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REVIEW

What is the role of lidocaine or phenytoin in tricyclic antidepressant-induced cardiotoxicity?

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Introduction. Tricyclic antidepressant (TCA) poisoning is a relatively common occurrence and remains a significant cause of mortality and morbidity. Deaths from TCA toxicity are typically due to cardiovascular events such as arrhythmias and hypotension. Cardiovascular toxicity may be multifactorial. However, the primary mechanism is a TCA-induced membrane-depressant or "quinidine-like" effect on the myocardium resulting in slowing down of phase 0 depolarization of the cardiac action potential and subsequent impairment of conduction through the His-Purkinje system and myocardium. This effect is manifest as QRS prolongation on the EKG, atrioventricular (AV) block, and impairment in automaticity leading to hypotension and ventricular dysrhythmia. Primary treatment strategies include sodium bicarbonate, hypertonic saline, and correction of any conditions that may aggravate this toxicity such as acidosis, hyperthermia, and hypotension. In cases of severe TCA toxicity, administration of sodium bicarbonate may be insufficient to correct the cardiac conduction defects. Use of lidocaine or phenytoin, both Vaughan Williams Class IB antiarrhythmic agents, has been reported as an effective adjunctive therapy in cases of severe cardiotoxicity. *Methods*. Thirty articles of interest were identified by searching PubMed, abstracts from meetings, and the reference sections of related primary and review articles and toxicological texts. *Role of lidocaine and phenytoin*. Lidocaine and phenytoin also cause sodium channel blockade, but unlike Class IA or IC agents do not depress phase 0 depolarization in healthy cardiac tissue. Lidocaine and phenytoin dissociate relatively quickly from cardiac sodium channels. Sodium channels have faster recovery times after exposure to lidocaine (1–2 s) and phenytoin (0.71 s), than with some TCAs such as amitriptyline (13.6 s), but not others (e.g., imipramine at 1.6 s). In experimental models of amitriptyline poisoning, lidocaine co-administration resulted in decreased sodium channel blockade compared to amitriptyline alone. This correlated with clinical improvement, including normalization of QRS interval, improved hypotension, and decreased mortality. It is postulated that lidocaine's rapid binding to the sodium channel may directly displace slower acting agents from the channel, leaving more channels unbound, and therefore be able to facilitate cardiac conduction. Phenytoin may act through a similar mechanism as lidocaine, although experimental studies suggest that it does not compete directly for the same sodium channel binding site as TCAs. Allosteric modulation of the TCA binding site may occur in the setting of phenytoin use. The evidence for using phenytoin in treating TCA-induced sodium channel blockade is less convincing than that for lidocaine. Human trials are limited to case series and, in most human exposures in which there appeared to be efficacy, the toxicity was not severe. *Conclusions*. Although there appears to be more evidence for the use of lidocaine than phenytoin as adjunctive treatment for TCA-associated cardiotoxicity, specific clinical indications and dosing recommendations remain to be defined. We recommend the use of lidocaine in cases in which cardiotoxicity (arrhythmias, hypotension) is refractory to treatment with sodium bicarbonate or hypertonic saline, or in which physiological derangement (e.g., severe alkalosis or hypernatremia) limits effective use of these primary strategies.

Keywords Tricyclic antidepressant; Poisoning management; Lidocaine; Phenytoin; IB agent

Introduction

Tricyclic antidepressant (TCA) poisoning is a relatively common occurrence and remains a significant cause of mortality and morbidity. In 2008, there were 11,033 cases of reported TCA overdose and 12 deaths in the United States.[1] TCA toxicity is protean, with the most serious effects occurring in the central nervous and cardiovascular systems. Overdose may result in seizure, delirium, sedation, arrhythmias, cardiac conduction delays, hypotension, and anticholinergic effects.[2] Current treatment includes decontamination, administration of sodium bicarbonate or hypertonic saline, hyperventilation, and supportive care.[3]

