Toxicology Today: What You Need to Know Now

Simon W. Lam, PharmD, BCPS1, Kristin M. Engebretsen, PharmD, DABAT2, and Seth R. Bauer, PharmD, BCPS1

Abstract
Clinicians are frequently confronted with toxicological emergencies and challenged with the task of correctly identifying the possible agents involved and providing appropriate treatments. In this review article, we describe the epidemiology of overdoses, provide a practical approach to the recognition and diagnosis of classic toxidromes, and discuss the initial management strategies that should be considered in all overdoses. In addition, we evaluate some of the most common agents involved in poisonings and present their respective treatments. Recognition of toxidromes with knowledge of indications for antidotes and their limitations for treating overdoses is crucial for the acute care of poisoned patients.

Keywords
toxicology, poisoning, overdose, antidotes

Introduction
All pharmacists should be aware of a general approach to treating the poisoned patient, regardless of their practice setting. Ambulatory care pharmacists are great resources for drug information in the community, and can provide evidence-based recommendations to their patients. Health-system pharmacists must be prepared to respond to questions from practitioners regarding severe cases of poisoning. Pharmacists can assist a team in caring for a poisoned patient by obtaining a thorough history and conducting a physical assessment, recommend a plan for rational management, and discuss further poison prevention with the patient or their loved ones. Additionally, health-system pharmacists should be aware of common antidotes and the treatment of specific poisonings in order to ensure these therapies are available in their institutions. The objectives of this review are to provide pharmacists with an overview of toxicology, describe the rapid assessment of the poisoned patient as they relate to common clinical toxidromes, and discuss the general management and treatment of common toxic substance exposures.

Epidemiology
Unintentional drug poisoning has surpassed other leading causes of accidental death in the United States and currently rates second only to motor vehicle crash deaths.1 In 2008, there were over 2.4 million cases of human toxic substance exposure reported to the American Association of Poison Control Centers National Poison Data System. Children under 6 years of age accounted for 51.9% of exposures, while adults above age 19 accounted for 34.4% of exposures. While children composed the majority of exposures, they only accounted for 2% of the fatalities. Most fatalities (76.2%) occurred in patients 20 to 59 years of age. Overall, the frequency of toxic exposures leading to a fatality was low (0.07%), but this proportion doubled from 1998 when only 0.035% of exposures led to death. The majority of exposures were unintentional (82.8%). The rate of unintentional drug overdose deaths has increased dramatically in the past two decades. The annual rate of mortality associated with drug overdose was less than two deaths per 100 000 people per year during the 1980s. That rate now approaches 10 deaths per 100 000 people per year in the United States.1

The majority of the intentional exposures (71.2%) were in participants 20 years or older. Ingestion was the most frequent route of exposure (79.3%), while 90.5% of cases involved exposure to only one substance. Analgesics were overall the most common type of toxic substance exposure in 2008 (13.3%), but there were differences in type of exposure based on age group. Analgesics and sedatives were commonly implicated in adult exposures (combined 31.9%), but were less

1 Cleveland Clinic, Department of Pharmacy, Cleveland, OH, USA
2 Regions Hospital, Emergency Medicine Department, St. Paul, MN, USA

Corresponding Author:
Simon Lam, Cleveland Clinic, Department of Pharmacy, 9500 Euclid Ave/JJN1-02, Cleveland, OH 44195, USA
Email: lams@ccf.org
common in children (combined 10.9%). Conversely, cosmetics/personal care products (13.5%) as well as foreign bodies (7.5%) were frequent exposures in children, but relatively uncommon in adults (3.8% and 1.6%, respectively). Sedatives were the most frequent substance leading to death despite accounting for only 6.6% of exposures. These statistics can help guide the clinician to the most likely type of substance exposure at the time of initial presentation.

**Diagnosis and Laboratory Evaluation**

A thorough physical examination and medication history is a crucial first step to the diagnosis of the patient exposed to a toxic substance. Unfortunately, the history provided by the patient may be incomplete or unreliable more than half the time. Additional information may be acquired through discussions with friends, family members, and by calling the pharmacy where the patient has prescriptions filled to see what medications the patient may have available to them. Pharmacies can also provide information regarding recent filling dates of prescriptions, which can aide in estimating the amount of drug ingested. If empty bottles are found near the patient, a conservative approach is to assume the patient ingested the full contents of the bottle. A rapid and focused physical assessment is frequently the key to identifying the unknown toxin(s). Many substances produce a constellation of features characteristic of the type of exposure, called a toxidrome. Assessment of the following 6 items will provide a practitioner with the resources to identify the majority of toxic syndromes: vital signs, mental status, pupil size, peristalsis, reflexes, and skin evaluation (color, texture, and appearance). Common toxidromes, their clinical features, and associated drug/toxin causes are listed in Table 1. Ordering and evaluation of particular laboratory tests are dependent on the signs and symptoms of the patient. In general, serum electrolytes, osmolality, and quantitative concentrations of acetaminophen and ethanol should be ordered for each patient. Prior to ordering a qualitative toxicology screen of the urine, it is important to ask yourself “Will getting a tox screen affect the management of a patient who has taken an overdose?” It has been reported that a “tox screen” will alter management of the poisoned patient in <5% of toxicology patients presenting to the emergency department. Qualitative toxicology urine screens may be of benefit in pediatric cases with suspected abuse or for legal, forensic or social service documentation. Of particular interest to the pharmacist is the anion gap (AG) associated with a metabolic acidosis and the osmol gap (OG), which can provide insight into the type of toxic exposure, and may change patient management.

The anion gap reflects unmeasured ions in the blood that counteract the positive charge of sodium and can be calculated using the formula: \( AG = (\text{sodium} + \text{potassium}) - (\text{chloride} + \text{bicarbonate}) \). Generally, potassium is omitted from the calculation of an anion gap because of its minimal contribution to the overall value. Rather, it is important to ensure that a corrected sodium value is used in the calculation (eg, in the case of dilutional hyponatremia seen with hyperglycemia). The anion gap is highly dependent on plasma proteins, most importantly albumin. In order to correct for hypo-albuminemia, a patient’s measured anion gap should be corrected using the following equation: \( AG_{\text{corrected}} = AG_{\text{measured}} + 2.5 \times (4 - \text{albumin}) \). The normal range for the anion gap can vary by laboratory, but an elevation in anion gap above >10 mEq/L suggests accumulation of acids in the blood. There are several drugs and toxins that can lead to an elevated anion gap and generally include toxic alcohols, toluene, methanol, uremia, diabetic ketoacidosis/alcoholic and starvation ketoacidosis, paraldehyde, iron, ibuprofen, isoniazid (INH), lactic acidosis (carbon monoxide, cyanide, hydrogen sulfide), ethylene glycol, and salicylates. Ethanol does not contribute to an anion gap. The pneumonic CAT MUD PILES summarizes the aforementioned etiologies on a metabolic acidosis with an anion gap. Drugs and toxins with low molecular weights increase the difference between

