A5: Antidotes in Depth

Paul M. Wax

INTRODUCTION

Sodium bicarbonate is a nonspecific antidote that is effective in the treatment of a variety of poisonings by means of a number of distinct mechanisms (Table A5–1). However, the support for its use in these settings is predominantly based on animal evidence, case reports, and consensus. It is most commonly used to treat patients with cyclic antidepressant (CA) and salicylate poisonings. Sodium bicarbonate also has a role in the treatment of phenobarbital, chlorpropamide, and chlorophenoxy herbicide poisonings and wide-complex tachydysrhythmias induced by Na⁺ channel blocking xenobiotics such as type IA and IC antidysrhythmics and cocaine. Correcting the life-threatening acidemia induced by methanol and ethylene glycol metabolism and enhancing formate elimination are other important indications for sodium bicarbonate. The use of sodium bicarbonate in the treatment of rhabdomyolysis, metabolic acidosis with elevated lactate, cardiac resuscitation, and diabetic ketoacidosis is controversial and not addressed in this Antidote in Depth.

TABLE A5–1. Sodium Bicarbonate: Mechanisms, Site of Action, and Uses in Toxicology

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PHARMACOLOGY

Sodium bicarbonate has a molecular weight of 84 Da. It is supplied in solution at approximately pH 8.0 (pH limits range from 7.0 to 8.5). The onset of action of intravenous (IV) sodium bicarbonate is within 15 minutes with a duration of action of 1 to 2 hours. Sodium bicarbonate increases plasma bicarbonate and buffers excess hydrogen ion. In normal individuals, the distribution volume for bicarbonate salts is approximately twice the extracellular fluid (ECF) volume. The apparent bicarbonate space (ABS) proportionally increases in severe acidemia, leading to higher bicarbonate requirements. Canine studies demonstrated that this effect is not due to the acidemia per se, but due to the tight correlation of extracellular bicarbonate concentrations with the ABS. Whether acidemic or alkalemic, low bicarbonate concentrations increase the apparent space of distribution in a highly dynamic manner. Human studies, in which the ABS is described by the equation, ABS = (0.36 + 2.44/[HCO₃⁻]) × body weight (kg), appear to support this concept.
ROLE IN MYOCARDIAL SODIUM CHANNEL TOXINS

The most important role of sodium bicarbonate in toxicology is the ability to reverse potentially fatal cardiotoxic effects of myocardial Na⁺ channel blockers such as CAs and other type IA and IC antidysrhythmics. Its mechanism of action in these cases appears to result from both an increase in [Na+] and a change in the proportion of the Na⁺ channel blocker ionized, resulting in an altered distribution away from its channel. Use of sodium bicarbonate for myocardial Na⁺ channel blocker overdose developed as an extension of sodium lactate use in the treatment of patients with toxicity from type IA antidysrhythmics. Noting similarities in electrocardiographic (ECG) findings between hyperkalemia and quinidine toxicity (ie, QRS widening), investigators in the 1950s began to use sodium lactate (which is rapidly metabolized in the liver to sodium bicarbonate) to treat quinidine toxicity. In a canine model, quinidine-induced ECG changes and hypotension were consistently reversed by infusion of sodium lactate. Clinical experience confirmed this benefit. Similar efficacy in the treatment of patients with procainamide cardiotoxicity was also reported.

The introduction of CAs during the 1960s also yielded reports of conduction disturbances, dysrhythmias, and hypotension occurring in overdose. Extending the use of sodium lactate for the type I antidysrhythmics to CA poisoning, uncontrolled observations in the 1970s showed a decrease in mortality rate from 15% to less than 3%. In 1976, sodium bicarbonate was reported successful in a pediatric series of CA-induced dysrhythmias. In this series, nine of 12 children who had developed multifocal premature ventricular contractions (PVCs), ventricular tachycardia, or heart block reverted to normal sinus rhythm with sodium bicarbonate therapy alone. An early canine experiment of amitriptyline-poisoning demonstrated resolution of dysrhythmias upon blood alkalinization to a pH above 7.40. Other methods of alkalinization, including hyperventilation and administration of the nonsodium buffer tris (hydroxymethyl) aminomethane (THAM), were also effective in reversing the dysrhythmias.

