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REVIEW ARTICLE

Sodium Acetate as a Replacement for Sodium Bicarbonate in Medical Toxicology: a Review

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Abstract Sodium bicarbonate is central to the treatment of many poisonings. When it was placed on the FDA drug shortage list in 2012, alternative treatment strategies to specific poisonings were considered. Many hospital pharmacies, poison centers, and medical toxicologists proposed sodium acetate as an adequate alternative, despite a paucity of data to support its use in medical toxicology. The intention of this review is to educate the clinician on the use of sodium acetate and to advise them on the potential adverse events when given in excess. We conducted a literature search focused on the pharmacology of sodium acetate, its use as a buffer in pathologic acidemia and dialysis baths, and potential adverse events associated with excess sodium acetate infusion. It appears safe to replace sodium bicarbonate infusion with sodium acetate on an equimolar basis. The metabolism of acetate, however, is more complex than bicarbonate. Future prospective studies will be needed to confirm the efficacy of sodium acetate in the treatment of the poisoned patient.

Keywords Sodium acetate · Sodium bicarbonate · Antidote · Drug shortage

Introduction

A shortage of sodium bicarbonate reported by the FDA in March 2012 arose from a "demand increase" in the drug [1]. The shortage recovered for the majority of sodium bicarbonate products during the first and second quarter of 2013, but drug shortages have increasingly plagued the medical community over the last several years, and future product availability remains unpredictable for sodium bicarbonate. Shortages of drugs such as diazepam, metoclopramide, ondansetron, phenytoin, and etomidate that have a great impact on emergency patient care are increasingly prevalent [1]. Effective alternatives exist when most common medications are in short supply. Sodium bicarbonate is unique as a therapeutic agent; even though it is a vital intervention in the treatment of several poisonings, it has no clearly accepted alternative in clinical use. Primary outcomes in sodium bicarbonate therapy include serum alkalinization, urine alkalinization, and sodium ion loading. Recommendations for a replacement antidote when sodium bicarbonate is unavailable have not been disseminated in the literature. The goal of this review is to enhance the understanding of sodium acetate pharmacology and to connect what we know of sodium acetate to its use in the management of specific poisonings during sodium bicarbonate drug shortages.

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Methods

We conducted an iterative search of the MEDLINE database using search terms "sodium acetate," "sodium bicarbonate," "drug shortage," "serum alkalinization," and "urine alkalinization" through January 2013. Non-English language manuscripts were excluded. The "related citations" feature was used to retrieve further references. Two authors reviewed titles and abstracts of all potential articles and selected those most pertinent to the use of sodium acetate in medical toxicology.

Sodium Bicarbonate in Medical Toxicology

The ideal replacement for sodium bicarbonate in medical toxicology applications should provide alkaline pH buffering

as well as additional sodium ions. Administration of sodium bicarbonate produces a transient increase in sodium ion concentration, while its buffering action raises serum and urine pH. In medical toxicology practice, sodium bicarbonate is most commonly used in the treatment of tricyclic antidepressant (TCA) and salicylate poisoning; it is also effective as an adjuvant therapy for cocaine-induced ventricular dysrhythmias [2] and poisonings with quinine, chloroquine, and other type 1A and 1C antidysrhythmics [3]; methanol and ethylene glycol [4]; 2,4-dichlorophenoxyacetic acid and other chlorphenoxy herbicides [5, 6]; and chlorine gas [7]. The rationale for sodium bicarbonate's therapeutic use varies by poisoning agent. When used for severe TCA poisoning, sodium bicarbonate raises the serum pH, increases the proportion of non-ionized drug, and putatively decreases binding of the TCA molecules to sodium channels [8, 9]. Injected sodium bicarbonate provides additional sodium ions and increases the sodium concentration gradient through the ion channel [9]. In contrast, the treatment of salicylate poisoning is more complex; the clinical endpoint of sodium bicarbonate infusion is to alkalinize urine to pH 7.5 or greater, which enhances salicylate elimination [10]. Sodium acetate has similar effects on serum and urine pH, as well as sodium ion concentration, and serves as a potential replacement for sodium bicarbonate in times of shortage.

