CHAPTER 66: TOXICOLOGY

ANDREW STOLBACH • LEWIS R. GOLDFRANK

HISTORY

Poisonings are recognized in the earliest recorded history. The word *toxicology* is derived from the Greek terms *toxikos* ("poison") and *toxikon* ("arrow into which arrowheads are dipped") (1, 2). In the 16th century, scientist Paracelsus made the astute observation that still holds strong: "What is there that is not poison? All things are poison and nothing [is] without poison. Solely, the dose determines that a thing is not a poison" (3). Today, we share Paracelsus’ appreciation of the dose-response relationship. One need not look further than basic elements such as oxygen or water to see that all substances can act as a poison at a specified dose. In modern medicine, the unique challenges posed by poisoned patients were recognized with the opening of the first poison control center in Chicago in 1953 (4); today, all 50 states are served by poison control centers. Medical toxicology, the care of poisoned patients, was first described in 1953 (5). Schultman AS, Williams KE, Caudrick JA. Does the addition of glutamine to enteral feeds affect patient mortality? Crit Care Med. 2003;31:2530–2536.

Throughout this chapter, any substance introduced to the body will be referred to as a xenobiotic. The terms *drug* and *pharmacological* identify the subgroup of xenobiotics that are commercially produced, while a toxicon is a xenobiotic produced by a biologic system, such as plant, animal, or fungi. An exposure occurs whenever a human comes into contact with a xenobiotic. Exposures may be dermal, oral, ophthalmic, or inhalational. Poisoning, intoxication, and toxicity characterize the harmful consequences of a xenobiotic exposure. Consistent use of these definitions should enhance the clarity of our discussion.

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Though identification of a toxic syndrome will not specify, the practice of “speedballing” (concurrent heroin and cocaine) the typical symptoms of a particular syndrome. For existing disease processes, patients do not always demonstrateBecause of coexisting assumption of other poisons or coexisting disease processes, patients do not always demonstrate the typical symptoms of a particular syndrome. For example, the practice of “speedballing” (concurrent heroin and cocaine abuse) might result in small, normal, or large pupils. Though identification of a toxic syndrome will not specifically identify the exact poison responsible, it will somewhat guide therapy. For instance, the presence of a sedative-hypnotic toxic syndrome (overdose) warrants support of the airway, whether the condition is a result of ethanol or diazepam abuse.

Electrocardiogram (ECG) should be obtained in most cases of suspected poisoning. In fact, several well-defined exposures (such as tetracycline antibiotics) will be identified based on a characteristic ECG. Xenobiotics such as cocaine or lidocaine can produce life-threatening dysrhythmias via direct myocardial effect. Xenobiotics can also produce dysrhythmias by causing an electrolyte abnormality. Exposure to hydrofluoric acid, even dermally, can result in hypocalcemia, resulting in QTC prolongation and torsades de pointes.

While most poisoned patients can be managed appropriately by physical examination and judicious use of laboratory studies alone, history should attempt to identify the specific xenobiotic exposure, the amount, the time and reason for exposure, and general medical history. At times, a specific antidote may be warranted based on the history (see Appendix).

A thoughtful use of laboratory studies is important in the management of poisoned patients. Electrolyte abnormalities complicate many severe poisonings. Therefore, serum chemistries are warranted for all critically ill patients. Blood gases and amino transferases should be judiciously used as well.

In contrast with the fundamental information provided in blood samples, a routine urine toxicologic screen rarely aids in management and is therefore not recommended. A urine toxicologic screen generally focuses on select drugs of abuse and omits the vast majority of potential toxins. Moreover, the analyses included in the commonly used qualitative urine screen may be too many false positives or false negatives. For example, fentanyl, a synthetic opioid, will not produce a positive result on an opiate screen, while dextromethorphan may yield a positive result for phencyclidine. Even a true positive result on an opiate screen, while dextromethorphan may yield a positive result for phencyclidine. Even a true positive result on an opiate screen, while

**TABLE 66.1**

<table>
<thead>
<tr>
<th>TOXIDROMES</th>
<th>Group</th>
<th>BP</th>
<th>P</th>
<th>R</th>
<th>T</th>
<th>Mental status</th>
<th>Pupil size</th>
<th>Peristalsis</th>
<th>Diaphoresis</th>
<th>Primary treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic</td>
<td>↓↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Delirium</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Benzo diazepines</td>
<td></td>
</tr>
<tr>
<td>Cholinergic</td>
<td>↓↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Normal/depressed</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Antipin, oximes</td>
<td></td>
</tr>
<tr>
<td>Ethanol, sedative-hypnotic</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Depressed</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Airway support</td>
<td></td>
</tr>
<tr>
<td>Opioid</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Depressed</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Naloxone</td>
<td></td>
</tr>
<tr>
<td>Withdrawal from opioids</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Agitated, disoriented</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Benzodiazepines</td>
<td></td>
</tr>
<tr>
<td>Withdrawal from ethanol or sedative-hypnotic</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Normal, anxious</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Opioids</td>
<td></td>
</tr>
</tbody>
</table>

BP: blood pressure; P, pulse; R, respiration; T, temperature.

In contrast to “shotgun” urine toxicologic screening, the acetaminophen concentration should be obtained following all overdoses where self-harm was intended. In one series, 1 in 365 individuals with suicidal ingestion and a history negative for acetaminophen ingestion had a potentially hepatotoxic acetaminophen concentration (7).

DETERMINING THE NEED FOR INTENSIVE CARE UNIT ADMISSION

Criteria that are traditionally used to determine whether patients need critical care do not necessarily apply to poisoned patients. For most patients, disposition is determined by how “sick” the patient is. In contrast, patients poisoned by dangerous xenobiotics but who appear well may require precautionary ICU admission and monitoring.

The factors that influence the need for critical care can be divided into three general categories: (a) patient characteristics, (b) xenobiotic characteristics, and (c) hospital unit capabilities (8).

All unstable poisoned patients require ICU care. Patients with significant laboratory abnormalities, unresponsiveness, inability to protect the airways, hypotension, dysrhythmias, or conduct abnormalities should be admitted to the ICU. Pre-existing medical conditions such as severe liver or renal insufficiency, congestive heart failure, or pregnancy may also influence disposition.

The disposition for minimally symptomatic patients is often determined by the xenobiotic involved rather than the clinical status of the patient. The most important considerations are the potential for deterioration or the requirement for a therapeutic agent with potentially adverse effects. Sustained-release products, potentially lethal doses, or xenobiotics that may cause dysrhythmias have the potential to cause rapid clinical deterioration. For this reason, asymptomatic patients with exposure to calcium channel blockers or sulfonylureas are often admitted to an ICU. Pre-existing medical conditions such as severe liver or renal insufficiency, congestive heart failure, or pregnancy may also influence disposition.

The single dose of acetaminophen generally thought to be required to produce toxicity is ≥150 mg/kg (11). In overdose, absorption of acetaminophen may be delayed, although peak absorption generally occurs at 2 hours, and rarely after 4 hours (12,13). Absorption may be expected to be further delayed in the presence of peristaltus-decreasing opioid or anticholinergic congestants, or if the acetaminophen is formulated for extended release. In overdose, metabolism by sulfation becomes saturated, and the formation of NAPQI exceeds that which can be detoxified by available glutathione (14). Because the toxic metabolite is formed in the liver, hepatic toxicity is the key clinical feature. N-acetyl-p-benzoquinoneminine (NAPQI), a toxic oxidant (11). Thiosulfating compounds, such as reduced glutathione, are used as electron donors to detoxify NAPQI.

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Clinical Manifestations

Acute acetaminophen toxicity has been divided into four clinical stages (16). Not every untreated patient will advance through each of these stages. Spontaneous improvement is possible at any point, but the stages of toxicity serve as a useful guide to the progression of symptoms. During stage I, the patient is either asymptomatic or has nonspecific clinical findings (nausea, vomiting, malaise), and no laboratory abnormalities are recognized. Stage II begins with the onset of liver injury, generally within 24 hours but always within 36 hours of ingestion (17). Symptoms are similar to other causes of hepatitis.
Initial laboratory findings include elevated aminotransferases (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]), but progress to signs of hepatic dysfunction, including prolonged prothrombin time (PT), metabolic acidosis, and hypoglycemia. Stage III represents the time of peak hepatotoxicity, usually 72 to 96 hours from ingestion. While AST and ALT may ultimately exceed 10,000 IU/L, creatinine, lactate, phosphate, and PT are better indicators of prognosis. Fatalities usually occur within 3 to 5 days of ingestion. When death does not occur, hepatic recovery is referred to as stage IV. Hepatic regeneration will be histologically and functionally complete in survivors.

Management

N-acetylcysteine is the key to managing acetaminophen poisoning. Because of its proven efficacy, decontamination with activated charcoal should only be considered if significant coingestants are expected. NAC is available for both oral and intravenous administration. The oral protocol for acute ingestions is a 140 mg/kg loading dose, followed by 17 doses of 70 mg/kg every 4 hours for a total of 72 hours. The intravenous regimen is 130 mg/kg over 45 minutes, followed by 30 mg/kg every 4 hours, and then 100 mg/kg over 16 hours. Both regimens have equal efficacy for simple acute ingestion, but the intravenous regimen has the advantage of a shorter course, and is the only route that has been studied adequately in patients with hepatic failure. Unlike oral NAC, parenteral NAC carries the risk of anaphylactoid reactions. The duration and route of treatment are determined by the type of presentation.

The simple, acute ingestion occurs when a single dose of acetaminophen is ingested over a short period of time, within 24 hours of presentation. There is little controversy in managing this type of ingestion. The serum acetaminophen concentration should be plotted against the number of hours following ingestion on the Rumack-Matthew nomogram to determine whether treatment with NAC is necessary [18]. The treatment line is a sensitive, but not specific, predictor of hepatotoxicity. The currently recommended line intersects 150 µg/mL at 4 hours, incorporating a 25% safety margin over the original nomogram line, which was itself nearly 100% sensitive for predicting hepatotoxicity. When the concentration at a specific time is plotted above the line, treatment is required. When treatment is initiated within 8 hours of ingestion, NAC has complete efficacy in preventing hepatotoxicity [19]. NAC should be started immediately in any patient with suspected acetaminophen poisoning when the laboratory result for the acetaminophen concentration is not expected to be available within 8 hours of the initial ingestion. Once the serum acetaminophen concentration is available, the decision whether to continue the NAC can be made based on the nomogram (Fig. 66.1). When there is uncertainty with regard to the exact time of ingestion, the physician should use the most conservative estimate (i.e., the earliest possible time) when using the nomogram. The risk of inadvertently failing to treat because of an incorrect history is mitigated by the safety margin associated with the nomogram.

The literature is less clear on the indications for the use of NAC for hepatotoxicity following suspected chronic acetaminophen use. The vast majority of people who take acetaminophen have no adverse clinical manifestations. Clinical trials involving daily dosing of 4 g of acetaminophen in both alcoholics and nonalcoholics showed that patients either have normal aminotransferase concentrations or very minor increases [20,21]. Despite its safety, hepatotoxicity from chronic use occurs. Because chronic acetaminophen use often occurs in the setting of comorbid conditions, the diagnosis can be difficult to establish with certainty. NAC should be administered to all patients with suspected acetaminophen hepatotoxicity until the diagnosis has been excluded.

The nomogram cannot be used for patients who present more than 24 hours after ingestion. In such cases, NAC should be started immediately upon presentation. If the patient has both an undetectable acetaminophen concentration and normal aminotransferases, acetaminophen overdose is highly unlikely, and NAC need not be continued. If either acetaminophen or aminotransferase concentrations are elevated (even minimally so), the patient should be administered 20 hours of IV NAC. Following the treatment period, intravenous and acetaminophen concentrations should be obtained again. At this point, if the aminotransferase concentrations are only minimally elevated, the patient was either minimally poisoned or acetaminophen was not the cause of the liver damage. When acetaminophen-induced hepatotoxicity is encountered, intravenous NAC should be administered as described above, but the maintenance dose should be continued until clinical improvement, liver transplantation, or death occur. Even in the presence of fulminating hepatic failure, IV NAC has been shown to decrease mortality, cerebral edema, and the need for vasopressors [22].

Hepatic Transplantation

Generally, patients with significant acetaminophen poisoning will have AST and ALT concentrations >1,000 IU/L by 24 to 48 hours after ingestion. The decision to perform hepatic
transplantation is particularly difficult in these patients, be-
cause those who survive without a transplant will make a com-
plete recovery, while the long-term complications of a trans-
plant are significant. Under ideal conditions, the clinician could
determine immediately which patients would survive without a trasnplant and which would not, so that the appropriate pa-
tients could be listed for a liver transplant and the procedure
could be performed before irreversible clinical deterioration.
In practice, it is not always clear. Several prognostic criteria are
available. The King’s College Hospital Criteria suggest that
pH < 7.3 after resuscitation or the combination of PT > 100,
creatinine > 3.3 mg/dL, and grade III or IV encephalopathy are
predictive of death in the absence of a transplant (23). Serum
phosphate has also been shown to be a good predictor. A 48-
hour serum phosphate concentration > 1.2 mmol/L has been
shown to be sensitive and specific for predicting the need for
transplant and the probability of death from acetaminophen
hepatotoxicity (24). Presumably, a low or normal phosphate
concentration is evidence that the phosphate is being utilized
by hepatocytes for adenosine triphosphate (ATP) generation.

