Physicians frequently encounter critically ill patients who were poisoned under a variety of circumstances. The wide range of clinical syndromes that occur as a result of overdose or recreational use of an ever-increasing array of available prescription and illicit drugs provides a continuous challenge to the intensive care physician. This article is the first of a three-part series to be published in CHEST; it discusses general management, laboratory tests, enhanced elimination, and emerging therapies. The second article will address the management of specific overdoses; the last will cover plants, mushrooms, envenomations, and heavy metals.

**Toxidromes**

Specific toxic syndromes (toxidromes) arise from similarities in the pharmacology of many poisons, permitting treatment to be started empirically, based on clinical presentation without definitive knowledge of the offending agent. The classic toxidromes include opioid, sedative-hypnotic, anticholinergic, cholinergic, and sympathomimetic (Table 1).

The classic opioid toxidrome results from the stimulation of opioid receptors by naturally occurring opiates, such as morphine and codeine, or by synthetic opioids, such as oxycodone, hydrocodone, hydromorphone, and fentanyl. The toxidrome is characterized by bradypnea, depressed mental status, and miosis. Miosis and a respiratory rate of ≤ 12 breaths/min are both sensitive (88% and 80%, respectively) and specific (90% and 95%, respectively) for predicting a response to naloxone. Opioids produce a general depression in autonomic activity; bradycardia,
hypotension, and hypothermia are common. Hypoactive bowel sounds are possible.4,5

This classic toxidrome may be obscured in mixed overdoses, and several opioids have unique clinical features of importance. Meperidine, propoxyphene, and tramadol can cause seizures.6-9 Miosis is not reliably present in the setting of tramadol or meperidine toxicity,10 or with mixed ingestions. Propoxyphene produces sodium channel blockade, which is associated with QRS prolongation and cardiovascular collapse,8,9 whereas potassium efflux blockade and QT prolongation are commonly observed with methadone toxicity.11 The rapid administration of high-dose IV fentanyl can induce chest wall rigidity, which can complicate ventilation.12

The sedative-hypnotic toxidrome also produces a generalized decrease in autonomic activity. Agents that may produce this toxidrome include benzodiazepines, benzodiazepine-like agents (eg, zolpidem), barbiturates, carisoprodol, chloral hydrate, ethanol, and baclofen. In most cases, CNS depression is enhanced via binding at postsynaptic y-aminobutyric acid type A channels, thereby promoting chloride influx and neuronal hyperpolarization.13 Characteristic clinical effects are anxiolysis and, as mentioned earlier, CNS depression. Respiratory depression and hypothermia may also occur.

The sympathomimetic toxidrome is often caused by stimulants such as cocaine and methamphetamine. Several over-the-counter and prescription medications, such as pseudoephedrine, caffeine, and agents used to treat attention deficit disorders (eg, methylphenidate), can also produce this toxidrome. Signs may include tachycardia, hypertension, hyperthermia, tachypnea, CNS excitation, and diaphoresis. Pupils are characteristically dilated but reactive.14,15 Agitation and muscular hyperactivity are common and may produce life-threatening hyperthermia.16

Sympathomimetics produce a general increase in sympathetic tone via several mechanisms, depending on the drug.17-19 These include increased release of catecholamines, inhibition of reuptake, direct receptor stimulation, and altered neurotransmitter metabolism.18 The differing modes of action may explain why cocaine intoxication responds well to benzodiazepines, whereas amphetamine-induced toxicity may be relatively resistant.20-23 Another example of a sympathomimetic, clenbuterol, is a long-acting direct β-agonist used for its anabolic and lipolytic properties. Its use may result in tachycardia, hyperglycemia, hypokalemia, and myocardial infarction.24,25

