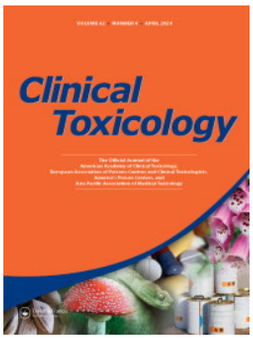

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Betty S. Chan & Nicholas A. Buckley

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COMMENTARY

Common pitfalls in the use of hypertonic sodium bicarbonate for cardiac toxic drug poisonings

Betty S. Chan[a,b] and Nicholas A. Buckley[b,c]

[a]Discipline of Critical Care, School of Clinical Medicine, University of New South Wales, Sydney, Australia; [b]New South Wales Poisons Information, Sydney, Australia; [c]Clinical Pharmacology, Faculty of Medicine and Health, Sydney University, Sydney, Australia

ABSTRACT

Background: Hypertonic sodium bicarbonate is advocated for the treatment of sodium channel blocker poisoning, but its efficacy varies amongst different sodium channel blockers. This Commentary addresses common pitfalls and appropriate usage of hypertonic sodium bicarbonate therapy in cardiotoxic drug poisonings.

Sodium bicarbonate works synergistically with hyperventilation: Serum alkalinization is best achieved by the synergistic effect of hypertonic sodium bicarbonate and hyperventilation ($PCO_2 \sim 30$–35 mmHg [0.47–0.6 kPa]). This reduces the dose of sodium bicarbonate required to achieve serum alkalinization (pH ~ 7.45–7.55) and avoids adverse effects from excessive doses of hypertonic sodium bicarbonate.

Variability in response to sodium bicarbonate treatment: Tricyclic antidepressant poisoning responds well to sodium bicarbonate therapy, but many other sodium channel blockers may not. For instance, drugs that block the intercellular gap junctions, such as bupropion, do not respond well to alkalinization. For sodium channel blocker poisonings in which the expected response is unknown, a bolus of 1–2 mmol/kg sodium bicarbonate can be used to assess the response to alkalinization.

Sodium bicarbonate can exacerbate toxicity from drugs acting on multiple cardiac channels: Hypertonic sodium bicarbonate can cause electrolyte abnormalities such as hypokalaemia and hypocalcaemia, leading to QT interval prolongation and torsade de pointes in poisonings with drugs that have mixed sodium and potassium cardiac channel properties, such as hydroxychloroquine and flecainide.

The goal for hypertonic sodium bicarbonate is to achieve the alkalinization target (~pH 7.5), not complete correction of QRS complex prolongation: Excessive doses of hypertonic sodium bicarbonate commonly occur if it is administered until the QRS complex duration is < 100 ms. A prolonged QRS complex duration is not specific for sodium channel blocker toxicity. Some sodium channel blockers do not respond, and even when there is a response, it takes a few hours for the QRS complex duration to return completely to normal. In addition, QRS complex prolongation can be due to a rate-dependent bundle branch block. So, no further doses should be given after achieving serum alkalinization (pH ~ 7.45–7.55).

Maximal dosing for hypertonic sodium bicarbonate: A further strategy to avoid overdosing patients with hypertonic sodium bicarbonate is to set maximum doses. Exceeding 6 mmol/kg is likely to cause hypernatremia, fluid overload, metabolic alkalosis, and cerebral oedema in many patients and potentially be lethal.

Recommendation for the use of hypertonic sodium bicarbonate in sodium channel blocker poisoning: We propose that hypertonic sodium bicarbonate therapy be used in patients with sodium channel blocker poisoning who have clinically significant toxicities such as seizures, shock (systolic blood pressure < 90 mmHg, mean arterial pressure <65 mmHg) or ventricular dysrhythmia. We recommend initial bolus dosing of hypertonic sodium bicarbonate of 1–2 mmol/kg, which can be repeated if the patient remains unstable, up to a maximum dose of 6 mmol/kg. This is recommended to be administered in conjunction with mechanical ventilation and hyperventilation to achieve serum alkalinization (PCO_2~30–35 mmHg [4-4.7 kPa]) and a pH of ~7.45–7.55. With repeated bolus doses of hypertonic sodium bicarbonate, it is imperative to monitor and correct potassium and sodium abnormalities and observe changes in serum pH and on the electrocardiogram.