An improved understanding of the mechanism and utility of sodium bicarbonate came from a series of animal experiments during the 1980s. In amitriptyline-poisoned dogs, sodium bicarbonate reversed conduction disturbances and ventricular dysrhythmias and suppressed ventricular ectopy. When comparing sodium bicarbonate, respiratory alkalemia (hyperventilation), hypertonic sodium chloride, and lidocaine, sodium bicarbonate, and hyperventilation proved most efficacious in reversing ventricular dysrhythmias and narrowing QRS prolongation. Although lidocaine transiently antagonized dysrhythmias, this antagonism was demonstrable only at nearly toxic lidocaine concentrations and was associated with hypotension. Furthermore, prophylactic alkalinization protected against the development of dysrhythmias in a pH-dependent manner.

In desipramine-poisoned rats, the isolated use of either sodium chloride or sodium bicarbonate was effective in decreasing QRS duration. Both sodium bicarbonate and hypertonic sodium chloride also increased mean arterial pressure, but hyperventilation or direct intravascular volume repletion with mannitol did not. In further studies both in vivo and on isolated cardiac tissue, alkalinization and

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increased sodium concentration improved CA effects on cardiac conduction. Although respiratory alkalemia and hypertonic sodium chloride each independently improved conduction velocity, this effect was greatest when sodium bicarbonate was administered.

Another study on amitriptyline-poisoned rats demonstrated that treatment with sodium bicarbonate was associated with shorter QRS interval, longer duration of sinus rhythm, and increased survival rates. Sodium bicarbonate seems to work independently of initial blood pH. Animal studies show that cardiac conduction improves after treatment with sodium bicarbonate or sodium chloride in both normal and acidemic animals. Clinically, CA-poisoned patients who were already alkalemic responded to repeat doses of sodium bicarbonate.

Although several authors suggest that the efficacy of sodium bicarbonate is modulated via a pH-dependent change in plasma protein binding that decreases the proportion of free drug, further study failed to support this hypothesis. The administration of large doses of a binding protein α,-acid glycoprotein (AAG) (to which CAs show significant affinity) to desipramine poisoned rats only minimally decreased cardiotoxicity. Although the addition of AAG increased the concentrations of total desipramine and protein-bound desipramine in the serum, the concentration of active free desipramine did not decline significantly. A redistribution of CA from peripheral sites may have prevented lowering of free desipramine concentration. The persistence of other CA-associated toxicities, antimuscarinic effects and seizures, also argues against changes in protein-binding modulating toxicity. In vitro studies performed in plasma protein-free bath further substantiate sodium bicarbonate's efficacy independent of plasma protein binding.

Sodium bicarbonate has a crucial antidotal role in myocardial Na-channel blocker poisoning by increasing the number of open Na-channels, thereby partially reversing fast Na-channel blockade. This decreases QRS prolongation and reduces life-threatening cardiovascular toxicity such as ventricular dysrhythmias and hypotension. The animal evidence supports two distinct and additive mechanisms for this effect: a pH-dependent effect and a sodium-dependent effect. The pH-dependent effect increases the fraction of the more freely diffusible nonionized xenobiotic. Both the ionized xenobiotic and the nonionized forms are able to bind to the Na-channel, but assuming myocardial Na-channel blockers act like local anesthetics, it is estimated that 90% of the block results from the ionized form. By increasing the nonionized fraction, less xenobiotic is available to bind to the Na-channel binding site (Fig. A5–1). The sodium-dependent effect increases the availability of Na ions to pass through the open channels. Decreased ionization should not significantly decrease the rate of CA elimination because of the small contribution of renal pathways to overall CA elimination (<5%).

**FIGURE A5–1.**
Blockade occurs by an ionized drug because the channel is a water (lipophobic) environment (*left*). As the drug becomes nonionized, it becomes more lipophilic and moves into the lipid bilayer of the membrane and away from the channel (*right*).
Although many anecdotal accounts support the efficacy of sodium bicarbonate in treating CA cardiotoxicity in humans, these reports are uncontrolled observations; controlled studies are unavailable. In one of the largest retrospective observational studies involving 91 patients who received sodium bicarbonate after CA overdose, QRS prolongation corrected in 39 of 49 patients who had QRS durations above 120 msec, and hypotension corrected within 1 hour in 20 of 21 patients who had systolic blood pressures below 90 mm Hg. Use of sodium bicarbonate was not associated with any complications in this study.