Sedative-hypnotic withdrawal syndrome can appear similar to the sympathomimetic toxidrome, and occurs with abrupt discontinuation of a sedative-hypnotic agent following prolonged use. In patients with alcohol withdrawal, seizures may result, with >90% occurring
within the first 48 h. Severe alcohol withdrawal occurs in 5% of patients with a history of alcohol dependence admitted to the hospital. The most severe presentation of ethanol withdrawal, delirium tremens, is characterized by altered sensorium, abnormal neuromuscular activity, and autonomic hyperactivity. With aggressive treatment, the mortality from alcohol withdrawal has declined to < 5%. The anticholinergic toxidrome results from a multitude of different classes of drugs, including tricyclic antidepressants, antihistamines, antipsychotics, and cyclobenzaprine. It may be more accurately referred to as an antimuscarinic toxidrome, and is characterized by the combination of mydriasis, dry flushed skin, delirium, hyperthermia, tachycardia, urinary retention, and hypotonic bowel sounds. Mydriasis is not always present, especially if coexisting antagonism is present. Progression and severity of anticholinergic effects are often dose related. At low doses, dryness of the mouth and skin may be noted; moderate doses lead to worsening anhidrosis, mydriasis, and tachycardia. At higher doses, central anticholinergic effects will occur, including ataxia, agitation, delirium, hallucinations, and coma. Mumbling, incoherent speech, visual hallucinations, and carphologia (picking at imaginary objects) can be encountered.

The cholinergic toxidrome is characterized by an increase in secretions, with findings of lacrimation, salivation, bronchorrhea, and urinary and fecal incontinence. It is classically produced by organophosphate insecticide poisoning, but may also be produced by other medications that affect acetylcholinesterase, such as edrophonium or physostigmine. Bradycardia is common, but tachycardia may result from stimulation of nicotinic receptors or hypoxia. Bronchorrhea, bronchospasm, bradycardia, and hypotension are ominous signs and indicate the need for aggressive therapy with atropine. Muscle weakness, including respiratory muscle paralysis, may occur because of nicotinic hyperstimulation and does not respond to atropine. Serotonin syndrome describes a combination of symptoms that is precipitated by the interaction or overdose of multiple proserotonergic medications, resulting in an increase in CNS serotonin activity. Initially, mild symptoms such as tachycardia and tremor may be noted. If the offending drugs are not removed, or in the case of ingestions of multiple serotonergic medications, more severe manifestations may develop, including hyperthermia, myoclonus, muscle rigidity, opsoclonus, agitation, delirium, and diaphoresis.

Neuroleptic malignant syndrome (NMS) is characterized by hyperthermia, altered mental status (AMS), autonomic instability, and lead-pipe rigidity (increased muscle tone without tremor or cog-wheeling). Unlike serotonin syndrome, which occurs following a predictable increase in synaptic serotonin concentrations, NMS is at least partially idiosyncratic. However, it should be noted that commencing neuroleptic therapy at high doses, or rapidly increasing the dose, can increase the risk of NMS. NMS can present along a spectrum; milder forms manifest simply with AMS and rigidity, whereas more severe forms have autonomic life-threatening autonomic instability, hyperthermia, and rhabdomyolysis. Prolonged hyperthermia is associated with a poor outcome. The syndrome generally follows therapeutic administration of a typical or atypical antipsychotic, but has also been reported following withdrawal of prodopaminergic medications such as levodopa/carbidopa. NMS is a diagnosis of exclusion; the differential diagnosis includes serotonin syndrome, anticholinergic toxicity, lethal catatonia, and malignant hyperthermia.

**TOXICOLOGY LABORATORY STUDIES**

Serum or urine assays to detect or quantify specific medications or illicit substances have clinical usefulness in many situations. In cases in which it is unclear whether a patient is intoxicated or whether an alternative diagnosis exists, these assays can be very helpful in ruling out or confirming specific drug intoxication as a cause of illness. For example, in a patient with delirium, tachycardia, and fever, a urine drug screen (UDS) that is negative for cocaine or methamphetamine might point the physician toward an infectious cause, whereas a positive UDS might direct him or her toward more specific treatment, such as the generous use of benzodiazepines, early intubation, and aggressive cooling measures. Specific drug assays will not be useful or affect the management of every patient, however, and when interpreting results, the physician must always consider the limitations of the particular test and whether the results “make sense,” considering the clinical findings.

