Toxicology: Pearls and Pitfalls in the Use of Antidotes

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• Toxicology • Antidotes • Acute poisoning • Toxin therapy

The management of the acutely poisoned patient first and foremost requires careful attention to the basic principles of emergency medicine. The patient's airway, breathing, and circulation must be evaluated and addressed systematically, and supportive care instituted expeditiously. With few exceptions, supportive care alone will effectively treat the majority of patients who present with acute poisoning. In 2008, according to the American Association of Poison Control Centers Toxic Exposure Surveillance System (TESS), besides decontamination, the most commonly instituted specific therapy in acute poisoning was the administration of intravenous fluids followed by the administration of oxygen.[1] In certain circumstances, however, prompt administration of a specific antidote may be required, and failure to identify these circumstances may lead to significant morbidity or mortality. This article aims to describe select antidotes, and to discuss their indications and the potential pitfalls with their use.

HIGH-DOSE INSULIN EUGLYCEMIC THERAPY FOR THE TREATMENT OF CALCIUM CHANNEL BLOCKER OVERDOSE

Acute calcium channel blocker (CCB) overdose is associated with significant morbidity and mortality. In 2008, the American Association of Poison Control Centers TESS reported 10,084 CCB exposures, of which 2232 were treated in health care facilities. Outcomes were defined as moderate in 361 cases and major in 74 cases, and there were 17 deaths.[1] The clinical features of severe CCB toxicity are the result of excessive blockade at L-type calcium channels located in myocardial cells, smooth muscle cells of the peripheral vasculature, and β cells in the pancreas. Antagonism of these channels produces decreased inotropy, bradycardia, myocardial conduction disturbances, peripheral vasodilation, and hypoinsulinemia, resulting in hyperglycemia. The combination of these effects can result in metabolic acidosis and refractory hypotension and shock.

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Significant CCB ingestions can pose a particular challenge to the emergency physician, because although the patient may initially appear well, hemodynamic decompensation can rapidly ensue.[2] In addition, conventional treatments produce variable responses, and often fail to restore hemodynamic stability.[3,4] These treatments include the administration of intravenous fluids to increase intravascular volume, calcium salts such as calcium gluconate or calcium chloride to increase transmembrane calcium flow, atropine to decrease vagal tone and increase heart rate, and the administration of vasoactive agents or glucagon. In some cases, intravenous pacing or an intra-aortic balloon pump may be necessary.[5]

High-dose insulin euglycemic therapy (HIET) consists of the infusion of high-dose regular insulin, most commonly as a bolus of 1 IU/kg followed by an infusion of 0.5 IU/kg per hour, along with the administration of supplemental glucose to maintain euglycemia (**Table 1**). HIET requires frequent blood glucose monitoring (every 30 minutes), and serum potassium should also be monitored and repleted as needed. The duration of therapy should be tailored to clinical response, in particular to hemodynamic parameters.[2]

The proposed mechanism by which HIET reverses hemodynamic collapse is through direct metabolic effects on myocardial cells.[6–8] It is hypothesized that in a state of shock, myocytes switch from the utilization of free fatty acids to glucose in order to meet metabolic demands. CCBs induce a state of hypoinsulinemia, preventing the uptake of glucose by myocytes and causing a loss of inotropy, decreased peripheral vascular resistance, and shock.[6–8] High doses of insulin might therefore be able to reverse these metabolic derangements.

Animal studies suggest that the administration of HIET may be more effective than conventional therapies. In a series of studies of verapamil-poisoned canines performed by Kline and colleagues,[6–8] HIET outperformed epinephrine, glucagon, and calcium chloride in increasing myocardial contractility, and resulted in improved survival. Although there are no randomized controlled trials in humans, there are numerous human case reports in the literature demonstrating the efficacy of HIET in improving blood pressure and hemodynamic collapse in patients refractory to other interventions including atropine, calcium chloride, glucagon, and vasoactive agents.[4–15]

It should not be overlooked, however, that there are many published case reports demonstrating the failure of HIET to reverse CCB-induced hemodynamic collapse. Some of these reports have in common the late initiation of HIET, after the development of severe symptoms,[16–18] and may indicate that HIET should be considered early in severe CCB toxicity rather than as a therapy of ''last resort.''

