Antidotes for toxicological emergencies: A practical review

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Purpose. Appropriate therapies for commonly encountered poisonings, medication overdoses, and other toxicological emergencies are reviewed, with discussion of pharmacists’ role in ensuring their ready availability and proper use.

Summary. Poisoning is the second leading cause of injury-related morbidity and mortality in the United States, with more than 2.4 million toxic exposures reported each year. Recently published national consensus guidelines recommend that hospitals providing emergency care routinely stock 24 antidotes for a wide range of toxicities, including toxic-alcohol poisoning, exposure to cyanide and other industrial agents, and intentional or unintentional overdoses of prescription medications (e.g., calcium-channel blockers, β-blockers, digoxin, isoniazid). Pharmacists can help reduce morbidity and mortality due to poisonings and overdoses by (1) recognizing the signs and symptoms of various types of toxic exposure, (2) guiding emergency room staff on the appropriate use of antidotes and supportive therapies, (3) helping to ensure appropriate monitoring of patients for antidote response and adverse effects, and (4) managing the procurement and stocking of antidotes to ensure their timely availability.

Conclusion. Pharmacists can play a key role in reducing poisoning and overdose injuries and deaths by assisting in the early recognition of toxic exposures and guiding emergency personnel on the proper storage, selection, and use of antidotal therapies.

Index terms: Antidotes; Dosage; Drugs; Hospitals; Pharmaceutical services; Pharmacists, hospital; Pharmacy, institutional, hospital; Poisoning; Protocols

Poisoning is a leading cause of morbidity and mortality in the United States; in fact, it is the second leading cause of injury-related mortality, and its incidence is rising. The American Association of Poison Control Centers’ National Poison Data System receives reports of more than 2.4 million human poison exposures and approximately 1300 poisoning-related deaths annually. However, it is likely that the associated mortality is much higher than those statistics would indicate, as it is estimated that only about 5% of U.S. poisoning deaths are reported to poison control centers.

Antidotes play a critical role in the care of poisoned or overdosed patients. Recently issued national consensus guidelines include a recommended list and the quantities of antidotes that should be readily available in hospitals that provide emergency care. Some of the antidotes should be available for immediate administration on a patient’s arrival, which requires stocking in the emergency department (ED) at most hospitals; other antidotes should be available within 60 minutes and can be stocked in the hospital pharmacy provided that prompt delivery to the ED can be assured. A recommended antidote stocking list and sample inventory log can be found in eFigure 1 and eTable 1.

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Supplementary material is available with the full text of this article at www.ajhp.org.
available at www.ajhp.org. This list should be adapted by each individual facility based on a needs assessment. Most importantly, this list should be decided on by vested parties (e.g., pharmacists, physicians, and other health care practitioners involved in providing emergency care and critical care).

One of the many roles of the ED pharmacist is participating in the management of toxicological emergencies. The goal of this review is to provide essential information to guide the appropriate use of antidotes. The antidotes discussed (in alphabetical order) are those whose use likely entails the greatest involvement of ED pharmacists. As recommendations may change, clinicians should always consult a regional poison control center (1-800-222-1222) to ascertain the most current recommendations on antidote use and to report exposures and poisonings.

### Antidotes for toxic-alcohol poisoning

The use of ethanol or, preferably, fomepizole for alcohol dehydrogenase (ADH) inhibition is a mainstay in the management of toxicity due to ingestion of methanol, ethylene glycol, or diethylene glycol.5-8 The toxicity of methanol and of ethylene glycol is well described, and each year in the United States there are about 5000 exposures that require treatment and 20–30 associated deaths reported to poison centers.2,9,10 Methanol and ethylene glycol, as parent compounds, are relatively nontoxic. However, they are metabolized by ADH to toxic metabolites that can cause end-organ damage and death. Methanol is metabolized via ADH to formic acid, which results in anion-gap metabolic acidosis and ocular toxicity. Retinal toxicity secondary to methanol poisoning is usually irreversible.6,11 Ethylene glycol is metabolized via ADH to glycolic acid, which results in anion-gap metabolic acidosis, and oxalic acid, which results primarily in renal toxicity due to the formation of calcium oxalate crystals.7,12 Both can produce irreversible CNS toxicity.

Poisoning by diethylene glycol (historically and tragically used as a glycerin substitute and also in household products such as wallpaper stripper and Sterno brand heating fuel13,14) is less common but associated with very high morbidity and mortality.15,16 Diethylene glycol is metabolized via ADH to hydroxyethoxyacetic acid and diglycolic acid and causes anion-gap metabolic acidosis, bilateral cortical necrosis, and sensorimotor polyneuropathy.17-20

**Ethanol.** For many years, ethanol has been used to inhibit ADH and limit the metabolism of methanol and ethylene glycol to their respective metabolites.21 The dose of ethanol needed to competitively inhibit ADH depends on the comparative affinity of the specific toxic alcohol for ADH. Most authorities recommend using a dose of ethanol sufficient to achieve and maintain a serum ethanol concentration of 100–150 mg/dL. In the presence of ethanol, the half-lives of ethylene glycol (in patients with normal renal function) and methanol are approximately 17.5 and 45 hours, respectively.6,7

Ethanol can be administered intravenously or orally. However, a commercial i.v. preparation of ethanol is no longer available, and extemporaneous preparation is too time-consuming to be considered satisfactory. A loading dose is necessary to quickly achieve the desired serum concentration of 100–150 mg/dL; then a maintenance dose is administered, using serum ethanol concentrations to maintain the desired target. Repeat evaluations of the serum ethanol concentration are required to ensure that the target level is achieved and maintained. Individual differences in ethanol metabolism occur due to pharmacogenetics and whether the patient is induced or becomes induced secondary to chronic ethanol exposure.6,7

The risks associated with ethanol administration include central nervous system (CNS) depression, hypoglycemia (due to decreased gluconeogenesis), nausea, and vomiting. Intravenous administration of ethanol poses an additional risk of phlebitis and hypertoncity with hypotension. Frequent assessment of the serum ethanol concentration and monitoring of venous blood glucose are required.