**MANAGEMENT OF SALICYLATE POISONING**

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Salicylates and Other Nonsteroidal
Anti-Inflammatory Drugs

The nonsteroidal anti-inflammatory drugs (NSAIDs) are widely
available both with and without prescription for relief of in-
flammation, pain, and fever. Salicylates are a subgroup of
NSAIDs that have unique features of toxicity and require dis-
tinct management. In this chapter, we will use the term NSAID
in reference to the nonsalicylate NSAIDs. ICU admission is
required when patients present with metabolic acidosis and
hemodynamic instability, or if they require bicarbonate infu-
sion or frequent measurements of salicylate concentration.

The therapeutic effects of salicylates and NSAIDs result from
the inhibition of cyclooxygenase (COX), a mediator of prosta-
glandin synthesis. The myriad medications in this class preclude discussion of the individual pharmacokinetic char-
acteristics. In general, they are renally eliminated. Because
they are designed to promote fast relief, therapeutic doses of
the immediate-release drugs produce significant concentrations
within an hour. However, when taken in overdose or as enteric-
coated or sustained-release formulations, absorption may be
greatly delayed, and maximal serum concentrations may not
be observed for hours after the ingestion.

In addition to these effects, salicylates also uncouple oxida-
tive phosphorylation, meaning that some of the proton gradient
across the mitochondrial matrix is dissipated in the formation
of heat, rather than ATP, forcing the production of lactate.

Clinical Manifestations of
Salicylate Poisoning

Acute salicylate poisoning may cause epigastric pain, nausea,
and vomiting. Salicylates induce hyperventilation (both tachyp-
nea and hyperpnea) by direct stimulation of the brainstem respi-
atory center (25). Neurologic signs and symptoms of sal-
icylate poisoning range from mild to severe, and include tinni-
tus, delirium, coma, and seizure. The initial feature of toxicity
is primary respiratory alkalosis. A primary metabolic acidosis
is characterized by the presence of lactic acid, ketoads, and
salicylic acids (26). The net result is an increased anion gap
metabolic acidosis. The simultaneous presence of a respiratory
alkalosis and metabolic acidosis can be difficult to interpret. Be-
cause the respiratory alkalosis initially predominates in adults,
the presence of an acidaemia or even normal pH indicates ad-
vanced poisoning.

Chronic salicylate poisoning presents with the same signs and
symptoms as acute poisoning, but typically occurs in el-
derly patients taking supertherapeutic amounts of salicylate to
treat a chronic condition. Chronic poisoning can be a chal-
lengeing diagnosis to establish because it is often not suspected.
Elderly salicylate-poisoned patients presenting with metabolic
acidosis and an altered sensorium may be initially miseduc-
nosed with sepsis, dehydratation, or cerebrovascular accident
(CVA) if a salicylate concentration is not obtained.

Serum salicylate concentrations only correlate loosely with
toxicity because the principal site of poisoning is the central
nervous system. The threshold for toxicity is usually consid-
ered to be 30 mg/dL when tumitus develops. Chronically poi-
noned patients have a lower salicylate concentration for the
same degree of illness because much of their total body burden
has redistributed into the central nervous system. The degree of
poisoning is determined by evaluating the serum concentration
in the context of the patient’s clinical appearance, laboratory
results, and acuity of the ingestion.
hyperpnea of salicylate poisoning does not necessarily represent “tiring,” and produces a helpful alkalosis. When intubation is unavoidable, patients should be administered 1 to 2 mEq/kg of bicarbonate prior to the procedure, intubated quickly, and hyperventilated afterward to avoid respiratory acidosis.

Early consultation with a nephrologist is recommended for seriously ill patients. Extracorporeal elimination is reserved for patients who are very ill, those who cannot tolerate alkalinization, or those with serum concentrations so elevated that their clinical status is expected to deteriorate. We recommend hemodialysis for severe acid-base disturbances, mental status changes, inability to tolerate alkalinization (renal failure or congestive heart failure), and serum concentrations of 100 mg/dL after acute poisoning and 60 mg/dL in chronic poisoning (Table 66.2).

**Clinical Manifestations of Overdose**

NSAIDs are considered safer than salicylates in therapeutic dosing. An acute overdose of NSAIDs can cause gastric injury. While chronic NSAID use is associated with interstitial nephritis, nephrotic syndrome, or anagistic nephropathy, acute overdose is sometimes accompanied by a reversible azotemia caused by vasoconstriction from decreased prostaglandin production (30). In severe overdose, the most consequential effects are elevated anion gap metabolic acidosis, coma, and hypotension (31).

**Management of Nonsteroidal Anti-inflammatory Drug Poisoning**

Activated charcoal should be administered if the patient presents within several hours of overdose. Good supportive care is the mainstay of therapy after NSAID overdose. NSAID elimination is not increased with alkalinization, and NSAIDs’ high degree of protein binding precludes removal with hemodialysis. Hemodialysis has been used to correct acidemia and electrolyte abnormalities in patients with multigorgan system failure.

**TABLE 66.2**

<table>
<thead>
<tr>
<th>INDICATIONS FOR HEMODIALYSIS IN SALICYLATE POISONING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Congestive heart failure (relative)</td>
</tr>
<tr>
<td>Acute lung injury</td>
</tr>
<tr>
<td>Persistent CNS disturbances</td>
</tr>
<tr>
<td>Progressive deterioration in vital signs</td>
</tr>
<tr>
<td>Severe acid-base or electrolyte imbalance, despite</td>
</tr>
<tr>
<td>appropriate treatment</td>
</tr>
<tr>
<td>Hepatic compromise with coagulopathy</td>
</tr>
<tr>
<td>Salicylate concentration (acute) &gt; 100 mg/dL or (chronic) &gt; 60 mg/dL</td>
</tr>
</tbody>
</table>

CNS, central nervous system.


**PSYCHIATRIC MEDICATIONS**

Psychiatric medications represent a disproportionate number of poisonings in the United States. Antidepressants, antipsychotics, and sedative-hypnotics accounted for more than half of all deaths reported to poison control centers in 2005 (6). This high mortality figure is a function of the prevalence of these ingestions, as these drugs do not have a high case-fatality rate. With sound supportive care, most patients can be managed successfully.

**Antipsychotic Medications**

The antipsychotics are categorized as either typical or atypical. The typical antipsychotics, which include haloperidol, chlorpromazine, and thioridazine, antagonize dopamine primarily at the D2 receptor. The newer medications, the atypical drugs, are exemplified by clozapine, olanzapine, quetiapine, risperidone, and ziprasidone, which have less dopaminergic antagonism and more serotoninergic effects than the typical antipsychotics. When antipsychotic medications produce coma, conduction abnormalities, or hyperthermia, these patients require ICU admission.

**Clinical Manifestations of Overdose**

The antipsychotics are a diverse group of medications, although useful generalizations can be made about their clinical manifestations. All produce sedation in overdose, though respiratory depression is usually not consequential. The drugs have varying degrees of muscarinic and α-adrenergic antagonism, often resulting in tachycardia and moderate hypotension (32). Many of the typical antipsychotics have type IA antidysrhythmic properties. Most of the typical and a few of the atypical drugs (notably ziprasidone) can cause QTc prolongation and torsades de pointes (33,34). Management of overdose of the antipsychotics generally only requires supportive care.

**Clinical Manifestations of the Neuroleptic Malignant Syndrome**

The dopamine antagonism required for control of psychosis can cause a group of distinct movement disorders that range in severity from mild to life threatening. These conditions—dystonia, akathisia, parkinsonism, tardive dyskinesia, and neuroleptic malignant syndrome (NMS)—are more likely to occur in the presence of the typical antipsychotics, although the atypical antipsychotics can cause them as well. The first four conditions mentioned above are of less concern to the intensivist than NMS, and will not be discussed. NMS is the most consequential of the movement disorders associated with the antipsychotics. The syndrome is characterized by the presence of altered mental status, muscular rigidity, hyperthermia, and autonomic dysfunction (35). While symptoms usually begin within weeks of starting treatment, they do occur in individuals that are taking the drug on a chronic basis. Risk factors include young age, male gender, extracellular fluid volume contraction, use of high-potency antipsychotics, depot...
drug preparations, concomitant lithium use, rapid increase in dose, or simultaneous use of multiple drugs (34). Diagnosis is not always clear because there is no reference standard. The differential diagnosis of hyperthermia and altered mental status is very broad. Other diagnoses to consider include infection, environmental hyperthermia, hyperthermia, serotonin syndrome, ethanol and sedative-hypnotic withdrawal, sympathomimetic intoxication, and anticholinergic intoxication.

Management of NMS begins with immediate treatment of life-threatening hyperthermia. Ice-water immersion and paralysis by neuromuscular blockade should not be delayed if temperature is > 106°F (41.1°C). In instances of environmental hyperthermia, a delay of cooling longer than 30 minutes has been associated with significant morbidity and mortality (36). Benzodiazepines should be titrated to sedation and muscle relaxation. When present, rhabdomyolysis, electrolyte disorders, and hypotension should be aggressively treated.

Bromocriptine, a centrally acting dopamine agonist given at 2.5 to 10 mg three to four times a day, may be of theoretical benefit even though it is not well studied. NMS may not be controlled for days after the introduction of bromocriptine. After signs and symptoms begin to improve, bromocriptine should be decreased by no more than 10% a day since decreasing the dose too rapidly may precipitate a relapse of NMS.

There is no evidence for the antidotal use of dantrolene in the management of NMS. Dantrolene is the drug of choice in malignant hyperthermia, a disorder affecting the sarcoplasmic reticulum that occurs in susceptible individuals receiving inhalational anesthetics or succinylcholine that some confuse with neuroleptic malignant syndrome because of their similar pharmacologic properties. All these effects result from increasing the frequency of opening of γ-aminobutyric acid (GABA)-mediated chloride channels in the central nervous system (CNS) (37). In overdose, these drugs produce somnolence, coma, and minimal decreases in blood pressure, heart rate, and respiratory rate.

Management of benzodiazepine overdose is supportive. Care of the comatose patient should focus on supporting the airway and blood pressure while waiting for the drug to be eliminated. There is a limited role for flumazenil, a competitive benzodiazepine antagonist; flumazenil can precipitate withdrawal in individuals who are tolerant to benzodiazepines and induce seizures in those with seizure disorders (38,39). Flumazenil may be indicated in patients without tolerance to benzodiazepines who suffer from a pure benzodiazepine overdose. Benzodiazepine overdoses in children may meet these criteria. When indicated, flumazenil should be given intravenously, 0.1 mg/minute, up to 1 mg. The dose can be repeated if the clinical response is inadequate. Because the duration of the effect of flumazenil is shorter than the effect of the benzodiazepine, recurrence of symptoms should be expected. Alternatively, redosing or a continuous IV infusion at 0.1 to 1.0 mg/hour may be administered. The clinician should determine that the risk/benefit analysis of flumazenil favors administration of the drug.

If there is any doubt as to whether the patient has tolerance to benzodiazepines, flumazenil should not be administered. Benzodiazepine poisoning can be managed effectively and safely with supportive care only, but benzodiazepine withdrawal precipitated by flumazenil can be life threatening.

### Cyclic Antidepressants

Until the introduction of the selective serotonin reuptake inhibitors (SSRIs), the cyclic antidepressants were the principal pharmacologic treatment available for depression. Roughly, 12% of the 11,198 cyclic antidepressant exposures reported to the AAPCC in 2005 had either a major outcome or fatality. While the cyclic antidepressant group is used in isolation, each in other their receptor affinities, they can be treated as a group.

The CAs are usually absorbed within hours of ingestion, although the antimuscarnic effects may delay absorption in overdose. The drugs also exhibit α-adrenergic antagonism, inhibition of reuptake of norepinephrine, and anticholinergic properties. Acting as type IA antidysrhythmics, CAs block sodium entry into myocytes during phase 0 of depolarization.

#### Clinical Manifestations

Important CNS effects include lethargy, delirium, coma, and seizures. Tachycardia and hypotension develop early in toxicity. The IA antidysrhythmic properties cause prolongation of the QRS interval. CAs also produce a characteristic rightward shift of the axis in the terminal portion of the QRS, best seen as an R wave in the terminal 40 msec of lead aVR (40) (Fig. 66.2).

