Poisonings and Overdoses

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Objectives:

- To describe physical examination and laboratory findings suggestive of intoxications
- To outline measures for the resuscitation and stabilization of the overdose patient
- To discuss use of interventions to decrease absorption of poisons and enhance elimination
- To review indicated interventions and antidotes for poisons and substances of abuse likely to be encountered in the ICU

Key words: antidotes; overdose; poisoning; substance abuse; toxicology

Intentional and accidental poisonings and substance abuse can result in the need for critical care support. In many cases, only supportive care is necessary until the effects of the toxin diminish. However, some poisonings require specific antidotes or interventions to decrease morbidity and mortality. General management principles of poisonings and substance abuse that are pertinent to intensive care management are presented, as well as interventions for specific overdoses that the intensivist is likely to encounter. Little evidence-based information is available and current recommendations are based on animal data, volunteer studies, case reports, pharmacologic data, and/or consensus opinion.

Clinical Presentation

Patients with possible overdose may be asymptomatic or present with life-threatening toxicities. The absence of symptoms on initial examination does not preclude potential deterioration and development of more severe symptoms. Life-threatening toxicities that often require intensive management include coma, seizures, respiratory depression, hypoxemia, arrhythmias, hypotension, hypertension, and metabolic acidosis.

Diagnosis

The diagnosis of the exact substance involved in an overdose or poisoning should not take precedence over resuscitation and stabilization of the patient (see "Management"). However, the initial evaluation of the patient may identify characteristic signs and symptoms that will enable the physician to make a specific diagnosis quickly and assist in directing optimal therapy.

History

Accurate information regarding the substance ingested, the quantity taken, and the time of ingestion should be collected, if possible. Establishing the time of ingestion is important to assess the significance of presenting symptoms. Drugs that may be accessible to the patient should be determined.

Physical Examination

Vital signs and the neurologic examination are particularly helpful in the initial evaluation of a patient. Tables 1 and 2 list drugs associated with changes in vital signs and neurologic alterations. Blood pressure may not be helpful in determining the toxin because of other systemic influences. Tachypnea is also fairly nonspecific and may result as a compensatory response to metabolic acidosis or hypoxemia due to pulmonary edema. Although the initial neurologic examination may be pertinent, it is also important to follow changes in neurologic function over time. Hypoactive bowel sounds may be associated with narcotic or anticholinergic agents, and hyperactive bowel sounds may result from poisoning with organophosphates.

Toxidromes

Findings on physical examination may enable the physician to characterize the poisoning into a classic "toxidrome." This categorization may allow the physician to direct diagnostic evaluation and define appropriate therapy (Table 3).

Laboratory Examination

Effective use of the laboratory may supplement the history and physical examination. An arterial

blood gas measurement will detect hypoxemia, hypercarbia, and significant acid-base disorders. In combination with electrolytes, a significant anion-gap acidosis may be diagnosed. The detection of an osmolal gap (> 10) through comparison of the measured osmolality with calculated osmolality—(2 × sodium + glucose / 18) + (BUN / 2.8)—may indicate the presence of methanol, ethanol, ethylene glycol, acetone, or isopropyl alcohol. An ECG should be obtained in unstable patients and when cardiotoxic drug ingestion is suspected.

Qualitative toxicology screens are performed on urine samples. These tests report only the presence or absence of a substance or class of drugs and are limited by the testing available at an institution. Qualitative toxicology screens are helpful in evaluating coma of unknown cause, distinguishing between toxicosis and psychosis, and (rarely) choosing a specific antidote. Qualitative test results seldom change the initial management of poisoned patients. Quantitative analyses provide serum levels and may direct specific therapies in selected cases. Quantitative levels that are particularly helpful in the patient with unknown poisoning are acetaminophen and salicylate levels. Other quantitative levels that may be useful include carbamazepine, carboxyhemoglobin, ethanol, methanol, ethylene glycol, theophylline, phenytoin, lithium, barbiturates, digoxin, and cyclic-antidepressant levels. Cyclic antidepressant levels confirm antidepressant ingestion, but the levels correlate poorly with toxicity.

Management

Resuscitation and Stabilization

The initial priorities are airway, breathing, and circulation. Intubation may be necessary to support oxygenation and ventilation or to protect the airway. Hypotension from toxins is more commonly due to venous pooling, rather than myocardial depression, and should be initially treated with isotonic

