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REVIEW ARTICLE

A Literature Review of the Use of Sodium Bicarbonate for the Treatment of QRS Widening

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Abstract Sodium bicarbonate is a well-known antidote for tricyclic antidepressant (TCA) poisoning. It has been used for over half a century to treat toxin-induced sodium channel blockade as evidenced by QRS widening on the electrocardiogram (ECG). The purpose of this review is to describe the literature regarding electrophysiological mechanisms and clinical use of this antidote after poisoning by tricyclic antidepressants and other agents. This article will also address the literature supporting an increased serum sodium concentration, alkalemia, or the combination of both as the responsible mechanism(s) for sodium bicarbonate's antidotal properties. While sodium bicarbonate has been used as a treatment for cardiac sodium channel blockade for multiple other agents including citalopram, cocaine, flecainide, diphenhydramine, propoxyphene, and lamotrigine, it has uncertain efficacy with bupropion, propranolol, and taxine-containing plants.

Keywords Sodium bicarbonate · Electrocardiogram · QRS widening · Tricyclic antidepressants

Introduction

Sodium bicarbonate is commonly used to reverse drug-induced sodium channel blockade. It is most widely known for its use in tricyclic antidepressant (TCA) toxicity. However, there are case reports of sodium bicarbonate therapy being used to treat QRS widening on the electrocardiogram (ECG) after a wide range of exposures including citalopram, cocaine, flecainide, diphenhydramine, propoxyphene, and lamotrigine [1–8]. The mechanism for its efficacy has not been fully elucidated, and it may differ depending on the drug responsible for toxicity. Regardless of the precise mechanism, it is frequently utilized for patients with drug-induced QRS widening. The purpose of this review is to examine the evidence regarding the mechanism of action, use, efficacy, and adverse effects of sodium bicarbonate in reversing sodium channel blockade for various agents that may widen the QRS.

Methods

Potentially relevant literature was identified in the PubMed database using the search terms "QRS," "sodium bicarbonate," "conduction," "conduction delay," "infusion," and "molar sodium lactate." All searchable years (dating back to 1946) were included. Additional search terms such as "sodium channel," "hyperpolarization," and "inactivation" were used to identify articles describing electrophysiologic principles. In addition, medical toxicology and critical care textbooks were used as a source of references and search terms [9–11]. In addition, generic drug names found in primary literature describing sodium channel blockade were also used as search terms. The search was limited to articles available in English. Articles were read and reviewed by the authors to determine if they were applicable to the purpose of this article.

History of Sodium Bicarbonate Therapy

As early as 1958, there are reports of using molar sodium lactate, which is metabolized to sodium bicarbonate, to treat

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QRS widening from quinidine and procainamide poisoning in both animals and humans [12–14]. Molar sodium lactate is first described in the literature for human use in 1955 by Bellet et al. for bradycardia, Stokes-Adams syndrome, and cardiac arrest [15]. Four years later, Bellet et al. published a brief report of molar sodium lactate narrowing the QRS in a quinidine toxic patient followed by a study showing similar effects in dogs. Bellet et al. postulated that the increase in pH resulting in hypokalemia improved conduction after quinidine toxicity [13]. However, Bailey hypothesized in his case reports of using molar sodium lactate for quinidine toxicity that the increase in sodium concentration was important for its effect [14]. The controversy of whether or not the effectiveness of sodium bicarbonate was due to sodium or alkalemia would continue to be debated in the following decades [16–18].

During the 1980s, the discussion of how to predict toxicity from TCAs was also debated during this period. Literature in the 1970s and early 1980s suggested that the serum concentration could be useful in determining clinical toxicity [19–21]. This hypothesis was challenged by Boenhert and Lovejoy's landmark study which has subsequently changed the focus of determining toxicity [22]. QRS widening became the standard measure for determining treatment thresholds with sodium bicarbonate although the precise QRS duration used to start therapy does vary by practitioner [23]. Furthermore, sodium bicarbonate is described in treatment protocols during the 1980s and 1990s [24, 25]. Since that time, it has been used to treat QRS widening induced by multiple agents with varying success.