Conclusions: Hypertonic sodium bicarbonate is an effective antidote for certain sodium channel blocker poisonings, such as tricyclic antidepressants, and when used in appropriate dosing, it works synergistically with hyperventilation to achieve serum alkalinization and to reduce sodium channel blockade. However, there are many pitfalls that can lead to excessive sodium bicarbonate therapy and severe adverse effects.

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CONTACT Betty S. Chan Betty.Chan1@health.nsw.gov.au Discipline of Critical Care, School of Clinical Medicine, University of New South Wales, Sydney, Australia.

Background

Hypertonic sodium bicarbonate is advocated for use in reducing the toxicity caused by Vaughan-Williams class 1A and 1C sodium channel blockade [1], particularly in patients with tricyclic antidepressant poisoning. It is well established to be effective in this setting, although there is debate about the exact mechanisms and whether the response is due to an increase in sodium concentration, alkalaemia or both. In addition, hyperventilation provides a synergistic effect and is essential to maintain serum alkalinization [2,3]. Sodium bicarbonate has also been used to manage other sodium channel blocker poisonings, such as cocaine and diphenhydramine [1]. However, the effectiveness of sodium bicarbonate has not been demonstrated in the management of many sodium channel blocker poisonings, and some, such as bupropion [4] and lamotrigine [5], do not appear to be as responsive.

The most clinically significant toxic effects of sodium channel blockers include seizures, shock, and ventricular dysrhythmias. Current recommended treatments for patients with sodium channel blocker poisoning include supportive care and early gastrointestinal decontamination using activated charcoal. Serum alkalinization is widely accepted as a management option to reduce cardiac toxicity. The exact electrocardiographic (ECG) changes that are an indication and the endpoint for sodium bicarbonate therapy lack consensus among physicians [6]. We discuss several potential pitfalls in the use of hypertonic sodium bicarbonate for managing cardiotoxic drugs.

Case vignette

A 31-year-old 90 kg female presented to the emergency department with a history of taking amitriptyline 5 g 30 min earlier. Her initial Glasgow Coma Scale was 15, which rapidly decreased to 8 approximately 30 min later. Her heart rate was 150 beats/min, and her blood pressure was 90/60 mmHg. An ECG was performed (Figure 1), which showed sinus tachycardia, QRS complex duration 160 ms, positive R wave (5 mm) in aVR, and R/S ratio of 1.3. The ECG demonstrated sodium channel-blocking effects, and the patient was at risk of shock, seizures, and ventricular dysrhythmias.

The patient was managed with hypertonic sodium bicarbonate (8.4%) 100 mmol and intubated endotracheally with rapid sequence induction. She was then hyperventilated to achieve a serum pH of 7.45–7.50. A large bore nasogastric tube was inserted to facilitate the administration of activated charcoal 50 g. A second dose of activated charcoal 50 g was given 4 h after the first dose. A repeat ECG performed 3 h post-ingestion showed some resolution of sodium channel blockade, with a heart rate of 120 beats/min, QRS complex duration 120 ms, and R/S 0.75, R wave 3 mm in aVR (Figure 2). The patient was extubated 34 h post-ingestion with an uneventful recovery and normalization of her ECG.

Hypertonic sodium bicarbonate works synergistically with hyperventilation to achieve serum alkalinization

As demonstrated in the case vignette, patients with sodium channel blocker poisoning, particularly tricyclic antidepressant overdose, appear to benefit from the synergistic effect of hypertonic sodium bicarbonate and hyperventilation to achieve serum alkalinization. Serum alkalinization reduces the free plasma concentrations of tricyclic antidepressants (weak bases with a pKa of 9–10), while hypertonic sodium bicarbonate also increases extracellular sodium concentration which might also counteract the sodium channel blockade [7,8]. Also worth highlighting is that the response on the ECG was rapidly obtained, but it was not completely reversed. As expected from the purported mechanisms, some sodium channel blockade features remained for many hours, presumably until plasma concentrations were very much lower.

