I   MANAGEMENT OF POISONING AND DRUG OVERDOSE

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Drug overdose and poisoning are leading causes of emergency department visits and hospital admissions in the United States, accounting for more than 250,000 emergency department visits[1] and 7,000 deaths[2] each year. Exposure to poison can occur in several ways. The patient may have ingested it accidentally or for the purpose of committing suicide, may be a victim of accidental intoxication from acute or chronic exposure in the workplace, may be suffering from unexpected complications or overdose after intentional drug abuse, or may be a victim of an assault or terrorist attack. Poisons can include drugs; chemicals; biotoxins in plants, mushrooms, or foods; and toxic gases. In all cases of poisoning, the clinician has several priorities: (1) immediately stabilize the patient and manage life-threatening complications; (2) perform a careful diagnostic evaluation, which includes obtaining a directed history, performing a physical examination, and ordering appropriate laboratory tests; (3) prevent further absorption of the drug or poison by decontaminating the skin or gastrointestinal tract; and (4) consider administering antidotes and performing other measures that enhance elimination of the drug from the body. For expert assistance with identification of poisons, diagnosis and treatment, and referral to a medical toxicologist, the clinician should consider consulting with a regional poison-control center.

Initial Stabilization

In many cases of poisoning, the patient is awake and has stable vital signs, which allows the clinician to proceed in a stepwise fashion to obtain a history and to perform a physical examination. In other cases, however, the patient is unconscious, is experiencing convulsions, or has unstable blood pressure or cardiac rhythm, thus requiring immediate stabilization [see Table 1].

The first priority is the airway. The airway's reflex protective mechanisms may be impaired because of drug-induced central nervous system depression (e.g., from opioids or sedative-hypnotic agents), excessive bronchial and oral secretions (e.g., from organophosphate insecticides), or swelling or burns (e.g., from corrosive agents or irritant gases). The airway should be cleared by the use of suction and by repositioning the patient; if the patient has an impaired gag reflex or other evidence of airway compromise, a cuffed endotracheal tube should be inserted. The adequacy of ventilation and oxygenation should be determined by clinical assessment, pulse oximetry, measurement of arterial blood gases, or a combination of these techniques. Supplemental oxygen should be administered, and if necessary, ventilation should be assisted with a bag/valve/mask device or a ventilator.[3] Even if the patient is not unconscious or hemodynamically compromised on arrival in the emergency department, continued absorption of the ingested drug or poison may lead to more serious intoxication during the next several hours. Therefore, it is prudent to keep the patient under close observation, with continuous or frequent monitoring of alertness, vital signs, the electrocardiogram, and pulse oximetry.

Management of Common Complications

COMA

Poisoning or drug overdose depresses the sensorium, the symptoms of which may range from stupor or obtundation to unresponsive coma. Deeply unconscious patients may appear to be dead because they may have nonreactive pupils, absent reflexes, and flat electroencephalographic tracings; however, such patients may have a complete recovery without neurologic sequelae as long as they receive adequate supportive care, including airway protection, oxygenation, and assisted ventilation.[4]

All patients with a depressed sensorium should be evaluated for hypoglycemia because many drugs and poisons can directly reduce or contribute to the reduction of blood glucose levels. A finger-stick blood glucose test and bedside assessment should be performed immediately; if such testing and assessment are impractical, an intravenous bolus of 25 g of 50% dextrose in water should be administered empirically before the laboratory report arrives.[5] For alcoholic or malnourished persons, who may have vitamin deficiencies, 50 to 100 mg of vitamin B_1 (thiamine) should be administered I.V. or I.M. to prevent the development of Wernicke syndrome.[5] If signs of recent opioid use (e.g., suspicious-looking pill bottles or I.V. drug paraphernalia) are in evidence or if the patient has clinical manifestations of excessive opioid effect (e.g., miosis or respiratory depression), the administration of naloxone may have both therapeutic and diagnostic value. Naloxone is a specific opioid antagonist with no intrinsic opioid-agonist effects.[6,7] Initially, a dose of 0.2 to 0.4 mg I.V. should be administered, and if there is no response, repeated doses of up to 4 to 5 mg should be given; doses as high as 15 to 20 mg may be administered if overdose with a resistant opioid (e.g., propoxyphene, codeine, or some fentanyl derivatives) is suspected.[6,7] Patients with opioid intoxication usually become fully awake within 2 to 3 minutes after naloxone administration. Failure to respond to naloxone suggests that (1) the diagnosis is

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Table 1   The ABCDs of Initial Stabilization of the Poisoned Patient

Airway
Position the patient to open the airway; suction any secretions or vomitus; evaluate airway protective reflexes; consider endotracheal intubation

Breathing
Determine adequacy of ventilation; assist ventilation, if necessary; administer supplemental oxygen

Circulation
Evaluate perfusion, blood pressure, and cardiac rhythm; determine QRS complex; attach continuous cardiac monitor

Dextrose
Quickly determine blood glucose by finger-stick test; give dextrose if patient is suspected of having hypoglycemia

Decontamination
Perform surface and gastric decontamination to limit absorption of poisons

Table 2   Mechanisms of Drug-Induced Hypotension

Mechanism	Selected Causes

Hypovolemia
  Vomiting and
   diarrhea
	Iron; arsenic; food poisoning; organophosphates and carbamates; mushroom poisoning; thallium

Sweating	Organophosphates and carbamates
Venodilatations	Barbiturates; other sedative-hypnotic agents
Depressed cardiac contractility	Tricyclic antidepressants; beta blockers; calcium antagonists; class IA and class IC antiarrhythmic agents; sedative-hypnotic agents
Reduced peripheral vascular resistance	Theophylline; beta$_2$-adrenergic stimulants; phenothiazines; tricyclic antidepressants; hydralazine

incorrect [*see* Factors to Be Excluded in Diagnosis, *below*]; (2) other, nonopioid drugs may have been ingested; (3) a hypoxic insult may have occurred before the victim was found and resuscitated; or (4) an inadequate dose of naloxone was given.

Flumazenil, a short-acting, specific benzodiazepine antagonist with no intrinsic agonist effects, can rapidly reverse coma caused by diazepam and other benzodiazepines.[5,7] However, it has not found a place in the routine management of unconscious patients with drug overdose, because it has the potential to cause seizures in patients who are chronically consuming large quantities of benzodiazepines or who have ingested an acute overdose of benzodiazepines and a tricyclic antidepressant or other potentially convulsant drug [*see* Sedative-Hypnotic Agents, *below*]. [5,7]

HYPOTENSION AND CARDIAC DYSRHYTHMIAS

The hypotension that commonly complicates drug intoxication has many possible causes [*see Table 2*].[8,9] Hypotension may result from volume depletion caused by severe drug-induced vomiting or diarrhea. In addition, relative hypovolemia may be caused by the venodilating effects of many drugs. Certain drugs or poisons can have direct negative inotropic or chronotropic effects on the heart, reducing cardiac output. Others can cause a severe reduction in peripheral vascular resistance. Some drugs or poisons can cause shock by a combination of these mechanisms.

Treatment of drug-induced shock includes rapid assessment of the likely cause, which is suggested by the history of exposure and the clinical findings. Hypotension with tachycardia suggests that the cause is volume depletion or reduced peripheral vascular resistance, whereas hypotension with bradycardia suggests that the cause is disturbance of cardiac rhythm or generalized cardiodepressant effects of the drug. Regardless of the etiology, most patients benefit from an I.V. bolus of fluid (e.g., 0.5 to 1 L of normal saline) and empirical pressor therapy with dopamine or norepinephrine.[10] However, if hypoperfusion persists, it may be necessary to insert a pulmonary arterial catheter to obtain more specific information about volume and hemodynamic status.

A variety of cardiac dysrhythmias may occur as a result of drug intoxication or poisoning [*see Table 3*]. In addition to the direct pharmacologic actions of the drug or poison, impaired ventilation and oxygenation may trigger disturbances of cardiac rhythm.[10]

Treatment of a cardiac dysrhythmia depends on its etiology. Because conventional advanced cardiac life support (ACLS) protocols were not designed with poisoning in mind, use of these guidelines may have inappropriate or dangerous effects. For example, a patient with tricyclic antidepressant intoxication (see below) may have wide-complex tachycardia resulting from severe depression of sodium-dependent channels in the myocardial cell membrane. However, use of the ACLS protocols for wide-complex tachycardia or possible ventricular tachycardia may lead the treating physician to administer procainamide, a class IA antiarrhythmic agent with cardiodepressant effects that are additive to those of the tricyclic antidepressants.[10] A patient with multiple premature ventricular contractions or runs of ventricular tachycardia after intoxication with chloral hydrate or inhalation of a chlorinated solvent would respond more readily to a beta blocker than to lidocaine, the drug recommended by the ACLS protocols.[11] Finally, cardiac dysrhythmias from digitalis intoxication are most appropriately treated with digoxin-specific antibodies (see below).

HYPERTENSION

Although hypertension is not commonly recognized as a serious pharmacologic effect of drug intoxication, it may have life-threatening consequences and requires aggressive treatment. Hypertension may result from generalized CNS and sympathetic stimulation (e.g., by amphetamines or cocaine) or from the peripheral actions of drugs such as phenylpropanolamine, a potent alpha-adrenergic agonist.[12] (Although the Food and Drug Administration removed phenylpropanolamine from the market in the United States in November 2000, patients may have access to phenylpropanolamine purchased before then; also, phenylpropanolamine is still available in other countries.) In addition, hypertension may result from the pharmacologic interaction of two agents, such as in the use of a stimulant or the ingestion of an inappropriate food by a person taking monoamine oxidase (MAO) inhibitors.[13] Severe hypertension can lead to intracranial hemorrhage, aortic dissection, or other catastrophic complications.[14,15]

Hypertension may be accompanied by tachycardia, as commonly occurs in cases of intoxication with generalized stimulants such as cocaine and amphetamine derivatives. Hypertension may also be accompanied by bradycardia or even atrioventricu-

Table 3   Causes of Cardiac Disturbances

Type of Disturbance	Selected Causes
Sinus tachycardia	Anticholinergic agents (e.g., diphenhydramine, atropine, tricyclic antidepressants); theophylline and caffeine; cocaine and amphetamines; volume depletion
Bradycardia or atrioventricular block	Beta blockers; calcium antagonists; tricyclic antidepressants; class IA and class IC antiarrhythmic agents; organophosphate and carbamate insecticides; digitalis glycosides; phenylpropanolamine (hypertension with reflex bradycardia)
Widening of the QRS complex	Tricyclic antidepressants; class IA and class IC antiarrhythmic agents; diphenhydramine; thioridazine; propoxyphene; hyperkalemia; hypothermia
Ventricular tachycardia or ventricular fibrillation	Tricyclic antidepressants; cocaine and amphetamines; theophylline; digitalis glycosides; fluoride or hydrofluoric acid burns (hypocalcemia); trichloroethane and numerous other chlorinated, fluorinated, and aromatic solvents; chloral hydrate; agents that cause prolongation of the QT interval (e.g., quinidine, sotalol)

lar (AV) block, which may occur after phenylpropanolamine overdose because of the reflex baroreceptor response.

Treatment is directed at the cause of the hypertension. In patients who have taken cocaine, amphetamines, or other generalized stimulants, mild or moderate increases in blood pressure may be reduced simply by providing a quiet environment and administering a sedative agent such as diazepam. In persons who have taken an overdose of phenylpropanolamine, administration of a specific alpha-adrenergic antagonist, such as phentolamine (2 to 5 mg I.V.), is extremely effective and usually leads to normalization of the slow heart rate or reversal of the AV block.[12] In general, beta blockers should not be used as single agents in the treatment of drug-induced hypertension, because their use may lead to unopposed alpha-adrenergic activity with paradoxically worsened hypertension.[16]

SEIZURES

Seizures may result from a number of factors, including a variety of drugs and poisons. The drugs that most commonly induce seizures are tricyclic antidepressants, cocaine and related stimulants, antihistamines, and isoniazid [see Table 4].[17] Prolonged or repeated convulsions can lead to serious complications, including hyperthermia, rhabdomyolysis, brain damage, and death. In addition, seizure activity causes metabolic acidosis, which may worsen cardiotoxicity in patients who have taken an overdose of a tricyclic antidepressant.[10,17] Seizures can also result from hypoxia, hypoglycemia, head trauma, stroke, or serious CNS infections [see Factors to Be Excluded in Diagnosis, below].

Treatment of seizures includes taking immediate steps to protect the airway and provide oxygen while administering anticonvulsant drugs. The blood glucose level should be determined and dextrose administered if needed [see Coma, above]. Initial anticonvulsant therapy consists of diazepam (5 to 10 mg I.V.), lorazepam (1 to 2 mg I.V.), or midazolam (3 to 5 mg I.V. or, if I.V.

access is not immediately available, 5 to 10 mg I.M.). Repeated doses are given if the initial therapy is ineffective. If convulsions persist, administer phenobarbital at a dosage of 15 to 20 mg/kg (1 to 1.5 g) I.V. over 20 to 30 minutes.[18] Phenytoin is not a first-line anticonvulsant agent for drug- or toxin-induced seizures. If seizure activity continues, the physician should consult with a neurologist and consider administering pentobarbital, another short-acting barbiturate, or propofol.[18] In addition, inducing neuromuscular paralysis (e.g., with pancuronium) should be considered to control the muscle hyperactivity, which may be necessary to control the hyperthermia, rhabdomyolysis, or metabolic acidosis. If neuromuscular paralysis is induced, however, the physician should be aware that seizure activity in the brain may persist but may not be apparent.[18] If isoniazid poisoning is suspected, administer pyridoxine (vitamin B$_6$), 5 g intravenously; or if more than 5 g of isoniazid was ingested, administer B$_6$ in an amount (in grams) equal to that of the isoniazid overdose.

HYPERTHERMIA

Hyperthermia is an underrecognized complication of poisoning and drug overdose that is associated with high morbidity and mortality.[19] It may result from the pharmacologic effects of the agent or as a consequence of prolonged muscle hyperactivity or seizures [see Table 5]. Severe hyperthermia (rectal temperature > 104° F [40° C]) that goes untreated may lead to brain damage, coagulopathy, rhabdomyolysis, hypotension, and, ultimately, death.[19]

Because it is immediately life threatening, hyperthermia warrants immediate and aggressive treatment.[19] Therapy is directed at the underlying cause, which is usually excessive muscle activity or rigidity. For mild or moderate cases, the physician should use appropriate pharmacologic agents (e.g., sedatives for cases of stimulant-induced psychosis and hyperactivity and anticonvulsants for cases of seizure), remove the patient's clothing, and maximize evaporative cooling by spraying the exposed skin with tepid water and fanning the patient. For severe cases, the most rapidly effective treatment is neuromuscular paralysis accompanied by maximal evaporative cooling.[19] In some cases, a specific antidote or therapeutic agent may be available [see Table 5].