**Fomepizole.** Fomepizole competitively inhibits ADH and is an effective and safe antidote for both ethylene glycol and methanol toxicity.6,7 In the presence of fomepizole, the half-lives of ethylene glycol (in patients with normal renal function) and methanol are 14.5 and 40 hours, respectively.22

The Food and Drug Administration (FDA)-approved regimen of fomepizole is an i.v. loading dose of 15 mg/kg over 30 minutes followed by a dose of 10 mg/kg every 12 hours, with the frequency of dosing increased to every 4 hours during hemodialysis.23 Fomepizole induces its own metabolism, presumably through the cytochrome P-450 2E1 isoenzyme; therefore, after 48 hours of drug administration, the fomepizole dose should be increased to 15 mg/kg every 12 hours.

Fomepizole is generally well tolerated. Adverse events reported with the use of fomepizole include mild irritation at the i.v. infusion site, headache, nausea, dizziness, drowsiness, and a bad or metallic taste in the mouth. Although there are no head-to-head comparisons of fomepizole versus ethanol for the management of toxic-alcohol poisoning, the former’s ease of administration and relative lack of serious adverse effects have elevated it to preferred status. The clinical advantages of fomepizole over ethanol are a much higher potency of ADH inhibition ($K = 0.1 \mu mol/L$, a 1000-fold higher affinity than that...
of ethanol), better maintenance of therapeutic blood concentrations, and fewer adverse effects; moreover, the administration of fomepizole is less labor-intensive. Additional and supportive therapy. In addition to antidote administration, hemodialysis should be considered in all toxic-alcohol exposures in which toxic metabolites have already formed, as evidenced by anion-gap metabolic acidosis or end-organ damage, and for patients with toxic serum methanol or ethylene glycol concentrations whose elimination of parent or toxic metabolites is expected to be inordinately prolonged (e.g., cases involving significant methanol exposure or ethylene glycol ingestion by a patient with renal impairment). Empiric hemodialysis is recommended if the serum methanol concentration is >25 mg/dL and if the serum ethylene glycol concentration is >50 mg/dL with renal insufficiency. Hemodialysis also should be considered in cases of severe isopropyl alcohol poisoning in patients with hemodynamic instability.

Intravenous administration of 50 mg of folic acid every six hours enhances methanol elimination and has been shown to prevent retinal toxicity in animal models. Also, urinary alkalinization (i.e., a urine pH of >8) with i.v. sodium bicarbonate enhances formate elimination and may reduce the distribution of formic acid to the eye.

Theoretically, the use of i.v. thiamine hydrochloride 100 mg and i.v. pyridoxine hydrochloride 50 mg every six hours should shunt the metabolism of ethylene glycol away from production of oxalic acid to production of less toxic metabolites; though there are no data from studies of humans to support this practice, these agents are well tolerated and the potential benefits outweigh any risks.

Implications for the pharmacist. Methanol or ethylene glycol toxicity should be suspected in a patient with anion-gap metabolic acidosis in whom laboratory testing reveals a low (or no) ethanol concentration, no ketones, and a normal lactic acid concentration (clinicians need to be aware that some test results can be skewed by glycolic acid, the toxic metabolite of ethylene glycol). Fomepizole and adjuvants that act as cofactors should be used as soon as toxic alcohols are included in the differential diagnosis. Fomepizole should be continued until the patient is no longer acidic and the toxic-alcohol serum concentration is presumed or confirmed to be <25 mg/dL. The availability of testing for toxic alcohols is limited.

Antidotes for calcium-channel-blocker and β-blocker toxicities

Toxicity due to calcium-channel blockers (CCBs) or β-blockers results in significant morbidity and mortality. The manifestations of toxicity are generally extensions of the drugs’ pharmacologic and therapeutic effects and often include hypotension, bradycardia, conduction block, and myocardial depression. Depending on the amount of the offending drug ingested and the patient’s underlying cardiovascular health, the patient could remain asymptomatic or progress to cardiovascular collapse.

Subtleties in presenting symptoms can help differentiate CCB and β-blocker poisoning. Patients experiencing a CCB overdose tend to remain awake and alert, even in the event of profound hypotension and bradycardia, while patients with β-blocker poisoning are more likely to have an altered mental status and respiratory depression. The more severe the CCB overdose, the more likely the patient is to exhibit hyperglycemia, because CCBs also inhibit the release of insulin from pancreatic β-cells via a calcium-dependent pathway. Children experiencing a β-blocker overdose may develop hypoglycemia, an uncommon symptom in adults. Dihydropyridine CCBs such as nifedipine are more potent peripheral vasodilators than nondihydropyridine CCBs; they have limited effects on cardiac rhythm and are more likely to cause hypotension with reflex tachycardia. Propranolol, a β-blocker with high lipophilicity and sodium-channel-blocking effects, is more likely than other β-blockers to cause patients to have a seizure and to exhibit a widened QRS complex on electrocardiography. Toxicity resulting from the ingestion of the combination of a β-blocker and a CCB can be particularly serious and life-threatening. Even at therapeutic doses, the ingestion of more CCB or β-blocker medication than is prescribed can be life-threatening in a patient with a tenuous cardiac history. Because of the pathophysiologic similarities of CCB toxicity and β-blocker toxicity, their management is similar. The treatment of patients with bradycardia and hypotension begins with fluids and atropine, but patients who are more than mildly poisoned typically do not have an adequate response to these therapies. Other treatment modalities include calcium, glucagon, hyperinsulinemia–euglycemia therapy (HIET), vasopressors, cardiac pacing, i.v. 20% fatty acid emulsion, extracorporeal circulatory support, and intra-aortic balloon pump therapy.