### Table 1. Selected toxidromes with their clinical findings and common causes

<table>
<thead>
<tr>
<th>Toxidrome</th>
<th>Clinical Findings</th>
<th>Common Drug/Toxin Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic</td>
<td>Dry mouth, dry skin, blurred vision, fever, flushing, tachycardia, psychosis, urinary retention, decreased GI motility, mydriasis</td>
<td>Anticholinergics, atropine, tricyclic antidepressants</td>
</tr>
<tr>
<td>Cholinergic</td>
<td>Salivation, lacrimation, increased urine production, diarrhea, emesis, bronchorrhea, diaphoresis, bradycardia, miosis</td>
<td>Organophosphates, carbamate</td>
</tr>
<tr>
<td>Sedative, hypnotic, and opiate</td>
<td>Confusion, depressed mental status, slurred speech, respiratory depression, bradycardia, hypotension, miosis (with opiates)</td>
<td>Benzodiazepines, barbiturates, opiates, ethanol</td>
</tr>
<tr>
<td>Beta-adrenergic antagonist (beta-blocker)</td>
<td>Bradycardia, hypotension, cardiac arrhythmias, congestive heart failure, bronchospasm, hypoglycemia, hyperkalemia, depressed mental status</td>
<td>Metoprolol, atenolol, carvedilol, propranolol</td>
</tr>
<tr>
<td>Beta- and alpha-adrenergic agonist</td>
<td>Tachycardia, hypertension, diaphoresis, agitation, mydriasis</td>
<td>Amphetamines, cocaine, phencyclidine</td>
</tr>
</tbody>
</table>
measured serum osmolality and calculated serum osmolarity, leading to an osmol gap. An osmol gap can be calculated using the formula: \( OG = (\text{measured osmolality}) - (\text{calculated osmolarity}) \), where calculated osmolarity = \( (\text{blood urea nitrogen} \times 2.8) + (\text{glucose} \div 18) + (\text{ethanol} \times 4.6) \). Elevations in OG are commonly caused by ingestion of methanol, acetone, ethanol, diuretics such as mannitol, sorbitol, and glycerol, isopropyl alcohol, and ethylene glycol. The listed etiologies are summarized in the pneumonic MAE DIE. It is important to remember that ethanol must be calculated in mg/dL not g/dL. The diagnosis of a poisoned patient is often difficult and involves interpretation of data from several sources. The expertise of practitioners at a poison control center is invaluable in the care of these patients. These specialists can be reached toll-free 24 hours a day at 800-222-1222.

Resuscitation and Initial Supportive Measures

Initial supportive measures are often necessary to stabilize the patient after exposure to a toxic substance. These procedures should focus on maintaining the patient’s airway, breathing, and circulation along with administering intravenous (IV) fluids and oxygen if necessary. The risk of aspiration (with resultant chemical pneumonitis or pneumonia) in comatose patients after overdose is approximately 10%. Airway patency is paramount and endotracheal intubation and mechanical ventilation should be considered if the patient is unable to protect his/her airway or respiratory failure is present. Removal of the suspected source of exposure to limit further exposure should be considered. This includes removal of clothing for dermal exposures and contact lenses for ocular exposures. In addition, irrigation of the skin and/or eyes with water should be performed if dermal or ocular exposure is suspected. Some practitioners recommend a “coma cocktail” for each poisoned patient, which consists of dextrose, oxygen, naloxone, and thiamine each in varying doses and formulations. The use of this combination of medications is controversial, and administration of each component should be considered individually, depending on the signs and symptoms of the patient.

Prevention of Absorption

While there are a number of routes of toxin exposure, the majority of exposures are due to ingestion. Prevention of absorption of the toxin from the gastrointestinal (GI) tract is an important therapeutic strategy to lower total toxic substance exposure. Common methods to prevent absorption include induction of emesis, gastric lavage, administration of activated charcoal, catharsis, and whole-bowel irrigation. Induction of emesis with syrup of ipecac was once commonly recommended for treatment of pediatric patients in the home. However, no clinical studies have shown improved outcome from the routine administration of syrup of ipecac in poisoned patients. Therefore, the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists recommend that routine administration of syrup of ipecac in the emergency department be abandoned.

Another method to remove toxins from the stomach after ingestion is gastric lavage. This procedure involves passing a large bore orogastric tube into the stomach, sequential administration of aliquots of liquid, and subsequent removal of the liquid. Gastric lavage is intended to directly remove the toxin from the stomach and is repeated until the return fluid is clear. Based on gastric emptying time, the procedure should be undertaken within 1 hour of ingestion. The data to support gastric lavage are sparse, with a potential for a number of adverse effects. Complications may be severe, including aspiration pneumonia, perforation of the esophagus, hypoxia, and cardiac arrhythmias. Consequently, consensus guidelines suggest gastric lavage should not be performed routinely, and the risks must be weighed against the potential for minimal benefit.

Administration of a single dose of activated charcoal to adsorb the ingested substance is one of the most frequently employed strategies to prevent absorption of the toxin. Although activated charcoal binds most substances, it does not adsorb acids, alcohols, alkalis, carbamates, hydrocarbons, or metals such as iron or lithium. This treatment is most effective if administered within 1 hour of ingestion, but may still bind toxin after 1 hour in cases where sustained release medications or drugs that delay gastric emptying have been ingested. Due to the risk for aspiration, an unprotected airway should be considered a contraindication to this therapy. Emesis is not an infrequent side effect of activated charcoal. The routine administration of a single dose of activated charcoal is not recommended in poisoned patients. Activated charcoal may be considered in patients with potentially toxic ingestions who present within 1 hour of ingestion of a toxin that is known to be adsorbed by active charcoal. The role of multidose activated charcoal will be discussed in the Enhanced Elimination section of this review.

Decreasing GI transit time with cathartics or whole-bowel irrigation may decrease intestinal absorption of drugs. Cathartics (such as sorbitol or magnesium citrate) induce an osmotic diarrhea, with the goal of decreasing the time the toxin remains in the gut. The administration of a cathartic alone is not recommended for decontamination. Sorbitol is occasionally added to activated charcoal to reduce the risk of constipation, but there are no data that single-dose activated charcoal produces constipation or that administration of a cathartic with activated charcoal changes outcome. Therefore, use of cathartics alone or in combination with activated charcoal is no longer recommended. Similar to cathartics, whole-bowel irrigation via enteral administration of polyethylene glycol electrolyte solution (PEG-ES) induces a liquid stool and has the potential to decontaminate the entire GI tract by physically expelling GI contents. PEG-ES is usually administered via a nasogastric or orogastric tube at 2 L/h for adults, and continued until the rectal effluent is clear. Contraindications to whole-bowel irrigation include the presence of ileus, bowel perforation, hemodynamic...
instability, intractable vomiting, or an unprotected airway. Whole-bowel irrigation is typically reserved for ingestion of substances that are not adsorbed by activated charcoal (such as iron and lithium), removal of ingested packets of illicit drugs, or for ingestion of sustained release or enteric-coated product formulations. Additional methods to prevent toxin absorption include endoscopic and surgical removal of the substance. These procedures are not frequently utilized, but may be necessary in the setting of bowel obstruction or bezoars.

Enhanced Elimination

The intent of enhancing elimination of a substance that has already entered the systemic circulation is to limit or reduce the sequelae of the toxin. This approach is often employed for patients in whom methods to prevent absorption are ineffective, or in patients that develop severe complications from their toxic substance exposure. Methods to increase clearance of the toxin include forced diuresis, urinary alkalinization, administration of multiple doses of activated charcoal, and extracorporeal removal through hemodialysis or hemoperfusion.

