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Official publication of the American College of Chest Physicians

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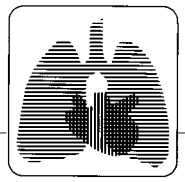
Chest 2003;123;897-922
DOI 10.1378/chest.123.3.897

ISSN:0012-3692



critical care review

Adult Toxicology in Critical Care*

Part II: Specific Poisonings

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(CHEST 2003; 123:897–922)

Key words: critical care; ICU; poisoning; toxicology; toxidromes

Abbreviations: ABCs = airway, breathing, circulation; CCB = calcium-channel blocker; DNS = delayed neuropsychiatric sequelae; FDA = US Food and Drug Administration; GABA = γ-aminobutyric acid; GHB = γ-hydroxybutyrate; MAO = monoamine oxidase; NAPQI = n-acetyl-p-benzoquinonimine; SSRI = selective serotonin re-uptake inhibitor

Acetaminophen

Acetaminophen (paracetamol) is the most common medicinal overdose reported to poison information centers. Alone or in combination with other drugs, it was implicated in 110,000 overdoses in the United States in 2000. Approximately 55,000 of these cases were treated in health-care facilities, 12,613 patients received N-acetylcysteine, 580 had major liver damage, and 210 died.[1] On a smaller scale, Bond et al[2] reported that of 137 patients presenting to an emergency department with acetaminophen ingestion, 92% had an acute ingestion and 122 patients (89%) reported a single supratherapeutic ingestion. Twenty-five patients (18%) were hospitalized for treatment; of these, 18 patients were treated with N-acetylcysteine based on the Rumack-Matthew nomogram. The remaining seven patients presented ≥ 18 h after ingestion with unmeasurable acetaminophen levels and six of them received N-acetylcysteine.[2] As these data show, the majority of exposures are not associated with significant morbidity or mortality; however, acetaminophen can cause severe and fatal hepatic injury.

After oral ingestion, acetaminophen is rapidly absorbed, achieving peak plasma levels in < 1 h. Primarily, the liver metabolizes acetaminophen, but the metabolic path can vary based on age and blood levels. At therapeutic doses, the half-life is 2 to 4 h. Ninety-five percent of the metabolites are nontoxic conjugates of glucuronide and sulfate. Glucuronidation is the primary route of acetaminophen metabolism in adults. Sulfation is an additional important pathway in young children.

Acetaminophen toxicity is due to a metabolite, which constitutes only 5% of acetaminophen metabolism. This metabolite, n-acetyl-p-benzoquinonimine (NAPQI), is produced by the hepatic cytochrome P-450 mixed-function oxidase enzyme system.[3] At usual therapeutic doses, this metabolite is rapidly detoxified by conjugating irreversibly with the sulfhydryl group of glutathione and excreted by the kidneys as mercapturic acid and cysteine conjugates. In overdose, the supply of glutathione is depleted and NAPQI is not detoxified. The toxic metabolite binds to macromolecules of hepatocytes inducing centrilobular hepatic necrosis with periportal sparing.[4] Local production of NAPQI makes the liver the primary target, but other organs can be affected (discussed later). The toxic threshold with the potential to produce liver damage is 150 mg/kg or 7.5 to 10 g in adults and 200 mg/kg in children (due to enhanced sulfation).[5–7] However, 4 to 6 g can cause injury in certain kinds of patients (see below).

There are four phases of acetaminophen toxicity.[5] Common in the first 24 h, or phase 1, are anorexia, malaise, pallor, diaphoresis, nausea, and vomiting. Phase 2 occurs 24 to 48 h after untreated overdose. Right-upper-quadrant pain and abnormalities of

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Manuscript received March 19, 2002; revision accepted July 12, 2002.

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liver function test results, which occur even while signs and symptoms of phase 1 improve, characterize this phase. If the patient progresses to phase 3 (48 to 96 h), symptoms of severe hepatotoxicity including encephalopathy, coagulopathy, and hypoglycemia will ensue. Liver function abnormalities typically peak in this period, with extreme elevations in alanine aminotransferase, aspartate aminotransferase (≥ 10,000 IU/L), total bilirubin, and prothrombin time. The rise in transaminases tends to be disproportionate to the rise in total bilirubin, which may help differentiate acetaminophen-induced hepatotoxicity from viral hepatitis, biliary obstruction, or cholestatic disease. Rare phase 3 sequelae include hemorrhagic pancreatitis, myocardial necrosis, and acute renal failure. Acute renal failure represents acetaminophen-induced acute tubular necrosis.[8] It rarely occurs in the absence of fulminant hepatic failure[9]; treatment with N-acetylcysteine may not prevent its occurrence.[10] Phase 4 involves the period beyond the fourth day postingestion. During this period, the patient may die, fully recover (without chronic liver disease), or undergo emergent liver transplantation. Declining hepatic enzymes signal recovery or massive hepatocellular necrosis. A rising prothrombin time, ammonia measure, and bilirubin levels accompany the latter. If the patient recovers, significant improvement will be evident between day 5 and day 7 postingestion.

The modified Rumack-Matthew nomogram (Fig 1) allows for stratification of patients into risk categories based on the relationship between the serum acetaminophen level and time after ingestion.[11] The lower line of this nomogram defines plasma levels 25% below those expected to cause hepatotoxicity. Points below this line are not concerning for the development of hepatotoxicity; points between the lower line and a parallel middle line suggest a possible risk for hepatotoxicity; points above the middle line but below a parallel upper line represent probable risk; points above the upper line are high risk. N-acetylcysteine is indicated for any acetaminophen level above the lower line (see below).

There are several situations in which the Rumack-Matthew nomogram is of limited use. First, serum acetaminophen levels obtained prior to 4 h postingestion are not interpretable because of ongoing drug absorption and distribution; conversely, patients presenting late may have undetectable serum concentrations despite having received a lethal dose. Second, in chronic ingestion or in overdose with an extended-release preparation, the nomogram is less predictive of toxicity.[12–15] Extended-release acetaminophen preparations exhibit a longer elimination half-life (up to 12 h compared to 2 to 3 h for immediate-release preparations), with a longer absorption phase. For extended-release preparation, samples for serial acetaminophen levels should be drawn every 4 to 6 h postingestion and plotted on the Rumack-Matthew nomogram. If any point is above the lower line, an entire course of N-acetylcysteine is indicated. N-acetylcysteine should also be administered for any signs of hepatotoxicity despite low acetaminophen serum levels. Third, the nomogram does not account for at-risk populations. Whereas 7.5 to 10 g of acetaminophen are toxic in healthy adults, 4 to 6 g may be enough in chronic alcohol users, patients with induced cytochrome P-450 enzymes, malnourished individuals, and patients with depleted glutathione stores (as in recent sublethal acetaminophen ingestion).[16,17] In these cases, N-acetylcysteine should be considered even if the serum acetaminophen level falls below the lower nomogram line. Fourth, accurate risk assessment requires an accurate time of ingestion, which is not always attainable.

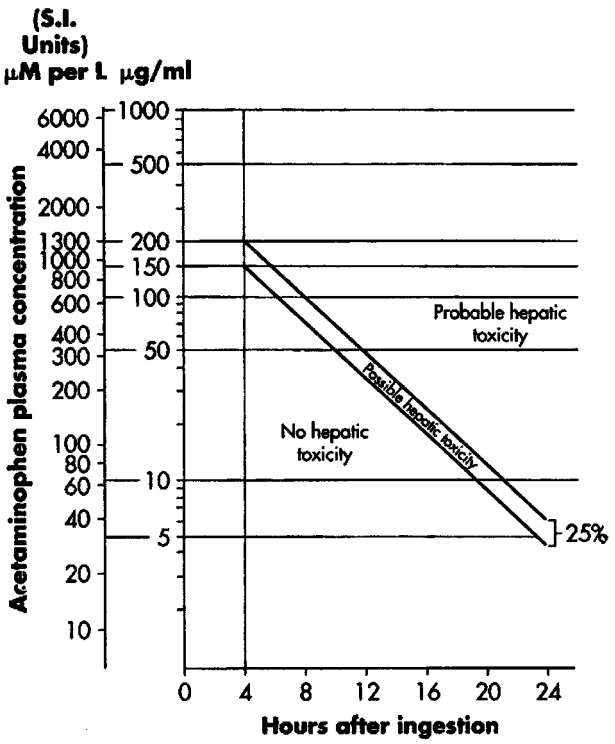

FIGURE 1. The Rumack-Matthew nomogram for predicting acetaminophen hepatotoxicity. This nomogram stratifies patients into three categories: probable hepatic toxicity, possible hepatic toxicity, and no hepatic toxicity. It is based on the relationship between acetaminophen level and time after ingestion. When this relationship is known, N-acetylcysteine is indicated for acetaminophen levels above the lower line. N-acetylcysteine is also indicated if serum acetaminophen level is > 5 μg/mL with an unknown time of ingestion (but < 24 h) and if serum acetaminophen levels are not readily available. The nomogram should be used only in relation to a single acute ingestion. See text for situations in which the nomogram may be of limited use. Reproduced with permission from Rumack and Matthew.[11]

A 1- to 2-h difference easily moves the borderline patient above or below the treatment line. A low threshold to treat is warranted in these situations. Bond et al[2] reported that the Rumack-Matthew nomogram could not be used in almost half of all patients hospitalized for treatment of acetaminophen ingestion, and an even higher proportion of those with bad outcomes.

Gastric lavage is reasonable if administered within 60 min of ingestion.[18] Activated charcoal is the modality of choice for gastric decontamination. It is unlikely that activated charcoal reduces the efficacy of oral N-acetylcysteine. Administration of N-acetylcysteine 2 h apart from activated charcoal to minimize interaction or increasing the dose of N-acetylcysteine after activated charcoal seem to be unnecessary.[19,20] Activated charcoal reduces the number of patients reaching toxic serum levels after ingesting > 10 g of acetaminophen and presenting within 24 h of ingestion. Activated charcoal can also reduce the need for a full treatment course of N-acetylcysteine and hospital stay.[21]

All patients with possible or probable risk of hepatic toxicity based on the Rumack-Matthew nomogram (*ie*, all patients with serum acetaminophen levels above the lower line) should receive N-acetylcysteine. N-acetylcysteine should also be administered if the acetaminophen level is > 5 μg/mL with an unknown time of ingestion (but < 24 h), if there is evidence of hepatotoxicity or if a serum acetaminophen level is not available. N-acetylcysteine can be discontinued if the initial plasma acetaminophen concentration is found to be nontoxic. Importantly, N-acetylcysteine should be considered in at-risk patients (as noted earlier) even if levels are nontoxic.

