EB MEDICINE

EM Critical Care

UNDERSTANDING AND CARING FOR CRITICAL ILLNESS IN EMERGENCY MEDICINE

Antidotes For Overdose: Timely And Effective Counteraction

Abstract

Knowledge of antidotes and how to administer them is necessary for appropriate management of overdose patients presenting to the emergency department. This issue reviews 5 commonly employed antidotes – N-acetylcysteine, sodium bicarbonate, glucagon, high-dose insulin, and intravenous lipid emulsion – including their indications, mechanisms of action, adverse effects, and dosing schedules. N-acetylcysteine, a glutathione precursor, can be used to both prevent and treat hepatotoxicity following acetaminophen overdose. Sodium bicarbonate is useful for urinary and serum alkalinization following salicylate overdose and enhancement of urinary elimination, while also promoting diffusion of salicylate from tissue to the serum. Sodium bicarbonate may also be used to overcome tricyclic antidepressant-mediated sodium-channel blockade. Glucagon activates an intracellular pathway downstream of beta-adrenergic receptors to alleviate hypotension and bradycardia in cases of beta blocker toxicity. High-dose insulin allows greater myocardial glucose utilization and improved microvascular perfusion for treatment of calcium-channel blocker overdose. Finally, intravenous lipid emulsion has been rigorously studied in the treatment of local anesthetic systemic toxicity, and it may have a role in management following overdose of other lipophilic cardiotoxic drugs.

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CME Objectives

Upon completion of this article, you should be able to:

1. Identify the indications for the use of antidotes in select patients.
2. Determine standard and patient-specific dosing options.
3. Explain the adverse effects that can occur with each antidote.

Prior to beginning this activity, see "Physician CME Information" on the back page.

Case Presentation

As you begin your shift in your rural ED, a local EMS crew arrives with a 53-year-old woman. The EMT states that the patient has a history of hypertension and depression and was found in her home by a family member, obtunded, with empty pill bottles on a nearby table. Vital signs in the field included: blood pressure, 100/60 mm Hg; heart rate, 60 beats/min; respiratory rate, 22 breaths/min; and oxygen saturation, 98% on room air. Blood glucose in the field was measured at 225 mg/dL. The nurses move the patient to a stretcher, obtain intravenous access, and place the patient on a monitor. Repeat vital signs show: blood pressure, 65/40 mm Hg; heart rate, 55 beats/min; respiratory rate, 24 breaths/min; and oxygen saturation, 100% on nonrebreather facemask. Examination of pill containers reveals empty bottles of verapamil XR and propranolol in addition to a nearly full bottle of imipramine. The patient remains obtunded, is not responsive to commands, and withdraws only to painful stimuli. You order a crystalloid fluid bolus and prepare your intubation equipment. A technician hands you an ECG showing sinus bradycardia at 50 bpm, QRS of 90 msec, and QTc of 400 msec. After successful endotracheal intubation, the nurse reports that the patient remains persistently hypotensive at 65/38 mm Hg despite a fluid bolus. You ask the pharmacist to prepare a norepinephrine infusion, and consider the use of an antidote. Which one should you choose?

Introduction

The quest for protection against poisoning harkens back to the time of Herodotus in the 5th century BC, when *terra sigillata* (a red clay from the Greek island of Lemnos mixed with goat's blood) was heralded as an antidote to all poisons.[1] While advances in emergency medicine and critical care have reduced the necessity for universal remedies, timely and focused use of antidotes can be lifesaving in the management of drug toxicity. This review will discuss the indications, pharmacology, adverse effects, and dosing of 5 antidotes commonly employed in emergency medicine: N-acetylcysteine, sodium bicarbonate, glucagon, high-dose insulin, and intravenous lipid emulsion.

N-acetylcysteine

N-acetylcysteine (NAC) is one of the most widely utilized antidotes in medical toxicology. When administered early following an acetaminophen (paracetamol) overdose, it possesses a remarkable ability to prevent the development of hepatic toxicity. The hepatoprotective properties of NAC were first noted in the 1970s, when both NAC and cysteamine (another nucleophilic sulfhydryl compound) demonstrated an ability to prevent hepatic necrosis following acetaminophen overdose, although NAC was also observed to cause far fewer adverse effects.[2,3] The United States Food and Drug Administration (FDA) approved oral NAC for use in 1985 and intravenous NAC in 2004. The most recent National Poison Data System annual report listed acetaminophen-combination drugs and acetaminophen alone as responsible for the fourth and sixth highest number of overdose fatalities, respectively.[4] Given its prevalence in multiple over-the-counter preparations, physicians must know when and how to successfully use NAC in the emergency department (ED).

Critical Appraisal Of The Literature

To identify primary relevant literature, the Ovid MEDLINE® library was queried using the search term *N-acetylcysteine* and *acetaminophen*. Results were reviewed for clinical and practical relevance. Controlled clinical studies, animal studies, review articles, editorials, commentaries, case reports, and case series were all identified for review. In addition, the reference sections of key textbooks in medical toxicology were reviewed.[5,6] The Cochrane Database of Systematic Reviews was also queried. A meta-analysis by their group concluded that NAC treatment was superior to placebo and should be given following acetaminophen overdose. However, the optimal regimen and selection criteria for treatment remained unclear.[7]

Query of the National Guideline Clearinghouse (www.guideline.gov) demonstrated no national guidelines specific to acetaminophen overdose. However, a position paper by the American Association for the Study of Liver Diseases on the management of acute liver failure recommended using NAC "in all patients where the quantity of acetaminophen ingested, serum drug level, or rising aminotransferases indicate impending or evolving liver injury" (Grade II-1) and "in cases of ALF [acute liver failure] in which acetaminophen ingestion is possible or when knowledge of circumstances surrounding admission is inadequate, but aminotransferases suggest acetaminophen poisoning." (Grade III)[8]

How Antidotes Work: N-acetylcysteine

Aside from rare cases of massive overdose, it is important to remember that acetaminophen itself is nontoxic. The majority of absorbed acetaminophen is conjugated with glucoronide or sulfate within the liver, forming inactive metabolites that are excreted in the urine. A small fraction (< 5%), however, is oxidized by the hepatic P450 system to form the reactive electrophile N-acetyl-p-benzoquinone imine (NAPQI).[5] Under normal conditions, NAPQI is quickly conjugated to an electron donor, glutathione, and also eliminated in the urine. In the overdose state, nontoxic metabolic pathways become saturated, and NAPQI production eventually overwhelms

available glutathione supplies. NAPQI is then free to covalently bind to and arylate sulfhydryl groups of key cellular proteins, resulting in hepatic necrosis. This is thought to occur when glutathione stores drop below 30% of normal.[2]