HYPOTHERMIA

Hypothermia may accompany drug overdose and is usually caused by environmental exposure combined with inadequacy of the patient's response mechanisms. These inadequate mechanisms may include impaired judgment (in patients who have taken opioids, sedative-hypnotic agents, or phenothiazines or who have underlying mental disorders), a reduced shivering response (in those who have taken phenothiazines or sedative-hypnotic agents), and peripheral vasodilatation (in those who have taken phenothiazines or vasodilators).[20] Severe hypothermia (core temperature < 82° F [28° C]) may cause the patient to appear to be dead and may be associated with barely perceptible blood pressure, heart rate, or neurologic reflexes. Hypotension, bradycardia, and ventricular arrhythmias may fail to respond to pharmacologic treatment until the patient is warmed.[20,21] Because no controlled trials comparing rewarming methods exist, management protocols vary institutionally and are often controversial.[20] Treatment of hypothermia is generally administered gradually because more aggressive management may precipitate cardiac dysrhythmias. Passive external rewarming is an acceptable treatment if the patient's condition is stable. Administration of a warmed mist inhalation or warmed I.V. fluids may be helpful, as

Table 4 Drug-Induced Seizures

Common Causes	Comments
Tricyclic antidepressants	Seizure activity and resulting metabolic acidosis often aggravate cardiotoxicity; protracted seizures with absent sweating may lead to hyperthermia; phenytoin worsens cardiotoxicity in animal models; treat with benzodiazepines or phenobarbital
Cocaine and amphetamines	Seizures are usually brief and self-limited; prolonged seizures suggest an alternative diagnosis or complication (e.g., hyperthermia or intracranial hemorrhage)
Theophylline	Seizures are often prolonged, recurrent, and refractory to anticonvulsant therapy; phenytoin is ineffective in animal models; administer high-dose phenobarbital (at least 15–20 mg/kg I.V.); for patients with serum theophylline levels > 100 mg/L or status epilepticus, consider hemoperfusion or hemodialysis
Diphenhydramine	Seizures are usually brief and self-limited; in patients with massive intoxication (e.g., > 4–5 g), tricycliclike cardiotoxicity may also occur
Isoniazid	Seizures are often accompanied by severe lactic acidosis; the specific antidote for seizures and coma is vitamin B$_6$ (pyridoxine), 5–10 g I.V., or, if the amount of ingested isoniazid is known, the equivalent gram-for-gram amount of vitamin B$_6$

Table 5 Drug-Induced Hyperthermia

Mechanisms	Selected Causes and Comments
Increased metabolic activity	Causes include salicylates, dinitrophenol, and cocaine and amphetamines
Reduced sweating	Causes include anticholinergic agents (e.g., tricyclic antidepressants, antihistamines, many plants, and some mushrooms)
Increased muscle activity or exertion	Causes include cocaine and amphetamines, phencyclidine, and exertional heatstroke
Neuroleptic malignant syndrome	Causes include haloperidol, related antipsychotic agents, and lithium; patients have lead-pipe rigidity, acidosis, and an elevated creatine kinase level that are caused by CNS dopamine blockade; specific treatment is bromocriptine (2.5–10.0 mg by nasogastric tube two to six times daily)[146]; treat severe hyperthermia with neuromuscular paralysis
Malignant hyperthermia	An inherited disorder of muscle cell function, commonly triggered by certain anesthetic agents (e.g., succinylcholine or halothane); causes severe muscle rigidity and acidosis not responsive to neuromuscular paralysis; treatment is dantrolene (2–5 mg/kg I.V.)[147]
Serotonin syndrome	Associated with the use of serotonin-enhancing agents (e.g., meperidine, dextromethorphan, fluoxetine, paroxetine, sertraline, L-tryptophan, or trazodone), especially in patients taking monoamine oxidase inhibitors; causes muscle rigidity, acidosis, and hyperthermia; treatment is neuromuscular paralysis; for mild cases, consider cyproheptadine (4 mg p.o. every hour for three or four dosages)[148] or methysergide (2 mg p.o. every 6 hr for three or four dosages)[149]

may gastric or peritoneal lavage with warmed fluids, although the heat transfer involved in these measures is variable. For profound hypothermia accompanied by evidence of severe hypoperfusion (e.g., cardiac arrest or ventricular fibrillation), more aggressive measures, such as partial cardiopulmonary or femorofemoral bypass, may be required.[20,21] Of note is that patients with severe hypothermia can withstand cardiorespiratory arrest longer than a normothermic patient—hence the old adage, "No one is dead until warm and dead."[21]

RHABDOMYOLYSIS

Rhabdomyolysis, a common complication of severe poisoning or drug overdose, may result from direct myotoxic effects of the agent, from prolonged or recurrent muscle hyperactivity or rigidity, or from prolonged immobility with mechanical compression of muscle groups.[22] Severe rhabdomyolysis (usually associated with markedly elevated serum creatine kinase levels) may cause massive myoglobinuria that results in acute tubular necrosis and renal failure. Myoglobinuria is usually recognized by the pink or reddish hue of spun serum or by a positive dipstick test for hemoglobin in the urine, with few or no red blood cells seen on microscopic examination. Severe rhabdomyolysis may also cause hyperkalemia, which results from loss of potassium from dead or injured cells.

Treatment of rhabdomyolysis includes measures to prevent further muscle breakdown (e.g., control of muscle hyperactivity and treatment of hyperthermia) and to prevent deposition of toxic myoglobin in the renal tubules. Unequivocally, the mainstay of treatment in rhabdomyolysis is aggressive volume expansion with normal saline early in the disease to maintain urine output of 200 to 300 ml/hr in those who can tolerate the fluid load.[22] Nonrandomized trials have also shown alkalinization of urine to be beneficial, but the role of mannitol and furosemide in rhabdomyolysis is less clear.[22]

Clinical Evaluation

Although the history recounted by patients who have intentionally taken a drug overdose may be unreliable, it should not be overlooked as a valuable source of information. If the patient is unwilling or unable to specify which drugs were taken and when they were ingested or to provide a pertinent medical history, family and friends may be able to do so. Family members should be asked about other medications available in the household and about exposure in the workplace and through hobbies. In addition, paramedics should be asked for any pill bottles or drug paraphernalia that they may have obtained at the scene.

A directed toxicologic physical examination may yield important clues about the drugs or poisons taken. Pertinent variables include the patient's vital signs, pupil size, lung sounds, peristaltic activity, skin moisture and color, and muscle activity; the presence or absence of unusual odors; and the presence or absence of track marks associated with I.V. drug abuse. Signs of one of the so-called autonomic syndromes [see Table 6] may suggest diagnostic possibilities and potential empirical interventions.[9]

The clinical laboratory may provide useful information that obviates an expensive and time-consuming toxicology screen. Recommended laboratory tests in the patient with an overdose of unknown cause include a complete blood count; measure-

Table 6 Autonomic Syndromes Induced by Drugs or Poisons

Autonomic Syndrome	Selected Causes	Empirical Interventions
Sympathomimetic (agitation; dilated pupils; elevated BP and HR; sweaty skin; hyperthermia)	Cocaine; amphetamines; pseudoephedrine	Induce sedation; initiate aggressive cooling; treat hypertension with phentolamine; treat tachycardia with beta blockers
Sympatholytic (lethargy or coma; small pupils; normal or low BP and HR; low temperature)	Barbiturates; opioids; clonidine; benzodiazepines	Give naloxone for suspected opioid overdose; consider flumazenil for benzodiazepine overdose
Cholinergic (pinpoint pupils; variable HR; sweaty skin; abdominal cramps and diarrhea)	Organophosphate and carbamate insecticides; chemical warfare nerve agents	Give atropine and pralidoxime; obtain measurements of serum and RBC cholinesterase activity
Anticholinergic (agitation; delirium; dilated pupils; tachycardia; decreased peristalsis; dry, flushed skin)	Atropine and related drugs; antihistamines; phenothiazines; tricyclic antidepressants	Obtain immediate ECG tracing to evaluate for poisoning with tricyclic antidepressants; consider physostigmine only if tricyclics are not involved

Table 7 Use of the Clinical Laboratory in the Initial Diagnosis of Poisoning

Test	Finding	Selected Causes
Arterial blood gases	Hypoventilation (elevated Pco_2)	CNS depressants (e.g., opioids, sedative-hypnotic agents, phenothiazines, and ethanol)
	Hyperventilation	Salicylates; carbon monoxide; other asphyxiants
Electrolytes	Anion-gap metabolic acidosis	Salicylates; methanol; ethylene glycol; carbon monoxide; cyanide; iron; isoniazid; theophylline
	Hyperkalemia	Digitalis glycosides; fluoride; potassium
	Hypokalemia	Theophylline; caffeine; beta-adrenergic agents (e.g., albuterol); soluble barium salts
Glucose	Hypoglycemia	Oral hypoglycemic agents; insulin; ethanol
Osmolality and osmolar gap	Elevated osmolar gap*	Ethanol; methanol; ethylene glycol; isopropyl alcohol; acetone
ECG	Wide QRS complex	Tricyclic antidepressants; quinidine and other class IA and class IC antiarrhythmic agents
	Prolongation of the QT interval	Quinidine and related antiarrhythmic agents
	Atrioventricular block	Calcium antagonists; digitalis glycosides
Plain abdominal x-ray	Radiopaque pills or objects	Iron; lead; potassium; calcium; chloral hydrate; some foreign bodies
Serum acetaminophen	Elevated level (> 140 mg/L 4 hr after ingestion)	Acetaminophen (may be the only clue to a recent ingestion)

*Osmolar gap = measured osmolality – calculated osmolality. Measured osmolality is performed in the laboratory using a freezing-point-depression device (do not use the vaporization method). Calculated osmolality = 2(Na) + [BUN/2.8] + [glucose/18]. The normal osmolar gap is 0 ± 5 mOsm/L.
BUN—blood urea nitrogen Pco_2—carbon dioxide tension

ments of glucose, electrolytes, blood urea nitrogen, creatinine, aspartate aminotransferase (AST), and serum osmolality (both measured and calculated); ECG; and plain abdominal x-ray (KUB [kidneys, ureters, and bladder] view) [*see Table 7*]. A quantitative serum acetaminophen level should be obtained immediately because acetaminophen overdose may be difficult to diagnose in the absence of a complete and reliable history, does not produce suggestive clinical or laboratory findings, and requires prompt administration of an antidote in patients with a serious acute ingestion if hepatic injury is to be prevented.[9,23,24]

Obtaining a thorough history, performing a careful physical examination, and using the clinical laboratory in a logical manner can often enable the physician to make a tentative diagnosis and to order specific quantitative measurements of certain drugs (e.g., salicylates, valproic acid, or digoxin) when the results of such tests may alter therapy. It is rarely useful, especially in the emergency management of a poisoning victim, to order a comprehensive toxicology screen. Generally, this test is performed at an outside reference laboratory at considerable expense, and patients often awaken and confirm the tentative diagnosis before results are available (usually 1 to 2 days after testing). In addition, many common dangerous drugs and poisons (e.g., isoniazid, digitalis glycosides, calcium antagonists, beta blockers, metals, and pesticides) are not included in the screening procedure; thus, a negative toxicology screen does not rule out the possibility of poisoning.[25] So-called drugs of abuse screens for opioids, amphetamines, and cocaine are commonly performed by hospital laboratories and are useful in identifying intoxication by these substances, but should not be mistaken for a comprehensive toxicologic screening test.

FACTORS TO BE EXCLUDED IN DIAGNOSIS

Whenever a patient with suspected poisoning or drug overdose is evaluated, the possibility that other illnesses are mimicking or complicating the presentation should always be considered. These illnesses include head trauma (e.g., in the ethanol-intoxicated patient, who often falls); cerebrovascular accident; meningitis; metabolic abnormalities, such as hypoglycemia, hyponatremia, and hypoxemia; underlying liver disease; and the postictal state. In any patient with altered mental status, computed tomography of the head and lumbar puncture should be considered.

Management Issues

DECONTAMINATION AFTER ACUTE INGESTION

Nowhere in the field of toxicology is there more controversy than in the debate about gastrointestinal decontamination.[26-29] Techniques for gut decontamination include emesis, gastric lavage, administration of activated charcoal, and whole bowel irrigation [*see Table 8*].

Ipecac-induced emesis, which as recently as a decade ago was the preferred technique for gut emptying, has been almost completely abandoned. One reason it has fallen out of favor is that treated patients run the risks of sudden, unexpected deterioration from the effects of the overdose and subsequent pulmonary aspiration; more important, however, is the lack of evidence of the efficacy of ipecac-induced emesis, especially when emesis is induced more than 1 hour after the ingestion.[26,30]

Gastric lavage is still an accepted method for gut decontamination in hospitalized patients who are obtunded or comatose, but several prospective, randomized, controlled trials have failed to show that emesis or lavage plus charcoal provides better clinical results than administration of activated charcoal alone. In one study,[30] patients given a regimen of activated charcoal and patients given a combination regimen of gastric lavage and charcoal showed no significant differences in all outcome parameters, including clinical deterioration, length of hospital stay, complications, and mortality. Studies of volunteers have shown that the amount of ingested material returned with gastric lavage is only about 30%.[26,29] However, many authors agree that it may still provide results if the ingested material has caused slowing of peristalsis (e.g., in the

case of anticholinergic agents or opioids) or pyloric spasm (e.g., in the case of salicylates) or is a potentially life-threatening amount of poison (e.g., 5 g of a tricyclic antidepressant).[26,27] Some investigators have suggested that gastric lavage is associated with an increased rate of complications, although adverse events are rare in clinical practice.[29]

Activated charcoal, a finely divided product of the distillation of various organic materials, has a large surface area that is capable of adsorbing many drugs and poisons.[27,29] Studies of volunteers and clinical trials have suggested that administration of activated charcoal without gastric lavage may be as effective as, or superior to, its administration after gut emptying.[26,29,30] Although it seems logical that gastric lavage in combination with the use of activated charcoal would be more effective than the use of activated charcoal alone, this hypothesis has not been proved. Most clinicians now employ oral activated charcoal without prior gut emptying in the awake patient who has taken a moderate overdose of a drug or poison; some clinicians still recommend lavage after a massive ingestion of a highly toxic drug.

There is no consensus about the use of cathartic agents with activated charcoal, although it seems logical to hasten passage of the charcoal-drug material from the intestinal tract. If cathartic agents are used, their potential adverse effects should be taken into account, especially in the very young or old (who may not be able to tolerate fluid shifts associated with osmotic cathartics such as sorbitol) or in patients with renal insufficiency (who may not be able to tolerate large doses of magnesium or sodium).

Whole bowel irrigation is a technique that was introduced for gut cleansing before surgical or endoscopic procedures and that has recently been adopted for gut decontamination after certain ingestions.[29] It involves the use of a large volume of an osmotically balanced electrolyte solution, such as Colyte or GoLYTELY, that contains nonabsorbable polyethylene glycol and that cleans the gut by mechanical action without net gain or loss of fluids or electrolytes. Whole bowel irrigation is well tolerated by most awake patients. Although no controlled clinical trials to date have demonstrated improved outcome, it is recommended for those who have ingested large doses of poisons that are not well adsorbed to charcoal (e.g., iron or lithium), for those who have ingested sustained-release or enteric-coated products, and for those who have ingested drug packets or other potentially toxic foreign bodies.[29,31]

ENHANCED ELIMINATION

Measures to enhance elimination of drugs and poisons are less popular than they were 20 years ago, primarily because it has since been recognized that the available techniques do not have a significant effect on total drug elimination of many of the most commonly ingested products and that they have little effect on the clinical course of intoxication.[8] In addition, hemodialysis and hemoperfusion are invasive procedures that require systemic anticoagulation and that are associated with potential morbidity. For a drug or poison to be considered for removal by hemodialysis or another procedure, it should have a relatively small volume of distribution, have a slow intrinsic rate of removal (clearance), and cause life-threatening intoxication that is poorly responsive to supportive measures.[8] Only a few drugs and poisons meet these criteria and are therefore efficiently removed by hemodialysis or hemoperfusion [see Table 9].