Calcium. Calcium plays an integral role in myocardial function and is necessary for automaticity, conduction, contraction, and vascular tone. In theory, the administration of exogenous calcium to patients with CCB toxicity should competitively increase calcium entry into the myocardium via nonblocked channels. Calcium has also been used to treat β-blocker toxicity.

Along with atropine, calcium is considered a first-line therapy for CCB or β-blocker toxicity. Patients with mild toxicity seem to have an
adequate response to calcium therapy; those with severe toxicity usually require additional therapies.

Calcium is available as either calcium chloride or calcium gluconate. Because of differences in the molecular weights of the chloride and gluconate components, 30 mL of 10% calcium gluconate is equivalent to 10 mL of 10% calcium chloride. Extravasation of calcium must be avoided. In particular, calcium chloride is extremely damaging to tissue should extravasation occur. For this reason, it is recommended that calcium chloride be administered through a central line or only with good peripheral venous access. Care should also be taken not to extravasate calcium gluconate, but the consequences are less severe, so the administration of calcium gluconate through a peripheral vein is more appropriate.

A reasonable starting dose in adults is 30 mL of calcium gluconate or 10 mL of calcium chloride, with additional doses administered in 15–20 minutes. After three doses, careful monitoring of ionized calcium is necessary to avoid dangerous hypercalcemia. Calcium is administered to improve hemodynamics.

Hypercalcemia may lead to an ileus, myocardial depression, hyporeflexia, and an altered mental status. The administration of calcium to a patient with cardioactive-steroid (e.g., digoxin) toxicity may lead to asystole and should be avoided.

Implications for the pharmacist.
To avoid hypercalcemia and its associated risks, close monitoring of the serum ionized calcium level is required, especially in patients receiving multiple doses of exogenous calcium. The use of calcium should be avoided in a patient with known or suspected digoxin toxicity.

Glucagon. It is glucagon’s ability to increase cardiac cyclic adenosine monophosphate (cAMP) directly and independently of the β-adrenergic receptor that has established its role in the management of β-blocker overdoses.29 The increase in cardiac cAMP enhances inotropy and chronotropy and may improve conduction. Glucagon can also be used to manage CCB toxicity because not only is it difficult to distinguish an overdose of a β-blocker from an overdose of a CCB, as the two types of medications are frequently consumed together, but also because the glucagon-induced increase in cAMP occurs regardless of whether the calcium channel is blocked. In severely poisoned patients, glucagon will likely be ineffective and additional interventions are necessary.29

Glucagon causes dose-dependent and rate-related nausea and vomiting with a risk of aspiration; thus, antiemetics such as metoclopramide and serotonin antagonists are often used in patients receiving the drug.29 Other adverse effects of glucagon can include hyperglycemia, followed by hypoglycemia in rare cases; gastrointestinal (GI) smooth-muscle relaxation and diarrhea; hypokalemia; and, rarely, allergic reactions. Tachyphylaxis with continued administration of glucagon is a theoretical concern.

Glucagon has a rapid onset of action and a short duration of effect, rarely longer than 15 minutes. As with other therapies used in toxicology, definitive glucagon dosing recommendations are lacking; a dosage of 50 µg/kg, or 3–5 mg up to a cumulative dose of 10 mg, is reasonable.24 This dose can be repeated as necessary. If there is a favorable response to glucagon boluses, a continuous infusion may be used.

Implications for the pharmacist.
The doses of glucagon necessary for the management of β-blocker or CCB toxicity are much higher than those typically used to induce hyperglycemic or antispasmodic effects. The endpoints for discontinuing glucagon infusions are not clear; however, it is reasonable that once a patient is hemodynamically stable for a minimum of 6 hours, a slow taper of a single agent at a time can be employed. Anecdotal evidence and clinical experience suggest that once therapy is discontinued, close observation is necessary for a minimum of 12 hours.

HIEt. The management and outcomes of patients severely poisoned by CCBs or β-blockers have improved substantially since the advent of HIEt.31,32 High-dose insulin has long been reported to be an inotrope.33 It was only in the late 1990s that HIEt was demonstrated to be effective in treating patients severely poisoned with CCBs or β-blockers.32 The mechanism of HIEt’s effectiveness has not been clearly delineated; the available data suggest it enhances carbohydrate use and energy production by myocardial cells, resulting in improved contractility.34,37 Because of the alterations in myocardial cell metabolism, it is not surprising that the beneficial effects of HIEt in patients with CCB or β-blocker toxicity are delayed, generally occurring after 15–60 minutes.37–39 Therefore, HIEt should be started early in the course of management. If a patient remains hypotensive and bradycardic after receiving fluids, atropine, calcium, and glucagon, HIEt should be administered. As HIEt is particularly effective in improving myocardial contractility, the early administration of HIEt may avoid the need for vasopressors or allow the use of lower doses, thereby reducing the potential for ischemic consequences.39

The major adverse effects associated with HIEt are hypoglycemia and hypokalemia. The sicker the patient is from a CCB overdose, the more likely it is that hypoglycemia will develop before HIEt is instituted; as the patient recovers, the need for supplemental glucose increases.30 Insulin causes an intracellular shift of serum potassium, and potassium supplementation should be considered when the serum potassium concentration is <3 meq/L.
HIET should begin with an i.v. loading dose of 1 unit/kg of regular insulin followed by an infusion of 0.5–1 unit/kg/hr. The infusion dosage can be increased every 20–30 minutes. Doses of 2.5–3 units/kg/hr have been used depending on the response. Experimental studies have used even higher doses. Serum glucose should be maintained at a concentration of >100 mg/dL during HIET. A maximum insulin dose has not been established. If the initial blood glucose concentration is <400 mg/dL, an i.v. loading dose of 0.5 g/kg dextrose should be administered with the insulin and followed by an infusion of 0.5 g/kg/hr of dextrose, with meticulous and frequent monitoring of serum glucose and potassium concentrations. This dose of dextrose can be administered in a concentrated form (e.g., a 20–25% solution) through a central line to avoid problems with fluid overload and venous irritation. The recommended goal is to maintain a serum glucose concentration of 100–250 mg/dL. A patient with a falling glucose concentration should be treated by increasing the amount of supplemental glucose (not by decreasing the insulin infusion) until the patient is hemodynamically stable.