N-acetylcysteine repletes glutathione, combines directly with NAPQI, and enhances sulfate conjugation of acetaminophen. N-acetylcysteine is virtually 100% effective when administered within the first 8 to 10 h,[22] although benefits may be seen for up to 24 h after ingestion, even after the onset of fulminant hepatic failure.[23] These effects include a lower incidence of hepatic encephalopathy and improved oxygen transport and consumption in the setting of fulminant hepatic failure.[24,25]

An initial oral loading dose of 140 mg/kg of N-acetylcysteine is followed by a maintenance dose of 70 mg/kg q4h for 17 doses. Limited data support the safety and efficacy of a shorter treatment course in certain cases. Woo and colleagues[26] conducted a retrospective, observational case study of short course treatment in patients with acute overdose and acetaminophen levels in the toxic range. Study patients received an oral loading dose of 140 mg/kg N-acetylcysteine followed by 70 mg/kg N-acetylcysteine q4h until the serum acetaminophen level was undetectable. Of the 75 patients, 25 (33.3%) were treated for < 24 h. The mean ($\pm$ SD) duration of therapy was 31 ± 16 h. The incidence of hepatotoxicity was low and comparable to that in patients treated in the standard way. Protocols using a 20-h IV course and a 48-h IV course have also been shown to be safe and effective.[27,28]

The dose is prepared using the standard 10% (100 mg/mL) or 20% (200 mg/mL) formulations diluted to a 5% solution in juice. If vomiting interferes with oral N-acetylcysteine use, the dose should be repeated with an antiemetic such as metoclopramide or ondansetron.[29,30] Occasionally, a nasogastric tube may be necessary. IV administration of N-acetylcysteine, using the same dose and dosing schedule, may be beneficial in patients unable to tolerate the oral preparation. Other indications for IV N-acetylcysteine include pregnancy and late presentation of acetaminophen overdose. Although IV administration is routinely used in Europe, the US Food and Drug Administration (FDA) has not approved the IV formulation of N-acetylcysteine.[31] There is no clear evidence that the oral route is superior to an IV route.[32] When oral N-acetylcysteine is administered IV, a micropore filter should be used. Yip et al[33] reported the IV use of oral N-acetylcysteine in 76 patients. Only four patients acquired adverse reactions, and none were life-threatening. Flushing requires no treatment. Urticaria, angioedema, and respiratory symptoms are treated with IV diphenhydramine and β_2-agonist bronchodilators. In case of a severe reaction, the infusion should be stopped and resumed 1 h after diphenhydramine has been administered. Anaphylactoid reactions to the IV drug have been reported.[34]

In the United States, acetaminophen-induced fulminant hepatic failure is one of the most common reasons for liver transplantation.[35] Among patients with acute fulminant hepatic failure who do not receive liver transplantation, survival is highest for acetaminophen-induced fulminant hepatic failure (57%).[36] In general, late presentation, grade 3 or 4 hepatic encephalopathy, prothrombin time prolongation, pH < 7.30, renal dysfunction, cerebral edema, and sepsis are indicators of poor outcome.[37] The usefulness of coagulation factors V and VIII as predictors of outcome in acetaminophen-induced fulminant hepatic failure remains controversial.[38,39] Investigators from King's College Hospital Liver Unit demonstrated that an APACHE (acute physiology and chronic health evaluation) II score[40] ≥ 15 provided an accurate risk of hospital mortality and identified patients in need of transfer for possible transplantation in the setting of acetaminophen-induced acute liver failure. Since intensivists are more familiar with APACHE II than with specialist

liver scores (*ie*, King's criteria),[41] this may expedite appropriate transfers to liver units.[42]

Alcohols

Ethylene glycol, methanol, and isopropanol are the most commonly ingested nonethanol alcohols. Ethylene glycol is odorless and sweet tasting. Blue or green fluorescent dye is added to most products that contain ethylene glycol, such as antifreeze, de-icers, and industrial solvents. This explains the positive urinary fluorescence under a Wood lamp.[43] However, this method of detection is of limited usefulness.[44] Methanol is also colorless and odorless but is bitter tasting and highly volatile. Methanol is present in many paint removers, duplicator fluid, gas-line antifreeze, windshield washing fluid, and solid canned fuel. Isopropanol is a colorless and bitter-tasting alcohol that has the smell of acetone or alcohol. It is found in rubbing alcohol, skin lotions, hair tonics, aftershave, deicers, and glass cleaners. All three are weak toxins by themselves; however, their metabolites can be very toxic.

Intoxication by nonethanol alcohols can present with signs and symptoms of inebriation and low or absent ethanol level. Ingestion history is important. Metabolic acidosis with an elevated anion gap and/or presence of an elevated osmolal gap are cardinal features of methanol and ethylene glycol poisoning. However, serious intoxication can occur without elevating the anion gap if there has been insufficient time to form acid metabolites, or if the patient started with a low baseline anion gap. Nonethanol alcohol intoxication can also occur without an increase in osmolal gap (explained in detail last month in part I of this review).[45–47]

Ethylene glycol is metabolized by alcohol dehydrogenase to glycoaldehyde and glycolic acid, and eventually to glyoxylic acid and oxalic acid. Accumulation and precipitation of oxalic acid to calcium oxalate in the renal tubules produces calcium oxalate crystals and contributes to the development of acute tubular necrosis. Hypocalcemia (because of precipitation by oxalate) and myocardial dysfunction are additional features of ethylene glycol poisoning. Ingestion of as little as 100 mL can be lethal in an adult patient. Significant toxicity is associated with serum levels > 50 mg/dL.

Ethylene glycol poisoning has a triphasic clinical course: stage 1 (30 min to 12 h postingestion) consists of inebriation, ataxia, seizures, variable levels of elevated anion gap metabolic acidosis with Kussmaul breathing, elevated osmolal gap, crystalluria, and hypocalcemia. Cerebral edema causes coma or death. Stage 2 (12 to 24 h) is dominated by myocardial dysfunction with high- or low-pressure pulmonary edema. Death in this stage is caused by myocardial dysfunction or aspiration pneumonia. Stage 3 (2 to 3 days) is dominated by acute renal failure due to acute tubular necrosis with an element of tubular obstruction from calcium oxalate precipitation.[48–50] Late (6 to 18 days) neurologic sequelae have also been described in survivors.[51,52]

Methanol is metabolized by alcohol dehydrogenase to formaldehyde, which is converted by aldehyde dehydrogenase to formic acid. Formic acid is the primary toxin responsible for metabolic derangements and ocular disturbances. Intoxication can occur through oral ingestion, inhalation, or dermal absorption. Only 30 mL can cause significant morbidity. Approximately 150 to 240 mL of 40% solution can be lethal (lethal serum levels are 80 to 100 mg/dL). Methanol causes an initial period of headache, inebriation, dizziness, ataxia, and confusion. As formic acid accumulates (6 to 72 h), the anion gap elevates and visual symptoms become more pronounced. Visual loss or optic nerve swelling on funduscopy suggest methanol intoxication. Pancreatitis is an additional feature of methanol poisoning.[53,54] Symptoms of ethylene glycol and methanol poisoning may be delayed if there is concomitant ethanol consumption, which inhibits conversion of these compounds to their toxic metabolites.

The treatment of ethylene glycol and methanol poisoning is very similar.[55] Inhibiting the formation of toxic metabolites by alcohol dehydrogenase and/or urgent dialytic removal of these alcohols and their metabolites are the cornerstones of therapy. Supportive measures include gastric lavage in the first hour postingestion. Bicarbonate infusion may improve metabolic acidosis, but buffer therapy has not been shown to improve outcome. Hypocalcemia and hypoglycemia should be corrected. Thiamine (50 to 100 mg), folate (up to 50 mg), and pyridoxine (100 mg) are usually administered.

Inhibitors of alcohol dehydrogenase include fomepizole (4-methylpyrazole) and ethanol. Fomepizole is preferred because it does not exacerbate the inebriated state or require blood monitoring.[56,57] The FDA has approved it for ethylene glycol and methanol poisoning. The protocol consists of a 15 mg/kg IV loading dose followed by a 10 mg/kg IV bolus q12h. After 48 h, the bolus dose should be increased to 15 mg/kg q12h to account for enhanced fomepizole metabolism. For both ethylene glycol and methanol, patients are treated until serum levels fall to < 20 mg/dL. Hemodialysis can be performed concurrently with fomepizole if clinically indicated. In ethylene glycol poisoning, hemodialysis is indicated when serum ethylene glycol levels are > 50 mg/dL, when there is significant and refractory

metabolic acidosis, or when there is evidence of end-organ damage. Dialysis is continued until ethylene glycol levels are undetectable and metabolic acidosis has resolved. In methanol poisoning, hemodialysis is indicated if serum methanol levels are >50 mg/dL, a lethal dose of methanol has been ingested, there is significant and refractory metabolic acidosis, or there is evidence of end-organ damage. Dialysis is continued until acidosis has resolved and serum methanol levels are <25 mg/dL.

Another inhibitor of alcohol dehydrogenase is ethanol (IV or orally). One protocol for therapeutic ethanol administration (maintaining a target serum level of 100 to 200 mg/dL) is as follows[58]: loading dose, 0.6 g/kg ethanol IV; maintenance doses are, 66 mg/kg/h ethanol by continuous IV infusion for nonalcoholic patients, 154 mg/kg/h ethanol by continuous IV infusion for alcoholic patients, and double continuous infusion rate for patients receiving dialysis.

IV ethanol is supplied as a 10% solution in 5% dextrose in water containing 10 g of ethanol per 100 mL of solution. Either dialysis bath supplementation with 200 mg/dL of ethanol or doubling the dose of IV ethanol infusion should maintain serum ethanol levels in the target range during hemodialysis.

Isopropanol is metabolized by alcohol dehydrogenase to acetone that is excreted through the kidneys and breath.[59] A combination of ketonemia (sweet-smelling breath; ketones in the urine; and absence of an elevated anion gap or metabolic acidosis), hemorrhagic gastritis, and an elevated osmolal gap suggests isopropyl alcohol consumption. A serum isopropanol level confirms the diagnosis. Supportive measures are usually sufficient in the treatment of these patients. Gastric lavage can be helpful if performed in the first hour postingestion. Hemodialysis is indicated when lethal doses have been ingested (150 to 240 mL of 40 to 70% solution) or when lethal serum levels are detected (400 mg/dL). Refractory shock or prolonged coma are other indications for dialysis.[60]

Amphetamines

During the past decade, methamphetamine use has increased rapidly in the United States, particularly in inner-city areas.[61] Common amphetamine and amphetamine-like prescription drugs include methylphenidate, dextroamphetamine, and pemoline, used primarily for narcolepsy and attention-deficit disorder; and various anorectic medications used for weight loss, including diethylpropion and phentermine. Illicit drugs include methamphetamine ("crank" or "ice"), and 3,4-methylenedioxymethamphetamine ("ecstasy").

Amphetamines exert their toxicity via CNS stimulation, peripheral release of catecholamines, inhibition of re-uptake of catecholamines, or inhibition of monoamine oxidase. They generally have a low therapeutic index. In overdose, they cause confusion, tremor, anxiety, agitation, and irritability. Additional features include mydriasis, tachyarrhythmias, myocardial ischemia, hypertension, hyperreflexia, hyperthermia, rhabdomyolysis, renal failure, coagulopathy, and seizures.[62,63] Severe hepatotoxicity requiring liver transplantation has been reported with ecstasy abuse.[64,65] Death may result from hyperthermia, arrhythmias, status epilepticus, intracranial hemorrhage, fulminant liver failure, or aspiration pneumonitis.[66]

Treatment is supportive, including maintenance of the airway and mechanical ventilation if necessary. Hypertension generally responds to systemic vasodilation with phentolamine or nitroprusside. Tachyarrythmias are best treated with esmolol or propranolol. Agitation, violent behavior and psychosis should be treated with butyrophenones (*ie*, haloperidol or droperidol), benzodiazepines, or phenothiazines. In a randomized controlled trial of 146 agitated patients with methamphetamine toxicity, droperidol treatment led to a more rapid and profound sedation than lorazepam.[67] If the rectal temperature exceeds 40°C, active cooling measures may become necessary. The value of using a muscle relaxant such as dantrolene in this setting is debated, particularly since it has potential side effects, including hepatitis.[68–70] Activated charcoal should be administered promptly with a cathartic. Gastric lavage is useful if performed within 1 h of ingestion. Dialysis and hemoperfusion are not effective.