Repeated oral doses of activated charcoal can reduce the elimination half-life of some drugs and poisons by interrupting enterohepatic or enteroenteric recirculation.[26,32] This technique was introduced in the late 1970s, after studies reported its efficacy in volunteers, and it was considered a benign, noninvasive treatment. However, reports of fluid depletion and shock caused by excessive coadministration of sorbitol, as well as the paucity of evidence of clinical benefit, have reduced the initial optimism about this treatment.[26,32]

Specific Drugs and Poisons

ACETAMINOPHEN

Acetaminophen is a widely used analgesic and antipyretic drug that is found in a number of over-the-counter and prescription products. When it is taken in combination with another drug that has acute toxic effects (e.g., an opioid), the more obvious and more rapidly apparent manifestations of the second drug may cause the clinician to overlook the subtle and nonspecific symptoms of acetaminophen poisoning. As a result, the op-

Table 8 Methods of Gastrointestinal Decontamination

Method and Technique	Useful Situations	Comments
Emesis: give syrup of ipecac, 30 ml p.o. in adults (15 ml in children), along with one to two glasses of water; may repeat after 30 min if no emesis occurs; alternatively, give 1–2 tbsp of liquid handwashing or dishwashing soap	Most useful in the home for children with recent ingestions; possibly useful for ingestion of sustained-release or enteric-coated pills	Contraindicated in ingestions of corrosive agents and most hydrocarbons, when the patient is lethargic, or when the ingested substance is likely to cause abrupt onset of coma or seizures
Gastric lavage: insert large-bore nasogastric or orogastric tube, empty stomach contents, and lavage with 100–200 ml aliquots of water or saline until clear	Useful in obtunded or comatose patients, in recent ingestions (< 1 hr), or in ingestion of anticholinergic agents or salicylates (delayed gut emptying)	Obtunded patient should have prior endotracheal intubation to protect airway; best position is left lateral decubitus to reduce movement of poison into small intestine
Activated charcoal: give 50–60 g of charcoal slurry p.o. or by gastric tube; goal is approximately 10:1 ratio of charcoal to ingested poison; usually given with one dose of a cathartic agent	Often useful because it adsorbs most drugs and poisons; may be equally effective when given alone as when given after emesis or lavage	Not effective for ingestions of iron, lithium, potassium, sodium, or alcohols; may need to repeat two or three times or more for large ingestions; repeated dosing may also enhance elimination of some drugs
Whole bowel irrigation: give Colyte or GoLYTELY, 1–2 L/hr p.o. or by gastric tube, until rectal effluent is clear or x-ray is negative for radiopaque materials	Useful in ingestions of iron, lithium, sustained-release or enteric-coated pills, and drug packets or other foreign bodies	Generally well tolerated; no significant fluid or electrolyte gain or loss occurs; most useful in awake, ambulatory patients; may reduce effectiveness of activated charcoal

Table 9 Methods of and Indications for Enhanced Drug Removal

Drug or Poison	Preferred Elimination Method and Indications
Carbamazepine	Hemoperfusion is indicated for severe poisoning with status epilepticus or cardiotoxicity; repeated doses of charcoal are of possible benefit for mild to moderate poisoning and for gut decontamination
Ethanol, isopropyl alcohol	Hemodialysis is rarely indicated because supportive care is generally successful; consider hemodialysis for deep coma with refractory hypotension
Lithium	Hemodialysis is indicated for severe neurologic manifestations (deep coma or seizures); I.V. saline is fairly effective for mild to moderate intoxication
Methanol, ethylene glycol	Hemodialysis is indicated for severe acidosis or for estimated or measured drug levels > 20–50 mg/dl
Phenobarbital	Hemoperfusion is indicated for refractory shock and drug levels > 200 mg/L; repeated doses of charcoal are of questionable clinical benefit
Salicylates	Hemodialysis is indicated for severe acidosis and drug levels > 100 mg/dl; consider hemodialysis at lower salicylate levels (> 60 mg/dl) in elderly patients with chronic, accidental intoxication
Theophylline	Hemoperfusion or hemodialysis is indicated for drug levels > 100 mg/L or status epilepticus; repeated doses of charcoal are indicated for less severe cases
Valproic acid	Hemodialysis or hemoperfusion is indicated for severe cases (coma, acidosis, and drug levels > 1,000 mg/L); repeated doses of charcoal are of theoretical benefit

laboratories. Clinical evidence of liver and kidney damage is usually delayed for 24 hours or more after ingestion. The earliest evidence of toxicity is elevated levels of hepatic aminotransferases (AST and alanine aminotransferase [ALT]), followed by a rising prothrombin time (PT) and bilirubin level. Hypoglycemia, metabolic acidosis, and encephalopathy are signs of a poor prognosis.[33]

Treatment

Oral activated charcoal should be administered. Ipecac-induced emesis is not recommended, because it often leads to protracted vomiting, which makes administration of the oral antidote difficult. A serum acetaminophen level should be obtained approximately 4 hours after ingestion, and the result should be plotted on the Rumack-Matthew nomogram [*see Figure 1*]. Ingestion of massive quantities of acetaminophen or a modified-release preparation or the coingestion of a drug that slows gastric emptying may result in delayed peak serum acetaminophen levels; in such cases, repeated measurements of serum concentrations should be obtained. If the acetaminophen level is above the probable toxicity line (many clinicians use the possible toxicity line instead), treatment should be initiated with acetylcysteine, 140 mg/kg orally as a loading dose followed by 70 mg/kg orally every 4 hours. If the patient has additional risk factors for hepatotoxicity (e.g., chronic alcohol abuse, chronic use of anticonvulsants or isoniazid, or unreliable history of time of ingestion), it is prudent to treat for toxicity even with levels below the lower possible toxicity line. Acetylcysteine, an antioxidant that substitutes for glutathione as a scavenger, is highly effective in preventing liver damage from acetaminophen toxicity,
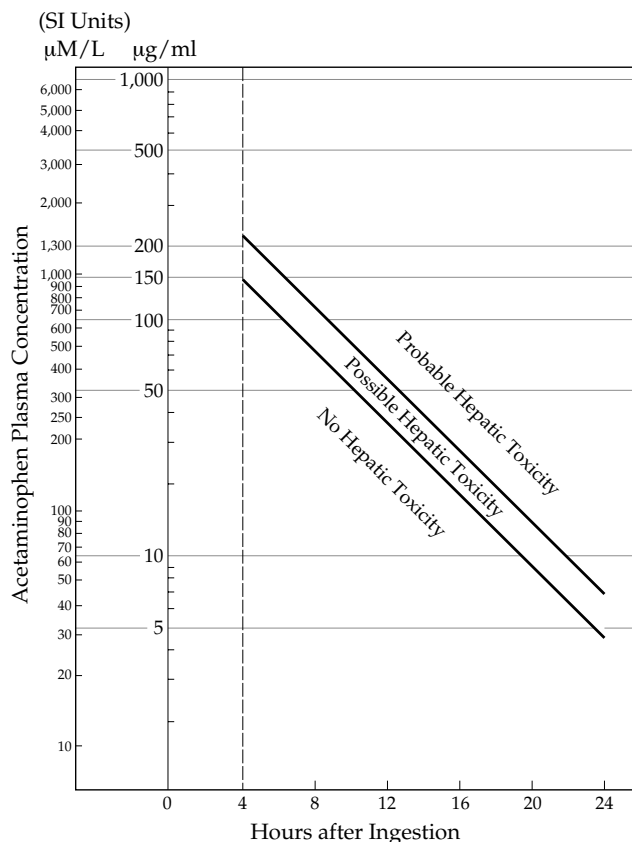
portunity to administer the highly effective prophylactic antidote acetylcysteine may be missed.

Acetaminophen is metabolized by various processes in the liver and, to a lesser extent, in the kidneys. One of the minor pathways of acetaminophen metabolism in the liver involves the cytochrome P-450 system, which generates a highly reactive intermediate metabolite. Normally, this toxic intermediate metabolite is readily scavenged by the intracellular antioxidant glutathione. In overdose, however, exhaustion of glutathione stores by production of the toxic intermediate metabolite allows the metabolite to react with cellular macromolecules, leading to cell injury and death. A similar process occurs in kidney cells.

The minimum acutely toxic single dose of acetaminophen is approximately 150 to 200 mg/kg, or about 7 to 10 g in adults.[33] Alcoholics are at risk for toxicity at lower doses, particularly when the drug is taken for several days, presumably because they have increased cytochrome P-450 metabolic activity and reduced glutathione stores.[34] Enhanced susceptibility to toxic effects has also been reported in persons who are fasting and in patients receiving long-term anticonvulsant therapy[35] or taking isoniazid.[34] Severe toxicity may result in fulminant hepatic and renal failure.[33]

Diagnosis

Early after acute ingestion of acetaminophen, the patient may have few or no symptoms.[36] Vomiting is not uncommon in those who have taken large doses. Other than what can be found in the patient's history, the only reliable early diagnostic clue is provided by a quantitative measurement of the serum acetaminophen level, which can be provided immediately by most hospital

Figure 1 **The Rumack-Matthew nomogram for acetaminophen poisoning.**

especially if therapy is initiated within 8 to 10 hours after the ingestion of acetaminophen.[36] It is less effective when initiated after 12 to 16 hours after acetaminophen ingestion; but it should be given in such cases anyway because it still has beneficial effects, presumably owing to its antioxidant and anti-inflammatory properties, and increases survival in patients with hepatic failure.[36] The treatment protocol approved by the FDA for the oral administration of acetylcysteine stipulates that 17 doses (approximately 3 days of therapy) be administered; however, shorter courses (20 hours of I.V. therapy, as is given in the United Kingdom and Canada, and 48 hours of I.V. therapy, as was given in one study) have been shown to be equally effective in patients who were treated within 8 to 10 hours after ingestion of acetaminophen.[36,37] At our institution, we usually administer oral acetylcysteine until 36 hours after the ingestion and then stop its administration if the liver enzymes (e.g., AST and ALT) reach normal levels. A retrospective study showed that the 36-hour regimen has a safety and efficacy profile similar to that of the traditional 72-hour protocol.[38] A longer course may be given to high-risk patients (e.g., patients who arrive in the emergency department late in the course of overdose or who have evidence of liver injury).[36]

Aggressive intervention is recommended to ensure that the loading dose is given within the first 8 hours of overdose. Occasionally, however, patients cannot tolerate oral acetylcysteine because the drug has a disagreeable odor and they are already vomiting. In such cases, it is advisable to administer a strong antiemetic (e.g., metoclopramide, 60 to 70 mg I.V. over 1 to 2 minutes) and to give the acetylcysteine through a gastric tube. Rarely, recalcitrant vomiting indicates the need to administer the drug by the I.V. route. Because the preparation is not approved for I.V. administration and may not be free of pyrogens, it should be administered slowly through a micropore filter. A slow I.V. infusion rate is also recommended because rapid administration can cause an anaphylactoid reaction (skin flushing and hypotension).[39,40]

ANTICHOLINERGIC AGENTS AND ANTIHISTAMINES

Intoxication with anticholinergic agents can involve a variety of over-the-counter and prescription products, including antihistamines, antispasmodic agents, antipsychotic drugs, and antidepressants. In addition, several plants and mushrooms (e.g., *Datura stramonium* [angel's trumpet],[41] *Atropa belladonna*, and *Amanita phalloides*) contain potent anticholinergic alkaloids [*see Amanita phalloides* Mushrooms, *below*]. Anticholinergic agents competitively inhibit the action of acetylcholine at muscarinic receptors. Antihistamines are commonly found in a variety of over-the-counter and prescription medications for the treatment of cough and cold symptoms, itching, dizziness, nausea, and insomnia. The most commonly used nonprescription antihistamine is diphenhydramine.

Diagnosis

Clinical manifestations of intoxication with anticholinergic agents include delirium, flushed skin, dilated pupils, tachycardia, ileus, urinary retention, jerky muscle movements, and occasionally hyperthermia. Coma and respiratory arrest may occur. Tricyclic antidepressants (see below) and phenothiazines may also cause seizures and quinidinelike cardiac conduction abnormalities. Therefore, an ECG should be obtained and the QRS complex and cardiac rhythm monitored in any patient who displays anticholinergic manifestations of intoxication.

Antihistamine intoxication is similar to anticholinergic poisoning and may also be associated with seizures[17] and tricyclic-

like cardiac conduction abnormalities.[42] The older nonsedating antihistamines terfenadine and astemizole were associated with prolongation of the QT interval and the occurrence of atypical (torsade de pointes) ventricular tachycardia both after overdose and after coadministration of macrolide antibiotics or other drugs that interfere with their elimination.[43] Because safer agents are available, both of these drugs were removed from the United States market by the manufacturers in 1999; however, the drugs are still commonly used in other countries.[44]

Treatment

Activated charcoal and a cathartic agent should be administered to patients with anticholinergic or antihistamine intoxication. Gastric lavage should be considered in cases of a large ingestion; this measure may be appropriate even if some time has passed, because ileus may delay gastric emptying. Coma and respiratory depression should be treated with the usual supportive measures. The physician should consider administering physostigmine, 0.5 to 2.0 mg in a slow I.V. infusion, in patients with pure anticholinergic intoxication (i.e., intoxication with agents other than tricyclic antidepressants or antihistamines) and severe delirium.[45] Drowsiness, confusion, and sinus tachycardia usually resolve without aggressive intervention. Prolongation of the QT interval and atypical ventricular tachycardia can be treated with magnesium, 1 to 2 g I.V., or overdrive pacing.

ANTICOAGULANTS

The anticoagulants include warfarin and the so-called superwarfarin rodenticides. Accidental intoxication with warfarin may result from long-term therapeutic overmedication or from the addition of a drug that interacts with it (e.g., allopurinol, cimetidine, nonsteroidal anti-inflammatory drugs, quinidine, salicylates, or sulfonamides). Acute ingestion of a single dose of warfarin rarely causes significant anticoagulation. However, a single dose of brodifacoum or one of the other superwarfarins can cause severe and prolonged anticoagulation that lasts for weeks to months.[46]

Diagnosis

All anticoagulants inhibit the hepatic production of clotting factors II, VII, IX, and X and prolong the PT. Circulating factors are not affected; the peak effect of anticoagulants on the PT is not seen until 36 to 48 hours after administration, when circulating factors are degraded. Severe anticoagulation can result in hemorrhage, which may be fatal.[46]

Treatment

Acute superwarfarin overdose should be treated with oral activated charcoal and a cathartic agent. A baseline PT should be obtained on presentation and 24 and 48 hours later. If prolongation of the PT occurs, the physician should administer oral vitamin K_1 (phytonadione), 25 to 50 mg/day, and monitor the PT; in rare instances, as much as 150 to 200 mg/day may be necessary to correct the PT. It may also be necessary to continue treatment for several weeks or even months.[47] Patients should not be treated prophylactically with vitamin K_1 after an acute ingestion, because such treatment would mask the rise in PT for about 3 to 5 days or more, preventing early diagnosis. As a result, the patient would require prolonged follow-up even in the case of a subtoxic ingestion.

Vitamin K_1 may be given subcutaneously or, cautiously, by the I.V. route to patients with severe prolongation of the PT.

