hyperglycemia while beta adrenergic blockers typically cause hypoglycemia. Toxicity presents within hours and is not delayed by 6 to 18 hours following overdoses of immediate release calcium channel antagonists.

9. **A.** Calcium chloride is usually given first for bradycardia related to a calcium channel blocker overdose, because it is readily available, can be administered quickly, and mechanistically helps to counteract the adverse effects of this type of overdose. Vasopressors like norepinephrine may be used to treat bradycardia and hypotension; however, they are typically given after or in addition to calcium. Many institutions require patients receiving continuous infusions of vasopressors to be admitted to the intensive care unit, which may prompt providers to see if patients can be successfully managed with intravenous calcium and supportive care first. Additionally, central access is preferred for vasopressor administration while intravenous calcium gluconate can be given safely through peripheral intravenous lines. Atropine may be used for bradycardia; however, it often does not reverse bradycardia from calcium channel antagonist overdoses because it does not target the mechanisms in which this type of overdose causes the bradycardia and hypotension. Lipid intravenous emulsion therapy would only be considered in cases refractory to standard of care treatment with calcium, vasopressors, or high-dose insulin therapy.

10. **C.** The anticholinergic toxidrome mnemonic consists of “hot as a hare” (fever), “red as a beet” (flushed skin), “blind as a bat” (mydriasis), “dry as a bone” (dry mouth, decreased sweating), “mad as a hatter” (delirium), and “full as a flask” (urinary retention). Tachycardia is also seen with anticholinergic toxicity. The opioid toxidrome consists of coma, respiratory depression, and miosis. Beta adrenergic blocker toxicity can result in hypotension, bradycardia, altered mental status, and hypoglycemia. Cholinergic toxicity results in diarrhea, urination, miosis, bronchospasm, bronchorrhea, bradycardia, emesis, lethargy, lacrimation, and salivation (“DUMBELLS” menumonic).

11. **D.** Physostigmine is the preferred antidote for moderate-to-severe anticholinergic toxicity without evidence of QRS prolongation on ECG. Patients treated with physostigmine have shorter recovery times and fewer complications compared to patients treated with benzodiazepines. Pralidoxime and atropine are treatments for cholinergic toxicity. Lorazepam may be used for anticholinergic toxicity; however, physostigmine is more effective than benzodiazepines at controlling agitation and reversing delirium associated with anticholinergic toxicity.

12. **A.** The opioid toxidrome consists of the triad of respiratory depression, coma, and miosis. Calcium channel blocker toxicity can result in hypotension, bradycardia, and hyperglycemia. Muscle fasciculations would be uncommon with opioid overdoses. Muscle fasciculations, miosis, and difficulty breathing can be observed along with other symptoms in patients experiencing cholinergic toxicity from organophosate insecticide poisonings or nerve gases. Vomiting, diarrhea, and hypotension are not common signs of an acute opioid overdose. Vomiting and diarrhea would be more characteristic of acute opioid withdrawal.

13. **D.** Naloxone will reverse respiratory and central nervous system depression related to opioid toxicity; however, it will not reverse the sedating properties of other medications or toxins with sedative hypnotic effects. Naloxone for opioid reversal is not administered orally so gastrointestinal motility does not factor in. Hyperglycemia does not impact naloxone’s ability to reverse opioids. Naloxone is still effective for patients with opioid dependence. Acute opioid withdrawal can be seen following naloxone administration in patients with a history of opioid dependence.

14. **D.** Sarin, a nerve agent, can cause seizures and increased secretions. Chlorine, hydrogen cyanide, and lewisite are other chemical weapons. Chlorine gas is a pulmonary irritant. Hydrogen cyanide is a “knock out” gas and exposures can lead to seizure, coma, hypotension, lactic acidosis, and cardiac arrest. Lewisite exposures cause painful blisters on the skin, shortness of breath, cough, gastrointestinal distress, and hypotension.

15. **B.** Nerve agents are well characterized by its anticholinesterase action and resultant cholinergic toxicity. Anticholinergics are competitive antagonists of acetylcholine at the muscarinic receptors and lead to a toxidrome that is almost the opposite of the cholinergic toxidrome seen with nerve agents. Calcium channel blockers inhibit. Opioids are agonists of the μ, κ, and δ receptors.