Given the small numbers of patients presenting to any given institution with CCB overdose and the variability of individual ingestion, it is unlikely that randomized prospective data on the efficacy of HIET will ever become available. However, this limitation is shared by all of the conventional therapies currently used in the treatment of CCB overdose. Both the animal data and human case reports provide some evidence that early treatment with HIET in conjunction with conventional measures may be of benefit. Given the significant potential for precipitous hemodynamic decline in patients who overdose on CCBs, emergency physicians should likely be prepared to initiate early and aggressive therapy that includes HIET.

INTRAVENOUS LIPID EMULSION

The administration of intravenous lipid emulsion (ILE) has rapidly emerged as a possible antidote for a variety of lipophilic cardiotoxic drugs. ILE conventionally provides calories in the form of free fatty acids to patients requiring total parenteral

Table 1
Antidotes discussed and their usage

Antidote	Primary Indication by Substance	Dose and Administration
High dose insulin euglycemic therapy (HIE)	**Severe calcium channel blocker poisoning**	• Bolus of Regular Insulin 1U/kg followed by infusion at 0.5–1.0 U/kg/h. Give 25 gm (50 cc of D50W) initially and monitor glucose frequently to prevent hypoglycemia. Monitor serum potassium and replace as needed to avoid hypokalemia.
Intravenous lipid emulsion (Intralipid)	**Lipophillic cardiotoxic agents**	• 1.5 mL/kg of 20% intralipid as an initial bolus followed by 0.25 mL/kg/min for 30–60 min. • Depending upon response, bolus could be repeated 1-2 times and infusion rate increased.
Hydroxocobalamin (Cyanokit, 5 g per kit)	**Cyanide**	• 5 grams as intravenous infusion over 15 min. • Depending on severity of poisoning, a second dose of 5 grams may be administered.
Oral *N*-Acetylcysteine(NAC) Mucomyst (Apothecon; Plainsboro, NJ) or equivalent, 10% or 20%	**Acetaminophen**	• **Loading dose**: 140 mg/kg diluted in juice or soda to produce a 5% solution • **Maintenance dose**: 70 mg/kg every 4 hours for 4 doses (uncomplicated cases)
Intravenous *N*-Acetylcysteine (NAC) Acetadote, 20%	**Acetaminophen**	• **Loading dose**: 150 mg/kg in 200 mL of 5% dextrose in water (D5W) over one hour • **Maintenance dose**: 50 mg/kg in 500 mL of D5W over four hours then 100 mg/kg in 1000 mL of D5W over 16 hours • Note: dosing based on ideal body weight; and, use smaller diluents doses of D5W in children
Crotalid Antivenom CroFab [Crotalidae polyvalent immune Fab (ovine)]; Protherics PLC; Cheshire UK	**Rattlesnake envenomation**	• Depending on severity of bite, initial dose ranges from 4-8 vials. • Repeat until there is a halt in progression of symptoms • Additional 2-vial doses every 6 hours for up to 18 hours, if needed

nutrition.[19] In addition, animal studies have suggested its effectiveness in resuscitation from the cardiotoxic effects of bupivacaine,[20,21] chlorpromazine,[22] clomipramine,[23] propranolol,[24] and verapamil.[19] The first case report of the use of ILE in humans appeared in the anesthesia literature in relation to the rare occurrence of cardiovascular collapse in the setting of regional anesthesia with ropivacaine.[25] Since then, numerous case reports have emerged demonstrating its efficacy in bupivacaine-induced cardiovascular collapse.[26–28]

In the last several years, the use of ILE in humans has been reported for overdoses of other lipid-soluble cardiac toxins. In a case report of a combined buproprion and lamotrigine overdose in which cardiac arrest had proved refractory to conventional treatment, ILE infusion was associated with the return of spontaneous circulation and a good patient outcome.[29] In a report of a combined quetiapine and sertraline overdose it was demonstrated to reverse coma, allowing the treating physicians to avoid intubation.[30] Finally, in a case of sustained-release verapamil overdose resulting in shock, its administration was temporally associated with a dramatic improvement in blood pressure and cessation of vasopressors and glucagon.[31] Although there is no standard protocol for ILE, a 1.5 mL/kg bolus of Intralipid 20% followed by an infusion of 0.25 mL/kg/min for 30 to 60 minutes has been described (see **Table 1**).[32]

Several mechanisms of action have been suggested. One theory is that ILE acts as a ''lipid sink,'' expanding the lipid compartment within the intravascular space, and sequestering lipid-soluble drugs from the tissues. The success of ILE in the treatment of poisoning by lipid-soluble drugs such as bupivacaine, propranolol, and verapamil supports this theory. Another explanation suggests that its efficacy is related to metabolic effects in the myocardium, specifically its ability to enhance fatty acid intracellular transport in myocardial cells.[19]