Barbiturates

Mild-to-moderate barbiturate overdose presents with reduced level of consciousness, slurred speech, and ataxia. At high doses, barbiturates cause hypothermia, hypotension, bradycardia, flaccidity, hyporeflexia, coma, and apnea. Patients with severe overdose may appear to be dead with absent EEG activity.

Cardiovascular depression is caused by a combination of decreased arterial tone and myocardial depression, leading to a high filling pressure, low cardiac output, and hypotensive state. Respiratory depression with hypercapnia and hypoxemia are common. In deep coma, the usual acid-base disturbance is a mixed respiratory and metabolic acidosis. Patients unresponsive to painful stimuli tend to be significantly more acidemic and hypoxemic than those who show some response to pain, a finding that

is not explained by differences in alveolar ventilation.[71] Hypoxemia may be aggravated by ventilation/perfusion mismatch and/or increased capillary permeability with development of the ARDS, possibly related to aspiration pneumonitis.

The diagnosis of barbiturate overdose is generally made on clinical grounds and confirmed by routine urine toxicology screening. Blood levels correlate with severity but rarely alter management.[72]

Treatment of barbiturate overdose first involves general supportive measures. There is no specific antidote. Gastric lavage is useful in acute massive overdose if performed within 60 min of ingestion.[18] Multidose activated charcoal decreases absorption and enhances elimination in life-threatening phenobarbital overdose.[73] Urine alkalinization (targeting a urinary pH > 7.5) increases elimination of phenobarbital, but not other barbiturates, and care must be taken not to cause pulmonary edema by volume overload.[50] Charcoal hemoperfusion is indicated in severe poisoning characterized by prolonged coma or refractory hypotension, but its role is disputed.[74–76] If depressed mental status persists, other conditions should be considered: head trauma with subdural or epidural hematoma, intracerebral hemorrhage, embolic stroke, electrolyte abnormalities, hypoxemia, hypothyroidism, liver or renal failure, CNS infection, seizures, and significant alterations in temperature.

Benzodiazepines

Benzodiazepines are used for a variety of purposes, such as hypnotics, anxiolytics, muscle relaxants, and sedatives. The half-life is dependent on the specific drug and can range from 2 h to several days. Because of widespread use, these drugs are frequently involved in drug overdoses, either as a single agent or combined with other toxins. Confirmation of exposure is rapidly available by urine toxicology screening.

Benzodiazepines enhance the inhibitory effects of the neurotransmitter γ-aminobutyric acid (GABA) causing generalized depression of the CNS. Symptoms in overdose range from slurred speech and lethargy to respiratory arrest and coma, depending on the dose and compound ingested. In general, patients in coma from benzodiazepine poisoning are hyporeflexic with small-to-midsized pupils that do not respond to naloxone administration. They do respond to the cautious administration of flumazenil.

Treatment of benzodiazepine overdose consists of initial supportive measures, gastric emptying if it can be performed in the first hour postingestion, activated charcoal,[77] and flumazenil. There is no role for forced diuresis, dialysis, or hemoperfusion. Flumazenil is a specific benzodiazepine antagonist that reverses sedation in postoperative patients and in intentional benzodiazepine overdose. Its effect on reversal of respiratory depression remains controversial.[78,79] Judicious use of flumazenil provides useful diagnostic information, as it does not antagonize the CNS effects of alcohol, barbiturates, tricyclic antidepressants, or narcotics. Although there are concerns regarding the precipitation of seizure activity in the setting of mixed tricyclic antidepressant-benzodiazepine overdose,[80,81] limited data suggest flumazenil is safe and effective in this setting.[82] Flumazenil could unmask seizures from any cause and increases the incidence of death in a rat model of combined cocaine/diazepam poisoning.[83] Flumazenil is not recommended in patients who use benzodiazepines therapeutically to control seizures or raised intracranial pressure.[84] Addicted patients may acutely withdraw after flumazenil administration.

The recommended initial dose of flumazenil is 0.2 mg (2 mL) IV over 30 s. A further 0.3-mg (3 mL) dose can be administered over 30 s if the desired clinical effect is not seen within 30 s. Additional 0.5-mg doses can be administered over 30 s at 1-min intervals as needed to a total dose of 3 mg. Doses > 3 mg are beneficial in a small number of patients.[85]

Patients should be monitored for re-sedation, particularly in overdose cases and in patients receiving high-dose, long-term, or long-acting benzodiazepines. Re-sedation may occur within 1 to 2 h after administration, so repeat doses or continuous infusion (0.1 to 0.5 mg/h) may be required to maintain therapeutic efficacy.[86] However, continuous infusion has not been shown to decrease complications.[87] Patients with liver dysfunction require downward adjustment in dose.[88] Patients with multidrug overdose, significant comorbidities, advanced age, and re-sedation after initial response to flumazenil should be admitted to an ICU.

β-Blockers

β-Blockers are competitive antagonists of β receptors. β_1-Receptors are found in the heart; β_2-receptors are found in bronchial tree and blood vessels. Some β-blockers (*eg*, acebutolol, betaxolol, pindolol, and propranolol) have myocardial membrane-stabilizing activity that can cause QRS widening and decreased myocardial contractility.

Clinical features of β-blocker overdose depend on the drug type, amount and timing of overdose, co-ingestions, and comorbidities. The diagnosis is usually established on clinical grounds; blood levels

are available but do not correlate closely with severity of overdose.[89] Factors associated with the risk of acquiring cardiovascular morbidity include coingestion of another cardioactive drug and a β-blocker with myocardial membrane-stabilizing activity (*eg*, acebutolol, betaxolol, pindolol, and propranolol).[90] The majority of patients (97%) acquire β-blocker toxicity within 4 h of ingestion. Asymptomatic patients with a normal ECG after 6 h generally do not require intensive care monitoring.[91]

Cardiovascular complications of β-blocker toxicity include hypotension, bradycardia, atrioventricular blocks of different degrees, and congestive heart failure with or without pulmonary edema. Hypotension is mainly due to decreased myocardial contractility rather than bradycardia. Other manifestations include bronchospasm, hypoglycemia, hyperkalemia, lethargy, stupor, coma, and seizures. Risk of seizure is highest with propranolol, particularly when the QRS complex is > 100 ms.[92] In a large retrospective review of 52,156 cases of β-blocker overdose, there were 164 deaths.[93] Propranolol was responsible for the greatest number of toxic exposures (44%) and implicated as the primary cause of death in a disproportionately higher percentage of fatalities (71%). Fifty-nine percent of patients went into cardiac arrest after reaching health-care personnel.

Treatment of β-blocker toxicity consists of initial supportive measures. Induced emesis is contraindicated because of the risk of sudden cardiovascular collapse.[92] Gastric lavage may help if the procedure can be undertaken within 60 min of ingestion. Activated charcoal can be used, but there is no clear role for multidose activated charcoal.[50]

Cardiovascular manifestations are best treated with combinations of fluid resuscitation, vasopressor agents, atropine, transvenous pacing, and glucagon. Glucagon effectively reverses myocardial depression and bradycardia. Its positive inotropic and chronotropic effect is mediated through adenyl cyclase, which increases cyclic adenosine monophosphate and intracellular calcium influx.[94] Improvements in bradycardia and hypotension are observed within a few minutes and may preclude the need for high-dose catecholamine infusion.[95] Glucagon is administered as bolus of 5 to 10 mg IV over 1 min followed by an infusion of 1 to 10 mg/h. The diluent provided by the manufacturer contains 2 mg of phenol per 1 mg of glucagon. In order to avoid phenol toxicity, dilution of glucagon in saline solution or dextrose is recommended. Phenol toxicity can induce hypotension and arrhythmias.[96–98] The use of an insulin-glucose infusion for β-blocker toxicity may prove to be superior to glucagon alone; this strategy is under investigation.[99]

Calcium-Channel Blockers

Calcium-channel blockers (CCBs) selectively inhibit the movement of calcium ions through the membrane of cardiac and vascular smooth muscle during the slow inward phase of excitation-contraction. These agents can have varying degrees of cardiovascular effects. Verapamil is more of a negative inotrope; nifedipine has more vasodilatory effects. Verapamil and diltiazem depress the sinus node and slow conduction through the atrioventricular node. The most common cardiovascular effect is hypotension, which generally occurs within 6 h of CCB overdose (except with sustained-release preparations in which toxicity may not be evident for 12 h). This commonly follows a period of nausea and vomiting. Hypotension is mainly secondary to peripheral vasodilation as opposed to myocardial depression. Conduction abnormalities are worsened with concurrent β-blocker ingestion[100] and existing cardiovascular disease. Lethargy, confusion, and coma have been attributed to CCB overdose. Seizures are uncommon. Hyperglycemia from suppression of insulin secretion has also been reported.

Gastric lavage may be useful for up to 8 h after ingestion of a sustained-release preparation. Whole-bowel irrigation has similarly been used for sustained-release preparations.[101] Multidose activated charcoal and hemodialysis are not very helpful. However, charcoal hemoperfusion may have a role in verapamil overdose in the setting of hepatic dysfunction.[102]

Hypotension is treated first with fluids. However, additional therapy is often required. Calcium gluconate (2 to 3 g total or 0.2 to 0.5 mL/kg of a 10% solution every 15 to 20 min to a total of four doses) is the preferred IV calcium agent.[103,104] Glucagon, administered as a bolus of 5 to 10 mg IV over 1 min followed by an infusion of 1 to 10 mg/h may decrease vasopressor requirements.[95,105] Several investigators have reported successful reversal of refractory shock in CCB toxicity with hyperinsulinemia-euglycemia therapy by continuous infusion of insulin at a rate of 0.5 IU/kg/h.[106,107] Larger trials are needed to confirm its safety and efficacy.

Carbon Monoxide

As a nonirritating, colorless, tasteless, and odorless gas, carbon monoxide is quite insidious. This gas is formed by incomplete combustion of carbon-containing materials (complete oxidation produces carbon dioxide). Carbon monoxide poisoning occurs in the setting of smoke inhalation, attempted suicide from automobile exhaust, and poorly ventilated burning charcoal or gas stoves. Carbon monoxide is also generated during hepatic metabolism of dichlo-

romethane (methylene chloride), a component of paint and varnish removers.[108,109] Although there has been a slight decline in deaths as a result of carbon monoxide poisoning, it remains the most common cause of death by poisoning in the United States. Up to 20% of all deaths due to this poisoning are considered to be accidental and unintentional in nature.[110]

Carbon monoxide binds to hemoglobin with an affinity that is 240 times greater than oxygen and decreases oxyhemoglobin saturation and blood oxygen-carrying capacity. Its toxicity results from a combination of tissue hypoxia and direct inhibition of cellular respiration through cytochrome oxidase blockade.

