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A Commentary on Treatment of Tricyclic Antidepressant Overdose

Rahul Sawhney[1*] **and Peter A McCullough**[2]

[1]*Baylor University Medical Center, Dallas, TX, USA*

[2]*Baylor Heart and Vascular Institute, Dallas, TX, USA*

[*]**Corresponding author:** Rahul Sawhney, Baylor University Medical Center, Dallas, TX, USA, Tel: 214 820-3275; Fax: 281 845-7064; E-mail: Rahul.Sawhney@BSWHealth.org

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Abstract

Tricyclic antidepressants are still widely used for depression and other indications today. These drugs have a narrow therapeutic window and can have significant toxicities, with their cardio toxicity being especially striking and potentially fatal. For these reasons, tricyclic antidepressants are a drug of choice for suicide attempts. A key component in the management of tricyclic antidepressant toxicity is the administration of intravenous sodium bicarbonate which has its own potential adverse effects. In this article, we provide a brief commentary on tricyclic antidepressant toxicity, potential treatments, and a brief case vignette to highlight possible morbidity from toxicity treatment itself.

Keywords: Amitriptyline; Tricyclic antidepressant; QTc prolongation; TCA overdose; QRS prolongation; EKG changes; Tricyclic antidepressant overdose

Introduction

Tricyclic Antidepressants (TCAs) were discovered in the 1950s and originally used for depression until they yielded way to selective serotonin/norepinephrine reuptake inhibitors due to their lower side effect profiles and toxicities [1]. Today, TCAs are reserved for refractory cases of depression but often used for other indications such as migraine prophylaxis, insomnia, and chronic pain [2-4]. Therefore, study of these drugs remains important due to their narrow therapeutic window and prevalence in suicide attempts [5,6]. While randomized control trials are lacking, treatment of TCA overdose has been relatively well defined through animal studies, retrospective reviews, expert opinion, and case reports. We provide a brief commentary on TCA toxicity, its treatment, possible adverse effects of treatment, and an illustrative vignette.

Discussion

TCAs are complex drugs that inhibit serotonin and norepinephrine reuptake with many of sites of action, including cardiac fast sodium channels, sodium channels, L-type calcium channels, central and peripheral muscarinic acetylcholine receptors, peripheral alpha-1 adrenergic receptors, Histamine (H_1 and H_2) receptors, and central nervous system Gamma-Aminobutyric Acid (GABA) A receptors [7-9]. Accordingly, TCAs can have significant toxicities related to these various channels/receptors and can be fatal with as little as ten times the daily dose [10,11]. TCAs are absorbed in the small intestine, metabolized in the liver, and are extremely lipophilic with a high volume of distribution [9].

The structure of TCAs consists of a triple-ring backbone with variable amine side chains which affect the degree of neurotransmitter reuptake blockade (Figure 1). Serotonin reuptake is blocked to a greater degree by tertiary amines-including imipramine and amitriptyline-while norepinephrine is blocked to a greater degree by secondary amines-including desipramine and nortriptyline. Tertiary amines with their increased serotonin reuptake blockade also act preferentially upon peripheral alpha-adrenergic, histamine H_1, and muscarinic M_1 receptors leading to more pronounced sedation, anti-cholinergic excess, and orthostasis. In contrast, secondary amines have increased norepinephrine reuptake blockade and less histamine/muscarinic receptor affinities thus leading to less sedation and hypotension [10].

Potential TCA toxicities vary across the organ systems but can include seizures, bone fractures, anti-cholinergic excess, anti-histamine excess, tremor, diaphoresis, atrioventricular conduction delay, tachyarrhythmias, hypotension, bradycardia, and sudden cardiac death. Initial supportive care for TCA toxicity follows the "airway, breathing, circulation" mantra and includes endotracheal intubation for those who cannot protect their airway, intravenous (IV) crystalloid for hypotension, and sodium bicarbonate for cardiac conduction abnormalities [7-9,12,13]. Following initial stabilization, oral activated charcoal can be given if within 2 hours of ingestion. Agitation and/or seizure activity can be managed with benzodiazepines; although these are used cautiously given the risk of over sedation from medication effect coupled with TCA induced anti-histamine excess. Admission to the intensive care unit is usually necessary [9].