Table 1. *Clues to Diagnosis in Poisoning: Vital Signs*

Vital Sign	Increased	Decreased
Blood pressure	Amphetamines / cocaine Anticholinergics Ephedrine Sympathomimetics	Antihypertensives Cyanide Cyclic antidepressants Ethanol Narcotics Organophosphates / carbamates Sedative / hypnotics
Heart rate	Amphetamines / cocaine Anticholinergics Carbon monoxide Cyanide Cyclic antidepressants Ethanol Sympathomimetics Theophylline	Barbiturates β-Blockers Calcium channel blockers Cholinergics Digitalis glycosides Sedative / hypnotics Organophosphates / carbamates γ-Hydroxybutyrate
Respiratory rate	Amphetamines Anticholinergics Carbon monoxide Hydrocarbons Organophosphates / carbamates Salicylates Theophylline	Alcohols Barbiturates γ-Hydroxybutyrate Narcotics Sedative / hypnotics
Temperature	Amphetamines / cocaine Anticholinergics β-Blockers Cyclic antidepressants Salicylates Sympathomimetics Theophylline	Barbiturates Carbon monoxide Ethanol Hypoglycemic agents Narcotics Sedative / hypnotics

fluids, rather than vasopressor agents. Oxygen should be routinely administered to the poisoning victim, pending assessment of oxygenation by arterial blood gas or pulse oximetry.

In the patient with a depressed level of consciousness, the following additional interventions should be considered:

- 50% glucose (25 to 50 g)
- Thiamine (100 mg IV)
- Naloxone (0.4 to 2 mg IV), especially with classic findings of miosis and respiratory depression
- Flumazenil is not routinely recommended. Consider in patients who have a clinical course compatible with a sedative overdose. Flumazenil is contraindicated in known cyclic-antidepressant overdoses and in chronic benzodiazepine users because of the risk of seizures.

Nonspecific Therapy

After stabilization, nonspecific interventions may be considered to decrease absorption of toxin from the GI tract or to enhance elimination. GI decontamination can be attempted with gastric emptying procedures (induced emesis, gastric lavage), adsorption of drugs (activated charcoal), and decreasing transit time in the GI tract (cathartics, whole bowel irrigation).

Induced Emesis: Induced emesis with ipecac is not recommended in adults. Ipecac is effective in inducing vomiting but is not necessarily effective in recovering toxins. Contraindications to the use of ipecac include hydrocarbon or corrosive ingestion, absent gag reflex, depressed mental status, a risk for CNS depression or seizures, and pregnancy. Potential complications include aspiration pneumonitis, Mallory-Weiss tear, and protracted emesis, which delays the use of activated charcoal.

Gastric Lavage: Gastric lavage is performed in the adult with a 36F to 40F Ewald tube inserted orally. Lavage is performed with aliquots of 100 to 200 mL of normal saline solution or water. Some studies indicated that the greatest benefit of lavage in obtunded patients occurs within 1 h of ingestion, but more recent studies have failed to confirm any benefit. Current recommendations suggest that gastric lavage should not be used routinely, and should be considered only in life-threatening cases of ingestion when lavage can be instituted within 1 h of ingestion. The airway must be protected in patients with depressed level of consciousness. Lavage is contraindicated in acid or alkali ingestions because of possible esophageal perforation and in the presence of a severe bleeding diathesis. Complications of lavage include aspiration pneumonitis, esophageal perforation, and cardiovascular instability.

Activated Charcoal: Activated charcoal is probably the best intervention in poisonings and should be administered in most cases of orally ingested toxins. The greatest benefit is within the first hour after ingestion. The appropriate dose of charcoal (1 g/kg) may be administered by an orogastric or nasogastric tube if patient cooperation is limited. Substances not adsorbed by activated charcoal include iron, lithium, cyanide, strong acids or bases, alcohols, and hydrocarbons. The only contraindication to the use of charcoal is known or suspected GI perforation.

Table 2. *Clues to Diagnosis in Poisoning: Neurologic Findings*

	Pinpoint (Miotic)	*Dilated (Mydriatic)*
Pupils	Barbiturates (late) Cholinergics Narcotics (except meperidine) Organophosphates Phenothiazine Phencyclidine	Alcohol Anticholinergics Antihistamines Barbiturates Ethanol Meperidine Phenytoin Sympathomimetics
Nystagmus	Alcohols Carbamazepine Carbon monoxide	Phencyclidine Phenytoin Sedative/hypnotics
Seizures	Amphetamines Anticholinergics Carbon monoxide Cocaine Cyanide Cyclic antidepressants γ-Hydroxybutyrate Isoniazid	Lithium Organophosphates Phencyclidine Phenothiazines Salicylates Strychnine Theophylline

Table 3. *Toxidromes*

Poisoning Syndrome	Symptoms
Cholinergic (SLUDGE)	Salivation, lacrimation, urination, defecation, GI upset, emesis. Also, bradycardia, fasciculations, confusion, miosis
Anticholinergic	Dry skin, hyperthermia, mydriasis, tachycardia, delirium, thirst
Sympathomimetic	Hypertension, tachycardia, seizures, CNS excitation, mydriasis
Narcotic	Miosis, respiratory depression, depressed level of consciousness
Sedative/hypnotic	Depressed level of consciousness, respiratory depression, hyporeflexia

Current recommendations for decreasing GI absorption of toxins emphasize the use of activated charcoal despite lack of proven benefit. In patients who are critically ill on hospital presentation or who have a potentially life-threatening ingestion, gastric lavage plus activated charcoal can be considered, although the benefit of lavage has not been established.

