REUE | Update

Bicarbonate: a traditional antidote or an antiarrhythmic agent?

Bicarbonato: ¿antídoto clásico o antiarrítmico?

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Bicarbonate has limited evidence as an antidote, and its presence in the scientific literature—within antidote reviews—is infrequent, and even less so in systematic reviews on the subject. However, it exerts a beneficial effect in certain poisonings based on its mechanism of action, which allows it to be considered a classic antidote in tricyclic antidepressant (TCA) intoxications.

This effect occurs because bicarbonate alters cell polarization and increases protein binding, thereby reducing the free fraction of the drug responsible for toxicity. In addition, it stabilizes the myocardium by increasing sodium levels and counteracting sodium channel blockade, and finally, it corrects acidosis if present, although its effect also occurs in the absence of acidosis and even in alkalosis.[1,2]

Between 1950 and 1980, TCAs were extensively used for the management of depression and other psychiatric disorders. Although selective serotonin reuptake inhibitors and other agents have largely replaced TCAs, they are still used for depression as well as for other indications such as neuropathic pain, migraine, enuresis, attention deficit, and panic disorders.

TCA intoxication is among the most frequent poisonings in adults, along with those caused by paracetamol, benzodiazepines, and alcohol, and—after opioid analgesic poisoning—it is associated with the highest mortality.[1] TCAs are rapidly absorbed in the GI tract. They exhibit high plasma protein binding and have a very large volume of distribution with a long elimination half-life exceeding 24 hours, which, in the case of amitriptyline, can reach 48 hours.[1] The toxic effects of TCAs arise from 4 main pharmacological properties: inhibition of synaptic reuptake of the neurotransmitters norepinephrine and serotonin, direct alpha-adrenergic blockade, membrane-stabilizing effects, and anticholinergic activity. Toxicity is considered high when the dose exceeds 10 mg/kg, but severity is determined by clinical, hemodynamic, and electrocardiographic manifestations, requiring an observation period of at least 12 hours.[3] Of note, among antidepressants, TCAs are the most toxic in overdose, whereas poisonings from second-generation antidepressants (bi- or tetracyclic) and selective serotonin reuptake inhibitors are generally less severe and typically do not cause cardiotoxicity.[3]

The cardiovascular effects of TCAs are due to inhibition of the fast sodium channels in myocardial and conduction tissue.[3] This effect causes a reduction in conduction velocity and an increase in repolarization duration and refractory period, similar to class I antiarrhythmic drugs.[4,5]

Possible electrocardiographic patterns include sinus tachycardia (the most frequent and least severe), sinus bradycardia, first-degree AV block, second- or third-degree AV block, T-wave flattening or inversion, QRS prolongation (> 0.10 s), QT prolongation, ventricular tachycardia, torsades de pointes, and other ventricular arrhythmias[3] (Figure 1).

Brugada syndrome and tricyclic antidepressants

In some cases of TCA intoxication, an electrocardiographic pattern similar to Brugada syndrome may appear (ST-segment elevation in right precordial leads V1–V3 associated with right bundle branch block) due to sodium channel blockade.[6,7] It is important to differentiate Brugada syndrome (a genetically determined channelopathy with an identifiable mutation) from Brugada phenocopy. Brugada phenocopy is associated with various clinical conditions characterized by a Brugada type I or II electrocardiographic pattern in the absence of true Brugada syndrome. It occurs in the presence of diverse underlying conditions, resolves completely once the triggering factor is removed, and is not accompanied by clinical symptoms. Definitive diagnosis requires negative results in sodium channel blocker challenge tests and negative genetic testing. Multiple metabolic, medical, and pharmacological conditions can lead to Brugada phenocopy. In the case of TCAs, they induce Brugada phenocopy, though its prog-