Implications for the pharmacist. The use of HIET has resulted in a decline in mortality among patients with severe CCB or β-blocker toxicity. There is a delay in the benefits of HIET, so it should be started early. A general rule of thumb is to initiate HIET when it is apparent that calcium and glucagon are ineffective or as soon as the decision is made to initiate a vasopressor.

Antidotes for cyanide poisoning

In the United States, there are now two types of cyanide antidotes available. The Lilly Cyanide Antidote Kit was the first and, for many years, the only such kit available; it contained amyl nitrite, sodium nitrite, and sodium thiosulfate. This combination of agents is now available as the branded Cyanide Antidote Package or as the generic Cyanide Antidote Kit, and the components are sold separately by various manufacturers. Nithiodote, recently approved by FDA, contains sodium nitrite and sodium thiosulfate. In 2006, FDA approved hydroxocobalamin, a novel cyanide antidote, available as the branded Cynokit.

Cyanide binds to the ferric ion on cytochrome oxidase and abruptly halts the electron transport chain and aerobic respiration, producing profound toxic effects. Cyanide also preferentially binds to the ferric ion of methemoglobin, but endogenous concentrations of methemoglobin are quite low.

Exposure to cyanide can occur during house fires, industrial accidents, and attempted suicides, and cyanide is a potential agent of chemical warfare. Smoke inhalation is one of the more common sources of exposure to cyanide in the United States. Suicide attempts involving the ingestion of commercially available cyanide salts have been reported. Cyanide overdose has been reported among workers in the gold, jewelry, and textile industries, in which the salts are frequently used. Cyanide exposure causes rapid, severe systemic toxicity and rapid cardiovascular collapse. Although there is no rapid test for the diagnosis of cyanide poisoning, an elevated lactate concentration (>8 mmol/L, or 72 mg/dL) and a venous blood gas with a high partial pressure of oxygen and a high oxygen saturation are, in the appropriate clinical context, highly suggestive of cyanide toxicity and warrant empiric antidotal therapy.

Amyl nitrite and sodium nitrite. The mechanism of action of amyl nitrite and sodium nitrite as antidotes for cyanide poisoning is to produce methemoglobinemia and vasodilation. Vasodilation may contribute to their therapeutic and adverse effects.

Intravenous sodium nitrite produces significant methemoglobinemia. The cyanide bound to cytochrome oxidase is then preferentially bound to methemoglobin, forming cyanomethemoglobin. Rhodanese, an endogenous enzyme, then facilitates the formation of thiocyanate, a much less toxic metabolite, which is renally excreted.

The creation of methemoglobinemia through the use of nitrites for cyanide poisoning entails some risk and, in particular, may be detrimental or even lethal to a patient with smoke inhalation and concurrent carboxyhemoglobinemia or lung injury. Neither carboxyhemoglobin nor methemoglobin is capable of carrying oxygen, so such patients can develop functional hypoxia. Therefore, the administration of the nitrite component of therapy for cyanide poisoning should be avoided in patients with smoke inhalation unless it can be demonstrated that the carboxyhemoglobin level is negligible. The dosage of nitrites should not be adjusted to achieve a predetermined methemoglobin concentration, since the formation of cyanomethemoglobin can potentially be misread as methemoglobin formation by an oximeter during patient monitoring. (A methemoglobin concentration above 20% should halt further nitrite administration.)

In the context of cyanide poisoning, the differences between nitrites lie in the route of administration and the degree of methemoglobinemia they produce. Amyl nitrite is inhaled, produces a minimal amount of methemoglobin, and is designed to be administered pending the establishment of i.v. access, as is often the case in the prehospital setting. Sodium nitrite is administered intravenously and results in a methemoglobin concentration of about 15% in healthy adults. In other scenarios of cyanide toxicity, particularly the
intentional ingestion of cyanide salts, amyl nitrite can be given to adults as one ampul (0.3 mL) inhaled until i.v. access is obtained, followed by 300 mg (10 mL of 3%) i.v. sodium nitrite over two to four minutes. Children should receive 6 mg/kg (0.2 mL/kg of 3%) sodium nitrite up to the adult dose, at the same rate. This dosing strategy has been established as safe in children with a hemoglobin concentration of ≥7 g/dL. Half of the recommended dosage can be administered if cyanide toxicity reappears or, for prophylaxis, two hours after the initial dosage.

Sodium thiosulfate. As noted above, cyanide is metabolized by the enzyme rhodanese to a less toxic metabolite, thiocyanate, which is renally eliminated. However, this metabolic pathway is capacity limited. Thiosulfate enhances the activity of rhodanese by donating a sulfur group, thereby increasing the amount of thiocyanate that rhodanese can produce. Sodium thiosulfate is relatively well tolerated, but there is a potential for nausea and vomiting, as well as rate-related hypotension.