The principal mechanism for the hepatoprotective effect of NAC is replenishment of depleted glutathione. Early animal studies suggested that NAC increases glutathione synthesis rather than directly reacting with NAPQI itself.[9] This is also supported by studies demonstrating NAC conversion in vivo to L-cysteine, which is then converted to glutathione.[10] Possessing its own sulfhydryl group, NAC may also provide a substrate for nontoxic sulfation of acetaminophen.[11] **(See Figure 1.)**

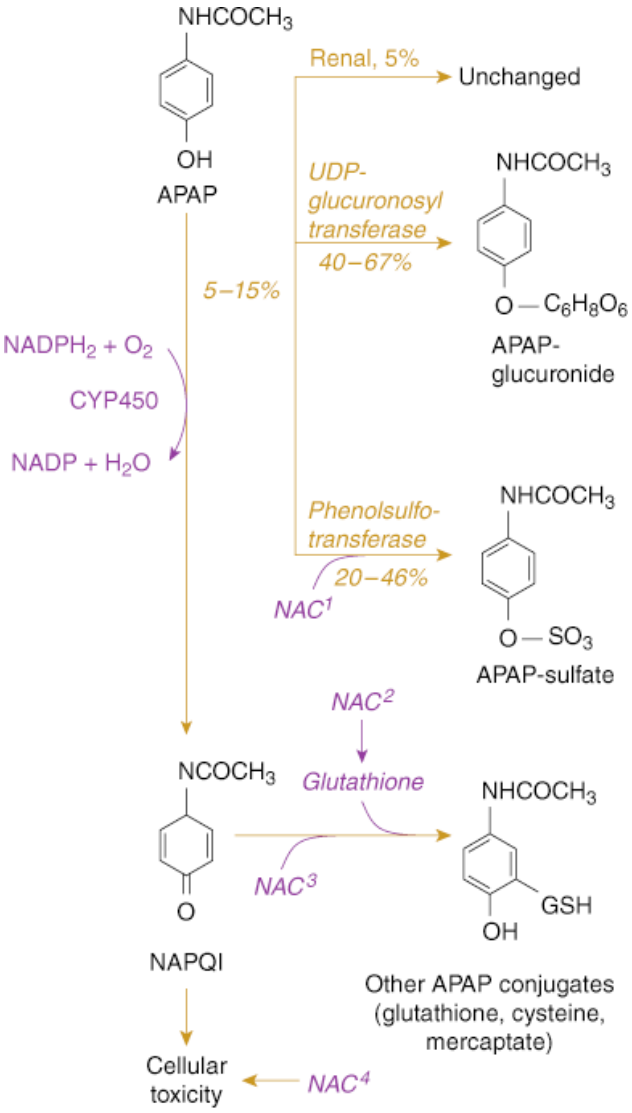
Of particular interest is the ability of NAC to provide benefit in even late-presenting patients with evidence of hepatic failure. In these cases, serum acetaminophen levels are often low or undetectable, yet initiation of NAC therapy may still lead to clinical improvement and recovery. A prospective randomized controlled trial comparing NAC to supportive care alone in 50 patients presenting with fulminant hepatic failure after acetaminophen overdose showed NAC to increase survival significantly and was associated with significantly lower rates of cerebral edema and the need for vasopressor use.[12] Retrospective studies of NAC use in similar populations have also shown lower rates of mortality and reduced rates of severe encephalopathy.[13] The mechanism of this benefit is not definitively known, but may involve improved peripheral oxygen extraction and microcirculatory blood distribution;[12,14] improved microcirculation via a direct vasodilatory effect on small vessels;[10] increased phagocytosis activity of neutrophils and decreased oxidative burst activity;[15] restored capacity of the intracellular proteolytic system to degrade toxic arylated proteins;[13] and NAC's own intrinsic antioxidant properties.[6]

Patient Selection

The decision to use NAC depends on several factors, including the clinical appearance of the patient, the time of presentation, and the ability of the receiving hospital to promptly obtain acetaminophen levels. Use of the Rumack-Matthew nomogram is appropriate for patients who present to the ED within 24 hours of a single acute ingestion.[16] **(See Figure 2, page 4.)** Patients with serum acetaminophen levels above the treatment line on the nomogram are at risk for development of hepatotoxicity and should be treated with NAC. Measurement of acetaminophen levels between 1 and 4 hours postingestion is only helpful if the initial level is undetectable (< 10 mcg/mL). In these cases, it is exceedingly unlikely that the patient will develop hepatotoxicity.[5]

The Rumack-Matthew nomogram should not be used after chronic ingestions (eg, patients who have taken supratherapeutic doses for several days) or if the time of ingestion is unknown. The decision to use NAC in these cases is less straightforward, but conservative recommendations suggest initiating treatment in any patient with evidence of ongoing hepatotoxicity (eg, elevated aspartate aminotransferase) or with supratherapeutic acetaminophen concentrations

Figure 1. Mechanism Of Action Of N-acetylcysteine

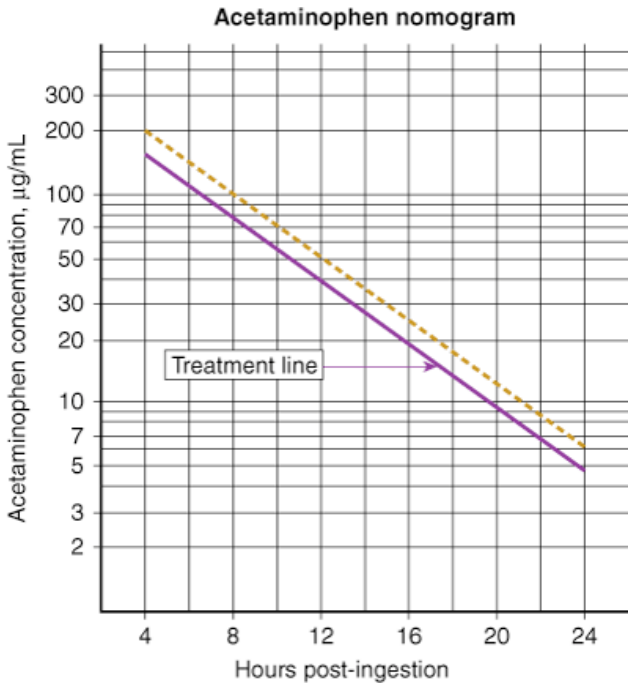


Abbreviations: APAP, acetyl-para-aminophenal (acetaminophen); $C_6H_8O_6$, ascorbic acid; CYP450, cytochrome P450; GSH, glutathione; H_2O, water; NAC, N-acetylcysteine; NADP, nicotinamide adenine dinucleotide phosphate; $NADPH_2$, hydrogenated nicotinamide adenine dinucleotide; NAPQI, N-acetyl-p-benzoquinone imine; OH, hydroxyl group; UDP, uridine diphosphate.

