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Esmolol for intractable ventricular arrhythmias in major amitriptyline toxicity

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SUMMARY

A massive tricyclic overdose of 10 g of amitriptyline resulted in cardiovascular collapse with multiple episodes of ventricular tachycardia and ventricular fibrillation despite aggressive attention to current recommended therapy of sodium bicarbonate and hypertonic saline, and correction of electrolytes. Second-line antiarrhythmic therapies failed to reduce the recurrent deterioration to malignant ventricular rhythms. Progression to extracorporeal support was avoided by the use of a titrated esmolol infusion. We discuss the physiological rationale by which esmolol may prevent tachyarrhythmia and fibrillation in severe amitriptyline toxicity.

BACKGROUND

Lethal ventricular arrhythmias are hard to treat in this toxicity. The evidence is scarce on best choice once first-line therapy fails. Beta-blockers had been used in the past successfully but with concerns about safety. The ultrashort acting beta-blockers like esmolol can be used more safely in this scenario, and should be reconsidered, particularly given the mechanism of ventricular arrhythmias in these poisonings.

CASE PRESENTATION

A woman in her 30s presented to a remote hospital after a very large intentional amitriptyline overdose of up to 10 g (up to 128 mg/kg). Her medical history included only major depressive disorder, and there was no family history of arrhythmia or cardiac disease.

She required immediate intubation for persisting coma and seizures. Sodium bicarbonate and hyper-ventilation were initiated for electrocardiographic (ECG) criteria of widened QRS and coma, and titrated to a pH of 7.55. After discussion with a toxicology specialist, intralipid was commenced and aeromedical retrieval was arranged. The aircraft was diverted to our hospital after two inflight episodes of ventricular fibrillation (VF) requiring defibrillation.

At our hospital, the patient continued to have frequent and intractable ventricular tachycardia progressing to fibrillation, requiring cardiopulmonary resuscitation (CPR) and defibrillation. She had aggressive electrolyte replacement aiming for potassium levels of 4.5–5, magnesium levels > 1.3 mmol/L and normal ionised calcium. Multiple repeated doses of sodium bicarbonate up to 1600 mmols and hypertonic saline 1500 mmols were administered, titrated to achieve a pH of 7.55, and Na > 155. The ECG showed sinus tachycardia with increasingly

broader complexes progressing to monomorphic VT of 200 beats/min with increasing automaticity then deteriorating to ventricular fibrillation, with no features of a torsades pattern or Brugada criteria. Further infusion of intralipid was given (6 hours after the first) and further magnesium infusion and then lidocaine infusion were all given without apparent effect. Inotropes and pressors were required to maintain a perfusing mean arterial blood pressure of > 60 mm Hg.

In view of the failure to resolve the arrhythmias and echocardiographic evidence of reducing ventricular function after multiple defibrillations, the patient was discussed with a tertiary cardiac intensive care unit (ICU) for consideration of extracorporeal cardiac support (ECMO). To support the progressively lower cardiac output and to facilitate transfer an intra-arterial balloon pump (IABP) was inserted.

Despite the above treatments, the patient continued to have VT/VF, a total of 28 episodes requiring CPR and defibrillation over the next 8 hours. It was observed that after a successful defibrillation the ECG would normalise when the rate was below 100 and begin to have progressively longer QT interval as the rate increased. Given that all treatment goals were being met and arrhythmias were continuing, a trial of intravenous esmolol (ultra-short acting B-blocker) was given. The patient's heart rate initially reduced to 60 beats/min and slowly increased to 100 over the next 30 min with no arrhythmias occurring.

When the heart rate returned above 100 beats/min, the ECG again displayed increased QRS duration (> 200 ms) and automaticity, provoking ventricular tachycardia which soon deteriorated to VF. An esmolol infusion was recommenced, targeting a heart rate of 80–100 beats/min. The ECG now showed a rate of 98 beats/min with QRS duration of 120 ms. The patient had no further arrhythmias with this therapeutic manoeuvre and was stable on transfer to the tertiary cardiac centre, with a reducing inotrope requirement. Attempts to stop or wean the esmolol infusion resulted in recurrence of tachycardia then VT/VF and the esmolol was continued for 72 hours. The IABP was weaned within 48 hours, and the patient extubated on day 7.