The severity of carbon monoxide poisoning depends on the concentration of carbon monoxide, duration of exposure, and minute ventilation. Carboxyhemoglobin concentrations up to 5% are generally well tolerated. Mild exposures (carboxyhemoglobin 5 to 10%) may result in headache and mild dyspnea. These levels can be seen in heavy smokers and commuters on polluted roads. Carboxyhemoglobin concentrations between 10% and 30% cause headache, dizziness, weakness, dyspnea, irritability, nausea, and vomiting. These symptoms may be mistaken for the flu or food poisoning. Patients with coronary artery disease are at risk for ischemia and infarction. Carboxyhemoglobin concentrations $>$ 50% result in coma, seizures, cardiovascular collapse, and death. It is important to note that carboxyhemoglobin levels do not always correlate well with clinical severity of carbon monoxide poisoning. Ten to 30% of survivors acquire delayed neuropsychiatric sequelae (DNS).[111–113] DNS has been described to occur from 3 to 240 days after apparent recovery. Its variable manifestations include persistent vegetative state, Parkinsonism, short-term memory loss, behavioral changes, hearing loss, incontinence, and psychosis. There is no accurate way of predicting which patients will acquire DNS. At 1 year, 50 to 75% of patients with DNS experience a full recovery.[113]

Clinicians must maintain a high index of suspicion for carbon monoxide poisoning, especially during cold weather. Important historical clues can aid in the diagnosis. These include cohabitants with similar symptoms, use of heating devices other than a furnace, or problems with a forced-air heating system.[114,115] Carboxyhemoglobin levels are determined by co-oximetry. Pulse oximetry cannot distinguish carboxyhemoglobin from oxyhemoglobin at the wavelengths that are commonly generated by standard pulse oximeters. Pulse oximetry overestimates oxyhemoglobin by the amount of carboxyhemoglobin present; therefore, pulse oximetry results may be "normal" despite high concentrations of carboxyhemoglobin.[116,117] Venous blood can also be used to predict carboxyhemoglobin levels.[118]

The most essential treatment for carbon monoxide poisoning is oxygen. Administration of 100% supplemental oxygen decreases the half-life of carboxyhemoglobin from 5 to 6 h on room air to 40 to 90 min. The addition of 4.5 to 4.8% carbon dioxide to a nonrebreathing circuit while breathing oxygen allows patients to maintain normocapnia while hyperventilating and avoids the development of respiratory alkalosis. In a study of seven healthy male volunteers, this simple method decreased the half-life of carboxyhemoglobin from 78 ± 24 to 31 ± 6 min.[119] This strategy requires further studying before routine use.

Hyperbaric oxygen (2.8 atmospheres within 6 h of exposure) further decreases the half-life of carboxyhemoglobin to 15 to 30 min. The role of hyperbaric oxygen in the management of carbon monoxide poisoning has been debated, and reviewed.[120] Evidence from available randomized controlled trials is insufficient to provide clear guidelines for the use of hyperbaric oxygen therapy in carbon monoxide poisoning. There is no clear evidence that unselected use of hyperbaric oxygen decreases the frequency of DNS at 1 month. Clearly, a multicenter, randomized, double-blind controlled trial is needed to better define the role of hyperbaric oxygen.[121] We believe that patients with potentially life-threatening exposures should receive at least one hyperbaric oxygen treatment (if hyperbaric capability is readily available).[122]

See addendum at the end of this text.

Cocaine

Cocaine may be snorted nasally, inhaled orally, or used IV. "Body packers" swallow multiple wrapped packages of cocaine in an attempt to smuggle the drug across national boundaries; "body stuffers" swallow or conceal wrapped packets of cocaine in various body cavities when law enforcement agents challenge them. Free-base cocaine, also known as *crack*, is absorbed more rapidly and is more potent.

Toxic effects of cocaine arise from excessive CNS stimulation and inhibition of neuronal uptake of catecholamines. Onset and duration of symptoms depend on route of administration, dose, and patient tolerance. Smoking and IV use produce symptoms within 1 to 2 min; oral use delays onset of symptoms by 20 to 30 min. The half-life of cocaine is approximately 60 min; however, its metabolites are detectable in blood or urine for 24 to 36 h after ingestion. Cocaine is often mixed with other substances of abuse including heroin ("speedball"), phencyclidine,

and alcohol. In the presence of ethanol, cocaine is transesterified in the liver to cocaethylene. Cocaethylene is similar to cocaine, but lasts longer and is more toxic.

Common CNS manifestations include euphoria, anxiety, agitation, psychosis, delirium, and seizures. Vasospasm, vasculitis, myocardial infarction with cardiac arrhythmias, and increased platelet aggregation may provoke ischemic cerebral infarcts.[123] Cardiovascular manifestations of cocaine include chest pain, myocardial ischemia and infarction, sudden death, arrhythmias, congestive heart failure, pulmonary hypertension, endocarditis, and aortic dissection.[124] Currently, there are no clinical parameters available to the physician that can reliably identify patients at very low risk for myocardial infarction, mandating that all patients with cocaine-associated chest pain be evaluated for myocardial infarction.[125] Respiratory complications of cocaine include status asthmaticus, upper airway obstruction (stridor), pulmonary hypertension, barotrauma, pulmonary edema, and alveolar hemorrhage. The inhalation of crack cocaine can cause an acute pulmonary syndrome characterized by dyspnea, diffuse infiltrates, and hemoptysis.[126] Severity ranges from mild respiratory distress to severe respiratory failure requiring intubation and mechanical ventilatory support. Another severe manifestation of cocaine abuse is rhabdomyolysis with myoglobinuria.[127] This in part may reflect a direct toxic effect of cocaine on muscle. Patients may be hyperthermic on presentation, with altered mental status, tachycardia, muscle rigidity, disseminated intravascular coagulation, hepatic dysfunction, and renal failure[128] resembling neuroleptic malignant syndrome.[129] Other contributors to the hyperthermic state include agitation and adrenergic stimulation causing vasoconstriction and ischemia. Botulism has also been associated with skin wounds resulting from cocaine use.[130]

Treatment of cocaine intoxication starts with the "ABCs" (airway, breathing, circulation), followed by immediate treatment of seizures, hyperthermia, and agitation if indicated. For orally ingested drug, activated charcoal should be administered to decrease further drug absorption. Gastric lavage and ipecac-induced vomiting are not recommended because of the risk of seizures and subsequent aspiration. In body packers (who are found frequently at hospitals near international airports), whole-bowel irrigation with a polyethylene glycol, electrolyte solution, 1 to 2 L/h, is a well tolerated, safe method of rapid elimination of drug packets from the GI tract.[131] Contraindications to whole-bowel irrigation include ileus, GI hemorrhage, and bowel perforation. Ideally, activated charcoal should be administered first, followed by the polyethylene glycol electrolyte solution.[132] Surgical removal of retained packages may be needed, particularly in patients with bowel obstruction or package perforation.[133] Endoscopic removal is not recommended since packet rupture may occur. Neither dialysis nor hemoperfusion effectively removes cocaine.

Perhaps the most important treatment strategy in cocaine intoxication is rapid treatment of agitation and hyperthermia. Active and passive patient cooling, sedation with benzodiazepines, and muscle paralysis with nondepolarizing neuromuscular blockers may be necessary. Cocaine-associated chest pain may be treated with nitrates and CCBs.[134] β-Blockers administered alone should be avoided due to blockade of β_2-mediated vasodilation and unopposed β-adrenergic stimulation. Propranolol worsens outcome in an animal model; esmolol produces an inconsistent antihypertensive response and may cause marked exacerbation of hypertension or hypotension[135]; and cocaine-induced coronary vasoconstriction may be potentiated by β-adrenergic blockade.[124] Labetolol, which blocks both α- and β-adrenergic receptors, may reverse cocaine-induced hypertension, but not cocaine-induced coronary vasoconstriction.[136,137] The combination of nitroprusside and a β-adrenergic blocking agent, or phentolamine alone or in addition to a β-blocker may successfully treat myocardial ischemia and hypertension.[138]

Treatment of respiratory complications is supportive.[139] Inhaled bronchodilators and corticosteroids generally improve cocaine-associated bronchospasm. Significant pneumothorax is treated with tube thoracostomy, and pneumomediastinum is watched expectantly.

Cyanide

Cyanide is found in a variety of synthetic and natural substances: plastics, glue removers, wool, silks, nylons, various seeds, and plants. Poisoning may occur through inhalation of hydrogen cyanide gas, a combustion byproduct of cyanide-containing products, sodium nitroprusside infusion, and very rarely absorption of cyanide-containing solutions or gas through skin. Cyanide is a rapidly acting poison, particularly when it is inhaled. The mechanism of toxicity involves the binding of cyanide to cellular cytochrome oxidase and resultant interference with aerobic oxygen utilization.

Once ingested, cyanide is detoxified by enzymatic conversion to the less toxic, renally excreted metabolite, thiocyanate. A small amount of cyanide is also detoxified by the vitamin B_{12} precursor, hydroxycobalamin. This chelating agent binds cyanide to form nontoxic cyanocobalamin.

Early manifestations of poisoning include anxiety, dyspnea, headache, confusion, tachycardia, and hypertension. These are rapidly followed by stupor or coma, seizures, fixed and dilated pupils, hypoventilation, hypotension, bradycardia, heart block, ventricular arrhythmias, and complete cardiopulmonary collapse.

The diagnosis of cyanide poisoning is usually made on clinical grounds, often in the setting of smoke inhalation where combined carbon monoxide and cyanide toxicity occurs. Blood cyanide levels > 0.5 mg/L are considered toxic.[140] Rapid onset of coma, seizures, and cardiopulmonary dysfunction in the presence of severe lactic acidosis or an elevated mixed venous oxyhemoglobin saturation (evidence of the blocking of aerobic oxygen utilization) should increase the suspicion of cyanide poisoning.[141] Funduscopic examination or direct examination of venous blood can demonstrate this "arteriolization" of venous blood. The bitter almond scent of hydrogen cyanide gas may also be present.

Treatment of cyanide poisoning tends to be effective if started early. Oxygen, decontamination, nitrites, and sodium thiosulfate are the main therapeutic modalities. Oxygen therapy at 100% fraction of inspired oxygen either by face-mask or endotracheal tube should be instituted immediately. Hyperbaric oxygen is as of yet unproved in cyanide poisoning.[142] Amyl and sodium nitrites induce formation of methemoglobin. Cyanide has a high affinity for the ferric iron contained in methemoglobin, thereby rendering methemoglobin an effective scavenger of unbound cyanide. Amyl nitrite is administered by inhalation of crushable pearls, which are inhaled for 15 to 30 s with 30 s of rest between inhalations. One pearl lasts approximately 2 to 3 min. This therapy induces a 5% methemoglobenemia and can be used in spontaneously breathing patients or in patients receiving ventilatory support until administration of sodium nitrite. Sodium nitrite is administered IV at a dose of 300 mg over 3 min to convert more hemoglobin to methemoglobin. Half this dose may be repeated after 2 h if there is persistent toxicity, and a tolerable degree of methemoglobinemia. Usually, methemoglobin levels remain $< 20\%$ and the reduction of total oxygen-carrying capacity by the combination of carboxyhemoglobin and methemoglobin is $< 21\%$.[143] Methylene blue should be avoided as a treatment of methemoglobinemia because it will release free cyanide.