Cardiac Sodium Channels

Normal Physiology

The QRS complex on the ECG represents the depolarization of the ventricles through voltage-gated sodium channels and corresponds to phase 0 of the action potential. The cardiac voltage-gated sodium channel is composed of one alpha subunit, which forms the pore of the channel, and multiple beta subunits. The cardiac sodium channel alpha subunit is characterized by four domains each containing six membrane spanning segments. The domains are numbered I–IV and the segments are numbered S1–S6. The pore module is thought to be located between S5 and S6. There is an inactivation gate that is located between domains III and IV which is hypothesized to "block the inner mouth of the channel pore" [26].

The sodium channels undergo three states: closed, activated (open), and inactivated. When the membrane is at the resting potential with a negative voltage gradient, the channel is closed. Upon a stimulus from another cell, the cell depolarizes and triggers the sodium channel to open and allow the influx of sodium, which is known as the activated state. The channel then becomes inactivated through either fast inactivation or slow inactivation. When channels undergo the structural change resulting in inactivation, no amount of electrical stimulus can open the channel, and this is known as the refractory period. Slow inactivation can occur over several seconds and may serve to regulate the excitability of the cell when it is undergoing repetitive depolarizations [27]. Fast inactivation is believed to occur through a "hinged lid" mechanism from the loop located in between domains III and IV on the inside of the cell. As the membrane returns to its resting potential, potassium channels allow efflux of potassium which cause hyperpolarization of the cell. It is during this period that the sodium channel closes and the inactivation gate moves out of the pore of the channel. However, the mechanism for the exact process to allow for the channel to go from the inactivated state to closed state not been fully delineated [28–31].

Modulation of Sodium Channels by Toxins

The modulation of sodium channels by toxins can occur while the sodium channel is in all states: activated, inactivated, and closed. For example, toxins including batrachotoxin, veratridine, aconitine, and grayanotoxin bind to the activated sodium channel and slow or prevent inactivation [30]. Flecainide also appears to favor binding to the activated channel though its binding pattern is not fully understood [32]. In addition, some toxins can bind to channels in multiple states. For example, it appears that cocaine binds to a similar site in both the activated and inactivated state [33]. Local anesthetics may have a higher affinity for the fast inactivated state of the sodium channel compared to the closed state [34]. Class Ib antiarrhythmics act on primarily inactivated sodium channels and bind to the sodium channel only for a short period of time that does not exceed the length of the cardiac cycle. Class Ic antiarrhythmics have a slow time of recovery and bind to sodium channels for a much longer period of time than diastole [35]. Class Ia antiarrhythmics have intermediate onset and offset kinetics [35]. In addition, quinidine and disopyramide (Class Ia agents) may bind to the open state [36]. Interestingly, the potential effect of Class Ic antiarrhythmic binding on activated sodium channels was discovered after Vaughan Williams created the Class I sub-classifications [37].

Sodium Bicarbonate as a Treatment for Sodium Channel Blockade

Mechanism of Action

The exact mechanism by which sodium bicarbonate acts to reverse sodium channel blockade has not been fully

elucidated. Increase in sodium concentration, change in pH, or a combination of these physiological alterations may be responsible for the clinical effects. Multiple older studies examined the effect of alterations of pH and sodium on the velocity of the upstroke of the action potential (Vmax) on isolated cardiac cells or conduction system preparations [38–40]. An increase in Vmax corresponds to a decrease in the time of phase 0 and, by inference, a shorter QRS. Furthermore, the mechanism of action of sodium bicarbonate varies by toxin.

There are multiple studies that favor the increase in sodium concentration as the property of sodium bicarbonate responsible for its clinical effect. Kohlhardt et al. examined the effect of sodium concentration on guinea pig papillary muscles exposed to procaine, lidocaine, and propafenone. He showed that the tonic Vmax block by procaine, lidocaine, and propafenone increased when there was a decrease in sodium concentration [39]. McCabe et al. studied the use of hypertonic saline versus sodium bicarbonate in reducing the QRS in swine given nortriptyline and found that a hypertonic saline solution narrowed the QRS more than sodium bicarbonate. Of note, the concentration of sodium in the hypertonic saline solution was five times that of the concentration of sodium in the sodium bicarbonate solution in this study [41].

