Tricyclic Poisoning—Successful Management of Ventricular Fibrillation Following Massive Overdose of Imipramine

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SUMMARY
Serious complications from tricyclic antidepressant (TCA) overdose are uncommon1,2,3. We present a case of massive imipramine overdose complicated by ventricular fibrillation and a prolonged period of cardiovascular collapse. A total of 400 mmol of sodium bicarbonate, 5 mg of adrenaline and 80 mg of sotalol were given during 50 minutes of cardiac arrest. The patient made a full recovery with no apparent neurological sequelae. The highest TCA plasma level we could find in the published literature was 4873 ng/ml4; our patient’s peak TCA level was 6000 ng/ml. Tricyclic antidepressant overdose is a common cause of intensive care unit admission. It has a low mortality rate.

Key Words: ANTIDEPRESSANTS: tricyclic, imipramine, ventricular fibrillation, overdose

Serious complications from tricyclic antidepressant (TCA) overdose are uncommon1,2,3. We present a case of massive imipramine overdose complicated by ventricular fibrillation and a prolonged period of cardiovascular collapse.

CASE HISTORY
The patient was a 27-year-old, 60 kg woman who had a history of postnatal depression requiring treatment with imipramine and electroconvulsive shock therapy. Three days after the birth of her second child, she became acutely depressed and presented to hospital following an overdose of 500 mg of imipramine. She was treated with 50 g of activated charcoal and 105 g of sorbitol orally. Physical examination was normal except for a dry mouth. She was admitted to the Intensive Care Unit for cardiovascular monitoring. Plasma imipramine levels were 950 ng/ml four hours after ingestion and 750 ng/ml at seven hours. Her ECG was normal throughout this period.

The following day, immediately prior to her transfer to the psychiatric ward, she suffered two grand mal seizures, five minutes apart, of 30 and 40 seconds duration. She was given diazepam 10 mg intravenously and hyperventilated with 100% oxygen using a bag and mask. She was haemodynamically stable. We suspected further TCA poisoning when an empty bottle of imipramine was found in the Intensive Care Unit bathroom. Ten minutes later, her ECG was noted to have a prolonged QRS duration (greater than 160 ms) and the QTc was in excess of 540 ms (Figure 1) (normal QTc is 390±40 ms). Her blood pressure was 90/60 mmHg. She was given 100 mmol of sodium bicarbonate intravenously. A few minutes later she developed ventricular tachycardia (Figure 2) with cardiovascular collapse. Attempts at defibrillation were unsuccessful.

She was intubated and external cardiac compression commenced. She was given a further 100 mmol of intravenous sodium bicarbonate, 1 mg of adrenaline and 1000 ml of normal saline. Her rhythm degenerated to ventricular fibrillation (Figure 3).

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FIGURE 1: Broad complex tachyarrhythmia.

FIGURE 2: Ventricular tachycardia.
the next 40 minutes she remained in ventricular fibrillation, despite a further 200 mmol of sodium bicarbonate, 2 mg of adrenaline and repeated attempts at DC cardioversion. Following the administration of 40 mg of intravenous sotalol and further defibrillation, she went into a broad complex ventricular rhythm with a systolic blood pressure of 50 mmHg (Figure 4). The rhythm then degenerated to multifocal ventricular ectopic beats (Figure 5).

A further 40 mg of sotalol and 2 mg of adrenaline were given. Arterial blood gases at this time were pH 7.42, $P_aO_2$ 450 mmHg, $P_aCO_2$ 16.7 mmHg and base excess –13. Three minutes after the administration of sotalol she reverted to sinus rhythm (which was preceded by a brief period of complete heart block). The QRS duration was now 120 ms with a QTc of 480 ms. The blood pressure remained low; an adrenaline infusion was commenced at 0.9 µg/kg/min, which was weaned over the next hour.

Her subsequent course was complicated by two further grand mal seizures each of less than 20 seconds duration. These were treated with intravenous diazepam 5 mg and a loading dose of phenytoin 800 mg. She remained acidaemic with an arterial pH of 7.22. She had a further episode of QRS broadening and profound hypotension which was treated with adrenaline 0.2 mg, sodium bicarbonate 100 mmol and 1000 ml of normal saline. The adrenaline infusion was again increased to 0.9 µg/kg/min and then weaned over the next eight hours. Arterial blood gases were performed every thirty minutes and the pH was maintained at greater than 7.5 with 50 mmol boluses of intravenous sodium bicarbonate and hyperventilation. Intravenous potassium chloride was given to maintain serum potassium at greater than 3.5 mmol/l.