Prospective validation of treatment criteria for use of sodium bicarbonate after CA overdose has not been performed. Common indications are conduction delays (as manifested by QRS above 100 msec or right bundle branch block), wide-complex tachydysrhythmias, and hypotension. Because studies demonstrate a critical threshold QRS duration (≥160 msec) at which ventricular dysrhythmias significantly increase in propensity, it seems reasonable that narrowing the QRS interval through use of sodium bicarbonate or hyperventilation may prophylactically prevent against development of dysrhythmias. Practice patterns vary considerably with regard to the use of sodium bicarbonate when the QRS interval is below 160 msec. Although sodium bicarbonate has no proven efficacy in either the treatment or prophylaxis of tricyclic antidepressant–induced seizures, seizures often produce acidaemia, which rapidly increases the risks of conduction disturbances and ventricular dysrhythmias. Administering sodium bicarbonate when the QRS duration is 100 msec or greater may establish a theoretical margin of safety in the event the patient suddenly deteriorates, without adding significant demonstrable risk. When the QRS duration is below 100 msec, given the minimal risk of seizures or dysrhythmias, prophylactic sodium bicarbonate administration is not indicated. In patients exhibiting a Brugada ECG pattern (right bundle branch block with downsloping ST segment elevation in V1–V3) and QRS widening after CA ingestion, sodium bicarbonate administration may narrow the QRS without reversing the Brugada pattern (Chap. 16).

Because cardiotoxicity may worsen during the first few hours after ingestion, sodium bicarbonate therapy should be initiated immediately if the QRS interval is greater than 100 msec. Because CA-induced hypotension responds to sodium bicarbonate, hypotension should also prompt sodium bicarbonate therapy. However, no evidence supports a role for sodium bicarbonate in CA-poisoned patients who present with altered mental status or seizures without QRS widening or hypotension.

Because the potential benefits of alkalinization in CA overdose usually outweigh the risks, sodium bicarbonate should be administered regardless of whether the patient has an acidemic or normal pH.

The time to resolution of conduction abnormalities during continuous bicarbonate infusion varies significantly, ranging from several hours to several days. In a case of poisoning from modified-release amitriptyline, sodium bicarbonate was required on multiple occasions over 110 hours after the initial ingestion to reverse ongoing Na⁺ channel conduction disturbances. Sodium
bicarbonate infusion usually is discontinued upon hemodynamic improvement and resolution of cardiac conduction abnormalities and altered mental status, although controlled data supporting such an approach are lacking.

Sodium bicarbonate is useful in treating patients with cardiotoxicity from other myocardial Na⁺ channel blockers that present with widened QRS complexes, dysrhythmias, and hypotension. Isolated case reports provide the bulk of the evidence in these situations. The utility of sodium bicarbonate in treating patients with type IA and IC antidysrhythmics, diphenhydramine, propoxyphene, quinine, and others has been demonstrated. 13, 28, 29, 95, 104, 110

Use of sodium bicarbonate in the treatment of patients with overdoses of amantadine, a xenobiotic with multiple myocardial channel effects has been suggested, but concurrent hypokalemia may limit its use. 100 Although the usefulness of sodium bicarbonate in reversing QRS prolongation, occasionally observed during fluoxetine and citalopram overdose has been reported, Na⁺ channel disturbances are uncommon in most cases of selective serotonin reuptake inhibitor (SSRI) overdose, and routine use of alkalinization therapy in this setting is unwarranted and might risk worsening QT effects by promoting hypokalemia. Sodium bicarbonate may help in the management of patients with other ingestions associated with type IA–like cardiac conduction abnormalities and dysrhythmias, such as carbamazepine, lamotrigine, and the phenothiazines thioridazine and mesoridazine, but documentation of benefit is limited to case reports. 44 Although sodium bicarbonate efficacy in the treatment of Taxus spp induced wide-complex dysrhythmias is reported, an animal study failed to detect any benefit. 87, 88 Bupropion’s reduction of cardiac intercellular coupling (ie, inhibition of gap junction communication), as opposed to Na⁺ channel blockade, 24 may explain the reported lack of efficacy of sodium bicarbonate in reversing QRS prolongation in bupropion poisoning. 119

Cocaine, a local anesthetic with membrane-stabilizing properties resembling other type I antidysrhythmics, may cause similar conduction disturbances. In several canine models of cocaine toxicity, sodium bicarbonate successfully reversed cocaine-induced QRS prolongation and improved myocardial function. 8 Of interest, sodium loading by itself failed to produce a benefit. Similar findings were demonstrated in cocaine-treated guinea pig hearts. 12 Of interest, sodium loading by itself failed to produce a benefit. Similar findings were demonstrated in cocaine-treated guinea pig hearts. 12 Patients with cocaine-induced cardiotoxicity responded to treatment with sodium bicarbonate and improved myocardial function. 14, 144 In many of these cases, simultaneous treatment with sedation, active cooling, and hyperventilation confounds the interpretation of sodium bicarbonate’s benefit.