Most UDS are immunoassays, in which the binding of an antibody to a recognized chemical structure produces a positive result. However, not all drugs in a class have a shared structure, so false-negative results are common. For instance, benzodiazepines, which are not metabolized to oxazepam, such as lorazepam and alprazolam, may be missed in some UDS. The cannabinoid screen detects a metabolite of 8-9-tetrahydrocannabinol and thus misses dissimilar compounds with cannabinoid effects, such as JWH-018, the synthetic cannabinoid found in “spice.” Alternatively, substances in other drug classes may posses a structure similar to that of the targeted substances, yielding a false-positive result.
For example, because of structural similarities with the tricyclics, diphenhydramine, cyclobenzaprine, carbamazepine, and quetiapine may cause a false-positive tricyclic antidepressant screen.\textsuperscript{48-53} Because of the frequent false-positives from a UDS, results should be considered preliminary until confirmed by gas chromatography-mass spectrometry. The test specificity varies, depending on the immunoassay used. A UDS may also remain positive for a prolonged period, so in many cases it will only suggest the historical use of an agent (Table 2).\textsuperscript{51,54} Urinary levels of most drugs do not correlate with intoxication.

Obtaining serum drug concentrations may also be useful in some circumstances. As examples, lithium, digoxin, valproic acid, carbamazepine, phenytoin, salicylate, and acetaminophen concentrations may all influence management (Table 3). Others, such as tricyclic antidepressants, are of less use because specific concentrations do not correlate well with clinical findings. However, in some cases they may be useful in confirming excessive exposure.

### Gaps

The anion gap (AG) is the difference between the measured dominant cations and anions, with a normal AG occurring between 4 and 12 mEq/L. An elevated AG usually results from increased unmeasured anions and assists in narrowing the differential for metabolic acidosis (Table 4). A low or negative AG may occur with lithium, bromide, or iodide.\textsuperscript{55,56} Hyperlipidemia or hypoalbuminemia may also cause a decreased AG.\textsuperscript{56-58}

The osmolal gap (OG) is the difference between the measured osmolality (mOsm/kg water) and the calculated osmolarity (mOsm/L) and is used to detect the presence of osmotically active substances (Fig 1).\textsuperscript{59,60}

### Coma Cocktail

Historically, the initial treatment of patients with undifferentiated AMS included use of a “coma cocktail,” which refers to IV administration of dextrose, thiamine, and naloxone. Rapid glucose testing is often available, in which case hypoglycemia can be confirmed and rapidly corrected. If rapid glucose analysis is unavailable, dextrose should be administered empirically.\textsuperscript{64}

Thiamine (vitamin B\textsubscript{1}) is administered routinely with dextrose, in a dose of 100 mg, to prevent precipitation of Wernicke encephalopathy. This concern is not evidence based and is attributed to a poorly described case series.\textsuperscript{65} However, Wernicke encephalopathy can complicate other medical conditions, including hyperemesis gravidarum.\textsuperscript{66} In suspected hypoglycemia, dextrose should not be withheld if thiamine is not available immediately.\textsuperscript{64} Furthermore, for true cases of suspected Wernicke encephalopathy, higher doses of thiamine are recommended.\textsuperscript{67}

### Table 2—Detection Period of Commonly Detected Drugs on a Urine Drug Screen

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approximate Detection Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine, methamphetamine</td>
<td>4 d</td>
</tr>
<tr>
<td>Barbiturates</td>
<td></td>
</tr>
<tr>
<td>Short acting (eg, pentobarbital)</td>
<td>24 h</td>
</tr>
<tr>
<td>Long acting (eg, phenobarbital)</td>
<td>3 wk</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td></td>
</tr>
<tr>
<td>Short acting (eg, lorazepam)</td>
<td>3 d</td>
</tr>
<tr>
<td>Long acting (eg, diazepam)</td>
<td>4 wk</td>
</tr>
<tr>
<td>Cocaine metabolite (benzoyleucgonine)</td>
<td>3 d</td>
</tr>
<tr>
<td>Marijuana (cannabinoids)</td>
<td></td>
</tr>
<tr>
<td>Single use</td>
<td>3 d</td>
</tr>
<tr>
<td>Long-term use</td>
<td>4 wk</td>
</tr>
<tr>
<td>Opiates (varies by agent)</td>
<td>4 d</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>8 d</td>
</tr>
</tbody>
</table>