Because of its relatively favorable adverse-effect profile, sodium thiosulfate should be given to all patients with suspected cyanide toxicity, including those with smoke inhalation. The recommended dosage of sodium thiosulfate for adults is 12.5 g i.v. (50 mL of 25% solution); for pediatric patients, it is 0.5 g/kg i.v. (2 mL/kg of 25% solution) up to the adult dose. One half of the initial dose can be administered two hours later if toxicity reappears or as a preventive measure. Intravenous sodium thiosulfate should be administered either as a bolus injection or infused over 10–30 minutes immediately after sodium nitrite via the same i.v. line.

Hydroxocobalamin. Vitamin B₁₂, or hydroxocobalamin, detoxifies cyanide and forms cyanocobalamin, which is renally excreted. Hydroxocobalamin is an appealing cyanide antidote because it is relatively safe, does not compromise the blood’s oxygen-carrying capacity, and, unlike the nitrites or sodium thiosulfate, does not produce hypotension. These features make hydroxocobalamin an ideal agent for empiric use in patients with smoke inhalation who are suspected to have cyanide toxicity. Hydroxocobalamin has been found effective for the treatment of acute cyanide poisoning in animal models; in one study of laboratory dogs rendered cyanide toxic, mortality was greatly reduced among dogs given hydroxocobalamin in comparison with those given placebo (21% versus 82%, respectively).

In healthy volunteers, the use of hydroxocobalamin has been linked to chromaturia, dose-dependent erythema, headache, GI distress, pruritus, dysphagia, and infusion-site reactions. Allergic reactions are less frequent but occasionally are severe enough to require intervention. In one study, 25% of volunteers who received hydroxocobalamin experienced a substantial rise in diastolic blood pressure, and three also had a rise in systolic blood pressure; these blood pressure changes were attributed to the effects of hydroxocobalamin on nitric oxide scavenging. A delayed pustular rash appeared on the face and neck of a few participants in that study and took several weeks to resolve.

Hydroxocobalamin is known to cause a reddish discoloration of the urine that typically resolves within 48 hours. Once hydroxocobalamin is administered, the use of laboratory tests that depend on colorimetric techniques is no longer valid, as both hydroxocobalamin and cyanocobalamin are bright red and will cause interference; assays for bilirubin, creatinine, aspartate transaminase (AST), iron, glucose, magnesium, and hemoglobin and most urine assays are among the tests affected.

There was a recent case report of a hydroxocobalamin-related colorimetric change resulting as a blood leak and shut down automatically. Discoloration of urine by hydroxocobalamin also has been reported to interfere with a spectroscopic assay for urinary thiocyanate that is often used to confirm cyanide exposure.

The use of hydroxocobalamin can also skew the results of serum carboxyhemoglobin determinations, falsely increasing or falsely decreasing the measured concentration. Therefore, if possible, blood samples should be drawn before the administration of hydroxocobalamin.

The empiric adult dose of hydroxocobalamin is 5 g, which can be infused over a period of 15 minutes, with the infusion repeated if necessary; the pediatric dose is 70 mg/kg, up to a maximum of the adult dose, administered at the same infusion rate.

There are no published data on the compatibility of hydroxocobalamin with other substances, and the drug should therefore not be administered through the same line as other agents. If another line is not available, sodium thiosulfate can be administered through the same line after hydroxocobalamin administration is completed, with care taken to avoid mixing and inactivating the hydroxocobalamin with sodium thiosulfate.

Implications for the pharmacist. Cyanide toxicity should be considered in patients with sudden cardiovascular collapse, especially in the appropriate context of occupational exposure (e.g., laboratory or industrial work) or in a fire victim with hemodynamic instability, elevated lactic acid, or coma. Cyanide antidotes should be immediately available in the ED.

Digoxin-specific antibody fragments

Digoxin-specific antibody fragments (Fab) are lifesaving agents
in the management of toxicity associated with the use of digoxin and other cardioactive steroids, including digitoxin and those derived from oleander, fox glove, lily of the valley, and toad venom. They are safe and effective in both adults and children with acute or chronic toxicity.

Digitalis, the most widely used cardioactive steroid, has a narrow therapeutic index. Cardioactive steroids act on the heart to enhance contractility, act on the conduction system of the heart to produce a variety of effects, and also act on the autonomic nervous system. The agents’ toxicity is related to an exaggeration of those effects and often involves an increase in intracellular calcium. Electrocardiographic changes secondary to digoxin toxicity can be marked and highly variable.

In patients with acute digoxin poisoning, empiric treatment with digoxin-specific Fab should be considered in any patient with a life-threatening or potentially life-threatening dysrhythmia, including severe sinus bradycardia or heart block unresponsive to atropine, as well as ventricular ectopy, tachycardia, or fibrillation. GI complaints are less common in the context of chronic digoxin poisoning, but confusion and an altered mental status are more frequent in the elderly and might suggest the need for digoxin-specific Fab in a patient with a chronically elevated serum digoxin concentration (>2.5 ng/mL). Patients at risk for chronic digoxin toxicity include elderly patients with declining renal function, patients who have received inappropriate dosages of digoxin, patients with electrolyte abnormalities, and patients administered drugs known to inhibit the elimination of digoxin.

Digoxin-specific Fab is generally well tolerated. The adverse-effect profile includes the potential for hypokalemia, worsening of heart failure, a rapidly conducted ventricular rate, and, rarely, allergic reactions.