ROLE IN ALTERING DISTRIBUTION AND ENHANCING ELIMINATION

Salicylates
Although there is no known specific antidote, judicious use of sodium bicarbonate is an essential treatment for salicylate toxicity. Through its ability to alter the concentration gradient of the ionized and nonionized fractions of salicylates, sodium bicarbonate is useful in decreasing tissue (eg, brain)
concentrations of salicylates and enhancing urinary elimination of salicylates. This therapy may limit the need for more invasive treatment modalities, such as hemodialysis.

Salicylate is a weak acid with a pKₐ of 3.0. As pH increases, the ionized proportion increases. Because of the presence of polar groups, ionized molecules penetrate lipid-soluble membranes less efficiently than do nonionized molecules. Consequently, when the ionized forms predominate, weak acids such as salicylates may accumulate in an alkaline milieu, such as an alkaline urine.

Although alkalinizing the urine to increase salicylate elimination is an important intervention in the treatment of patients with salicylate poisoning, increasing the serum pH in patients with severe salicylism may prove even more consequential by protecting the brain from a lethal central nervous system (CNS) salicylate burden. In these patients, using sodium bicarbonate to “trap” salicylate in the blood (ie, keeping it out of the brain) may prevent clinical deterioration of salicylate-poisoned patients. Salicylate lethality is directly related to primary CNS dysfunction, which, in turn, corresponds to a “critical brain salicylate concentration.” At physiologic pH, at which a very small proportion of the salicylate is in the nonionized form, a small change in pH is associated with a significant change in amount of nonionized molecules. For example, whereas at a pH of 7.4, 0.004% of the salicylate molecules are in the nonionized form, at a pH of 7.2, 0.008%, of the salicylate is in the nonionized form. In experimental models, lowering the blood pH produces a shift of salicylate into the tissues. Hence, acidemia in patients with significant salicylate poisonings can be devastating. In salicylate-poisoned rats, increasing the blood pH with sodium bicarbonate produced a shift in salicylate out of the tissues and into the blood. This change in salicylate distribution did not result from enhanced urinary excretion because occlusion of the renal pedicles failed to alter these results.

Enhancing the elimination of salicylate by trapping ionized salicylate in the urine is also beneficial. Salicylate elimination at therapeutic concentrations is predominantly first-order hepatic metabolism. At these low concentrations, without alkalinization, only approximately 10% to 20% of salicylate is eliminated unchanged in the urine. With increasing concentrations, enzyme saturation occurs (Michaelis-Menten kinetics); thus, a larger percentage of elimination occurs as unchanged free salicylate. Under these conditions, in an alkaline urine, urinary excretion of free salicylate becomes even more significant, accounting for 60% to 85% of total elimination. The relationship between salicylate clearance and urine pH \( \log(\text{salicylate clearance}) = [(0.52 \times \text{pH}) - 2.1]\) would suggest that increasing urine pH from 5.0 to 8.0 could increase the amount of salicylate cleared by almost 40-fold.

The exact mechanism of pH-dependent salicylate elimination has generated controversy. The pH-dependent increase in urinary elimination initially was ascribed to “ion trapping,” which is the filtering of both ionized and nonionized salicylate while reabsorbing only the nonionized salicylate. However, limiting reabsorption of the ionizable fraction of filtered salicylate cannot be the primary mechanism responsible for enhanced elimination produced by sodium bicarbonate. Because the quantitative difference between the percentage of molecules trapped in the ionized form at a pH of 5.0 (99% ionized) and a pH of 8.0 (99.999% ionized) is small, decreases
in tubular reabsorption cannot fully explain the rapid increase in urinary elimination seen at a pH above 7.0.