Sodium Acetate Use in Acid–Base Disorders

Several lines of evidence converge to suggest comparable efficacy of sodium acetate with that of sodium bicarbonate as a buffer in the correction of severe acidemia associated with metabolic acidosis [11–13]. First, comparison of acetate and bicarbonate infusions demonstrated equal efficacy in the correction of acidemia of uremic acidosis without adverse hemodynamic instability [11]. Second, sodium acetate is also effective in the correction of acidemia secondary to diarrhea [12]. Finally, sodium acetate has been used in the treatment of hyperchloremic acidosis in trauma patients [13]. None of these studies link infusion of sodium acetate with hypotension or other adverse events historically associated with sodium acetate dialysate. The data are, however, limited regarding the safety or efficacy of sodium acetate in medical toxicology applications.

Pharmacology of Sodium Acetate

Acetate is the conjugate base of acetic acid and is used as a buffer in many biochemical applications. In vitro, the Brønsted–Lowry concept would describe acetate as a proton acceptor; in vivo, the increase in serum pH by sodium acetate infusion is more completely understood by Stewart's approach to acid–base homeostasis [14, 15]. In brief, a solution that increases the body's strong ion difference (the concentration of strong cations minus strong anions) will increase serum pH [15]. After injection and cellular uptake, the two-carbon acetate anion forms acetyl CoA and enters the citric acid cycle; the final by-products, carbon dioxide and water, are in a rapid equilibrium with bicarbonate through the catalyst activity of carbonic anhydrase [16, 17]. Thus, the infusion of sodium acetate increases the strong ion difference by causing a net increase in cations, as the acetate anion is metabolized out of the system. Based on Stewart's theory, the increased strong ion difference leads to alkalemia. This is the basis for many balanced crystalloid solutions that use acetate (Plasma-Lyte®) or lactate (lactated Ringer's solution) to partially replace chloride anions. Sodium bicarbonate infusion can be thought of in a similar manner, whereby the end result is added sodium cations, an increased strong ion difference, and, in turn, increased pH. Sodium bicarbonate metabolism, however, is dependent on the near instant catalyst action of the ubiquitous enzyme, carbonic anhydrase. In contrast, acetate has numerous and complex metabolic pathways; this may reflect adverse events associated with sodium acetate overload.

Sodium acetate metabolism was thought to occur primarily in the liver, but that has been disproved by several studies [18, 19]. Schumann et al. measured metabolic products of labeled acetate to assess the citric acid cycle and gluconeogenesis in the human liver [19]. The results of this analysis were inconsistent with hepatic metabolism alone, and the authors conclude that acetate cannot be used as a marker for gluconeogenesis or citric acid cycle activity in the liver. Acetate metabolism occurring in skeletal muscle accounts for the observation that liver disease does not adversely affect the handling of infused sodium acetate [19, 20].

Studies regarding the disposition of sodium acetate were primarily derived from the nephrology literature of 30 to 40 years past, when the drug was most commonly used as a dialysate buffer. Of note, the sodium acetate load during dialysis is much larger than that during standard intravenous infusion, and adverse events reported with dialysis may not parallel sodium acetate infusions in medical toxicology. This is highlighted by Tolchin et al. who suggested that sodium acetate used during dialysis may saturate its metabolic pathways; in a single dialysis treatment using a 40-mM sodium acetate bath and lasting 4 h, approximately 90 % of the acetate load is converted to bicarbonate [21]. Under these conditions, the authors calculated a maximum metabolic threshold of 48 μM/min/kg body weight [21]. As the sodium acetate load exceeds this level, acetate levels increase without an equimolar rise in bicarbonate. This rate of infusion translates to approximately 200 mM per h for a 70-kg person. A sodium acetate solution of 150 mEq in 1 L D5W infused at 200 mL/h would provide 30 mM per h, well below this theorized threshold of acetate metabolism. In