Cathartics: Cathartics have been routinely administered with charcoal, based on the assumption that they decrease GI transit time, help limit drug absorption, and serve as an adjunct to charcoal therapy. However, there is no evidence of efficacy. Sorbitol is the most commonly used cathartic. Care must be taken with the very young and with elderly patients because electrolyte abnormalities can ensue due to diarrhea.

Whole Bowel Irrigation: Whole bowel irrigation involves large volumes of polyethylene glycol electrolyte solution given over time (1 to 2 L/h) to mechanically cleanse the bowel. This method has been recommended for ingested substances that are not adsorbed by activated charcoal (*ie*, iron and lithium), ingestions of sustained-release or enteric-coated products, and ingestions of illicit drug packets. This method may not be practical for many patients; further study is required to determine any benefit in toxic ingestions. Contraindications to this intervention include ileus, GI obstruction or perforation, hemodynamic instability, and intractable vomiting; CNS or respiratory depression and inability to cooperate are relative contraindications.

Enhanced Elimination: Measures to increase elimination of toxic substances attempt to utilize the normal detoxification mechanisms performed by the liver and kidney. Multiple doses of charcoal for drugs with an enterohepatic circulation may have the greatest potential utility. This technique may be helpful in poisonings with barbiturates, carbamazepine, dapsone, and theophylline. Although multiple doses of charcoal have been used in poisonings with cyclic antidepressants, digoxin and phenytoin, proof of effectiveness is lacking. The dosing regimen has not been standardized, but currently not < 12.5 g/h or an equivalent amount at other intervals is recommended. Smaller doses administered more frequently may decrease the occurrence of vomiting. Repeat doses of charcoal should not contain a cathartic. Adequate gastric emptying must be assured before administration of a subsequent dose.

Forced diuresis to accelerate renal excretion of drugs has little clinical effect and may predispose to volume overload. Alkaline diuresis is effective in promoting the elimination of barbiturates and salicylates. Two ampules of sodium bicarbonate can be added to 1 L of dextrose 5% in water solution, and the rate of administration should be determined by the patient's ability to handle the fluid load and the maintenance of urine pH > 7. Acidification of urine has been proposed for ingestions involving phencyclidine, strychnine, amphetamines, and quinine. However, the metabolic consequences of acidification weigh against any clinical usefulness of this measure. Dialysis may be considered for life-threatening ingestions involving water-soluble substances of low molecular weight. Drug overdoses in which dialysis may be beneficial include alcohols, amphetamines, phenobarbital, lithium, salicylates, theophylline, and thiocyanate. Hemoperfusion is useful with the same compounds that are dialyzable and involves the passing of blood through a filtering device that contains charcoal or a synthetic resin as an absorbent. Charcoal hemoperfusion may be helpful in elimination of carbamazepine, phenobarbital, phenytoin, and theophylline. Hemodialysis and hemoperfusion are efficient methods of removing poisons but are costly, require trained personnel, and may be associated with complications. Use of continuous arteriovenous or venovenous hemoperfusion in poisoning has been reported on a limited basis.

Specific Therapy

Although management of many toxic ingestions involves only the nonspecific therapy outlined above, some toxins have specific interventions or antidotes. Table 4 lists toxins and their respective antidotes. Specific poisonings are discussed in detail below. Attention should be directed to managing those poisonings that most frequently result in death: analgesics, antidepressants, stimulants and street drugs, cardiovascular drugs, alcohols, and sedatives and hypnotics.

Specific Drug Poisonings

Acetaminophen

Knowledge of appropriate management of acetaminophen ingestions is important to prevent

significant toxicity and mortality. Acetaminophen levels should be obtained in all multiple drug overdoses ≥ 4 h after ingestion. The Rumack-Matthew nomogram determines the need for *N*-acetylcysteine (NAC) therapy (140 mg/kg oral loading dose; 70 mg/kg orally every 4 h for 72 h) if the level plots above the "possible hepatic toxicity" line. NAC serves as a substitute for glutathione, which normally metabolizes toxic metabolites of acetaminophen. Activated charcoal adsorbs acetaminophen and many co-ingestants. Charcoal interferes only slightly with the effectiveness of NAC, and the dose of NAC does not require adjustment. NAC is most effective in the first 8 h but is recommended up to 24 h after a significant ingestion. It is also reasonable to administer NAC > 24 h after ingestion if toxic levels of acetaminophen are present. Late administration of NAC may be potentially beneficial in fulminant hepatic failure due to acetaminophen toxicity. The nomogram is useful only for single acute ingestions, and there are no firm guidelines for administration of NAC in chronic ingestions or multiple ingestions over time. A course of NAC should be strongly considered if hepatic enzymes are elevated at presentation. Antiemetics are frequently needed to improve tolerance of oral NAC. The local Poison Control Center should be contacted for other NAC regimens, such as IV administration for refractory vomiting or shorter courses of therapy.