Forced diuresis is the process of stimulating urine excretion. In salicylate toxicity this can be accomplished by expanding intravascular volume through fluid administration, administering diuretics to facilitate excretion, or a combination of these therapies. In theory, expanding intravascular volume through fluid administration should increase glomerular filtration rate and increase elimination of filtered drugs. Unfortunately, data to support this theory are lacking. The excretion of salicylates depend more on urine pH than urine flow rate. Diuretics may further complicate treatment as they may compete with salicylates for secretion by the renal tubules and therefore increase salicylate toxicity. Diuretics may prevent rehydration or worsen electrolyte disorders in already dehydrated patients. Due to potential complications of pulmonary edema and electrolyte disturbances, forced diuresis by volume expansion, diuretic therapy, or a combination of these therapies is not recommended. Administration of IV sodium bicarbonate to raise the pH of the urine above 7.5 may prevent tubular reabsorption of weak acids that are ionized at higher pHs. The elimination of drugs reabsorbed in the kidney corresponds directly with urine flow rate, thus relatively high rates of urine output (above 1 mL/kg per hour) are needed. Alkalization of the urine can be achieved through sodium bicarbonate boluses and maintained with an infusion. Complications of urinary alkalization include hypokalemia, hypernatremia, and volume overload. Urinary alkalization is recommended for patients with overdoses of salicylates, methotrexate, phenobarbital, chlorpropamide, chlorophenoxy herbicides, tricyclic antidepressant overdose, and for correcting metabolic acidosis in toxic alcohol ingestions. Methotrexate elimination is increased with increased urine pH, but data to support sodium bicarbonate administration in methotrexate overdose are not conclusive. Urine alkalization enhances elimination of phenobarbital and may be used in conjunction with multiple doses of activated charcoal which increases clearance rate. Other than in the setting of the previously mentioned poisonings, urinary alkalization is not recommended.

While a single dose of activated charcoal is given to adsorb toxin present in the GI system and prevent its systemic absorption, administration of multiple doses of activated charcoal (MDAC) is intended to increase elimination. MDAC adsorbs parent drug and metabolites that are excreted into the bowel through enterohepatic circulation or diffuse into the gut from the circulation. Although the optimal administration technique of MDAC is unknown, doses of 0.5-1 g/kg every 4 hours or an infusion via nasogastric tube ≥12.5 g/h have been suggested for adults. Contraindications to MDAC include an unprotected airway and the presence of intestinal obstruction. Although bowel obstruction and constipation have been reported with MDAC, concurrent administration of a cathartic is not recommended. Administration of multiple doses of activated charcoal should be considered if a patient develops life-threatening complications after ingestion of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. Although MDAC has been shown to increase the elimination of these medications, these alterations in pharmacokinetics have not been associated with improved clinical outcomes.

The use of an extracorporeal technique to remove a toxin, such as hemodialysis or hemoperfusion, is reserved for specific toxins when conservative approaches to therapy have failed. In order to be effectively removed by hemodialysis, a drug must have minimal protein binding (<80%), a low volume of distribution (<1 L/kg), low molecular weight (<500 daltons), and high water solubility. Hemodialysis should be considered for patients who develop life-threatening complications after ingestion of toxic alcohols, valproic acid, salicylates, metformin, or lithium. Both conventional hemodialysis and continuous renal replacement therapy (CRRT) may be used for drug removal. There are advantages and disadvantages to each modality. Major limitations to conventional hemodialysis are hypotension during the procedure and redistribution of the toxin after cessation. In patients who are hemodynamically unstable as a consequence of their ingested toxin, hemodialysis may further exacerbate the hypotension and CRRT may be a better option. Although CRRT may less frequently cause hypotension, this may also lead to a lower clearance of the toxin. Longer periods (>4 hours) of intermittent hemodialysis or frequent sessions may be necessary to remove ingested toxins with a high volume of distribution, which will clear drug from not only the central compartment but other compartments as well. The merits and indication of each dialysis modality should be decided on a case-by-case basis.

Drugs with a relatively high molecular weight or lipid solubility are not easily removed by hemodialysis, but may be amenable to hemoperfusion. During hemoperfusion, the blood passes through an external cartridge with a substance able to adsorb the toxin (usually charcoal). The limiting factors with hemoperfusion involve the affinity of the toxin to adsorb to the substance in the cartridge and a low volume of distribution. Although this procedure is effective in removing barbiturates and theophylline, its use is declining due to its inability to...
correct acidosis, its unfamiliarity to practitioners, and a short shelf-life (and thus a lack of supply) of the cartridges.\textsuperscript{28}

**Antidotes**

Antidotes may be life-saving in certain emergencies, and all institutions that provide emergency care must have a plan for procuring these medications (Table 2). An expert consensus panel recommends that the following 12 antidotes are available for immediate administration on patient arrival: atropine, calcium chloride, calcium gluconate, cyanide antidote kit or hydroxocobalamin, digoxin immune fab, flumazenil, glucagon, methylene blue, naloxone, physostigmine, pyridoxine, and sodium bicarbonate.\textsuperscript{29} Health-system pharmacists can play a vital role in the stocking of these medications, their appropriate quantities, and reducing inappropriate use.

**Specific Poisonings**

**Acetaminophen**

Acetaminophen (APAP), alone or in combination, was the second leading cause of poison-related fatalities in the United States in 2008.\textsuperscript{2} The acute ingestion dose with the potential to induce liver damage is 150 mg/kg (\textasciitilde 10 g) in adults and 200 mg/kg in children. Acetaminophen is rapidly absorbed and achieves peak plasma concentrations usually within 4 hours after overdose. Approximately 90\% of APAP normally undergoes hepatic glucuronide and sulfate conjugation to form inactive metabolites, which are then eliminated in the urine. The remaining fraction (about 5\%) is oxidized by the cytochrome P450 system, resulting in the formation of a highly reactive intermediate metabolite called N-acetyl-p-benzoquinoneimine (NAPQI), which is usually detoxified by glutathione to non-toxic conjugates. However, during acute overdoses, the supply of glutathione is depleted, which leads to NAPQI accumulation. This metabolite binds to macromolecules and exhibits an oxidative cytotoxic effect leading to hepatocyte and other tissue damage.\textsuperscript{30}

The clinical presentation of APAP overdose can be divided into 4 phases. Phase 1 commonly occurs in the first 24 hours following ingestion and patients may exhibit anorexia, nausea, vomiting, and diaphoresis. During phase 2, which occurs 24 to 48 hours after untreated overdose, damaged hepatocytes, increased liver function tests (LFTs), and right upper quadrant pain may be seen. In phase 3, occurring 48 to 96 hours after ingestion, symptoms manifest as multi-organ toxicity including encephalopathy, coagulopathy, hypoglycemia, peaked LFTs at extreme elevations, jaundice, and renal failure. Phase 4 of APAP overdose is characterized by full recovery, death, or emergent liver transplantation.

The goal of treatment for APAP overdose is to prevent or reduce progression of toxicity. This is usually accomplished through 2 strategies: reducing absorption and detoxification. The most important strategy for the management of APAP overdose is the administration of N-acetylcysteine (NAC) to detoxify NAPQI. The administration of NAC should not be delayed or interrupted by therapies for reducing absorption.

The administration of NAC is the mainstay of therapy for the treatment of APAP overdose. Proposed mechanisms for NAC include increasing glutathione synthesis and availability, providing inorganic sulfate which promotes noncytochrome P450 metabolism pathways, and substituting for glutathione by directly binding to NAPQI.\textsuperscript{31} The Rumack-Matthew nomogram is used to assess need for NAC therapy in APAP overdose.\textsuperscript{32} Patients who present within 4 to 24 hours after APAP ingestion with a serum concentration above the lower line are candidates for NAC therapy. Although the Rumack-Matthew nomogram is a useful guide to determine the appropriate use of NAC treatment in single acute overdose, its use is not applicable when APAP concentrations are obtained outside of the 4 to 24 hours from ingestion time period, for multiple ingestions occurring within an acute time frame or for chronic ingestions. The nomogram also does not account for patients at high risk for liver toxicity, such as malnourished patients, chronic alcohol users, those patients with underlying liver disease or patients on enzyme inducing medications. Lastly, an accurate assessment of the potential for liver toxicity associated with APAP requires an accurate time of ingestion, which may frequently be unobtainable. These cases should be referred to a regional poison control center for further guidance and clinicians should have a low threshold to treat with NAC.