More specifically, cardiac conduction abnormalities associated with TCA toxicity include prolongation of QRS duration, Corrected QT Interval (QTc), and right-axis deviation on Electrocardiogram (ECG) [7-9,14]. Increased QRS duration is an independent predictor of seizures and ventricular arrhythmias in acute TCA overdose [15]. Prolonged QTc occurs both in therapeutic and toxic doses of TCAs and is mediated by class 1a antiarrhythmic type inhibition of cardiac fast sodium channels with resultant lengthening of the cardiac action potential [7,16]. If cardiac conduction delays are noted, terminal right-axis deviation is greater than 120 degrees, and/or hypotension is refractory to fluid resuscitation, serum alkalinization should be attempted with an IV bolus of 2-3 ampules of sodium bicarbonate (50 mEq/ampule). This can be repeated after 5 minutes if no response is noted. Following initial boluses, a sodium bicarbonate infusion should

be started and maintained until QRS widening resolves after which the infusion can be tapered [7,12,17,18]. Serum alkalinity can also be maintained with hyperventilation if the patient is intubated [19,20]. Using the QTc interval to guide therapy has not been reported; rather, the literature cautions that serum alkalinization inevitably leads to hypokalemia which can further prolong the QTc [7]. Increased serum pH decreases the affinity of TCAs for sodium channels while increased extracellular sodium concentration increases the trans membrane electrochemical gradient and reduces TCA blockade of cardiac fast sodium channels [12,21]. With this treatment usually 80% of patients will have narrowing of their QRS duration and more than 90% will have improvement of their hypotension [22].

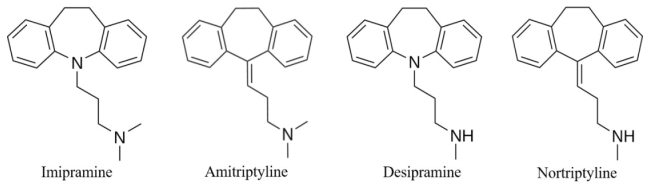

Figure 1: Tricyclic antidepressants and their structures. The triple-ring backbone denotes the drug class while the number of side chain amine substitutions denotes the subclass: imipramine and amitriptyline are tertiary amines (two methyl groups attached to terminal side chain) while desipramine and nortriptyline are secondary amines (one terminal side chain methyl group).

Lipid Emulsion (LE) therapy has been described in cases of refractory arrhythmia or hemodynamic instability. The most likely mechanism for its efficacy is the 'lipid sinks' theory in which the lipophilic TCA is engulfed in the lipid molecule and rendered ineffective [23]. 20% lipid emulsion is infused as a 1.5 mL/kg bolus up to 2-3 times, followed by a 0.25 mL/kg/min infusion for 30-60 minutes [24]. Use of this therapy is not first line however due to significant possible adverse effects including fat embolism, pancreatitis, infection, acute lung injury, and acute respiratory distress syndrome [23,25]. Current guidelines recommend usage of LE in TCA toxicity with hemodynamic instability unresponsive to sodium bicarbonate and/or impending cardiac arrest [26,27].

We recently encountered a case of TCA toxicity in which 18 ampules of sodium bicarbonate were rapidly administered based on guidance from a regional Poison Control Center due to significant prolongation of QRS duration and corrected QT interval (QTc) on ECG (Figure 2). Subsequent serum chemistries revealed acute hypernatremia (142-161 mEq/L in 3 hours), hypokalemia (3.6-2.8 mEq/L), and profound metabolic alkalosis (serum bicarbonate 21-45 mEq/L). Sodium bicarbonate was discontinued in favor of serum alkalinization through hyperventilation and the hypernatremia was slowly corrected with IV dextrose and free water. Hypokalemia was treated with intravenous potassium chloride with gradual resolution of the prolonged QTc. The serum pH was maintained between 7.5 and 7.55. Within 24 hours the ECG abnormalities improved (Figures 3 and 4), serum chemistries returned to normal, and the next day the patient was discharged. 1 month later, an ECG obtained for an unrelated emergency department visit showed resolution of QRS widening and QTc prolongation (Figure 5).

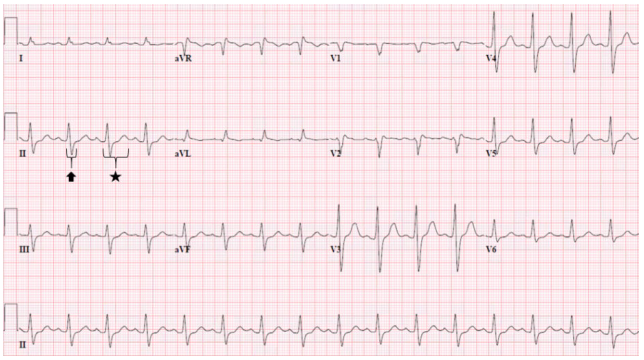

Figure 2: Significant cardiac conduction abnormalities noted on ECG 1 hour after arrival and 2 hours post-amitriptyline ingestion. QRS duration increased to 152 ms (arrow) and QTc prolonged to 538 ms (star). QRS axis is normal.

