Intravenous Sodium Bicarbonate

Recommendations and information provided in Drug Shortage Alerts are compiled by experts in the field. Practitioners always are advised to consult with staff to ensure response to any drug shortage is in line with internal policies and procedures.

Summary

- Intravenous sodium bicarbonate syringes and vials are affected by this shortage, caused in part by a manufacturer discontinuation. The American Society of Health-System Pharmacists offers general details on the overall shortage.
- This summary provides information on the shortage’s impact in the intensive care unit specifically, providing management strategies, pharmacotherapeutic considerations, and safety considerations.
- The recommendations provided are based on a combination of the current evidence as well as the need for conservation during this shortage.
- A detailed, cited review is included here.

Pharmacotherapeutic Considerations

- The use of intravenous sodium bicarbonate and management strategies in the setting of shortages is indication-dependent. Please refer to the detailed review for more information.
- Sodium acetate is given as an alternative; however, it is also on shortage and supplies are sporadic. Trometamol (tris-hydroxymethyl aminomethane or THAM) is not commonly used (and therefore not expected to be in abundant supply). Given the limitations in the setting of renal insufficiency, as well as its adverse effect profile, this agent is not appropriate for all patients.

Safety implications

- Lack of prefilled syringes in code boxes may present safety issues in emergent situations.
- Use of alternatives that are not commonly used presents safety concerns and a potential for errors throughout the entire medication use process. As such, a heightened awareness for errors is warranted during the prescribing, preparation, and administration processes.
## Management Strategies

<table>
<thead>
<tr>
<th>Select Indications in the Critically Ill</th>
<th>Recommendation</th>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of contrast-induced nephropathy in those at risk</td>
<td>0.9% NaCl 1 mL/kg/h for 6-12 h before and 6-12 h after procedure</td>
<td>Use of sodium bicarbonate associated with mixed results; studies have differing therapeutic end points</td>
</tr>
<tr>
<td></td>
<td>For emergent procedures: 0.9% NaCl 3 mL/kg bolus, followed by 1 mL/kg/h for 6-12 h after procedure</td>
<td>Identify patients at high risk and minimize modifiable risks (concomitant nephrotoxins, etc.)</td>
</tr>
<tr>
<td>Urinary alkalinization to enhance drug elimination</td>
<td>Optimal alternatives will be agent-specific; see review for details</td>
<td>Evidence to support use of sodium bicarbonate is limited for most agents, with the best data in relation to enhancing elimination of high-dose methotrexate</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>Aggressive resuscitation with 0.9% NaCl</td>
<td>Sodium bicarbonate offers no significant improvement over aggressive fluid resuscitation with 0.9% NaCl</td>
</tr>
<tr>
<td>Hyperkalemia (acute management)</td>
<td>Insulin 10 units IV push with 50% dextrose 50 mL +/- inhaled β&lt;sub&gt;2&lt;/sub&gt; agonists</td>
<td>Sodium bicarbonate therapy has little use in the routine treatment of hyperkalemia unless severe metabolic acidosis is present</td>
</tr>
<tr>
<td>Sepsis-induced acidosis</td>
<td>Sodium bicarbonate not recommended in patients with pH ≥7.15</td>
<td>Studies do not support that sodium bicarbonate enhances catecholamine effectiveness</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>Sodium bicarbonate not recommended</td>
<td>Treat underlying shock/source of acidemia</td>
</tr>
<tr>
<td>Alternative buffers</td>
<td>THAM and sodium acetate may be considered in select patients with severe acidemia</td>
<td>Avoid THAM in patients with renal insufficiency</td>
</tr>
</tbody>
</table>
Use sodium acetate with caution in patients with hepatic dysfunction

| IV, intravenous; THAM, trometamol |

Impact on Intensive Care
- Lack of availability of a buffering solution can present challenges for the management of acidotic patients, potentially resulting in prolonged acidosis and the subsequent physiologic effects, which may include but are not limited to: depression of myocardial contractility, tachycardia, vasoconstriction, dysrhythmias, and central nervous system depression.
- Outsourcing the production of sodium bicarbonate syringes and continuous infusions (a strategy some pharmacies may employ to obtain more supply) can represent increased drug acquisition costs.