#### Management

Gastrointestinal decontamination should be considered in every patient. If the history suggests a recent large ingestion, gastric lavage may be attempted. Acute ingestions of 10 to 20 mg/kg of most CAs can cause significant poisoning (41). Activated charcoal should be administered. Serum drug concentrations may be obtained but do not correlate well with toxicity (42). The ECG is the most important diagnostic test when managing CA overdose. A terminal 40-msec QRS axis of 130 to


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**Chapter 66:** Toxicology

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**Cyclic Antidepressants**

**Management**

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Pharmacology

Lithium is thought to increase serotonin release and increase receptor sensitivity to serotonin, as well as modulate the effects of norepinephrine on its second-messenger system (47). Like sodium, lithium is a monovalent cation. The kidney handles lithium and sodium similarly. Lithium is freely filtered by the glomerulus, and 80% is reabsorbed, with 60% occurring in the proximal tubule (48). Immediate-release lithium preparations produce peak serum concentrations within hours, but sustained-release lithium may not peak for 6 to 12 hours. The generally accepted therapeutic range of lithium is 0.6 to 1.2 mmmol/L, although in both overdose and therapeutic dosing, clinical signs and symptoms may serve as a better guide than the serum concentration.

Clinical Manifestations of Overdose

Acute and chronic lithium toxicity have similar neurologic features, although acute toxicity is usually associated with significant gastrointestinal manifestations. Acute toxicity occurs when an individual without a body burden of lithium takes a supratherapeutic dose of the drug. Chronic toxicity is usually the result of decreased elimination of the drug in a patient who is receiving a fixed dose (e.g., after developing renal insufficiency). Acute-on-chronic toxicity occurs when a patient with a pre-existent total body drug takes a supratherapeutic dose. In acute toxicity, a large ingestion of lithium—a gastrointestinal irritant—will initially cause gastrointestinal symptoms, such as vomiting and diarrhea. Neurotoxicity (which is clinically more significant) will be delayed until the drug has been absorbed and is redistributed into the CNS. In chronic lithium toxicity, gastrointestinal symptoms may be completely absent.

Neurotoxicity manifests itself as disorders of movement and alterations in mental status. In very mild toxicity, only a fine tremor will be present, but in more advanced poisoning, fasciculations, hyperreflexia, dysarthria, and nystagmus may be seen as well (49). Mental status changes range from confusion to coma and seizures (49).

Nephrogenic diabetes insipidus and hypothyroidism occur following chronic therapeutic lithium use but are not features of overdose. The syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) is a chronic neurologic disorder with many of the same features of lithium neurotoxicity. The distinction is that SILENT persists even when the body burden of lithium is eliminated. The mechanism is not completely elucidated but may involve demyelination. SILENT has been reported both as a result of chronic therapeutic use and as a sequela of lithium intoxication (50).

Management

Gastrointestinal decontamination should be considered after acute lithium toxicity. Since lithium does not bind to activated charcoal, activated charcoal should only be considered when a mixed overdose is suspected (51). When sustained-release preparations are ingested, whole bowel irrigation has been shown to decrease serum lithium concentration (52). Whole bowel irrigation can be performed by administering 2 liters of polyethylene glycol orally every hour (25 mL/hour in children) until the rectal effluent is clear. After both acute and chronic toxicity, intravenous fluids should be given to optimize intravascular volume. The volume-depleted patient will have a decreased glomerular filtration rate and increased real absorption.

270 degrees discriminated patients with CA toxicity from those without toxicity in one study (43). While the terminal 40-msec QRS toxicity is a good indicator of exposure, QRS duration is a better indicator of severity of poisoning. In another series, no patients with QRS >160 msec had ventricular dysrhythmias and no patients with a QRS duration >100 msec had seizures (42).

The decision to administer sodium bicarbonate should be based on the ECG. Sodium bicarbonate should be administered if the QRS duration is >100 msec. Both the high sodium concentration and alkaline pH of sodium bicarbonate solution are responsible for its salutary effects. The sodium load increases the sodium gradient across the poisoned myocardial sodium channel, resulting in a narrowing of the QRS complex. The bicarbonate raises the pH, reducing CA binding to the sodium channel. Sodium bicarbonate should be administered as a 1 to 2 mEq/kg bolus during continuous ECG monitoring. If the complex narrows, sodium bicarbonate can be administered as an infusion. If the complex remains unchanged, the diagnosis of CA poisoning should be reconsidered. The sodium bicarbonate infusion may be performed by adding 150 mEq of bicarbonate to 1 L of D5W and infusing at twice the maintenance rate. The arterial pH should be targeted to 7.50 to 7.55. Occasional repeat boluses of 1 to 2 mEq/kg may be necessary. Hypertonic sodium chloride (3% NaCl) may be indicated when the QRS complex widens and the serum pH precludes further alkalization. Hyperventilation may be used to induce alkalemia in intubated CA-poisoned patients. Hyperventilation may be utilized in those patients who cannot tolerate the fluid or sodium load from sodium bicarbonate. Although hyperventilation did not have an effect in one experimental model, it has been used clinically with success (44,45).

If hypotension persists despite fluid resuscitation and vasoressors become necessary, the direct-acting drug, norepinephrine, may be superior to the indirect-acting dopamine, because intracellular catecholamines may be depleted or depleted. Seizures should be rapidly controlled. Convulsions will result in a metabolic acidoses, causing even more avid binding of the CA to the cardiac sodium channels, potentially resulting in more cardiotoxicity. Benzo diazepines can be safely administered, and propofol or barbiturates are also appropriate. Phenytoin, a type IA antidyssrhythmics, may worsen cardiac toxicity and is therefore not indicated (46).

Therapy should continue until vital signs and ECG improve. In most instances, CA poisoning results in a rapid deterioration within hours of overdose—most severe within hours of presentation. Unless there has been a significant secondary injury (such as from shock), those who survive to 24 hours are expected to make a complete recovery. Because of their protein binding, hemodialysis is ineffective at removing significant quantities of CAs.

Lithium

Lithium is used in the treatment of bipolar affective disorders. Patients will require ICU admission when they have signs of CNS toxicity, do not tolerate fluid therapy, or have serum concentrations >2 mmmol/L, which may result in rapid deterioration. Of 5,359 exposures reported to the AAPCC, 5.7% were classified as major or fatal.
of lithium. When fluid deficits are restored, 0.9% saline can be administered at twice the maintenance rate or approximately 200 mL/hr in adults to aid in elimination of lithium.

Extracorporeal elimination may be necessary to treat lithium toxicity. Lithium can be removed by hemodialysis due to its low volume of distribution and limited protein binding. Although hemodialysis can only remove the lithium residing in the vascular compartment, the elimination of serum lithium will allow the remaining intracellular lithium to redistribute into the plasma. Thus, although lithium concentrations may rebound following dialysis, the tissue burden has actually decreased. The indications for dialysis are not universally agreed upon. Hemodialysis should be performed when there are signs of significant end-organ damage, when lithium cannot be eliminated without dialysis, or when the serum concentration is elevated such that severe toxicity is highly likely. We recommend dialysis when there is significant CNS toxicity such as delirium, obtundation, coma, or seizures, when a patient with milder toxicity cannot eliminate lithium efficiently (renal insufficiency) or tolerate saline resuscitation (congestive heart failure); or in the presence of a serum lithium concentration >4.0 mmol/L following acute poisoning or >2.3 mmol/L following chronic poisoning. Since repeat dialysis may be necessary, the clinician should reapply the above criteria 4 hours after dialysis is completed to determine if dialysis should be repeated.

A common clinical pitfall is to deny dialysis to patients with an elevated lithium concentration and signs of toxicity because consecutive lithium concentrations have shown a small decrease. The clinician concludes that the lithium will eventually be eliminated without dialysis, so dialysis should not be helpful. Because the duration of exposure to the toxic lithium levels may predispose the patient to SILENT, it is better to be exposed to a neurotoxin for a few hours than a few days. While this area is not adequately studied, it seems prudent to hemodialyze these patients.

### TOXICOLOGIC BRADYCARDIA: DIGOXIN, β-ADRENERGIC ANTAGONISTS, AND CALCIUM CHANNEL BLOCKERS

In 2005, the AAPCC NPED reported more than 30,000 exposures to cardioactive steroids (including digoxin), β-adrenergic antagonists, and calcium channel blockers. This figure includes 1,085 major outcomes and 167 fatalities (6). These xenobiotics have a narrow therapeutic index, drawing a fine line between therapeutic dosing and poisoning. The individuals who take these medications usually have underlying cardiovascular disease, making management of overdose even more challenging.

#### Digoxin

Digoxin is a cardioactive steroid derived from the foxglove plant. Though digoxin and digitoxin are the only pharmaceuticals in the class, plants such as oleander, yellow oleander, dogbane, and red squill contain cardioactive steroids with similar toxicity. While some of these plants cause a great deal of morbidity worldwide, this chapter will deal primarily with digoxin, which causes more morbidity than any other cardioactive steroid in North America. Of 2,828 reported exposures to cardiac steroid medications in 2005, 7.4% were classified as major or fatal (6).

Digoxin has multiple therapeutic and toxic cardiovascular effects, all of which result from inhibition of the Na⁺-K⁺-ATPase. The Na⁺-K⁺-ATPase extrudes sodium from the myocardial cell, creating a sodium gradient that drives an Na⁺-Ca²⁺-antipporter that moves calcium extravascularly. The inhibition of the Na⁺-K⁺-ATPase by digoxin increases intracellular Ca²⁺, which therapeutically triggers Ca²⁺-mediated Ca²⁺ release from the sarcoplasmic reticulum (Fig. 66.3). Ca influx through the cell membrane triggers Ca release through sarcolemmal Ca²⁺ channels, which is commonly called Ca-mediated Ca release.

Digoxin also slows conduction through the sinoatrial (SA) and atrioventricular (AV) nodes, probably through direct and vagally mediated mechanisms (53). In therapeutic use, digoxin decreases heart rate and increases isotropy. In overdose, the increased intracellular Ca²⁺ brings the cell closer to threshold, resulting in increased automaticity.

Digoxin does not exert its therapeutic and toxic effects until it redistributes from the serum into the myocardium. Digoxin has a large volume of distribution, precluding elimination by hemodialysis. Digoxin is mostly eliminated renally, although there is some hepatic metabolism. The maximal effect from a drug loses the ability to excrete it effectively. Both syndromes have similar cardiovascular manifestations, but acute toxicity may feature more prominent gastrointestinal symptoms. Acute poisoning may result in nausea, vomiting, and abdominal pain, whereas chronic poisoning develops more insidiously. In addition to gastrointestinal symptoms, chronic poisoning may present with weakness, confusion, or delirium (54,55).

Bradycardia with a preserved blood pressure typically occurs in digoxin toxicity. The ECG is the most important test in establishing the diagnosis. Because digoxin has multiple cardiac effects, there is no single ECG manifestation that is consistently seen in patients with digoxin toxicity. Almost any rhythm is possible, with the exception of a rapidly conducted supraventricular rhythm. The most common rhythm disturbance on initial ECG is the presence of ventricular ectopy (56). The ECG could potentially exhibit increased automaticity from elevated resting potential, conduction disturbance from AV and SA nodal block, both, or neither. The ectopy may degrade into ventricular tachycardia or ventricular fibrillation. If conduction disturbance predominates, the ECG may demonstrate sinus bradycardia or varying degrees of AV block.

The laboratory provides clues to toxicity. The therapeutic range for digoxin is usually reported as 0.5 to 2.0 ng/mL. Serum digoxin concentration should be interpreted in the context of the history and ECG. Digoxin is a cardiotonic, and serum concentrations do not necessarily reflect the degree of poisoning. Digoxin requires several hours to redistribute from the serum to the tissues. Shortly after an acute ingestion, the serum concentration may overestimate toxicity, while a mild increase in

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serum concentration of a patient chronically on digoxin may underestimate the high extent of the increased tissue burden. Serum potassium concentration is a better predictor of illness following acute ingestions. A study of 91 digitoxin-poisoned patients performed in the pre-digoxin-specific antibody fragment era found no mortality when the potassium concentration was less than 5.0 mEq/L and 50% mortality when the potassium concentration was 5.0 to 5.5 mEq/L (57).

**Management of Toxicity**

Because acute toxicity can cause vomiting, activated charcoal and gastric lavage may be of limited value.

Atropine can be given intravenously in 0.5-mg doses for bradycardia, although it is probably not important to “correct” the heart rate if the blood pressure is preserved. If necessary, potassium should be supplemented. Hypokalemia inhibits the function of the Na⁺-K⁺-ATPase, and thereby exacerbates digoxin poisoning. A pitfall in managing digoxin-poisoned patients is the administration of calcium in response to the recognition of hyperkalemia. When hyperkalemia is the result of an increase in total body burden of potassium, such as in renal failure, calcium is the treatment of choice. However, calcium administration is not recommended in the setting of digoxin poisoning where extracellular distribution of potassium is the result of a poisoned Na⁺-K⁺-ATPase, not an increase in total body potassium. Under these circumstances, increasing extracellular calcium may accentuate toxicity.

**Digoxin-specific Immune Fragments**

Administration of digoxin-specific antibody fragments (Fab) is the most important intervention in digoxin-poisoned patients. Fab are prepared by cleaving the Fc fragment from IgG. The resulting Fab fragments are much less immunoreactive than the whole IgG antibodies. In a large series, digoxin-specific
antibody fragments caused allergic reaction in 0.8% of patients (58).