(> 20 mcg/mL) until further risk stratification can be performed.[5,17] Patients presenting after suspected chronic acetaminophen ingestion with normal liver function tests and undetectable or therapeutic acetaminophen levels are unlikely to require antidotal therapy. As previously noted, NAC therapy may be beneficial for use in late-presenting patients with fulminant hepatic failure. In these cases, NAC should be initiated even if serum acetaminophen levels are low or undetectable.

Both oral and intravenous NAC are safe and effective treatments for acetaminophen toxicity. Oral NAC has an unpleasant odor (similar to sulfur or rotten eggs) and may cause nausea and vomiting, though first-pass hepatic metabolism may theoretically produce higher local concentrations in the target organ.[18] While some studies have suggested no change in peak NAC levels and half-life when administered with activated charcoal, both can cause GI distress and the available data are limited and conflicting.[6,19] A prudent recommendation is to use intravenous NAC after activated charcoal administration. Intravenous NAC has been associated with fewer side effects and shorter duration of hospitalization in some limited, small studies.[20,21] Anaphylactoid reactions have been reported in up to 38% of patients receiving intravenous NAC, but these are rarely severe, respond to standard treatment, and therapy can typically be restarted safely without complication.[21] Patients with nausea and vomiting that is unresponsive to antiemetics, who have altered or depressed mental status, or who have fulminant hepatic failure should receive intravenous NAC.

Figure 2. Rumack-Matthew Nomogram



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Practical Considerations: Adverse Effects Of N-acetylcysteine

Both oral and intravenous NAC are well tolerated and largely free of severe adverse effects. The potential for anaphylactoid reactions following intravenous NAC use merits discussion. These reactions are characterized by urticaria, pruritus, angioedema, bronchospasm, and hypotension. Reactions typically occur within the first hour of treatment and are dose-dependent. Not surprisingly, these reactions occur more often after iatrogenic accidental overdose. They are not immunoglobulin E-mediated and do not require previous exposure to NAC. Patients with a history of asthma or atopy appear to be at increased risk for the development of an anaphylactoid reaction. However, treatment should not be withheld as these reactions are usually self-limiting. Slowing the infusion rate in high-risk patients (eg, those with a history of severe asthma) may prevent some reactions, but this has not been definitively proven. Treatment for adverse effects includes antihistamines, corticosteroids, inhaled beta agonists, and epinephrine (though epinephrine use is rarely indicated). Indeed, steroids are probably unnecessary, given the time of onset and the frequently rapid resolution of symptoms following discontinuation of NAC therapy. Nevertheless, physicians should be aware that fatal anaphylactoid reactions, worsening of asthma, respiratory arrest, and status epilepticus have been reported in association with intravenous NAC use. It should be noted, however, that the status epilepticus case was associated with massive NAC overdose.[21-24]

Emergency physicians should also be aware of NAC's ability to affect prothrombin time. Multiple studies have demonstrated a dose-dependent increase of prothrombin time following NAC administration in patients without hepatotoxicity, particularly during the initial infusion. This is likely via a decrease in the activity of factors II, VII, IX, and X.[25-27] In the absence of other signs of liver failure, physicians should not mistake this as evidence of clinical deterioration.

Special Circumstances: N-acetylcysteine Use In Pregnant Patients

Both oral and intravenous NAC have been used to treat acetaminophen toxicity in pregnant patients.[17,28] High first-pass hepatic metabolism of oral NAC has led to concern for inadequate antidote delivery to the fetus, but some studies have reported similar maternal and fetal NAC concentrations following oral treatment.[17] Reference texts generally list pregnancy as an indication for

intravenous NAC therapy. The FDA lists NAC as pregnancy category B.

Duration Of Treatment

Multiple protocols have been created for NAC administration. Perhaps the most widely utilized is a 21-hour intravenous protocol, which includes a loading dose of 150 mg/kg for 1 hour, followed by 50 mg/kg for 4 hours, and then 100 mg/kg for 16 hours. While convenient, this protocol relies on a fixed time period, regardless of clinical status. In 2007, Dart and Rumack proposed a patient-tailored therapy that defined clinical endpoints for cessation of NAC administration.[29] This protocol recommended administering a loading dose of NAC and treating until the following: (1) acetaminophen level is zero or near zero; (2) serum alanine aminotransferase level is normal or significantly improving; and (3) the patient is clinically well. The advantages of this approach are that it can be applied to all patients (regardless of time of ingestion or initial clinical appearance) and it avoids early cessation of treatment in patients who have not recovered after 21 hours.

Sodium Bicarbonate

Many toxicologic substances have, historically, been treated with sodium bicarbonate. This antidote exerts activity at sodium channels, can affect tissue distribution via changes in drug ionization, may enhance urinary elimination of certain xenobiotics, and can aid in treatment of a nongap metabolic acidosis. Current use of sodium bicarbonate for the poisoned patient in the ED is most relevant for treatment of overdose of 2 classes of medications: salicylates and tricyclic antidepressants (TCAs).

Critical Appraisal Of The Literature

The Ovid MEDLINE® library was queried using the terms *sodium bicarbonate* and *salicylates* as well as *sodium bicarbonate* and *tricyclic antidepressants*. Prospective studies, retrospective reviews, case reports and case series, animal studies, literature reviews, surveys, and editorials and letters were all identified and reviewed for relevance. Reference sections of key textbooks in medical toxicology were reviewed as well.[30-32]

The Cochrane Database of Systematic Reviews and the National Guideline Clearinghouse were queried, though no review specific to urinary alkalinization or the use of sodium bicarbonate for treatment of salicylate or tricyclic antidepressant toxicity was discovered. However, a position paper on urine alkalinization by the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists was published in 2004.[33] This comprehensive review recommended urine alkalinization as a first-line treatment for patients with "moderately severe salicylate poisoning who do not meet the criteria for hemodialysis."

How Antidotes Work: Sodium Bicarbonate

While sodium bicarbonate is utilized for overdose of both salicylates and TCAs, the pharmacologic mechanism responsible for the clinical benefit differs. Each will be considered in turn, beginning with salicylates.