Recommendations for management of extended-release forms of acetaminophen include determination of acetaminophen levels 4 and 8 h after ingestion and initiation of NAC if either level is potentially toxic.

Alcohols

Ethylene glycol and methanol ingestions can result in significant morbidity and mortality. Clinical manifestations, metabolic derangements, and management are similar for both alcohols.

Cardiopulmonary and neurologic symptoms may include pulmonary edema, hypotension, ataxia, seizures, and coma. Abdominal pain, nausea, and vomiting are frequent. Visual disturbances (blurred vision, photophobia, blindness, optic disc hyperemia) suggest methanol toxicity, and the finding of urinary calcium oxalate crystals may indicate ethylene glycol ingestion. Significant symptoms may be delayed up to 24 h after methanol ingestion. Both ingestions are classically characterized

Table 4. *Antidotes and Interventions for Specific Toxins*

Toxin	Antidote or Intervention
Acetaminophen	*N*-acetylcysteine
Arsenic/mercury/gold/lead	BAL (dimercaprol)
Benzodiazepines	Flumazenil
β-Blocker	Glucagon, calcium (?), pacing
Calcium channel blocker	Calcium, glucagons, pacing
Carbon monoxide	100% oxygen, hyperbaric oxygen
Coumarin derivatives	Vitamin K_1
Cyanide	Nitrites, thiosulfate, hydroxocobalamin
Cyclic antidepressants	Blood alkalinization
Digoxin	Digoxin-specific Fab fragments
Ethylene glycol	Ethanol, fomepizole
Heparin	Protamine
Oral hypoglycemic agents/insulin	Glucose 50%, somatostatin
Iron	Deferoxamine
Isoniazid	Pyridoxine
Lithium	Hemodialysis
Methanol	Ethanol
Narcotics	Naloxone
Nitrites	Methylene blue
Organophosphates/carbamates	Atropine, pralidoxime
Salicylates	Urinary alkalinization, hemodialysis
Theophylline	Multiple-dose charcoal, hemoperfusion

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by an anion gap metabolic acidosis and an osmolal gap. An anion gap metabolic acidosis may not be present initially if sufficient time has not elapsed for metabolism to toxic acids or high levels of ethanol prevent metabolism of other alcohols. An osmolar gap may not be present in late presentations if the alcohol has already been metabolized to acid. Most institutions are unable to provide blood levels of methanol or ethylene glycol in a timely manner, and treatment is initiated based on the clinical history and acid-base status.

Treatment of ethylene glycol and methanol ingestion includes the following:

- Maintenance of a secure airway
- Gastric lavage may be considered within 1 h of ingestion.
- Activated charcoal if other substances have potentially been ingested (does not adsorb alcohols)
- 50% glucose if indicated
- Thiamine, folate, multivitamin supplement
- Ethanol orally or IV to maintain blood level at 100 to 150 mg/dL—ethanol is preferentially metabolized by alcohol dehydrogenase.
- Fomepizole (4-methylpyrazole), an inhibitor of alcohol dehydrogenase that does not cause CNS depression, may substitute for ethanol.
- Hemodialysis for visual impairment, renal failure, pulmonary edema, significant or refractory acidosis, level of > 25 mg/dL
- Bicarbonate for acidosis is advocated by some clinicians.

Isopropyl alcohol is more potent than ethanol and results in similar manifestations at lower doses. Isopropyl alcohol ingestions are characterized by an osmolar gap and ketonemia/ketonuria but no metabolic acidosis. Treatment is supportive and may require intubation and mechanical ventilation for respiratory depression. Hemodialysis is reserved for evidence of hypoperfusion and failure to respond to supportive therapy.

Amphetamines/Methamphetamines

Amphetamines, methamphetamines, and related agents cause release of catecholamines, which results in a sympathomimetic toxidrome characterized by tachycardia, hyperthermia, agitation, hypertension, and mydriasis. Hallucinations (visual and tactile) and acute psychosis are frequently observed. Acute adverse consequences include myocardial ischemia and arrhythmias, seizures, intracranial hemorrhage, stroke, rhabdomyolysis, necrotizing vasculitis, and death.

An amphetaminelike drug, 3-4-methylenedioxymethamphetamine, is a designer drug associated with "rave" parties. It is commonly known as ecstasy, XTC, E, and MDMA, and acts as a stimulant and hallucinogen. It increases release of serotonin and inhibits serotonin reuptake in the brain. Bruxism and jaw clenching are clues to use of ecstasy. Complications are usually a result of drug effects and nonstop physical activity. Hyponatremia and liver injury progressing to fulminant failure have also been reported.

