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# Management of sodium-channel blocker poisoning: the role of hypertonic sodium salts

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**Abstract. – Sodium-channel blockers act by slowing sodium influx into myocytes through voltage gated channels.**

**Many substances have sodium-channel blocking properties and many others show this effect when taken in overdose.**

**Sodium-channel blocker poisoning, associated with a high death rate, is characterized by a variety of clinical presentation, depending on the pharmaceutical agent involved.**

**Sodium bicarbonate or lactate, increasing serum pH and extracellular concentration of the ion, displace the drug from its receptor sites and can be used for the treatment of cardiac toxicity in the setting of sodium-channel blocker poisoning.**

**In spite of this theoretical assumption, the role played by hypertonic sodium salts is not well elucidated and conflicting results have been reported.**

**Authors review the pathophysiologic mechanisms of sodium-channel blocker poisoning and the evidences in literature concerning the efficacy of hypertonic sodium salts in the treatment of the related toxicity.**

*Key Words:*

Sodium channel blockers, Poisoning, Sodium bicarbonate, Sodium lactate, Class IC drugs, Tricyclic antidepressant.

## Introduction

Sodium-channel poisoning is a potentially life-threatening condition characterized by a variety of clinical presentation depending on the pharmaceutical agent involved[1,2].

Many substances have sodium-channel blocking properties, but tricyclic antidepressants and Vaughan Williams class IC antiarrhythmic agents remain the most common causes of sodium-channel blocker poisoning[3].

Sodium salts increase serum pH and extracellular concentration of the ion with displacement of the drug from its receptor sites, and can be administered as therapeutic agents[4].

Despite this theoretical assumption, conflicting results have been presented and optimal treatment has not been established.

The aim of this paper is to analyze the electrophysiological bases of sodium-channel blocker poisoning and the evidences in regard to the therapeutic use of hypertonic sodium salts in the treatment of the myocardial toxicity.

## Electrophysiology

Ionic movement across the cell membrane creates the cardiac action potential. The membrane is not permeable to the ions and in the different phases of the action potential are involved specific voltage gated channels that control inward and outward currents[5].

The function of the voltage-gated sodium channels was fully elucidated by Hodgkin and Katz[6] in 1949, in a classic study performed on the great axon of the squid. In the heart, they play a role in the depolarization of sodium-dependent myocardial cells (atria, ventricles and His-Purkinje fibers) that occurs with a conformational change (activated state), rapid opening of the channel and the subsequent massive sodium influx (phase 0).

This state is followed by other two additional changes in the conformation of the channel that becomes first inactivated (inactivated state), and then capable of activating again (resting state)[5].

Unlike sodium-dependent myocardial cells, very little $Na^+$ influx occurs instead during the phase 0 of calcium-dependent cells, such as sinoatrial and atrioventricular nodes.

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Heart rate modulates the conformational changes, increasing tachycardia the number of channels in active and inactive states per unit time[1].

Sodium-channel blockers bind to the transmembrane channels and reduce the number available for the depolarization, with a delay of the phase 0 and a slowing in the conduction of atria, ventricles and His-Purkinje fibers: this effect has been described as *quinidine-like effect*, in reference to the antiarrhythmic drug[7,8].

In calcium-dependent cells, a slowed depolarization during phase 4 is the main electrophysiological effect[1,9].

The reduction of intracellular sodium concentration due to the blockade of sodium channels results in a decrease of sodium-calcium exchange and a fall in intracellular calcium, effect that explains the potential decrease in myocardial contractility.

At high doses, some sodium channel blockers (i.e. lidocaine, quinidine) block calcium channels directly.

## Electrocardiographic Manifestations of Sodium-Channel Blockers Poisoning

The principal alteration on the electrocardiogram is a QRS complex widening; rarely, the QRS complexes may take the pattern of bundle branch blocks[10].

In severe poisonings, the QRS widening becomes so profound that a differential diagnosis between supraventricular and ventricular rhythms can be impossible.

A slowing of the intraventricular conduction and a unidirectional conduction block create the development of a re-entrant circuit, with possible onset of ventricular tachycardia that can degenerate into ventricular fibrillation[11].