The use of hypertonic sodium bicarbonate per se does not necessarily raise arterial blood pH. Sodium bicarbonate combines with hydrogen atoms and generates carbon dioxide and water. This extra carbon dioxide would normally be rapidly cleared by pulmonary hyperventilation. This will often not occur if the patient is comatose and has respiratory depression from a drug overdose. If the extra carbon dioxide is not eliminated, this results in respiratory acidosis [9–11]. Even if the patient is intubated, there may be inadequate adjustment of mechanical ventilation to eliminate excess carbon dioxide, leading to intracellular acidosis from the diffusion of carbon dioxide into cells [9]. Respiratory acidosis should be managed with hyperventilation rather than more sodium bicarbonate, as the latter could exacerbate hypercapnia and intracellular acidosis [10,11]. We recommend routinely utilizing hyperventilation (PCO_2∼ 30–35 mmHg [4-4.7 kPa]) to maintain serum alkalinization (pH∼ 7.45–7.55), which should generally prevent the worsening of hypercapnia and respiratory acidosis [2,3].

Variability in response to sodium bicarbonate treatment

Sodium channel blockers exert their effects through different mechanisms on the voltage-gated sodium channels by blocking either the activated, inactivated, or closed state or acting at the intercellular junction [1]. Serum alkalinization is not expected to be effective in all cases of sodium channel blocker poisoning. Sodium channel blockers are very diverse and have critical differences in their pharmacokinetic properties (e.g., different pKa and protein binding) and mechanisms of action that determine their responses to pH changes and, thus, their response to hypertonic sodium bicarbonate therapy [12]. For instance, bupropion, which causes the QRS complex to widen, does not typically respond to sodium bicarbonate therapy as it reduces intercellular coupling at the gap junction [1, 4, 13].

Drugs that are not weak bases may have no favourable change in free concentrations or sodium channel blockade with alkalinization. For example, lamotrigine has a pKa of 4.7 and very different pH-related effects on binding kinetics to sodium channels [12]. There is considerable uncertainty regarding whether hypertonic sodium bicarbonate is favourable or even harmful based on limited case series, but further studies are needed to evaluate its response to bicarbonate therapy [5].