\textit{N}-acetylcysteine can be administered either orally or intravenously. The traditional oral regimen entails a loading dose of 140 mg/kg, followed by 70 mg/kg given every 4 hours for 17 doses.\textsuperscript{33} However, shorter oral regimens are now being employed.\textsuperscript{33} One of the most common IV regimens includes a loading dose of 150 mg/kg infused over 15 to 60 minutes, followed by 50 mg/kg over 4 hours and then 100 mg/kg over 16 hours.\textsuperscript{34} In a meta-analysis of patients with high risk of developing hepatotoxicity based on the Rumack-Matthew nomogram, similar outcomes were found in those treated with oral or IV NAC.\textsuperscript{35} A recent retrospective study with historical controls, which compared the use of IV NAC versus oral NAC in 4048 patients, also found similar rates of hepatotoxicity.\textsuperscript{36} Administration of oral NAC can be challenging given the unpleasant odor and frequent nausea and vomiting secondary to toxic ingestion. Doses can be mixed with carbonated beverages to mask the taste and smell. Intravenous NAC is associated with anaphylactoid reactions, which is more common with the 1-hour loading dose infusion than the subsequent doses. The anaphylactoid reaction associated with IV NAC is secondary to histamine release.\textsuperscript{37} Therefore, stopping the IV infusion of NAC and administering diphenhydramine will usually eliminate this reaction. The IV NAC infusion may then be restarted at a slower rate. In a large multicenter study which evaluated 2086 patients treated with IV NAC, the incidence of anaphylactoid reactions was 7.1\%. The choice of IV or oral NAC depends on the clinical scenario. Abbreviated oral administration may be less expensive and may be more convenient for patients without evidence of hepatic toxicity. However, the use of oral NAC may be precluded by altered mental status, nausea, and
vomiting. There are sparse data for patients who present with acetaminophen-induced fulminant hepatic failure. In a randomized, placebo-controlled trial, Keays and colleagues evaluated 50 patients with acetaminophen-induced fulminant hepatic failure. The use of IV NAC in this study was associated with a 28% absolute risk reduction in mortality.38 Patients who presented with fulminant hepatic failure were treated with IV NAC beyond 20 hours with 6.25mg/kg per hour until there was Table 2. Antidotes and Indications

<table>
<thead>
<tr>
<th>Antidote</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antivenom, Crotalinae (rattlesnake)</td>
<td>Envenomation by Crotalinae species</td>
</tr>
<tr>
<td>Antivenom, Latrodectus mactans (Black widow spider)</td>
<td>Black widow spider envenomation</td>
</tr>
<tr>
<td>Antivenom, Micrurus fulvius (Coral snake)</td>
<td>Envenomation by Eastern coral snake (Micrurus fulvius) or Texas coral snake (Micrurus fulvius tenere)</td>
</tr>
<tr>
<td>Atropine</td>
<td>Cholinesterase Inhibitors</td>
</tr>
<tr>
<td>Atropine and glycopyrrolate</td>
<td>Organophosphate and carbamate Insecticide Intoxication</td>
</tr>
<tr>
<td>Benzodiazepines (diazepam, lorazepam, midazolam)</td>
<td>Anxiety and agitation, convulsions, hypertension, muscle relaxant, alcohol or sedative-hypnotic withdrawal, conscious sedation, nerve agent poisoning, serotonin syndrome, NMS, chloroquine toxicity.</td>
</tr>
<tr>
<td>Benztrapine</td>
<td>Acute dystonic reactions associated with neuroleptics or metoclopramide</td>
</tr>
<tr>
<td>Bicarbonate, Sodium</td>
<td>Metabolic acidosis, urinary alkalinization (salicylates, phenobarbital), cardiotoxicity as evidenced by sodium channel blockade resulting in prolonged QRS (TCAs, citalopram, venlafaxine, flecainide, quinidine, procainamide)</td>
</tr>
<tr>
<td>Botulinum Antitoxin</td>
<td>Botulism</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>NMS from neuroleptic drugs or levodopa withdrawal</td>
</tr>
<tr>
<td>Calcium</td>
<td>Symptomatic hypocalcemia from intoxication by fluoride, oxalate or IV anticoagulant citrate</td>
</tr>
<tr>
<td>Charcoal, Activated</td>
<td>Limit drug or toxin absorption</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>Mild to moderate symptoms of serotonin syndrome</td>
</tr>
<tr>
<td>Dantrone</td>
<td>Malignant hyperthermia</td>
</tr>
<tr>
<td>Deferasirox (Exjade)</td>
<td>Transfusion hemosiderosis</td>
</tr>
<tr>
<td>Deferoxamine</td>
<td>Iron</td>
</tr>
<tr>
<td>Digoxin-specific antibody fragments (Fab)</td>
<td>Digoxin</td>
</tr>
<tr>
<td>Dimercaprol (BAL)</td>
<td>Lead poisoning/encephalopathy</td>
</tr>
<tr>
<td>Edetate calcium disodium</td>
<td>Lead poisoning/encephalopathy</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>Rapid reversal of benzodiazepine overdose-induced coma and respiratory depression</td>
</tr>
<tr>
<td>Fomepizole</td>
<td>Methanol, ethylene glycol, diethylene glycol</td>
</tr>
<tr>
<td>Glucagon</td>
<td>BB or CCB</td>
</tr>
<tr>
<td>Hydroxocobalamin (Cyanokit)</td>
<td>Cyanide</td>
</tr>
<tr>
<td>Insulin (HDl) &amp; Glucose</td>
<td>BB or CCB</td>
</tr>
<tr>
<td>l-Carnitine</td>
<td>Valproic acid-induced hyperammonemia or valproic acid-induced elevated AST/ALT</td>
</tr>
<tr>
<td>Leucovorin (folinic acid)</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Lipid 20% (Intralipid)</td>
<td>Resuscitation from lipid soluble xenobiotic (CCB, BB, bupropion, TCA, local anesthetics)</td>
</tr>
<tr>
<td>Methylene blue</td>
<td>Methemoglobinemia</td>
</tr>
<tr>
<td>N-Acetylcysteine (NAC)</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Opioid-induced respiratory depression, clonidine</td>
</tr>
<tr>
<td>Nitrites and sodium thiosulfate (Cyanide Antidote Kit)</td>
<td>Cyanide</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Sulfonylurea-induced hypoglycemia</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Control of tonic-clonic seizures and status epilepticus (not first-line)</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Hypertensive crisis associated with: stimulant overdose, MAOI interactions and clonidine withdrawal or extravasation of vasoconstrictive agents</td>
</tr>
<tr>
<td>Phystostigmine</td>
<td>Anticholinergic toxicity</td>
</tr>
<tr>
<td>Pralidoxime</td>
<td>Cholinesterase inhibitors</td>
</tr>
<tr>
<td>Prontamine</td>
<td>Reversal of heparin anticoagulation</td>
</tr>
<tr>
<td>Prussian blue</td>
<td>Contamination by radioactive cesium or thallium</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Succimer</td>
<td>Lead poisoning</td>
</tr>
<tr>
<td>Unithiol (DMPS)</td>
<td>Intoxication by mercury, arsenic and lead</td>
</tr>
<tr>
<td>Vitamin K (Phytonadione)</td>
<td>Excessive anticoagulation caused by coumarin and indanedione derivatives</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BAL, British anti-lewisite; BB, beta adrenergic blocking agent; CCB, calcium channel blocking agent; DMPS, dimercapto propane sulfonate; HDl, high dose insulin; MAOI, monoamine oxidase inhibitors; NMS, neuroleptic malignant syndrome; TCA, tricyclic antidepressant.
complete recovery from encephalopathy or death. No studies evaluated oral NAC for the treatment of acetaminophen-induced fulminant hepatic failure. Therapy with NAC is frequently recommended to be continued at least until acetaminophen levels are undetectable and LFTs are consistently trending downward.\textsuperscript{39,40}

**Toxic Alcohols**

**Toxic alcohol ingestions.** Alcohol ingestion is the 6th leading cause of adult toxicological exposure and accounted for 6.7% of all reported poisoning-related fatalities in 2008.\textsuperscript{2} Ethylene glycol is commonly found in gas line antifreeze, de-icers, braking fluid, and industrial solvents; while methanol is present in paint removers, cleaning solvents, and various automotive fluids. The toxicities associated with both of these toxic alcohols are caused by their respective toxic metabolites.