Contributors
Farooq Bandali, PharmD, BCPS
Michael Bentley, PharmD, FCCM
Katie Burenheide, MS, PharmD, BCPS
Emily Hutchinson, PharmD, BCPS
Rachel Kruer, PharmD, BCPS
John Lewin, PharmD, MBA
Liz Ramos, BS, PharmD, BCPS

Reviewers
Gail Gesin, PharmD
Nicholas Ward, MD, FCCM
Scott Bolesta, PharmD, BCPS
Antoinette Spevetz, MD, FCCM, FACP
Intravenous Sodium Bicarbonate Shortage: Alternative Strategies for the ICU

Contributors
Farooq Bandali, PharmD, BCPS
Michael Bentley, PharmD, FCCM
Katie Burenheide, MS, PharmD, BCPS
Emily Hutchinson, PharmD, BCPS
Rachel Kruter, PharmD, BCPS
Liz Ramos, BS, PharmD, BCPS

Reviewers
Scott Bolesta, PharmD, BCPS
Gail Gesin, PharmD
Judi Jacobi, PharmD, FCCM, FCCP, DPNAP, BCPS
John Lewin, PharmD, MBA
Antoinette Spevetz, MD, FCCM, FACP
Nicholas Ward, MD, FCCM

In 2012, healthcare systems continue to be challenged with drug shortages and are forced to make decisions regarding allocation of scarce resources. In making these difficult decisions, clinicians are turning to the literature more than ever, seeking alternatives and reappraising the evidence. Given the current sporadic availability of intravenous sodium bicarbonate, the Society of Critical Care Medicine Drug Shortages Task Force has compiled this evidence-based resource, providing a brief summary of current evidence for alkali therapy in select conditions in the critically ill. It is intended to serve as a resource for members in managing this shortage at their institutions. The recommendations combine the current evidence with the need for conservation during this shortage.

Contrast-Induced Nephropathy

Extracellular volume expansion is beneficial for patients at risk for contrast-induced nephropathy (CIN). The best agent to use depends on the patient population or clinical situation. Comparing trials that investigate isotonic saline or isotonic sodium bicarbonate is challenging due to several factors, including timing of fluid administration and defined outcome. For example, several investigators have shown no difference in mortality or the need for renal replacement therapy with either therapy even though their primary objective (a decreased incidence of CIN) was met. Identifying those at greatest risk is imperative (e.g., preexisting renal disease, hypertension, diabetes mellitus, heart failure, hypovolemia, elderly, concomitant nephrotoxins) in order to limit contrast exposure and avoid known nephrotoxins. In high-risk patients, contrast agents with a high osmolarity may be more likely to cause CIN. Iso-osmolar nonionic contrast agents have a lower risk compared with these older (hyperosmolar ionic) and second-generation (low-
In addition to the use of iso-osmolar nonionic contrast agents at the lowest dose possible, CIN prevention strategies also should consider isotonic saline for volume expansion, minimizing or spacing repeated procedures, prevention of volume depletion, and avoidance of nephrotoxins (e.g., nonsteroidal anti-inflammatory drugs). The choice of a preferred hydration solution is not clear. In the face of a national sodium bicarbonate shortage, a reasonable approach for planned procedures is to administer 0.9% sodium chloride, 1 mL/kg/h, beginning 6 to 12 hours before the procedure and continuing for 6 to 12 hours afterwards. For patients who require urgent or emergent procedures, a reasonable choice may be 0.9% sodium chloride with or without a 3 mL/kg bolus, depending on volume status, followed by 1 mL/kg/h started as soon as possible and continuing for 6 to 12 hours.