“Diffusion theory” offers a reasonable alternative explanation. Fick’s law of diffusion states that the rate of flow of a diffusing substance is proportional to its concentration gradient. A large concentration gradient between the nonionized salicylate in the peritubular fluid (and blood) and the tubular luminal fluid is found in alkaline urine. Because at a higher urinary pH, a greater proportion of secreted nonionized molecules quickly becomes ionized upon entering the alkaline environment, more salicylate (ie, nonionized salicylate) must pass from the peritubular fluid into the urine in an attempt to reach equilibrium with the nonionized fraction. In fact, as long as nonionized molecules are rapidly converted to ionized molecules in the urine, equilibrium in the alkaline milieu will never be achieved. The concentration gradient of peritubular nonionized salicylates to urinary nonionized salicylates continues to increase with increasing urinary pH. Hence, increased tubular diffusion, not decreased reabsorption, probably accounts for most of the increase in salicylate elimination observed in the alkaline urine.16

Sodium bicarbonate is indicated in the treatment of salicylate poisoning for most patients with evidence of significant systemic toxicity. Although some authors have suggested alkali therapy for asymptomatic patients with concentrations above 30 mg/dL,118 limited data support this approach. For patients with chronic poisoning, salicylate concentrations are not as helpful and may be misleading; clinical criteria remain the best indicators for therapy. Patients with contraindications to sodium bicarbonate use, such as severe acute kidney injury (AKI) or chronic kidney disease (CKD) and acute respiratory distress syndrome (ARDS), should be considered candidates for intubation and subsequent hyperventilation, but extracorporeal removal is often required because of the difficulty and dangers of intubation.

Dosing recommendations depend on the acid–base considerations. For patients with hypobicarbonatemia, IV administration of 1 to 2 mEq of sodium bicarbonate per kilogram of body weight is recommended.112 Alkalization can be maintained with a continuous sodium bicarbonate infusion of 150 mEq in 1 L of D5W at 150 to 200 mL/h (or about twice the maintenance requirements in a child). Continued titration with sodium bicarbonate over 4 to 8 hours is recommended until the urinary pH reaches 7.5 to 8.0.109,112 The addition of the dextrose is important because salicylate toxicity may cause hypoglycemia.112 Achieving a urinary pH of 8.0 is difficult but is the goal. Fastidious attention to the patient’s changing acid–base status is required. Systemic pH should not rise above 7.55 to prevent complications of alkalemia. Hypokalemia can make urinary alkalization particularly problematic.122 In hypokalemic patients, the kidneys preferentially reabsorb potassium in exchange for hydrogen ions. Urinary alkalization will be unsuccessful as long as hydrogen ions are excreted into the urine. Thus, appropriate potassium supplementation to achieve normokalemia may be required to alkalinize the urine.122

In the past, proper urinary alkalization was thought to require forced diuresis to maximize salicylate elimination.30,60 Suggestions included administering enough fluid (2 L/h) to produce a urine output of 500 mL/h. Because forced alkaline diuresis appears unnecessary and is potentially harmful as a
result of its unnecessarily large fluid load, the goal is alkalinization at a rate of approximately twice maintenance requirements to achieve a urine output of 3 to 5 mL/kg/h.

**Phenobarbital**

Although cardiopulmonary support is the most critical intervention in the treatment of patients with severe phenobarbital overdose, sodium bicarbonate may be a useful adjunct to general supportive care. The utility of sodium bicarbonate is particularly important considering the long plasma half-life (~100 hours) of phenobarbital. Phenobarbital is a weak acid (pKₐ, 7.24) that undergoes significant renal elimination. As in the case of salicylates, alkalinization of the blood and urine may reduce the severity and duration of toxicity. In a study of mice, the median anesthetic dose for mice receiving phenobarbital increased by 20% with the addition of sufficient sodium bicarbonate to increase the blood pH from 7.23 to 7.41, demonstrating decreased tissue concentrations associated with increased pH. The animal evidence has been extrapolated to humans to suggest that phenobarbital-poisoned patients in deep coma might develop a respiratory acidosis secondary to hypoventilation, with the acidemia enhancing the phenobarbital transfer into the brain, thus worsening CNS and respiratory depression. Alternatively, increasing the pH with bicarbonate, ventilatory support, or both would enhance the phenobarbital efflux from brain, thus lessening toxicity. Given phenobarbital's relatively high pKₐ, significant urinary phenobarbital accumulation is evident only when urinary pH is increased above 7.5. As the pH approaches 8.0, a threefold increase in urinary elimination occurs. The urine-to-serum ratio of phenobarbital, although much higher in alkaline urine than in acidic urine, remains less than unity, thereby suggesting less of a role for tubular secretion than in salicylate poisoning.