Many questions remain, including the identification of potential safety hazards. ILE is contraindicated in patients with known egg allergies, disorders of fat metabolism, and liver disease.[19] In patients receiving total parenteral nutrition (TPN), high triglycerides resulting from ILE infusion may alter immunity, lung function, and hemodynamics.[19] Yet TPN patients receive intravenous lipid emulsion for an extended period of time, rather than as short-term rescue dosing. With bolus dosing and at high doses, ILE can potentially result in pulmonary and fat emboli.[19] Finally, there is also evidence to suggest that ILE is contraindicated in acute myocardial infarction, because free fatty acids administered during ischemia may increase myocardial damage through lipid peroxidation.[19]

For now, ILE is an intriguing antidote that holds the promise of a potential ''intravascular decontamination'' method for lipophilic drugs. The use of ILE as an adjunctive therapy to standard Advanced Cardiac Life Support protocols in the rare setting of cardiac arrest due to the administration of regional anesthesia with bupivacaine seems justified. Case reports of its use in the setting of lipophilic drug overdose are compelling, but more research is needed. Although it is too early to consider ILE a stand-alone therapy in the setting of lipophilic drug overdose, it should be considered when conventional therapies fail.

THE USE OF HYDROXOCOBALAMIN IN SMOKE INHALATION VICTIMS

Inhalation of smoke accounts for more fire-related morbidity and mortality than burns.[33] Fire smoke contains a complex mixture of gases released from the combustion of natural and synthetic materials, which contribute to smoke inhalation-associated death. Among these are carbon monoxide (CO) and hydrogen cyanide (HCN).

CO binds to hemoglobin with 250 times the affinity of oxygen and shifts the oxygen hemoglobin dissociation curve to the left.[34] This results in decreased carrying capacity of hemoglobin for oxygen (functional anemia) and impaired delivery of oxygen to vital tissues, resulting in cellular hypoxia, cardiovascular collapse, and death. HCN inhibits oxidative phosphorylation by binding to cytochrome oxidase in the electron transport chain. The end result is similar to CO, in that cellular hypoxia ensues, causing lactic acidosis, cardiovascular collapse and death.

Studies on smoke exposure victims indicate that CO and HCN are often both present.[33] Whereas CO can be quickly detected in venous or arterial blood with the use of cooximetry, cyanide levels cannot be obtained rapidly in most hospitals. A surrogate marker, lactic acidosis, may be elevated in cyanide exposure, but can also be present in CO poisoning.

Management of smoke inhalation involves removal of the victim from further exposure, airway support, and the administration of supplement oxygen. CO poisoning is usually treated with high-flow oxygen, and sometimes hyperbaric oxygen, whereas HCN poisoning requires the administration of a specific antidote.

The conventional cyanide antidote kit (consisting of amyl nitrite, sodium nitrite, and sodium thiosulfate) may be unsuitable for the empiric treatment of the undifferentiated smoke inhalation victim. Amyl nitrite and sodium nitrite work through the induction of methemoglobinemia. Cyanide preferentially binds to methemoglobin, preventing or delaying its binding to the cytochrome oxidase in the electron transport chain. However, methemoglobinemia also reduces the oxygen-carrying capacity of blood, and can therefore exacerbate CO toxicity and hypoxemia from lung injury due to smoke inhalation. Furthermore, both amyl nitrite and sodium nitrite can cause vasodilation and exacerbate hypotension.[35] Therefore, empiric use of these agents is not recommended in smoke inhalation victims. The third component of the kit, sodium thiosulfate, does not induce methemoglobinemia, but enhances the elimination of cyanide by acting as a sulfhydryl donor in the conversion of cyanide to thiocyanate. Although sodium thiosulfate can be given alone, it has been suggested that its delayed onset of action, and limited penetration into the brain and mitochondria, may make it a less effective antidote.[35]