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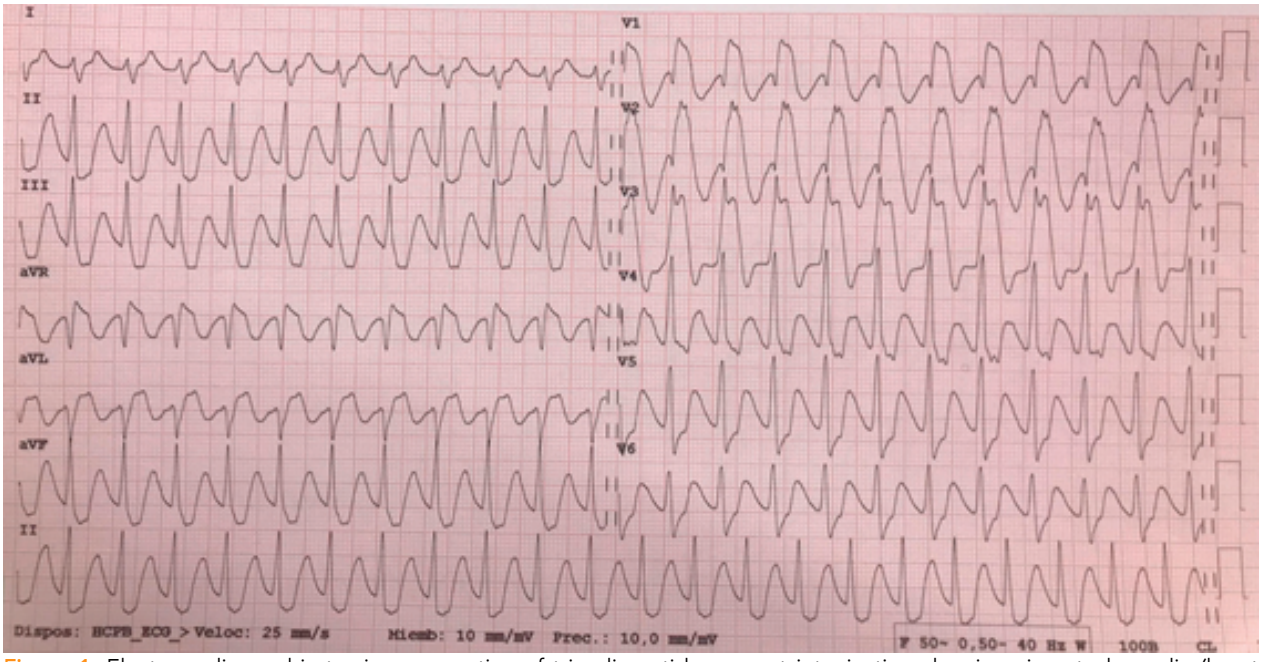

Figure 1. Electrocardiographic tracing suggestive of tricyclic antidepressant intoxication showing sinus tachycardia (heart rate 140 bpm), QRS widening (156 ms), and prolonged QTc (QT, 423 ms; QTc, 641 ms).
(Image courtesy of Dr. Salgado, Hospital Clínic de Barcelona).

nosis remains unclear.[8] The prevalence of Brugada phenocopy in the general population does not exceed 0.1%; however, it is higher among patients with TCA overdose, prompting studies aimed at analyzing the incidence of this pattern in such patients.[6] Brugada syndrome is a genetic cardiac disorder related to sodium channel dysfunction, without evidence of structural heart disease. It is associated with a high risk of sudden cardiac death in middle-aged adults. Sodium channel–blocking drugs, such as class IA or IC antiarrhythmics, are used to unmask the Brugada electrocardiographic pattern and aid in diagnosis.[6]

In cases of Brugada phenocopy, the electrocardiographic pattern disappears when TCA concentrations fall < 1 µmol/L. The appearance of this pattern raises the question of whether it implies a high risk of sudden death due to an underlying Brugada syndrome on baseline ECG. In many of these patients, electrophysiological studies have been performed, but administration of flecainide or ajmaline failed to reproduce ST-segment elevation, and no significant increase in sudden death risk was observed vs those who, despite TCA overdose, had a normal ECG.[9] Therefore, electrophysiological studies are not required in asymptomatic patients with TCA-induced Brugada phenocopy and transient Brugada ECG pattern.[10] In any case, there is insufficient scientific evidence to consider this Brugada phenocopy pattern benign; what is clear is that sodium channel blockade by TCAs and other drugs can cause electrocardiographic abnormalities and death due to ventricular arrhythmias resulting from sodium channel inhibition.