Clinical studies examining the role of alkalinization in phenobarbital poisoning have been inadequately designed. Many are poorly controlled and fail to examine the effects of alkalinization, independent of coadministered diuretic therapy. In one uncontrolled study with phenobarbital overdoses, a 59% to 67% decrease in the duration of unconsciousness in patients occurred in patients administered alkali compared with nonrandomized control subjects. In other older studies, treatment with sodium lactate and urea reduced mortality and frequency of tracheotomy to 50% of control subjects, enhanced elimination, and shortened coma. In a later human volunteer study, urinary alkalinization with sodium bicarbonate was associated with a decrease in phenobarbital elimination half-life from 148 to 47 hours. However, this beneficial effect was less than the effect achieved by multiple-dose activated charcoal (MDAC), which reduced the half-life to 19 hours. In a nonrandomized study of phenobarbital-poisoned patients comparing urinary alkalinization alone, MDAC alone, and both methods together, both the phenobarbital half-life decreased most rapidly and the clinical course improved most rapidly in the group of patients who received MDAC alone. Interesting, the combination approach proved inferior to MDAC alone but was better than alkalinization alone. The authors speculated that when both treatments were used together, the increased ionization of phenobarbital resulting from sodium bicarbonate infusion might have decreased the efficacy of MDAC. These studies suggest that MDAC is more efficacious than urinary alkalinization in the treatment of phenobarbital-poisoned patients, although both approaches are beneficial and indicated.
Sodium bicarbonate therapy does not appear warranted in the treatment of patients with ingestions of other barbiturates, such as pentobarbital and secobarbital, which either have a pKₐ above 8.0 or are predominantly eliminated hepatically.

Methotrexate
Urinary alkalization with sodium bicarbonate is routinely used during high-dose methotrexate cancer chemotherapy therapy. Methotrexate is predominantly eliminated unchanged in the urine. Unfortunately, methotrexate, as well as its metabolites DAMPA (4-amino-4-deoxy-10-methylpterioic acid) and 7-hydroxymethotrexate, are poorly water soluble in acidic urine. Under these conditions, tubular precipitation of the methotrexate may occur, leading to AKI and decreased elimination, increasing the likelihood of methotrexate toxicity. Administration of sodium bicarbonate (as well as intensive hydration) during high-dose methotrexate infusions increases methotrexate solubility and the elimination of methotrexate and its metabolites.

Chlorophenoxy Herbicides
Alkalization is indicated in the treatment of patients with poisonings from weed killers that contain chlorophenoxy compounds, such as 2,4-dichlorophenoxyacetic acid (2,4-D) or 2-(4-chloro-2-methylphenoxy) propionic acid (MCPP). Poisoning results in muscle weakness, peripheral neuropathy, coma, hyperthermia, and acidemia. These compounds are weak acids (pKₐ 2.6 and 3.8 for 2,4-D and MCPP, respectively) that are excreted largely unchanged in the urine. In an uncontrolled case series of 41 patients poisoned with a variety of chlorophenoxy herbicides, 19 of whom received sodium bicarbonate, alkaline diuresis significantly reduced the half-life of each by enhancing renal elimination. In one patient, resolution of hyperthermia and metabolic acidosis and improvement in mental status were associated with a transient elevation of serum concentration, perhaps reflecting chlorophenoxy compound redistribution from the tissues into the more alkaline blood. The limited data suggest that the increased ionized fractions of the weak-acid chlorophenoxy compounds produced by alkalization is trapped in both the blood and the urine as demonstrated both with salicylates and phenobarbital; thus, its use ameliorates toxicity and shortens the duration of effect.

ROLE IN CORRECTING METABOLIC ACIDEMIA

Toxic Alcohols
Sodium bicarbonate has two important roles in treating patients with toxic alcohol ingestions. As an immediate temporizing measure, administration of sodium bicarbonate may reverse the life-threatening acidemia associated with methanol and ethylene glycol ingestions. In rats poisoned with ethylene glycol, the administration of sodium bicarbonate alone resulted in a fourfold increase in the median lethal dose. Clinically, titrating the endogenous acid with bicarbonate greatly assists in reversing the consequences of severe acidemia, such as hemodynamic instability and multiorgan dysfunction.

The second role of bicarbonate in the treatment of toxic alcohol poisoning involves its ability to favorably alter the distribution and elimination of certain toxic metabolites. In cases of methanol
poisoning, the proportion of ionized formic acid can be increased by administering bicarbonate, thereby trapping formate in the blood compartment. Consequently, decreased visual toxicity results from removal of the toxic metabolite from the eyes. In cases of formic acid (pKₐ of 3.7) ingestion, sodium bicarbonate decreases tissue penetration of the formic acid and enhances urinary elimination.