An alternative antidote, hydroxocobalamin, has been used in France since the 1980s. Hydroxocobalamin is the natural form of vitamin B_{12a}, which directly binds to cyanide to form nontoxic cyanocobalamin (vitamin B_{12}). In multiple animal models, hydroxocobalamin was an effective antidote even when given after cyanide exposure rather than as prophylaxis.[36–38] Hydroxocobalamin's efficacy was compared with saline in dogs administered intravenous potassium cyanide.[38] In the saline-treated dogs, the overall mortality rate was 82% (14/17), whereas 79% (15/19) and 100% (18/18) of the dogs treated with 75 mg/kg or 150 mg/kg, respectively, survived. Although no efficacy data are available in humans (due to the ethical issues of a placebo controlled trial), a prospective noncomparative trial in victims of fire-smoke inhalation and documented cyanide exposure demonstrated a survival rate of 72% (50/69) in patients treated with 5 to 15 g intravenously.[33] In addition, 82% (41/50) of the survivors showed no neuropsychiatric sequelae. Many of the patients in this study were also shown to have concomitant CO exposure, suggesting that the antidote is safe for administration in the setting of concomitant CO exposure. A retrospective review of 101 smoke inhalation victims treated with hydroxocobalamin showed a survival rate of 41.7%, and of 38 patients found in cardiac arrest, 21 had return of spontaneous circulation.[39]

The recommended dosing for hydroxocobalamin (Cyanokit) is an intravenous initial infusion of 5 g over 15 minutes (see **Table 1**). Depending on the severity of the

poisoning and the clinical response, a second dose of 5 g may be administered.[40] The most frequently reported adverse effect of hydroxycobalamin is a red discoloration of the urine and skin that does not appear to be of any clinical significance, but can last for several days.[39] This red discoloration may also affect some laboratory tests that depend on colorimetric assays. Temporary increases in blood pressure, headache, nausea, and injection site reactions have also been reported.[40] Allergic reactions have been observed in a small number of individuals, but are relatively mild and have responded quickly to standard treatment.[36]

Hydroxocobalamin seems to be a safe and effective therapy in the undifferentiated smoke inhalation victim, and has a limited side effect profile. Of importance is that the use of sodium thiosulfate alone may also be an effective and cheaper option, but no trials directly comparing the 2 antidotes have been carried out. Until then, both drugs should be considered options for the treatment of this patient population.

INTRAVENOUS *N*-ACETYLCYSTEINE FOR THE TREATMENT OF ACETAMINOPHEN POISONING AND SHORT-COURSE THERAPY

Acetaminophen is one of the most common causes of poisoning worldwide.[41] According to the American Association of Poison Control Centers TESS, in the United States in 2008 alone, acetaminophen was responsible for more than 26,000 visits to health care facilities and approximately 74 deaths.[1] In overdose, acetaminophen is metabolized by the P450 system of the liver to the toxic metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI), resulting in the destruction of liver cells.[42] *N*-Acetylcysteine (NAC) prevents hepatic injury primarily by restoring hepatic glutathione, which binds to NAPQI to form nontoxic metabolites.[42]

Intravenous NAC was first suggested as an antidote for acetaminophen toxicity in 1974, and NAC was first introduced to the United States as an oral preparation with a 72-hour treatment protocol.[41] Following its introduction, a multicenter study involving 2540 patients over 9 years showed that 6.1% of patients who received oral NAC within 10 hours of their ingestion developed hepatotoxicity.[43] This result was a marked improvement when compared with historical controls, and contributed to the widespread acceptance of NAC for the treatment of acetaminophen overdose.

Over the years, emergency physicians have become familiar with the use of NAC. When no approved intravenous formulation was available, physicians could administer the oral form intravenously after running it through a micropore filter. In 2004, the Food and Drug Administration (FDA) approved an intravenous formulation of NAC (Acetadote). The approved 20-hour dosing regimen for Acetadote is identical to that used for many years in Canada and Europe, and is considerably shorter than the conventional 72-hour oral NAC regimen. Acetadote's ease of use and shorter course have made intravenous NAC a popular choice for treatment of acetaminophen overdose. According to data collected by the American Association of Poison Control Centers in the 4 years from 2004 to 2008, the use of intravenous NAC jumped from 3807 to 11,895 instances and exceeded the use of oral NAC by approximately 150.[1,44] That same time period saw the use of oral NAC decrease from 15,333 to 11,764 uses.[1,44]

The dosing regimens of the oral and intravenous formulations of NAC are listed in **Table 1**. There are no formal studies comparing the use of intravenous versus oral NAC, but experience suggests that they are equally efficacious. Intravenous NAC may be advantageous in the patient with an altered level of consciousness, or when there is significant nausea and vomiting precluding the use of oral medications. It should be noted, however, that oral NAC is generally well tolerated, especially when

given in conjunction with an antiemetic. While both therapies are relatively inexpensive, intravenous NAC costs approximately $470 for a 20-hour course compared with $50 for a 72-hour course of oral NAC,[41] and there may be additional administration costs for intravenous use.