However, other studies favor alterations in pH as the more important property for reversal of sodium channel blockade. For example, Bou-Abboud and Nattel showed that only changing the pH on canine Purkinje fibers in Tyrode solution with imipramine resulted in a significant change in Vmax and no change in Vmax for increasing the sodium concentration. It also appeared that alkalosis decreased the hyperpolarizing effect of imipramine on the inactivation curve [38]. Parker et al. showed that sodium bicarbonate reduced the QRS in cocaine-poisoned dogs but that sodium chloride did not narrow the QRS [42]. A study by Stone et al. showed that treatment with trishydroxyaminomethane (THAM) in dogs for amitriptyline-induced QRS widening was effective in reducing the QRS [43]. THAM is an amino alcohol which is capable of accepting a proton and increases the blood pH with a higher buffering capacity than sodium bicarbonate. Another contributing factor to the mechanism of alkalemia in reducing QRS widening is that alkalemia increases protein binding and decreases the amount of free drug. A study by Levitt et al. demonstrated a 42 % decrease in free amitriptyline in an in vitro study using human plasma and changing the plasma pH from 7.35 to 7.83 [44]. The clinical significance of this finding is somewhat controversial [45, 46].

There are also studies which favor a combined effect of increased sodium concentration and increased pH as the mechanism of sodium bicarbonate as a treatment for sodium channel blockade. The Bou-Abboud and Nattel study described above also examined canine Purkinje fibers exposed to mexilitine and flecainide. In these studies, increasing the pH and sodium concentrations both individually and together produced a significant change in Vmax [38]. In addition, Sasyniuk et al. showed that in canine Purkinje fibers exposed to amitriptyline, the addition of sodium bicarbonate resulted in a significantly higher increase in Vmax compared to either a high sodium or high pH, low PCO_2 solution [47]. In summary, the in vitro and animal data support that both the sodium and bicarbonate have effects on the action potential which could explain the effect of reducing QRS duration in humans.

Method of Administration

Currently, there are no clear dosing guidelines or evidence regarding the preferred method of administering sodium bicarbonate with respect to boluses, infusions, or treatment duration. Proposed methods of administration include boluses of a 1 mEq per 1 mL (8.4 %) solution at a quantity of 1–2 mEq/kg to obtain a serum pH of 7.45–7.55 and an infusion of 150 mEq mixed with 1 L of 5 % dextrose in water at a rate to maintain that pH [48]. Furthermore, regarding recommendations by U.S. Poison Center medical directors, Seger et al. found that 71 % of directors recommended bolus dosing followed by infusion and 24 % of directors recommended a bolus dose alone. Seventy-eight percent recommended a bolus dose of 1–2 mEq/kg [23]. A protocol by Walsh recommended 1–3 mEq/kg bolus followed by hyperventilation if the patient was intubated to maintain a serum pH of 7.4–7.5 [49]. Hoffman et al. in their retrospective study on the use of sodium bicarbonate for cyclic antidepressants describe the use of boluses and infusions to maintain a serum pH of 7.50–7.55. The concentrations in the infusions were most often either 88 or 176 mEq/L and the rates were not specified. Of note, boluses were used without infusion in two of their patients [50]. Shannon et al. also recommend maintaining a sodium bicarbonate infusion to achieve an arterial blood pH of 7.45–7.55 for 24 hours to treat TCA cardiotoxicity [48]. Pentel and Benowitz recommended a treatment duration of 24–48 h with resolution of ECG abnormalities [26].

Indications

Antidepressants

TCAs are some of the most widely studied drugs treated with sodium bicarbonate therapy. However, the mechanism, initiation, and duration of therapy remain poorly understood. In vitro studies have demonstrated that sodium bicarbonate can increase Vmax which should correspond to a decrease in the time of phase 0 of the action potential. In addition, there are in vitro and animal studies that favor alkalosis and hypertonic sodium loading separately and in combination [38, 40, 41, 64]. Human case reports and series on treating TCA poisoning with sodium bicarbonate began in the 1970s [58, 60]. By the 1980s, sodium bicarbonate began appearing in more

general treatment guidelines and continued to be studied experimentally [40, 44, 49, 61, 80].