However, because vitamin K_1 does not restore clotting factors immediately, patients who have active bleeding may require fresh frozen plasma or whole blood. Because coagulopathy after a superwarfarin overdose may last for weeks to months, high-dose oral vitamin K_1 therapy (5 mg/kg over 24 hours) may be necessary for outpatient therapy.[48]

BETA BLOCKERS

Beta blockers are used for the treatment of hypertension, angina pectoris, migraine, and cardiac arrhythmias. Propranolol is the prototypical beta blocker but is also the most toxic [see Table 10].[49] All of these agents act competitively at beta-adrenergic receptors; at therapeutic doses, some have a degree of selectivity for $beta_1$- or $beta_2$-adrenergic receptors that is not apparent at high doses. Propranolol and a few of the other agents also have depressant effects on the myocardial cell membrane that are similar to those of quinidine and the tricyclic antidepressants.[50]

Diagnosis

Beta blockade typically causes hypotension and bradycardia. Severe overdose may cause cardiogenic shock and asystole. Bronchospasm and hypoglycemia may also occur. In addition, propranolol overdose may cause widening of the QRS complex and CNS intoxication, including seizures and coma.[50] Most patients with beta-blocker poisoning manifest symptoms within 6 hours after an acute ingestion.[51]

Treatment

Treatment of overdose with a beta blocker includes aggressive gut decontamination. In cases of a large or recent ingestion, gastric lavage and the administration of activated charcoal and a cathartic agent should be initiated.

Hypotension and bradycardia are unlikely to respond to beta-adrenergic–mediated agents such as dopamine and isoproterenol; instead, the patient should receive high dosages of glucagon (5 to 10 mg I.V. followed by 5 to 10 mg/hr). Glucagon is a potent inotropic agent that does not require beta-adrenergic receptors to activate cells.[50,52] When glucagon fails, an epinephrine drip may be more beneficial in increasing heart rate and contractility than isoproterenol or dopamine. If pharmacologic therapy is unsuccessful, transvenous or external pacing should be used to maintain heart rate.[50,52] Use of hemodialysis in atenolol poisoning has been reported.[50]

CALCIUM ANTAGONISTS

Calcium channel blockers are used for the treatment of angina pectoris, hypertension, hypertrophic cardiomyopathy, migraine, and supraventricular tachycardia. These agents have a relatively low toxic-to-therapeutic ratio, and life-threatening toxicity can occur after accidental or intentional overdose. Calcium antagonists block the influx of calcium through calcium channels and act mainly on vascular smooth muscle, resulting in vasodilatation, reduced cardiac contractility, and slowed AV nodal conduction and sinus node activity. The most commonly used calcium antagonists in the United States are nifedipine, verapamil, and diltiazem. Although each of these agents has a different spectrum of activity, this selectivity is usually lost in overdose.[50]

Diagnosis

Manifestations of intoxication with a calcium antagonist include hypotension and bradycardia. Bradycardia may result from AV block or sinus arrest with a junctional escape rhythm.

The QRS complex is usually normal. Severe poisoning may cause profound shock followed by asystole. Overdose with sustained-release forms of nifedipine and verapamil, which are very popular, may be associated with delayed onset of toxicity.[53]

Treatment

Treatment of overdose of an orally administered calcium antagonist includes aggressive gut decontamination. Gastric lavage and administration of activated charcoal are recommended. For patients who have ingested a large dose of a sustained-release preparation, the physician should consider whole bowel irrigation[53] in combination with administration of repeated doses of activated charcoal; in such cases, the patient should be observed closely for possible delayed-onset effects.

Hypotension should be initially treated with boluses of fluid, vasopressors, and I.V. calcium chloride (10 ml of a 10% solution) or calcium gluconate (20 ml of a 10% solution).[54] Doses of calcium should be repeated as needed; in some case reports, as much as 5 to 10 g of calcium has been given.[55] Calcium administration may improve cardiac contractility but has less effect on AV nodal conduction or peripheral vasodilatation. Infusion of glucagon (5 to 10 mg I.V.) or epinephrine has been recommended for patients with unresponsive hypotension; in one reported case, cardiopulmonary bypass was also shown to be effective. In a verapamil-toxic canine model, the survival rate was higher with high-dose insulin therapy (insulin-dextrose infusion) than with high doses of epinephrine, calcium chloride, or glucagon. A small, uncontrolled case series of patients with calcium channel blocker poisoning showed improvement with high-dose insulin therapy, but a prospective, controlled trial is still pending.[56] Hemodialysis and hemoperfusion are not effective.[50]

CARBON MONOXIDE

Carbon monoxide is a colorless, odorless, nonirritating gas that is produced by the combustion of organic material. It is responsible for more than 5,000 deaths in the United States each year, most occurring from suicidal inhalation. Sources of carbon monoxide include motor vehicle exhaust, improperly vented gas or wood stoves and ovens, and smoke generated by fire. Children riding under closed canopies in the backs of pickup trucks have been poisoned from the exhaust, and campers have been poisoned by using propane stoves or charcoal grills inside their tents.[57] The blizzards that hit the eastern United States in the winter of 1996 produced reports of carbon monoxide poisoning associated with snow-obstructed vehicle exhaust systems.[58]

Tissue hypoxia, which occurs as a consequence of the high affinity of carbon monoxide for hemoglobin, is the major pathophysiologic disturbance in carbon monoxide poisoning: at a carbon monoxide concentration of only 0.1%, as many as 50% of hemoglobin binding sites may be occupied by carbon monoxide. In addition to reducing the oxygen-carrying capacity of the blood, carbon monoxide interferes with release of oxygen to the tissues. Carbon monoxide may also inhibit intracellular oxygen utilization by binding to myoglobin and cytochromes.[59]

Diagnosis

Carbon monoxide poisoning produces the symptoms and signs commonly associated with hypoxia, such as headache, confusion, tachycardia, tachypnea, syncope, hypotension, seizures, and coma. Clinical manifestations depend on the duration and intensity of exposure: an acute, sizable exposure may produce rapid unconsciousness, seizures, and death, whereas prolonged,

Table 10 Toxicity of Common Beta Blockers[150]

Drug	Usual Daily Dose (mg)	Cardioselective	Myocardial Cell Membrane Depression
Acebutolol	400–800	+	+
Atenolol	50–100	+	–
Labetalol	200–800	–	+
Metoprolol	100–450	+	Variable
Nadolol	40–240	–	–
Propranolol	40–360	–	++

low-level exposure may cause vague and nonspecific symptoms such as headache, dizziness, nausea, and weakness. Mild cases may be mistakenly diagnosed as influenza or migraine headache. So-called classic features of carbon monoxide poisoning, such as cherry-red skin coloring and bullous skin lesions, are not always present. Survivors of severe carbon monoxide poisoning may be left with permanent neurologic sequelae. These sequelae can include gross deficits, such as a permanent vegetative state or parkinsonism, or more subtle deficits, such as memory loss, depression, and irritability. In some cases, delayed neurologic deterioration may occur after 1 to 2 weeks.[59,60]

Laboratory findings may include metabolic acidosis and cardiac ischemia on ECG. The oxygen tension is usually normal because carbon monoxide binds to hemoglobin but does not disturb levels of dissolved oxygen; therefore, the calculated oxygen saturation is falsely normal. Furthermore, indirect measurement of oxygen saturation by pulse oximetry is inaccurate because of the similar absorption characteristics of oxyhemoglobin and carboxyhemoglobin.[61] Thus, correct diagnosis depends on direct spectrophotometric measurement of oxyhemoglobin and carboxyhemoglobin in a blood sample or direct measurement of exhaled carbon monoxide. Carboxyhemoglobin levels greater than 20% to 30% are usually associated with moderate symptoms of intoxication, and levels greater than 50% to 60% are associated with a serious or fatal outcome. There is considerable variability, however, and levels do not always correlate with symptoms.[59]

Treatment

The victim of carbon monoxide poisoning should immediately be removed from the site of exposure and given supplemental oxygen in the highest available concentration. Oxygen competes with carbon monoxide for hemoglobin binding sites, and administration of 100% oxygen can reduce the half-life of carboxyhemoglobin to approximately 40 to 60 minutes, thereby restoring normal oxygen saturation within about 2 to 3 hours. It should be noted that it is difficult to deliver 100% oxygen unless the patient is endotracheally intubated. Hyperbaric oxygen (HBO) administered in a sealed chamber can deliver oxygen at a pressure of 2.5 to 3.0 atm and has been reported to speed recovery and reduce neurologic sequelae.[59,62] Proponents of hyperbaric oxygen therapy assert that this treatment can reduce cerebral edema and quell lipid peroxidation and other postinjury mechanisms of cellular destruction.[59,63] However, hyperbaric chambers are not readily available, and until recently, the few clinical studies to have compared HBO therapy with 100% oxygen at ambient pressure produced conflicting or inconclusive results or were otherwise unsatisfactory.[64,65]

A recent report from Australia describes a randomized, double-blind, placebo-controlled (with sham HBO treatments) study of hyperbaric versus normobaric oxygen in a large number of patients with significant carbon monoxide poisoning; the authors found that HBO provided no greater benefit than normobaric oxygen.[66] Although the role of HBO in carbon monoxide poisoning is questionable, proponents of HBO generally advise its use for patients who have a history of unconsciousness, a detectable neuropsychiatric abnormality on bedside testing, or a carboxyhemoglobin level greater than 25%.[59] Because of concerns about the higher affinity of carbon monoxide for fetal hemoglobin, the recommended threshold for treatment of young infants and pregnant women is usually lower.[67] However, there are no controlled studies evaluating HBO therapy in pregnancy.

In patients with carbon monoxide poisoning associated with smoke inhalation, the physician must also consider the potential role of other toxic gases produced during combustion, such as cyanide, phosgene, nitrogen oxides, and hydrogen chloride, as well as the possibility that direct thermal injury to the airway and respiratory tract has been caused by inhaled soot or steam.

COCAINE, AMPHETAMINES, AND OTHER STIMULANTS

Cocaine is now used by as many as six million persons in the United States.[68] In 1991, acute cocaine-related emergencies accounted for more than 100,000 hospital visits; in 1997, cocaine abuse was the leading cause of drug-related deaths (3,465 mentions by medical examiners).[1] Cocaine and the amphetamines [*see Table 11*] stimulate the CNS and the sympathetic nervous system and may act directly on peripheral adrenergic receptors.[68,69] Although cocaine also has local anesthetic properties and may cause sodium channel blockade in high doses, the clinical manifestations and treatment of cocaine overdose are essentially the same as those of amphetamine overdose. These drugs can be taken orally or can be snorted, smoked, or injected. So-called crack cocaine is a crudely prepared nonpolar derivative of the hydrochloride salt that is more easily volatilized and is thus the preferred form for smoking. The combined use of ethanol and cocaine may create the highly potent metabolite cocaethylene, which has a longer half-life than does cocaine and may contribute to the development of delayed toxic effects.[69,70]

Another common drug of abuse, particularly among teenagers and young adults, is methylenedioxymethamphetamine (MDMA), or ecstasy. National surveys suggest a marked increase in the prevalence of MDMA use in the United States. A survey of 14,000 college students reported a 69% increase in the use of MDMA between the years 1997 and 1999.[71] Additionally, the number of emergency room visits in which MDMA was involved soared by over 1,600%, from 253 in 1994 to 4,500 in 2001.[72] Although MDMA is an amphetamine derivative

Table 11 Common Stimulant Drugs

Drug	Street Names
Cocaine	Coke, crack (free-base cocaine)
Methamphetamine	Speed, crystal, ice
3,4-Methylenedioxymethamphetamine (MDMA)	Ecstasy
Methylphenidate	Ritalin*
Methcathinone†	Cat

*Ritalin is the trade name, not the street name.
†An illegally synthesized ephedrine derivative.

with psychoactive properties similar to the hallucinogen mescaline, MDMA toxicity appears to be related to its stimulant properties. The subjective effects of MDMA include euphoria, sexual arousal, enhanced sensory perception, increased endurance, and greater sociability.[73] Adverse reactions from MDMA abuse reported in the literature include hyperthermia, hyponatremia, seizures, hepatitis, cerebrovascular accidents, and cardiac arrhythmias.[73] As MDMA use rises, health care providers are likely to see more patients with adverse reactions from this drug.

Methylphenidate (Ritalin) toxicity may be an increasing cause of sympathomimetic toxicity in children. Between 1990 and 1995, the prevalence of methylphenidate treatment in the United States increased 2.5-fold; by mid-1995, approximately 2.8% of youths 5 to 18 years of age were receiving methylphenidate for attention deficit disorders.[74] Methylphenidate toxicity is most commonly the result of therapeutic error in children treated with the drug.[75] Abuse of methylphenidate has been reported, but its prevalence remains uncertain.[76]

Diagnosis

Clinical manifestations of mild stimulation include euphoria, alertness, and anorexia. More severe intoxication causes agitation, psychosis, tachycardia, hypertension, and diaphoresis. The pupils are usually dilated. Severe poisoning may result in convulsions, hypertensive crisis (e.g., intracerebral hemorrhage or aortic dissection), and hyperthermia.[15,16] Consequences of severe hyperthermia include shock, brain damage, coagulopathy, and hepatic and renal failure.[19]

The differential diagnosis includes acute functional psychosis, acute exertional heatstroke, and intoxication with other drugs. Phencyclidine, a ketaminelike dissociative anesthetic, may produce stimulant effects, but victims of overdose often have a waxing-and-waning encephalopathy with periods of flaccid stupor or coma.[15] Anticholinergic agents (see above) may also cause dilated pupils, tachycardia, and agitation, but these toxins usually cause the skin to be dry and flushed; stimulants generally cause the skin to be pale, clammy, and diaphoretic.

Treatment

Mild or moderate intoxication with a stimulant can often be successfully managed by administering a sedative agent, such as diazepam or lorazepam, and by providing the patient with a quiet room. If hypertension is severe and does not improve after sedation, phentolamine (2 to 5 mg I.V. at 5- to 10-minute intervals) or nitroprusside (0.5 to 10 mg/kg/min) should be administered. For patients with tachycardia or ventricular arrhythmias, a short-acting beta blocker such as esmolol (50 to 100 mg/kg/min) is recommended, although it should be cautioned that beta blockers may worsen hypertension because of unopposed alpha-adrenergic effects of the stimulant drug.[16] Wide-complex dysrhythmias in cocaine overdose should be treated with sodium bicarbonate.[68] Severe hyperthermia should be treated aggressively to prevent brain damage and multiorgan complications [see Hyperthermia, above].

Because acute myocardial infarction may occur even in young persons with normal coronary arteries, all patients with chest pain should be evaluated carefully for evidence of ischemia.[16] Other causes of chest pain in these patients may include mechanical trauma to the chest wall, pneumomediastinum from hard coughing or the Valsalva maneuver, or pectoral muscle ischemia.[16]

CORROSIVE AGENTS

A number of agents with caustic or corrosive properties [see Table 12] are used for a variety of purposes in industry, as cleaning agents in the home, and in hobbies. Exposure to these agents may occur accidentally or as a result of suicidal ingestion. In some cases, the corrosive effect of these agents is a direct result of the high concentration of hydrogen (H^+) or hydroxyl (OH^-) ions and can be predicted from the very low or very high pH of the product. In other cases, toxicity may result from the product's oxidizing, alkylating, or other cytotoxic effects. Systemic toxicity can occur as a result of absorption across burned skin or after ingestion (e.g., in the case of hydrofluoric acid, phenol, or paraquat) [see Table 12].[77]

Diagnosis

Manifestations of toxicity usually occur immediately after exposure to the corrosive or caustic agent and include burning pain and erythema at the site of exposure. Immediate effects occur most commonly with acids. Injury caused by alkali burns can evolve over several hours and takes the form of a penetrating liquefaction necrosis. Burns may also be delayed in cases of exposure to hydrofluoric acid (hydrogen fluoride in aqueous solution); the toxicity of this agent is mediated through its fluoride component, which combines with calcium and magnesium ions. With hydrofluoric acid burns, pain and swelling may not be apparent until several hours after exposure, especially after exposure to relatively dilute solutions.