The most commonly reported adverse side effect of intravenous NAC is anaphylactoid reactions, which may occur in up to 15% of patients.[45] Most symptoms are mild and include rash and pruritus; however, 1% are severe and may include bronchospasm, tachycardia, and hypotension.[42] Depending on the severity of the reaction, treatment includes the administration of diphenhydramine, corticosteroids, and bronchodilators. Although a decrease in the infusion rate of intravenous NAC may result in a decreased incidence of anaphylactoid reactions, studies have produced conflicting results.[45,46] Nonetheless, the manufacturer has changed the recommended initial infusion rate from 15 minutes to 60 minutes.

Studies have shown that patients with a family history of allergy and asthmatics are at increased risk of anaphylactoid reactions to NAC.[47] Death has been reported in a patient with a history of asthma,[48] and physicians should be particularly cautious with the administration of intravenous NAC in this patient population. In addition, an inverse correlation has been observed between serum *N*-acetyl-para-aminophenol concentrations and anaphylactoid reactions,[47,49–52] suggesting that acetaminophen itself has protective properties against the adverse effects of NAC. This unexpected finding suggests that physicians should use the oral formulation in patients with low or borderline acetaminophen concentration. Finally, dosing errors with the intravenous infusion have also led to deaths.[53,54] Dilutional hyponatremia and seizures developed in a child receiving the adult volume of intravenous NAC.[55] For pediatric patients, volumes should be adjusted to body weight, and normal saline solution should be used as the diluent.

The conventional oral NAC regimen has a recommended duration of therapy of 72 hours, whereas the intravenous preparation has a recommended 20-hour protocol. This discrepancy can often lead to confusion over when to stop treatment. Evidence supports the use of a shortened protocol in patients with acute acetaminophen overdose, who receive their first dose of NAC (either intravenously or orally) within 8 hours of arrival in the emergency department.[56,57] Patients should have repeat acetaminophen measurements and liver function test performed at the end of the 20-hour protocol to ensure the absence of liver damage and nondetectable acetaminophen levels. A critical mistake is the use of the 20-hour regimen in the setting of delayed presentations, and large or chronic acetaminophen ingestions. Premature cessation of therapy in this setting has resulted in hepatotoxicity.[58]

In summary, NAC is a safe and effective therapy for the treatment of acetaminophen overdose, and has been used by emergency physicians for several decades. The introduction of an FDA-approved intravenous formulation has greatly increased this route of administration. Physicians must be aware of the risk of anaphylactoid reactions, especially among asthmatics and those with low serum acetaminophen levels. Dosing errors, in particular among pediatric patients, have led to deaths. The shortened (20-hour) protocol is appropriate for patients with acute ingestions, who receive NAC within 8 hours of ingestion, and have normal liver function tests and undetectable acetaminophen levels at the end of treatment.

CROTALIDAE POLYVALENT IMMUNE FAB (OVINE; FabAV) and thrombocytopenia

Each year, there are approximately 8000 venomous snakebites in the United States, most of which are caused by the Crotalidae (pit viper) family.[59] Snake venoms are

complex mixtures of substances that function to immobilize, kill, and predigest prey.[34] In humans these substances precipitate tissue destruction at the bite site, and have hemotoxic, neurotoxic, and other systemic effects. The relative predominance of these effects is variable and depends on the species of snake, as well as geographic and seasonal factors.[34]

The clinical presentation after a significant rattlesnake bite includes stinging and burning pain at the site of the bite, accompanied by progressive swelling and erythema. Petechiae, ecchymosis, and hemorrhagic blebs may develop over several hours. Hypovolemic shock and local compartment syndrome may occur secondary to fluid and blood sequestration in the affected area.[34] Neurotoxic effects may result in nausea, vomiting, weakness, muscle fasciculations, a metallic taste in the mouth, and perioral and peripheral paresthesias. Venom-induced hematologic effects can include thrombocytopenia and coagulopathy.

The evaluation of the snakebite victim begins with an assessment of the bite site and identification of systemic toxicity. The affected area should be measured, and the leading edge of swelling demarcated and frequently reassessed. Complete blood cell count, coagulation studies, chemistry panel, and creatine phosphokinase along with fibrinogen and D-dimer levels should be obtained. It should be noted that approximately 25% of rattlesnake bites are ''dry'' bites, in which no envenomation has occurred.[59] In such cases there will be minimal to no swelling at the bite site, with no progression of symptoms over time and no systemic symptoms. Patients with apparent dry bites should be observed for at least 12 hours to ensure that no delayed symptoms develop before being sent home. Patients with signs or symptoms of envenomation should be given antivenom.