Ethylene glycol is metabolized by alcohol dehydrogenase to intermediate metabolites of glycoaldehyde and glycolic acid. Glycolic acid is converted to oxalic acid for urinary excretion.\textsuperscript{41} Accumulation of oxalic acid can result in precipitation of calcium oxalate crystals leading to acute tubular necrosis, central nervous system (CNS) damage, and cranial nerve damage. Furthermore, the hypocalcemia caused by oxalate precipitation can cause myocardial dysfunction. Similar to ethylene glycol, methanol is also metabolized by alcohol dehydrogenase, which forms formaldehyde and eventually formic acid. Formic acid is the metabolite responsible for the toxic metabolic and ocular effects.\textsuperscript{41}

The clinical presentation of both ethylene glycol and methanol is similar. It includes inebriation, nausea, vomiting, altered mental status, headaches, metabolic acidosis, and a wide osmol gap. The progression of ethylene glycol toxicity can lead to cerebral edema, renal failure, myocardial dysfunction, pulmonary edema, neurologic deficits, and death. As little as 100 mL of ethylene glycol may be lethal in adults and substantial toxicity has been associated with serum concentrations >50 mg/dL.\textsuperscript{52} Progression of methanol toxicity and accumulation of formic acid can lead to visual loss, optic nerve swelling, metabolic acidosis, and death. Toxic serum concentrations have never been established. Toxicity may vary given the time of evaluation, coingestion of ethanol, and degree of acidosis. Therefore, until more data are available, any concentration >20 mg/dL is currently regarded as toxic and should be considered for treatment. It is important to remember that signs and symptoms of ethylene glycol and methanol toxicity may be delayed with ethanol coingestion due to preferential binding of ethanol to alcohol dehydrogenase.

Treatment of toxic alcohol ingestion can be broadly divided into 3 categories: supportive treatments including treating metabolic derangements and electrolyte abnormalities; inhibition of alcohol dehydrogenase using either ethanol or fomepizole; and dialysis.\textsuperscript{42,43} In addition, sodium bicarbonate can be administered to correct metabolic acidosis, to enhance the renal elimination of glycolate and formate, and to inhibit the precipitation of calcium oxalate in the renal tubules. Both fomepizole and ethanol can be used to inhibit alcohol dehydrogenase metabolism of methanol and ethylene glycol to toxic metabolites. Ethanol, administered IV or orally to maintain a target serum concentration of 100 to 200 mg/dL, has been used to prevent adverse effects from toxic alcohol ingestion.\textsuperscript{44} Of note, IV ethanol as a 5% infusion is no longer commercially available and its use requires compounding the infusion using 98% ethanol vials. Alcohol dehydrogenase has a stronger affinity for ethanol, thus causing the metabolism of either methanol or ethylene glycol to be spared and allowing them to be excreted unchanged. Therapeutic concentrations of ethanol should be maintained until symptoms have improved and serum concentrations of toxic alcohols are undetectable. The therapeutic administration of ethanol is challenging given the unpredictable interpatient variability in dosing and pharmacokinetics. This may be particularly troublesome in a chronic alcohol user because of the baseline induction of alcohol dehydrogenase. Furthermore, ethanol can cause other unwanted side effects including acidosis, hypoglycemia, and altered mental status, which clouds the patient baseline symptoms of toxic alcohol ingestion. These inherent issues with ethanol administration make it less favorable than fomepizole.\textsuperscript{42,43}

Fomepizole is a competitive inhibitor of alcohol dehydrogenase that is Food and Drug Administration (FDA)-approved for treatment of ethylene glycol and methanol poisonings. Fomepizole should be administered as a loading dose of 15 mg/kg IV over 30 minutes followed by a maintenance dose of 10 mg/kg IV every 12 hours until the patient is asymptomatic with serum concentrations of either toxic alcohols <20 mg/dL.\textsuperscript{41,45} Fomepizole is metabolized by the liver via cytochrome P450 and induces its own metabolism. Therefore, the maintenance dose should be increased to 15 mg/kg every 12 hours if therapy is continued for more than 48 hours. Fomepizole is readily dialyzable and the dosing interval should be shortened to every 4 hours during hemodialysis.\textsuperscript{45} Fomepizole is well tolerated at therapeutic doses with most common side effects being headache, nausea, and dizziness.\textsuperscript{41,45}

Dialysis is an integral part in the management of toxic alcohol ingestion. In general, dialysis is indicated if there are evidences of significant ingestion (serum concentration of either alcohol > 50 mg/dL), refractory metabolic acidosis, or end-organ damage.\textsuperscript{46}

**Iatrogenic toxic alcohol.** Propylene glycol is used as a solvent for many intravenous medications that are commonly used in the critically ill population. Propylene glycol is generally safe; however, large doses have been associated with increase serum osmolality, lactic acidosis, and renal failure. The World Health Organization recommends a maximum consumption of no more than 25 mg/kg per day when used as a food additive; however, no maximum dose is recommended for intravenous use as a medication solvent. Many medications, such as lorazepam, phenobarbital, pentobarbital, diazepam, phenytoin, sulfamethoxazole / trimethoprim, etomidate, and nitroglycerin, contain considerable amounts of propylene glycol.\textsuperscript{47} Patients receiving one or more of these medications can quickly exceed...
the maximum daily recommended propylene glycol consumption. In a recent trial, metabolic derangements associated with propylene glycol toxicity were observed in 4 (19%) of 21 patients who received either diazepam or lorazepam intravenously. Propylene glycol toxicity is a potentially life-threatening iatrogenic complication that is easily avoidable. Patients on high-dose lorazepam (>0.1 mg/kg per hour) or on prolonged therapy should be closely monitored for propylene glycol toxicity. An elevated osmolar gap may be the strongest predictor of serum propylene glycol concentrations.

**Tricyclic Antidepressants**

Antidepressants are the third leading cause of overdose-related deaths in 2008, with the majority of cases involving tricyclic medications. The tricyclic antidepressants (TCAs) have 7 normal pharmacological effects, which are magnified during overdoses and responsible for their toxic effects. These include inhibition of serotonin and norepinephrine reuptake, direct alpha adrenergic blockade, antihistaminic effects, sodium and potassium channel blockade, GABA inhibition, and muscarinic antagonism. The main toxicities can be divided into anticholinergic effects, cardiovascular effects, and CNS effects. In a series of 316 patients with TCA overdose, coma and grand mal seizures were seen in 17% and 4% of patients, respectively. Fatalities from TCA overdose are primarily caused by cardiac toxicity and tend to occur within 24 hours of ingestion. The cardiac toxicity usually consists of sinus tachycardia and QRS and QTc prolongation. A QRS interval of >0.1 seconds may be a significant predictor of seizures and QRS duration >0.16 seconds is associated with ventricular arrhythmias. Alternatively, an R wave >3 mm in AvR was shown to be comparable to the sensitivity of the QRS in predicting seizure activity and dysrhythmias. Hypotension may ensue due to alpha-blockade and decreased myocardial contractility.