Treatment

Treatment of toxicity from corrosive or caustic agents must be initiated rapidly to reduce injury. Exposed areas should be flushed with copious amounts of plain water and any contaminated clothing removed (health providers must be careful not to become exposed while assisting victims). For patients whose eyes have been exposed to the agent, the physician should use an eyewash fountain or should splash water into the face, then pour water directly over the eyes from a pitcher or glass. Patients who have ingested a corrosive agent should drink one to two glasses of water. Although use of gastric lavage is controversial because of concerns about possible mechanical damage to the esophagus, our gastrointestinal consultants recommend gastric intubation with a small flexible tube as soon as possible after corrosive-liquid ingestion, to remove as much of the injurious material as possible. Neutralizing agents should not be administered in an attempt to normalize the pH; they may modify the pH too far in the opposite direction, and the heat of neutralization may cause thermal injury. There are a few exceptions to this rule; for example, after exposure to hydrofluoric acid, soaking the skin in a solution or gel that contains calcium (e.g., 2.5% calcium gluconate gel) or magnesium or in benzalkonium chloride may bind the toxic fluoride ion before it can be absorbed[78]; calcium is sometimes injected subcutaneously or by the intra-arterial route for deeper burns. For management of exposure to hydrofluoric acid, the physician should consult a regional poison-control center, a medical toxicologist, or a plastic or hand surgeon.

CYANIDE

Cyanide (the CN^- anion or a salt that contains this ion) is a highly toxic chemical that is used in a variety of industries, including electroplating, chemical synthesis, and laboratory analysis.[79] Cyanide is also released in the I.V. administration of nitroprusside. Acetonitrile, which is found in some glue removers for

Table 12   Corrosive Agents

Corrosive or Caustic Agent	Comments
Mineral acids (e.g., hydrochloric, sulfuric, nitric, and phosphoric acids)	Produce rapidly painful coagulation necrosis of skin and eyes; inhalation of mists or vapors can cause irritation, bronchospasm, and chemical pneumonitis
Hydrofluoric acid	Highly electronegative fluoride ion causes deep tissue injury, which may have a delayed onset; systemic absorption from the skin or after ingestion may cause fatal hypocalcemia or hyperkalemia[151,152]
Caustic alkalis (e.g., sodium, potassium, calcium, and ammonium hydroxides)	Injury is often progressive and deep because of tissue saponification and resulting liquefaction necrosis
Phenol (carbolic acid)	Liquid and vapor are rapidly absorbed across the skin, causing severe systemic toxicity (shock, convulsions, and coma)[153]; isopropyl alcohol may speed its removal from skin[154]
Paraquat	Ingestion causes severe corrosive injury; systemic absorption leads to progressive and ultimately fatal pulmonary fibrosis[155]

artificial fingernails, is metabolized to cyanide and has caused death in children.[79] Natural sources of cyanide (cyanogenic glycosides) include cassava, apricot pits, and several other plants and seeds. Hydrogen cyanide gas is generated from the combustion of many natural and synthetic materials that contain nitrogen and is a common component of the smoke generated by fire [*see* Smoke Inhalation, *below*].[80]

Cyanide is a highly reactive chemical that binds to intracellular cytochrome, blocking the utilization of oxygen. The resulting cellular asphyxia leads to headache, confusion, dyspnea, syncope, collapse, and death.[79,81] Although these effects occur rapidly after inhalation of hydrogen cyanide gas, symptoms of intoxication may be delayed for minutes after the ingestion of cyanide salts or even for hours after the ingestion of cyanogenic glycosides or acetonitrile.[79]

Diagnosis

Diagnosis of cyanide poisoning is based on a history of possible exposure (e.g., in a laboratory worker who attempts to commit suicide; in a person who has ingested laetrile, a cyanogenic glycoside; in a victim of smoke inhalation; or in a patient who has received a rapid high-dose infusion of nitroprusside) and the presence of characteristic symptoms. Any victim of smoke inhalation who has altered mental status should be suspected of having been poisoned with cyanide as well as with carbon monoxide. The so-called smell of bitter almonds may be present after cyanide ingestion, but only about 50% of the general population has the ability to perceive this odor. Severe lactic acidosis is usually present. Because cyanide blocks the cellular utilization of oxygen, venous blood may have an elevated oxygen content; a venous oxygen saturation of greater than 90% suggests the diagnosis.

Treatment

Once cyanide poisoning is suspected, immediate measures must be taken to prevent further exposure and to provide an antidote. For an ingestion, oral activated charcoal should be immediately administered; although the adsorption of cyanide to charcoal is relatively low, a standard dose of charcoal (e.g., 50 to 60 g) is sufficient to adsorb several hundred milligrams of cyanide salts. If charcoal is not available and there will be a delay before the patient reaches the hospital, emesis should be induced with ipecac. If ipecac is not available, emesis should be induced by mechanical gagging.

The antidotes for cyanide poisoning consist of nitrites, which oxidize hemoglobin to methemoglobin; in turn, methemoglobin binds free cyanide ions. If I.V. access is not immediately available, break a pearl of amyl nitrite and have the victim inhale the contents. As soon as possible, administer sodium nitrite, 300 mg I.V. The other antidote is sodium thiosulfate (12.5 g I.V.), which enhances the conversion of cyanide to the less toxic thiocyanate by the endogenous enzyme rhodanese. Although nitrites produce serious side effects (methemoglobinemia reduces the oxygen-carrying capacity, and vasodilatation may cause hypotension), sodium thiosulfate is relatively benign and can be used empirically as a single agent when the diagnosis is uncertain. Other potential antidotes include cobalt ethylenediaminetetraacetic acid (cobalt EDTA) and vitamin B_{12a} (hydroxocobalamin), but these agents have not been approved for use in the United States, and hydroxocobalamin, although used in the United States for treatment of pernicious anemia, is not available in a concentrated high-strength form needed for antidotal treatment of cyanide poisoning.[79]

DIGITALIS GLYCOSIDES

Digitalis glycosides are found in a variety of plants, including foxglove, oleander, and rhododendron,[82] and have been used for centuries to treat heart failure. Digoxin is the most commonly prescribed digitalis glycoside. Digitalis poisoning may occur after accidental or suicidal acute overdose, as a result of chronic accumulation (usually because of renal insufficiency or overmedication), or as a drug interaction. There have been many reports of elevated digoxin levels resulting from the interaction of digoxin with commonly used drugs, such as quinidine, amiodarone, and macrolide antibiotics.[83] Digitalis glycosides inhibit the Na^+,K^+-ATPase pump, which returns potassium to cells and increases the intracellular calcium concentration.[84]

Diagnosis

After an acute overdose, serum potassium levels are often elevated and AV nodal conduction is impaired, leading to varying degrees of AV block. Additionally, gastrointestinal symptoms of nausea, vomiting, and anorexia are often described after acute digitalis poisoning. With chronic poisoning, in contrast, ventricular dysrhythmias (e.g., ventricular ectopic beats or bidirectional ventricular tachycardia) predominate, and the potassium level is often normal or low, perhaps in part because of long-term coadministration of diuretic agents. The digitalis level is usually markedly elevated; however, if the sample is drawn within a few hours of overdose or the last therapeutic dose, the result may be misleading because the drug has not been fully distributed to tissues.[85]

Treatment

Management of acute digitalis poisoning includes gut decontamination with the oral administration of activated charcoal and, if the ingestion was large and occurred shortly before presentation, gastric lavage. Ipecac is not recommended, because it may enhance the vagotonic effects of the digitalis. Initially, sinus

bradycardia or uncomplicated AV block should be treated with atropine (0.5 to 2 mg I.V.). A temporary pacemaker may be needed in patients with persistent symptomatic bradycardia; however, such patients should also receive digoxin-specific antibodies.

Digoxin-specific antibodies (e.g., Digibind) are indicated for patients with manifestations of severe intoxication (marked hyperkalemia and symptomatic dysrhythmias). These antibodies are derived from sheep and then cleaved to leave only the Fab fragment, which is small enough to be filtered and eliminated by the kidney after binding to digoxin. Extensive clinical experience with dixogin-specific antibodies has shown that they are safe and highly effective, with peak activity occurring within 20 to 30 minutes after administration.[7] The dose of digoxin-specific antibodies depends on the type of intoxication [*see Table 13*]. After acute ingestion, the serum level of drug does not predict the body burden because of ongoing tissue distribution[85]; therefore, the dose of digoxin-specific antibodies is calculated by estimating the amount of drug ingested. In patients with chronic poisoning in whom a steady-state digoxin level can be obtained, the body burden can be estimated on the basis of the serum level and the average apparent volume of distribution. When the ingested dose is not known or a steady-state level cannot be obtained, patients should be treated empirically: initially, one to five vials should be administered, depending on the severity of toxicity. It may also be appropriate to start with small doses and to titrate them to clinical effect in patients who have preexisting disease that requires residual digitalis effect (e.g., those with congestive heart failure or atrial fibrillation).

ETHANOL, METHANOL, AND ETHYLENE GLYCOL

Ethanol (grain alcohol) is probably the most widely used drug in the United States, and complications related to acute intoxication, as well as related medical illness and trauma, are commonly encountered. Ethanol-related illnesses account for nearly 20% of the national expenditure for hospital care, and ethanol is involved in about 50% of all fatal motor vehicle accidents.[86] Ethanol is frequently ingested with other drugs, both in suicide attempts and in recreational drug abuse. Ethylene glycol (antifreeze) and methanol (wood alcohol) are other alcohols that cause profound and often fatal poisoning when mistakenly ingested as substitutes for ethanol.

Ethanol

Diagnosis Acute ethanol intoxication produces an easily recognized state of inebriation that includes disinhibition,

slurred speech, ataxia, stupor, and coma.[15] Loss of protective reflexes in the airway may permit pulmonary aspiration of gastric contents, possibly causing respiratory arrest in those who are in a deep coma. In most states, a blood ethanol level above 80 to 100 mg/dl is considered sufficient evidence to charge a driver with the crime of driving while intoxicated. A level above 300 mg/dl is generally considered sufficient to cause deep coma and respiratory arrest; however, because tolerance to ethanol develops, chronic drinkers with these levels are often awake and even able to ambulate.[15] Acute ethanol ingestion can also cause hypoglycemia because of the inhibitory effect of ethanol on gluconeogenesis.

Treatment Treatment of ethanol intoxication usually consists of supportive care. The blood ethanol level decreases at an average (but variable) rate of about 20 mg/dl/hr,[15] and most patients are awake and ambulatory within 6 to 12 hours or less. The physician should protect the airway and, if necessary, intubate the trachea and assist ventilation. The patient should be evaluated for hypoglycemia, and glucose-containing fluids should be given as necessary; vitamin B_1, 100 mg I.V. or I.M., should be administered to malnourished or chronic alcoholic patients. Hypotension, although uncommon, may result from vasodilatation and dehydration and usually responds to an I.V. bolus of fluid. Although such patients often come to medical attention because of falls, even those without a history of trauma should be examined for occult injuries (especially to the head, neck, and abdomen) because inebriated patients often have such injuries. In addition, serious infections, vitamin deficiencies (especially of vitamin B_1 and folic acid), and metabolic abnormalities also occur frequently in chronic alcoholic patients[16]; if any of these are present, they should be treated.

Methanol and Ethylene Glycol

Diagnosis Methanol or ethylene glycol poisoning produces an initial clinical picture that is similar to that of ethanol intoxication. However, these alcohols are gradually metabolized to highly toxic organic acids that can have disastrous effects [*see Table 14*]. After a delay of up to several hours, the patient develops severe metabolic acidosis and evidence of endorgan injury from the accumulation of the toxic acid metabolites. Diagnosis of methanol or ethylene glycol poisoning is based on the patient's history of exposure and the presence of severe metabolic acidosis. The osmolar gap is usually elevated, especially early after ingestion when the parent compounds are present, but toxic products can be present with a seemingly normal osmolar gap.[87] The serum lactate level is relatively low despite a large anion gap.[88]

Treatment If methanol or ethylene glycol poisoning is suspected, immediate measures should be instituted to reduce absorption, prevent metabolism, and remove the toxic acid metabolites.[88] If the ingestion occurred shortly before presentation (i.e., less than an hour), gastric lavage should be performed; activated charcoal does not efficiently adsorb the alcohols. Metabolism of the alcohols can be prevented by giving ethanol or fomepizole (4-methylpyrazole), which competitively inhibit the enzyme alcohol dehydrogenase. If ethanol is used, a loading dose of approximately 750 mg/kg orally or I.V. usually produces an ethanol level of about 100 mg/dl[88]; an infusion of 100 to 150 mg/kg/hr is given to maintain this level. An ethanol drip is difficult to manage, and the ethanol may contribute to obtunda-

Table 13 Dosing of Digoxin-Specific Antibodies

Type of Intoxication	Dose Needed to Provide Complete Binding of Digoxin
Acute ingestion*	Administer one vial (40 mg) for each 0.5 mg of digoxin expected to be absorbed (because bioavailability is 80%, multiply ingested dose by 0.8 to estimate absorbed dose)
Chronic intoxication†	Use the following formula to calculate the number of vials needed: $$\frac{\text{Serum digoxin level (ng/ml)} \times \text{body weight (kg)}}{100}$$

*Dose of digoxin-specific antibodies is based on the estimated amount of digoxin ingested.
†Dose of digoxin-specific antibodies is based on the steady-state serum digoxin level.

Table 14 Poisoning with Ethylene Glycol, Isopropyl Alcohol, or Methanol

Alcohol	Metabolic Products	Treatment
Ethylene glycol	Oxalic, hippuric, and glycolic acids cause severe anion-gap metabolic acidosis; calcium oxalate crystals precipitate in tissues and kidneys[156]	Fomepizole or ethanol infusion; perform hemodialysis if there is severe acidosis, if serum level > 20–50 mg/dl, or if osmolar gap > 10 mOsm/L
Isopropyl alcohol	Acetone causes characteristic odor; toxicity includes CNS depression, but there are no toxic acid by-products[157]	Isopropyl alcohol is a potent CNS depressant and gastric irritant, but its toxicity is usually managed supportively
Methanol	Formic acid causes severe anion-gap metabolic acidosis and visual disturbances that can lead to blindness and death[158]	Fomepizole or ethanol infusion; perform hemodialysis if there is severe acidosis, if serum level > 20–50 mg/dl, or if osmolar gap > 10 mOsm/L

tion. Fomepizole is easier to administer, has few side effects, and, if initiated early after ethylene glycol ingestion, may eliminate the need for dialysis (this is not the case for methanol). Although costly, fomepizole therapy may be less expensive than the combined costs of hemodialysis, intensive care, and serial blood work during an ethanol drip.[88] Administration of folic acid (50 mg I.V. every 4 hours), vitamin B_1 (100 mg I.M. or I.V. every 6 hours), and vitamin B_6 (pyridoxine; 50 mg I.V. every 6 hours) is also recommended to enhance the metabolism of the toxic organic acids, and sodium bicarbonate should be given as needed to restore normal serum pH and enhance renal elimination of the toxic acid metabolites.