The dosage calculation for digoxin-specific Fab can be made according to the known ingested digoxin dose, according to the serum digoxin concentration, or empirically. The empiric dosing for acute toxicity is 10–20 vials (each 38- or 40-mg vial binds 0.5 mg of digoxin); the empiric dosing for acute toxicity is 10–20 vials, according to the serum digoxin concentration, or empirically. The empiric dosing for acute toxicity is 10–20 vials (each 38- or 40-mg vial binds 0.5 mg of digoxin); the empiric dosing for acute toxicity is 10–20 vials, according to the serum digoxin concentration, or empirically. The empiric dosing for acute toxicity is 10–20 vials (each 38- or 40-mg vial binds 0.5 mg of digoxin); the empiric dosing for acute toxicity is 10–20 vials, according to the serum digoxin concentration, or empirically. The empiric dosing for acute toxicity is 10–20 vials, according to the serum digoxin concentration, or empirically. The empiric dosing for acute toxicity is 10–20 vials, according to the serum digoxin concentration, or empirically. The empiric dosing for acute toxicity is 10–20 vials, according to the serum digoxin concentration, or empirically. The empiric dosing for acute toxicity is 10–20 vials, according to the serum digoxin concentration, or empirically. The empiric dosing for acute toxicity is 10–20 vials, according to the serum digoxin concentration, or empirically.

Flumazenil

The intentional ingestion of benzodiazepines is a common cause of overdoses. Flumazenil is a competitive antagonist at the benzodiazepine-receptor binding site on γ-aminobutyric acid-A. Typically, when benzodiazepines are ingested in overdose, the patient exhibits a toxicome, or toxic syndrome, of CNS depression with relatively normal vital signs. Deaths attributed solely to the oral ingestion of benzodiazepines are rare.

While the idea of using flumazenil to reverse benzodiazepine toxicity may be tempting, the risks usually outweigh the benefits. In a benzodiazepine-dependent patient, flumazenil can precipitate symptoms of benzodiazepine withdrawal, including seizures. Additionally, in cases of multiple-drug ingestion, flumazenil may remove the protective effect of the benzodiazepine and unmask cardiac arrhythmias and seizures. Therefore, the use of flumazenil in overdose patients is discouraged unless it can be determined with certainty that only a benzodiazepine was ingested and that the patient is not benzodiazepine dependent and has no history of seizure.

Flumazenil also may serve a role in the treatment of children who present with altered mental status in whom possible ingestion of a benzodiazepine is suspected as the sole toxic exposure. In this scenario, invasive diagnostic techniques such as computed tomography of the head and lumbar puncture may be avoided. In such cases, flumazenil therapy will not reduce the required ED observation time; but if the child improves clinically, flumazenil can
help confirm the diagnosis of benzodiazepine toxicity.

Flumazenil can also be used to reverse CNS depression associated with benzodiazepine administration during procedural sedation if the patient is known not to be benzodiazepine dependent. The initial dosage of flumazenil is 0.2 mg/min administered via a slow i.v. infusion. In the context of conscious sedation, many patients respond to total doses of 0.4 mg while some patients may require a total dose of up to 1 mg.81 The reversal of benzodiazepine toxicity occurs rapidly after flumazenil administration; if re sedation occurs, doses can be repeated at intervals of no less than 20 minutes. Resedation after flumazenil therapy is most likely to develop if >10 mg of midazolam or a longer-acting benzodiazepine is used for conscious sedation. No more than 3 mg of flumazenil should be given in one hour. In general, if re sedation is not observed within two hours of the administration of a 1-mg dose of flumazenil, subsequent serious re sedation is unlikely.81,82

Implications for the pharmacist.
Due to the associated risk–benefit ratio, flumazenil is rarely indicated in the management of acutely poisoned patients.89 These patients often have an unclear history, which makes the administration of flumazenil potentially dangerous. Flumazenil does not consistently reverse hypoventilation secondary to benzodiazepine use.80 In the rare instances when flumazenil may be considered, it is important to ascertain that the patient is not taking benzodiazepines chronically, has a normal electrocardiogram, and is not experiencing toxicity due to a polydrug ingestion. In the context of reversal of conscious sedation, it is important to ensure that the patient has no contraindications to flumazenil, as described above.

Intravenous fat emulsion

Intravenous fat emulsion (IFE) has long been used to supply calories in the form of free fatty acids to patients requiring parenteral nutrition. More recently, fatty acid emulsion has been used as an antidote for drug-induced cardiovascular collapse; the first supportive studies were laboratory investigations demonstrating the successful use of fatty acid emulsion in increasing the lethal threshold in animal models of bupivacaine-induced cardiac toxicity.85,86,87 Since those early animal studies, there have been multiple case reports of patients successfully resuscitated after cardiovascular collapse due to toxicity from local anesthetics.80–84 Those promising results led investigators to hypothesize that IFE would produce similar results in other scenarios of drug toxicity caused by lipid-soluble drugs such as CCBs, β-blockers, and tricyclic antidepressants.95–98 A case report by Sirianni et al.99 demonstrated the role of IFE in reversing the effects of an intentional overdose of bupropion and lamotrigine. The mechanism of action has not been precisely elucidated, but the “lipid sink” theory (i.e., lipophilic molecules of a local anesthetic partition into a lipemic plasma compartment, making them unavailable to the tissue) is foremost at this time;99 other actions that might contribute to the beneficial effects of IFE include the direct activation of myocardial calcium channels100 and the modulation of myocardial energy by providing the heart with energy in the form of fatty acids.84,85

Despite the promising case reports, research on the risks and benefits of IFE as an antidote for toxin-induced cardiovascular collapse remains in the popularity phase. Recently reported data from animal studies suggest that IFE has very limited adverse effects at the doses currently recommended.101 Potential IFE-related adverse events include the development of fat embolism, or sludging, as well as interference with certain laboratory analyses due to the resultant lipemic blood; other unknowns include the potential for drug interactions with other therapeutic interventions such as HIET.

IFE should be considered a first-line antidote for bupivacaine-induced toxicity.86,87,90–92 It should also be considered in a patient with presumed toxin-induced cardiovascular collapse after the failure of advanced supportive care measures, including other accepted antidotal therapy. In addition to local anesthetics, potentially toxic agents that should be considered possibly amenable to IFE therapy include those that are lipophilic and toxic to the myocardium (e.g., tricyclic antidepressants; CCBs, especially verapamil and diltiazem; bupropion; propranolol).