Salicylates

The use of sodium bicarbonate for aspirin poisoning can be traced to a small case series from the 1960s describing "forced alkaline diuresis" resulting in prompt recovery following overdose.[34] The term "urinary alkalinization" is applicable to management of salicylate overdose and refers to administration of intravenous sodium bicarbonate to achieve an alkaline urine (typically with a goal pH of 7.5-8). The rationale for this therapy is derived from the principles of general chemistry. Weakly acidic drugs (such as salicylic acid with a pKa of 3.0) exist in both ionized and nonionized forms. Increasing the pH of the drug's environment (eg, urine, serum) favors increased concentration of the ionized fraction of the drug. This is important, as the ionized drug crosses membranes far less rapidly than the nonionized lipophilic species. Therefore, increasing the pH of the urine will "trap" ionized salicylate and prevent diffusion across the renal epithelium back into systemic circulation, and allow elimination of the drug in the urine.[35,36] This process is referred to as "ion trapping." As pKa is a logarithmic function, small changes in pH will have a disproportionately larger effect on clearance.[37] Increased tubular diffusion due to the creation of a large concentration gradient of nonionized salicylate between peritubular fluid and tubular luminal fluid in alkaline urine is another likely source of enhanced elimination. A final benefit of sodium bicarbonate use in salicylate toxicity is alkalinization of the serum. This increases ionized salicylate concentration in the serum, preventing further diffusion of salicylate across membranes into target organs, while also promoting salicylate movement from tissue (especially the central nervous system) into serum. **(See Figure 3, page 6.)** This is a key clinical feature, as morbidity from salicylate poisoning is primarily related to central nervous system toxicity.[31,38]

Tricyclic Antidepressants

A different rationale exists for the use of sodium bicarbonate following TCA overdose. TCAs cause cardiotoxicity by blocking the rapid inward movement of sodium ions into the fast sodium channel, slowing phase 0 depolarization of the action potential in the distal His-Purkinje system and the ventricular myocardium. This is represented by a widened QRS on

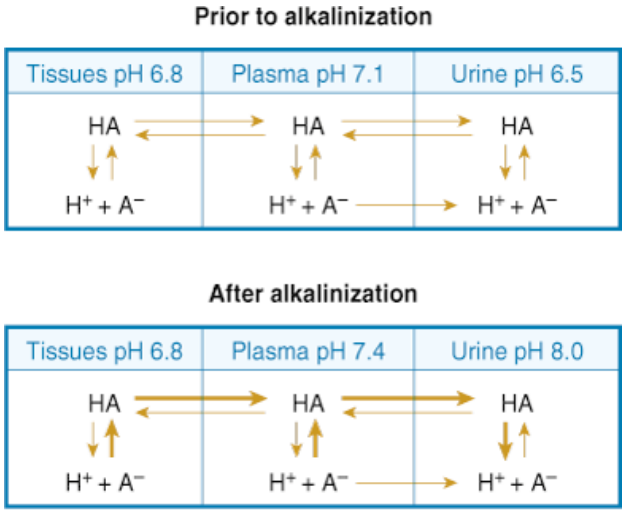
electrocardiogram (ECG). Impaired depolarization slows anterograde conduction, decreases myocardial inotropy, and increases susceptibility to reentry ventricular dysrhythmias. The benefit of sodium bicarbonate is primarily due to an increased extracellular sodium concentration overcoming sodium channel blockade.[39-44] **(See Figure 4, page 7.)** Furthermore, in vitro studies of cardiac and smooth muscle have demonstrated increased cardiac contractility in alkaline versus acidic environments, and acidosis is known to exacerbate TCA toxicity.[45,46] Serum alkalinization may increase free TCA protein binding, though this is less likely to be clinically relevant, as TCAs are lipophilic and possess a high volume of distribution.[47] It is likely that both sodium loading and alkalinization play a role in sodium bicarbonate therapy for TCA cardiotoxicity.

Patient Selection

There are no standard, specific indications for urinary alkalinization in the salicylate-poisoned patient. As mentioned previously, the American Academy of Clinical Toxicology recommends sodium bicarbonate for patients with moderately severe poisoning who are not candidates for dialysis (such as patients with pulmonary edema, acute lung injury, or cerebral edema). Some authors have suggested alkalinization for any patient with a serum salicylate level > 30 mg/dL.[31,48] A conservative recommendation is to initiate alkalinization in any patient with supratherapeutic salicylate levels and evidence of systemic toxicity (eg, tinnitus, respiratory alkalosis, anion gap metabolic acidosis). However, patients with pulmonary edema, acute lung injury, or clinical signs of cerebral edema (eg, seizures, altered mental status) should be concurrently evaluated for hemodialysis. Standard recommended dosing for infusion is 3 ampules of 7.5% sodium bicarbonate (135 mEq) in 1 L of 5% dextrose in water (D5W) administered at 1 to 2 times the maintenance fluid rate.[30]

A similar lack of consistency is found in recommendations for sodium bicarbonate use following TCA overdose. A 2003 survey of poison center medical directors found that 100% of participants would administer this therapy for a widened QRS on ECG, but QRS width for initiation ranged from 90 msec to 160 msec. A majority (53%) recommended giving bicarbonate for QRS > 100 msec.[49] Hypotension and other wide-complex tachydysrhythmias are also indications for administration of sodium bicarbonate boluses, with initial doses of 1 to 2 mEq/kg.[32] As serum alkalinization is likely beneficial, an infusion should also be initiated with a goal arterial pH of 7.5 to 7.55.

Figure 3. Sodium Bicarbonate Mechanism Of Action



Abbreviations: A, conjugate base; H, hydrogen/proton.

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Practical Considerations: Adverse Effects Of Sodium Bicarbonate

The most common complication of urinary alkalinization is hypokalemia. This is due to both potassium loss in the urine and intracellular shifts of potassium in the presence of alkalemia. This can affect therapy, as sodium reabsorbed in the distal renal tubule will be exchanged for hydrogen ions in the presence of hypokalemia, frustrating attempts to maintain an alkaline urine.[35] Hypokalemia may also be observed during bicarbonate therapy for TCA overdose, potentially increasing the risk of dysrhythmia. Physicians must closely monitor serum potassium levels when using this antidote.

Calcium levels should also be monitored, as hypocalcemia has been reported as a consequence of bicarbonate therapy.[50] Systemic alkalemia carries its own theoretical risk, including cerebral vasoconstriction and impaired tissue oxygenation secondary to a leftward shift of the oxygen-hemoglobin dissociation curve. Therefore, most authors discourage exceeding an arterial pH of 7.55.[40,47,51]

Duration Of Treatment

Salicylate-poisoned patients should receive treatment until the following criteria are met: 1) the patient is clinically well (normal mental status, no acid-base disturbance); and 2) salicylate levels are < 20 mg/dL and clearly trending down.