In cases in which QRS widening or ventricular arrhythmias persist, despite aggressive use of sodium bicarbonate or hypertonic saline, lidocaine and phenytoin are typically recommended (UpToDate(TM), eMedicine(TM)).[4,5] Lidocaine and phenytoin are Vaughan Williams Class IB antiarrhythmic

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agents that, by different mechanisms, slow down sodium conductance through cardiac sodium channels, thus slowing the conduction of the cardiac action potential. Class IB agents differ from other Class I antiarrhythmic drugs by a particular way in which they interact with the sodium channel. Class IB agents bind to and dissociate from these channels very quickly whereas Class IA agents, such as quinidine or procainamide, and Class IC agents, including flecainide and propafenone, have slower association/dissociation binding kinetics. The sodium channel to which Class I agents bind is also one of the primary sites of TCA-associated cardiotoxicity and the resultant slowing of depolarization, in particular affecting phase 0 of the cardiac action potential, is described as a "quinidine-like effect."

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Methods

A PubMed search (1948-July, 2009) was conducted for the keywords "tricyclic antidepressant," and, specifically, "imipramine," "desipramine," "nortriptyline," "amitriptyline," "poisoning" or "overdose," and "lidocaine" or "phenytoin." This generated 105 individual abstracts; these were all evaluated and 21 were deemed relevant to the question of treatment of TCA toxicity with lidocaine or phenytoin. Additionally, the journal *Clinical Toxicology* (1968–2010) was searched using the same keywords as the PubMed search. Included in this review were abstracts from the *North American Congress of Clinical Toxicology* (NACCT) and the *Congress of the European Association of Poison Centres and Clinical Toxicologists* (EAPCCT) over the same time period. Additional articles were identified by reviewing the reference sections of related primary and review articles and toxicology texts. In total, 25 peer-reviewed articles, a mix of case reports, case series, animal studies, and review articles were deemed relevant. We also expanded our search to include lidocaine and/or phenytoin treatment of poisonings caused by related quinidine-like compounds, including cocaine and dextropropoxyphene. This generated five additional articles.

Cardiovascular effects of TCAs

Cardiac toxicity represents the most significant cause of TCA mortality, with most deaths attributable to arrhythmias or hypotension.[2] Within cardiac tissue, TCAs have myriad effects. Their anticholinergic properties result in an increased sinus rate. Sinus tachycardia is the most common arrhythmia noted in TCA overdose and occurs at doses lower than those producing conduction delays.[6] TCAs inhibit neuronal reuptake of several neurotransmitters, including dopamine, norepinephrine, and serotonin. Increased concentration of these catecholamines in cardiac tissue can contribute to sinus tachycardia and transient hypertension, and may initiate or contribute to ventricular arrhythmias.[7]

TCAs also bind to the hERG channel. This channel involves the rapid delayed rectifying current that conducts potassium out of the myocyte. Inhibition of the hERG channel affects cardiac myocyte repolarization that may appear as QT prolongation. This may increase the risk of torsades de pointes, a malignant ventricular arrhythmia, although the tachycardia also commonly seen in TCA overdose may be somewhat protective in this context.

Additionally, and perhaps most importantly, TCAs cause inhibition of cardiac sodium channels and slowing of phase 0 depolarization, resulting in lengthening of the cardiac action potential.[8,9] This can result in conduction delays (appreciated by widened QRS duration on a 12-lead EKG), ventricular arrhythmias, and hypotension. TCAs share this "quinidine-like" or "membrane-stabilizing" effect with many other medications, including Class IA and IC antiarrhythmics (e.g., procainamide, quinidine, flecainide, and propafenone), the beta-blocker propranolol, anticonvulsants (e.g., phenytoin and carbamazapine), antihistamines (e.g., diphenhydramine), and even certain narcotics (e.g., dextropropoxyphene) and cocaine.[10]