Modified with permission from Chattergoon et al\textsuperscript{51} and McQuillen and Anderson.\textsuperscript{54}

### Table 3—Specific Serum Concentrations That May Affect Management

- Acetaminophen
- Carbamazepine
- Cooximetry (carboxyhemoglobin, methemoglobin, sulhemoglobin)
- Digoxin
- Selected metals (iron, lead, mercury; based on history and clinical findings)
- Lithium
- Phenytoin
- Salicylate
- Theophylline, caffeine
- Toxic alcohol (ethylene glycol, isopropanol, methanol)
- Valproic acid

Concentrations of sodium, BUN, creatinine, glucose, and measured osmolality, which are used in determining the OG, must be obtained simultaneously in order to increase validity. The normal OG ranges from −14 to 10.\textsuperscript{54,60} Ethanol, ethylene glycol, methanol, isopropanol, excipients (eg, propylene glycol), ketones, and shock states can raise the OG.\textsuperscript{61,62} It is important to remember that the large normal range for the OG may allow a patient to have a “normal” value despite a clinically significant gap for that patient.

The arterial oxygen saturation gap is the calculated percentage saturation (based on $P_{O_2}$ and pH) minus the percentage saturation measured by multiwavelength cooximetry (not simple pulse oximetry). An arterial oxygen saturation gap of >5% usually results from elevated levels of carboxyhemoglobin, methemoglobin, or sulhemoglobin. Cyanide poisoning does not result in an increased oxygen saturation gap.\textsuperscript{63}
The purpose of administering naloxone, a competitive opioid receptor antagonist, is to reverse opioid-induced respiratory depression. An ideal therapeutic goal is to prevent intubation without precipitating withdrawal. As such, a reasonable starting dose is 0.2 to 0.4 mg IV. This can be increased rapidly to a dose of 2 to 10 mg if no effect is achieved. The typical half-life is 30 to 80 min, so additional doses may be required for reversal of resedation.68,69 If multiple doses are administered, a continuous infusion of two-thirds the minimal effective dose may be administered per hour.70 Repeated doses of naloxone are often needed for agents with long half-lives, such as methadone or extended-release oxycodone. In addition to precipitation of opioid withdrawal, adverse reactions to naloxone include development of non-cardiogenic pulmonary edema or seizures (with tramadol or meperidine).64,71-77

Table 4—MUDPILES Mnemonic for Causes of Anion-Gap Acidosis

| M | Methanol, metformin |
| U | Uremia |
| D | Diabetic ketoacidosis |
| P | Paraldehyde, propylene glycol, propofol |
| I | Iron, isoniazid, ibuprofen |
| L | Lactate |
| E | Ethanol (alcoholic ketoacidosis), ethylene glycol |
| S | Salicylates, starvation ketoacidosis |

GI DECONTAMINATION

GI decontamination refers to any measures undertaken to minimize absorption of the toxin from the GI tract. These measures have traditionally included activated charcoal (AC), syrup of ipecac, gastric lavage, and whole-bowel irrigation (WBI). Because of a lack of proven benefit and undesirable side effects, however, the use of ipecac and gastric lavage are no longer recommended routinely.80-82

AC is most likely to be of benefit if given within 1 h of ingestion, although patients with certain ingestions, such as salicylate, may benefit from delayed administration.83,84 The recommended dose is 0.5 to 1 g/kg in children or 25 to 100 g in adults. Importantly, AC does not bind well to hydrocarbons, alcohols, or most metals (except thallium).85 Aspiration is a potential complication and may result in prolonged hospitalization, lung injury, or death.83,86-89 Therefore, AC administration is contraindicated unless the

<table>
<thead>
<tr>
<th>ALCOHOL</th>
<th>CONVERSION FACTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetoacetate</td>
<td>10.2</td>
</tr>
<tr>
<td>Acetone</td>
<td>5.8</td>
</tr>
<tr>
<td>Beta hydroxybutyrate</td>
<td>10.4</td>
</tr>
<tr>
<td>Ethanol</td>
<td>4.6</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>6.2</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>6.0</td>
</tr>
<tr>
<td>Methanol</td>
<td>3.2</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>7.2</td>
</tr>
</tbody>
</table>