The point at which to begin treatment with sodium bicarbonate therapy in terms of QRS widening is not standardized. In a landmark study by Boenhart and Lovejoy, the incidence of seizures was found to be 33 % in patients who had a QRS of greater than 100 msec. In addition, the incidence of dysrhythmias was 50 % in patients who had a QRS of greater than 160 msec. However, no patients had seizures or dysrhythmias below these thresholds, respectively [22].

Concerning other antidepressants, there are case reports of sodium bicarbonate being used to treat QRS prolongation by citalopram and escitalopram [3, 53]. Lung et al. describe a case of a patient with a QRS of 160 msec after ingesting citalopram and olanzapine which narrowed to 116 msec with the administration of a 100 mEq bolus of sodium bicarbonate [54]. In addition, there is a case report of QRS widening after a fluoxetine ingestion being effectively treated with sodium bicarbonate by Graudins et al. Although the patient described also reported ingesting hydroxyzine, his comprehensive urine and serum drug screens were positive for fluoxetine, norfluoxetine, and acetaminophen and negative for hydroxyzine [67].

Bupropion causes QRS widening but may do so through a different mechanism than sodium channel blockade. Interestingly, the QRS prolongation associated with bupropion does not appear to be responsive to sodium bicarbonate therapy as described in several case reports [72–74]. With regards to a possible mechanism for this finding, Caillier et al. used patch clamp techniques to determine that bupropion did not significantly change sodium current amplitude or steady-state activation/inactivation. They used male guinea pig hearts and showed that the change in action potential from bupropion was similar to glycyrrhetinic acid and heptanol which are known to decrease cardiac intracellular coupling [75]. However, there is a study in guinea pigs where sodium bicarbonate did not show a significant effect on ECG changes induced by amitriptyline and doxepin which is contrary to human data [76]. Therefore, guinea pigs may not be an ideal model for sodium bicarbonate's effect in treating human toxin-induced QRS widening. In addition, even in earlier literature, bupropion was noted to have a different effect on the shape of the action potential in mammalian cardiac tissue [81]. This finding may explain why sodium bicarbonate is less effective in human overdose cases since the sodium channel is not significantly involved.

Antiarrhythmics

Multiple case reports demonstrate the successful use of sodium bicarbonate in the reversal of QRS widening due to numerous antiarrhythmic agents including class Ia, class Ic, and beta-blockers. For class Ia antiarrhythmics, there are case reports for the use of molar sodium lactate (metabolized to sodium bicarbonate) for quinidine and procainamide [12–14, 68]. In addition, there is a case report of procainamide toxicity resulting in pacemaker failure where sodium bicarbonate and sodium lactate were used to reverse the pacemaker latency and sensing/capture dysfunction [68]. For class Ic antiarrhythmics, Goldman et al. used a total bolus of 300 mEq sodium bicarbonate to treat a patient with flecainide poisoning resulting in ventricular tachycardia and a QRS of greater than 160 msec. After treatment, the patient's QRS narrowed to 128 msec. An infusion of 50 mEq sodium bicarbonate in an unknown amount of normal saline was continued but the duration of the infusion was not specified [66]. There are two case reports of sodium bicarbonate being used to treat QRS prolongation induced by propafenone [69, 70]. There are no in vivo studies regarding the use of sodium bicarbonate for lidocaine or mexilitine toxicity. However, the in vitro study by Bou Abboud and Nattel showed that raising the sodium concentration and pH resulted in an increase in Vmax using canine Purkinje fibers exposed to mexilitine [38].

Some beta-blockers also produce sodium channel blockade. Love et al. studied propranolol toxicity in dogs and treatment with sodium bicarbonate. While the QRS did decrease, it was not statistically significant. In addition, the control dogs who received dextrose also had a narrowing QRS with time [77]. The clinical significance of this study in humans has not been determined.