Not all wide-complex tachyarrhythmias associated with TCA poisoning can be attributed to the toxic effects of TCA at sodium channels. Other factors such as acidosis, tissue hypoperfusion, or increased excitability in the setting of inhibition of catecholamine reuptake also increase the risk of ventricular tachycardia. TCA poisoning often results in acidosis, either from respiratory depression or metabolic acidosis caused by poor tissue perfusion or persistent seizure activity.[2] Systemic acidosis can aggravate TCA cardiotoxicity and has been shown to worsen both hypotension and cardiac action potential delay.[11] Treatments that produce serum alkalinization have been shown to improve cardiac function and decrease arrhythmias.[3]

Primary treatment of TCA-associated cardiotoxicity

Primary treatment of TCA-associated cardiotoxicity – as well that caused by related agents – is aimed at reducing the sodium channel blocking effects of these drugs by inducing hypernatremia and/or systemic alkalinization. As early as the 1950s, sodium lactate was used to reverse the effects of procainamide and quinidine, drugs that affect cardiac sodium channels in a manner similar to TCA's.[12] Sodium bicarbonate has been used extensively in the treatment of TCA and related drug toxicity for the past 35 years.[3,13,14]

Intravenous (IV) hypertonic sodium bicarbonate produces a rise in both serum sodium concentration and serum pH. Its efficacy in treating TCA poisoning was first documented in the 1970s, when Brown et al.[13] observed resolution of TCA-induced arrhythmias in five children following sodium bicarbonate administration. Numerous subsequent animal studies,[6,13,15,16] case reports,[14,17,18] and case series[19] have demonstrated sodium bicarbonate's efficacy in reducing TCA-induced conduction delay, QRS widening, arrhythmias,

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and hypotension. Sodium bicarbonate has also been shown to be effective in the treatment of cardiotoxicity related to other sodium channel blocking agents, including encainide, flecainide, cocaine, and propafenone.[10]

The extent to which sodium bicarbonate's efficacy results from the increase in sodium concentration as compared to its effect on serum alkalinization remains unclear. Serum alkalinization by other means, specifically hyperventilation and administration of the nonsodium buffer tris(hydroxymethyl)aminomethane, also appears effective in reversing TCA-induced dysrhythmias and hypotension.[15,20] This effect may be due in part to an increase in plasma protein binding by TCAs at alkaline pH, with a subsequent decrease in available unbound drug.[15] Additionally, at higher pH, the proportion of nonionized TCA is greater and it is postulated that the nonionized form may have lower affinity for sodium channels. However, rapid equilibration between unbound TCA concentrations and tissue concentrations, independent of protein binding, is likely to limit the effect that changes in protein binding have on toxicity.[5] It is more likely that the primary effect of increased pH is directly at the ion channel. Experiments performed using human atrial myocytes have demonstrated increased dissociation of imipramine from sodium channels in the presence of alkalosis.[21]

Sodium administration by itself, in the absence of serum alkalinization, is also effective. Hypertonic saline has been shown to be at least as effective as sodium bicarbonate in narrowing the QRS duration and suppressing ventricular arrhythmias in TCA overdose.[22,23] Work performed in canine Purkinje fibers has shown that the effect of serum sodium concentration and increased pH is additive in treating amitriptyline-induced cardiotoxicity.[24] *In vitro* studies have shown that a combined treatment strategy, raising extracellular sodium concentration to 160 mmol/L and pH to 7.6, reduces cardiac toxicity due to flecainide, mexiletine, and imipramine.[24]

Cardiac defibrillation should be considered for the treatment of wide-complex tachycardia that does not respond to sodium and sodium bicarbonate administration, especially in hemodynamically unstable patients.

Adjunctive treatment of TCA cardiotoxicity

In addition to the treatment strategies involving sodium loading or serum alkalinization, several adjunctive agents have been utilized in cases of TCA cardiotoxicity. Phenytoin, lidocaine, and magnesium are mentioned often in the primary literature and in bedside clinical resources (UpToDate™, eMedicine™)[4,5] as adjunctive treatments for TCA toxicity and TCA-related arrhythmias. Magnesium is often used both empirically for prolonged QT intervals and specifically to treat torsades de pointes, whereas phenytoin and lidocaine are recommended for the treatment of refractory membrane-depressant effects.