If the measured or estimated serum level of the toxic alcohol is greater than 50 mg/dl or if severe metabolic acidosis is present, hemodialysis is indicated to remove the parent compounds and their metabolites. During hemodialysis, the ethanol infusion is usually increased twofold, and fomepizole is administered every 4 hours to replace the respective drugs that are lost during the procedure.[88]

γ-HYDROXYBUTYRIC ACID (GHB)

γ-Hydroxybutyric acid (GHB) is a naturally occurring four-carbon compound that was first synthesized in 1960. Since then, the drug has been used for various clinical purposes, including induction of general anesthesia, treatment of alcohol withdrawal and narcolepsy, and even as a protective agent during tissue ischemia.[89] In the United States, it has been available only under an FDA investigational new drug (IND) exemption for the treatment of narcolepsy. However, in the late 1980s, GHB gained popularity among some bodybuilders who believed it could enhance muscle mass through stimulation of growth hormone release. It is now promoted popularly as a sleep aid, a diet agent, and a euphorigenic drug. Its increasing use has been accompanied by a number of reports of severe and fatal effects. Its illegal recreational abuse has become a part of the underground drug culture (e.g., at rave parties and dance clubs). It has also been used to facilitate rape and assault because it produces rapid loss of consciousness. Innovative ways to continue GHB use despite FDA and Drug Enforcement Administration (DEA) restrictions have included the sale of precursors of the drug such as γ-butyrolactone (GBL) and 1,4-butanediol, marketed as dietary supplements at health food stores and on the Internet under several trade names (e.g., Renew Trient and Revivarant). These precursors are metabolized to GHB in the body, and toxic effects are similar or identical to those of GHB.[90] After numerous reports of adverse reactions to these agents, including one death, the FDA asked manufacturers on January 21, 1999, to recall their GBL-containing products and warned consumers to avoid taking these products.[90]

Diagnosis

Clinically, patients poisoned by GHB or analogues usually present with profound CNS and respiratory depression, with possible loss of laryngeal reflexes and apnea. Symptoms usually last less than 4 to 6 hours, and patients often have sudden awakening and agitation, particularly in response to painful stimuli (e.g., intubation).[91] Concurrent sinus bradycardia, myoclonic movements, and vomiting are common. Delirium and tonic-clonic seizures have been reported. There is an additive effect of GHB when it is taken in conjunction with sedative agents or alcohol. GHB is absorbed within 10 to 15 minutes, and because of its short half-life of 27 minutes, plasma blood levels are undetectable within 4 to 6 hours of therapeutic ingestion.[89] A recent report suggests that GHB dependence may lead to severe withdrawal after sudden discontinuance. Symptoms are similar to alcohol withdrawal but may last 7 to 14 days; these patients often require very large doses of benzodiazepines and barbiturates to control agitation.[92]

Treatment

There is no specific antidote for GHB. Therapy consists of airway protection, with rapid-sequence intubation if needed [*see* Initial Stabilization, *above*]. Because of the short half-life of GHB, patients without complications from GHB (e.g., prolonged hypoxia, aspiration, or untoward effects of mechanical ventilation) are often extubated and discharged from the emergency room within 3 to 7 hours.[91] Symptomatic bradycardia can be successfully treated with atropine.[91] Decontamination measures, such as gastric lavage and activated charcoal, are of little benefit because of GHB's rapid absorption, although it should be considered for large overdoses or if a coingestion is suspected. GHB withdrawal can be treated in the same manner as alcohol withdrawal, although physicians should recognize the potential need for a longer treatment period.[93]

IRON

Iron poisoning is typically seen in children who accidentally ingest their parents' iron supplements, but intentional overdose occasionally occurs in adults.[94] Iron in large quantities is corrosive to the gastrointestinal tract, causes nausea and vomiting, and sometimes causes bloody emesis and diarrhea. Intestinal perforation occasionally occurs. Shock may result from volume loss and fluid shifts, as well as from iron-induced peripheral vasodilatation. In addition, free iron is cytotoxic, and coma, metabolic acidosis, and liver failure may develop from excessive, acute systemic absorption.[94]

Diagnosis

Diagnosis of acute iron poisoning may be based on a history of exposure or may be suspected in a patient with severe gas-

troenteritis and hypotension, especially if such a patient also has metabolic acidosis, hyperglycemia, and leukocytosis.[94] A plain x-ray of the abdomen (KUB view) may reveal radiopaque iron tablets. Serum iron levels in patients with severe poisoning are usually higher than 600 to 1,000 mg/dl, although lower levels may be seen if the sample is drawn late in the course of intoxication. In the past, it was common to estimate the quantity of free iron by subtracting the total iron-binding capacity (TIBC) from the serum iron level. However, it has since been shown that the TIBC is falsely elevated during iron poisoning, and this value is no longer considered useful for the purpose.[95]

Treatment

Treatment of acute iron overdose includes gut decontamination, I.V. administration of fluids, and, possibly, chelation with deferoxamine. Patients who are in shock should receive vigorous I.V. fluid replacement. Because activated charcoal does not bind iron, it should not be given unless overdose of other drugs is also suspected. Gastric lavage may be useful in patients who have taken liquid iron preparations or chewable products; however, if intact tablets are seen on x-ray, it is unlikely that they can be removed through even the largest-bore gastric hose. Attempts to render the iron insoluble by gastric lavage with bicarbonate- or phosphate-containing solutions have proved ineffective or dangerous. Currently, the recommended method of gut decontamination in patients with large ingestions is whole bowel irrigation,[23,29] which is achieved by administering polyethylene glycol–electrolyte solution (e.g., GoLYTELY or Colyte), 1 to 2 L/hr by nasogastric tube for several hours, until the rectal effluent is clear and the x-ray shows no radiopacities.

Therapy with deferoxamine, a specific chelator of iron, is indicated in patients who have evidence of severe poisoning, but such therapy should not replace thorough gut decontamination and aggressive volume replacement.[94] The I.V. route is preferred, and an initial dosage of 10 to 15 mg/kg/hr should be given. Dosages as high as 40 to 50 mg/kg/hr may be given in particularly severe cases of poisoning. The iron-deferoxamine complex imparts an orange or vin rosé color to the urine that is sometimes used as evidence of the continued presence of chelatable (free) iron. Inasmuch as serum iron levels are readily available in most hospitals, the so-called vin rosé test is seldom used as an indication to continue therapy. Many clinicians stop administering deferoxamine as soon as the serum iron level is lower than 350 mg/dl, because prolonged infusions have been associated with acute respiratory distress syndrome (ARDS).[7]

ISONIAZID

Isoniazid is widely used in the treatment of tuberculosis. Long-term use of isoniazid has been associated with hepatitis and peripheral neuropathy [see 4:VIII Chronic Hepatitis and 7:XIV Chemotherapy of Infection]. Acute overdose of isoniazid is a well-known cause of seizures and metabolic acidosis.[96,97] Isoniazid causes acute toxicity by competing with pyridoxal 5´-phosphate (the active form of vitamin B_6), resulting in lowered γ-aminobutyric acid (GABA) levels in the brain. It also inhibits the hepatic metabolism of lactate to pyruvate. As little as 1.5 g of isoniazid may cause toxicity, with severe toxicity likely to occur after administration of 5 to 10 g.

Diagnosis

Acute overdose of isoniazid causes confusion, seizures, and coma; the onset is abrupt, often occurring within 30 to 60 min-

utes of ingestion. Lactic acidosis is often severe, and its severity is disproportional to the duration or intensity of seizure activity. Diagnosis is based on a history of isoniazid ingestion and should be suspected in any person who experiences the acute onset of seizures and who may be taking the drug (e.g., persons who have tuberculosis or AIDS and recent immigrants who test positive on the purified protein derivative [PPD] skin test). Results of testing for serum isoniazid levels are not generally available immediately, and routine toxicology screens do not ordinarily test for the drug.

Treatment

Activated charcoal should be administered to any person who is suspected of having isoniazid intoxication. Emesis should not be induced because of the risk of abrupt onset of seizures and coma. Gastric lavage is appropriate in cases of large, recent ingestion. Seizures should be treated initially with diazepam, 5 to 10 mg I.V., or with lorazepam, 1 to 2 mg I.V. Vitamin B_6 is a specific antidote and should be given to all patients who have taken more than 3 to 5 g of isoniazid. In cases in which the amount of isoniazid ingested is unknown, the dose is 5 to 10 g I.V.; if the amount is known, an equivalent gram-for-gram amount of vitamin B_6 should be given.[96] Administration of vitamin B_6 effectively stops resistant seizures and improves metabolic acidosis. It has also reportedly reversed isoniazid-induced coma.[98]

LEAD

Lead poisoning primarily occurs in the occupational setting, with exposure occurring over a period of months or years. However, lead is a ubiquitous metal found in the paint of older houses, car batteries and radiators, some pottery glazes and solders, and some folk medicines[99]; thus, it may be encountered by hobbyists, home-repair buffs, and those who use ceramic cookware.

Diagnosis

The clinical manifestations of lead poisoning are sufficiently variable and nonspecific that lead poisoning should be suspected in any patient who has multisystem illness, especially if the illness involves the neurologic, hematopoietic, and gastrointestinal systems.[99] Lead poisoning rarely results from a single ingestion, although such occurrences have been reported.[31] More commonly, exposure occurs repeatedly and gradually. Patients typically have cramplike abdominal pain or nausea and may have chronic systemic symptoms such as irritability, malaise, and weight loss. Other manifestations of lead poisoning include peripheral motor neuropathy (wristdrop) and anemia, which is often microcytic and accompanied by basophilic stippling. Lead encephalopathy, manifested by coma and seizures, is rare.

Chronic lead poisoning has been misdiagnosed as porphyria, in part because they both involve alteration of heme metabolism.[100] Diagnosis of lead poisoning is usually based on the lead level in whole blood. Symptoms generally occur in patients with lead levels above 25 to 40 mg/dl, but lower levels have been associated with impaired neurobehavioral development in children.[101] Lead levels above 80 mg/dl are often associated with severe overt toxicity. The free erythrocyte protoporphyrin (FEP) concentration, which is elevated (> 35 mg/dl) in persons with chronic intoxication, has been used to screen large populations for lead poisoning but is not sufficiently sensitive for the identification of low blood lead levels (< 30 mg/dl) in children.

Treatment

For patients with an acute ingestion of lead (e.g., a fishing weight, bullet, or curtain weight), a plain x-ray of the abdomen should be obtained. If the object is in the stomach, there is a risk that the action of stomach acid may create enough absorbable lead to cause systemic toxicity; therefore, the object should be removed by the use of cathartic agents, whole bowel irrigation, or endoscopy. Objects that clearly lie beyond the pylorus are likely to pass uneventfully into the stool, but confirmation of this supposition should be obtained by close follow-up with repeated x-rays and measurement of blood lead levels.[31]

Several chelating agents are available for the treatment of patients with acute or chronic intoxication who are symptomatic and have elevated blood lead levels.[101,102] The oldest chelating agent, dimercaprol, is reserved for patients with lead encephalopathy (but even this use is controversial). For less severe intoxication, the physician should administer I.V. calcium EDTA or oral succimer (meso-2,3-dimercaptosuccinic acid, or DMSA). Triple-chelation therapy with dimercaprol, EDTA, and oral succimer has been used in conjunction with whole bowel irrigation following an extremely high lead level in a 3-year-old child with encephalopathy.[102] A recent trial suggests that succimer does not provide any benefit in children with chronically elevated blood lead levels between 20 and 44 μg/dl.[103] However, the findings of this study, the indications for treatment, and the recommended agents and doses are controversial; the physician should consult with a specialist in occupational medicine or toxicology or contact a regional poison-control center for specific advice about the doses and side effects of these drugs.

Health care providers should be aware that the Occupational Safety and Health Administration (OSHA) has provided specific guidelines for monitoring and managing workers who have been exposed to lead [see CE:VI Occupational Safety and Health]; these guidelines stipulate that such workers be removed from exposure if a single blood lead level exceeds 60 μg /dl or if the average of a series of three successive periodic screening levels exceeds 50 μg /dl.[104] For further information, a regional OSHA office or an occupational medicine specialist should be consulted. (A directory of regional offices is available at the OSHA Web site, at http://www.osha.gov.) Finally, because household members of persons who have been occupationally exposed to lead may be contaminated by the poisoned individual, household members should also be evaluated for lead poisoning even if they are apparently asymptomatic, and measures should be taken to reduce or prevent further exposure.

LITHIUM

Lithium is a simple cation that is widely used for the treatment of manic-depressive illness and other psychiatric disorders. It is also used to elevate the white blood cell count in patients with severe leukopenia. Lithium is excreted renally, and severe intoxication usually results from drug accumulation caused by renal impairment or excessive overmedication. An acute single overdose, however, is less likely to result in severe poisoning.

Diagnosis

The usual therapeutic level of lithium is 0.6 to 1.2 mEq/L. Chronic intoxication can occur with levels only slightly above 1.2 mEq/L, but patients with acute overdose may remain asymptomatic despite having much higher levels early after ingestion of the drug.[105] Manifestations of lithium intoxication include confusion, lethargy, tremors, and muscle twitching. The ECG may show flattening of T waves, the presence of U waves, and prolongation of the QT interval. In severe cases, coma and convulsions may occur.[105] Symptoms may take several days to weeks to resolve, and some patients are left with permanent neurologic impairment.[106] Other toxic effects of lithium intoxication are nephrogenic diabetes insipidus and neuroleptic malignant syndrome [see Table 5]. These effects can occur at therapeutic levels of the drug.

Treatment

Treatment of acute lithium overdose consists mainly of gut decontamination and fluid therapy. Because lithium is poorly adsorbed to activated charcoal, administration of this agent is not necessary unless the physician suspects that another drug has also been ingested. Gastric lavage or ipecac-induced emesis may reduce the gastric burden of lithium. Whole bowel irrigation should be considered, especially if the patient has ingested a sustained-release form of the drug.[105] Limited experimental and anecdotal evidence suggests that administration of sodium polystyrene sulfonate reduces absorption and enhances elimination of lithium, although its role in acute lithium overdose remains to be established.[107]

Fluid therapy is an essential part of treatment of lithium intoxication. The physician should restore volume with 1 to 2 L of normal saline, then continue the I.V. administration of fluids at a rate sufficient to produce urine at a rate of about 100 ml/hr. The indications for hemodialysis in the setting of lithium toxicity are controversial. A recent review article recommends the following guidelines for hemodialysis: a lithium level greater than 6 mEq/L in any patient; a lithium level greater than 4 mEq/L in any patient on long-term lithium therapy (in contrast to an acute overdose); or a lithium level of 2.5 to 4.0 mEq/L in any patient with severe neurologic symptoms, renal insufficiency, hemodynamic instability, or neurologic instability.[105] One poison-control center–based study did not observe any significant difference in lithium toxic patients in whom hemodialysis was recommended by the poison-control center but not performed and in whom hemodialysis was performed.[108] These authors recommend reserving hemodialysis for severe cases of lithium toxicity. Blood should be drawn at least 8 to 12 hours after the last dose of lithium is given to prevent misinterpretation caused by falsely high levels before drug distribution in tissues. Serial lithium measurements should be obtained until the level clearly drops, to exclude ongoing absorption or rebound after hemodialysis. Consultation with a regional poison-control center, medical toxicologist, and nephrologist should be obtained early to help manage a lithium-toxic patient.

METHEMOGLOBINEMIA-INDUCING AGENTS

Methemoglobin is an oxidized form of hemoglobin that is incapable of carrying and delivering oxygen normally. A number of oxidant drugs and chemicals can convert hemoglobin to its oxidized form, causing methemoglobinemia.[109] These agents include local anesthetics (e.g., benzocaine and lidocaine), antimicrobial agents (e.g., chloroquine, dapsone, primaquine, and sulfonamides), analgesics (e.g., phenazopyridine and phenacetin), nitrites and nitrates (e.g., amyl nitrite, butyl nitrite, isobutyl nitrite, and sodium nitrite), and several miscellaneous drugs and chemicals (e.g., aminophenol, aniline dyes, bromates, chlorates, metoclopramide, nitrobenzene, nitrogen oxides, and nitroglycerin). Persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency and congenital methemoglobin reductase deficiency

are more likely than persons without these conditions to accumulate methemoglobin after exposure to an oxidant.