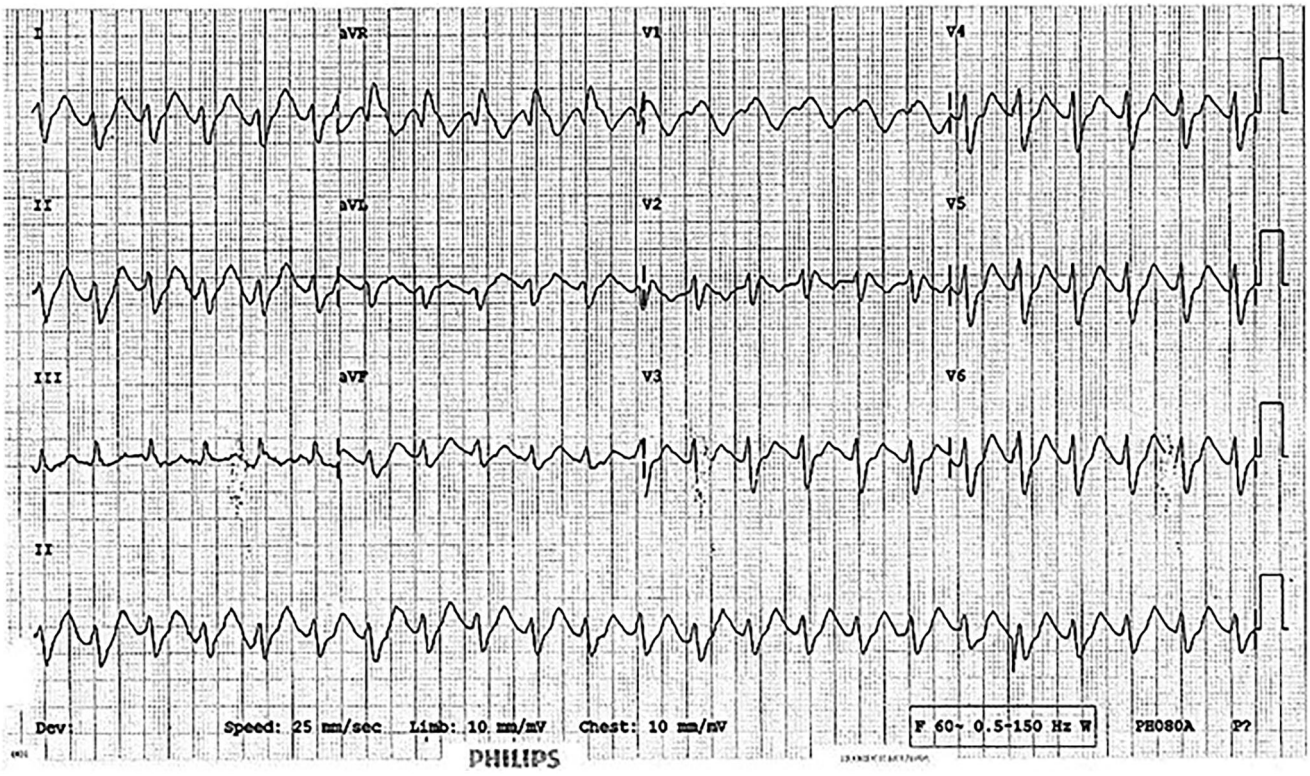

Figure 1. Twelve-lead electrocardiogram of the patient upon arrival in the emergency department.

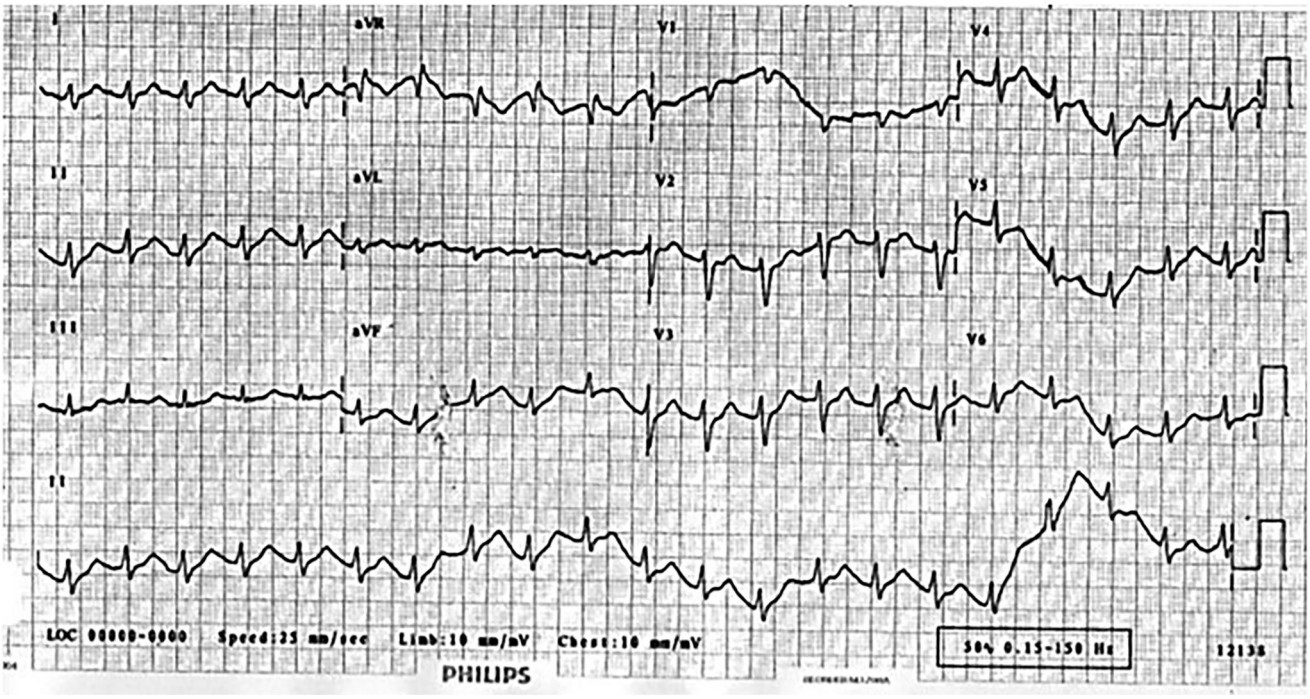

Figure 2. Twelve-lead electrocardiogram of the patient 3 h post ingestion.