**Urinary Alkalinization to Enhance Drug Elimination**

Urinary alkalinization is defined as increasing urinary pH to ≥7.5. Intravenous sodium bicarbonate has been used for this purpose to treat toxicity from phenobarbital, salicylates, methotrexate, and chlorophenoxy herbicides. The strongest supporting evidence is in patients receiving high-dose methotrexate. Raising the urinary pH significantly increases methotrexate solubility, which prevents precipitation and increases elimination to minimize the risk of nephrotoxicity. Acetazolamide has been studied as an alternative to sodium bicarbonate in such cases. In a small, nonrandomized, single-arm study, the urinary pH was maintained ≥7.5 for approximately 30 hours utilizing oral or intravenous (IV) acetazolamide, 500 mg every 6 hours. After this point, 46% of patients required an intermittent dose of IV sodium bicarbonate to maintain the urinary pH at goal. Based on these results, acetazolamide may initially be effective at alkalinization, but co-administration with oral sodium bicarbonate may be necessary to prevent the development of low serum bicarbonate concentrations and the subsequent reduction in urinary pH seen after 30 hours. Another potential alternative to IV sodium bicarbonate is IV sodium acetate. Although comparative data are lacking, sodium acetate theoretically would alkalinize the urine similarly to sodium bicarbonate in patients without severe hepatic failure. Oral sodium bicarbonate or other oral forms of alkali therapy (e.g., citrate salts) may also be titrated to the target urinary pH in advance of treatment with high-dose methotrexate.

Alkalinization of the urine may also be used with severe, symptomatic salicylate overdose where hemodialysis is not available or contraindicated. Intravenous sodium bicarbonate in severe salicylate toxicity will increase renal elimination when the urinary pH is maintained at ≥7.5. Sodium bicarbonate-induced serum alkalemia may reduce the risk of severe central nervous system toxicity by shifting salicylates from tissue to the blood. Acetazolamide should not be administered as an alternative as the potential resulting metabolic acidosis can increase salicylate toxicity. For toxicity associated with phenobarbital, multiple-dose activated charcoal (MDAC) is the most efficient method of reducing serum concentrations. A study comparing three treatment groups (MDAC, IV sodium bicarbonate, and a combination of the two) found that enhanced elimination of serum phenobarbital concentrations was most profound with
use of MDAC given every 4 hours until phenobarbital concentrations were no longer toxic.\textsuperscript{17} The addition of IV sodium bicarbonate to MDAC and IV sodium bicarbonate alone were less effective. Therefore, IV sodium bicarbonate should be avoided for the treatment of phenobarbital overdose with MDAC as it may lead to a reduced efficacy of MDAC.\textsuperscript{13}

Evidence supporting urinary alkalinization for treatment of chlorophenoxy herbicide toxicity is limited. In patients with life-threatening levels, renal elimination may be increased by decreasing passive reabsorption in the nephron.\textsuperscript{11-13} As in salicylate toxicity, alkalinization of the serum and urine may “trap” chlorophenoxy compounds, reducing the negative effects of herbicide overdoses.\textsuperscript{13} Use of sodium acetate, if available, may achieve similar effects.

**Rhabdomyolysis**

The benefit of urinary alkalinization with IV sodium bicarbonate in the setting of rhabdomyolysis is controversial. The theoretical benefits are prevention of tubular cast development, reduction in urate crystallization from hyperuricemia, and avoidance of free-radical cellular damage leading to nephrotoxicity.\textsuperscript{18,19} However, sodium bicarbonate has not been shown to have a significant benefit over aggressive fluid resuscitation with saline in the prevention of renal failure. Studies assessing sodium bicarbonate for rhabdomyolysis have been small and retrospective, and have significant confounding variables that may have affected results.\textsuperscript{18,20-23} Intravenous sodium bicarbonate may have a limited role in rhabdomyolysis for patients who develop a hyperchloremic metabolic acidosis secondary to large-volume 0.9% sodium chloride administration.\textsuperscript{19} Given the limited amount of evidence suggesting benefit, however, aggressive resuscitation with saline is preferred, reserving IV sodium bicarbonate for more critical indications where the benefit has been more clearly demonstrated.