Do not assume that falling salicylate levels alone indicate clinical improvement, as this may be indicative of drug diffusion from the serum into tissue (especially the central nervous system) and may represent a harbinger of decompensation.[35,38] As for patients with TCA toxicity, sodium bicarbonate is

generally stopped once the hemodynamics and mental status of the patient have improved and there is improvement (not necessarily normalization) of abnormal ECG findings.[32]

Glucagon

Glucagon is a polypeptide hormone secreted by pancreatic alpha cells. Its cardioactive properties were noted as early as 1960, when animal studies reported positive inotropic and chronotropic effects.[52] The first human case utilizing glucagon for treatment of beta blocker overdose was reported in 1973.[53] Despite the considerable history of glucagon utilization for beta blocker toxicity, it should be noted that no controlled human trials exist demonstrating glucagon's efficacy for this indication. However, because animal studies and case reports constitute the basis for many interventions in medical toxicology and, given glucagon's safety profile and practitioner comfort using this drug, it remains standard therapy for beta blocker overdose and adjunctive therapy for calcium channel blocker overdose.

Critical Appraisal Of The Literature

The Ovid MEDLINE® library was queried using the terms *glucagon* and *beta blocker* as well as *glucagon* and *calcium-channel blocker*, and reference sections of key textbooks were reviewed.[54,55] Review articles, animal studies, and case reports were identified, but no controlled human studies were found. Queries of the Cochrane Database and the National Guideline Clearinghouse produced no results.

How Antidotes Work: Glucagon

Stimulation of beta-adrenergic receptors activates the enzyme adenylate cyclase, leading to cyclic adenosine monophosphate production, phosphorylation of L-type calcium channels, and subsequent calcium influx into myocardial cells.[56] This calcium entry is necessary for contraction and action potential generation in sinoatrial nodal cells. Beta blocking agents interrupt this process. Glucagon receptors located downstream of the beta receptor activate adenylate cyclase, initiating the same cellular cascade. As such, the cardioactive properties of glucagon are catecholamine independent. Glucagon-facilitated calcium entry may also explain positive inotropic and chronotropic effects in patients poisoned by calcium-channel blockers.[57-62] **(See Figure 5, page 8.)**

An additional mechanism for cardiac effects involves glucagon metabolism by cardiac tissue into "mini-glucagon," an active terminal fragment. Mini-glucagon stimulates phospholipase A_2, releasing arachidonic acid, which increases contractility through a calcium-mediated pathway.[55] Finally, glucagon can inhibit phosphodiesterase, preventing cyclic adenosine monophosphate breakdown.[54]

Patient Selection

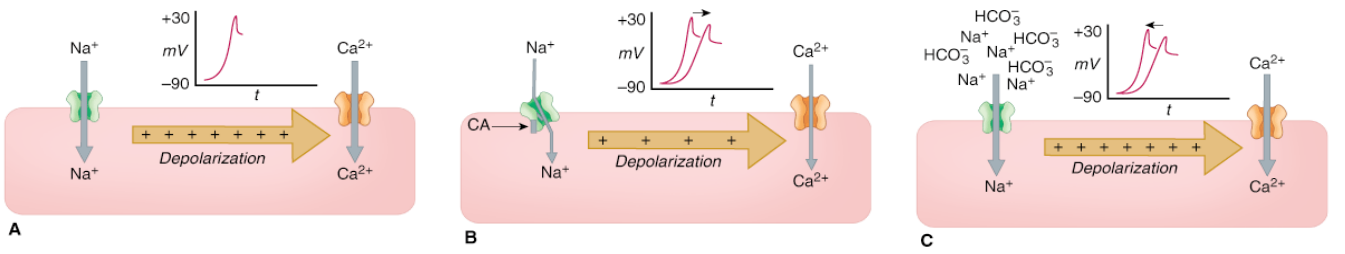
Despite a paucity of controlled trials, glucagon remains a safe and reasonable option for patients poisoned with beta blockers who present with hypotension and/or bradycardia. An initial bolus of 5 to 10 mg should be given (pediatric dose, 50 mcg/kg). If a favorable response is seen, repeat boluses can be given, though a continuous infusion (1-5 mg/hr) is the kinetically advantageous option, given glucagon's short duration of action. Cardiovascular effects typically persist for 10 to 15 minutes.[53]

Glucagon should be considered adjunctive therapy in the management of calcium-channel blocker toxicity. While high-dose insulin is likely the superior antidote for these cases, both can be used concurrently for hypotension and bradycardia following calcium-channel blocker overdose.

Practical Considerations: Adverse Effects Of Glucagon

Nausea and vomiting are the most common side effects of glucagon therapy. These are dose-dependent and can be treated with antiemetics. Hyperglycemia is a predictable consequence of this antidote, given

Figure 4. Effect Of Sodium Bicarbonate On Depolarization



A. Sodium depolarizing the cell, propagating conduction and allowing cardiac depolarization

B. Tricyclic antidepressant blockade of sodium channel, slowing the rate of rise of the action potential

C. Raising the sodium gradient across the affected channel counteracts drug-induced effects

Reprinted with permission. Nelson LS, Levin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE. *Goldfrank's Toxicologic Emergencies.* 9th edition, Figure 73-1. Available at: http://www.accessemergencymedicine.com.

its role in management of hypoglycemia, and may occasionally require treatment with insulin.[58] Hypokalemia and hypocalcemia are possible, but usually do not require intervention. Finally, patients given repeat doses of glucagon may develop tachyphylaxis (an acute decrease in response), necessitating higher doses or alternate therapies.[63]

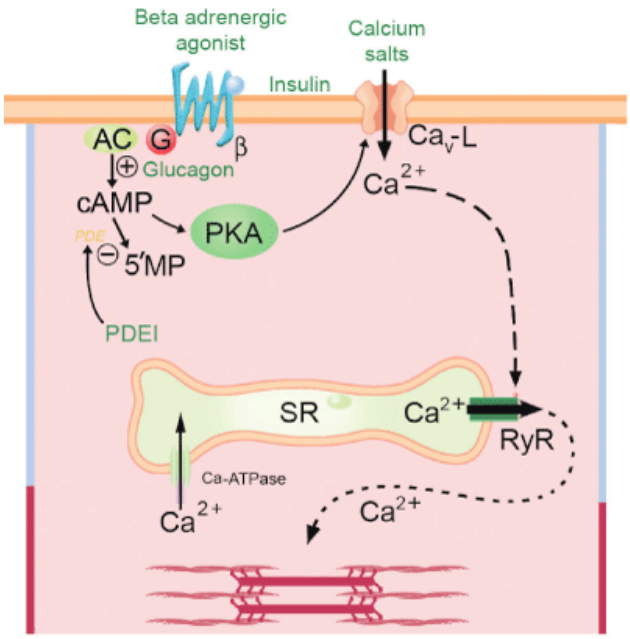
Special Circumstances: Glucagon Use in Pregnant Patients

Glucagon is listed as FDA category B for pregnant patients.[55]

High-Dose Insulin

Discussion of the use of insulin as an antidote focuses on its role in high-dose insulin therapy (also known as hyperinsulinemia/euglycemia) for the management of calcium-channel blocker and beta blocker toxicity. Published experience with high-dose insulin spans over 15 years, including many case reports, case series, and prospective animal studies demonstrating efficacy and safety. Nevertheless, recent poison center reviews of treatment guideline compliance reveal underutilization of high-dose insulin, likely due to physician discomfort and unfamiliarity with dosing recommendations.[64,65]

Figure 5. Glucagon Mechanism Of Action



Abbreviations: AC, adenylate cyclase; ATPase, adenosine triphosphatase; Ca, calcium; cAMP, cyclic adenosine monophosphate; G, G protein; PDE, phosphodiesterase; PDEI, phosphodiesterase inhibitor; PKA, protein kinase A; RyR, ryanodine receptor; SR, sarcoplasmic reticulum.