Table 1 Serum alkalinization with sodium acetate

	Indications and goals of therapy	Sodium bicarbonate	Sodium acetate
Bolus	Initial rapid treatment of QRS widening, severe cardiac arrhythmias, and salicylism; goal serum pH 7.5–7.55	1–2 mEq per kg body weight infused over 1–2 min	1 mEq per kg body weight infused over 15–20 min
Maintenance infusion	Maintaining alkaline serum pH (pH 7.5–7.55)	150 mEq diluted to 1 L with dextrose 5 % in water; infuse at twice the maintenance rate	150 mEq diluted to 1 L with dextrose 5 % in water; infuse at twice the maintenance rate

contrast, an intravenous bolus of 50 mEq sodium acetate given over 1–2 min (25–50 mM/min) far exceeds the body's ability to metabolize acetate. By this rationale, bolus administration of sodium acetate over a short period of time (1–2 min) may lead to acetate overload and potentially negative sequelae. We will discuss alternative bolus administration of sodium acetate later in this review.

Adverse Events from Sodium Acetate

Sodium acetate has fallen into disuse as a dialysate buffer due to adverse events associated with its administration, including myocardial depression, hypotension, and hypopnea resulting in hypoxemia [22–24]. Sodium acetate, when given in excess during dialysis, is funneled to alternative metabolic pathways, leading to increased nitric oxide concentrations and resulting hemodynamic instability [25]. Several animal studies have reported decreased systemic vascular resistance (SVR) in response to sodium acetate [26–28]. Research into the association of pooled protein fraction infusion and hypotension implicated sodium acetate, at concentrations as low as 16.8 mEq/L, as the cause of hypotension [26]. This has not been reproduced in other studies. Sodium acetate dialysate buffer, when compared head-to-head with sodium bicarbonate dialysate, consistently lowers SVR [27, 28]. Hypopnea, often in the setting of hypoxemia during dialysis with sodium acetate, may arise from loss of carbon dioxide in the absence of a bicarbonate buffer; chemoreceptors then recognize serum hypocarbia and reduce respiratory drive [22]. More recent observations include flushing reactions when sodium acetate is given by intravenous bolus; this may also represent increases in nitric oxide production arising from saturated metabolic pathways of sodium acetate. In addition, specific features of sodium acetate may complicate certain poisonings. Hyperpyrexia has been observed in patients undergoing hemodialysis with a sodium acetate bath [25]. Mechanistic studies in which sodium acetate was infused in rats identified uncoupling of oxidative phosphorylation, a finding that may theoretically complicate the treatment of salicylism. The negative sequelae associated with dialysis using sodium acetate buffer may not, however, parallel the continuous infusion of sodium acetate in medical toxicology applications. The acetate load during dialysis, as discussed previously, seems to far exceed what is given during sodium acetate infusion, but knowledge of the potential negative sequelae of sodium acetate will help clinicians when faced with an iatrogenic overdose of sodium acetate.

Dosing Recommendations for Sodium Acetate in Specific Poisonings

Sodium acetate for infusion is available in 2 and 4 mEq/mL concentrations. Sodium acetate infusion should be prepared in a similar manner to sodium bicarbonate. Dosing instructions for sodium acetate are presented in Table 1. Several features of sodium acetate administration should be noted. First, sodium acetate is diluted in dextrose 5 % water and not normal saline. In addition, the common practice of rapid bolus administration of sodium bicarbonate (over 1–2 min) in the setting of QRS widening or other consequences of sodium channel dysfunction associated with TCAs (and other type 1A and 1C antidysrhythmics) should not be replicated with sodium acetate; the rate of sodium acetate metabolism and the physiologic response to sodium acetate in high concentrations make rapid bolus potentially dangerous. When using sodium acetate as a replacement therapy for sodium bicarbonate boluses in the treatment of cardiotoxicity associated with sodium channel antagonists, we recommend slowing the bolus infusion to 15–20 min, rather than the typical 1–2 min for sodium bicarbonate. Based on the theoretical maximum metabolic rate of sodium acetate, this dosing strategy should provide a relatively rapid increase in serum pH and reduce the likelihood of acetate-induced hypotension. The added effect of increasing molar