The use of IFE for the reversal of cardiotoxicity is not approved by FDA, and the dosing of IFE for this indication is unclear. Based on the published case reports of the successful use of IFE, a reasonable dosing strategy in adults is 20% IFE 100 mL (or 1.5 mL/kg) administered over 1–2 minutes by i.v. push. The bolus dose can be repeated if necessary.99 Some reports described the use of a continuous infusion of IFE at a rate of 0.25–0.5 mL/kg/min for 30–60 minutes after the bolus dose. The maximum dose of IFE has not been established.83,84

Implications for the pharmacist.
IFE has changed the management of bupivacaine-induced cardiotoxicity.87 Before the use of IFE, patients with cardiac arrest secondary to bupivacaine use were rarely resuscitated.92,93 Today, IFE should be used in any patient with bupivacaine-induced cardiac toxicity. The likely scenario for IFE use in the ED is treatment of a patient experiencing toxin-related cardiovascular collapse who is not improving with aggressive standard resuscitation measures and other accepted antidotal therapies. Toxins that are lipophilic and cause cardiac toxicity are most likely to respond
to IFE therapy, but data supporting such use of IFE are limited.

**N-acetylcysteine**

*N*-acetylcysteine (NAC) is a lifesaving therapy in the management of acetaminophen poisoning.102-109 While acetaminophen is still present in the plasma, NAC acts as an antidote, primarily by replenishing glutathione stores. Secondarily, it acts as a glutathione substitute and replenishes sulfate. These mechanisms of action all serve to either limit the formation of the toxic metabolite or to detoxify it; in this way, if NAC is administered in a timely fashion, acetaminophen toxicity can be prevented.108,109

The Rumack-Matthew nomogram is used to predict whether patients will develop hepatotoxicity, defined as a serum AST concentration of >1000 units/L, based on an initial plasma acetaminophen concentration obtained four or more hours after a single acute ingestion of acetaminophen. Indications for the initiation of NAC include a serum acetaminophen level on or above the Rumack-Matthew nomogram; situations in which a serum acetaminophen level is not available within eight hours of a potentially toxic ingestion; and hepatotoxicity, as defined by clinical symptoms or liver enzyme elevations above baseline.

Once fulminant hepatic failure has occurred, whether it is acetaminophen related or not, and even when all of the acetaminophen has already been metabolized, i.v. NAC therapy is still beneficial and may be life saving.105 In patients with severe reactive airway disease, oral NAC (which rarely produces an anaphylactoid reaction) might be preferred to i.v. NAC. Improper dilution or dosing has resulted in overdoses of NAC, leading to hyponatremia, cerebral edema, and death.105,110,117,119

The FDA-approved dosing of oral NAC is 140 mg/kg as a loading dose followed by 70 mg/kg every four hours for a total of 17 doses. The oral dose must be repeated if emesis occurs within one hour. Although oral NAC is rarely associated with anaphylactoid reactions, nausea and vomiting occur frequently, may delay the time to administration of an effective dose, and often require the administration of an antiemetic.120,121

The benefits of NAC outweigh the risks in pregnant patients with acetaminophen toxicity who meet the criteria for NAC administration. Although there are conflicting data, i.v. NAC is often recommended with the belief that i.v. NAC more readily crosses the placenta.122,123

NAC should not be discontinued until the acetaminophen concentration is undetectable or lower than the level of sensitivity; the AST concentration is normal or significantly improved; the synthetic function of the liver has improved, as evidenced by an International Normalized Ratio of <2; and there is no evidence of an altered mental status due to hepatic encephalopathy.124

**Implications for the pharmacist.** The decision to treat with NAC must be made quickly and based on multiple factors, including the determination of a toxic acetaminophen level and the time since overdose. NAC is nearly 100% hepatoprotective if given within the first eight hours of an overdose, and its efficacy decreases every hour after that.108 Although most effective if given early, NAC has a clear role in late therapy and has been shown to decrease mortality.117,125

NAC therapy should be continued until acetaminophen is undetectable, the AST concentration is improving, and evidence of hepatic failure is no longer present. If treatment is necessary beyond the standard 21-hour dosing regimen for i.v. NAC, the third part of the protocol (6.25 mg/kg/hr) should be continued. Unusually high or prolonged serum acetaminophen concentrations may require a change in the NAC protocol; consultation with a poison center is critical.
Naloxone

The most commonly used antidote in the ED setting, naloxone is a competitive antagonist at all opioid receptors, including the µ-opioid receptor. It is a well-established antidote for respiratory depression secondary to opioid toxicity. The efficacy and safety of naloxone are dose dependent. In a previously opioid-naïve patient experiencing an opioid overdose, even high doses of naloxone can be given safely. However, in an opioid-dependent patient, an inappropriate dose of naloxone has the potential to precipitate opioid withdrawal and to produce or worsen acute lung injury. Therefore, it is advisable to start with a dose of 0.04 or 0.05 mg in all patients and adjust the dose upward in increments of 0.04–0.05 mg; that approach can safely reverse the respiratory depressant effects of the opioids without producing unwanted and potentially dangerous withdrawal. Opioid withdrawal with abrupt catecholamine release, especially in an apneic patient, is likely to induce vomiting and aspiration or acute lung injury.