Local Anesthetics

There is scant literature regarding the use of sodium bicarbonate as an antidote for local anesthetic toxicity with the exception being cocaine. There are multiple case reports as well as animal studies showing the effectiveness of sodium bicarbonate as a treatment for cocaine-induced sodium channel blockade [6, 7, 42, 55–57]. Wang describes two cases of cocaine intoxicated patients with QRS widening being successfully treated with sodium bicarbonate. The QRS was reported in one patient at 120 msec [56]. In addition, Kalimullah and Bryant as well as Kerns et al. describe cases of severe cocaine overdose resulting in cardiac arrest being effectively treated with sodium bicarbonate [6, 55]. Dayan et al. describe three fatal cases of dibucaine poisoning in children where bicarbonate was used in two of the three cases [82]. Although lidocaine is a known sodium channel blocker, there are no reports of QRS widening being treated with sodium bicarbonate. In addition, lidocaine has been used to treat toxicity induced by other sodium channel blockers with the hypothesis that lidocaine's fast kinetics with sodium channel binding reduce the fraction of blocked sodium channels when used with a sodium channel blocker with slower kinetics [83].

Antimalarials

Sodium bicarbonate has been used to treat cardiac toxicity of chloroquine, hydroxychloroquine, and quinine with varying

Table 1 Agents where sodium bicarbonate appears to be effective

Agent	Human data (references)	Animal data (references)	In vitro data (references)
Chloroquine/hydroxychloroquine	Case report [51]	Rat study [52]	
Citalopram/escitalopram	Case reports [1, 3, 53, 54]		
Cocaine	Case reports [6, 7, 55, 56]	Canine [42, 57]	
Cyclic antidepressants	Case reports, retrospective series [19, 50, 58, 59]	Canine, rat, swine [41, 60–63]	Canine Purkinje fibers, human atrial myocytes [64]
Diphenhydramine	Case report [2, 65]		
Flecainide	Case reports [8, 66]		
Fluoxetine	Case report [67]		
Lamotrigine	Case reports [4, 5]		
Quinidine	Case report [12, 13]		
Procainamide	Case reports [12, 68]		
Propafenone	Case reports [69, 70]		
Propoxyphene	Case report [71]		

effects. Data is limited to animal studies and human case reports. Curry et al. studied sodium bicarbonate in chloroquine-poisoned rats and the QRS narrowed faster with the administration of sodium bicarbonate. Although the results were clinically significant, the results showed only an overall mild difference in the rate of narrowing (0.23 msec/min) [52]. Gunja et al. describe hydroxychloroquine toxicity resulting in QRS prolongation in two patients being treated with sodium bicarbonate. Both patients survived the overdose; however, they were each treated with potassium and epinephrine and one patient was also given high dose diazepam [51]. Sodium bicarbonate has been described as part of a treatment strategy for chloroquine toxicity though there is more focus on high dose diazepam and epinephrine therapy [84, 85]. There is a case report of quinine toxicity resulting in death where a small dose of sodium bicarbonate ("1/2 ampule") was used [86].

Other Sodium Channel Blocking Agents

Sodium bicarbonate has been used to treat diphenhydramine overdoses resulting in QRS widening [2, 65]. Sharma et al. describe three cases of diphenhydramine toxicity with maximum QRS values ranging from 102 to 162 msec treated effectively with sodium bicarbonate [65]. Lamotrigine has also been implicated in causing sodium channel blockade and has also been shown to be responsive to sodium bicarbonate therapy [4, 5]. Propoxyphene toxicity can also result in QRS widening and sodium channel blockade. In addition, Stork et al. describe a case of QRS widening after propoxyphene overdose being treated with sodium bicarbonate although the serum concentration of propoxyphene is not reported [71].

Lastly, in more esoteric ingestions, sodium bicarbonate has been effective in yew berry seed poisoning as detailed by Peirog et al. They describe a 24-year-old male patient who ingested 168 yew seeds (*Taxus cuspidate*) with an initial QRS of 172 msec which narrowed to 84 msec after a bolus dose of 100 mEq of sodium bicarbonate [78]. However, a study in swine examining the effect of sodium bicarbonate on QRS prolongation induced from an extract of the leaves of *Taxus* media, the QRS did not narrow with the administration of sodium bicarbonate [79]. The seeds and leaves contain taxines that can disrupt sodium-potassium transport and cause conduction abnormalities. However, the berries do not contain significant amounts of toxin [78, 79].

Please see tables 1 and 2 for a summary of the agents and data presented in this section.