Sinus bradycardia results from the slowing in the depolarization of sinoatrial node, but with sodium-channel blocker agents having anticholinergic and/or adrenergic effects (i.e. tricyclic antidepressants), sinus tachycardia is very common.

In these cases, when bradycardia occurs, it is an indication that $Na^+$ channels blockade is so profound that the increase in heart rate in response to muscarinic antagonism is not possible[1].

In contrast, class IC antiarrhythmic drugs and other agents devoid of these properties are far more likely cause of bradyarrhythmias, such as junctional or ventricular escape and eventual asystole[12,13].

As mentioned above, tachyarrhythmias, preventing complete repolarization, increase the number of channels in active and inactive states per unit time, with a decline in the $V_{max}$ (upslope of phase 0 of a myocardial cell).

This phenomena is further enhanced in the face of sodium-channel blockade because more binding sites are offered to the drug, as reflected in an increase of QRS lengthening at faster heart rates[7].

The structural similarity between $Na^+$ and $K^+$ channels can explain the prolonged repolarization observed with some sodium-channel blockers (i.e. tricyclic antidepressants, IA antiarrhytmic drugs, phenothiazines).

The lengthening of QT interval, due to an impairment of outward $K^+$ currents, is a potential trigger for the occurrence of *torsades de pointes*, uncommon in poisoning with agents having anticolinergic properties for the protective role played by the increase in heart rate[14-16].

A rightward axis shift in the terminal 40 ms of the QRS axis is a sensitive (83%) and specific (63%) marker for tricyclic toxicity.

This alteration is detected as a negative deflection of the final portion of QRS complex on lead I [a deep S wave] and a positive deflection of the terminal portion of lead aVr (a large R wave)[17].

## Clinical Features of Sodium-Channel Blocker Poisoning

Sodium-channel blocker poisoning is not characterized by a specific symptomatology.

Anticholinergic properties produce agitation, respiratory depression, tachycardia, mydriasis, anhydrosis, depressed gastrointestinal motility and urinary retention.

At high concentration most sodium-channel blockers show proconvulsant activity due to a variety of mechanisms: inhibition of the GABA system (i.e. lidocaine), activation of a sodium ouabain-sensitive current (i.e. enaminones), stimulation of 5-TH2C receptors (i.e. cocaine, mepryicaine, tricyclic antidepressants), H1 receptors antagonism and neuronal noradrenaline activating effect [i.e. imipramine)[18-21].

Hypertension, tachycardia and diaphoresis, effects of adrenergic stimulation, characterize cocaine intoxication[22].

Myocardial depression, often associated with vasodilation (i.e. quinidine, tricyclic antidepressants, phenothiazines), results in severe hypotension.

Block of $K^+$ efflux (i.e. chloroquine, quinine, disopyramide) produces hypoglycaemia by insulin release[23,24].

Severe poisonings, apart from the substance involved, are characterized by coma and profound respiratory depression.

## Hypertonic Sodium Salts in the Management of Sodium-Channel Blockers Poisoning

Hypertonic sodium salts, bicarbonate or lactate, are considered the treatment of choice for cardiac toxicity in the setting of sodium-channel blocker poisoning, although conflicting results have been presented in literature and optimal treatment has not been established.

Most of the available data derives from *in vitro* experiments, animal studies and human case reports, with no randomized clinical trials supporting treatment recommendations.

Concerning i*n vitro* research, toxicity has been measured by the drug-induced decrease in $V_{max}$ [maximal change in voltage per unit time] and improvement of toxicity has been defined as an increase in $V_{max}$.

Interpretation of data derived from experiments conducted in animals (dog, guinea-pig, rabbit, rat) requires caution because of important potential interspecies differences in sensitivity to sodium-channel blockers, and the difficulty in relating directly the drug concentration to a corresponding concentration in humans.

Clinical research has been focused on the decrease of QRS prolongation induced by the treatment, the improvement of hypotension and the effects on heart rate[25].

A review of the literature shows that case reports, mostly limited to tricyclic antidepressants and Vaughan Williams class IC antiarrhythmic agents poisonings, vary widely in the extent of clinical details, severity of poisoning and treatment used.