Critical Appraisal Of The Literature

The Ovid MEDLINE® library was queried using the search terms *insulin* and *calcium channel antagonist* as well as *insulin* and *beta blocker*. Case reports, case series, prospective observational studies, prospective animal and in vitro studies, reviews, and editorials were identified for review. Reference sections of key texts in medical toxicology were reviewed.[66,67] Searches of the Cochrane Database and the National Guideline Clearinghouse revealed no results discussing the use of high-dose insulin for the poisoned patient.

How Antidotes Work: High-Dose Insulin

During normal physiologic conditions, free fatty acid beta oxidation accounts for 60% to 80% of myocardial energy production.[68] This process produces more energy than glucose utilization, but it requires more oxygen. Indeed, there is an inverse relationship between free fatty acid consumption and myocardial efficiency.[69] As such, myocytes switch to glucose for an energy substrate when under physiologic stress.

Insulin release from the pancreas is a calcium channel-dependent process, and is inhibited following calcium channel blocker overdose, leading to a hypoinsulinemic state.[70] Insulin deficiency, along with increased hepatic glycogenolysis, explains the hyperglycemia frequently seen with calcium-channel blocker toxicity. Providing high-dose insulin enables greater glucose utilization by cardiac myocytes, a highly efficient process for energy production that does not increase myocardial oxygen requirements.

Improved glucose uptake is not the only mechanism responsible for the inotropic properties of insulin. Insulin is not a vasopressor; it is a vasodilator of systemic, pulmonary, and coronary vasculature via enhancement of endothelial nitric oxide synthase. Rapid improvement of microvascular perfusion has the effect of increasing cardiac output despite lowering systemic vascular resistance.[71] Given these properties, insulin's inotropic effects are better observed via clinical parameters (mental status, skin warmth/color, urine output, and peripheral pulses) rather than improved systolic or mean arterial pressure.

Finally, insulin may improve cardiac contractility via stimulation of calcium entry into myocytes via sodium-calcium exchange and the calcium-dependent adenosine triphosphatase (ATPase) pump of the sarcoplasmic reticulum.[68]

Patient Selection

There is compelling evidence to initiate high-dose insulin therapy for any patient with drug-induced cardiogenic shock, especially if hyperglycemia is present. High-dose insulin should be started early for patients presenting with hypotension follow-

ing calcium-channel blocker overdose. This is more effective than using high-dose insulin as a rescue therapy. Most reviews and reference texts advise an initial bolus of 1 unit/kg followed by a continuous infusion of 0.5 to 1 unit/kg/h. The infusion dose can be titrated up if no response is seen after 30 minutes. A conservative maximum recommended infusion dose is 2 unit/kg/h, though infusions > 8 unit/kg/h have been reported.[72] While published incidence rates of hypoglycemia with high-dose insulin are low, supplemental dextrose (0.5 g/kg bolus followed by 0.5 g/kg/h infusion) should be given to patients with blood glucose levels < 200 mg/dL.[66,71]

Animal studies and published case reports support high-dose insulin use for beta blocker toxicity as well.[73,74] However, unlike cases of calcium-channel blocker toxicity, an insulin-deficient state is not seen following beta blocker overdose. Physicians should, therefore, be vigilant in monitoring for hypoglycemia in these cases.

Practical Considerations: Adverse Effects Of High-Dose Insulin

The most obvious and frequently described adverse effect of high-dose insulin therapy is hypoglycemia. While several case series have reported a low incidence of hypoglycemia, it is still observed, even when supplemental dextrose is administered at the outset of therapy.[64,72,75] Blood glucose should be measured every 30 minutes until the patient is clinically stable, and then every 1 to 2 hours for the duration of high-dose insulin administration.[66]

Intracellular shifts of potassium, magnesium, and phosphorus can be anticipated with insulin treatment as well. Potassium levels should be normal prior to initiation of therapy. While clinically significant hypokalemia rarely occurs, supplementation may be required if potassium levels fall below 2.8 mEq/L.[66] Supplementation of other electrolytes is typically unnecessary.

Duration Of Treatment

The insulin infusion can gradually be tapered down and off as the patient's clinical condition improves and stabilizes. As mentioned previously, clinical parameters (such as urine output, skin color, and mental status) may be better indications of the effects of high-dose insulin rather than rigid hemodynamic measurements. Hypoglycemia may occur after insulin is discontinued, due to gradual release from lipid stores, so glucose measurements should continue every 4 to 6 hours for at least 24 hours after cessation of high-dose insulin therapy.[71]

Intravenous Lipid Emulsion

No recent innovation in antidotal therapy has captured the attention of emergency medicine, critical care, and anesthesiology as intravenous lipid emulsion (ILE). Composed of medium- and long-chain triglycerides, free fatty acids, and phospholipids, ILE has been a component of parenteral nutrition since 1961 and, more recently, it has been used as a drug delivery system. In 1998, Weinberg et al made the chance observation that rats pretreated with lipid emulsion showed increased resistance to cardiac toxicity associated with bupivacaine administration.[76] Pioneering work by Weinberg and other investigators has since demonstrated ILE's benefit in the treatment of local anesthetic systemic toxicity and cardiotoxicity from many other lipophilic agents. The first clinical report of successful ILE deployment for drug toxicity was published in 2006.[77] Numerous other reports, along with in vitro studies, animal models, and editorials warning of overuse of the new "silver bullet," have followed.