Treatment for TCA overdose includes supportive measures such as gastric lavage with sodium bicarbonate. TCAs are rapidly absorbed by the GI tract and have a large volume of distribution, long and unpredictable half-life, high lipid-solubility, and high protein binding. These pharmacokinetic features make strategies to decrease absorption such as gastric lavage futile if performed beyond one hour of ingestion. Furthermore, strategies to enhance elimination such as hemodialysis and hemoperfusion are also ineffective. Activated charcoal may be used, but there is no role for MDAC. Caution should be used with activated charcoal since the anticholinergic effects of TCAs may potentiate charcoal-induced bowel obstruction. Sodium bicarbonate should be administered for prolongation of the QRS interval >0.1 second (or an R wave >3 mm in AvR), for wide complex dysrhythmias, hypotension, and seizure activity. Sodium bicarbonate may be continued for 12 to 24 hours after the QRS interval returns to normal and the patient’s mental status improves. Alkalization of the serum with sodium bicarbonate should have a target pH goal of 7.50 to 7.55. Sodium bicarbonate most likely works by correcting sodium channel blockade. However, it also corrects metabolic acidosis, resulting in improved myocardial contractility. In addition, it serves to reverse the effect of an acidic environment to increase the fraction of free drug available which increases TCA toxicity.

Other supportive measures include administration of antiarrhythmic agents, vasopressors, and antiseizure medications. In general, antiarrhythmic medications should not be routinely recommended. The correction of hypotension, acidosis, and hypoxia will reduce the cardio-toxic effects of TCAs. If antiarrhythmics are used, class 1a (quinidine, procainamide, disopyramide) and class 1c (flecainide) agents should be avoided due to their potential of exacerbating cardiac effects due to further prolongation of the QT interval. Similar effects occur with class 3 anti-arrhythmic drugs (bretylium, amiodarone). Lidocaine has been reported to be effective in the treatment of ventricular arrhythmias in patients with TCA overdose. Seizures are usually self-limiting, but when treatment is necessary, benzodiazepines are the treatment of choice. In severe cases, unresponsive to traditional therapies, high-dose insulin and intravenous lipid emulsion (ILE) therapy have been reported to be of benefit.

**Calcium Channel Blockers and Beta-Blockers**

Cardiovascular agents are the fifth most common category of drugs associated with adult exposures and accounts for 7.6% of all ingestion-related mortality. Of 117 single cardiovascular drug ingestion-related fatalities in 2008, β-blockers and calcium channel blockers (CCB) accounted for 56 cases (48%).

The clinical manifestation of β-blocker (BB) overdose may vary according to their lipid solubility, membrane-stabilization effect, and metabolism. In general, the cardiovascular complications of BB overdose include hypotension, bradycardia, atrioventricular block, and heart failure. β-blockers with myocardial membrane-stabilizing activity, such as acebutolol, betaxolol, pin dolol, and propranolol, can cause QRS interval widening and are associated with more cardiovascular morbidity. Other toxicities associated with β-blocker overdose include bronchospasm, hypoglycemia, hyperkalemia, altered mental status, and seizures. The risk of seizures appears to be greater for lipid-soluble β-blockers (propranolol, metoprolol, acebutolol, and timolol), particularly when the QRS complex is >0.1 seconds. Toxicities usually occur within 6 hours of ingestion; however, there may be delayed toxicity from extend release preparations.

Treatment for cardiovascular toxicities from BB and CCB overdose consists of fluid resuscitation, administration of calcium, atropine, and inotropic support for myocardial depression. Despite inconsistent response rates, glucagon continues to be used for β-blocker overdoses. Glucagon is an endogenous peptide that binds to a GS-protein receptor, and activates adenylate cyclase resulting in increased concentrations of intracellular cAMP, thereby bypassing the blocked β-adrenergic receptor. Glucagon has positive inotropic and chronotropic effects. Glucagon receptors are mainly expressed in liver. It is administered as a 5 to 10 mg IV bolus over 1 minute. For responders,
an IV infusion of 5 to 10 mg/h should be initiated. Common side effects of glucagon include nausea, vomiting, hyperglycemia, and hypocalcemia. Due to glucagon’s adverse side effect profile, high cost, and limited availability, glucagon is being replaced with high-dose insulin (HDI) therapy. Catecholamine vasopressors that work through the adrenergic receptors (blocked by BB) do not appear to be of benefit for cardiogenic shock in animal models. Their use has been shown to be associated with increased mortality when compared to HDI therapy.63 Calcium channel blockers have varying degrees of cardiovascular effects. Verapamil and diltiazem have stronger negative inotropic and chronotropic effects, while dihydropyridines (ie, nifedipine and amlodipine) have more peripheral vasodilatory properties. However, in overdose, this selectivity is lost and all CCBs exhibit severe myocardial depression. Verapamil is the CCB most commonly associated with serious morbidity and mortality.64 Toxicities of CCBs include bradycardia, hypotension and altered mental status, which generally occur within 6 hours of ingestion. Fluid resuscitation and the administration of calcium should be the first-line treatment choices for symptomatic patients with CCB overdose. Calcium increases blood pressure and inotropy by increasing intracellular calcium concentrations. However, the effect of calcium is frequently short-lived or ineffective in severe overdoses. Calcium chloride should only be administered through a central line as extravasation may result in tissue necrosis. Calcium chloride 1 to 2 g should be administered followed by an infusion of 20 to 50 mg/kg per hour.6 Patients refractory to calcium should be considered for HDI therapy. Vasopressor support has not been shown to be of benefit either alone or in addition to HDI therapy in a dihydropyridine animal model of toxicity.65 Vasopressin is a peptide hormone that directly stimulates vasopressin receptors in the periphery resulting in vasoconstriction. Case reports of the successful use of vasopressin in CCB overdose have been reported, however, animal studies have not supported its efficacy. Vasopressin should be reserved for cases refractory to standardized treatment, if used at all. It has been proposed that insulin increases plasma concentrations of calcium, improves hyperglycemic acidosis, improves myocardial carbohydrate utilization, and exerts strong inotropic effects.66 The dose of HDI normally includes a bolus of 0.5 to 1 unit/kg and then an infusion of HDI is started at 1 to 10 units/kg per hour. Doses as high as 21 units/kg per hour have been reported without adverse effects.67 If the serum blood glucose is less than 200 mg/dL, a bolus of dextrose 25 g is recommended prior to administration of the insulin bolus. Dextrose concentrations should be monitored every 10 minutes while increasing insulin doses and checked every 30 minutes after insulin dosing has stabilized. Concentrated dextrose administered through a central line will likely be required to avoid hypoglycemia and fluid overload. Due to insulin’s significant lipid solubility, dextrose administration may need to be continued for up to 24 hours after discontinuation of the insulin infusion. Potassium concentrations should be monitored every 30 to 60 minutes until insulin dosing has stabilized and then every 4 to 6 hours during HDI therapy. Potassium should be supplemented as needed but concentrations should be maintained in the low normal laboratory range. Intravenous lipid emulsion (ILE) therapy has also been reported to be successful in multiple animal models of verapamil overdose but has not been shown to be of benefit in animal models of nifedipine toxicity.70,71 No optimal regimen of ILE has been established, but current recommendations include use of 20% Intralipid with an initial 1.5 mL/kg initial IV bolus, followed by 0.25 mL/kg per min for 30 to 60 minutes. Boluses may be repeated 1 to 2 times for persistent asystole and the infusion rate may be increased for hypotension. Side effects due to intralipid administration have been minimal thus far.73