Sodium bicarbonate

Although sodium bicarbonate cannot be considered an antidote in the classical sense of the word, it is the cornerstone of treatment for this type of intoxication, as it reverses hypotension, arrhythmias (Figure 2), and conduction disorders. Alkalinization is performed with the goal of achieving and/or maintaining a pH > 7.45 (ideally 7.50).

Among the indications for using bicarbonate as an antidote in TCA intoxication are: QRS widening > 100 ms (QRS > 100 ms being the best predictor of seizures; > 160 ms, the best predictor of arrhythmias), R wave in aVR > 3 mm, presence of acidosis, severe arrhythmias, hemodynamic instability, and neurological involvement in cases of TCA ingestion > 1 g.[5]

Use and dosage of sodium bicarbonate

Bicarbonate is usually available in 1 M (8.4%) ampoules of 10 mL, equivalent to 1 mEq/mL; therefore, each 10 mL ampoule corresponds to 10 mEq = 0.84 g of sodium bicarbonate. There are no fixed doses for its use as an antidote, but high doses should always be employed to prevent severe complications. The electrocardiographic signs of TCA intoxication resolve with the administration of 1–2 mEq/kg of sodium bicarbonate. Treatment can begin with a bolus of 50–150 mEq of 1 M bicarbonate, which may be repeated every 3–5 minutes if needed.[10] This can be followed by an infusion of 250 mL of 1 M bicarbonate over 4–5 hours (50 mEq/h), continuing with 1/6 M bicarbonate over 6 hours, and repeating if necessary. In any case, administration should not exceed 250 mEq per 6 hours, and continuous monitoring of both therapeutic effects and limits is required,[11] along with careful observation for hypokalemia. Electrocardiographic monitoring and alkalinization should be maintained for at least 12–24 hours after normalization of ECG abnormalities.[3] This period may vary significantly due to the redistribution of TCAs from tissues.