Current recommendations are supported by a little evidence and there are questions that remain unsolved.

### Molecular Mechanism

Molecular mechanism by which hypertonic sodium salts reverse $Na^+$ channel blockade is not clear and can include changes in diastolic potential, in action potential duration (APD), in ionized $Ca^{++}$ and in the direct interaction between drug and receptor[26].

First evidences emphasized the role of alkalinization, that decreases the free concentration of the drug, but following studies demonstrated that the effect is independent of protein binding[27,28].

The dissociation of the blocking agent from the channel could be related to the rise in $Na^+$ concentration [mass effect], and this would explain the assumed benefits of hypertonic saline solution reported in literature[29-31].

Electrostatic repulsion has been postulated to explain the reduction in $Na^+$ channel drug-blocking action when $(Na^+)_0$ is increased, and changes in the magnitude of $I_{Na}$ as result of altered $(Na^+)_0$ have been thought to be important[26].

However, because the heterogeneity of $Na^+$ channel blockers binding to the channel, alkalinization and sodium loading are not necessarily effective for all substances, and their relative roles for various drugs are incompletely known.

Among Vaughan Williams class IC antiarrhythmic agents and tricyclic antidepressants, for instance, the effect of disopyramide is not altered by sodium bicarbonate that, in contrast, strongly inhibits the pharmacological action of flecainide and imipramine.

The effect of sodium bicarbonate is entirely due to alkalinization in case of imipramine, but both increase in pH and rise in $Na^+$ concentration contribute to the interaction with flecainide[26].

### Timing of Administration

In clinical practice, hypertonic sodium salts are administered when QRS complexes reach 120 ms, but this practice is empirical and there are not controlled studies demonstrating changes in the outcome of patients free from ventricular arrhythmias and hypotension[1].

Moreover, although prolonged QRS is a marker of intraventricular conduction delay, it does not necessarily indicate impaired myocardial contractility or cardiotoxicity, and reliance on this parameter should be critically re-evaluated to determine its prognostic value on life-threatening events[32].

### Dosage

The dose of hypertonic sodium salts to administer is not well defined.

In clinical practice, the average dose of hypertonic sodium bicarbonate is 1 mEq/kg bolus, with a range of 0,55 to 3 mEq/kg, but doses of 5 to 6 mEq/kg in animal models (dogs, rats) have been reported[33,34].

Bolus is followed by a hypertonic sodium bicarbonate drip, with an average dose of 15 to 20 mEq/h[1].

No evidences support such dosage, but this choice seems to be the most effective in reaching and maintaining a target pH of 7.50 to 7.60, with only a modest rise in $Na^+$ concentration.

If therapy with intravenous bicarbonate is combined with hyperventilation, careful monitoring of the pH is imperative to avoid severe alkalemia (pH >7.60)[35].

No recommendations concerning the length of the therapy can be provided on the basis of the literature.

### Therapeutic Response

Conflicting results have been presented in literature concerning the efficacy of the treatment with hypertonic sodium salts in course of sodium-channel blocker poisoning.

There are numerous cases or case series in which patients with sodium-channel blocker poisoning responded favourably to sodium bicarbonate (normalization of QRS prolongation, disappearance of arrhythmias, resolution of neurological symptomatology, improvement of vital signs) in a temporally consistent manner[3,8,36-44].

In other cases, therapy with sodium bicarbonate did not result in any clinical improvement or contributed to adverse effects[35,45-49].

A number of patient-or circumstance-specific factors and inaccuracy or incompleteness of the collected data, limit the value of many reports reviewed.

## Conclusions

Hypertonic sodium salts have been used to treat toxicity of a variety of sodium-channel blocker poisoning.

As more substances having sodium-channel blocking properties become available, the incidence of this poisoning may be expected to increase, and clinician, particularly the emergency physician, should be familiar with this potential fatal condition.

A little evidence supports the treatment with hypertonic sodium salts, and current recommendations have not been based on randomized clinical trials.

Drugs can differ widely in the response to sodium bicarbonate or lactate, suggesting caution and advising against an extensive use, since such therapy may not be beneficial for all sodium-channel blocker poisonings.

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