For example, for a patient presenting after methanol ingestion, and $Na = 140 \text{ mEq/L}$, $BUN = 14 \text{ mg/dL}$, $Glu = 90 \text{ mg/dL}$, $EtOH = 46 \text{ mg/dL}$, measured serum osmolality = 390:

\[
\text{Calculated Osmolarity} = \frac{(2 \times 140) + (14/2.8) + (90/18) + (46/4.6)}{300}
\]

\[
\text{Osmol Gap} = \text{Measured Osmolality} - \text{Calculated Osmolarity} = 390 - 300 = 90
\]

\[
\text{Estimated serum methanol in mg/dL} = \frac{\text{Osmol Gap Increase} \times CF_{\text{methanol}}}{80 \times 3.2} = 256 \text{ mg/dL}
\]
patient is able to protect his or her airway or has been intubated. Common side effects include vomiting, abdominal bloating, constipation, or diarrhea. Relative contraindications include anticipated endoscopy or abdominal surgery. Cathartics (eg, sorbitol) should not be used. Importantly, the routine use of AC has not been demonstrated convincingly to reduce morbidity or mortality.

Unlike single-dose charcoal, which is used for gastric decontamination, the administration of repeated, scheduled doses of charcoal is a form of enhanced elimination and is referred to as multiple-dose AC. Although multiple-dose AC has been recommended and shown to decrease serum levels for various agents (theophylline, dapsone, phenobarbital, carbamazepine, and quinine), its use has not been demonstrated to improve patient-oriented outcomes (eg, mortality). Its routine use is not recommended.

WBI involves administering large volumes (1.5–2 L/h) of a polyethylene glycol-based solution to facilitate rapid transit of a toxin through the GI tract. In volunteer studies, WBI was effective in decreasing absorption of enteric-coated aspirin and sustained-release lithium tablets. Although it is not recommended routinely, WBI should be considered following ingestion of highly toxic, extended-release preparations such as verapamil, metals such as iron (especially those preparations with high concentrations of elemental iron), or asymptomatic drug packers. Contraindications include compromised airway, ileus, and bowel obstruction. As in the case of charcoal, data demonstrating improved clinical outcomes are lacking.

Endoscopy has been used to remove button batteries or drug bezoars, whereas laparotomy has been used to remove illicit drug packets (body packers or stufferers). Button batteries lodged in the esophagus or trachea mandate endoscopic removal. Symptomatic leakage of sympathomimetic drug packets generally mandates immediate laparotomy, whereas leakage of packets of heroin can be managed more conservatively. Bowel obstruction due to drug packet ingestion also requires operative management.

### Enhanced Elimination

All xenobiotics, or exogenous chemicals, achieve effectiveness and toxicity based on the ability to reach target tissues. Pharmacokinetic variables include absorption, distribution, metabolism, clearance, and elimination. Extracorporeal elimination techniques (EETs) seek to reduce or prevent toxic concentrations in target tissue. The ability of EETs to remove a xenobiotic depends on the xenobiotic’s molecular weight, protein binding, and apparent volume of distribution (Vd). Substances with a small Vd (< 1 L/kg) have limited penetration into tissue and maintain a relatively high intravascular concentration. Low molecular weight, low Vd, high water solubility, and low protein binding allow the xenobiotic to be removed more effectively by hemodialysis (HD) because the xenobiotic can cross the filtration membrane easier and dissolve into the dialysate.

The main EET used in the management of poisoning is HD, which can both reduce drug/metabolite concentrations and correct fluid and electrolyte abnormalities. A list of xenobiotics that undergo significant clearance by HD is given in Table 5. Hemoperfusion has advantages over HD for the treatment of some poisonings because of its ability to remove substances with high protein binding, such as carbamazepine, but is no longer available in most US centers.