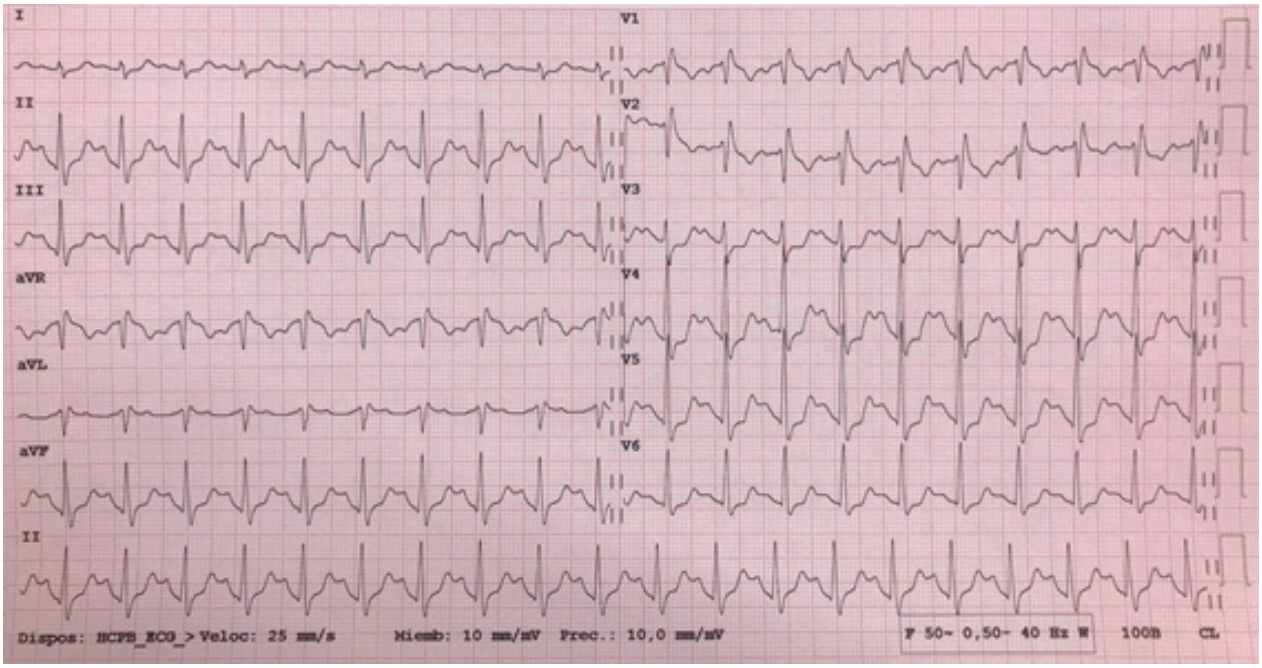

Figure 2. Progressive normalization of the ECG after bolus infusion of 80 mEq of 1 M bicarbonate (heart rate, 122 bpm; QRS, 129 ms; QT, 326 ms; QTc, 465 ms).
(Image courtesy of Dr. Salgado, Hospital Clínic de Barcelona).

Discontinuation of alkalinization should be done gradually, reducing the infusion rate by 25% every hour.

The limits for bicarbonate administration in correcting TCA-induced cardiovascular disturbances include resolution of the triggering disorder and/or the appearance of pH > 7.55, base excess > 10 mEq/L, plasma sodium > 150 mEq/L, significant hypervolemia (CVP >15 cmH_2O), or signs of pulmonary or cerebral edema.[3]

Another alternative for alkalinization in TCA intoxication is hypertonic saline (15 mEq/kg), which can also improve hypotension—sometimes even more effectively than bicarbonate, according to some studies.[12] Hyperventilation-induced respiratory alkalosis has minimal effect when used alone and does not modify QRS duration, producing only a modest improvement in hypotension.[12]

This effect of bicarbonate is not only beneficial in TCA intoxication but also in poisonings involving drugs that block ion channels and cause electrocardiographic widening of QRS and QT intervals, such as class Ia (procainamide) or Ic (flecainide) antiarrhythmics. These drugs, in turn, are contraindicated for treating arrhythmias associated with TCA intoxication.

Indications in cardiopulmonary resuscitation

In the toxicology section of the Advanced Life Support Guidelines published by the American Heart Association (AHA) in 2020, recommendations are presented based on a review of the scientific literature. With a class II recommendation and level C evidence, they state that the administration of hypertonic sodium bicarbonate solution (8.4%, 1 mEq/mL) for sodium channel blockade due to TCAs and other toxic substances is supported by human observational studies and animal experiments. Apart from its use in poisonings, bicarbonate is an alkalinizing agent primarily used to treat metabolic acidosis resulting from various disorders—such as diabetic ketoacidosis, diarrhea, renal disease, and shock. Although dose-finding studies are lacking, an initial dose of 1–2 mEq/kg (equivalent to 1–2 mL/kg of 8.4% bicarbonate), repeated as needed to achieve clinical stability while avoiding severe hypernatremia or hypokalemia, has been historically recommended and appears effective.[13,14] In cases of cardiac arrest, prolonged resuscitation according to standard clinical practice guidelines is mandatory, along with rapid infusion of 1 M sodium bicarbonate—and, if necessary, temporary extracorporeal circulation may be instituted for several hours while awaiting cardiac clearance of the drug.

Conclusions

In conclusion, and in response to the question posed in this article's title, bicarbonate acts more as an antidote—a substance that counteracts the harmful effects of another—than as an antiarrhythmic. It will only act as such under conditions in which a triggering or proarrhythmic substrate exists.

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