Sodium thiosulfate acts as a sulfur donor to rhodenase and other sulfur transferases and thereby enhances conversion of cyanide to thiocyanate.[144] The dose is 12.5 g (50 mL of a 25% solution) IV over 10 min. Half this dose may be repeated after 2 h for persistent toxicity. Sodium thiosulfate may result in thiocyanate toxicity, particularly in the setting of renal insufficiency, but thiocyanate is readily dialyzable. Co-administration of thiosulfate with nitroprusside (in a ratio of 1:10 thiosulfate to nitroprusside) effectively eliminates the possibility of cyanide intoxication during nitroprusside infusion without altering the efficacy of nitroprusside.[145]

Hydroxycobalamin is a promising antidote capable of reducing RBC and plasma cyanide concentrations. In healthy adult smokers, hydroxycobalamin, 5 g IV, decreased whole-blood cyanide levels by 59%.[146] The currently recommended dose of hydroxycobalamin in acute cyanide poisoning is 4 to 5 g IV administered as a one-time dose.[147–149] However, the FDA has not approved its use in the United States.

Gastric emptying is recommended for acute ingestions, followed by activated charcoal. Induced emesis is not recommended because of the risk of rapid cyanide-induced deterioration in clinical status and subsequent risk of aspiration. There is no role for hemodialysis or hemoperfusion except to clear high levels of thiocyanate.

Cyclic Antidepressants

The American Association of Poison Control Centers has recently reported that antidepressants were second only to analgesics as a cause of overdose-related death. Sixty-nine percent of antidepressant fatalities were secondary to tricyclic antidepressants.[1] Cyclic antidepressants (including the tricyclics, tetracyclics, bicyclics, and monocyclics) are among the most commonly encountered causes of self-poisoning. Tricyclic antidepressants include amitriptyline, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and amoxapine. These drugs are used for depression, chronic pain syndromes, obsessive-compulsive disorder, panic and phobic disorders, eating disorders, migraines, insomnia, and peripheral neuropathies. The development of newer and safer antidepressants, such as the selective serotonin re-uptake inhibitors (SSRIs) has caused a decline in use of cyclic antidepressants. Compared to SSRI overdose, tricyclic antidepressant overdoses are more likely to cause severe toxicity, admission to the ICU, and death.[150,151] In overdose, these drugs mainly affect the CNS and cardiovascular system. Anticholinergic effects and inhibition of neural re-uptake of norepinephrine and/or serotonin are responsible for CNS toxicity. Cardiovascular manifestations stem from anticholinergic effects, inhibition of neural uptake of norepinephrine or serotonin, peripheral α-adrenergic blockade, and membrane depressant effects.

The clinical presentation may be divided into

anticholingeric effects, cardiovascular effects, and seizures. Anticholinergic manifestations include mydriasis, blurred vision, fever, dry skin and mucous membranes, lethargy, delirium, coma, tachycardia, ileus, myoclonus, and urinary retention. These effects are commonly summarized by the phrase: "hot as a hare, dry as a bone, red as a beet, mad as a hatter."

Cardiovascular toxicity consists of sinus tachycardia with prolongation of the QRS, QTc, and PR intervals. Occasionally, sinus tachycardia with QRS prolongation is difficult to distinguish from ventricular tachycardia, which also occurs in cyclic antidepressant overdose. Torsades des pointes is relatively rare. Importantly, a limb-lead QRS interval longer than 0.10 s has been shown to predict seizures and QRS duration $>$ 0.16 s has been associated with ventricular arrhythmias.[152] The degree of interrater agreement in the measurement of QRS interval is adequate enough to make this measurement a useful part of the overall assessment of toxicity.[153] Although the ECG can neither unequivocally rule in nor rule out impending toxicity, it is a valuable bedside tool in combination with other clinical data gathered during patient assessment.[154] A maximal limb-lead QRS duration $<$ 0.1 s is rarely associated with seizures or ventricular arrhythmias. Various forms of atrioventricular block may accompany cyclic antidepressant overdose. Right bundle-branch block is common. Hypotension is mainly due to venodilation and a direct drug effect on myocardial contractility. Seizures may be short-lived and self-limited, or prolonged and refractory to treatment. Neurologic deterioration may be abrupt and unpredictable. Metabolic acidosis from seizures or arrhythmias promotes unbinding of the drug from proteins and contributes to increased toxicity.[155]

The diagnosis of cyclic antidepressant overdose depends on a compatible history and clinical features with a high index of suspicion. Cyclic antidepressant overdose should be considered in all patients with QRS prolongation. Confirmation of exposure is available by urine toxicology screening. Blood levels are not generally followed because of the reliability of the QRS duration to predict severity.

Treatment of cyclic antidepressant overdose involves initial supportive measures aimed at identifying and treating life-threatening problems. Serum alkalinization remains the mainstay of therapy. Patients should immediately receive sodium bicarbonate (1 to 2 mEq/kg IV) when there is widening of the QRS interval to decrease the fraction of free drug. Sodium bicarbonate should be continued until there is narrowing of the QRS interval or serum pH exceeds 7.55. Hyperventilation is an alternate strategy in intubated patients. The ECG should be followed closely for 48 to 72 h.[156] After initial stabilization, gastric lavage (within 2 h of ingestion) followed by activated charcoal is the preferred method of gastric decontamination. Emesis should not be induced because of the possibility of abrupt deterioration in mental status and seizures leading to high risk of aspiration. Activated charcoal can be administered without gastric lavage[157]; there is no role for multidose activated charcoal,[73] particularly since anticholinergic-induced ileus increases the risk of charcoal-induced bowel obstruction. Because of high lipid solubility and protein binding, dialysis and hemoperfusion are not effective.

Lidocaine is the drug of choice in cyclic antidepressant overdose complicated by refractory ventricular arrhythmias. Support for the use of phenytoin comes largely from anectodal reports. Based on the available data, we do not recommend this drug for either prophylaxis or treatment in cyclic antidepressant overdose.[158,159] Bretylium can exacerbate hypotension. Class 1a antiarrhythmics (*eg*, procainamide) can add to cardiac toxicity and should be avoided in the setting of ventricular arrhythmias. Temporary ventricular pacing may be required in high-grade blocks.

Hypotension tends to be refractory to fluid resuscitation. Many patients will require vasopressor support with a drug such as norepinephrine.[160–162] Pulmonary edema, both cardiogenic and noncardiogenic, has been reported.[163,164] Although a pulmonary artery catheter may help direct therapy, there is concern regarding the arrhythmogenic potential of right-heart catheterization in this setting.

Diazepam, lorazepam, and phenobarbital can be used for the treatment of seizures. Phenytoin should be reserved for refractory cases. Paralysis or deep sedation with propofol may be indicated for refractory seizures (as may be seen in amoxapine overdose) to control temperature and muscle breakdown.[165] Continuous EEG monitoring is required to guide antiseizure medications during paralysis.

Experimental therapies include glucagon[166,167] and monoclonal antibodies to tricyclics.[168–170] Physostigmine should not be used in cyclic antidepressant overdose because of the potential for seizures and asystole.

Lethality from cyclic antidepressant overdose lies primarily in their cardiac toxicity and tends to occur in the first 24 h of arrival. Most patients acquire symptoms within the first 6 h after ingestion.[171] Patients with altered mental status, seizures, hypotension, metabolic acidosis, and cardiac arrhythmias require ICU monitoring. Patients should remain in the ICU up to 12 h after discontinuation of all

therapeutic interventions, and should be asymptomatic and demonstrate a normal ECG and arterial pH before transfer.[172,173]

γ-Hydroxybutyrate

γ-Hydroxybutyrate (GHB), also known as *liquid ecstasy*, *liquid G*, *date-rape drug*, or *fantasy*, has become a popular drug of abuse among young individuals. In the 1980s, the drug was promoted to bodybuilders as a growth hormone stimulator and muscle-bulking agent. Recreationally, it was claimed to cause euphoria without a hangover and to increase sensuality and disinhibition. In 1990, GHB was banned outside of clinical trials approved by the FDA. However, products such as Revivarant (Philips Pharmatech; Largo, FL) containing a precursor of GHB (γ-butyrolactone) continued to be available until a recent ban by the federal government.[174,175]

GHB is derived from GABA, and is thought to function as an inhibitory transmitter through specific brain receptors for GHB and possibly through GABA receptors.[176] Experimentally, GHB increases stage IV of nonrapid eye movement sleep (slow-wave deep sleep).[177] In controlled clinical trials of narcoleptics, it decreases cataplexy, sleep paralysis, hypnagogic hallucinations, and daytime sleep attacks.[178,179]

Clinical manifestations of GHB depend on the dose ingested. Regular use has been shown to produce tolerance and dependence. Abrupt discontinuation can produce withdrawal delirium and psychosis.[180,181] Low doses of GHB can induce a state of euphoria. Emesis, hypothermia, symptomatic bradycardia, hypotension, and respiratory acidosis on arterial blood gas analysis have all been described.[182] Higher doses can result in deep coma and death.[183]

Treatment of GHB poisoning is mainly supportive. It is important to keep in mind that patients may have co-ingested other drugs of abuse, especially ethanol and amphetamines.[182] Mechanical ventilation may be necessary for a short period of time; most patients regain consciousness spontaneously within 5 h of ingestion.[182] Naloxone is not helpful. Yates and Viera[184] described the use of physostigmine, 2 mg IV, in the emergency department to reverse coma in two patients with GHB overdose. Both patients awoke in < 5 min after the administration of a single dose of physostigmine. The use of physostigmine to reverse coma in GHB overdose is controversial since rapid recovery is the norm and there are risks, particularly when there is co-ingestion of a cyclic antidepressant.[185]

Laboratory diagnosis of GHB ingestion is a challenge. Normal toxicology screens do not include GHB. However, in cases of drug-facilitated sexual assault, it may be important to document GHB ingestion. Specialized laboratories can detect GHB in both urine and blood by gas chromatography-mass spectroscopy.[186,187] GHB can also be detected by hair analysis.[188]

Lithium

Lithium is a monovalent cation used for treatment of bipolar affective disorders. It is rapidly absorbed through the GI tract. There is virtually no protein binding and a small volume of distribution (0.66 to 0.8 L/kg). Lithium is eliminated by glomerular filtration; 80% of excreted lithium undergoes tubular reabsorption; even more is reabsorbed in states of dehydration. The elimination half-life, which is approximately 18 h in healthy adults, is prolonged in the elderly or in patients receiving long-term therapy.[189] Volume depletion and renal insufficiency are common precipitants of lithium overdose. Deliberate acute lithium overdose by ingestion with suicidal intent also commonly occurs.[190] Chronic use can result in nephrogenic diabetes insipidus, renal insufficiency, hypothyroidism, and leukocytosis.