Although the use of a Class IB agent may seem counterintuitive for treating sodium channel blockade, it is just this effect in the context of specific pharmacodynamic and pharmacokinetic interactions with these receptors that may be responsible for IB efficacy in treating TCA-associated cardiotoxicity.

Phenytoin

Of the aforementioned adjunctive agents, phenytoin has been the most studied. Phenytoin acts as a Class IB antiarrhythmic and in normal cardiac tissue either has no effect or minimally increases the rate of phase 0 depolarization.[25] Animal experiments have shown conflicting results, with some studies showing benefit and an equal number or more showing no benefit. Kulig et al.[26] demonstrated that pretreatment with phenytoin was effective in preventing ventricular arrhythmias in dogs that had been administered toxic concentrations of amitriptyline. However, Mayon and Ruiz[27] showed that IV pretreatment with phenytoin in rabbits did not alter the fatal dose of amitriptyline or the dose at which QRS prolongation or ventricular arrhythmia was noted. Callaham et al.[28] showed an increase in ventricular tachycardia in dogs that were treated with phenytoin before amitriptyline dosing.

Human data are limited and no randomized controlled trials have been performed to date. In a small case series, 10 patients exhibiting cardiac conduction abnormalities due to TCA poisoning were administered low doses of IV phenytoin (5–7 mg/kg) shortly following presentation to an emergency department (ED). Eight of these patients presented with combined first degree AV block and intraventricular conduction delay; one had first degree AV block alone, and one had intraventricular-conduction defect alone. Eight had ingested amitriptyline (dose range 1,500–4,400 mg), one had ingested doxepin (3,600 mg), and one had ingested an unknown amount of amitriptyline and perphenazine. Supportive measures were employed (fluids, oxygen); all other pharmacological treatment (e.g., sodium bicarbonate, hypertonic saline) was withheld. Five of the patients showed normalization of their PR interval and QRS duration within 46 min of treatment; the remaining five patients showed improvement immediately following administration of phenytoin, and normalization within 14 h of presentation to the ED. The mean decrease in PR interval following treatment was 29 ms, occurring in a mean time of 36 min. The mean decrease in QRS duration was 24 ms, occurring in a mean time of 39 min. It should be noted, however, that none of the patients was hemodynamically unstable before treatment, and none exhibited significant acidosis or alkalosis on arterial blood gas measurement. One of the patients did experience an episode of profound hypotension – initially unresponsive to fluid and dopamine infusion – approximately 6 h after phenytoin administration.[29]

In one prospective study,[30] only published as an abstract, seven patients presenting to an ED with TCA-related toxicity

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were administered IV phenytoin and compared to seven matched control patients who did not receive phenytoin. All patients had QRS durations greater then 100 ms; three patients in the phenytoin group had ventricular arrhythmias (bigeminy and hypotension, ventricular tachycardia, idioventricular rhythm and hypotension). The average dose of phenytoin administered was 915 mg (14.5 mg/kg), infused at rates <25 mg/min, with peak plasma concentrations of 22 ± 7.5 mg/L. In the phenytoin group, QRS duration decreased by 55 ± 25% (range 25–100%) in 58 ± 38 min from the patient's baseline QRS. QRS duration for controls did not change spontaneously in 3 h, and narrowed by only 25 ± 26% in 5.7 ± 3.5 h ($p < 0.005$ compared with phenytoin group). In each of the three cases of ventricular arrhythmia, the rhythm normalized during phenytoin administration.[30] This report is somewhat confusing to interpret. Including "100%" decrease in QRS duration in the phenytoin group suggests that the resulting QRS duration would be 0. Although this could technically be true if the patient became asystolic or died, this was not clarified in the abstract. Additionally, even a median or mean decrease of 55% would involve a patient's QRS changing from 150 to 73 ms which seems unlikely.