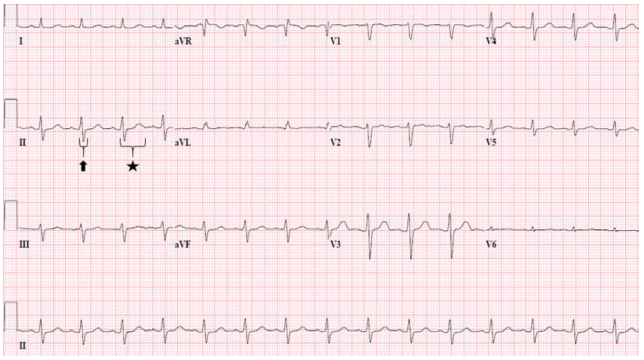

Figure 3: Convalescence of ECG changes 48 hours following sodium bicarbonate treatment with QRS duration 110 ms (arrow) and QTc 494 ms (star). QRS axis is normal.

This case demonstrated a serious potential side effect of intensive sodium bicarbonate therapy. Similar serum chemistry abnormalities, albeit within a less dramatic timeframe, have been described with massive bicarbonate therapy in another reported case [13]. A rapid increase and then decrease in serum sodium can potentially lead to seizures and/or osmotic demyelination syndrome with resultant permanent neurologic damage [28,29]. Alkalinization of the plasma is associated with hypokalemia which can worsen the QTc prolongation and potentially lead to ventricular arrhythmias [30]. This was notable in our case as the QTc on presentation was prolonged at baseline (presumably due to therapeutic TCA use), worsened considerably with iatrogenic hypokalemia from bicarbonate treatment, and took much longer to return to normal than the QRS duration. Thus, bicarbonate therapy should be administered carefully with monitoring of pH, serum sodium, potassium, bicarbonate, and the QRS and QTc intervals on ECG.

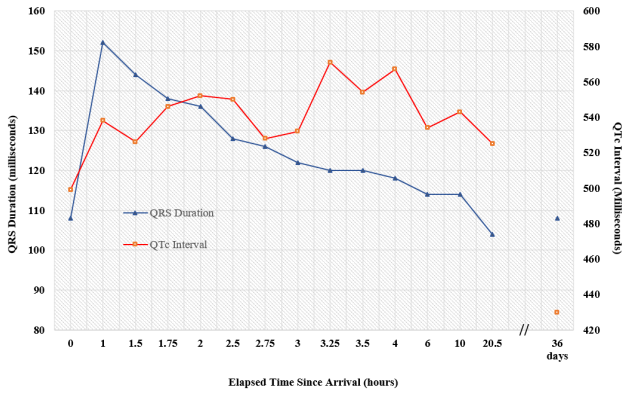

Figure 4: Time lapse of ECG changes from arrival to nearly 24 hours post treatment with follow up values showing complete resolution after 1 month. QTc calculated using Bazett's formula.

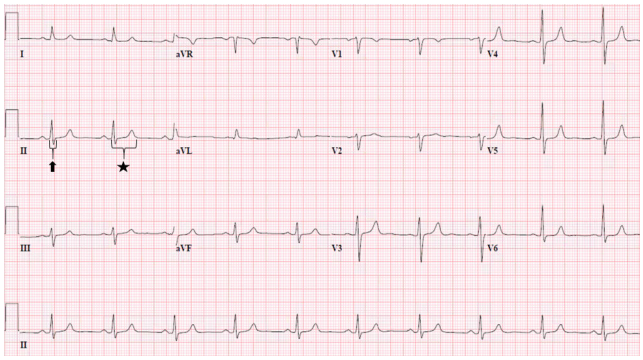

Figure 5: ECG obtained during an unrelated visit to the emergency department 3 months later. Resolution of ECG changes with QRS duration 108 ms (arrow) and QTc 430 ms (star). QRS axis is normal.

Conclusion

Treatment of TCA toxicity is multifaceted and includes a combination of IV fluids, careful use of sodium bicarbonate, and supportive care. Due to the complex physiology of TCAs and the variety of sites on which they act, assiduous attention must be paid to pH, serum chemistries, and ECG during the course of treatment. Aggressive sodium bicarbonate therapy may be necessary to narrow the QRS duration but may result in QTc prolongation and additional, potentially life-threatening, metabolic abnormalities.

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Conflicts of Interest

Both authors report neither conflicts of interest nor industry relationships that are relevant to the content of this article.

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