Lithium has a low therapeutic index (target range, 0.5 to 1.25 mEq/L). Most cases of intoxication are associated with levels > 1.5 mEq/L and are due to unintentional overdose during chronic therapy. Serum levels following acute lithium ingestion correlate poorly with intracellular lithium levels and clinical symptoms. A closer correlation exists between serum levels and clinical symptoms in chronic and acute-on-chronic intoxications. Severe toxicity may occur at a lower serum level in chronic lithium ingestion than in acute intoxication. Relatively mild intoxications (levels < 2.5 mEq/L) cause tremor, ataxia, nystagmus, choreoathetosis, photophobia, and lethargy. At higher levels of intoxication (2.5 to 3.5 mEq/L), agitation, fascicular twitching, confusion, nausea, vomiting, diarrhea, and signs of cerebellar dysfunction may predominate. Severe toxicity (> 3.5 mEq/L) is characterized by worsening neurologic dysfunction (seizures, coma), and cardiovascular instability (sinus bradycardia, hypotension). Decreased serum anion gap (< 6 mEq/L) is an interesting consequence of severely elevated lithium levels and may be an important clue to the diagnosis.

With adequate therapy, morbidity and mortality of lithium intoxication remains low.[191] Treatment consists of supportive care including seizure control and use of vasopressors for hypotension refractory to fluids. Gastric lavage is the preferred method of gastric decontamination. Lithium is adsorbed poorly by activated charcoal; therefore, it is not indicated in the absence of co-ingestions. Sodium polystyrene

sulfonate (Kayexalate; Sanofi-Synthelabo; New York, NY) does bind to lithium and may decrease its absorption,[192] but may also cause hypokalemia.[193] Multiple doses of sodium polystyrene sulfonate may result in GI dialysis and further lower serum lithium levels, but this therapy is unproven in human subjects.[194] Whole-bowel irrigation with polyethylene glycol has also been used to successfully decrease absorption of sustained-release lithium in normal volunteers.[195] Enhancement of elimination with saline solution diuresis and forced alkaline diuresis are not very effective and can be dangerous.[196,197]

Lithium is the prototypical dialyzable intoxicant because of its low molecular weight, lack of protein binding, water solubility, low volume of distribution, and prolonged half-life. Indications for hemodialysis include the following: (1) serum levels $>$ 3.5 mEq/L in an acute ingestion; (2) serum levels $>$ 2.5 mEq/L in chronic ingestion, symptomatic patients, or patients with renal insufficiency; and (3) serum levels $<$ 2.5 mEq/L but following a large ingestion, so that rising levels are anticipated.[198] After hemodialysis, drug levels may increase as the drug redistributes requiring repeat dialysis.[199] Four hours of hemodialysis should reduce serum lithium concentrations by approximately 1 mEq/L. Continuous arteriovenous or venovenous hemofiltration/hemodialysis may also be considered.[200,201]

Methemoglobinemia

Methemoglobin is formed by oxidation of circulating hemoglobin. Contrary to reduced (Fe^{2+}) hemoglobin, methemoglobin (Fe^{3+}) is incapable of binding and transporting oxygen. Under normal circumstances, a small amount of methemoglobin is formed by auto-oxidation. Reduced cytochrome b5 reacts with circulating methemoglobin to restore hemoglobin and oxidized cytochrome b5; the RBC enzyme reduced nicotinamide adenine dinucleotide-cytochrome b5 reductase (methemoglobin reductase) regenerates reduced cytochrome b5 and thereby ensures insignificant concentrations of methemoglobin in circulating blood.[202]

Methemoglobinemia arises from a variety of etiologies including hereditary, dietary or drug-induced, and idiopathic.[203] Acquired methemoglobinemia, which can be severe and life threatening, generally occurs in the setting of oxidant drugs or toxin exposure (Table 1).

A 50% concentration of methemoglobin decreases hemoglobin concentration in half. In addition, methemoglobinemia shifts the oxyhemoglobin dissociation curve to the left, thereby interfering with offloading of oxygen in peripheral tissues. In mild methemoglobinemia ($<$ 15% of the total hemoglobin), patients generally remain asymptomatic despite evidence of cyanosis. One possible exception is the patient with critical coronary artery disease who may acquire angina or myocardial infarction in the presence of mild functional anemia. Higher methemoglobin concentrations result in dyspnea, headache, and weakness. Severe methemoglobinemia ($>$ 60%) is associated with confusion, seizures, and death.

Arterial blood gases with co-oximetry are capable of measuring the absorption of four or more wavelengths, enabling it to directly measure levels of oxyhemoglobin, reduced hemoglobin, carboxyhemoglobin, and methemoglobin. Pulse oximetry, however, estimates oxygen saturation by emitting a red light (wavelength of 660 nm) absorbed mainly by reduced hemoglobin and an infrared light (wavelength of 940 nm) absorbed by oxyhemoglobin.[204] Methemoglobin absorbs equally at both wavelengths. At high methemoglobin levels (35%), the oxygen saturation by pulse oximeter tends to regress

Table 1—*Selected Drugs/Toxins Associated With Acquired Methemoglobinemia*

Acetanilid
Amyl nitrite
Butyl nitrite
Bromates
Aniline dyes
Benzocaine
Bupivacaine
Chlorates
Chloroquine
Dapsone
Flutamide
Herbicides
Isobutyl nitrite
Isosorbide dinitrate
Lidocaine
Loxosceles gaucho venom
Methyl nitrite
Metoclopramide
Nitric oxide
Nitroethane
Nitrobenzene
Nitroglycerin
Nitroprusside
Pesticides
Petrol octane booster
Phenacetin
Phenazopyridine
Potassium ferricyanide
Prilocaine
Primaquine
Pyridium Plus (Warner Chilcott, Inc.; Rockaway, NJ)
Silver nitrate
Sodium chloride
Sodium nitrite
Sulfonamides

toward 85% and plateaus at that level despite further increments in methemoglobin levels. Thus, if the actual oxygen saturation by co-oximetry is $> 85\%$, the pulse oximeter would be underestimating it; if it is $< 85\%$ by co-oximetry, it would be overestimating oxygen saturation.[205] Therefore, pulse oximetry may become unreliable in this setting, registering falsely high in patients with severe methemoglobinemia and falsely low with mild methemoglobinemia. In addition, methylene blue can also cause false elevation in methemoglobin levels measured by co-oximetry and pulse oximetry.[206] "Chocolate colored" venous blood that does not change color on exposure to air is another clue to methemoglobinemia.[207]

Treatment of methemoglobinemia involves general supportive measures and removal of the inciting drug or toxin. The preferred mode of gastric decontamination is gastric lavage followed by activated charcoal. Methylene blue, a dye capable of reversing drug/toxin-induced methemoglobinemia by increasing conversion of methemoglobin to hemoglobin, should be considered in symptomatic patients. A dose of 1 to 2 mg/kg (0.1 to 0.2 mL/kg of a 1% solution) IV administered over 5 min generally results in a significant reduction in methemoglobin level within 30 to 60 min. A repeat dose of methylene blue may be administered after 60 min if needed. Additional repeat doses may be required in patients who have received a long-acting oxidant drug such as dapsone; however, excessive doses of methylene blue may paradoxically increase oxidant stress and methemoglobinemia. Contraindications to methylene blue include glucose-6-phosphate dehydrogenase deficiency (where methylene blue may cause hemolytic anemia), renal failure (due to renal excretion of the antidote), and reversal of nitrite-induced methemoglobinemia during treatment of cyanide poisoning. Failure to respond to methylene blue suggests cytochrome b5 reductase deficiency, glucose-6-phosphate dehydrogenase deficiency, or sulfhemoglobinemia. Additional therapies of possible value in severe conditions include exchange transfusion and hyperbaric oxygen.[208]

Opioids

Opioid stimulation of opiate receptors induces a generalized depression of the CNS. The severity of overdose depends on dose, drug type, and patient tolerance. Symptoms range from lethargy to respiratory arrest and coma. Respiratory failure can arise through a number of mechanisms: alveolar hypoventilation, aspiration pneumonitis, and noncardiogenic pulmonary edema (which occurs by unknown mechanisms).[209,210] Noncardiogenic pulmonary edema occurs early in the course of acute overdose and may also be caused by treatment of overdose with naloxone. In a retrospective review of 27 patients presenting to the emergency department with heroin-induced noncardiogenic pulmonary edema, only a third of patients required mechanical ventilation and all patients but one were extubated at 24 h.[211] Inhaled heroin can trigger status asthmaticus.[212,213]

Opioid poisoning can also cause hypotension, bradycardia, decreased gut motility, rhabdomyolysis, muscle flaccidity, hypothermia, and seizures. Seizures are most common with propoxyphene[214] and meperidine. Particularly implicated in lowering the seizure threshold is the meperidine metabolite, normeperidine, which can cause seizures in the therapeutic dosing range,[215] particularly if there is renal insufficiency.[216] Seizures unresponsive to naloxone may be treated with IV diazepam or lorazepam. Ongoing seizures suggest either body packing or body stuffing of heroin, or a secondary process.

Examination during opioid overdose classically reveals small, pinpoint-sized pupils that respond to naloxone administration. Lack of miosis does not rule out opioid poisoning as coexisting toxins or comorbidities such as anoxic brain injury may influence pupil size.

The majority of opioid-related deaths are due to IV heroin, which is seven times more toxic than morphine.[217] Most deaths occur in chronic abusers 20 to 40 years old.[218] Up to a third of fatalities have experienced a nonfatal overdose in the prior year. A minority of deaths (17%) occurs in first-time users.[219] Co-ingestion of other toxic agents is common.[220]

The diagnosis of opioid toxicity and overdose is often made on clinical grounds. Investigators in Los Angeles have proposed that clinical criteria can diagnose opioid toxicity as accurately as response to naloxone in patients with acute alteration of mental status. The combination of Glasgow coma scale score of ≤ 12 with respirations ≤ 12 breaths/min, miotic pupils, or circumstantial evidence of drug use, had a sensitivity of 92% and specificity of 76% for diagnosing opiate overdose.[221] The excellent performance of this clinical criterion may not be reproducible in all cities. Rapid response to naloxone corroborates opioid exposure; however, not every patient who responds to naloxone has an opiate overdose—and not every patient with a heroin overdose responds to naloxone. Naloxone is obviously helpful in opioid overdose, but its indiscriminate use should be discouraged.[222] Opioid exposure is confirmed by urine toxicology screening; however, certain opioids such as fentanyl are not detected by routine urine toxicology screening.[223] Blood toxicology screening is more

sensitive and may confirm opioid intoxication in rare instances when the urine toxicology screen result is false-negative.[224]

Treatment of opioid overdose involves initial supportive measures (ABCs). In cases of oral ingestion, gastric lavage should be attempted after ensuring adequate airway protection. Since opioids decrease gut motility, the usefulness of gastric lavage may extend to several hours postingestion.[18] Activated charcoal should follow gastric lavage. Small-bowel obstruction after activated charcoal has been described.[225] There is no role for forced diuresis, dialysis, or hemoperfusion.