**Opioids and Benzodiazepines**

Opioid and benzodiazepine overdoses are common causes of patients presenting to the ED unresponsive or with a decreased level of consciousness. These overdoses may also occur in the hospital setting as a function of iatrogenic supratherapeutic opioid or benzodiazepine administration, particularly in the postoperative period or in at-risk patient populations (eg, geriatrics). Opioid overdoses produce symptoms consisting of a classic triad of: decreased level of consciousness, decreased respiratory drive, and miosis. The severity of the symptoms ranges based on the dose, agent, and patient tolerance. Other symptoms of opioid overdose include decreased gastric motility, hypotension, and seizures. Seizures are more common with meperidine and propoxyphene overdoses.68 Most fatal opioid overdoses involve chronic heroin abusers or multiple undetected fentanyl patches.74

Opioid overdose is usually diagnosed based on the presence of a classic triad of symptoms including miosis, bradypnea, and a decreased level of consciousness. Opioid exposure can be confirmed with urine and/or blood toxicology screening but does not influence management. Many clinicians also rely on response to urine and/or blood toxicology screening but does not influence management. Many clinicians also rely on response to naloxone as a marker of opioid exposure. Naloxone is a synthetic opioid receptor antagonist with a rapid onset of action that is frequently used in opioid overdoses. The required IV naloxone dose typically ranges from 0.04 to 0.4 mg.75 If the initial naloxone dose does not produce a clinical response, additional doses may be given, up to a total of 10 mg. In general, if no improvements in mental status and respiratory drive are seen after 10 mg of IV naloxone, then alternate causes of symptoms should be sought. For responders, the onset of response is usually within minutes and lasts for 45 to 90 minutes. Patients may require repeat boluses every 20 to 60 minutes to maintain clinical response. A continuous naloxone infusion may also be given. The infusion dose should be administered hourly at one-half to two-thirds of the initial dose that was required to reverse the respiratory depression. Adverse effects to high doses of naloxone are rare; however, clinicians should be aware of the propensity for withdrawal symptoms induced by administration of naloxone, including agitation and dysphoria. Long-acting opioid antagonists, such as nalmefene and naltrexone, should not be administered as first-line therapies since unwanted withdrawal symptoms may persist for an undue amount of time.

Benzodiazepines bind to γ-aminobutyric acid and enhance its inhibitory effects causing generalized CNS depression.
Symptoms in overdose are usually exaggerations of their normal pharmacologic actions, including lethargy, respiratory arrest, and coma. Flumazenil is a specific benzodiazepine antagonist capable of reversing unwanted sedative effects. The recommended initial dose of flumazenil is 0.2 mg IV, with repeated doses of 0.2 to 0.5 mg IV at 1-minute intervals. Doses >3 mg are usually not helpful and failure to respond to this dose should warrant further investigation into other causes of altered mental status. Patients who received high-dose, long-term, or long-acting benzodiazepines may experience re-sedation 1 to 2 hours after flumazenil administration. Repeated doses or a continuous IV infusion (0.1 to 0.5 mg/h) may be required in those situations. Flumazenil is usually well-tolerated; however, it may precipitate seizures and withdrawal symptoms in (often unknown) chronic benzodiazepine users. Flumazenil may also precipitate seizures in patients with a known underlying seizure disorder, head injury, or co-ingestion with others drugs which may lower seizure threshold. Seizures after flumazenil administration may require high-dose benzodiazepines or barbiturate therapy. However, recent studies on the actual incidence of seizures after flumazenil administration are mixed. One review suggests that use of flumazenil in patients who also ingested pro-convulsants had a three-fold increase in the rate of seizures, while two other studies suggested no difference in the risk of seizures for those patients given flumazenil (even in patients who ingested pro-convulsant drugs) as compared to those patients who did not receive flumazenil. Future studies are needed to clarify how and when flumazenil should be used.

**Serotonin Syndrome**

Serotonin syndrome (SS) was initially described in the 1960s resulting from a condition of serotonergic hyperstimulation. Serotonin syndrome is an iatrogenic drug-induced disorder with no other known endogenous cause. The pathophysiology of SS is primarily an increase in serotonergic activity and resultant stimulation of post synaptic 5HT receptors in the brain stem although other receptors such as 5-HT and 5-HT may also play a role. Increased serotonin neurotransmission is mediated via 5 mechanisms: (1) Augmentation of serotonin synthesis (L-triptophan); (2) Inhibition of serotonin metabolism (MAOIs); (3) Increase in serotonin release (cocaine, amphetamines); (4) Direct stimulation of postsynaptic serotonin receptors (Lithium, Buspirone); and (5) Inhibition of serotonin uptake (SSRI’s, Mirtazapine). The most common mechanism of increased serotonergic activity and resultant SS is via inhibition of serotonin uptake. Overdose of serotonergic drugs results in the clinical diagnosis of SS in only 16% of cases. More commonly, SS is associated with therapeutic administration of multiple serotonergic medications and/or increases in dosage regimens.

Clinical features of serotonin toxicity are characterized by a triad of clinical symptoms consisting of (1) autonomic instability, (2) neuromuscular hyperactivity, and (3) mental status changes in the presence of a serotonergic agent. However, the toxic effects of serotonin do not have a clearly defined set of clinical attributes to define a syndrome. Diagnosis of SS is usually based upon either Sternbach’s or Hunter’s criteria (Table 3). Hunter’s criteria have been shown to be somewhat more sensitive (84% vs 75%) and more specific (97% vs 96%) than Sternbach’s criteria. Sternbach’s criteria requires the presence of 3 out of 10 clinical features associated with a known serotonergic agent whereas Hunter’s criteria is based upon clinical features such as clonus, agitation, diaphoresis, tremor, hyperreflexia, hypertonia, and temperature, with clonus being the most important finding. Temperatures >38.5°C and/or marked hypertonia or rigidity is suggestive of severe toxicity with a high risk of progression to respiratory compromise and need for intubation. There are no confirmatory laboratory tests for SS. Differential diagnosis should include anticholinergic toxicity, malignant hyperthermia, and neuroleptic malignant syndrome (Table 3). Treatment of SS is primarily supportive with removal of any precipitating medications. Benzodiazepines may be used for control of agitation, tremors, and seizure activity. The most commonly reported antidote for the use of serotonin toxicity is cyproheptadine. Cyproheptadine is a 5HT2 antagonist. It is not available in parenteral form. Therefore, the oral liquid or tablets must be crushed and administered through a gastric tube. Three case reviews found rapid reversal of mydriasis with use of cyproheptadine in SS, but cyproheptadine was not found to alter or abbreviate the illness. Chlorpromazine has also been used successfully. Known adverse effects with chlorpromazine are hypotension, dystonic reactions, and theoretically lowered seizure threshold. Propranolol is a beta blocker with 5-HT antagonism and has mixed reported success in the literature. Unfortunately, propranolol is not recommended as it may result in significant hypotension in the face of autonomic instability. Olanzapine, a mixed 5-HT2 and 5-HT3 antagonist, has been suggested as an antidote. Administration of olanzapine is not recommended as it may induce neuroleptic malignant syndrome or possibly worsen serotonin toxicity. Symptoms typically resolve in 24 to 72 hours after removal of the serotonergic agent and initiation of good supportive care. Temperature must be monitored closely and patients with temperatures >41.1°C should be treated aggressively with cooling measures, sedation, neuromuscular paralysis, and endotracheal intubation, as needed.

**Salicylates**

Salicylate toxicity and its associated treatments have not significantly changed in the past 20 years. Salicylates rated 13th in the top 25 categories associated with the largest number of fatalities for 2008, reported by the American Association of Poison Control Centers National Poison Data System. Prognosis depends on prompt recognition and treatment. Mortality can increase to 15% to 25% if diagnosis and
treatment is delayed in severe poisoning. This is of concern as practitioners see fewer salicylate intoxications and become less familiar with aspirin overdoses.