Although case reports have suggested that naloxone may be useful in reversing toxicity due to clonidine, ibuprofen, valproic acid, and captopril, the reported effects were quite variable, often minor, and usually inadequate. Buprenorphine is a partial µ-agonist whose toxic effects cannot be easily reversed with naloxone. Buprenorphine has a very high affinity for the µ-receptor and most likely affects µ-receptor subtypes in a dose-dependent and variable manner; this makes reversal with naloxone tricky, and a bell-shaped dose–response curve has been described, indicating that a dose too low or too high will be ineffective. In one experimental model, adults required an i.v. naloxone loading dose of 2–3 mg followed by a continuous infusion of 4 mg/hr for one hour before the respiratory depressant effects of buprenorphine were reversed; dosages greater than 4 mg/hr were actually ineffective, consistent with a bell-shaped dose–response relationship.

The i.v. route of naloxone administration is preferred due to a predictable, quick, and titratable onset of action. Oral or sublingual administration result in poor absorption and limited effects. Although naloxone is well absorbed with other parenteral routes of administration (intralingular, endotracheal, intranasal, subcutaneous, and intramuscular), a delayed onset of action or difficulty in titrating the dose makes those routes less desirable.

An initial naloxone dose of 0.04–0.05 mg i.v. in both opioid-dependent and opioid-naïve adult patients is recommended. Increasing the dose until reversal of respiratory depression maximizes the benefits while minimizing the potential for significant opioid withdrawal. Titration can be accomplished by doubling the dose every one to two minutes or escalating the dose from 0.05 mg to 0.1 mg to 0.4 mg to 2 mg to 10 mg. During dose titration, bag-valve mask ventilation should be used as necessary. Although there is not a consensus on the initial dose, starting with a lower dose of naloxone (0.04–0.05 mg) rather than the “standard” 2-mg dose is considered best practice. A lack of sufficient patient response to treatment with 10 mg of naloxone should call into question a diagnosis of isolated opioid toxicity. Patients experiencing an overdose of synthetic opioids (e.g., buprenorphine, fentanyl, methadone) often require higher doses of naloxone but generally respond to doses of 10 mg.

Due to the relatively short half-life of naloxone, the duration of its clinical effect is generally 30–90 minutes. This relatively brief duration of effect is critical to clinicians because the duration of effect of the opioid is frequently much longer than that of naloxone and, therefore, respiratory depression may recur. Repeat doses or a continuous infusion at an hourly dose equal to two thirds of the initial dose of naloxone may be necessary, so close monitoring of the patient is required in the ED. It is recommended that the naloxone infusion be started at two thirds of the hourly dose that was effective in reversing the respiratory depression. This is based on a pharmacokinetic study done in the 1980s.

Octreotide

A long-acting synthetic analog of somatostatin, octreotide is used in toxicology to counteract the insulin-releasing properties of the sulfonylurea and miglitolide oral hypoglycemics. Sulfonylureas and miglitolide stimulate insulin release by binding to adenosine triphosphate (ATP)-sensitive potassium channels on the beta-islet cell of the pancreas, increasing intracellular ATP concentrations, which increases intracellular calcium concentrations. Octreotide inhibits pancreatic beta-islet cell insulin release via G-protein-coupled receptors that inhibit cAMP production; this decreases intracellular calcium influx, thereby causing a decrease in insulin release.

Octreotide is used as an adjunct to dextrose to manage hypoglycemia induced by sulfonylureas and other exogenous causes of insulin release. Octreotide limits the production of hypoglycemia and decreases the need for supplemental dextrose in such cases. There are no published data from randomized clinical trials confirming the unique effects of octreotide in patients with sulfonylurea-induced hypoglycemia. One study of human volunteers confirmed the ability of octreotide to reduce dextrose requirements in fasting patients given sulfonylureas. Case reports described the reversal of sulfonylurea-induced hypoglycemia with octreotide in both adults and children. Vallurupalli described two patients...
with sulfonylurea-induced hypoglycemia and congestive heart failure who had blood glucose concentrations of 31 and 36 mg/dL, respectively, due to inadequate oral intake of glucose and underlying renal failure. Despite repeat doses of dextrose, both patients remained hypoglycemic. One of those patients received two doses of octreotide 50 µg 12 hours apart; after the initial dose, the first blood glucose value was 62 mg/dL, and the concentration rose to 121 mg/dL after the second dose. In the second case reported by Vallurupalli, the patient initially received 25 µg of octreotide subcutaneously, but the hypoglycemia persisted until two additional doses of 50 µg given 12 hours apart were administered.

Adverse effects associated with several doses of octreotide are minimal and may include diarrhea and abdominal discomfort. Octreotide has a relatively benign adverse-effect profile with short-term use, and it is therefore recommended that octreotide be considered in any patient with recurrent hypoglycemia after a single dose of i.v. hypertonic dextrose (0.5–1 g/kg) when the differential diagnosis includes sulfonylurea toxicity. The use of i.v. dextrose should be followed by feeding the patient.

Subcutaneous administration is the most frequently described method of octreotide delivery in the scientific literature. The usual adult dose of octreotide is 50 µg subcutaneously, with doses repeated every six hours as needed.

Implications for the pharmacist.

Octreotide decreases insulin release from the pancreas when secondary to an insulin secretagogue. In otherwise healthy patients (i.e., patients without diabetes) with an intact pancreas, the administration of exogenous dextrose to reverse the hypoglycemia caused by ingestion of an oral hypoglycemic induces the pancreas to release more insulin, which can exacerbate the hypoglycemia. Some clinicians advocate the use of octreotide after the first hypoglycemic episode, although most suggest that it should be initiated after the second hypoglycemic event. The duration of effect of the ingested xenobiotic causing the hypoglycemia should help determine the initial number of doses of octreotide and the duration of monitoring after the last dose of octreotide.

Conclusion

Pharmacists can play a key role in reducing poisoning and overdose injuries and deaths by assisting in the early recognition of toxic exposures and guiding emergency personnel on the proper storage, selection, and use of antidotal therapies.

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