Management of amphetamine intoxication is primarily supportive. Gastric lavage has little role, since absorption after oral ingestion is usually complete at the time of presentation. The patient should be carefully assessed for complications, including measuring of core temperature, obtaining an ECG, and evaluating laboratory data for evidence of renal dysfunction and rhabdomyolysis. IV hydration for possible rhabdomyolysis is warranted in individuals with known exertional activities pending creatine phosphokinase results. Benzodiazepines, often in high doses, are useful for control of agitation.

Benzodiazepines

Benzodiazepine overdoses rarely result in death unless other sedating drugs (*eg*, alcohol, narcotics) are also ingested. A benzodiazepine receptor antagonist, flumazenil, is available as a diagnostic tool and adjunctive treatment. Flumazenil should not be considered a substitute for intubation in patients with significant respiratory depression. Its use is contraindicated in suspected cyclic-antidepressant overdoses and in patients physically dependent on benzodiazepines because of the risk of seizures. The initial dose of flumazenil is 0.2 mg over an interval of 30 s, followed by doses of 0.3 mg and 0.5 mg every minute up to a cumulative dose of 3 mg. Resedation is likely due to the short half-life of flumazenil (0.7 to 1.3 h) compared with benzodiazepines. Flunitrazepam is a potent benzodiazepine banned in the United States that is associated with rape. It may not be detected by most urine drug screens.

β-*Blockers*

β-Adrenergic blockers produce toxicity through bradycardia and hypotension. Hypotension often results from negative inotropic effects rather than bradycardia. Glucagon is considered the initial drug of choice because it produces chronotropic and inotropic effects and does not act via β-receptors. An initial dose of 2 to 3 mg of glucagon is given IV and an infusion of 2 to 5 mg/h can be initiated, adjusted for desired clinical effects, and then tapered over 12 h as indicated. Transcutaneous pacing and transvenous pacing may be considered in cases refractory to glucagon. Additional drugs that have had variable efficacy in β-blocker overdoses include atropine, epinephrine, isoproterenol, and dopamine. Phosphodiesterase inhibitors such as milrinone, intra-aortic balloon pump, or cardiopulmonary bypass may be considered if there is no response to these interventions. In some cases, calcium and insulin euglycemia have been reported to be beneficial.

Calcium Channel Blockers

Calcium-channel-blocker overdose should be considered in the hypotensive, bradycardic patient, particularly if there is a history of hypertension. In the presence of hemodynamic instability, 10 mL of 10% calcium chloride should be administered IV. Calcium is effective in reversing negative inotropic effects and conduction abnormalities in ~ 50% of overdoses. Higher doses of calcium may be required for beneficial effects. As in β-blocker overdose, glucagon may have beneficial effects. Transcutaneous and transvenous pacing are additional options in refractory cases. Successful treatment has also been reported with amrinone and insulin euglycemia (insulin 0.1 to 10 U/kg/h and glucose 10 to 75 g/h).

Carbon Monoxide

Carbon monoxide is a colorless, odorless gas that has 240 times greater affinity for hemoglobin as oxygen. Carboxyhemoglobin reduces oxygen-carrying capacity and also shifts the oxyhemoglobin dissociation curve to the left. Carbon monoxide also exerts direct cellular toxic effects. The clinical manifestations of carbon monoxide poisoning are nonspecific. The most common findings are headache, dizziness, and nausea; more severe exposure can result in chest pain, disorientation, seizures, coma, dyspnea, weakness, arrhythmias, and hypotension. Although the diagnosis of carbon monoxide poisoning is confirmed by an increased carboxyhemoglobin level, decisions for aggressive therapy with 100% oxygen should be based primarily on a clinical history suggestive of exposure. High-flow oxygen or intubation with administration of 100% oxygen should be initiated as soon as possible while confirmatory tests are obtained. An ECG, chest radiograph, and arterial blood gas measurement should be obtained to assess severity of toxicity. The finding of metabolic acidosis implies significant exposure with inadequate oxygen availability at the tissue level. The use of hyperbaric oxygen in the setting of carbon monoxide poisoning is controversial but may be considered for any patient with a depressed level of consciousness, neurologic findings other than headache, cardiac instability, carboxyhemoglobin level > 25 to 40%, or persistent symptoms after normobaric oxygen treatment for 4 to 6 h. A recent clinical trial suggests that hyperbaric oxygen decreases the incidence of postexposure cognitive deficits.