Digoxin-specific Fab should be administered to anyone with digoxin-induced cardiotoxicity, a serum potassium concentration \( \geq 5.0 \text{ mEq/L} \) after an acute overdose, or a serum digoxin concentration \( \geq 15 \text{ ng/mL} \) at any time or \( \geq 10 \text{ ng/mL} \) at 6 hours postingestion (59).

Digoxin-specific Fab are given by intravenous infusion and dosed according to serum concentration (Table 66.3). In the presence of suspected severe toxicity, treatment should not be dependent on nor await serum digoxin concentration results.

The first clinical effect of Fab should be seen within 20 minutes and a maximal response within several hours (60). Following immune-specific antibody fragment administration, the serum digoxin concentration determined by most laboratories will be a total digoxin concentration, which will include the antibody-bound digoxin. The result will be a very elevated value without clinical utility. The determination of free digoxin concentration, which is available at some institutions, would not be affected.

TABLE 66.3
DIGOXIN-SPECIFIC FAB DOSE CALCULATION

<table>
<thead>
<tr>
<th>Condition</th>
<th>Formula</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>When serum digoxin concentration (SDC) known:</td>
<td>No. of vials = ( \frac{\text{SDC (ng/mL)} \times \text{patient weight (kg)}}{100} )</td>
<td>Empiric therapy 10-20 vials (adult or pediatric)</td>
</tr>
<tr>
<td>When both SDC and dose unknown:</td>
<td>No. of vials = Amount ingested (mg) / 5 mg/vial</td>
<td>Empiric therapy 1-3 vials (Pediatric)</td>
</tr>
</tbody>
</table>

β-Adrenergic Antagonists and Calcium Channel Blockers

In 2005, the National Poisoning and Exposure Database received 18,207 reports of exposures to β-adrenergic antagonists (including 60 fatalities and 523 major outcomes) and 10,300 reports of exposures to calcium channel blockers (75 fatalities and 384 major outcomes) (6).

The β-adrenergic antagonists and calcium channel blockers represent a diverse group of medications with a wide range of clinical indications. There is, however, an overlap in the clinical effects and the management of overdose of these medications. The description of each class is described individually, whereas the discussion of appropriate management is integrated.

β-Adrenergic Antagonists

β-Adrenergic receptors are coupled to G proteins, which activate adenylyl cyclase, resulting in increased production of ATP from cyclic adenosine monophosphate (cAMP). The cAMP activates protein kinase A (PKA), which initiates a series of phosphorylations. Phosphorylation of L-type calcium channels on cell membranes increases intracellular calcium, which allows more activation of the SR and further calcium release from the SR, causing muscle contraction. The calcium influx also brings pacemaker cells closer to threshold. The net result is increased inotropy and chronotropy (61).

Most of the β-adrenergic antagonists are exclusively metabolized or biotransformed in the liver and then renally eliminated. The exception to the rule is atenolol, which is exclusively renally eliminated.

Clinical Manifestations of Overdose

All β-adrenergic antagonists have the potential to produce bradycardia and hypotension in a dose-dependent fashion. However, there are subtle differences among the agents in terms of receptor selectivity, lipid solubility, membrane-stabilizing activity, and potassium channel blockade that result in varied clinical manifestations.

β-Adrenergic antagonists differ from each other in their selectivity for α-, β₁-, and β₂-adrenergic receptors. Drugs with α- and β-adrenergic antagonist effects, such as labetalol and carvedilol, produce more hypotension and afterload reduction. The more β₁-selective drugs, including metoprolol and atenolol, have less potential for β₂-related adverse effects such as bronchospasm. The more lipid-soluble β-adrenergic antagonists, such as propranolol, penetrate the CNS more readily, causing obtundation or seizures prior to hemodynamic collapse (62). Membrane-stabilizing activity, similar to type I antiarrhythmic activity, produces shortening of the QRS interval, tachycardias, and hypotension. The membrane-stabilizing effect is usually associated with propranolol and other lipid-soluble drugs, although it has been observed after overdose with others (63,64). Sotalol and acebutolol can produce QTc prolongation due to potassium channel blockade, which may result in torsades de pointes (65).

Calcium Channel Blockers

The calcium channel blockers (CCBs) are formulated as both immediate and sustained release, but in overdose, the effects of either type may be prolonged. The CCBs undergo hepatic metabolism.

There are three major classes of CCBs: Dihydropyridines (including amlodipine, nifedipine, and others ending with the suffix “-pine”), phenylalkylamines (verapamil), and benzothiazepine (diltiazem). In practice, it is more clinically useful to divide them into two classes: the dihydropyridines and the nondihydropyridines. All of the drugs inhibit the function of L-type calcium channels. The dihydropyridines have greater affinity for calcium channels in vascular smooth muscle than the myocardium (66).

Clinical Manifestations of Overdose

The most consequential clinical features of CCB overdose are cardiovascular. All of the CCBs produce hypotension, but effects on heart rate and contractility vary based on the class of the particular drug. As a result, they cause hypotension with a reflex tachycardia. Diltiazem, in contrast, produces little peripheral blockade, but does suppress contractility and conduction through the SA and AV nodes, resulting in bradycardia and decreased inotropy. These cardiac effects can be much
more difficult to treat than the peripheral vasodilation of the dihydropyridines. In severe poisoning, heart block or complete cardiac arrest occurs. Yerapamil, which is active in the peripheral vasculature and in the myocardium, produces a combination of the effects of the dihydropyridines and diltiazem. For this reason, yerapamil is considered to be the most dangerous of the CCBs, although any of them can cause death in overdose.

CCBs have effects outside the cardiovascular system. The blockade of L-type calcium channels in pancreatic β-cells, where they trigger the blockade of insulin release, may result in hypoglycemia (67).

**Management of Overdose of β-adrenergic Antagonists and Calcium Channel Blockers**

Patients who initially present without symptoms may rapidly become very ill. Patients with these overdoses should be taken very seriously and treated aggressively. Many antidotes have been investigated, with varying degrees of clinical success. Patients with β-adrenergic antagonist and CCB overdose do not benefit from removal with hemodialysis. There is no single antidote for either β-adrenergic antagonists or CCBs. The optimal treatment consists of a combination of the treatments described below.

Gastrointestinal decontamination should be considered in all patients. Gastric lavage may be indicated if there are pills still expected to be in the stomach (usually in the first hour or two after ingestion). Activated charcoal should be administered. Whole bowel irrigation with polyethylene glycol is indicated for patients with a history of ingesting sustained-release drugs. Initial management for hypotension will be intravenous crystalloid fluid. Although intravenous atropine, 0.5 mg to 1 mg, may be given for bradycardia, studies of atropine efficacy in CCB toxicity are not definitive (68).

Calcium has a role not only in calcium channel blocker toxicity, but also for β-adrenergic antagonist poisoning (69,70). Increasing extracellular calcium helps to overcome calcium channel blockade and increase intracellular calcium, typically with greater improvement in blood pressure than heart rate. The ideal dosing of calcium is not yet established. An intravenous bolus of 13 to 25 mEq of Ca²⁺, 10–20 mL of 10% calcium gluconate, or 13 to 25 mL of 10% calcium chloride or 30–60 mL of 10% calcium gluconate can be followed by repeat boluses or an infusion of 0.5 mg/kg/hour of Ca²⁺ (71). Calcium concentration should be closely monitored.

Glucagon, an endogenous polypeptide hormone released by pancreatic α-cells, has significant isotropic effects mediated by its ability to activate myocardial adenylate cyclase by itself, effectively bypassing the β-adrenergic receptor (72). Because calcium channel opening occurs “downstream” from adenylate cyclase, glucagon may not be as effective for overcoming calcium channel blockade. Glucagon should be given intravenously, at an initial dose of 3 to 5 mg (30 μg/kg in children), up to 10 mg. The total initial dose that produces a response should be given hourly as an infusion (73). Glucagon may cause hyperglycemia or vomiting, but neither complication should limit the therapy if it is effective.

Hyperinsulinaemia/euglycemia therapy should be instituted early in patients with moderate to severe poisoning. Insulin is a positive inotrope and may independently increase Ca²⁺ entry into cells (74). Insulin may allow the myocardium, which usually relies on fatty acids, to use more carbohydrate for metabolism (75). As with other therapies for poisoning with these agents, the ideal dose is not known. We recommend an intravenous bolus of 1 unit/kg, followed by an infusion of 0.5 to 1 unit/kg/hour. The initial bolus should be preceded by a 1 g/kg bolus of dextrose, followed by an infusion to maintain euglycemia. An initial infusion of 0.5 g/kg/hour of dextrose can be instituted and then adjusted based on the subsequent glucose concentration. Although some clinicians are understandably apprehensive about using a dose of insulin that is 10-fold greater than the typical diabetic ketoacidosis regimen, the regimen has been successfully used clinically and in animal models of both β-adrenergic antagonists and calcium channel blocker poisoning (76,77).

In severe poisoning, all of the above measures should be performed, as well as institution of inotropes and vasoactive drugs. Intra-aortic balloon counterpulsation should also be considered if cardiac output is severely compromised. These patients may be ideal for this procedure because, unlike with most other causes of cardiogenic shock, their cardiac output can recover in a relatively short period of time.

**TOXIC ALCOHOLS**

The term toxic alcohols refers in particular to methanol and ethylene glycol, which are the most important chemicals in the class because they are both of high potential toxicity and wide availability. In 2005, the NPED received 6,220 reports of exposure to ethylene glycol, including 5.4% classified as major or fatal, and 2,276 exposures to methanol, with 3.2% major or fatal (6).

The toxic alcohols have numerous industrial and consumer uses. Methanol is commonly found in windshield wiper fluid and ethylene glycol in automobile antifreeze, and isopropanol is a ubiquitous topical disinfectant. Since specific laboratory testing is usually not available for these chemicals, establishment of the diagnosis of toxic alcohol poisoning will necessitate skilled use of the serum osmolality and anion gap.

The toxic alcohols are readily absorbed and have a volume of distribution similar to total body water. Both the parent compounds and the toxic metabolites are dialyzable. It is not the toxic alcohols themselves that produce significant toxicity, but their metabolites. Methanol and ethylene glycol are metabolized in a stepwise fashion by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) to the clinically important metabolites formic acid (methanol) and glycolic, glyoxylic, and oxalic acid (ethylene glycol) (Figs. 66.4 and 66.5). Isopropanol is less clinically consequential, as it is converted by ADH to acetone, which is an end product rather than a substrate of ALDH.

Because ADH preferentially metabolizes ethanol over all other alcohols, no significant metabolism of toxic alcohols will occur while high concentrations of ethanol are present. When ADH is inhibited, the parent compounds are eliminated very slowly without metabolism. In the absence of ADH, ethylene glycol is readily eliminated with a half-life of 8.5 hours while methanol, which is eliminated as a vapor, has a half-life of 30 to 54 hours (78–80).

When suspected, toxic alcohol poisoning requires ICU admission. Patients may be obtunded and require therapeutic medication infusions and hemodialysis that cannot be accomplished in general inpatient units.
Clinical Manifestations

The physical examination may be unremarkable. All of the toxic alcohols can produce significant CNS depression, and a compensatory tachypnea may be present if there is a metabolic acidosis. Acetone, generated from ADH metabolism of isopropanol, produces nausea, hypotension, hemorrhagic gastritis, and tachycardia, but these are not usually life threatening (81). Formate, a methanol metabolite, can produce blindness from toxicity to the retina and optic nerve (82).

Laboratory studies can suggest—but not establish or exclude—the diagnosis of toxic alcohol poisoning. Metabolites of methanol or ethylene glycol may cause an elevated anion gap metabolic acidosis. The hallmark laboratory finding of isopropanol poisoning is ketonemia without acidosis. Ethylene glycol may cause nephrotoxicity when the primary metabolite oxalic acid precipitates as calcium oxalate crystals in the renal tubules (83).

If a serum toxic alcohol concentration is available, the diagnosis can be established rapidly, and management is expected in a timely manner, dialysis should be presumptively started empirically as soon as the diagnosis is considered.

Management

There are several clinical presentations that suggest poisoning with a toxic alcohol, and each requires different management considerations. The first type of patient presents without acidoses and either a history of ingesting ethylene glycol or methanol or a very elevated osmolar gap. The physician should immediately begin an ADH inhibitor and obtain toxic alcohol concentrations (when available). Later, the decision to continue treatment or begin hemodialysis can be made based on the presence of a toxic alcohol in a high concentration. If the result is not expected in a timely manner, dialysis should be presumptively performed.

The second scenario is the patient who presents with an unexplained elevated anion gap metabolic acidosis that is not explained by the presence of lactate, ketoadipic acid, or urea. In such cases, the diagnosis should be considered, and ADH inhibition and hemodialysis should be instituted. One test that is very helpful in this scenario is a serum ethanol concentration. As long as there is elevated ethanol concentration present in the serum, toxic alcohols cannot be converted into their metabolites. Therefore, if a patient has a very elevated ethanol concentration, his or her elevated anion gap metabolic acidosis cannot be explained by toxic alcohol poisoning, unless the ethanol was consumed only hours after the ingestion of the toxic alcohol.