**Hyperkalemia Management**

Hyperkalemia is most commonly cause by renal insufficiency and/or medications (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, spironolactone). Other causes include cell death (e.g., rhabdomyolysis, tumor lysis, burns, hemolysis), excessive intake, and metabolic disturbances. Severe hyperkalemia can cause flaccid paralysis and lethal arrhythmias that require aggressive management. Goals of treatment are to antagonize the effects of potassium on excitable cell membranes, redistribute extracellular potassium into cells, and enhance elimination of potassium from the body.\textsuperscript{24}

Hyperkalemia produces classic electrocardiographic (EKG) changes, which include peaked T waves, widening of the QRS complex, loss of the P wave, “sine wave” confirmation or ventricular fibrillation and asystole. These changes may be modified by factors such as extracellular fluid pH, calcium concentration, sodium concentration, and the rate of rise of plasma potassium concentration. Exogenous calcium directly antagonizes the myocardial effects of hyperkalemia without lowering potassium, even in patients who have normocalcemia.\textsuperscript{25} Those with concomitant digoxin toxicity should not receive calcium due to potentiation of the effects of digoxin. Calcium and digoxin co-
administration is contraindicated. Hypertonic 3% sodium chloride may be of benefit in hyperkalemic patients with hyponatremia and electrocardiographic changes, but clinicians should assess them for potential volume overload with this therapy. The role of hypertonic 3% sodium chloride has not been established in eunatremic patients with hyperkalemia.

Review articles suggest the best strategy to redistribute extracellular potassium intracellularly is to administer an IV insulin infusion with dextrose and inhaled \( \beta_2 \) agonists (albuterol or levalbuterol). Hemodialysis remains the most reliable tool for removing potassium from the body in patients with kidney failure. Other agents that have been used to reduce potassium in emergent situations include aminophylline and sodium bicarbonate. Aminophylline is effective for acute treatment of hyperkalemia but less effective than an insulin-dextrose infusion. Sodium bicarbonate is less effective than insulin-dextrose and albuterol in lowering potassium levels. Loop diuretics and/or resins enhance potassium elimination. Forced diuresis with a loop diuretic (e.g., furosemide) causes the excretion of potassium. Resins, such as sodium polystyrene, exchange sodium for potassium in the gastrointestinal tract. For every 1 g of sodium polystyrene administered, approximately 1 mEq of potassium is removed. Sodium polystyrene should be administered with sorbitol to help prevent constipation. While these agents are part of the overall management of hyperkalemia, they are not indicated for acute management and are not considered replacements for sodium bicarbonate.

**Sepsis-Induced Acidosis**

The use of sodium bicarbonate for acute metabolic acidosis in the critically ill has been long debated. Some have argued that its use in severe acidemia is both ineffective and potentially harmful. Others have suggested that alkali therapy should be the standard of care for patients with severe acidosis.

Lactic acidosis is a common complication in patients presenting with severe sepsis. Animal studies suggest that metabolic acidosis is associated with cardiac dysfunction. For example, a drop in pH (from 7.4 to <7.2) may cause a decrease in cardiac output, contribute to vasodilatation, and ultimately lead to hypotension. However, the most recent Surviving Sepsis Campaign (SSC) guidelines recommended against the use of sodium bicarbonate in patients with lactic acidosis and pH ≥7.15 (grade 1B). Because of insufficient data, sodium bicarbonate has not been recommended for severe acidosis (pH <7.15). Two small studies comparing saline and sodium bicarbonate failed to show any meaningful benefit in the small number of patients with pH <7.15. Additionally, although acute metabolic acidosis is believed to induce catecholamine resistance, these studies did not reveal any reduction in vasopressor requirement when sodium bicarbonate therapy was administered.

The key to correction of acidemia is treatment of the underlying process. Some have suggested the use of sodium bicarbonate in patients with severe metabolic acidosis (pH <7.1) and evidence of cardiovascular compromise. Unfortunately, these recommendations are not based on firm evidence. At this time, there is insufficient
information to routinely recommend the use of sodium bicarbonate in patients with sepsis-induced severe acidosis.