Cocaine

Significant morbidity and mortality are associated with cocaine use by all routes, including nasal insufflation, IV administration, smoking, and oral ingestion. Toxicities include intracranial hemorrhage (subarachnoid and intraparenchymal), cerebrovascular accidents, seizures, noncardiogenic pulmonary edema, arrhythmias, hypertension, myocardial ischemia, barotrauma, bronchospasm, bowel ischemia, hyperthermia, and rhabdomyolysis. These potential morbidities should be considered in any critically ill cocaine abuser, and treatment should be initiated as indicated. Chest pain thought to be ischemic usually responds to nitroglycerin and/or benzodiazepines. Aspirin should be administered. Phentolamine is considered a second-line agent for chest pain. Thrombolysis for myocardial infarction should be considered only when other interventions have failed and immediate angiography and angioplasty are not available. In severe hypertension, labetolol may be the drug of choice because it has both α- and β-adrenergic blocking properties. In most cases, IV fluid hydration should be instituted until

rhabdomyolysis can be excluded. Rhabdomyolysis is enhanced by high environmental temperatures and increased physical activity. The agitation and combativeness frequently associated with cocaine use can usually be controlled with benzodiazepines. If frank psychosis is present, neuroleptics such as haloperidol are indicated, although there is a potential concern of lowering the seizure threshold.

Cyanide

Cyanide exposure is rare, but may occur in occupational settings involving metal extraction, electroplating, chemical synthesis, and firefighting. Cyanide inhibits cytochrome oxidase, which halts oxidative phosphorylation. Metabolic acidosis and decreased oxygen consumption result. Symptoms include nausea and vomiting, agitation, and tachycardia. Serious poisonings can result in seizures, coma, apnea, hypotension, and arrhythmias. Additional complications include rhabdomyolysis, hepatic necrosis, and ARDS. Diagnosis may be difficult in the absence of an exposure history. A cyanide antidote kit (Taylor Pharmaceuticals; San Clemente, CA) is used for management. Several other therapies may be useful:

- Amyl nitrite pearls are an immediate source of nitrite to induce methemoglobinemia. Methemoglobin has a higher affinity for cyanide than cytochrome oxidase.
- 10% sodium nitrite IV to induce methemoglobinemia
- 25% sodium thiosulfate IV enhances conversion of cyanide to thiocyanate, which is excreted by the kidneys.

Hydroxocobalamin has also been used for cyanide poisoning and relies on the formation of nontoxic cyanocobalamin (vitamin B_{12}). Mixed evidence exists for use of hyperbaric oxygen in cyanide poisoning.

Cyclic Antidepressants

Antidepressant overdoses account for the second largest number of deaths from poisoning in the United States. Toxicities include arrhythmias, seizures, depressed level of consciousness, and hypotension. Life-threatening events occur within the first 6 h of hospitalization; most often, they occur within 2 h of presentation. Serum levels may confirm ingestion but do not correlate with toxicity. Altered mental status is the best predictor of a significant ingestion and risk of complications. Cyclic antidepressants slow sodium influx into myocardial cells, resulting in intraventricular conduction delays, wide complex arrhythmias, and negative inotropy. The ECG may be normal in significant ingestions or demonstrate a QRS > 0.10 s or amplitude of the terminal R wave in aVR ≥ 3 mm. Management should include the following measures:

- Maintain a secure airway.
- Stabilize vital signs.
- ECG monitoring
- Consider gastric lavage.
- Activated charcoal administration
- Alkalinization of blood with sodium bicarbonate to pH of 7.45 to 7.55 for prolonged QRS or wide complex arrhythmias
- $MgSO_4$ for *torsades de pointes*
- Benzodiazepines for seizures
- Norepinephrine or phenylephrine for refractory hypotension rather than dopamine
- Additional doses of activated charcoal for significant morbidity

Sodium bicarbonate uncouples the cyclic antidepressant from the myocardial sodium channels and alkalinization with bicarbonate may be superior to hyperventilation. In an animal study, hypertonic saline solution was most effective in treatment of a wide QRS complex, but this therapy has not been evaluated in humans. Bicarbonate may also be beneficial for seizures and hypotension unresponsive to other interventions. Physostigmine is not indicated in cyclic antidepressant overdose.

γ-Hydroxybutyrate

γ-Hydroxybutyrate (GHB) is a naturally occurring metabolite of γ-aminobutyric acid, which was banned in 1991 due to reported toxicities. Clinical effects of GHB ingestion may include hypothermia, loss of consciousness, coma, respiratory depression including arrest, seizurelike activity, bradycardia, hypotension, and death. Concomitant use of alcohol results in synergistic CNS and respiratory effects. More recently, γ-butyrolactone (GBL) and 1,4-butanediol (BD), which are precursors of GHB, have been abused with resultant manifestations similar to GHB. The benefit of activated charcoal is unknown

because of the rapid absorption of these substances. Although patients usually recover spontaneously in 2 to 96 h, supportive therapy with airway protection and mechanical ventilation may be necessary. Use of physostigmine to reverse CNS effects is not recommended. A GHB withdrawal syndrome of agitation and delirium has been reported in high-dose, frequent abusers.