The advantages of HD are technical ease and availability. Because HD removes xenobiotics only from circulating blood, intercompartmental transfer or prolonged absorption may require prolonged or recurrent treatments. This scenario commonly occurs with the treatment of lithium toxicity, where levels can rise again because of redistribution many hours after HD is completed. In cases where rebound is a concern, a precartridge level should be obtained before terminating HD. Because HD may also remove therapeutic medications, the dosing interval of some drugs may need to be decreased.

Newer EET techniques include molecular adsorbent recirculating system, sustained low-efficiency dialysis, extended daily dialysis, and continuous renal replacement therapy (CRRT). These techniques may aid in the treatment of poisoned patients but in general should be considered adjunctive therapy. Additionally, several studies have failed to show that CRRT is safer in hypotensive patients.

### Specific Xenobiotics Removed by HD

Salicylates have a low molecular weight, a relatively small Vd, and significant protein binding, but after overdose, the fraction of unbound drug increases.

<table>
<thead>
<tr>
<th>Xenobiotics Removed by Hemodialysis</th>
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</thead>
<tbody>
<tr>
<td>Salicylates</td>
</tr>
<tr>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Theophylline</td>
</tr>
<tr>
<td>Methanol</td>
</tr>
<tr>
<td>Ethylene glycol</td>
</tr>
<tr>
<td>Methanol</td>
</tr>
<tr>
<td>Diethylene glycol</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
<tr>
<td>Propylene glycol</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
</tr>
<tr>
<td>Valproic acid</td>
</tr>
<tr>
<td>Carbamazepine</td>
</tr>
</tbody>
</table>

This list contains some of the more common substances for which hemodialysis is effective, but not all cases will require hemodialysis.

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800
allowing for effective HD.\textsuperscript{106} There are no specific evidence-based guidelines for when to initiate HD in the treatment of salicylate toxicity. Generally, AMS, pulmonary edema, seizures, and elevated and rising salicylate concentrations despite aggressive supportive care, or serum levels nearing 100 mg/dL following an acute overdose, typically require emergent use of HD.\textsuperscript{107}

Li\textsuperscript{+} has a low molecular weight, minimal protein binding, and a small Vd. As with salicylate toxicity, clear, evidence-based guidelines for when to initiate HD do not exist. Furthermore, because HD has not been demonstrated to improve clinical outcomes with Li\textsuperscript{+} toxicity, there is some variability in clinical practice and controversy surrounding the best treatment. Many medical toxicologists believe the decision as to whether to remove Li\textsuperscript{+} via HD should be based more on clinical findings, such as the presence of encephalopathy or neurotoxicity, then on levels alone.\textsuperscript{108} Acute Li\textsuperscript{+} ingestion may result in predistribution levels well above 4 mEq/L within the first few hours of ingestion, but may produce only minimal clinical effects. Alternatively, some propose that Li\textsuperscript{+} should be removed by HD before it reaches the CNS.\textsuperscript{109} Newer forms of extracorporeal therapy such as CRRT have been proposed for use in Li\textsuperscript{+} toxicity based on the ability to slowly remove lithium and eliminate rebound. However, because of limited evidence supporting CRRT, HD is still the recommended modality for extracorporeal removal of Li\textsuperscript{+}.\textsuperscript{106}

Ethylene glycol and methanol have low molecular weights, limited protein binding, and a small Vd.\textsuperscript{109} HD effectively removes both the parent compounds and their toxic metabolites while correcting pH, fluid status, and electrolytes.\textsuperscript{110} Fomepizole, a safe and effective inhibitor of alcohol dehydrogenase, has changed the indications of HD following methanol or ethylene glycol ingestions. Before fomepizole, the threshold for initiating HD was a plasma concentration of 50 mg/dL.\textsuperscript{111} Currently, if a patient is treated with fomepizole, elevated concentrations of toxic alcohols alone should not prompt use of HD.\textsuperscript{112} However, significant metabolic acidosis or renal dysfunction associated with any specific toxic alcohol level is likely to require HD.\textsuperscript{111} Although isopropanol may also be removed by HD, it is metabolized to acetone and causes much less toxicity, making HD unnecessary in the vast majority of cases.