Salicylate toxicity is characterized by 5 primary clinical manifestations:

(1) GI effects, (2) acid-base disturbances, (3) neurological effects, (4) acute lung injury (ALI), and (5) hyperthermia. Gastric irritation and corrosive injury from salicylates may result in nausea, vomiting, decreased gastric motility, hematemesis, and rarely gastric perforation. These side effects contribute to dehydration and electrolyte disturbances. In severe salicylate poisoning, 4 to 6 L per square meter may be lost secondary to insensible losses and vomiting. Electrolyte imbalances are common in salicylate toxicity secondary to gastrointestinal losses, renal excretion, and metabolic shifts. Hypokalemia, secondary to emesis and renal losses, stimulates potassium and hydrogen ion exchange in the renal tubules, resulting in hydrogen ion excretion in the urine. Adequate urinary alkalinization may not be possible if hypokalemia is not corrected first.

Salicylates directly stimulate the respiratory center producing tachypnea and hypercapnea. Toxicity of the pulmonary vasculature is mediated through increased capillary permeability and delivery of high-protein exudate to interstitial or alveolar spaces, resulting in pulmonary edema. Acute lung injury is more prevalent in chronic salicylate intoxication, the elderly, smokers, and patients who present with neurological symptoms and acidosis. The classic respiratory finding in salicylate toxicity is respiratory alkalosis. Respiratory acidosis may be seen secondary to hypoventilation with coingestion of CNS depressants, or in severe cases of salicylate-induced respiratory fatigue. Although respiratory alkalosis is the classic early finding, moderate and severely intoxicated patients will present with or rapidly progress to a mixed metabolic picture. In moderate to severe toxicity, accumulation of salicylic acid, pyruvic acid, and lactic acid induces a metabolic acidosis. The combination of pulmonary and metabolic events generate the classic acid-base disturbance of respiratory alkalosis with a metabolic acidosis in salicylate toxicity.

Neurological effects may range in severity from lethargy to seizures and coma. Central nervous system manifestations are always an ominous finding and are representative of increased concentrations of salicylates in the CNS. Rising CNS concentrations facilitate neuronal uncoupling of oxidative phosphorylation, and pulmonary edema may ensue. Salicylate neurotoxicity has also been correlated with decreased CNS glucose concentrations despite normal serum glucose concentrations. Therefore, dextrose should be considered in any patient presenting with altered mental status and suspected salicylate toxicity. Uncoupling of oxidative phosphorylation may further result in increased heat production and the inability to dissipate heat. Rapid elevation in temperature in salicylate toxicity is typically a premorbid finding.

No antidote for salicylate intoxication exists. Management of salicylate toxicity includes supportive care, limiting further salicylate absorption and enhancing elimination. The optimal method of GI decontamination for salicylates has not been proven. In vitro studies demonstrate that a gram of activated charcoal can adsorb 550 mg of salicylic acid and a 10:1 ratio of AC to salicylates appears to result in maximum efficacy for adsorption. Multidose-activated charcoal may be of benefit for enteric-coated preparations or bezoar formation. The use of MDAC to enhance gastrointestinal dialysis is controversial. A porcine model of MDAC...
after IV administration of aspirin did not result in enhanced clearance when venous bicarbonate was kept at ≥15 mEq/L and urine pH was kept at ≥7.5.105,106 Whole bowel irrigation may also be considered in the prevention of salicylate absorption for enteric-coated preparations. However, a study by Mayer et al found that neither MDAC nor WBI was efficacious in enhancing the excretion of previously absorbed salicylates.104 Single-dose AC should be considered in patients exhibiting ongoing absorption that have no other contraindications. Multidose AC is not recommended and if used should be limited to 2 to 4 doses.

IV fluid administration to replace intravascular depletion is crucial in the management of salicylate poisoning. Salicylate excretion is dependent on renal flow rate but even more so on urinary pH.105 Forced diuresis has not been shown to enhance elimination of salicylates more than alkalinization alone.106 Forced diuresis is not recommended as it may precipitate fluid overload, electrolyte abnormalities, and pulmonary edema.

Alkalinization is the mainstay of enhancing salicylate excretion and decreasing toxicity. Because aspirin is a weak acid, it may be ionized and “trapped” at urine pH ≥ 7.5.107 Renal clearance of salicylates can be increased 20-fold if urine pH is increased from 5 to 8.105,106 Alkalinization of the serum traps salicylates and inhibits further redistribution to tissues or the CNS.108 Goals of alkalinization include a urine pH of 7.5 to 8 and an arterial pH of 7.45 to 7.55.108 Alkalinization may be accomplished by administering sodium bicarbonate 1 to 2 mEq/kg IV bolus followed by an infusion of 150 mEq of sodium bicarbonate placed in 1 liter of 5% dextrose in water (D5W) and infused at 1.5 to 2 times the rate of IV maintenance fluids.95 Complications of overzealous alkalinization include fluid overload, alkalemia, hypernatremia, and CHF. Extracorporal techniques should be considered in any patient who has a very high salicylate concentration, severe fluid or electrolyte imbalance, deteriorating vital signs, ALI, ARF, or altered mental status. The preferred method of extracorporal removal is hemodialysis because of its ability to correct underlying acid-base imbalances while removing salicylates. Hemoperfusion is not commonly employed for reasons previously discussed.

Routine laboratory monitoring of salicylate concentrations is not recommended in patients presenting with overdose who are asymptomatic and have no history of salicylate ingestion.109 Therapeutic dosing of salicylates usually results in peak concentrations within 1 to 2 hours. In overdose, bezoars may form and result in varying times to peak concentrations. West et al reported delayed salaslate toxicity occurring as late as 67 hours postingestion.110 Salicylate concentrations should be obtained immediately in patients exhibiting symptoms consistent with salicylate toxicity. Salicylate levels should be repeated every 2 to 6 hours depending on the severity of the patient’s symptoms and prior concentrations. Salicylate concentrations should only be interpreted in association with the patient’s acid base status as salicylate toxicity is enhanced in acidosis. Salicylate concentrations should be monitored until the patient’s symptoms resolve and at least 2 downward trending salicylate concentrations have been obtained.

Finally, although airway management is a critical aspect of supportive care, sedatives and endotracheal intubation with mechanical ventilation pose a significant risk in the salicylate poisoned patient. In a study by Stolbach et al, mechanical ventilation was associated with respiratory acidosis, a decrease in serum pH and clinical deterioration.94 Decreases in respiratory rate and/or increases in PCO2 cause a respiratory acidosis that can rapidly shift salicylates from the serum to the CNS or other tissues resulting in significant clinical deterioration or death. If airway management is required, alkalinization with sodium bicarbonate should be maximized and maintenance of the patient’s ventilation rate should be equivalent or greater than the patient’s own respiratory rate to avoid increasing PCO2 concentrations and resultant respiratory acidosis.

Conclusions

Preparing emergency medicine and critical care pharmacists for acute toxicological emergencies is critical for effective patient care of the patient presenting with toxic ingestions. Pharmacists can have an integral role in the management of patients with acute poisonings through provision of drug information and therapeutic recommendations. Supportive care and initial stabilization are important in all poisonings. Certain poisonings may benefit from interventions to decrease toxin absorption or enhance elimination, while others may benefit from specific antidotes. All pharmacists should be familiar with the evaluation, initial resuscitation and stabilization, specific beneficial interventions and antidotes for common toxicodromes.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research and/or authorship of this article.

References