Diagnosis

Methemoglobinemia causes cellular asphyxia. Symptoms of mild to moderate methemoglobinemia include headache, nausea, dizziness, and dyspnea. Methemoglobin levels as low as 15% can cause the patient to appear cyanotic despite having a normal oxygen tension. The blood usually has a dark or chocolate-brown appearance. Although pulse oximetry is abnormal, the reported drop in oxygen saturation does not correlate with the actual reduction in oxyhemoglobin saturation, and specific testing for methemoglobinemia should be performed.[110]

Treatment

Mild methemoglobinemia (methemoglobin levels < 15% to 20%) usually resolves spontaneously, requiring no treatment. Patients who have more severe intoxication should be given the antidote methylene blue (1 to 2 mg/kg I.V. [0.1 to 0.2 ml/kg of a 1% solution] over several minutes).[109] The dosage may be repeated once. Although symptoms and signs usually resolve quickly, methemoglobinemia may recur with the administration of long-acting oxidants such as dapsone [see 5:IV Hemoglobinopathies and Hemolytic Anemias].[109]

OPIOIDS

The opioids and opiates include several synthetic and naturally occurring compounds that are widely used for their analgesic properties. Common opium derivatives include morphine, heroin, hydrocodone, and codeine. Synthetic opioids include fentanyl, methadone, and butorphanol. Preparations of hydrocodone or codeine for oral use commonly contain aspirin or acetaminophen, which may themselves be responsible for serious toxicity in an overdose. Opioids stimulate several receptors in the CNS, resulting in sedation and reduced sympathetic outflow.[6,7] Excessive opioid effect may cause coma and blunting of the respiratory response to hypercapnia. The opioids meperidine and dextromethorphan may cause serious rigidity and hyperthermia in persons who are taking MAO inhibitors or other serotoninergic drugs (e.g., selective serotonin reuptake inhibitors [SSRIs]).[111]

Diagnosis

Patients may have opioid intoxication as a result of unintentional overdose or attempted suicide. Signs of intoxication include lethargy or coma, pinpoint pupils, and respiratory depression. Acute noncardiogenic pulmonary edema may occur.[6] Seizures are not typical but may occur with acute propoxyphene overdose; repeated therapeutic doses of meperidine can also cause seizures, especially in persons with renal failure because of accumulation of the metabolite normeperidine.

Diagnosis of opioid intoxication is usually not difficult in a person who is in a coma and has pinpoint pupils and apnea.[5,6] Paramedics may discover I.V. drug paraphernalia or empty prescription bottles at the scene. Exposure to other drugs, however, may complicate the clinical picture.

Treatment

The physician should immediately establish that the airway is not obstructed and that ventilation is adequate and then administer supplemental oxygen as necessary. After these initial measures, the specific opioid antagonist naloxone should be given (0.2 to 2 mg I.V. or S.C.). A recent trial has shown similar results with subcutaneous and intravenous naloxone.[112] Persons who are suspected of chronic narcotic abuse should be started with smaller doses of naloxone to minimize the severity of an acute withdrawal reaction. Patients usually become fully awake within a few minutes after administration. If the initial dose is not effective, additional doses (up to 15 to 20 mg if opioid intoxication is strongly suspected) should be given until a satisfactory response is achieved. The plasma half-life of naloxone is about 60 minutes, which is shorter than that of most of the opioids whose actions it reverses; therefore, patients who respond to the antidote should be observed for at least 3 hours after the last dose for the recurrence of sedation. Traditionally thought to be an innocuous drug, naloxone has been associated with an approximately 1.6% complication rate. Complications include asystole, seizures, pulmonary edema, and severe agitation.[6]

Oral ingestion of an opioid should be treated with activated charcoal. Gastric lavage should be considered in cases of large or recent overdose. There is no role for hemodialysis or other enhanced removal procedures in the treatment of opioid overdose.

ORGANOPHOSPHATES AND RELATED AGENTS

Organophosphates and carbamates are widely used as pesticides,[113] and several of the nerve agents developed for chemical warfare[114] are rapidly acting and potent organophosphates. All of these poisons inhibit the enzyme acetylcholinesterase, preventing the breakdown of acetylcholine at cholinergic synapses. Whereas the organophosphates may cause permanent damage to the enzyme, carbamates have a transient and reversible effect. Many of these agents are well absorbed through intact skin. Persons may be exposed accidentally while working with or transporting the chemicals or as a result of accidental or suicidal ingestion.

Diagnosis

Excessive activity of acetylcholine may occur at nicotinic, muscarinic, and CNS cholinergic receptors. The most common presenting symptoms of poisoning are abdominal cramps and vomiting accompanied by sweating and hypersalivation [see Table 15]. The patient usually has small or pinpoint pupils. Because of the mixed effects of poisoning on sympathetic ganglia and parasympathetic synapses, the heart rate may be either slow or fast. Life-threatening manifestations of acetylcholinesterase inhibition include muscle weakness with respiratory arrest, as well as severe bronchospasm. Significant volume loss may result from excessive sweating, salivation, vomiting, and diarrhea.[113]

Treatment

Contaminated clothing should be removed immediately and all exposed areas washed thoroughly with soap and water. Rescue personnel should take precautions to avoid secondary contamination from direct contact with the victim's skin, clothing, or vomitus. Xylene or other solvent vapors emanating from the victim are not life threatening to medical personnel but may cause dizziness, nausea, and headache. In patients who have ingested an organophosphate or a carbamate, gastric lavage should be performed with the use of a closed-container unit and activated charcoal should be administered.

Specific therapy includes administration of atropine and pralidoxime (2-PAM). Atropine is not a physiologic antidote but can reverse excessive muscarinic stimulation, thereby alleviating abdominal cramps, bronchospasm, and hypersalivation. It does not reverse muscle weakness. All patients with organophosphate poisoning should also be given 2-PAM because it can

Table 15   Manifestations of Excessive Activity of Acetylcholine

Site of Activity	Clinical Manifestations
Postganglionic muscarinic receptors	Bradycardia; miosis; salivation; lacrimation; bronchorrhea; increased peristalsis; sweating
Autonomic ganglia	Tachycardia; hypertension
Skeletal muscle nicotinic receptors	Muscle fasciculations followed by weakness; neuromuscular paralysis
CNS cholinergic receptors	Agitation; seizures

chemically restore the enzyme acetylcholinesterase; in persons who go untreated, the organophosphate's binding to acetylcholinesterase may become permanent (the so-called aging effect). Because carbamates have a transient effect, 2-PAM therapy is not needed in patients who have been poisoned with these agents. However, because the exact product causing cholinergic excess is often not known initially or because it may be a mix of organophosphate and carbamate, 2-PAM may be initiated empirically. Additionally, several case reports suggest that 2-PAM may be useful in carbamate poisoning.[115]

The dosage of 2-PAM is 1 to 2 g I.V. initially, followed by a continuous infusion of 200 to 500 mg/hr, depending on the patient's response. The infusion should be continued until the patient can be weaned from the drug without experiencing recurrence of weakness or muscarinic manifestations. This process may take several days in persons who have been exposed to highly lipid-soluble agents such as fenthion or dichlorvos.[7] A so-called intermediate syndrome has been described in which some patients experience recurrent muscle weakness several days after initially successful treatment[116]; this syndrome may be caused by neurotoxic components of the agent, continued toxicity from a lipid-soluble product, or inadequate 2-PAM therapy.

SALICYLATES

Aspirin (acetylsalicylic acid) and other salicylates are widely used for their antipyretic, anti-inflammatory, and analgesic effects and can be found alone or in combination in a number of prescription and over-the-counter products (e.g., oil of wintergreen, Pepto-Bismol). Salicylates interfere with the metabolism of glucose and fatty acids; they also uncouple oxidative phosphorylation, leading to inefficient production of adenosine triphosphate, accumulation of lactic acid, and production of heat. Poisoning may result from an acute single ingestion (usually in a dose > 200 mg/kg) or from chronic overmedication.[117] Chronic poisoning occurs most commonly in elderly persons who regularly take large doses of aspirin (e.g., for osteoarthritis) and who gradually begin to take larger doses or in whom renal insufficiency develops. In such cases, the diagnosis of salicylism is often overlooked, and patients may be assumed to have sepsis, gastroenteritis, or pneumonia on admission to the hospital.[117]

Diagnosis

The most common initial manifestation of salicylate poisoning is hyperventilation, which occurs largely as a result of central stimulation of respiratory drive and partly in response to metabolic acidosis. Measurement of arterial blood gases usually reveals respiratory alkalosis with predominant alkalemia and un-

derlying metabolic acidosis. Other findings include tinnitus, confusion, and lethargy. Patients with severe intoxication may experience coma, seizures, hyperthermia, noncardiogenic pulmonary edema, and circulatory collapse. The serum salicylate level in such cases usually exceeds 100 mg/dl (1,000 mg/L), although patients with chronic intoxication may experience severe effects with much lower serum levels.[118]

Treatment

For patients with an acute ingestion, activated charcoal should be administered and gastric lavage considered if the ingestion was large (e.g., > 10 to 15 g). Because salicylates cause pylorospasm and delay gastric emptying, lavage may be successful even after a delay of several hours. For a patient who has taken a massive ingestion, extra dosages of activated charcoal (50 to 60 g every 4 to 6 hours for the first 1 to 2 days) may be needed to achieve the desired 10-to-1 ratio of charcoal to drug. Massive ingestions, as well as those involving enteric-coated aspirin, may lead to prolonged or delayed absorption and the potential for catastrophic worsening after 1 to 2 days.[117] In such cases, close observation of the patient should be maintained, and measurement of the serum salicylate level should frequently be performed until the level clearly drops into the therapeutic range (10 to 20 mg/dl).

Enhanced elimination procedures can effectively reduce elevated salicylate levels. Alkalinization of the urine traps the ionized form of salicylate in the kidney tubules, increasing renal elimination.[110] To initiate alkalinization, the physician should add 100 mEq of sodium bicarbonate to 1 L of 5% dextrose in quarter-normal (0.225%) saline, then infuse the solution at 200 ml/hr while monitoring the pH of the urine (the goal is to achieve a pH of 7 to 8). It may be difficult to perform alkalinization in patients with volume and potassium deficits without first replacing these losses. Hemodialysis rapidly lowers serum salicylate levels and can restore fluid and electrolyte balances. Hemodialysis is recommended for patients who are unable to tolerate fluid challenges (e.g., as in cerebral edema or pulmonary edema) and those who have worsening renal insufficiency, severe metabolic acidosis, or a serum salicylate level greater than 100 mg/dl (1,000 mg/L).

SEDATIVE-HYPNOTIC AGENTS

The sedative-hypnotic agents include the barbiturates (e.g., phenobarbital, pentobarbital, butalbital, and amobarbital) and the benzodiazepines (e.g., alprazolam, diazepam, lorazepam, and triazolam), as well as several other drugs, such as meprobamate, glutethimide, ethchlorvynol, chloral hydrate, zolpidem, and buspirone. These drugs cause generalized depression of CNS activity and are commonly used to alleviate anxiety or to induce sleep. The mechanisms of action and pharmacokinetics are different for each drug group.[11,119,120]

Diagnosis

Overdose of a sedative-hypnotic drug causes lethargy, ataxia, and slurred speech. In patients with severe poisoning, coma and respiratory arrest may occur, especially when sedative-hypnotic drugs are combined with other depressants, such as ethanol. The blood pressure and pulse rate are usually decreased, the temperature may be low because of exposure and venodilatation, and the pupils are usually small (although they may be dilated in patients with glutethimide overdose). Patients who are in a deep coma may appear to be dead because they may have absent reflexes, fixed pupils, and even flat EEG tracings.[121] In patients with chloral hydrate overdose, ventricular ectopy and ventricular

tachycardia may develop; these effects are caused by generation of the metabolite trichloroethanol, which, like other chlorinated hydrocarbons, can sensitize the myocardium to the effects of epinephrine.[122] In cases of phenobarbital overdose, blood levels of the drug can be obtained in most hospital laboratories, but in cases of overdose of most of the other sedative-hypnotic agents, blood levels are neither clinically useful nor readily available.

Treatment

The physician should maintain an unobstructed airway and administer supplemental oxygen, then intubate the trachea and assist ventilation, if necessary. Uncomplicated hypothermia should be treated with gradual passive external rewarming. I.V. crystalloids should be administered to patients with low blood pressure; if necessary, dopamine and other pressor agents should be given. For patients with ventricular arrhythmias caused by chloral hydrate overdose, propranolol (1 to 5 mg I.V.) or esmolol (25 to 100 mg/kg/min) should be given.[122] Activated charcoal should be administered. For cases of massive ingestion, gastric lavage should be considered.

Flumazenil is a specific benzodiazepine antagonist that has been proved effective in reversing the coma caused by benzodiazepine overdose. It has a rapid onset of action after I.V. administration (0.5 to 3.0 mg); because its effects last for only about 2 to 3 hours, resedation may occur. Flumazenil is contraindicated in patients with a known or suspected overdose of a tricyclic antidepressant and in patients who have been given a benzodiazepine for control of status epilepticus, because flumazenil may induce seizures in these patients. It should also not be used in patients who have increased intracranial pressure and who are receiving benzodiazepines for sedation. The use of flumazenil in persons who have been taking large quantities of benzodiazepines for long periods may provoke an acute withdrawal syndrome.[5,7]

Enhanced removal procedures are rarely needed in patients with sedative-hypnotic overdose because most will recover with airway management, assisted ventilation, and other supportive measures. When supportive measures fail, hemoperfusion can effectively reduce blood concentrations of phenobarbital, pentobarbital, meprobamate, glutethimide, and ethchlorvynol.[123]

THEOPHYLLINE

Although no longer a first-line drug, theophylline is still used for the treatment of asthma and other bronchospastic disorders, congestive heart failure, and neonatal apnea. It is available in regular and sustained-release formulations for oral use. Aminophylline, the ethylenediamine salt of theophylline, is used for I.V. infusions. Theophylline intoxication may occur after an acute single overdose or as a result of chronic overmedication.[124] Chronic intoxication may also be caused by reduced theophylline metabolism resulting from the addition of an interfering drug (e.g., cimetidine or erythromycin) or from an intercurrent illness (e.g., congestive heart failure or liver failure). The normal elimination half-life, 4 to 6 hours, may be prolonged to more than 20 hours in theophylline overdose.

Diagnosis

Acute theophylline overdose causes vomiting, tremors, and tachycardia. Laboratory findings include hypokalemia, hypophosphatemia, and hyperglycemia. These metabolic effects, as well as tachycardia and vasodilatation, are thought to be mediated through excessive beta$_2$-adrenergic stimulation. If serum theophylline levels exceed 100 mg/L, seizures, hypotension, and

ventricular arrhythmias are likely to develop.[124] The seizures are often refractory to anticonvulsant therapy. Serum drug levels may not peak for 16 to 24 hours after theophylline ingestion, especially if the drug was in a sustained-release formulation.

Chronic intoxication may develop gradually, with toxicity possibly occurring at serum drug levels that are much lower than those associated with acute overdose: seizures have been reported to occur at levels as low as 14 to 35 mg/L.[124] Unlike the findings in acute overdose, hypokalemia and hypotension are not common.