**Urinary Alkalinization:** Some drugs become ionized and undergo ion trapping in urine at elevated urine pH, limiting reabsorption and enhancing elimination. Table 6 includes xenobiotics in which urinary alkalinization is recommended.\textsuperscript{113} A general goal of urinary alkalinization is to maintain a urine pH \( \geq \) 7.5,\textsuperscript{114} although in the case of salicylate, increased renal salicylate clearance occurs up to about pH 8.5. There is no standard method of producing alkaluria. Many physicians infuse 150 mEq NaHCO\textsubscript{3} in 1 L of 5% dextrose in water (D\textsubscript{5}W) solution. Potassium supplementation is usually needed in the absence of hyperkalemia to prevent paradoxical urinary aciduria from distal tubular reabsorption of Na\textsuperscript{+} in exchange for protons rather than K\textsuperscript{+}.

### Emerging Therapies

Several therapies have emerged in recent years for the treatment of poisonings. These include hyperinsulinemic euglycemia (HIE) therapy for the treatment of severe calcium channel blocker (CCB) toxicity, IV lipid emulsion (ILE) therapy for shock due to lipophilic drugs, and hydroxocobalamin for the treatment of cyanide toxicity.

#### Hyperinsulinemia Euglycemia

Toxicity from CCB poisoning is characterized by hypotension, hypokalemia, cardiac dysrhythmias, metabolic acidosis, and hyperglycemia. The hyperglycemia is multifactorial in origin. First, CCB impair calcium influx through the L-type calcium channels in the pancreatic ß cells, resulting in impaired insulin release. In addition, CCB poisoning results in impaired intracellular signaling and insulin resistance.\textsuperscript{115} During CCB toxicity, the myocardial cells change their preferred energy substrate from free fatty acids to glucose.\textsuperscript{116} High-dose insulin therapy has been shown to promote cellular uptake of glucose into adipose and muscle tissue, reduce cytosolic calcium concentration, and promote intracellular potassium movement.\textsuperscript{116,117} The use of HIE may increase

<table>
<thead>
<tr>
<th>Table 6—Xenobiotics For Which Urinary Alkalinization Increases Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylates\textsuperscript{a}</td>
</tr>
<tr>
<td>Chlorpropanamide</td>
</tr>
<tr>
<td>2,4-dichlorophenoxyacetic acid</td>
</tr>
<tr>
<td>Diflunisal</td>
</tr>
<tr>
<td>Fluoride</td>
</tr>
<tr>
<td>Mecoprop (MCPP, a chlorphenoxy herbicide)</td>
</tr>
<tr>
<td>Methotrexate</td>
</tr>
<tr>
<td>Phenobarbital\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The most recent recommendations of the American Academy of Clinical Toxicology and the European Association of Poison Control Centres and the Clinical Toxicologists Position Statement is that based on volunteer and clinical studies, urine alkalinization should be considered as first line treatment for patients with moderately severe salicylate poisoning who do not meet the criteria for hemodialysis.\textsuperscript{112}

\textsuperscript{b}Phenobarbital is the only barbiturate shown to benefit from urinary alkalinization.
myocardial contractility and mean arterial pressure, but typically does not reverse bradycardia or conduction defects. Clinical improvement often begins approximately 30 min after therapy is commenced. Although there is moderate human experience with HIE, its use in CCB toxicity has not been validated prospectively and may be associated with potential adverse effects including hypoglycemia and hypokalemia. However, it is unlikely that a prospective randomized controlled trial on HIE will ever be conducted.

Although various guidelines for the use of HIE exist, one approach involves giving an IV bolus of 1 unit/kg of insulin, followed by a maintenance insulin infusion of 0.5 to 1 unit/kg/h. Glucose should be monitored frequently. Unless the patient is significantly hyperglycemic, an initial bolus of 1.0 g/kg of glucose should be given followed by a continuous glucose infusion of 0.5 g/kg/h. This infusion should be titrated based on the patient’s blood sugar level. Hyperinsulinemic euglycemic therapy is most likely to be of benefit in patients who are hyperglycemic and in those with decreased cardiac contractility.