If a serum toxic alcohol concentration is available, the diagnosis can be established rapidly, and management is
CHOLINERGIC COMPOUNDS

Acetylcholine is the neurotransmitter found throughout the parasympathetic nervous system, in the sympathetic nervous system at the level of the ganglia and sweat glands, and at the neuromuscular junction (Fig. 66.6). The cholinergic syndrome describes the condition of excess acetylcholine characterized by the sum of the parasympathetic, somatic, and sympathetic effects. Cholinergic compounds are used as medications, pesticides, and weapons. In 2005, the AAPCC received reports of ten fatalities and 62 major effects related to organophosphate and carbamate insecticides. The World Health Organization estimates that at least 1 million unintentional poisonings and 2 million suicide attempts occur annually worldwide from these insecticides (88).

Acetylcholine is inactivated in the synapse by acetylcholinesterase (AChE). Inhibition of AChE causes an excess of the neurotransmitter in the synapse. The two most important classes of AChE inhibitors are the carbamates and the organic phosphorous compounds. The carbamates inactivate AChE by carbamylation, while the organic phosphorous compounds do so by phosphorylation. The carbamates and organic phosphorous compounds are both absorbed by ingestion, by inhalation, and through skin.

There are some generalizations that can be made about the two classes. Organic phosphorous compounds have a greater delay to onset of action. After ingestion, peak concentrations have been reported at 6 hours (89). Many of the organic phosphorous agents are activated in the liver, resulting in a further delay to peak action. In contrast, many of the carbamates have peak concentrations within 40 minutes following ingestion (90). The organic phosphorous compounds are generally very lipophilic. Redistribution from fat allows measurable serum concentrations for up to 48 days, while carbamates may be almost completely eliminated within days (91,92). Organic phosphorous compounds exhibit peripheral and CNS effects, while the carbamates do not readily cross into the CNS, resulting in a predominance of peripheral symptoms (93). Most importantly, organic phosphorous compounds exhibit “aging,” whereby the reversible inhibition of AChE becomes permanent. Aging can take minutes to days, depending on the particular compound. Carbamates, in contrast, spontaneously hydrolyze from the active site of AChE and do not age.

ICU admission is required for those with respiratory compromise, hemodynamic instability, or the need for administration of large amounts of atropine.

Clinical Manifestations

Diagnosis is often established by recognition of the muscarinic signs: salivation, lacrimation, urination, defecation, bradycardia, bronchoconstriction, and bradyarrhythmias. Acetylcholine initially acts as an agonist, but in excess becomes an antagonist at the neuromuscular junction, producing weakness, fasciculations, and paralysis. Simulation of nicotinic receptors at the sympathetic ganglia produces tachycardia and mydriasis.

Management

The first management priorities involve securing the airway when necessary and decontaminating the patient's skin to
Chapter 66: Toxicology

Sympathetic Parasympathetic

ACh

Adrenal medulla
↑ circulating epinephrine
Skin (diaphoresis)

CNS
• Confusion
• Agitation
• Hallucinations
• Coma
• Convulsions
Mydriasis
Bronchodilation
Tachydysrhythmia
Hypertension
Urinary retention
Hyperglycemia


protect caregivers and prevent further absorption. After initial stabilization, atropine should be administered. The presence of tachycardia is not a contraindication to atropine. The goal of “atropinization” is reversal of the muscarinic symptoms. Atropine is titrated to effect the resolution of bronchospasm and bronchorrhea. The initial dose of 1 mg IV atropine (0.05 mg/kg in children) can be doubled every 2 minutes until muscarinic signs are controlled. There is variation in the amount of atropine required, ranging from one to hundreds of milligrams (92).

If CNS anticholinergic toxicity develops prior to resolution of peripheral muscarinic signs, the peripherally acting antimuscarinic agent, glycopyrrolate, may be given, initially at 1 mg IV and then titrated to symptomatic relief. A common clinical pitfall is to interpret froth from the patient’s mouth as a sign of cardiogenic pulmonary edema and respond with fluid restriction. On the contrary, cholinergic-poisoned patients have large volume losses from diaphoresis and bronchorrhea.

Oximes are used to supplement antimuscarinic therapy. The oximes improve both muscarinic and nicotinic signs, primarily by restoring activity to phosphorylated AChE. Since oximes will not restore activity once aging has occurred, they must be administered early in the clinical course of AChE inhibitor poisoning. Oxime therapy is recommended for both organic phosphorous compounds and carbamates because oximes may have salutary effects following carbamate poisoning and because the toxic agent in question is not always known with certainty. Even in carbaryl poisoning, adequate atropinization overcomes any deleterious effect of pralidoxime (94). Pralidoxime (2-PAM) is the oxime most frequently available in the United States. Administer 1 to 2 g IV over 30 minutes (20–40 mg/kg in children, to a maximum of 2 g). Significant poisoning may require a continuous infusion of 500 mg/hour (10–20 mg/kg/hour in children, up to adult dose) (95).

Diazepam should be administered to patients severely poisoned by organic phosphorous compounds. Although human data are not available, animal studies show a survival benefit possibly unrelated to the GABAAergic effects of diazepam (96). Because severely poisoned patients will require endotracheal intubation, diazepam can be administered very safely.

Diagnostic Studies

AChE inhibitor poisoning is a clinical diagnosis. Although red blood cell cholinesterase and butyrylcholinesterase are inhibited by carbamates and organic phosphorous compounds, their activity may remain depressed after clinical signs and symptoms have resolved. There may be a clinical role for these tests in mild cases when the diagnosis is unclear. Electromyography (EMG) may be a sensitive indicator of toxicity before clinically apparent symptoms have occurred (97).

Delayed Manifestations

In the acute setting, the physician should be vigilant for recurrence of cholinergic signs after apparent resolution and for a distinct form of toxicity called the intermediate syndrome. The intermediate syndrome—so called because it occurs after acute, but before delayed, toxicity—may occur 24 to 96 hours after organic phosphorous poisoning. The intermediate syndrome consists of upper body weakness, cranial nerve palsies, and areflexia. The syndrome appears to be self-limited,
but can last up to 30 days and be severe enough to require intubation (98,99). We recommend continuing pralidoxime infusion at 500 mg/hour when this diagnosis is considered. Since organic phosphorous compounds are very lipophilic, redistribution from fat stores may result, causing delayed toxicity days after apparent resolution (100). Discharge can be considered when the patient has been asymptomatic without additional treatment for 1 to 2 days.

CYANIDE

Cyanide salts are widely available and may be used in suicidal or homicidal poisoning. Because jewelers, laboratory workers, and industrial workers often have ready access to cyanide, a relationship to these industries may be an important historical clue. Cyanide poisoning should also be considered in all fire victims, as it is released when certain synthetic and natural fibers undergo combustion. Cyanide poisoning most frequently occurs after the ingestion of a cyanide salt or inhalation of the gas hydrogen cyanide. In both forms, cyanide is rapidly absorbed. The most important toxic effect of cyanide is inhibition of cytochrome oxidase of the electron transport chain (101). Despite the presence of oxygen, cells cannot oxidize electrons from nucleotide adenine diphosphate (NADH) to oxygen, and generate ATP, resulting in anaerobic metabolism and producing lactic acid. Small quantities of cyanide are detoxified by the enzyme, rhodanese, which catalyzes the transfer of sulfur from thiosulfate, yielding thiocyanate. Poisoning results when this system is overwhelmed by large concentrations of cyanide.

Clinical Manifestations

The history may be very helpful in establishing the diagnosis. Cyanide should be considered in anyone who rapidly loses consciousness after ingestion or inhalational exposure. Signs and symptoms resemble those of hypoxia: headache, lethargy, seizures, and coma in the absence of cyanosis.

Management of Cyanide Poisoning

Cyanide poisoning requires treatment before laboratory confirmation is available, so treatment must be instituted based on clinical suspicion. As soon as cyanide poisoning is considered, 100% oxygen should be administered, intravenous access established, and fluids given. The remainder of treatment depends on the route of exposure.

Because the symptoms of cyanide poisoning are similar to those associated with hypovolemia or carbon monoxide poisoning, the diagnosis is difficult to establish with certainty. Laboratory studies will show a lactic acidosis. In one series, a plasma lactate concentration > 8 mmol/L in patients with clinical suspicion of poisoning was 94% sensitive and 70% specific for cyanide toxicity (102).

The cyanide antidote kit consists of amyl nitrite, sodium nitrite, and sodium thiosulfate. Each individual component is beneficial, whereas together they have synergistic activity (103). The nitrites derive their efficacy by generating methemoglobin, which has a greater affinity for cyanide than cytochrome oxidase. When reduced oxygen-carrying capacity is suspected (due to anemia or carboxyhemoglobinemia), the nitrites should be omitted. For this reason, the nitrites should be avoided in patients presenting following smoke inhalation. Such individuals may not tolerate further compromise in their oxygen distribution associated with an increase in methemoglobin.

Amyl nitrite is a volatile liquid. The ampule encasing should be broken and held in front of the patient’s mouth for 1.5-second intervals with 15-second breaks. Once intravenous access is established, sodium nitrite can replace the amyl nitrite. Sodium nitrite is administered 10 mL IV in adults (0.2 mL/kg in children). In 2 hours, the dose can be repeated at half the initial dose (104). A methemoglobin concentration should be obtained 30 minutes after nitrite administration, with a target concentration of 20% to 30%. Sodium thiosulfate, the final component of the kit, functions by providing substrate to rhodanese, facilitating conversion of cyanide to thiocyanate. The dose is 50 mL in adults and 1.65 mL/kg in children, and the drug may be repeated in 2 hours at half the initial dose if symptoms persist. Another potential antidote, hydroxocobalamin, will become available in the United States shortly. Hydroxocobalamin combines with cyanide to form cyanocobalamin (vitamin B12) (105). In animal models, it has synergism with thiosulfate (106). Hydroxocobalamin should be given IV at 70 mg/kg (to a maximum of 5 g) in a separate infusion site from thiosulfate.

CYANIDE, THIOCYANATE, AND NITROPRUSSIDE

Nitroprusside contains an iron molecule coordinated to five cyanide molecules and one molecule of nitric oxide. Cyanide molecules are slowly liberated after nitroprusside is infused, but usually at a rate that can be detoxified by endogenous pathways. Risk factors for accumulation of cyanide are prolonged infusion, high infusion rate, and poor nourishment. If the diagnosis is suspected, the infusion should be discontinued and hydroxocobalamin and thiosulfate administered. A more likely complication of nitroprusside use is thiocyanate toxicity. Thiocyanate, which does not cause any symptoms at low concentrations, is cleared renally. Bioaccumulation occurs in patients with impaired renal function, causing delirium, hallucinations, seizures, and rash. In patients receiving >2 μg/kg/min and in those with renal insufficiency, serum thiocyanate concentrations should be checked after 48 to 72 hours of infusion. The infusion should be discontinued if the thiocyanate concentration is >10 mg/dL (107). Dialysis can be effective for thiocyanate accumulation, but should be reserved for only the most severely compromised patients (108).

METHEMOGLOBIN

Methemoglobinemia results from the formation of deoxyhemoglobin, which is caused by inappropriate oxidation of heme iron. Under normal conditions, iron in deoxyhemoglobin remains in the reduced ferrous state, Fe2+, and the heme is available to bind oxygen. After oxygen binds, iron assumes the oxidized ferric state, Fe3+. Methemoglobin, which is normally formed in small quantities, is formed when a hemoglobin iron moiety is exposed to oxidative stress and converted to
the ferric state in the absence of binding oxygen. Methemoglobin is unable to bind oxygen and increases the affinity of normal hemoglobin for oxygen. Thus, the result of methemoglobin formation is decreased oxygen delivery and a leftward shift in the oxygen dissociation curve. Due to the physiologic systems available to reduce methemoglobin to functional hemoglobin, low-level methemoglobin production may be a protective mechanism against oxidant damage to erythrocytes. The most important mechanism of methemoglobin reduction is catalyzed by the enzyme, methemoglobin reductase (cytochrome b₄, reductase), using NADH generated from the Embden-Meyerhof glycolytic pathway. Congenital methemoglobinemia is a rare condition caused by methemoglobin reductase deficiency (109). This enzyme is also relatively deficient until approximately 4 months, making infants prone to methemoglobinemia when it recurs.

Most individuals with methemoglobinemia can be treated and discharged from the emergency department. Patients with methemoglobinemia may require ICU admission when it recurs following initial treatment, either from continued absorption of an inducer or continued metabolism of a drug to a methemoglobin inducer.