Treatment

In cases of acute ingestion of theophylline, activated charcoal should be given. Gastric lavage should be considered for large ingestions (more than 15 to 20 tablets). However, it is unlikely that lavage will remove intact sustained-release tablets, and severe or fatal intoxication may ensue despite aggressive attempts at decontamination.[125] Although some toxicologists have suggested administering repeated doses of activated charcoal in combination with whole bowel irrigation for massive ingestions of sustained-release medications, this approach remains controversial.[125]

Hypotension should be treated with esmolol (25 to 100 mg/kg/min) rather than a beta-adrenergic agonist because the hypotension is probably caused by beta$_2$-adrenergic–mediated vasodilatation.[126] Seizures should be treated with phenobarbital (15 to 20 mg/kg I.V.) rather than with phenytoin, which is ineffective.[125] For patients with recurrent seizures and for those with serum theophylline levels of around 100 mg/L or greater, excess theophylline should be removed as quickly as possible by hemodialysis or hemoperfusion.[127] Administration of multiple repeated doses of activated charcoal [*see* Enhanced Elimination, *above*] can effectively shorten the elimination half-life of theophylline, but such administration is often not practical in the critically ill patient.

TRICYCLIC ANTIDEPRESSANTS AND RELATED COMPOUNDS

Tricyclic antidepressants, also known as cyclic antidepressants, were once a leading cause of seizures and death from acute drug overdose.[123] Although most of the newer SSRI antidepressants are much less toxic [*see Table 16*], tricyclic antidepressants are still commonly used for the treatment of depression, enuresis, and other disorders.

The toxicity of the tricyclic antidepressants is caused by various pharmacologic properties of this class of agents, including anticholinergic activity, inhibition of norepinephrine reuptake, alpha-adrenergic blockade, and, most important, depression of the fast sodium channel in cardiac cells (the so-called quinidine-like or membrane-depressant effect). This last property is responsible for prolongation of conduction and depressed cardiac contractility.[128] Ingestion of approximately 1 g of a tricyclic antidepressant is likely to produce severe toxicity.

Diagnosis

Initially, persons with tricyclic antidepressant overdose have anticholinergic signs, including tachycardia; dilated pupils; reduced peristalsis; muscle twitching; and dry, flushed skin. Lethargy and slurred speech are common. The abrupt onset of seizures, coma, and hypotension signals severe toxicity, which may occur within 30 to 60 minutes of ingestion or may be delayed because of slowed gut absorption. In patients with severe intoxication, the ECG shows a QRS complex that is usually

wider than 0.12 second[128,129]; however, this finding may initially be absent if the drug has not been absorbed or in cases of overdose with amoxapine or another noncardiotoxic drug. In some patients, right-axis deviation of the terminal 40 msec of the QRS complex may represent early evidence of a conduction disturbance.[129] Death may result from profound depression of cardiac conduction and contractility; respiratory arrest; or complications of pulmonary aspiration, aspiration pneumonia, or hyperthermia (caused by muscle twitching and seizures coupled with the absence of sweating).

Treatment

The physician should administer activated charcoal. Gastric lavage should be considered for patients with massive ingestions (e.g., > 4 to 5 g), especially if less than 1 hour has elapsed since the overdose. All patients should be monitored closely for at least 6 hours; any person with altered mental status, evidence of anticholinergic toxicity, or cardiac conduction abnormalities should be admitted to the hospital and monitored closely. The physician should maintain an unobstructed airway, intubate the trachea, and assist ventilation if needed.

Seizures should be treated with benzodiazepines and pheno-

barbital (see above). Physostigmine should not be administered, because it may cause seizures and can worsen cardiac conduction disturbances. Initially, hypotension should be treated with I.V. boluses of normal saline. If there is evidence of depression of the sodium channel (i.e., a wide QRS complex), sodium bicarbonate should be administered at a dosage of 50 to 100 mEq I.V.[10,128] Repeated doses may be given as needed, although the serum pH should be monitored for excessive alkalemia. If hypotension does not respond to administration of fluids and sodium bicarbonate, dopamine or norepinephrine should be given. Norepinephrine may be more effective than dopamine in some patients, possibly because of tricyclic antidepressant–induced depletion of norepinephrine, but in one study, no difference between these agents was found.[128] Partial cardiopulmonary bypass has been suggested for patients with refractory hypotension and agonal cardiac rhythm, although there is little likelihood of survival.[54] There is no known role for hemodialysis or hemoperfusion in this setting.

Food Poisoning

A variety of toxins may produce illness after consumption of fish, shellfish, or mushrooms. Illness caused by bacterial or viral contamination of food, including botulism, is discussed elsewhere [*see 7:V Anaerobic Infections*].

SEAFOOD

The mechanism of toxicity varies with each toxin [*see Table 17*]. In general, the seafood-associated toxins are heat stable; therefore, cooking does not render the food safe to eat. In some cases (e.g., ciguatera and paralytic shellfish poisoning [PSP]), the poisons are highly potent neurotoxins elaborated by dinoflagellates, which are then consumed by fish or concentrated by filter-feeding clams and mussels. Scombroid poisoning results from bacterial overgrowth in inadequately refrigerated fish (although the fish may look and smell fresh); scombrotoxin is a mixture of histamine and histaminelike compounds produced by the breakdown of histidine in the fish flesh. Tetrodotoxin is produced by microorganisms associated with the puffer fish (as well as the California newt and some species of South American frogs) and concentrated in various internal organs. Although the fish is deadly and ranks as the leading cause of fatal food poisoning in Japan, it is also considered a delicacy; extreme care is required in preparation of this fish by specially trained chefs to separate the edible muscle from

Table 17 Seafood Poisonings[159]

Type	Onset	Common Sources	Syndrome	Treatment
Ciguatera	1–6 hr	Barracuda, red snapper, grouper	Gastrointestinal upset, paresthesias, sensation of hot and cold reversal, itching, weakness, myalgias, orthostatic hypotension	Supportive; ?mannitol
Paralytic shellfish poisoning	30 min	Bivalve mollusks (mussels, clams), associated with algae bloom (red tide)	Gastrointestinal upset, paresthesias, ataxia, weakness, respiratory muscle paralysis, respiratory arrest	Supportive
Scombroid	Minutes to hours	Tuna, mahi-mahi, bonito, mackerel	Gastrointestinal upset, flushed skin, urticaria, wheezing	Antihistamines
Tetrodotoxin	30 min	Puffer fish (fugu), sunfish, porcupine fish	Vomiting, paresthesias, perioral tingling, muscle weakness, respiratory paralysis, respiratory arrest	Supportive

the toxin-containing organs. Poisoning from saxitoxin (the culprit in PSP) has recently been reported in persons who ate puffer fish caught in waters near Titusville, Florida.[130]

Diagnosis

Signs and symptoms of seafood poisoning vary with the toxin [*see Table 17*]. Diagnosis is based on the clinical presentation and history of ingested seafood. In some cases, laboratory confirmation can be carried out with the assistance of the regional or state health department.

Treatment

In general, treatment is supportive. For neurotoxic poisonings such as PSP and tetrodotoxin, prompt medical attention may be required to prevent death from sudden respiratory arrest. Scombroid poisoning is often treated with H_1 and H_2 histamine blockers (e.g., diphenhydramine and cimetidine). For ciguatera poisoning, previous anecdotal reports have suggested benefit from mannitol, but a recent randomized, controlled blinded trial showed that mannitol did not relieve symptoms of ciguatera poisoning and resulted in more side effects than normal saline.[131] Ciguatera poisoning can produce chronic symptoms, which may resemble multiple sclerosis or chronic fatigue syndrome.[132] Improvement in chronic symptoms has been reported in patients treated with amitriptyline or fluoxetine[133,134]; polyneuropathy has responded to gabapentin.[135] Recurrence of symptoms, which may be worse than the initial attack, can be triggered by ingestion of fish or alcohol.

AMANITA PHALLOIDES MUSHROOMS

The *A. phalloides* mushroom ("death cap") has been known and feared for at least two millennia and continues to cause serious illness and death, although in recent years, mortality has declined because of the availability of orthotopic liver transplantation for patients with fulminant liver failure. This mushroom, as well as several others that contain the cellular toxin amanitin (also known as amatoxin), are found throughout Europe and the United States. Most victims are amateur or novice mushroom hunters who mistake this mushroom for another, edible species. The toxin is heat stable and is not destroyed by cooking. Once absorbed, it binds to RNA polymerase and inhibits cellular protein synthesis. Hepatocytes and rapidly dividing cells are most sensitive.

Diagnosis

Severe abdominal cramps, vomiting, and diarrhea begin about 8 to 12 hours or longer after a meal. Diarrhea can be so severe that it results in severe volume depletion and cardiovascular collapse. After apparent recovery from the gastrointestinal syndrome, patients can develop rapidly progressive hepatic failure.

Treatment

Treatment of suspected amatoxin poisoning includes aggressive fluid replacement and administration of activated charcoal by mouth to bind any unabsorbed toxin in the gut and to prevent enterohepatic reabsorption, which can be significant.[136] Patients who develop severe liver injury with encephalopathy are candidates for emergency liver transplantation. Various antidotes have been described over the years, including high-dose intravenous penicillin G, corticosteroids, thioctic acid, and silibinin (an extract of the milk thistle plant), but none have proved to be effective in controlled studies, and neither thioctic acid nor

silibinin is available in the United States.[136] (Milk thistle extract can be found in some stores selling dietary and nutritional supplements, however.)

MONOSODIUM GLUTAMATE

Monosodium glutamate (MSG) is a food additive used to enhance flavor and add body to prepared foods. It is also found as a component of hydrolyzed vegetable protein. Consumption of MSG can invoke, in susceptible persons, a syndrome originally coined the Chinese-restaurant syndrome and now known as the MSG symptom complex. The syndrome, which begins about 15 to 30 minutes after ingestion, includes a burning sensation or pressure in the face, behind the eyes, and in the chest, neck, shoulders, forearms, and abdomen. Headache, syncope, and, rarely, cardiac arrhythmias have been described. Not everyone who ingests MSG experiences the reaction. The etiology of the syndrome is not clearly understood. Symptoms usually last no more than 2 to 3 hours, and there is no specific treatment.[137-139]

HERBAL REMEDIES AND DIETARY SUPPLEMENTS

Approximately 25% of patients use alternative therapies, such as herbal products, for a health problem[140] [*see CE:XII Complementary and Alternative Medicine*]. Herbal products are not subject to FDA approval, because they do not undergo the scientific testing required of conventional therapies. They cannot be promoted specifically for treatment, prevention, or cure of a disease. However, the Dietary Supplement Health and Education Act of 1994 has allowed these products to be sold and labeled with statements describing their professed effects. With increasing use and availability of herbal medications, poison-control centers and health care providers are commonly encountering patients with adverse effects from impure products, drug interactions, and intentional ingestions. *Ginkgo biloba* has been suggested to have antiplatelet effects, and cases of spontaneous hyphema and bilateral subdural hematomas have been reported.[141] The additional risk of warfarin must be considered in patients taking *Ginkgo biloba*. Ephedra (Ma Huang) is a common ingredient in herbal weight-loss products (herbal fen-phen), stimulants (herbal ecstasy), decongestants, and bronchodilators. The active moiety in Ephedra is ephedrine and related alkaloids. Serious adverse reactions, including hypertension, seizures, arrhythmias, heart attack, stroke, and death, have been reported.[142] St. John's wort (*Hypericum perforatum*), touted as a natural antidepressant, has been shown to inhibit serotonin, dopamine, and norepinephrine reuptake and thus presents the possibility of interaction with MAO inhibitors and other serotoninergic drugs.[142]

Adverse events associated with most herbal products are largely undescribed, and there are few specific antidotes. Emergency and supportive measures should therefore be instituted as necessary [*see* Management of Common Complications, *above*]. To enhance research and knowledge in this area, all such events should be reported to poison-control centers and to the FDA's MedWatch Program (800-FDA-1088; http://www.fda.gov/medwatch).

Smoke Inhalation

Smoke inhalation injury is the most common cause of mortality among fire victims, accounting for up to 75% of deaths.[81] Fires produce heat and smoke, although the latter is the chief culprit in inhalation injuries.[143] Smoke comprises a varying mixture of particles and gaseous chemicals that are pyrolysis products of

substances that become toxic only when burned.[144] Smoke components can be broken down into simple asphyxiants, chemical asphyxiants, and irritants. Simple asphyxiants (e.g., methane and carbon dioxide) displace oxygen, thus decreasing F_IO_2 (fraction of inspired oxygen) and resulting in hypoxemia. Chemical asphyxiants (e.g., carbon monoxide, cyanide, and hydrogen sulfide) cause systemic toxicity and cellular hypoxia by interrupting transport or utilization of oxygen [*see* Specific Drugs and Poisons, *above*].

Irritant gases have a direct cytotoxic effect on the oropharynx and the respiratory tract. Toxicity depends on the physical and chemical properties of the gas, which are often divided into two major groups on the basis of their water solubility. Highly water-soluble gases (e.g., ammonia, acrolein, hydrogen chloride, and sulfur dioxide) are readily absorbed in the mucous membranes along the upper respiratory tract, causing local irritation of the eyes, nose, and throat. Compounds with intermediate solubility (e.g., chlorine and isocyanates) cause upper and lower respiratory tract injury. Substances that are less water soluble (e.g., phosgene and nitrogen dioxide) do not dissolve readily in the mucous membranes of the upper respiratory tract and can reach the distal airway, producing delayed-onset pulmonary toxicity.[81,144]

DIAGNOSIS

Clinical symptoms vary with the location of tissue injury, which in turn depends on the solubility and the concentration of exposure. Manifestations of toxicity may include conjunctival irritation, rhinitis, oropharyngeal erythema and burns, coryza, hoarseness, stridor, wheezing, coughing, and noncardiogenic pulmonary edema. Onset of pulmonary edema may be delayed up to 12 to 24 hours or longer when the patient has been exposed to low-solubility gases such as phosgene and nitrogen dioxide.[81]

TREATMENT

Management at the scene of the exposure should include evacuation of all persons from further exposure to the smoke. Rescuers should take precautions to avoid personal exposure and should use a self-contained breathing apparatus. Although the clinician rarely has access to information regarding the constituents of the smoke, initial treatment of all victims should focus on the airway [*see* Initial Stabilization, *above*]. All patients should receive supplemental oxygen in the highest concentration while arterial blood gas and carboxyhemoglobin levels are pending [*see* Carbon Monoxide, *above*]. For patients who do not require immediate airway protection (e.g., those who are without respiratory distress, coma, or stridor), a careful plan should be sought for identifying those at high risk for potential deterioration. Many authors recommend fiberoptic bronchoscopy to help identify supraglottic and subglottic airway injury.[81] An important caveat is that lack of upper airway injury (e.g., oropharyngeal burns or singed nasal hairs) neither precludes nor predicts future airway demise. Patients should be risk-stratified on the basis of history (e.g., closed-space fire, particular materials in the fire, loss of consciousness, or history of reactive airway disease) before final disposition. Patients with any sign of airway injury or clinically significant smoke inhalation should be observed overnight. A normal initial chest radiograph is not a reliable indicator of pulmonary injury.[145] If exposure to a low-solubility toxin is likely (e.g., phosgene or nitrogen dioxide), manifestation of pulmonary injury may be delayed for 12 to 24 hours. Bronchodilators should be used for bronchospasm, but unlike in asthma and chronic obstructive pulmonary disease, use of

steroids has not been shown to be beneficial in smoke inhalation patients.[81] Patients with suspected cyanide poisoning should receive sodium thiosulfate [*see* Cyanide, *above*].

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