Table 2 Urine alkalinization with sodium acetate

	Infusion	Goal of treatment
Sodium acetate	150 mEq diluted to 1 L with dextrose 5 % in water; infuse at twice the maintenance rate	Maintain urine pH of >7.5

concentration of sodium ions to enhance sodium channel activity should also be maintained at this rate of infusion. As with sodium bicarbonate, the goal of sodium acetate infusion in TCA overdose should be narrowing of the QRS complex [9]. No consensus recommendations guide the administration of sodium acetate serum alkalinization for TCA toxicity due to the paucity of prospective research. Most recommendations use a threshold of QRS of >100 ms as a trigger for treatment [29]. Similarly, goals of treatment are also ill defined, but a target pH of 7.5 to 7.55 is reasonable [29]. Physicians should consult a medical toxicologist for treatment decisions related to the use of sodium acetate in TCA toxicity.

No prospective studies evaluate the efficacy of sodium acetate infusion in urine alkalinization for salicylate toxicity. We infer from the prior literature using sodium acetate to correct acidemia; however, that sodium acetate is also capable of producing adequate alkaluria to increase renal salicylate excretion. A recent case report describes using sodium acetate, during the bicarbonate shortage, to alkalinize the urine for salicylate elimination [30]. The authors successfully treated the patient and achieved adequate urine alkalinization, without ill consequence. Dosing instructions for sodium acetate in urine alkalinization are found in Table 2. Urine alkalinization is indicated for symptomatic patients with elevated salicylate levels and adequate renal function [31]. Goal of therapy is to increase urine pH to 7.5. Sodium acetate infusion is not a replacement for early hemodialysis or aggressive volume replacement in severe overdoses, and maintaining an adequate urine output is tantamount to expedient salicylate clearance.

There are no reports of sodium acetate maintenance infusion causing severe adverse events, but its use in hemodialysis suggests that hypotension is a potential complication [13, 14, 30]. Sodium acetate infusion decreases systemic vascular resistance, while TCA cardiotoxicity decreases myocardial contractility. These cumulative effects create conditions similar to distributive shock. Initial treatment of hypotension, therefore, should be directed at volume replacement with 0.9 % saline. Severe hypotension refractory to adequate volume expansion should be treated with norepinephrine infusion to increase systemic vascular resistance and cardiac output. Other potential pitfalls of administering an unfamiliar antidote include failing to dilute sodium acetate concentrate or using the wrong diluent, both of which would lead to administration of hypertonic solutions of sodium acetate and an excess concentration of sodium, acetate, or both. When using a new or unfamiliar antidote, the guidance of a medical toxicologist is invaluable.

Conclusion

As drug shortages become more frequent, emergency physicians must develop agile treatment paradigms for different conditions. Similarly, as medical toxicologists, we must be prepared to provide guidance when ideal antidotes are unavailable. Although the sodium bicarbonate shortage is temporarily resolved, it should serve to stimulate discussion regarding future antidote shortages. It also provides the opportunity to reevaluate a long-established treatment modality. When developing guidelines for the treatment of common poisonings, antidote shortages should be anticipated, and alternative medications should be included in the guidelines. In this way, we provide the solution before the problem develops.

We do not recommend the routine use of sodium acetate when sodium bicarbonate is available; during shortages, however, sodium acetate provides an inexpensive and apparently safe alternative. At our institution, one ampule of 50 mEq sodium bicarbonate costs $0.76, compared to one ampule of 100 mEq sodium acetate, which costs $1.25. Sodium acetate is stable in solution compared to sodium bicarbonate; a solution of sodium bicarbonate stored in a polyolefin bag begins to lose buffering capability after only 2 days due to diffusion of carbon dioxide through the bag's surface, while a solution of Plasma-Lyte® containing 27 mM/L of sodium acetate, stored in a polyolefin bag, remains stable for 3 years [32, 33]. Despite these benefits, limited data guide its use in medical toxicology practice. Physicians managing life-threatening overdoses traditionally treated with sodium bicarbonate should consult a medical toxicology service or poison control center for further guidance on the use of sodium acetate.

Conflict of Interest None.

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