Some clinicians are concerned about using phenytoin in the setting of severe TCA-associated cardiotoxicity as the diluents of phenytoin, propylene glycol, and ethanol in particular, might exacerbate TCA-induced hypotension. Using the classification of recommendations and level of evidence by the American Heart Association and other organizations, we rate these recommendations as Class IIB, level of evidence B. Class IIB is defined as benefit greater or equal to risk and additional studies are needed. Level of B evidence means efficacy is less well established, there is conflicting evidence or nonrandomized trials exist that are supporting the recommendation. Thus, treatment with phenytoin may be considered.

Lidocaine

Lidocaine is a Vaughan Williams Class IB antiarrhythmic agent which shares many properties with phenytoin and is referenced as a second-line agent in the treatment of TCA toxicity and TCA-related arrhythmias.[7] There is evidence to suggest that lidocaine's effectiveness in treating TCA-related cardiotoxicity may be predicated, at least in part, on competitive binding. Much of the data to support this notion comes from ex vivo studies using lidocaine with agents that act in a similar manner as TCA's at cardiac sodium channels, specifically dextropropoxyphene and cocaine.

Dextropropoxyphene is a weak mu-opiod receptor agonist that also exhibits potent sodium channel blocking effects, similar to lidocaine, procainamide, and quinidine, although it is classified as a Vaughan Williams Class IC antiarrhythmic whereas most TCAs and quinidine are Vaughan Williams Class IA drugs. Both Class IA and Class IC drugs slow down phase 0 depolarization of the cardiac action potential as described in the introduction. Toxicity can result in hypotension, ventricular arrhythmia, QRS duration prolongation, and cardiovascular collapse.[31]

Experiments using *in vitro* rabbit myocytes have demonstrated a use-dependent block of inward sodium current by dextropropoxyphene, similar to that caused by TCAs.[32] When the rabbit myocytes were exposed to lidocaine with dextropropoxyphene, however, a relative decrease in this steady state blockade was observed. The authors noted that dextropropoxyphene alone exhibited a slow block recovery time – nearly 21 s – whereas lidocaine-induced block of sodium current resolved within 2–3 s. The authors suggest that lidocaine's rapid on/off kinetics may result in more sodium channels being unbound and thus available to propagate an action potential.[32]

This effect has also been described between lidocaine and cocaine. Cocaine exhibits properties similar to IC antiarrhythmic drugs (e.g., flecainide and propafenone) and in animal studies exhibits relatively slow on/off and binding dissociation with cardiac sodium channels.[33] Like TCAs, cocaine in high doses can result in conduction delay, increased QRS duration, and development of ventricular arrhythmias.[34] In a guinea-pig myocyte model, lidocaine added to a cocaine-containing perfusate decreased QRS duration 60% from that due to cocaine alone. The magnitude of the reversal was similar to that caused by treatment with sodium bicarbonate.[35,36] Studies using a canine papillary muscle preparation showed that the presence of lidocaine improved cocaine-delayed phase 0 conduction velocity, and shifted the curve correlating cocaine concentration and reduction of conduction velocity to the right.[37] Finally, in mice exposed to toxic concentrations of cocaine, pretreatment with lidocaine reduced overall mortality.[38]

In an *ex vivo* rabbit myocyte model of TCA toxicity, Barber and colleagues[39] demonstrated a competitive binding effect between amitriptyline and lidocaine. Amitriptyline was noted to induce a use-dependent blockage of inward sodium current, with slow recovery time (13.6 ± 3.2 s) in myocytes. In the presence of lidocaine, at pulse frequencies of lower than 1 Hz, less block of sodium current was noted than with amitriptyline alone. This same experiment failed to show the same direct relationship between phenytoin and amitriptyline.[39]

Finally, in experiments using a swine model of nortriptyline toxicity, lidocaine administration caused displacement of nortriptyline from binding sites in pulmonary tissue. Lidocaine also resulted in normalization of nortriptyline-induced QRS widening.[40]