Isoniazid

Isoniazid toxicity produces seizures (often intractable), an anion-gap metabolic acidosis, coma, and hepatic toxicity. The treatment of choice is intensive supportive care and the use of pyridoxine (vitamin B_6) 5 g IV or a dose equivalent to the amount of isoniazid ingested). Hemoperfusion or hemodialysis may be considered, particularly in patients with renal insufficiency.

Lithium

Although arrhythmias are reported, neurologic abnormalities are the major manifestation of acute and chronic lithium toxicity. CNS manifestations include lethargy, dysarthria, delirium, seizures, and coma. Symptoms of GI distress, polyuria, and polydipsia may be present. A decreased anion gap is suggestive of a severely elevated lithium level. Patients who chronically ingest lithium are more prone to toxic effects. Serum lithium levels of > 2.5 to 4 mmol/L may be considered life-threatening, depending on the clinical findings. Whole bowel irrigation may be considered in serious toxicity as lithium is not adsorbed by charcoal. Volume resuscitation should be aimed at restoring adequate urine output, but forced diuresis is not effective in enhancing lithium excretion. Diuretics can worsen toxicity and should be avoided. Hemodialysis is indicated in life-threatening toxicity, which may include renal dysfunction, severe neurologic dysfunction, volume overload or levels of ≥ 4 mmol/L in acute ingestion or ≥ 2.5 mmol/L in chronic ingestions. Owing to redistribution between intracellular and extracellular compartments, a rebound increase in lithium level can occur 6 to 8 h after dialysis. Continuous arteriovenous and venovenous hemodiafiltration have also been used to remove lithium and may be associated with less rebound. Sodium polystyrene sulfonate has been suggested to decrease lithium absorption, but evidence of clinical benefit is lacking and complications of hypokalemia, hypernatremia, and fluid overload may result.

Narcotics

Naloxone should be used to reverse the morbidity of respiratory depression and depressed level of consciousness associated with narcotic overdose. An initial dose of 2 mg should be administered IV unless the patient is known to be addicted, in which case lower initial doses should be used to prevent sudden withdrawal symptoms. Doses > 2 mg may be required to reverse the effects of propoxyphene, codeine, pentazocine, methadone, oxycodone, hydrocodone, and fentanyl. Naloxone can be administered at doses up to 10 mg and occasionally up to 20 mg. Naloxone can also be administered by the intramuscular, sublingual, and endotracheal routes if IV access is not established. Continuous infusion may be necessary because all narcotics have a longer half-life than naloxone. The initial hourly infusion dose should be one half to two thirds of the amount (in milligrams) that was needed to initially reverse the respiratory depression. Noncardiogenic pulmonary edema may also occur with narcotics and can be managed with supportive care that may require intubation and mechanical ventilation.

Organophosphates/Carbamates/Nerve Gas

Organophosphate and carbamate poisoning producing a cholinergic syndrome are uncommon in the United States but prevalent in developing countries. Some nerve gases (sarin) that may be used in terrorist attacks also produce similar toxicity. Cholinergic poisoning exerts potential deleterious effects on three systems: (1) the muscarinic (parasympathetic) system, inducing bronchorrhea, bradycardia, and salivation, lacrimation, urination, defecation, GI upset, and emesis (the "SLUDGE" syndrome; Table 3); (2) the nicotinic autonomic system, resulting in muscle weakness; and (3) the CNS, including confusion, slurred speech, and central respiratory depression. Pulmonary toxicity from bronchorrhea, bronchospasm, and respiratory depression is the primary concern. Both IV atropine and pralidoxime (30 mg/kg bolus followed by > 8 mg/kg/h infusion recommended by the World Health Organization) are indicated. Atropine does not reverse nicotinic manifestations; therefore, patients with significant respiratory muscle weakness require the use

of pralidoxime. Large amounts of atropine may be required, and the initial dose is usually 2 to 4 mg, repeated every 5 min. The end point of atropinization is clearing of secretions from the tracheobronchial tree. An intermediate syndrome of respiratory paralysis, bulbar weakness, proximal limb weakness, and decreased reflexes may develop 24 to 96 h after resolution of the cholinergic crisis.

Salicylates

Salicylates are found in many over-the-counter preparations. Patients with chronic rather than acute ingestions of salicylates are more likely to require intensive care. Symptoms of salicylate poisoning include tinnitus, nausea and vomiting, and depressed level of consciousness. In addition, fever, an anion-gap metabolic acidosis, coagulopathy, prolonged prothrombin time, transient hepatotoxicity, and noncardiogenic pulmonary edema may be present. The clinical presentation of salicylate toxicity may be mistaken for sepsis. A salicylate level should be measured initially and may need to be repeated to assess for continued absorption (especially with enteric-coated products). The Done nomogram used to estimate the severity of an acute salicylate overdose may not reliably correlate with observed toxicity. Acidemia predisposes to more severe toxicity because more drug crosses the blood-brain barrier. Gastric lavage may be considered for significant ingestions, and activated charcoal should be administered. Alkalinization of the urine (pH $\geq$ 7.5) is indicated to enhance salicylate excretion if serum levels are > 35 mg/dL. Supplemental potassium is often needed. Hemodialysis may be indicated with levels of > 100 mg/dL, refractory seizures, persistent alteration in mental status, or refractory acidosis.