DIFFERENTIAL DIAGNOSIS

There was no family history suggesting that the patient had an underlying familial or genetic tendency to VF such as Brugada syndrome, where the use of amitriptyline can block sodium channels I_{Na} , I_{to} and I_{Kr} leading to unmasking of Brugada



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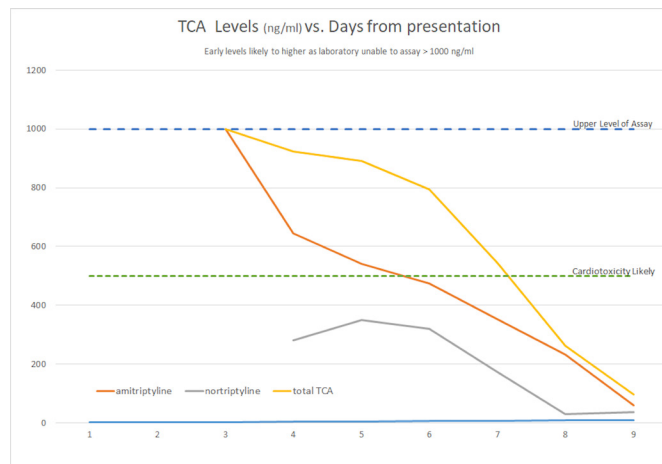


Figure 1 Amitriptyline/nortriptyline levels versus days from presentation. The tricyclic levels from the first days of the admission were higher than the upper level of the assay.

ECG phenotype, or exacerbate a Congenital prolonged QT syndrome.^{1 2} It is unlikely that she had undiagnosed critical coronary arterial disease in view of her age and subsequent follow-up. The patient had taken one of the largest overdoses we are aware of, as much as 10 g of amitriptyline, and this was evidenced by retrospective amitriptyline levels from the day of admission being beyond the limits of the assay (>1000 $\mu\text{mol/L}$), quantifiable by day 4 as 994 $\mu\text{mol/L}$ and normalising to 232 $\mu\text{mol/L}$ by day 10 (see figure 1). Some people with cytochrome p phenotypes can have delayed clearance of amitriptyline, but this is not routinely assessable.

DISCUSSION

The most common mode of death in tricyclic antidepressant (TCA) overdoses that reach hospital is refractory hypotension with progressive cardiac dysfunction due to contractile failure. The mechanisms leading to low cardiac output and hypotension are numerous.³

Spontaneous ventricular tachycardias and fibrillation are less common, but dramatically increase the risk of death. Slowed depolarisation and subsequent repolarisation of the cardiac action potential throughout myocardial conducting and contractile tissue leads to a relatively longer refractory period owing to use-dependant sodium channel blockade.⁴⁻⁶ Acidosis, hypokalaemia, hypoxaemia, hyperthermia, hypotension and excessive adrenergic stimulation may also predispose to arrhythmias.⁷ Blockade of the hERG human potassium channel by amitriptyline may also cause increased automaticity and arrhythmias in this setting of excessive adrenergic activity.⁸

In animal models, it appears that the combination of increased sinus node rate and prolonged QRS is key to the occurrence of VT/VF here.^{6 9} Models first proposed in the 1970s predicted that block produced by tertiary amine local anaesthetics (like amitriptyline) may be enhanced by depolarisation, and that recovery from depolarisation-induced block is time dependant. As the heart rate increases, the diastolic period is shortened and there is insufficient time for complete drug unbinding between beats. The increasing presence of drug-associated (blocked) sodium channels reduces maximum sodium current and conduction velocity in cardiac muscle, resulting in QRS prolongation, and increases the likelihood of re-entrant type arrhythmias.¹⁰