Naloxone, a specific opioid antagonist with no opioid agonist properties, can reverse opioid-induced sedation, hypotension, and respiratory depression. It is administered IV at an initial dose of 0.2 to 0.4 mg. Endotracheal use has also been described.[226] A lower initial dose (0.1 to 0.2 mg) should be administered to patients with opioid dependence to avoid acute withdrawal, or if there are concerns regarding concurrent stimulant overdose. If naloxone does not produce a clinical response after 2 to 3 min, an additional 1 to 2 mg IV may be administered to a total dose of 10 mg. In general, a lack of response to 10 mg of naloxone is required to exclude opioid toxicity, although doses >10 mg may be required to antagonize the effects of propoxyphene, diphenoxylate, methadone, and pentazocine.[227] Opioid antagonism typically occurs within minutes of naloxone administration and lasts for 45 to 90 min. Repeat boluses may be needed every 20 to 60 min to maintain an adequate clinical response. Alternatively, a continuous naloxone infusion may be used (0.4 to 0.8 mg/h). Severe side effects to naloxone are rare, but pulmonary edema and seizures have been reported.[228–230] Noncardiogenic pulmonary edema, which tends to occur in the first few hours after acute overdose, may be difficult to distinguish from aspiration pneumonitis with ARDS[217]; however, improvement is generally more rapid in opioid-induced pulmonary edema. Supplemental oxygen and mechanical ventilation with positive end-expiratory pressure may be required to achieve adequate arterial oxygen saturation.[209] Since central venous pressure is low, diuresis may aggravate hypotension.

Organophosphates and Carbamate Insecticides

Most insecticides used in the United States are organophosphates (also used as warfare nerve agents) or carbamates. The use of these compounds has increased because of their rapid degradability in the environment. Both compounds exert their toxicity through inhibition of acetylcholinesterase. Organophosphates are irreversible inhibitors of acetylcholinesterase; carbamate inhibition of acetylcholinesterase is reversible. The accumulation of acetylcholine at the synapses gives rise to the cholinergic syndrome. Carbamates do not produce CNS toxicity due to poor penetration of the CNS.

Most intoxications occur through the GI tract. However, insecticides can also be absorbed through the skin, conjunctiva, and respiratory tract. Organophosphates are typically lipophilic and rapidly absorbed.[231] In the United States, most exposures are accidental, but in some developing countries, organophosphates are commonly used for suicide.[232] Poisoning has occurred through contaminated food[233]; emergency department personnel have also been inadvertently poisoned through contact with poisoned patients.[234]

Signs and symptoms of acute toxicity occur within the first 12 to 24 h after exposure.[235] Symptoms can be nonspecific, but commonly include weakness, blurred vision, nausea, vomiting, headache, abdominal pain, and dizziness. Signs include miosis (85% of patients), vomiting (58%), salivation (58%), respiratory distress (48%), depressed mental status (42%), and muscle fasciculations (40%).[236] In one large study, tachycardia occurred more often than bradycardia.[237] Other cardiac complications include noncardiogenic pulmonary edema, arrhythmias, and conduction abnormalities. An odor of garlic in the breath or sweat may be noted.

Clinical features of organophosphate poisoning can be secondary to overstimulation of muscarinic, nicotinic, and central receptors. Muscarinic overstimulation tends to be sustained and is characterized by SLUDGE (**S**alivation, **L**acrimation, **U**rination, **D**iarrhea, **GI** cramps, and **E**mesis), blurred vision, miosis, bradycardia, and wheezing. Nicotinic overstimulation is more transient and presents with muscular weakness and fasciculations, which can progress to paresis and paralysis, hypertension, and tachycardia. Organophosphates, as opposed to carbamates, can penetrate the blood brain barrier and overstimulate central receptors inducing anxiety, confusion, seizures, psychosis, and ataxia.

The diagnosis of organophosphate poisoning is aided by measurement of cholinesterase activity in the blood. The two principal cholinesterases are RBC cholinersterase (also called acetylcholinesterase), which is present in RBC and nerve endings, and pseudocholinesterase, which is found primarily in liver and serum. Both are inhibited by organophosphates and carbamates, and although clinical toxicity is due primarily to their action on acetylcholinesterase, pseudocholinesterase is more readily quantified. When measured, acetylcholinesterase is considered

more specific. A falsely low pseudocholinesterase may be seen in patients with liver disease, anemia, or malnutrition. It may also represent a genetic variant (familial succinylcholine sensitivity). Normal levels of enzyme activity do not exclude poisoning because of wide variations in normal levels. In the absence of baseline plasma acetylcholinesterase levels, use of sequential postexposure plasma acetylcholinesterase levels can be helpful in confirming the diagnosis of organophosphate exposure.[238] Typically in severe poisoning, levels are < 20% to 50%. However, the plasma acetylcholinesterase level may not correlate with severity of intoxication.[239] Because of these limitations, the diagnosis of organophosphate and carbamate poisoning remains primarily a clinical one.

During initial patient stabilization, special attention should be paid to the respiratory status. Bronchoconstriction, excess secretions, muscle weakness, and altered mental status increase the risk of respiratory failure. In agricultural exposures, it is extremely important to remove all contaminated clothing and cleanse the hair and skin thoroughly to decrease skin absorption. Health-care workers must take precautions to protect themselves from accidental exposure by wearing protective gloves and gowns.[234] Activated charcoal is indicated to limit further drug absorption. Gastric lavage may be useful if done immediately postingestion.

Symptomatic patients should receive atropine immediately. Treatment should not await results of acetylcholinesterase or pseudocholinesterase levels. Atropine competitively blocks acetylcholine at muscarinic receptors but has no effect on nicotinic receptors. Thus atropine should not increase heart rate significantly. Atropine crosses the blood-brain barrier and can cause CNS toxicity. Effects can be difficult to distinguish from organophosphate poisoning. In this situation, substituting atropine with an anticholinergic that does not cross the blood-brain barrier (such as glycopyrrolate) allows for further anticholinergic administration without CNS effects.[240] The dose of atropine required to achieve atropinization (mydriasis, dry mouth, increased heart rate) varies considerably, depending on the severity of poisoning. Doses of up to 40 mg/d are not uncommon. If atropinization occurs after 1 to 2 mg of atropine, the diagnosis of acetylcholinesterase inhibitor poisoning should be questioned. The initial dose of atropine is 2 mg IV (6 mg IV for life-threatening cases) followed by 2 mg every 15 min until adequate atropinization has occurred.

Pralidoxime reverses muscarinic and nicotinic effects of organophosphate poisoning. In carbamate poisoning, pralidoxime is generally not needed because of rapid resolution of symptoms and the reversible nature of enzyme inhibition. Pralidoxime reactivates phosphorylated cholinesterase enzyme and protects the enzyme from further inhibition. Administration prior to irreversible inactivation of cholinesterase is crucial, preferably within the first 6 h of poisoning. Pralidoxime is still effective in the first 24 to 48 h after exposure, especially when highly lipophilic organophosphates have accumulated in fat and are gradually released. After this critical period of time, restoration of cholinesterase function requires regeneration of the enzyme, a process that may take weeks to complete. The antimuscarinic effects of pralidoxime allow for faster atropinization with lower doses of atropine. The initial dose of pralidoxime is 1 to 2 g IV over approximately 10 to 20 min. Clinical response should be evident in < 30 min. In cases where there is no improvement in muscle fasciculations or weakness, the same dose can be repeated in 1 h. A continuous infusion is then administered at a rate of 200 to 500 mg/h, titrated to achieve the desired effect. Continuous infusion of pralidoxime may be necessary for > 24 h depending on the half-life and lipid solubility of the poison, after which the dose may be gradually reduced and stopped while the patient is observed for signs of recurrent muscle weakness.

Serious complications of organophosphates and carbamates include respiratory failure, ventricular arrhythmias, CNS depression, and seizures. On average, most patients will require 5 to 14 days of intensive care monitoring. Recovery from carbamate poisoning is quicker than recovery from organophosphates. Between 60% and 70% of patients will require mechanical ventilation. Mortality has been reported between 15% to 36%.[241,242]

Phencyclidine

Phencyclidine or "angel dust" has variable anticholinergic, opioid, dopaminergic, CNS-stimulant, and α-adrenergic effects. It can be smoked, snorted, ingested orally, or injected IV. Phencyclidine is frequently combined with other co-ingestants such as ethanol, marijuana, and lysergic acid diethylamide.

McCarron et al[243] evaluated 1,000 patients presenting with acute phencyclidine intoxication. The incidence of violence was 35%, bizarre behavior was noted in 29% of cases, and agitation was seen in 34% of cases. Only 46% of patients were alert and oriented; the others demonstrated alterations in mental status ranging from lethargy to coma. Nystagmus (which may be vertical and horizontal) and hypertension occurred in only 57% of cases. Grand mal seizures, muscle rigidity, dystonic reactions, or

athetosis were rare. Diaphoresis, hypersalivation, bronchospasm, and urinary retention occurred in < 5% of cases. Twenty-eight cases (2.8%) were apneic, and 3 cases (0.3%) presented in cardiac arrest. Hypoglycemia and elevated serum creatine phosphokinase, uric acid, and aspartate aminotransferase/alanine aminotransferase were common. Rhabdomyolysis can complicate phencyclidine intoxication and cause acute renal failure.[244] Hypertensive crisis[245] and intracranial and subarachnoid hemorrhage have been reported.[246,247]

The diagnosis of phencyclidine intoxication should be considered in patients with fluctuating behavior, signs of sympathomimetic overstimulation, and vertical nystagmus. The finding of pinpoint pupils in an agitated patient suggests phencyclidine toxicity. Phencyclidine exposure is confirmed by qualitative urine toxicology screening; drug levels do not correlate with the severity of clinical findings.[243]

Treatment of phencyclidine intoxication starts with initial supportive measures. There is no role for emesis or gastric lavage. Activated charcoal is useful. Although urine acidification and diuretics may enhance drug elimination,[248] they may also exacerbate myoglobinuric renal failure and are therefore not recommended. Because of its large volume of distribution, dialytic therapies are not effective in phencyclidine intoxication.

Violent psychotic behavior may require physical restraints to ensure patient and staff safety. Haloperidol appears to be the drug of choice to treat phencyclidine psychosis.[249] Adding a benzodiazepine (*eg*, lorazepam, 1 mg) to each dose of haloperidol may expedite control of the difficult patient. Other causes of agitation should be considered in patients with phencyclidine overdose who do not seem to respond.

Severe hypertension that does not respond to calming strategies should be treated with nitroprusside or labetolol. β-Blockers alone should be avoided because of the risk of unopposed α activity worsening hypertension and increasing the risk of cerebrovascular accidents.

Salicylates

Salicylates are common ingredients in a variety of prescription and nonprescription preparations. The most common is acetylsalicylic acid or aspirin. Other medications containing salicylates include Soma Compound, (Wallace Lab; Cranbury, NJ) Norgesic (3M Pharmaceuticals; St. Paul, MN), Darvon Compound-65 (Eli Lilly; Indianapolis, IN), Trilisate (Choline magnesium trisalicylate; Purdue Frederick; Norwalk, CT), Percodan (Endo Pharmaceuticals; Chadds Ford, PA), and Pepto-Bismol (bismuth subsalicylate; Proctor and Gamble Pharmaceuticals; Cincinnati, OH). Ingestion of topical products containing salicylates such as Ben-Gay (Pfizer; New York, NY), salicylic acid (keratolytic), and oil of wintergreen or methyl salicylate (one teaspoon contains 7,000 mg of salicylate) can cause salicylate toxicity.[250,251]

The incidence of salicylate poisoning has been declining in the pediatric population because of reliance on alternative analgesics and the use of child-resistant containers. Improvements in packaging and package size restrictions have reduced the likelihood of severe intentional poisonings in adults.[252,253]

Once ingested, acetylsalicylic acid or aspirin is rapidly converted to salicylic acid, its active moiety. Salicylic acid is readily absorbed from the stomach and small bowel. At therapeutic doses, salicylic acid is metabolized by the liver and eliminated in 2 to 3 h. Therapeutic serum levels are 10 to 30 mg/dL. Chronic ingestion can increase the half-life to > 20 h.[254]

Clinical features of aspirin intoxication occur in most people with serum levels > 40 mg/dL; in chronic intoxication, severe poisoning occurs at lower serum levels (particularly in elderly patients). At toxic levels, salicylates are metabolic poisons that affect a multitude of organ systems by uncoupling oxidative phosphorylation and interfering with the Krebs cycle.[255]

Minor intoxication causes tinnitus, vertigo, nausea, vomiting, and diarrhea. Significant ingestions in adults result in respiratory alkalosis or a mixed metabolic acidosis and respiratory alkalosis (unless co-ingestion of a CNS depressant causes respiratory acidosis).[256,257] Respiratory alkalosis occurs through direct central stimulation. Uncoupling of oxidative phosphorylation leads to accumulation of organic acids (including lactic acid and ketoacids) and a metabolic acidosis with an elevated anion gap. Salicylic acid itself contributes only minimally to the measured anion gap (3 mEq/L with a 50 mg/dL level).