**Clinical Manifestations**

Although the diagnosis of methemoglobinemia is commonly confirmed by co-oximetry, it can be established presumptively based on symptoms and signs, and via pulse oximetry. Symptoms of methemoglobinemia are those associated with hypoxia. The severity of symptoms is determined by the concentration of methemoglobin and the patient’s underlying comorbidities. At low concentrations of methemoglobin (0%–15%), patients may be asymptomatic, and as concentrations rise (20%–50%), patients may manifest decreased exercise tolerance and dyspnea. At higher concentrations (50%–70%), metabolic acidosis, seizures, and coma result. Concentrations greater than 60% or 70% can cause death in previously healthy individuals (111).

Cyanosis is an important physical examination finding that occurs when methemoglobin concentration is 1.5 g/dL. This corresponds to a concentration of 10% in an individual with a total hemoglobin concentration of 15 g/dL. In contrast, 5 g/dL of deoxyhemoglobin is required to produce cyanosis, corresponding to an oxygen saturation of 66% in the same patient. As a result, patients who are cyanotic from methemoglobinemia will not appear as ill as those who are cyanotic from impaired oxygenation.

Pulse oximetry aids in diagnosis before co-oximetry has been obtained. Methemoglobin interferes with pulse oximetry in a somewhat predictable manner (112). Pulse oximetry reads absorbance of light at two wavelengths (660 nm and 940 nm), so chosen because they are the best to distinguish the absorption spectra of oxyhemoglobin and deoxyhemoglobin. Based on the ratio of absorption between the two wavelengths, the pulse oximeter uses an algorithm to estimate the percentage of total hemoglobin as oxyhemoglobin. Methemoglobin, however, has greater absorption than either oxyhemoglobin or deoxyhemoglobin at those wavelengths. When it is present in modest concentrations, the pulse oximeter will no longer be able to meaningfully calculate oxygen saturation. In a dog model, increasing methemoglobin concentrations caused the pulse oximeter oxygen saturation (SpO₂) to decrease and then plateau at 84% to 86%. In the clinical setting, methemoglobin does not produce this straightforward plateau in SpO₂, but does consistently generate readings between 70% and 90% (111). The oxygen saturation derived from the arterial blood gas is not measured in the same fashion as SpO₂, and will not reflect the methemoglobin concentration. The oxygen saturation from a blood gas is a calculated saturation based on the pO₂, and should be normal in the setting of methemoglobinemia. A difference between the SpO₂ and arterial blood gas–calculated oxygen saturation may suggest methemoglobinemia.

**Methemoglobin Inducers**

Acquired methemoglobinemia is most frequently seen after exposure to a drug, although it can also be found in infants without drug exposure who are ill with a metabolic acidosis or diarrhea (113,114). The drugs that have been associated with methemoglobin formation are extensive. Dapsone, nitrites, nitrates, benzocaine, and sulfonamides are consistently implicated in producing methemoglobinemia (115) (Table 66.4).

It is not entirely clear why some individuals develop methemoglobinemia after exposure to these drugs and others do not. Although there is clearly a dose-response effect, host factors such as coexisting medical illness and metabolic variables play a role in methemoglobin development.

**Management of Methemoglobinemia**

When cyanosis is recognized and methemoglobinemia is considered, administer 100% oxygen by nonrebreather mask. Unless the patient is asymptomatic, methylene blue should be administered and given intravenously, 1 to 2 mg/kg over 5 minutes. Methylene is reduced by nicotinamide adenine dinucleotide phosphate (NADPH) to leukomethylene blue. Leukomethylene blue, in turn, reduces methemoglobin to hemoglobin. Clinical improvement should be seen within minutes of administration. Because the medication itself has a blue color, oxygen saturation reported by pulse oximetry may transiently worsen. A repeat dose of methylene blue may be required if the methemoglobin concentration is high or if there is ongoing oxidative stress.

Some authors recommend against giving methylene blue, an oxidizing agent, to individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Patients with this condition suffer from hemolytic anemia when exposed to drugs that create oxidative stress. Because G6PD is required to activate methylene blue, a deficiency in the enzyme may lead to a lack of efficacy of the anistote. The administration of methylene blue is appropriate when clinically indicated unless there is a strong history of G6PD deficiency. In such cases, hyperbaric oxygen or exchange transfusion should be considered. If the G6PD-deficient patient presents with severe methemoglobinemia, methylene blue should be administered and the patient monitored closely for hemolysis.

**Dapsone-induced Methemoglobinemia**

Both dapsone and its hydroxylamine metabolites are responsible for methemoglobin formation. The cytochrome P450...
Carbon monoxide poisoning is a serious health concern. It can lead to irreversible tissue damage and even death if not treated promptly.

### Clinical Manifestations

Initially, patients may complain of headache, nausea, and dizziness. Because of the vague nature of the complaints, CO poisoning may be misdiagnosed as a viral illness. The diagnosis should be considered when more than one person in a home presents with the same symptoms. Alteration in mental status, coma, seizures, and syncope are signs of severe poisoning. Indicators of tissue hypoxia, such as tachypnea, tachycardia, and ECG changes, may be seen as well. CO can cause dysrhythmias or an acute MI (122); the intensity of signs and symptoms is related to the duration and severity of exposure and comorbid conditions. Pulse oximetry will interpret carboxyhemoglobin as hemoglobin, so the SpO₂ will be falsely normal (123).

### Conversion of Dapsone to Metabolites

The conversion of dapsone to these metabolites is inhibited by cimetidine (116). Cimetidine should be administered intravenously, to patients with dapsone-induced methemoglobinemia. Initially, patients should be administered intravenously, 300 mg every 6 hours, to patients with dapsone-induced methemoglobinemia.

### Carbon Monoxide Monoxide

In their latest annual report, the AAPCC received more than 16,000 reports of carbon monoxide (CO) exposure, including 176 major effects and 66 fatalities (6). These figures, while very concerning, underestimate morbidity and mortality from carbon monoxide, which is considered the leading cause of poisoning death in the United States.

### Common Etiologies of Methemoglobinemia

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Carbon monoxide is a hemotoxin, a neurotoxin, a cardiac toxin, and an inhibitor of cytochrome oxidase. Some of these properties are more important in acute toxicity, while others cause chronic effects. Carbon monoxide binds to hemoglobin with greater affinity than does oxygen, and causes a leftward shift of the oxyhemoglobin dissociation curve, causing a decrease in delivery of oxygen to cells. Although the formation of carboxyhemoglobin can impair oxygen delivery sufficiently to cause mortality, inhibition of oxygen delivery does not fully explain why carboxyhemoglobin concentrations of 50% are often fatal whereas a similar degree of anemia might be well tolerated. The formation of carboxyhemoglobin is inadequate to explain the chronic cardiac and neurologic sequelae of CO. CO inhibition of cytochrome oxidase persists for days after carboxyhemoglobin concentration has normalized (117). CO is associated with damage to the brain endothelium, resulting in lipid peroxidation (118,119). It also binds to myoglobin with high affinity, making it a direct skeletal and cardiac muscle toxin (120).

CO results from the incomplete combustion of carbonaceous fuels. CO is tasteless, odorless, and colorless. The initial clue to the presence of CO in the home may be the alarm from a CO detector. During natural disasters, when electricity is unavailable, people may use generators indoors, allowing CO from exhaust to permeate the home. Even when a home heater is used appropriately, it can lead to CO poisoning if the outflow is obstructed. In automobiles, a functioning catalytic converter minimizes the release of CO. Other internal combustion engines, such as lawnmowers, Zambonis, and outboard motors on boats, do not usually have catalytic converters and can cause CO poisoning. Methylene chloride, an important source of CO that is not a product of combustion, is heptically metabolized to CO by the liver. Methylene chloride is used as a paint stripper and can be absorbed dermally, inhalationally, or by ingestion (121). Unlike other sources of CO poisoning, where carboxyhemoglobin begins to decline as soon as the patient is removed from the exposure, peak carboxyhemoglobin concentration will occur hours after exposure to methylene blue as the parent compound is metabolized to CO.

CO poisoning does not usually require ICU admission; this is only necessary for patients who are comatose or obtunded, those with signs of cardiotoxicity, and those with significant burns or other comorbidities.

### Table 66.4: Common Etiologies of Methemoglobinemia

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Carbon monoxide poisoning does not usually require ICU admission; this is only necessary for patients who are comatose or obtunded, those with signs of cardiotoxicity, and those with significant burns or other comorbidities.

### Clinical Manifestations

Initially, patients complain of headache, nausea, and dizziness. Because of the vague nature of the complaints, CO poisoning may be misdiagnosed as a viral illness. The diagnosis should be considered when more than one person in a home presents with the same symptoms. Alteration in mental status, coma, seizures, and syncope are signs of severe poisoning. Indicators of tissue hypoxia, such as tachypnea, tachycardia, and ECG changes, may be seen as well. CO can cause dysrhythmias or an acute MI (122); the intensity of signs and symptoms is related to the duration and severity of exposure and comorbid conditions. Pulse oximetry will interpret carboxyhemoglobin as hemoglobin, so the SpO₂ will be falsely normal (123). The diagnosis of CO poisoning is aided by obtaining the carboxyhemoglobin concentration, which can be taken from either a venous or arterial sample. The normal carboxyhemoglobin concentration will be falsely normal (123).
concentration is less than 5%, but smokers may have a concentration of up to 10% (124). Carboxyhemoglobin concentration is an indicator of exposure, but do not correlate with the degree of toxicity (125). When there is a delay from exposure to measurement of carboxyhemoglobin, the concentration loses further value as a clinical tool. This is more likely if the patient has been receiving supplemental oxygen, which decreases the half-life of carboxyhemoglobin.

**Chronic Sequelae**

For those who survive an acute CO exposure, there may be significant chronic neurologic and cardiovascular effects. Delayed neurologic sequelae (DNS) follow the resolution of initial symptoms, sometimes days to weeks later, and include dementia, movement disorders, and memory impairment (126).

**Diagnostic Studies**

In patients with chest pain, shortness of breath, palpitations, or neurologic deficits indicating severe exposure, an electrocardiogram should be performed, and serum cardiac markers should be obtained. Pregnancy status should be determined in women of childbearing age.

Elevated serum cardiac markers during moderate and severe acute toxicity predict long-term mortality (127). The pathophysiology of chronic cardiovascular effects of carbon monoxide poisoning probably involves CO poisoning of cardiac myoglobin, but needs further study.

Within 12 hours of exposure, loss of consciousness occurs, and changes on a computed tomography (CT) scan of the brain may be seen. Characteristic findings include symmetric, low-density changes in the globus pallidus, putamen, and caudate nuclei (128). A normal CT scan is a good prognostic indicator. In a series of 18 patients, a negative CT within 1 week of admission was associated with good outcome (129).

**Management**

As soon as the diagnosis is considered, the patient should be administered 100% oxygen, and the carboxyhemoglobin concentration should be obtained. Without supplemental oxygen, studies have found that the half-life of carboxyhemoglobin in blood is 4 to 6 hours. With oxygen, it has been found to range from 1 to 2 hours (130).

The most important decision is whether to administer hyperbaric oxygen (HBO). While HBO decreases the half-life of carbon monoxide even more rapidly than 100% normobaric oxygen, this is not a clinically important objective. Most patients who are brought to a hospital will survive whether or not they receive HBO. The value of HBO is its potential to decrease morbidity, not mortality. Specifically, HBO may reduce delayed neurologic sequelae. In animal models, HBO prevents brain lipid peroxidation and regenerates CNS cytochrome oxidase after CO exposure (131,132).

The use of HBO for CO poisoning is controversial. Both acid and base produce damage to the oropharynx, esophagus, stomach, and respiratory tract. Acids and alkalis produce damage to the oropharynx, esophagus, stomach, and respiratory tract. Acid and alkali produce damage to the oropharynx, esophagus, stomach, and respiratory tract.
hyperemia without ulceration; grade II burns demonstrate ulcers, but do not damage periesophageal tissues; grade II lesions are subdivided into IIa (noncircumferential) and IIb (circumferential) lesions; and grade III describes burns with deep ulceration and damage to surrounding tissues. The classification of the burn predicts chronic sequelae: Grade IIB and III injuries may heal with strictures and dysphagia, and may perforate. When esophageal perforation is suspected, or when there is airway injury, patients should be admitted to the ICU.

Clinical Manifestations

The lack of oral burns does not exclude significant esophageal injury, nor does the presence of oral lesions guarantee visceral burns. The physical examination following caustic ingestion can be deceiving. A series of pediatric patients found visceral burns in 37.5% of patients without oral burns and 50% of patients with oral burns (141). Deroofing, edysmophagia, and abdominal pain are common findings following significant caustic exposure. However, a series of acid ingestions noted abdominal pain or tenderness in less than half of patients with gastric injury (138).

Pulmonary aspiration may lead to coughing and respiratory distress. Absorption of acid from the stomach may cause acidemia following ingestion. Alkalins are not systemically absorbed in consequential amounts, but a metabolic acidosis may be present if significant injury has occurred.

Management

Endoscopy should be performed in all adult patients presumed to have significant exposures in order to establish the severity of the burn. If endoscopy is normal, the patient can be safely discharged, while patients with severe injury are rapidly stabilized and referred for surgical care before their condition worsens. Endoscopy should be performed as early as possible, ideally within 12 hours. Wound strength is weakest between 5 days and 2 weeks postingestion, when the perforation risk is greatest.