Prevention of sinus tachycardia in experimental amitriptyline toxicity by sinus node destruction, beta-blockers, direct vagal

stimulation, physostigmine and specific bradycardia agents like zatebradine effectively prevent ventricular tachyarrhythmias, as well as reduce QRS prolongation.^{6 9 11 12}

Beta-blockade infusion was chosen in our patient to reduce the heart rate because we observed that the QRS and QT prolongation increased with rate, and arrhythmias and triggered automaticity occurred exclusively when the heart rate was >110 and QRS prolonged, and we hoped to prevent the tachycardia and ventricular arrhythmias despite the risks of reduced cardiac contractility.

Any potential reduction in contractility or blood pressure could be offset by careful titration of esmolol to a safe rate, the restoration of a perfusing rhythm, and in extremis the use of a cardiac support device such as IABP or ECMO. In this case, we minimised the dose of esmolol by titrating to a pulse range of less than 100 beats/min and more than 80beats/min. The malignant rhythm reappeared once the pulse rate was over 110 beats/min at several different times in her course. It was a successful intervention suggested by the fact that premature cessation of esmolol infusion on two occasions led to tachycardia and recurrence of ventricular tachycardia then fibrillation.

Currently first-line therapy of amitriptyline cardiac toxicity is generous use of IV sodium bicarbonate to provide sodium ions and alkalinisation.¹³⁻¹⁶ Five to 7.5% hypertonic sodium has been shown to have as good or better effect than dilute sodium bicarbonate in reversing hypotension and QRS, and both are more effective than alkalinisation by hyperventilation alone, suggesting that the sodium dose is important.¹⁷ Intra-lipid infusion ('lipid rescue') was recommended by the toxicologist, commenced at the referring hospital and was continued as recommended, with no apparent benefit. Positive anecdotes of successful use of intralipid are not supported by clinical trails and human or animal models so far.¹⁸⁻²⁰

There is no consensus over the recommended 'second line' therapy of magnesium, lidocaine or phenytoin for ventricular tachyarrhythmias, and sodium channel blockers such as flecainide, procainamide and amiodarone are strongly contra-indicated.²¹⁻²⁴ There are no trials comparing them, but currently small case series and animal models favour lidocaine.^{5 23} Physostigmine was observed to reduce anticholinergic symptoms, tachycardia and arrhythmias, but avoided due to adverse events.²⁵ Long-acting beta-blockers have been used in past decades, with some successful cases but

Learning points

- ▶ Resistant ventricular arrhythmias greatly increase the risk of death in tricyclic antidepressant toxicity and can be difficult to treat.
- ▶ The type of sodium channel blockade caused by tricyclics means that recovery from depolarisation-induced block is time dependant, suggesting that an increased heart rate can lead to greater risk of ventricular arrhythmia occurrence.
- ▶ Second line medications to treat VT or VF in TCA toxicity have poor evidence and efficacy, and although extra-corporeal cardiovascular support is an option, it is not always available.
- ▶ In severe amitriptyline toxicity complicated by intractable ventricular arrhythmias unresponsive to the typical first and second-line therapies, and attention to homeostasis, that a titrated short acting beta-blocker infusion can be considered, and may be lifesaving.

significant concerns about reducing ventricular contractility and worsening shock.^{26–29}

The antiarrhythmic mechanism of betablockers is complex and depends on the specific mechanism of the arrhythmia.³⁰ In this situation, the ventricular arrhythmias may have been caused by triggered activity due to afterdepolarisations in a situations where the action potential is already prolonged by the rate dependant block, as well as the profound sympathetic stimulation of cardiac arrest.

We propose that in cases of severe amitriptyline toxicity complicated by intractable ventricular tachycardia and arrhythmias unresponsive to the typical first-line and second-line medications, and where all care has been given to controlling homeostasis by optimisation of potassium, magnesium, calcium, pH, oxygenation and perfusing blood pressure, that a titrated short acting beta-blocker infusion can be considered

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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