For many years, the only available antivenom was the equine-derived Antivenin Crotalidae polyvalent (ACP), and a significant proportion of patients receiving this antidote developed both immediate and delayed-onset hypersensitivity reactions. In retrospective studies, the incidence of acute allergic reactions from ACP (including hypotension and anaphylaxis) ranged between 23% and 56%, and virtually all patients who received more than 12 vials developed serum sickness.[34]

In 2000, Crotalidae polyvalent immune fab (ovine; FabAV) became available as an alternative to ACP. FabAV is derived from sheep immunized with the venom of 1 of 4 species of rattlesnake (*Crotalus atox*, *Crotalus adamantus*, *Crotalus scutulatus*, and *Agkistrodon piscivorus*). Papain is used to cleave the immunogenic Fc fragment from the IgG antibody, producing a purified Fab fragment antivenom. Experience using Crofab compared with ACP indicates a substantially reduced incidence of allergic reactions and serum sickness with apparently equal efficacy.[60] Because of its improved safety profile, FabAV has essentially replaced ACP for the treatment of rattlesnake bites in the United States (see **Table 1** for a description of dosing regimens).

The adoption of FabAV as the treatment of choice in snakebite victims has coincided with the documentation of recurrent thrombocytopenia and thrombocytopenia refractory to additional doses of antivenom. Published case reports and postmarketing surveillance describe patients with thrombocytopenia that is initially responsive to antivenom, but refractory to additional doses of FabAV when it recurs.[61–65] Boyer and colleagues[66] conducted a multicenter, prospective clinical trial designed to detect recurrent and persistent coagulation abnormalities after FabAV administration. These investigators showed that 53% (20 of 38 patients) had recurrent, persistent or late coagulopathy from 2 to 14 days after envenomation. Even more concerning are reports of clinically significant bleeding in association with thrombocytopenia.[61]

These findings were not previously reported following the administration of the ACP antivenom. Some investigators have hypothesized that the smaller molecular weight

of FabAV compared with ACP allows for more rapid renal clearance, resulting in recurrent symptoms. This theory, however, does not explain why some patients' recurrent thrombocytopenia is resistant to further FabAV administration. Others suggest that delayed coagulation abnormalities were simply not recognized with the use of the ACP, because clinicians did not repeat coagulation studies after discharge. In a retrospective review, Bogdan and colleagues[67] tried to reevaluate patients treated with ACP for recurrent coagulopathy. Unfortunately, in a review of 354 consecutive cases, they found only 31 with adequate follow-up testing, but 14 of these 31 cases (45%) did reveal recurrent coagulopathy.

Whether recurrent and refractory thrombocytopenia is a function of the new FabAV antivenom or just a newly recognized phenomenon, it may result in a real risk of clinically significant bleeding. Clinicians must be aware of this risk, and should follow coagulation parameters closely after the discontinuation of antivenom therapy. Recurrent thrombocytopenia should be treated with additional antivenom in consultation with a poison control center or a medical toxicologist.

SUMMARY

Although the majority of poisonings require only supportive care, the emergency physician must recognize when the use of an antidote is required, and understand the risks and benefits of the treatment rendered. This article focuses on several selected antidotes, their indications, and potential pitfalls in their use. Both HIE therapy for the treatment of CCB overdose and the use of ILEs for the treatment of lipophilic cardiotoxic drug overdoses represent cutting-edge therapies that hold promise for poisonings that currently have limited treatment options. Further study may shed light on their effectiveness and continue to define their side effect profiles. Hydroxycobalamin is an antidote that has the potential to replace the cyanide antidote kit for the treatment of cyanide exposure in the undifferentiated smoke inhalation victim. Preliminary evidence suggests that it is effective and has minimal side effects. Further study comparing it with sodium thiosulfate alone (a cheaper and potentially equally efficacious option) should be conducted. NAC is a well-established antidote with a newly FDA-approved intravenous formulation and shortened protocols for administration. With its increasing use, physicians must be aware of the risks associated with anaphylactoid reactions and dosing errors. Physicians must also understand the limited indications for the shortened protocol, as premature cessation of therapy can result in irreversible hepatotoxicity. Finally, several years into use of the new rattlesnake antivenom, FabAV, delayed and refractory thrombocytopenia and bleeding complications have been documented in snakebite victims. It remains to be seen whether these complications result from the new therapy or represent greater detection from improved follow-up.

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