The clinical implications of this competitive binding model are unclear, but could be important. Specific TCAs have significantly different kinetics with respect to sodium channel blockade. Although amitriptyline exhibits a relatively high time to block recovery at 13.6 s, imipramine, at 1.6 s, is similar to lidocaine.[32] Thus, there may be greater relative efficacy in lidocaine treatment of TCA exposures with slower sodium channel recovery times such as amitriptyline and nortriptyline than imipramine or desipramine. For

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other sodium channel antagonists, these recovery times also appear to play a role as the majority of literature describing efficacy with lidocaine is in treating toxicity after exposure to agents such as propoxyphene and cocaine, both with recovery times similar to amitriptyline. Further study is warranted to determine if increased time to sodium channel recovery correlates with cardiotoxicity (arrhythmias, conduction delay, hypotension), and if the administration of a "competitive" agent, such as lidocaine or phenytoin, will result in decreased toxicity.

There is currently limited data with regard to lidocaine treatment of TCA-related toxicity in animal models, from human data and from clinical experience. Nattel and Mittleman[41] demonstrated a decrease in amitriptyline-induced ventricular ectopy with the administration of lidocaine in dogs. The effect was transient, however, and was associated with hypotension. In separate experiments, lidocaine had no effect on arrhythmias induced by amitriptyline in four dogs,[42] and successfully converted only 1 of 10 rats with TCA-related ventricular arrhythmias.[43]

Human data are limited to one case report involving imipramine and one case series and one case report of lidocaine used for dextropropoxyphene-associated cardiotoxicity. These reports suggest a beneficial effect of lidocaine in the treatment of sodium channel blockade.

Dolara and Franconi[44] in 1977 described the case of a 6-year-old boy who was presented to a pediatric hospital comatose and convulsing, approximately 4 h after ingesting 1 g of imipramine. The patient was profoundly hypotensive as well and developed ventricular tachycardia shortly after arrival. He was given pyridostigmine 5 mg IM and an IV infusion of hypertonic saline (608 mmol/L at 0.1 mL/s), then a 1% lidocaine IV infusion. Minutes after the lidocaine was initiated, the patient's tachyarrhythmia reverted and his blood pressure normalized.

In a retrospective analysis of 35 cases of TCA poisoning, Langou et al.[45] described 13 patients who exhibited frequent ventricular ectopy (defined as greater than 60 premature ventricular contractions per hour), presumably as a result of cardiotoxicity. All 13 received supportive care, including IV fluids and respiratory support; none received sodium bicarbonate or hypertonic saline. IV lidocaine (2.0 ± 0.5 mg/min) was used to control ventricular ectopy in all 13 cases; all improved clinically and exhibited no ventricular ectopy after 36–72 h.

Whitcomb et al.[32] described a patient in extremis following ingestion of dextropropoxyphene who was given lidocaine with subsequent and rapid clinical improvement. The patient presented initially with seizures and hypotension. She received lorazepam and a phenytoin load was initiated (then subsequently terminated when her hypotension worsened). The patient then received four lidocaine 100 mg boluses, each of which transiently normalized the prolonged QRS duration and reversed her hypotension. An infusion of lidocaine (2 mg/min) was initiated following the fourth bolus dose. The patient stabilized and showed gradual clinical improvement over the next 12 h.

Conclusions

Lidocaine appears to act by competitively binding at the same site on cardiac sodium channels as TCAs, while phenytoin's actions in decreasing TCA cardiotoxicity appear more complicated and may include allosteric modulation of the TCA binding.

The effect of lidocaine appears to be greater for certain TCAs such as amitriptyline and nortriptyline, which have the slowest sodium channel recovery times. Based on the limited evidence available, we recommend the use of lidocaine over phenytoin for TCA toxicity when cardiotoxicity persists despite the treatment with sodium bicarbonate and/or hypertonic saline. Lidocaine may also be considered when severe alkalosis and/or hypernatremia limit the effective use of sodium bicarbonate, which is the primary therapy. Lidocaine should be particularly considered for TCA exposures with slower sodium channel recovery times such as amitriptyline and nortriptyline.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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