It is reasonable to consider a trial of hypertonic sodium bicarbonate 1–2 mmol/kg therapy in patients with most sodium channel blocker poisonings. However, if there is no obvious improvement in ECG changes and haemodynamic status after achieving serum alkalinization, then this should be taken as an indication that further doses of sodium bicarbonate are unlikely to be beneficial.

Sodium bicarbonate can exacerbate toxicity from drugs acting on multiple cardiac channels

Hypertonic sodium bicarbonate is recognized for its potential to cause hypokalaemia, hypocalcaemia and QT interval prolongation [14,15]. This poses particular concerns in patients who have ingested single or mixed drugs with potassium

and sodium channel-blocking properties. Several sodium channel blocking drugs, including hydroxychloroquine, chloroquine, quinidine and flecainide, are also potent potassium channel blockers [16]. Risks of torsade de pointes from QT interval prolongation are exacerbated by bradycardia, a common feature in flecainide poisoning [16].

While tricyclic antidepressants also block potassium channels and can cause some QT interval prolongation this is partly due to the increase in QRS complex duration [17–20], this is not the dominant feature, and torsade de pointes is extremely rare [21]. Very few clinical toxicologists recommend the use of hypertonic sodium bicarbonate therapy to manage isolated QT interval prolongation in patients with tricyclic antidepressant poisoning [6]. Indeed, sodium bicarbonate may exacerbate QT interval prolongation by lowering serum potassium and calcium concentrations, and sodium bicarbonate should never be used to treat QT interval prolongation as there are other clearly effective and recommended strategies [22].

The goal for hypertonic sodium bicarbonate is to achieve the alkalinization target (∼pH 7.5), not complete correction of QRS complex prolongation

It is recognized that tricyclic antidepressant poisoning is associated with QRS prolongation (≥100 ms) [23] and terminal right axis deviation in aVR, evidenced by a dominant R wave of ≥3 mm or R/S ratio of ≥0.7 [24–26]. The maximal limb lead QRS complex duration of ≥100 ms is one of several biomarkers of tricyclic antidepressant toxicity and has frequently been used as an indication for treatment.

However, it has been reported that changes in QRS complex duration and the terminal right axis deviation in aVR may take up to a week to resolve [20]. Moreover, QRS complex prolongation could be attributable to pre-existing or rate-dependent bundle branch block. Thus, we recommend that QRS complex <100 ms should not be employed as a guide for the endpoint of sodium bicarbonate therapy. Instead, achieving serum alkalinization (∼pH 7.45–7.55) should signify the endpoint for hypertonic sodium bicarbonate therapy.

Maximal dosing for hypertonic sodium bicarbonate therapy

The dose of hypertonic sodium bicarbonate required to achieve a pH of 7.5 is typically only 1–3 mmol/kg or 100–200 mmol in total. Further doses are likely to have fewer benefits and increased risks.

In a small non-randomized study that compared 31 patients who received hypertonic sodium bicarbonate with 338 patients who did not have hypertonic sodium bicarbonate treatment for managing poisonings associated with acidosis, salicylate, QRS ≥100 ms or cardiac arrest, hypertonic sodium bicarbonate therapy was associated with adverse cardiovascular events (adjusted odds ratio [aOR]: 9.4), QTc prolongation (aOR: 126.7) and increased mortality (aOR 5.1) [27]. Patients who received hypertonic sodium bicarbonate therapy were more unwell, and much of this is likely explained by reverse causation. However, the study also revealed significantly increased odds of adverse outcomes with greater doses and longer duration of sodium bicarbonate therapy ($P < 0.05$), raising concerns about whether some adverse outcomes are related to excessive doses.