Critical Appraisal Of The Literature

As with antidotes previously discussed, the Ovid MEDLINE® library was queried with the search terms *lipid emulsion antidote* and *lipid emulsion therapy*, producing case reports, retrospective chart reviews, animal studies, poison center surveys, literature reviews, and editorials selected for review. While searches of the Cochrane Database and the National Guideline Clearinghouse failed to produce results, the American College of Medical Toxicology and the American Society of Regional Anesthesia and Pain Medicine have produced practice advisories regarding the use of ILE. The American College of Medical Toxicology interim position statement does not list specific indications, stating that the use of ILE is "solely discretionary and is based on the clinical judgment of the treating physician;" that there are "no standard of care requirements" regarding use; and, in situations of significant hemodynamic instability from lipophilic drug toxicity, ILE is a "reasonable consideration for therapy, even if the patient is not in cardiac arrest."[78] The American Society of Regional Anesthesia and Pain Medicine advisory includes a Class IIa recommendation to consider ILE administration at the first sign of local anesthetic systemic toxicity, following airway management.[79]

How Antidotes Work: Intravenous Lipid Emulsion

Several mechanisms have been proposed to explain ILE's effects. The "lipid sink" theory postulates that administration of ILE expands the lipid phase within the serum, drawing lipophilic drugs into this "sink" and away from target organs (eg, the myocardium). Bupivacaine and other local anesthetics are highly lipophilic, as are other substances that have been successfully treated by ILE in the laboratory or described in case reports (eg, verapamil, barbiturates, and TCAs). Isolated rat studies have shown ILE to be capable of

reducing overall bupivacaine content by 70%,[80] and radiolabeled bupivacaine added to plasma drawn from animals treated with ILE moves preferentially to the lipid phase.[81] However, other animal studies have shown no increase in serum drug concentrations following treatment with ILE,[82] or very low drug recovery following ILE treatment and subsequent plasma exchange,[83] suggesting alternate mechanisms to the lipid sink. Some authors have suggested that lipemic serum may enhance enteric absorption of the ingested drug, potentially increasing toxicity.[84]

Local anesthetics inhibit carnitine acylcarnitine translocase (a necessary transport enzyme in the mitochondrial metabolism of fatty acids) and adenosine triphosphate (ATP) synthase in the electron transport chain. ILE may provide a large substrate to overwhelm this blockade, improving ATP generation by enhancing cellular energy substrate. This "bioenergetic" theory is supported by animal studies demonstrating failed resuscitation with ILE after pretreatment with free fatty acid oxidation inhibitors.[85] This could argue against ILE use in cardiogenic shock. As previously discussed, there is a myocardial preference for carbohydrates in the stressed state.

ILE may also have positive inotropic effects by increasing myocyte calcium levels via action at calcium channels. As demonstrated by in vitro studies, free fatty acids are able to directly activate voltage-gated calcium channels.[80] ILE may also activate the cytoprotective Akt pathway or compete with drugs for ion channel binding.[86] Finally, ILE has been shown to be protective against ischemia-reperfusion injury.[87] These pathways are not mutually exclusive, and it is likely that several mechanisms are responsible for ILE's benefit in lipophilic cardiotoxic drug overdose.

Patient Selection

The available evidence currently supports the use of ILE as an early antidotal therapy for patients with clinical signs of local anesthetic systemic toxicity. Early clinical manifestations of local anesthetic systemic toxicity are predominantly neurologic and include altered mental status, agitation, lightheadedness, and visual disturbances, and potentially progressing to seizures or significantly depressed mental status. The heart is more resistant to local anesthetic toxicity, although bupivacaine may cause cardiovascular collapse more readily than other agents of this class. As such, bupivacaine toxicity may present with hypotension and bradycardia, progressing quickly to ventricular dysrhythmia.[81] ILE should be initiated immediately if any neurologic or cardiovascular compromise develops following administration of these agents.

Use of ILE for other drug toxicity is less straightforward. Case reports describing benefit from ILE have been published for many agents, including calcium-channel blockers, beta blockers, TCAs, antipsychotics (eg, quetiapine [Seroquel®, Seroquel XR®), bupropion (Wellbutrin®, Wellbutrin XL®, Zyban®, Forfivo XL®, Aplenzin®), chloroquine (Aralen®, Plaquenil®), glyphosate, and cocaine.[88-94] While encouraging, these reports and the available animal evidence do not yet support the use of ILE as a first-line agent for drug-induced cardiotoxicity. Rather, its judicious use should be considered if standard supportive measures and other antidotal therapies fail to restore hemodynamic stability.

Practical Considerations: Adverse Effects Of Intravenous Lipid Emulsion

While adverse effects are rare (or rarely reported), lipemia following ILE administration has been associated with pancreatitis, hyperamylasemia, pyrogenic reactions, gross hematuria, and deep venous thrombosis.[95-99] It may predispose the patient to systemic infection, especially yeast infection.[87] The incidence of adverse effects appears to be associated with prolonged infusions and doses > 4 mL/kg.[96]

Of particular concern is the potential risk of acute lung injury. Oleic acid (which comprises approximately 22% of free fatty acids in some common ILE preparations) has been associated with acute lung injury in animal studies. However, preexisting pulmonary compromise was necessary in these models for ILE-associated pulmonary injury to occur.[80,97] While rare, physicians should be aware that patients with acute respiratory distress syndrome are at increased risk for transient changes in oxygenation and pulmonary vascular tone while receiving ILE.

Finally, ILE has the potential to interfere with spectrophotometric analysis of several laboratory studies, including aspartate aminotransferase, hemoglobin and methemoglobin, electrolytes, base excess, coagulation testing, and arterial blood gas analysis.[80,87,91,98,100] Bench models suggest that ultracentrifugation of samples may ameliorate laboratory interference, but this is not universally effective.[98]

Special Considerations: Intravenous Lipid Emulsion In Pediatric Patients

A recent literature review identified 14 cases of ILE administration in pediatric patients (aged < 18 years).[101] In this series, ILE was used to treat toxicity from local anesthetics (7 patients), TCAs (2 patients), calcium-channel blockers (2 patients), antipsychotics (2 patients), and a mixed bupropion/lamotrigine overdose (1 patient). Positive benefit was noted in 13 of the 14 patients. One case of pancreatitis was reported. Based on limited available clinical experience, ILE appears to be safe in the pediatric population.

Dosing And Duration Of Treatment

While optimal ILE dosing has not been defined, a recent survey of poison center medical directors found that > 95% advise an initial bolus of 1.5 mL/kg followed by an infusion of 0.25 mL/kg/min.[102] The bolus may be repeated 1 to 2 times and the infusion increased to 0.5 mL/kg/min for patients with declining hemodynamic stability. Dosing recommendations are based on lean body mass. Large doses and prolonged infusions may increase the risk of adverse effects. Dosing should not exceed 10 mL/kg over the first 30 minutes. As with dosing, optimal duration of ILE treatment is unclear. The American Society of Regional Anesthesia practice advisory recommends continuing ILE infusion for at least 10 minutes after achieving hemodynamic stability.[79]

Table 1. Overdose Indications For Antidotes

Antidote	Overdosed Medication
N-acetylcysteine	Acetaminophen
Sodium bicarbonate	Salicylates, tricyclic antidepressants
Glucagon	Beta blockers (first-line), calcium-channel blockers
High-dose insulin	Calcium-channel blockers (first-line), beta blockers
Intravenous lipid emulsion	Local anesthetics, consider for tricyclic antidepressant, calcium-channel blocker, beta blocker, or bupropion overdose resistant to standard therapy

Summary

A summary of the indications for antidotes and their recommended treatment regimens is provided in **Tables 1 and 2**.