Early treatment of acidemia with sodium bicarbonate is strongly recommended in cases of methanol and ethylene glycol poisoning. Sodium bicarbonate should be administered to toxic alcohol-poisoned patients with an arterial pH below 7.30. More than 400 to 600 mEq of sodium bicarbonate may be required in the first few hours. In cases of ethylene glycol toxicity, sodium bicarbonate administration may worsen hypocalcemia, so the serum calcium concentration should be monitored. Combating the acidemia, however, is not the mainstay of therapy, and concurrent administration of IV fomepizole or ethanol and consideration for hemodialysis are almost always indicated.

**Metformin**

Metformin toxicity, either from overdose or therapeutic use in the setting of AKI or CKD, may cause severe, life-threatening metabolic acidemia with an elevated lactate concentration. The use of high-dose sodium bicarbonate to correct the metabolic acidemia, as well as extracorporeal removal of the metformin, is recommended in these cases.

**ROLE IN NEUTRALIZATION**

**Chlorine Gas**

Nebulized sodium bicarbonate serves as a useful adjunct in the treatment of patients with pulmonary injuries resulting from chlorine gas inhalation. Inhaled sodium bicarbonate neutralizes the hydrochloric acid that is formed when the chlorine gas reacts with the water in the respiratory tree. Although oral sodium bicarbonate is not recommended for neutralizing acid ingestions because of the problems associated with the exothermic reaction and production of carbon dioxide in the relatively closed gastrointestinal tract, the rapid exchange in the lungs of air with the environment facilitates heat dissipation. In a sheep model of chlorine inhalation, animals treated with 4% nebulized sodium bicarbonate solution demonstrated a higher PO₂ and lower PCO₂ than did the normal, saline-treated animals. There was no difference, however, in 24-hour mortality or pulmonary histopathology. In a retrospective review, 86 patients with chlorine gas inhalation were treated with nebulized sodium bicarbonate. Sixty-nine patients were sent home from the emergency department, 53 of whom had clearly improved. In a more recent study, 44 patients who were diagnosed with reactive airway dysfunction syndrome after an acute exposure to chlorine gas were randomized to receive either nebulized sodium bicarbonate (4 mL of 4.2% sodium bicarbonate solution) or nebulized placebo. Both groups also received IV corticosteroids and inhaled β₂-adrenergic agonists. Compared with the placebo group, the nebulized sodium bicarbonate group had significantly higher forced expiratory volume in 1 second (FEV₁) values at 120 and 240 minutes.
and scored significantly higher on a posttreatment quality of life questionnaire. Nebulized sodium bicarbonate failed to demonstrate a benefit in the treatment of chloramine gas exposure. 

**ROLE IN RENAL PROTECTION**

**Contrast Media**

Although multiple meta-analyses suggest that hydration with sodium bicarbonate prevents contrast-induced nephropathy (CIN), other studies suggest no benefit. A randomized trial of 119 patients compared an infusion of 154 mEq/L of either sodium bicarbonate or sodium chloride before (3 mL/kg for 1 hour) and after (1 mL/kg/h for 6 hours) iopamidol administration. CIN, defined as a 25% or greater increase in serum creatinine concentration within 2 days of contrast, occurred in eight patients in the sodium chloride group and one patient in the sodium bicarbonate group. In another study comparing sodium bicarbonate with sodium chloride before emergency coronary angiography or intervention, the incidence of CIN was also significantly lower in the sodium bicarbonate group than in the sodium chloride group (7% vs. 35%). However, in another recent study, an equal number of patients from the sodium bicarbonate and sodium chloride groups developed CIN. It is suggested that increasing renal medullary pH with sodium bicarbonate infusion might protect the kidneys from oxidant injury by slowing free radical production. Although the addition of N-acetylcysteine to a sodium chloride hydration regimen to prevent CIN does not appear to offer any benefit compared with the use of only sodium chloride hydration, the use of N-acetylcysteine and sodium bicarbonate together provides benefit compared with N-acetylcysteine and sodium chloride hydration. Whether N-acetylcysteine plus sodium bicarbonate is superior to sodium bicarbonate alone remains unproven.

**Other Indications**

Adverse effects and safety concerns may be associated with the dissociation of the dimercaprol (British anti-Lewisite {BAL}) metal binding that occurs in acid urine. Because dissociation of the BAL–metal chelate occurs in acidic urine, the urine of patients receiving BAL should be alkalinized with hypertonic sodium bicarbonate to a pH of 7.5 to 8.0 to prevent renal liberation of the metal. Sodium bicarbonate may provide a renal protection benefit after exposure to depleted uranium. Animal studies suggest that sodium bicarbonate in conjunction with a chelator such as deferiprone may accelerate uranium excretion and reduce uranium nephrotoxicity.