Administration of sodium bicarbonate 400 mmol (approximately 6 mmol/kg) leads to a 10 mmol/L increase approximately in the serum sodium concentration [2]. This is around the maximum change that will not lead to dangerous shifts in serum osmolality. Even greater doses can potentially precipitate serious complications such as volume overload, pulmonary oedema, cerebral oedema, hypernatraemia, metabolic alkalosis, electrolyte abnormalities and even death [9,28]. Therefore, we recommend that hypertonic sodium bicarbonate is used typically in doses of 1-2 mmol/kg with a maximum total dose of 6 mmol/kg [2,28]. In our experience those not responding to such doses do not respond to greater doses. This is concordant with the literature. We are unaware of any cases in which doses of this magnitude have been used with no response, and there has been a substantial improvement with further doses. However, there are certainly several cases that demonstrate disastrous results with further doses.

Recommendation for the use of hypertonic sodium bicarbonate in sodium channel blocker poisoning

We propose that hypertonic sodium bicarbonate therapy be used in patients with sodium channel blocker poisoning who have clinically significant toxicities such as seizures, shock (systolic blood pressure < 90 mmHg, mean arterial pressure <65 mmHg) or ventricular dysrhythmia [7]. These patients will almost invariably also have QRS complex prolongation and increased R wave in aVR; typically QRS > 120 ms and R/S ratio in aVR > 0.7 [25,29]. In the management of patients with sodium channel blocker poisoning, such as cyclic antidepressant overdoses, which are known to respond to sodium bicarbonate and serum alkalinization, we recommend initial bolus dosing of hypertonic sodium bicarbonate of 1–2 mmol/kg, which can be repeated if the patient remains unstable, up to a maximum dose of 6 mmol/kg. This is recommended to be administered in conjunction with mechanical ventilation and hyperventilation to achieve serum alkalinization (PCO_2∼30–35 mmHg [4-4.7 kPa]) and a pH of 7.45–7.55 [2]. With repeated bolus doses of hypertonic sodium bicarbonate, it is imperative to monitor and correct potassium and sodium abnormalities and observe changes in serum pH and ECG.

In cases of cyclic antidepressant poisoning for whom airway protection is necessary, it is prudent to administer a single bolus dose of sodium bicarbonate 50–100 mmol prior to intubation. This approach aims to prevent respiratory acidosis during the peri-intubation period. It is likely that the total dose of hypertonic sodium bicarbonate required will be reduced when hyperventilation is employed in conjunction to achieve serum alkalinization [2]. For patients with sodium channel blocker poisoning, it is generally not recommended

to use hypertonic sodium bicarbonate exclusively for treating a QRS complex duration $\geq$100 ms.

Conclusions

We recommend using hypertonic sodium bicarbonate therapy for patients experiencing life-threatening toxicities such as shock, ventricular dysrhythmias or seizures due to sodium channel blocker toxicities such as cyclic antidepressant poisoning. It is generally futile and dangerous to exceed 6 mmol/kg and should not be used to achieve a complete correction of QRS complex duration $<$100 ms. Sodium bicarbonate therapy is recommended concurrently with hyperventilation to achieve serum alkalinization (pH$\sim$ 7.45–7.55) and good supportive care. It is important to recognize that not all patients with sodium channel blocker poisoning will have a positive response to hypertonic sodium bicarbonate treatment. Furthermore, hypertonic sodium bicarbonate can exacerbate QT interval prolongation and may increase the toxicities of drugs with potassium channel-blocking properties. For unstable poisoning with non-cyclic antidepressant sodium channel blockers, a trial of sodium bicarbonate 1–2 mmol/kg is recommended. Electrocardiogram changes may be utilized as a diagnostic tool for risk assessment, in conjunction with clinical evaluation, to monitor patient response to treatment. However, it is important to note that normalization of ECG might not be achieved within the first few hours of therapy.

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ORCID

Betty S. Chan http://orcid.org/0000-0003-0083-282X
Nicholas A. Buckley http://orcid.org/0000-0002-6326-4711

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