Case Conclusion

You deduced that the patient's physiology was potentially consistent with both calcium-channel blocker (verapamil) and beta blocker (propranolol) toxicity. Although tricyclic antidepressant (imipramine) overdose was possible, the patient had a normal QRS interval and would not have benefited from administration of sodium bicarbonate at that time. Additionally, the presence of hyperglycemia made you suspicious of calcium-channel blocker overdose. You elected to give boluses of both high-dose insulin (1 U/kg) and glucagon (10 mg). Twenty minutes after administration,

Table 2. Antidote Treatment Recommendations

Antidote	Treatment Recommendations
N-acetylcysteine	• Loading dose of 150 mg/kg for 1 hour, then 50 mg/kg for 4 hours, and then 100 mg/kg for 16 hours. • Patient-tailored therapy: Administer a loading dose of N-acetylcysteine and treat until the following: (1) acetaminophen level zero or near zero; (2) serum alanine aminotransferase normal or significantly improving; and (3) the patient is clinically well.
Sodium bicarbonate	Salicylate poisoning • Infusion dosing of 3 ampules of 7.5% sodium bicarbonate (135 mEq) in 1L of 5% dextrose in water (D5W) administered at 1 to 2 times the maintenance fluid rate. • Continue treatment until: 1. The patient is clinically well (normal mental status, no acid-base disturbance). 2. Salicylate levels are < 20 mg/dL and clearly trending down. Tricyclic antidepressant overdose • Initial sodium bicarbonate dose of 1 to 2 mEq/kg. Initiate infusion with a goal arterial pH of 7.50 to 7.55. • Continue treatment until: 1. The patient has clinically improved (hemodynamics and mental status); and 2. There is improvement (not necessarily normalization) of abnormal ECG findings.
Glucagon	• Initial bolus of 5 to 10 mg (pediatric dose, 50 mcg/kg). If favorable response, repeat boluses can be given, though a continuous infusion (1-5 mg/h) is the kinetically advantageous option.
High-dose insulin	• Initial bolus of 1unit/kg followed by a continuous infusion of 0.5 to 1 unit/kg. Infusion dose can be titrated up if no response is seen after 30 minutes. A conservative maximum recommended infusion dose is 2 unit/kg/h. • Taper insulin infusion gradually down and off as the patient's clinical condition improves and stabilizes. Clinical parameters (eg, urine output, skin color, and mental status) may be better indications of the effects of high-dose insulin rather than rigid hemodynamic measurements. Hypoglycemia side effect • Supplemental dextrose (0.5 g/kg bolus followed by 0.5 g/kg/h infusion) for patients with blood glucose levels < 200 mg/dL. • Glucose measurements should continue every 4 to 6 hours for at least 24 hours after cessation of high-dose insulin therapy.
Intravenous lipid emulsion	• Initial 1.5 mL/kg bolus followed by an infusion of 0.25 mL/kg/min. The bolus may be repeated 1 to 2 times and the infusion increased to 0.5 mL/kg/min for declining hemodynamic stability. Dosing recommendations are based on lean body mass. Dosing should not exceed 10 mL/kg over the first 30 minutes. • Continue intravenous lipid emulsion infusion for at least 10 minutes after achieving hemodynamic stability.

the patient's blood pressure improved to 100/70 mm Hg, with a heart rate of 75 beats/min. Repeat blood glucose measurement was 210 mg/dL. You started a continuous infusion of high-dose insulin (1 U/kg/h) and glucagon (5 mg/h) and called the intensivist for admission. You advised the admitting physician that if the patient's hemodynamics deteriorated despite current management, intravenous lipid emulsion could be considered.

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Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

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1. **Potential mechanisms for the hepatoprotective effects of NAC include all of the following, EXCEPT:**
   a. Glutathione repletion
   b. Providing a substrate for nontoxic sulfation
   c. Interrupting enterohepatic recirculation
   d. Improvement of microcirculatory blood flow

2. **Which of the following regarding anaphylactoid reactions associated with NAC is FALSE?**
   a. They are immunoglobulin E-mediated.
   b. They are dose-dependent and usually occur early in treatment.
   c. Asthmatic patients are at increased risk.
   d. They frequently resolve rapidly following discontinuation of treatment.

3. **Which finding on an ECG is most important in determining whether to use sodium bicarbonate following TCA overdose?**
   a. Shortened PR
   b. Prolonged QTc
   c. Prolonged QRS
   d. Abnormal axis

4. **A common adverse effect following urinary alkalinization with sodium bicarbonate is:**
   a. Hypernatremia
   b. Prolonged QTc on ECG
   c. Abdominal pain
   d. Hypokalemia

5. **Which of the following regarding antidotal use of glucagon is TRUE?**
   a. It is supported by several controlled human trials.
   b. It is first-line therapy following TCA overdose.
   c. It works primarily by activation of adenylate cyclase, located downstream of the beta receptor.
   d. It is not associated with tachyphylaxis.

6. **Which of the following is NOT a potential side effect of glucagon?**
   a. Seizures
   b. Hyperglycemia
   c. Hypokalemia
   d. Nausea and vomiting

7. **Which of the following is NOT a possible mechanism for insulin's positive inotropic effect?**
   a. Improvement of microvascular perfusion
   b. Improved myocardial free fatty acid utilization
   c. Stimulation of calcium entry into myocytes
   d. Increase in myocardial glucose utilization

8. **What is the recommended initial bolus dose of high-dose insulin?**
   a. 0.1 U/kg
   b. 1 U/kg
   c. 10 U/kg
   d. 100 U

9. **Currently available evidence supports early use of ILE for systemic toxicity of which of the following?**
   a. Beta blockers
   b. Antipsychotics
   c. Salicylates
   d. Local anesthetics

10. **Proposed mechanisms for inotropic effects of ILE include all of the following, EXCEPT:**
    a. Increased myocardial calcium levels
    b. Expansion of the serum lipid phase, drawing lipophilic drugs away from target organs
    c. Inhibition of carnitine acylcarnitine translocase
    d. Improvement in mitochondrial fatty acid metabolism

CME Information

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Goals: Upon completion of this article, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

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