Table 2 Agents where sodium bicarbonate appears to have uncertain efficacy

Agent	Human data (references)	Animal data (references)	In vitro data (references)
Bupropion	Case reports [72–74]	Guinea pig hearts, rat neonatal myocytes, rat atria, canine ventricular tissue, crayfish axons [75, 76]	Human embryonic kidney cells [75]
Propranolol		Canine study [77]	
Taxine	Case report (QRS narrowed) [78]	Swine study (no effect) [79]	

Complications of Sodium Bicarbonate Therapy

The most well-known and expected complication of sodium bicarbonate therapy is hypokalemia [87]. Hypokalemia occurs due to an extracellular shift of hydrogen ions with an intracellular shift of potassium ions to compensate for alkalosis. There is a case of sodium bicarbonate causing hypokalemia and ventricular tachycardia in a patient being treated for acidosis [88]. This complication can be treated with potassium repletion and careful attention to electrolytes. There are two cases of fatal alkalosis in tricyclic-poisoned patients [89]. Sodium bicarbonate also has been associated with hypocalcemia and hypernatremia [90, 91]. Hypocalcemia may be caused by alterations in urinary pH resulting in less calcium reabsorbed. Sodium bicarbonate may induce calcium binding to albumin and carbonate resulting in a decreased ionized calcium level [11]. Hypocalcemia from sodium bicarbonate resulting in hypotonia with both Chvostek's sign and Trousseau's sign has been described by Fox. This patient improved with cessation of sodium bicarbonate therapy and administration of calcium. This patient was also mildly hypokalemic with a serum potassium concentration of 3.1 mEq/L, had prominent U waves on ECG, and received supplemental potassium [90]. Possible hypocalcemia can be addressed by monitoring serum calcium concentration and providing calcium repletion as needed. Lastly, alkalemia with a pH of greater than 7.48 was associated with higher risk of mortality in medical and surgical patients and risk of mortality increased as the pH rose [92].

Discussion

Sodium bicarbonate is used to narrow QRS widening induced by multiple medications and toxins. The mechanism is not fully elucidated, and it may vary by agent. Sodium bicarbonate may work by raising the sodium concentration to overwhelm sodium channel blockade, increasing the pH which may either reduce free drug levels or alter the polarization of the cell, or via a combination of both mechanisms.

There is good evidence that sodium bicarbonate is effective for treating QRS widening from tricyclic antidepressant poisoning. The evidence is limited and/or uncertain that sodium bicarbonate can be used to reverse QRS widening induced by cocaine, propafenone, flecainide, escitalopram/citalopram, diphenhydramine, fluoxetine, lamotrigine, quinidine, procainamide, and chloroquine/hydroxychloroquine. In addition, although evidence is limited, sodium bicarbonate does not appear to be effective for treating QRS widening from bupropion toxicity. Sodium bicarbonate also may not reverse QRS widening from propranolol and taxine-induced cardiac toxicity.

There are no studies to determine the optimal dosing of sodium bicarbonate. One common protocol for adults is to give 50–100 mEq (one to two 50 cc ampules of 8.4 % sodium bicarbonate solution) as a bolus. This bolus dosing is then followed by an infusion of 150 mEq of sodium bicarbonate mixed with 1 L of 5 % dextrose in water at a rate of 150 cc/h for a serum pH of 7.45–7.55 [48]. For children, a common dosing pattern is 1–2 mEq/kg as the bolus dose followed by the infusion with the concentration described above at a rate of 1.5 times the maintenance intravenous fluid rate. The monitoring of the pH can be performed using venous blood gases, which is important to ensure that the patient does not become overly alkalemic. Given the risk of hypokalemia, frequent potassium monitoring is also important with repletion given carefully.

Conclusion

Sodium bicarbonate has been shown to be an effective antidote for narrowing QRS widening caused by TCA poisoning. Whether the mechanism of sodium bicarbonate as an antidote for sodium channel blockade is via increased sodium concentration, increased pH, or a combination of both still needs to be refined and may vary by toxin. Future directions of potential research include exploring the most effective dosing regimens, clarifying the mechanism of action, and determining other possible applications of sodium bicarbonate as an antidote for sodium channel blockade.

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