The exact timing as to when to start HIE is somewhat controversial. Given the lack of controlled trials, its use certainly cannot be recommended as first-line therapy. However, because its use as a “last ditch” effort seems to be associated with failure, it seems reasonable to start HIE shortly after a patient fails to improve with standard therapies including vasopressors. Hyperinsulinemic euglycemic therapy is most likely to be of benefit in patients who are hyperglycemic and in those with decreased cardiac contractility.

IV Lipid Emulsion

Based on limited data, the use of ILE has been cited as standard of care for treating neurotoxicity or cardiotoxicity due to local anesthetics. In 2006, the first cases of ILE use in humans were reported and involved successful resuscitation after cardiac arrest following local anesthetic toxicity. Animal models have demonstrated benefit in the management of bupivacaine, clonidine, verapamil, and possibly propranolol. There is also a case of prolonged cardiac arrest due to lanostigmine and bupropion whose successful resuscitation involved ILE.

The exact mechanism of ILE is unknown, but likely involves decreasing the toxin’s Vd by shifting lipophilic drugs into the vascular compartment and limiting target tissue concentration. Other theories include inhibition of mitochondrial metabolism of lipids, impairment of fatty acid delivery to mitochondria, and activation of potassium and calcium channels involved with local anesthetic toxicity.

Use of ILE should be considered for patients with severe toxicity due to a lipophilic drug who do not respond to standard measures. ILE is available in 10%, 20%, and 30% solutions, and several dosing regimens have been suggested. No prospective human studies have been performed. Based on human experience and animal research, one regimen involves administering 1.5 mL/kg of a 20% ILE over 1 min, followed by a continuous infusion of 0.25 mL/kg/min for 60 min. If there is no response to the initial bolus, it can be repeated twice in 5-min increments. If hypotension persists, the maintenance infusion can be increased to 0.5 mL/kg/min. Pyrogenic reactions, hyperlipidemia, pulmonary injury, hepatosplenomegaly, thrombocytopenia, and fat embolism are theoretic concerns. When administered as a resuscitative drug, however, few adverse events have been described. Because of the lipemia, laboratory studies may be difficult to analyze transiently or may produce spurious results. It is important to recognize that propofol is not a substitute for ILE, because of myocardial depressant effects and different lipid content.

Hydroxocobalamin

Traditional therapy for cyanide toxicity involves the administration of nitrites (to produce methemoglobinemia) and sodium thiosulfate (to convert cyanide into thiocyanate). These therapies may not be ideal for patients who have high carboxyhemoglobin levels. Hydroxocobalamin (Cyanokit) is an alternative cyanide antidote now approved by the US Food and Drug Administration. Hydroxocobalamin is vitamin B12, the precursor for cyanocobalamin (vitamin B12). It combines with cyanide to form cyanocobalamin, which is then excreted renally. The typical treatment dose is 5 g IV, which can be repeated once if needed. In a swine model, the administration of hydroxocobalamin and sodium thiosulfate appeared to be as effective as sodium nitrite and sodium thiosulfate in the treatment of cyanide toxicity. When using both antidotes, they cannot be administered in the same IV because of incompatibility. Hydroxocobalamin has some side effects. Although not necessarily undesired, it can augment mean arterial pressure because of the nitric oxide scavenging effects of cobalamin. Use of hydroxocobalamin transiently produces a pink discoloration of tissue and blood, abnormal cooximetry measurements, and altered serum values for aspartate aminotransferase, bilirubin, creatinine, magnesium, and iron. Because of the blood discoloration, HD machines may interpret a “blood leak” incorrectly and delay or prevent the use of HD. An aceneiform rash and erythema are commonly encountered.
CONCLUSIONS

Severe clinical illness can occur following overdose or exposure to certain chemicals and illicit substances. Many agents produce toxidromes, which allows the physician to identify a probable poisoning syndrome and empirically determine the most appropriate management. Knowledge of the various routes of decontamination, emerging antidotal therapies, and opportunities for enhanced elimination allow for provision of optimal care in the critical care setting. Many cases of poisoning present diagnostic and therapeutic challenges. It is recommended that physicians consult a medical toxicologist or regional poison control center (800-222-1222) to discuss individual cases to assist in the management of each patient.

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