The exception to universal endoscopy may be a subset of pediatric patients based on a series of 79 patients younger than 20 years of age when no serious esophageal injuries were observed in patients who lacked stridor or the combination of drooling, odynophagia, and abdominal pain (142). A group of investigators found no lesions in asymptomatic pediatric patients (143). The lack of oral burns does not exclude significant esophageal injury, nor does the presence of oral lesions guarantee visceral burns. The physical examination following caustic ingestion may heal with strictures and dysphagia, and may perforate. When esophageal perforation is suspected, or when there is airway injury, patients should be admitted to the ICU.

HYDROFLUORIC ACID

Hydrofluoric acid (HF) is a weak acid, and does not have important tissue-corrosive properties. HF and ammonium bifluoride have numerous industrial uses. HF dissolves metal oxides and glass, making it useful in rust removal and glass etching. Because of these properties, HF is stored in plastic, not glass.

HF is an important dermal, ophthalmic, pulmonary, and systemic toxin. HF penetrates deeply into tissues before dissociating into protons and fluoride ions. Although the protons cause some damage, the most important toxic effects result from fluoride ions binding the divalent cations calcium and magnesium (147). The consumption of these cations leads to neuropsychic pain and cell death. HF ingestions and exposures resulting in electrolyte abnormalities require ICU admission.

Clinical Manifestations

HF produces a clinical syndrome distinct from the caustic agents and requires specific therapy. In small dermal exposures, HF produces severe pain with limited dermal findings. Large exposures by any route, including dermal, can produce severe hypocalcemia and death.

Most unintentional HF exposures are dermal. The severity of HF exposure is determined by the duration of exposure, concentration, and extent of surface area exposed. Solutions with low fluoride concentration may cause severe pain beginning hours after the exposure, with a very unremarkable physical examination. An area that appears normal or merely mildly erythematous may be extremely painful. High-concentration industrial preparations may cause immediate pain, with hyperemia and ulceration (148). Similarly, ophthalmic exposures result in pain, chemosis, and damage to conjunctiva and corneal epithelium (149).

The most consequential effects of HF poisoning are systemic. Systemic toxicity can result from ingestions or dermal exposures. Dermal exposures to concentrated HF covering as little as 2.5% body surface area have resulted in systemic toxicity, although typical fatal dermal exposures are larger (150,151). Fluoride ions scavenging divalent cations, causing hyperkalemia may be seen as well (152). The electrocardiogram may reflect these electrolyte abnormalities. Lengthening of the QRS and QT intervals or presence of peaked T waves may be early indicators of toxicity. The proximal cause of death is usually dysrhythmias; ventricular fibrillation and sudden cardiac arrest have been described (153,154).

Management

The most important concern in small dermal injuries is pain control. The mainstay of therapy is calcium gluconate. The calcium derives its efficacy from binding fluoride ions. Calcium chloride should only be used topically. Should calcium extravasate, the solution itself can cause tissue damage. Other
ANTIDIABETIC AGENTS

Diabetes is characterized by an inability to maintain normal blood glucose concentration due to deficiency of insulin, resistance to insulin, or a combination of both. The medications used to treat diabetes are collectively known as antidiabetic agents, while a subset of these drugs are properly called hypoglycemics. The hypoglycemics include insulin and those drugs that promote the release of endogenous insulin. The terms hypoglycemic agents and antidiabetic agents are not synonymous, because many diabetic medications (metformin, thiazolidinediones) cannot produce hypoglycemia. In 2005, the AAPCC received reports of 8,695 exposures to sulfonylureas and biguanides, including 244 major exposures and 28 deaths (6). The antidiabetics are a diverse group of drugs, but some important generalizations can be made. The sulfonylureas, meglitinides, and thiazolidinediones are very highly protein bound, and thus not amenable to extracorporeal removal. Insulin and metformin are completely renally eliminated, while most of the sulfonylureas have active hepatic metabolites with urinary excretion of both active metabolites and the parent drug. By far, the most important pharmacokinetic parameter of the hypoglycemics is duration of action. Of great clinical importance, the duration of action of insulin and the sulfonylureas is greatly increased in overdose. Insulin is available in multiple forms. Short-acting insulin preparations are designed to reduce postprandial hyperglycemia, while long-acting forms are intended to create a constant basal level of insulin. In therapeutic subcutaneous doses, it has onset of action within an hour and duration of action of less than 5 hours. Ultralente insulin, the longest-acting insulin commonly used, does not take effect for 4 to 6 hours but lasts as long as 36 hours (161). Regular insulin, lente, and NPH fall in between lispro and ultralente insulin. In overdose, the formation of deposits of the drug in tissues can slow release and greatly prolong the duration of action. The vascularity of the site of injection will also influence the duration of hypoglycemia. The sulfonylureas generally have a duration of action of 12 to 24 hours in therapeutic doses. Chlorpropamide, a first-generation sulfonylurea, may promote insulin release for up to 72 hours (162). As in the case of insulin, the duration of action is prolonged in overdose, resulting in delayed hypoglycemia (163). Meglitinides, intended to prevent postprandial hyperglycemia, induce insulin release for only 1 to 4 hours. There is not yet enough data on their pharmacokinetics in overdose, but it appears likely that duration of action would be increased in overdose.

Clinical Manifestations

The most important signs and symptoms of the aptly classified hypoglycemics are manifestations of decreased serum glucose. The diagnosis of hypoglycemia is established by interpreting a serum glucose concentration in the context of a patient’s clinical status. In one study, the serum glucose threshold for symptoms of hypoglycemia was 78 mg/dL in poorly controlled diabetics and 53 mg/dL in nondiabetes (164). Manifestations of hypoglycemia can be classified as either autonomic or neuroglycopenic. The former result from an increase in counterregulatory hormones (e.g., epinephrine), while the latter are due to a lack of glucose substrate available for the brain. The autonomic symptoms include tremor, diaphoresis, hunger, and nausea. Neuroglycopenic features of hypoglycemia can manifest as almost any conceivable neurologic deficit, including coma, agitation, seizure, hemiplegia, or mild confusion. Typically, the autonomic symptoms precede neuroglycopenic symptoms, thereby serving as a warning of hypoglycemia before the brain is deprived of a critical level of glucose. However, the autonomic symptoms may be blunted or absent in diabetics or patients taking β-adrenergic antagonists (165). The onset and duration of hypoglycemia is unpredictable after overdose. Of less clinical importance, the hypoglycemics can also produce electrolyte abnormalities such as hypokalemia, hypomagnesemia, and hypophosphatemia (166). These are reported more frequently in very large insulin overdoses (167).

Metformin does not produce hypoglycemia itself, but is often formulated with drugs that do, such as glipizide or glyburide. Metformin and its biguanide predecessor, phenformin, are associated with lactic acidosis. The biguanides promote anaerobic metabolism and inhibit lactate metabolism (168). Lactic acidosis is rare, but is more likely in the setting of liver disease, renal insufficiency, heart failure, other acute illness,
or acute overdose (169,170). Hepatotoxicity is reported from therapeutic use of thiazolidinediones and acarbose, but there are limited data on acute overdose of these drugs (171,172).

**Management**

A rapid bedside serum glucose concentration should be obtained as soon as hypoglycemia is considered. If the diagnosis of hypoglycemia is established, 1 g/kg intravenous dextrose should be given. Because high concentrations of dextrose can be irritating, children should receive 25% dextrose solution and infants 10% dextrose solution. As soon as a normal mental status is restored, the patient should be fed. Each 50-mL vial of 50% dextrose supplies 100 kcal of short-lived simple carbohydrate. In contrast, a meal will supply hundreds of “sustained-release” kilocalories. Glucagon should not be administered unless intravenous access is delayed and the patient cannot be fed. Glucagon will not be effective in patients with depleted glycogen stores.

If hypoglycemia recurs after it is initially corrected, the treatment is determined by the causative agent. Recurrent insulin-induced hypoglycemia should be treated with a dextrose infusion. Administer a 10% to 20% solution and titrate to maintain glucose in a normal range. A 5% dextrose solution is inappropriate for glucose maintenance.

Octreotide, a somatostatin analogue, is indicated for hypoglycemia following sulfonylurea use. Octreotide should be given subcutaneously, 50 μg every 6 hours (4–5 μg/kg/day in divided doses in children). Dextrose alone might not be sufficient to manage sulfonylurea-induced hypoglycemia. Because sulfonylureas potentiate endogenous β-islet cell insulin release, supplemental dextrose will induce more insulin release, with transient corrections and subsequent recurrence of hypoglycemia. Octreotide inhibits the β-islet cell calcium channel, inhibiting sulfonylurea-induced insulin release (173,174).

There are no significant adverse effects of short-term octreotide use. Octreotide should be continued for 24 hours. After octreotide is discontinued, the patient should be observed for 24 hours. There are limited data in the literature regarding meglitinide toxicity. With a mechanism of action similar to the sulfonylureas, the meglitinides are shorter acting. Based on their shorter duration of action, we would expect they would be less likely to produce recurrent hypoglycemia, but we have no data to support this assumption. Until we have more experience with overdose of these drugs, it is prudent to manage meglitinide overdose similarly to sulfonylureas.

Metformin-associated lactic acidosis should be considered in patients taking an overdose of metformin, children exposed to more than one or two tablets, and those patients who take metformin therapeutically who also have renal insufficiency, hepatic insufficiency, heart failure, or another acute illness. The diagnosis is established by obtaining a serum chemistry, lactate concentration, and serum pH. The primary therapy is supportive. Although the role of bicarbonate in metformin-associated lactic acidosis is unclear, supplemental bicarbonate should be used to maintain the pH above 7.1. Although metformin is highly protein bound, hemodialysis can be used to correct refractory acidosis (175).

Adults who present with a history of sulfonylurea overdose and children who may have been exposed to sulfonylureas should be observed for 24 hours, even in the absence of hypoglycemia. Similarly, patients who present with hypoglycemia from long-acting forms of insulin should be observed for 24 hours as well.

**NATURAL TOXINS**

**Plants**

This brief discussion focuses on a few important plants that might necessitate intensive care management. In 2005, there were 76 major outcomes resulting from plant exposure that were reported to the AAPCC.

**Belladonna Alkaloids**

Plants such as jimsonweed (Datura stramonium) contain numerous anticholinergic compounds. They are used recreationally, often in the form of teas, for their hallucinatory effects. Toxicity is identified by the presence of anticholinergic symptoms: tachycardia; hyperthermia; dry, flushed skin; urinary retention; and agitation. One hundred jimsonweed seeds contain nearly 6 mg of atropine and similar alkaloids (176). In addition to supportive care, physostigmine can be given when the diagnosis is relatively certain. Physostigmine is administered 1 to 2 mg IV slowly over 5 minutes. Physostigmine should be discontinued and the diagnosis reconsidered if cholineric symptoms develop. If there is improvement or no change in the patient’s condition, physostigmine can be readministered after a 10- or 15-minute delay.

**Nicotine and Nicotineline Alkaloids**

Nicotine poisoning occurs from inhaled, transdermal, and ingested nicotine. A dose of 1 mg/kg can be lethal in an adult (177). A cigarette contains 13 to 30 mg of nicotine, but most of it is not delivered to the smoker when the cigarette is used as intended. The largest portion of the nicotine is protonized but not inhaled. As much as 5 to 7 mg of nicotine remains in the cigarette butt, a potentially lethal dose for a child (178). Workers handling tobacco can be poisoned from nicotine as well (179). Signs and symptoms of nicotine toxicity result from activation and then inhibition (from overstimulation) of nicotinic receptors. Gastrointestinal signs include nausea, vomiting, and diarrhea. Early cardiovascular toxicity involves hypotension from nicotinic stimulation of the sympathetic ganglia, but hypotension eventually occurs. The most important signs and symptoms result from nicotinic agonist effects at the neuromuscular junction. Early toxicity causes fasciculation, which gives way to paralysis. Management is supportive. Vasodepressor agents may be necessary to maintain blood pressure, and intubation may be indicated to support respiration during paralysis.

**Cicutoxin**

Cicutoxin is found in Cicuta spp., such as water hemlock. The toxin is found throughout the plant, which is often eaten by adults who misidentify it as wild parsley, turnip, or parsnip (180). The mechanism of cicutoxin poisoning is unclear. Early
symptoms are primarily gastrointestinal and begin soon after ingestion. Later, cicutoxin can cause status epilepticus, renal failure, and rhabdomyolysis (181).

Sodium Channel-altering Plants
Aconitine, from Aconitum spp., opens sodium channels, increasing cellular excitability (180,182). Increased sodium influx delays repolarization, which in turn delays conduction. Slow conduction of peripheral nerves can lead to decreased sensation, weakness, paralysis, and CNS seizures. Vagal and cardiac myocyte sodium channel effects lead to bradycardia, atrioventricular blockade, increased automaticity, or asystole. Aconitine is found in Aconitum napellus (monkshood) and Chinese herbal remedies. Management is supportive. Gastrointestinal decontamination should be performed. Cardiac complications have been successfully managed with a ventricular assist device (183).