**Sodium Bicarbonate Therapy in Diabetic Ketoacidosis**

Diabetic ketoacidosis (DKA) is caused by reduced insulin levels, decreased glucose utilization, and increased gluconeogenesis from elevated counter-regulatory hormones, including catecholamines, glucagon, and cortisol. DKA primarily affects patients with type 1 diabetes, but also may occur in type 2 diabetes.40

Current reviews do not recommend the use of sodium bicarbonate therapy in DKA.40-45 Insulin therapy increases the plasma bicarbonate concentration by inhibiting lipolysis and ketone production and promoting the regeneration of bicarbonate. Exogenous bicarbonate therapy has been shown to worsen hypokalemia and intracellular acidosis, delay ketone-anion metabolism, and possibly produce a paradoxical central nervous system acidosis, hypoxemia, and increased acetoacetate levels.46 No published trials have demonstrated a mortality difference with or without bicarbonate use in DKA; however, most excluded patients with severe metabolic acidemia.41

In one case-control study, 61 patients with DKA and cerebral edema (CE) were identified.47 Variables that were associated with CE were lower partial pressures of arterial carbon dioxide and higher serum urea nitrogen concentrations compared with the matched control and random control groups. Bicarbonate treatment was the only therapeutic variable associated with greater risk of CE. To ensure that physicians were not administering bicarbonate in response to deteriorating mental status, Glaser et al evaluated the timing of bicarbonate administration in relation to the onset of CE symptoms.47 When compared to the matched control group, the same number of patients in the cerebral edema group had neurological deterioration within 2 hours of administering bicarbonate. No studies have examined the risk of CE in the adult population, as CE has been rarely reported.47

A more recent systematic review concluded that the evidence does not support the use of bicarbonate for the emergent treatment of DKA, especially in the pediatric population, in view of possible clinical and physiological harm and the lack of clinical or sustained physiological benefits. The evidence is insufficient to recommend bicarbonate administration in more extreme DKA (pH <6.9).41

**Alternative Buffers to Sodium Bicarbonate**

Trometamol (tris-hydroxymethyl aminomethane or THAM), an amino alcohol and weak alkali (pKa=7.8), reduces arterial [H+] and increases the bicarbonate concentration through hydration of CO₂.48-50 THAM has been shown to improve contractility and relaxation in animal heart models, which may be explained by this CO₂ consuming effect.49, 50 It rapidly distributes to the extracellular space and quickly restores pH and acid-base regulation; at steady state, it slowly penetrates cells and acts as a direct intracellular buffer.48,49 THAM is minimally metabolized and its protonated form is excreted renally.48,49 The initial loading dose of THAM acetate may be estimated using the following formula:
THAM (mL of 0.3 mol/L solution) = lean bodyweight (kg) x base deficit (mmol/L).

An IV dose of 250 mL is expected to produce a degree of buffering similar to that of 75 mEq sodium bicarbonate. The maximum daily dose is 15 mmol/kg for an adult (or approximately 3.5 L of a 0.3 mol/L solution). THAM has potential side effects that include hypoglycemia, hyperkalemia, hyponatremia, and extravasation-related necrosis (less extravasation risk with THAM acetate, the formulation available in the United States), and the risk of these adverse events is magnified at supratherapeutic doses. The use of THAM should be avoided in patients with renal insufficiency. Acid-base status, ventilation, electrolytes, and glucose should be monitored closely when THAM is administered.

Sodium acetate, an alkalinizing salt, was first substituted for sodium bicarbonate as a hemodialysis fluid bath, and it has since been studied as a continuous infusion for the slow correction of a metabolic acidosis. Unfortunately, use as a hemodialysis fluid bath may cause hemodynamic instability. In a recent study of 78 trauma patients who received continuous infusions of sodium acetate for fluid resuscitation, no difference in hemodynamic instability was noted between the sodium acetate- and sodium chloride-treated patients; however, a faster resolution of acidosis was observed in those who received sodium acetate versus the sodium chloride control group. The rate of sodium acetate buffering effect is determined by hepatic oxidization of acetate to bicarbonate.

Patients with hepatic dysfunction are at higher risk of developing an elevated lactate levels with sodium acetate infusion.

In summary, both THAM and sodium acetate are viable alternatives to sodium bicarbonate in the treatment of metabolic acidosis under certain conditions. Sodium acetate is also in short supply in many regions in the United States. In addition, THAM is considerably more expensive than sodium bicarbonate. These factors, as well as the patient-specific characteristics, should be considered in selecting treatment.

References