Selective Serotonin Reuptake Inhibitors

Poisoning with selective serotonin reuptake inhibitors (SSRIs) is usually less severe than poisoning with cyclic antidepressants. Acute overdoses may result in nausea, vomiting, dizziness, and less commonly, CNS depression and arrhythmias. There are reports of cardiac toxicity responding to administration of sodium bicarbonate. Therapeutic doses, overdoses of SSRIs alone, or SSRI overdoses in combination with other agents can cause serotonin syndrome, which may be life-threatening. This syndrome may be precipitated by SSRIs, monoamine oxidase inhibitors, serotonin precursors (L-tryptophan), lithium, meperidine, and nonselective serotonin reuptake inhibitors (*eg*, imipramine, meperidine, trazodone). Clinical manifestations include altered mental status (agitation, coma), autonomic dysfunction (blood pressure fluctuation, hyperthermia, tachycardia, diaphoresis, diarrhea), and neuromuscular abnormalities (tremor, rigidity, myoclonus, seizures). Management of an overdose should include activated charcoal, but the benefit of gastric lavage has not been determined. Intensive supportive care may be necessary, including cooling, sedatives, anticonvulsants, and mechanical ventilation. The role of other agents, such as serotonin antagonists (propranolol, cyproheptadine, methysergide), bromocriptine, or dantrolene in the treatment of serotonin syndrome is not established. Most cases of serotonin syndrome resolve in 24 to 72 h.

Theophylline

Theophylline toxicity is characterized by nausea, vomiting, and agitation. More serious complications include arrhythmias and seizures. Toxicity is more likely to occur following chronic theophylline use compared with an acute overdose in an individual not taking theophylline. Activated charcoal should be administered to decrease GI absorption. An initial theophylline level should be obtained, as well as a subsequent level 1 h later. Unfortunately, sustained-release preparations of theophylline may form conglomerates in the stomach and allow for continued absorption, despite aggressive interventions. Hypokalemia is commonly present in theophylline overdose and should be treated aggressively to prevent any contribution to the initiation of arrhythmias. Seizures are often poorly responsive to phenytoin but may respond to benzodiazepines. Any patient with a life-threatening complication and/or a level of > 60 mg/L with chronic ingestion or a level of > 80 to 90 mg/L with an acute ingestion should be considered for hemoperfusion or hemodialysis. Multiple doses of charcoal are indicated to enhance elimination of theophylline in patients with less severe manifestations.

Herbal medicines are the most common form of alternative therapy in the United States, and can be marketed without testing for safety or efficacy. Poisoning may result from product misuse, from contamination of the product, or through interaction with other medications. Cardiac toxicity may result from aconitine and cardiac glycosides. Aconitine or related compounds are common ingredients in Asian herbal medications. Symptoms include paresthesias, hypersalivation, dizziness, nausea, vomiting, diarrhea, and muscle weakness. Sinus bradycardia and ventricular arrhythmias can occur. No antidote is available, but atropine may be considered for bradycardia or hypersalivation. Cardiac glycosides or digoxinlike factors can be found in many herbal preparations, particularly teas and laxatives. Toxicity is similar to digoxin toxicity, with visual disturbances, nausea, vomiting, and arrhythmias. A digoxin level should be obtained but may not correlate with clinical findings because numerous cardiac glycosides will not cross-react in the digoxin immunoassay. With significant toxicity, digoxin-specific antibodies should be administered. CNS stimulation is characteristic of preparations containing ephedrine and pseudoephedrine, which are often found in products marketed as "herbal ecstasy." A typical sympathomimetic syndrome can result with tachycardia, hypertension, mydriasis, and agitation. Seizures, stroke, myocardial infarction, arrhythmias, liver failure, and death have also been reported. Supportive care is indicated similar to management of other sympathomimetic syndromes. Ginkgo biloba has been reported to result in spontaneous bleeding including subdural hematomas, which may be due to antiplatelet activating factor effects. Treatment for bleeding includes supportive care and blood products as needed. Garlic may also result in bleeding as a result of inhibition of platelet aggregation, and ginseng has been associated with hypoglycemia. Kava-containing dietary supplements are possibly associated with hepatic failure requiring transplantation. Contaminants found in some products, such as mercury, arsenic, lead, antihistamines, etc., may cause toxicities.

Suggested Readings

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