**ADVERSE EFFECTS AND SAFETY ISSUES**

The use of sodium bicarbonate has associated risks. Concerns regarding excessive alkalemia, hypernatremia, fluid overload, hypokalemia, and hypocalcemia have all been raised. The package insert urges caution in patients with congestive heart failure, severe renal insufficiency, and preexisting edema with sodium retention. Regarding its use to treat salicylism, early on, patients with pure respiratory alkalosis often have alkaluria and alkalemia and do not require urinary
alkalinization. Young children who rapidly develop metabolic acidosis often require alkalinization but should be at less risk for complications of this therapy. However, because hypertonic sodium bicarbonate has been reported to cause hypernatremia, decreased cerebrospinal fluid pressure, and possible intracranial hemorrhage in children younger than 2 years, the 4.2% solution may be preferred in these patients. Extravasation has been reported to cause local tissue damage. Dobutamine and norepinephrine are incompatible with sodium bicarbonate solutions, and calcium solutions may cause precipitation.

PREGNANCY AND LACTATION

According to the Food and Drug Administration (FDA), sodium bicarbonate is a Category C drug. The World Health Organization rates sodium bicarbonate as compatible with breastfeeding.

DOsing AND Administration

For the treatment of QRS prolongation in the setting of myocardial sodium channel poisoning, 1 to 2 mEq/kg of sodium bicarbonate should be initially administered IV as a bolus over a period of 1 to 2 minutes. Greater amounts may be required to treat patients with unstable ventricular dysrhythmias. Similar boluses can be repeated as needed to achieve a blood pH of 7.50 to 7.55. Because sodium bicarbonate has a brief duration of effect, a continuous infusion usually is required after the initial IV boluses. The treatment endpoint is the narrowing of the QRS interval. Excessive alkalemia (pH >7.55) and hypernatremia should be avoided. To prepare a sodium bicarbonate infusion three 50 mL ampules should be placed in 1 L of 5% dextrose in water (D.W) and run at twice maintenance with frequent checks of QRS, potassium, and pH depending on the fluid requirements and blood pressure of the patient. Frequent evaluation of the fluid status should be performed to avoid precipitating pulmonary edema. An optimal duration of therapy has not been established.

For the treatment of salicylate poisoning, sodium bicarbonate can be administered by bolus or infusion using the dosing strategies described earlier until the urinary pH approaches 8. Careful and frequent monitoring of the urinary pH and serum potassium is critical to ensure optimal treatment. In salicylate-poisoned patients with altered mental status, aggressive administration of sodium bicarbonate may be required to ensure that the serum pH is greater than at least 7.40 to 7.45.

FORMULATIONS

The most commonly used sodium bicarbonate preparations are an 8.4% solution (1 M) containing 1 mEq each of sodium and bicarbonate ions per milliliter (calculated osmolarity of 2000 mOsm/L) and a 7.5% solution containing 0.892 mEq each of sodium and bicarbonate ions per milliliter (calculated osmolarity of 1786 mOsm/L). Fifty-milliliter ampules of the 8.4% and 7.5% solutions therefore contain 50 and 44.6 mEq of sodium bicarbonate, respectively. The common infant formulation is a 4.2% solution packaged as a 10 mL injectable ampule. This yields 5 mEq per container (0.5 mEq each of
sodium and bicarbonate ions per mL). According to the package insert, the FDA approved indications for sodium bicarbonate include the “treatment of certain drug intoxications, including barbiturates (where dissociation of the barbiturate-protein complex is desired), in poisoning by salicylates or methyl alcohol, and in hemolytic reactions requiring alkalinization of the urine to diminish nephrotoxicity of blood pigments. Urinary alkalinization is also used in methotrexate therapy to prevent nephrotoxicity.”

**SUMMARY**

- **Sodium bicarbonate** remains an important antidote in the treatment of a wide variety of xenobiotic exposures.

- **Sodium bicarbonate** is effective in patients poisoned by myocardial sodium channel blockers by providing sodium through its effects on drug ionization and subsequent diffusion from the sodium channel binding site.

- **Sodium bicarbonate** is effective for salicylates, phenobarbital, methotrexate, and other weak acids because of its ability to “ion trap” in blood or urine compartments and mitigate target organ accumulation.

- Nebulized sodium bicarbonate may be effective in neutralizing inhaled acids such as chlorine gas.

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