Other effects include noncardiogenic pulmonary edema, mental status changes, seizures, coma, GI bleeding, liver and renal failure, hypoglycemia (including low cerebrospinal fluid glucose), and death.[258] Thisted et al[259] described the clinical findings in 177 consecutive admissions to an ICU with acute salicylate poisoning. Neurologic abnormalities occurred in 61% of patients, acid-base disturbances in 50%, pulmonary complications in 43%, coagulation disorders in 38%, fever in 20%, and circulatory disorders such as hypotension in 14%. In a 2-year

review of salicylate deaths in Ontario, 31.4% of the patients were dead on arrival.[260] ICU mortality of severe salicylate poisoning has been reported to be 15%.[259]

The lethal adult dose is approximately 10 to 30 g or 150 mg/kg (≥ 35 tablets). Lethality correlates poorly with serum levels. A critical review of the commonly used Done nomogram[254] has revealed that is of no value in the assessment of acute or chronic salicylism.[261] Its use may be misleading when there is an incorrect time of ingestion, ingestion of more than a single dose, use of enteric-coated preparations,[262] or long-term use of salicylates. Elderly patients are particularly at risk for unintentional poisoning; a high index of suspicion is thus required to avoid delays in diagnosis that may contribute to higher mortality.[263] Patients with chronic intoxication commonly present with CNS injury,[264] noncardiogenic pulmonary edema,[265] or isolated elevation of the prothrombin time.

Optimal management of a salicylate poisoning depends on whether the exposure is acute or chronic. Gastric lavage and activated charcoal (1 g/kg) are useful for acute ingestions but not in cases of chronic salicylism. The use of multidose activated charcoal to enhance elimination is controversial.[266] Empiric administration of dextrose helps avoid low cerebrospinal fluid glucose levels.

Administration of bicarbonate to raise plasma pH to between 7.45 and 7.5 induces urinary alkalinization, which in turn increases renal clearance. Raising urinary pH from 6.1 to 8.1 results in an > 18-fold increase in renal clearance by preventing nonionic tubular back-diffusion.[267] This decreases the half-life of salicylates from 20 to 24 h to < 8 h. Care must be taken to avoid hypokalemia, which prevents excretion of alkaline urine by promoting distal tubular potassium reabsorption in exchange for hydrogen ion. Urinary alkalinization must be used with caution in the presence of alkalemia due to salicylate-induced hyperventilation. Forced diuresis does not appear to increase the efficacy of urinary alkalinization and may precipitate volume overload. Repetitive determination of serum salicylate levels should be obtained to confirm a declining level.

Salicylates can be removed by hemodialysis. Indications for hemodialysis include a serum level > 120 mg/dL acutely, or > 100 mg/dL 6 h postingestion, refractory acidosis, coma or seizures, noncardiogenic pulmonary edema, volume overload, and renal failure.[268] In chronic overdose, hemodialysis may be necessary for a symptomatic patient with a serum salicylate level > 60 mg/dL.

SSRIs (Serotonin Syndrome)

With the increased use of SSRIs, psychiatrists, emergency department physicians, and intensivists should expect to see increasing numbers of patients with serotonin syndrome.[269] The increased use of these medications reflects their relatively nontoxic drug profile compared to other antidepressants (such as the tricyclics and monoamine oxidase inhibitors).[270] The list of SSRIs and noncyclic serotoninergic antidepressants has been growing rapidly in the last decade: sertraline, paroxetine, fluoxetine, fluvoxamine, citalopram, trazodone, nefazodone, and venlafaxine. Although SSRIs and selective monoamine oxidase (MAO) inhibitor antidepressants are relatively nontoxic when taken alone, combinations of MAO inhibitors or tryptophan and either SSRIs or tricyclic antidepressants with serotomimetic effects may result in serotonin syndrome and death.[271] Thus, in general, SSRI antidepressants should not be combined with MAO inhibitor antidepressants or other agents that have serotomimetic effects.[272,273] Other serotomimetic agents associated with this syndrome include 3,4-methylenedioxy-methamphetamine, dextromethorphan, and meperidine.[274] The presumed pathophysiologic mechanism involves brainstem and spinal cord activation of the 1A form of serotonin (5-hydroxytryptamine) receptor.

Because of the long half-life of some of these drugs, toxic combination therapy may not be apparent for days to weeks. Many of the newer antidepressants are associated with a risk for clinically significant drug interactions, in part due to cytochrome P450 inhibition.[275,276]

Clinical manifestations can be mild, moderate, or severe.[277] The most frequent features are changes in mental status, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, flushing, fever, nausea, and diarrhea. In severe cases, disseminated intravascular coagulation, convulsions, coma, muscle rigidity, myoclonus, autonomic instability, orthostatic hypotension, and rhabdomyolysis can occur.[272] Other findings include hyponatremia and syndrome of inappropriate antidiuretic hormone secretion.[278,279] Fortunately, recovery is usually seen within 1 day and death is rare.

The diagnosis of serotonin syndrome should be considered in any patient with compatible clinical features, particularly if there is a history of depression and use of serotonergic drugs. Additionally, it is important to consider serotonin syndrome in any agitated patient presenting to the emergency department.[280] Blood and urine assays are currently not readily available and are not included in routine toxicology screening panels.

Treatment of serotonin syndrome starts with dis-

continuation of the suspected serotonergic agent and institution of supportive measures. The ABCs of basic life support should be addressed sequentially. Gastric lavage should be considered in patients with early acute ingestion (within 1 h). Activated charcoal should be administered. Dialysis and hemoperfusion are not effective. Further data are needed to address the safety and efficacy of serotonin antagonists such as methysergide and cyproheptadine.[281] There are anecdotal reports of success with these agents.[282] Chlorpromazine, diphenhydramine, and benzodiazepines have also been used in the treatment of this condition.[283,284]

Theophylline

Theophylline is a dimethylxanthine bronchodilator used in the management of patients with obstructive lung disease. Despite declining use, it remains an important cause of intoxication with significant morbidity and mortality.[285] The reasons for toxicity include the following: narrow and low therapeutic index, patient and physician dosing errors, and conditions that decrease drug clearance (*ie*, drug interactions, smoking cessation, and the development of congestive heart failure or hepatic dysfunction).[286] Mild toxicity can occur within the therapeutic range. Significant toxicity generally occurs with plasma levels > 25 mg/L. Intoxication may result from either an acute ingestion or chronic use. For the same plasma level, chronic intoxication causes more severe clinical sequelae due to larger total body stores of drug.[285,287,288]

Clinical features of theophylline toxicity are classified into neurologic, cardiovascular, and metabolic categories.[289] Seizures can occur in chronic intoxications at serum levels of 35 to 70 mg/L; in acute intoxication, seizures are less likely unless serum levels exceed 80 to 100 mg/L.[285,290] Uncontrolled seizures may occur and lead to hyperthermia and rhabdomyolysis. Tachyarrhythmias (both supraventricular and ventricular) can occur at theophylline levels of 20 to 30 mg/L. However, at these serum levels, the need for antiarrhythmic therapy is uncommon.[291] Cardiovascular collapse can occur at levels > 50 mg/L. Metabolic abnormalities are common and include hypokalemia, hypomagnesemia, hyperglycemia, hypophosphatemia, hypercalcemia, and respiratory alkalosis.[292]

The preferred mode of gastric decontamination is gastric lavage followed by activated charcoal for ingestions > 50 mg/kg. Gastric lavage may be useful for several hours after ingestion of sustained-release preparations. Because of high risk of seizure, emesis is contraindicated. Since theophylline undergoes significant enterohepatic circulation, multidose activated charcoal (without sorbitol) can enhance elimination.[73] Theophylline levels should be monitored every 2 to 3 h to ensure decreasing values.

Seizures should be treated with benzodiazepines. Refractory seizures are an indication for phenobarbital. Phenytoin can worsen theophylline-induced seizures and should be avoided.[290,293,294] Supraventricular tachyarrhythmias are best controlled by β_1-cardioselective β-blockers (metoprolol, esmolol). β-Blockers must be used with extreme caution in patients with obstructive airways disease and should not be used if active bronchospasm is present. Hypotension secondary to β_2-adrenergic stimulation should be treated with fluids and phenylephrine. Nonselective β-blockers such as propranolol or esmolol have been used to treat cases of refractory hypotension.[295–297] Lidocaine and other standard agents are suitable for ventricular arrhythmias. CCBs may be useful in the management of sustained supraventricular tachycardias.[298–300] Aggressive electrolyte repletion may be required, but consider that low serum potassium levels may be secondary to intracellular shift, not total body potassium deficit. Nausea may be refractory to agents other than ondansetron.[301,302]

Patients presenting with life-threatening conditions such as refractory seizures, hypotension, or unstable arrhythmias are candidates for extracorporeal drug removal. Other indications for extracorporeal drug removal are the following: a plasma level > 100 mg/L 2 h after an acute ingestion (after initial charcoal therapy), a plasma level > 50 mg/L in chronic ingestion, and a 2-h level > 35 mg/L associated with clinical instability or high risk of adverse outcome and/or prolonged intoxication. High-risk characteristics include the following: chronic intoxication, intolerance of oral charcoal or intractable emesis, impaired theophylline metabolism (congestive heart failure, cirrhosis, severe hypoxemia), increased susceptibility to cardiovascular toxicity and seizures, or respiratory failure. Charcoal hemoperfusion is the extracorporeal removal procedure of choice. It is twice as effective as dialysis, which remains an acceptable alternative.[303] Sequential and simultaneous "in-series" hemodialysis and hemoperfusion has also been described.[304,305] Other techniques such as plasmapheresis and exchange transfusion have been successfully used in pediatric and neonatal patients.

Addendum

Since the submission of this manuscript, a large, double-bind, randomized, controlled trial of hyperbaric oxygen treatment vs normobaric oxygen treatment in carbon monoxide poisoning has been published. Weaver et al[306] demonstrated that three hyper-

baric oxygen treatment sessions (2 to 3 atmospheres at intervals of 6 to 12 h) within a 24-h period of exposure significantly reduced DNS both at 6 weeks and 12 months.

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