Mushrooms
Forty-six major outcomes and six deaths from mushroom ingestions were reported to poison control centers in 2005 (6). The vast majority of mushroom exposures do not result in significant morbidity, and most of the fatalities that occur are caused by only a few of the many mushroom species in North America. Identification of mushrooms is challenging and best left to the mycologist. However, because each of the clinically important toxic mushrooms causes a distinct clinical syndrome, the physician should be able to identify the toxicologic manifestations of several mushrooms. Mushroom toxins have been divided into ten groups (184). We will discuss the most common exposures and those most likely to require ICU care.

Gastrointestinal Toxin-containing Mushrooms
Most reported exposures are to mushrooms containing gastrointestinal toxins. Hundreds of types of mushrooms fall into this category. The most notable clinical feature of ingestion of these mushrooms is the development of vomiting and diarrhea within several hours of ingestion. With few exceptions, mushrooms that cause gastrointestinal symptoms within 6 hours belong to this category and will not cause life-threatening symptoms. The early onset of vomiting following exposure to gastrointestinal toxin-containing mushrooms clinically differentiates them from the cyclopeptide-containing mushrooms. Treatment of exposure to these mushrooms is supportive, and symptoms are generally self-limited. These mushrooms rarely lead to toxicity requiring ICU admission.

Cyclopeptide-containing Mushrooms
Three of five fatalities from mushrooms in 2004 were related to cyclopeptide-containing mushrooms. Historically, mortality from these mushrooms is high, although improvements in critical care have improved the prognosis. The most prominent member of this group is Amanita phalloides and other Amanita species. Amanita phalloides contains numerous cyclopeptides, but the most important are a group called the amatoxins. Amatoxins are heat stable and present in lethal concentrations in mushrooms as small as 20 g (184).

Clinical Manifestations and Management. Amatoxins cause endocrine, renal, and CNS injury, but the hepatic effects are the most consequential. Patients will be asymptomatic for the first few hours after ingestion. In 5 to 24 hours, patients will have watery diarrhea. Hepatic toxicity is evident on day 2 with elevations in bilirubin, AST, and ALT. Signs of fulminant hepatic failure such as encephalopathy and coagulopathy follow. Hyponatremia results not just from hepatic failure, but from direct pancreatic toxicity (185). Cyclopeptides may also cause decreased levels of thyroid hormone and increased calcitonin.

Because patients do not seek help until symptoms develop, it is not uncommon for patients to present to a healthcare facility with volume depletion and early hepatic injury. Good supportive care and prevention of secondary complications are the keys to management. Activated charcoal should be administered 1 g/kg every 2 to 4 hours in order to adsorb any toxin remaining in the gut and interrupt the potential enterohepatic circulation (186). Many therapies to mitigate hepatotoxicity have been investigated, with no substantial or reproducible evidence of efficacy.

Although there are no data to support its use in Amanita poisoning, NAC effectively treats hepatic failure from other hepatotoxins, such as acetaminophen. Administer NAC intravenously, according to the acetaminophen protocol: 150 mg/kg over 45 minutes, 30 mg/kg over 4 hours, and 100 mg/kg over 16 hours. Continue the final infusion until the patient expires, definitively recovers, or receives liver transplant.

Silibinin, extracted from milk thistle, improved hepatic markers and mortality in a dog model of Amanita poisoning, but was not found beneficial in a meta-analysis of human studies (187). Because a clinical trial will likely never be conducted, and in light of its experimental benefits, we recommend orally administered silybin, 20 to 50 mg/kg/day. Silybin is not a Food and Drug Administration-approved drug, but is available at health food stores.

High-dose penicillin had some effectiveness in a dog model of Amanita poisoning, possibly by blocking hepatic uptake of amatoxin (188). Therapy includes intravenous penicillin G, 1 million units/kg/day in divided doses (189).

The criteria for liver transplantation have not been clearly established. Transplantation is not without risk, and those who survive fulminant hepatic failure from Amanita without transplantation are expected to make a full recovery. Ideally, the decision to transplant should be delayed until it is clear the patient will not recover. Some consider transplantation for those with encephalopathy and prolonged PT, persistent hyponatremia, metabolic acidosis, increased serum ammonia, aminotransferases, and hypofibrinogenemia (184). Patients should be referred to transplantation centers early in their clinical course so that they may be listed early, and transport should be avoided when they are gravelly ill.

Gyromitrin-containing Mushrooms
Gyromitra mushrooms are found throughout the United States. These mushrooms contain gyromitrin (N-methyl-N-formyl hydrazine), which is hydrolyzed to monomethylhydrazine (MMH). MMH inhibits the formation of pyridoxal-5-phosphate (PLP), an enzyme cofactor synthesized from pyridoxine (vitamin B6). Of great importance, PLP is a cofactor for glutamic acid decarboxylase, the enzyme in the CNS that converts glutamate to GABA. Inhibition of PLP by monomethylhydrazine results in excessive excitation relative to inhibition.
Clinical Manifestations and Management. The initial phase of toxicity, occurring 5 to 10 hours after ingestion, is manifest by nonspecific clinical features including nausea, vomiting, diarrhea, and headache, and ultimately leads to intractable seizures (184). Patients ingesting Gyromitra spp. should receive activated charcoal, 1 g/kg. Seizures may not respond to benzodi- azeptines alone. If Gyromitra spp. ingestion is considered, or if a patient presents with seizures after mushroom ingestion, pyridoxine 70 mg/kg IV should be given. Pyridoxine serves as substrate for pyridoxine phosphokinase, allowing some PLP to be generated despite inhibition by MMH.

Allenic Norleucine–containing Mushrooms

The nephrotoxic Amanita smithiana contains the amino acid toxin allenic norleucine (amino-hexadienoic acid) and possibly 1,2-amino-6-pentenionic acid (184). All known exposures to these mushrooms have occurred in the Pacific Northwest of the United States. These serve as important exceptions to the “rule” that mushrooms that cause early gastrointestinal toxicity do not cause significant end-organ damage later.

Clinical Manifestations and Management. Initial symptoms, which include nausea, vomiting, diarrhea, and abdominal cramping, may begin within an hour of ingestion. The most important clinical features of toxicity develop later. Acute renal failure, indicated by elevations in blood urea nitrogen (BUN) and creatinine, manifest 4 to 6 days following ingestion (190). Activated charcoal should be administered when patients present after ingesting mushrooms from the Pacific Northwest. Management of nephrotoxicity is supportive. Patients who require hemodialysis undergo the procedure two to three times per week for approximately 1 month (184).

Orellanine- and Orellinine-containing Mushrooms

Cortinarius orellanus, found in North America, contains the toxin orellanine, which is converted by photochemical degradation to another toxin, orellinine (184). Orellanine and orellinine are important causes of mushroom-induced nephrotoxicity. Orellanine is activated by the P450 system. These molecules generate oxidative damage by sustained redox cycling.

Clinical Manifestations and Management. Symptoms begin 24 to 36 hours after ingestion. Patients report headache, chills, polydipsia, nausea, and vomiting. Early laboratory findings of hematuria, leukocyturia, and proteinuria indicate interstitial nephritis. Later, renal failure develops, characterized histologically by tubular damage and fibrosis of tubules with relative glomerular sparing (191,192). Hepatotoxicity is an uncommon feature. Management is supportive. Administer activated charcoal if patients present early. Some patients will rapidly improve, whereas others require chronic hemodialysis (193).

OTHER RESOURCES

This chapter is intended to be a review of common and consequential xenobiotic exposures. Goldfrank’s Toxicologic Emergencies (McGraw-Hill, 2006) contains a more comprehensive review of all the substances discussed here. The regional poison center (1-800-222-1222) is an excellent resource for further information and recommendations specific to your patient.

Owing a great deal to the success of prevention measures, significant poisonings are relatively rare events. In 2005, there were fewer than 20,000 patients with major effects and deaths reported to the AAPCC. Although this figure underestimates total poisoning, it represents a very small number of patients per hospital per year. Because each ICU sees a paucity of these patients, many critical care physicians do not see enough of them to develop familiarity with their care. We encourage close collaboration between ICU physicians, regional poison centers, and toxicologists to provide the best possible care to poisoned patients.

TREATMENT REFUSAL

Patients with toxicologic emergencies are often suicidal and self-destructive, and may have an altered level of consciousness. We have an ethical obligation to our patients to allow them to guide their own treatment. At times, this means that the patient will decide against the physician’s recommendation. In order to refuse care, the patient must demonstrate the capacity to understand his or her condition and the implications of treatment refusal. The refusal must be voluntary in the absence of a medical or psychiatric condition precluding the ability to make such a decision. The hospital has the right to physically restrain a person who has an altered level of consciousness for the purpose of evaluation and intervention (194). There is a potential for legal liability whenever the medical staff physically restrain a patient, retain a patient against his or her will, or allow a patient to refuse a life-saving therapy. The physician and hospital staff can reduce liability by thoroughly documenting the patient’s decision-making process and by involving psychiatric consultation in determining the patient’s capacity. When in doubt, the physician should consult the hospital’s legal department.

References

# APPENDIX

## SELECTED ANTIDOTES WITH COMMON DOSES

<table>
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<tr>
<th>Xenobiotic</th>
<th>Antidote and dose</th>
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| Acetaminophen | N-acetylcysteine: IV: 150 mg/kg infused over 60 min, followed by 50 mg/kg over 4 h, then 100 mg/kg over 16 h  
Oral: 140 mg/kg, followed by 70 mg/kg every 4 h for 17 doses |
| β-Adrenergic antagonists | Atropine (for bradycardia): 0.5–1 mg IV  
Glucagon: 3–5 mg IV (50 μg/kg in children) up to 10 μg/h  
Calcium: 13–25 mL of CaCl₂ IV bolus (10–20 mL of 10% calcium chloride or 30–60 mL of 10% calcium gluconate)  
Hyperinsulinaemia/euglycaemia: Insulin 0.5–1 U/kg/h accompanied by 0.5 g/kg/h dextrose, titrated to maintain euglycaemia |
| Calcium channel blockers | Atropine (for bradycardia): 0.5–1 mg IV  
Calcium: 13–25 mL of CaCl₂ IV bolus (10–20 mL of 10% calcium chloride or 30–60 mL of 10% calcium gluconate)  
Glucagon: 3–5 mg IV (50 μg/kg in children) up to 10 μg/h  
Hyperinsulinaemia/euglycaemia: Insulin 0.5–1 U/kg/h accompanied by 0.5 g/kg/h dextrose, titrated to maintain euglycaemia |
| Cholinergic compounds | Atropine: 1 mg IV (0.05 mg/kg in children) doubled every 2 min until muscarinic symptoms are controlled  
Pralidoxime: Adults: 1–2 g IV over 30 min followed by 500 mg/g infusion for sickest patients.  
Children: 20–50 mg/kg (max 1–2 g) infused IV over 30–60 min and then 10–20 mg/kg/h (max 500 mg/h) |
| Cyanide | Adults: 1. Sodium nitrite: 300 mg (10 mL of a 3% conc.) infused IV over 2–5 min  
2. Sodium thiosulfate: 12.5 g (50 mL of a 25% conc.) infused IV over 10–20 min or as a bolus  
3. Hydroxocobalamin IV 70 mg/kg (up to 5 g)  
Children: 1. Sodium nitrite: 6–8 mL/m² (0.2 mL/kg of a 3% conc., up to adult dose) infused IV over 2–5 min  
2. Sodium thiosulfate: 7 g/m² (0.5 g/kg, up to adult dose) infused over 10–30 min or as a bolus |
| Cyclic antidepressants | Sodium bicarbonate: 1 mL/kg IV bolus, followed by infusion of 150 mL in 1 L of D5W, infused at twice maintenance rate |
| Digoxin | Digoxin-specific Fab: Known level: # of vials = [wt (kg) × level (ng/mL)]/100 rounded up to nearest vial. Empiric dosing: Acute: 10–20 vials. Chronic: Adults 3–6 vials; children: 1–2 vials. Usually given as IV infusion over 30 min (administer as IV bolus for asystole) |
| Ethylene glycol, methanol | Fomepizole: 15 mg/kg infused IV over 30 min; next 4 doses at 10 mg/kg every 12 h; additional doses at 15 mg/kg every 12 h if needed  
Ethanol (when fomepizole not available): 0.8 g/kg infused IV over 20 to 60 min, followed by initial infusion of 100 mg/kg/h |
| Methemoglobin | Methylene blue: 1–2 mg/kg IV over 5 min followed by a 30-mL fluid flush |
| Salicylates | Sodium bicarbonate: 150 mL in 1 L of D5W, infused at twice maintenance rate. Activated charcoal, 1g/kg every 4 h |
| Sulfonylurea-related hypoglycaemia | Octreotide: 30 μg SQ every 6 h. Children: 1.25 μg/kg (up to adult dose) SQ every 6 h |