The plasma imipramine level at the time of the first grand mal seizure was 3800 ng/ml. Two hours later it reached 6000 ng/ml; it was 2700 ng/ml at eight hours and 1500 ng/ml at twenty-four hours. No tablets were recovered during subsequent gastric lavage. A further dose of activated charcoal and sorbitol was given and this was repeated every four hours until TCA levels were below 1000 ng/ml.

A total of 400 mmol of sodium bicarbonate, 5 mg of adrenaline and 80 mg of sotalol were given during 50 minutes of cardiac arrest. The patient made a full recovery with no apparent neurological sequelae.

**DISCUSSION**

The case presented highlights the complications and management issues associated with major TCA overdose. The highest TCA plasma level we could find in the published literature was 4873 ng/ml; our patient’s peak TCA level was 6000 ng/ml.

Tricyclic antidepressant overdose is a common cause of intensive care unit admission. It has a low mortality rate. In one review of 259 intensive care admissions following TCA overdose, only two patients died. Ellison et al showed that seizures occurred in 10% of TCA overdoses and the mortality rate in these patients was 10%. In a review by Golbery et al, ventricular fibrillation or tachycardia occurred in 4% of cases of TCA overdose. All patients who developed a life-threatening complication of TCA poisoning did so within six hours of presentation to hospital, and no life-threatening arrhythmias occurred after 24 hours.

The relationship between TCA plasma levels and clinical toxicity is unclear. Petit et al showed that levels of 1000 ng/ml or more are associated with serious toxicity; however, serious cardiac arrhythmias and seizures may still occur with levels below this. The primary value in measuring TCA levels is to confirm the diagnosis of overdose rather than to predict morbidity. Treatment should never await a drug

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level. Early treatment should be instituted based upon neurological signs (impairment of consciousness and seizures) and ECG characteristics. A QRS duration of less than 100 ms is associated with a negligible risk of either seizures or ventricular arrhythmias. A QRS duration of greater than or equal to 100 ms is associated with a 34% incidence of seizures, and a duration of 160 ms or more with a 14% incidence of arrhythmias. The QRS duration has also been shown to return to normal within 24 hours after overdose, regardless of the 24 hour serum drug level.

An important step in the early management of TCA poisoning is alkalization of the blood. This will alter TCA plasma protein binding from 82% at pH of 6.7 to 98% at a pH of 7.5, thereby decreasing the free concentration of TCA. pH should be maintained at greater than 7.5 by hyperventilation and intravenous sodium bicarbonate. Sodium bicarbonate therapy may also be useful because of the sodium load, as sodium ions may help reverse the TCA induced blockade of sodium channels. These measures will help to narrow the QRS complex, improve conduction and decrease arrhythmias.

Another important therapy in TCA overdose is activated charcoal, which effectively binds TCAs and can decrease plasma levels by up to 60% in 6 hours. In addition, multiple doses of activated charcoal decrease the plasma half-life of TCAs. Charcoal haemoperfusion, dialysis and forced diuresis are ineffective because of the very high tissue binding of these drugs.

TCA overdose typically produces impaired atrioventricular conduction, tachycardia, ventricular and supraventricular arrhythmias. These result from anti-cholinergic properties of TCAs, along with sodium channel blockade (prolonging the PR, QRS and QTc intervals), decreased automaticity and alpha adrenergic blockade.

Recommendations regarding antiarrhythmic choice in TCA poisoning are based on anecdotal experience rather than on controlled trials. The ideal agent should have minimal effect on QT interval so as not to exacerbate the QT effect of TCA overdose. Class 1B agents (lignocaine and phenytoin) are theoretically useful antiarrhythmics because they do not slow conduction or depress myocardial contractility. In an in vitro study, Barber et al showed that lignocaine (but not phenytoin) may produce partial reversal of TCA induced sodium channel blockade.

Phenytoin has two useful clinical properties in the treatment of TCA overdose. It has been shown to narrow the QRS widening caused by TCA poisoning and is useful in the prevention and treatment of seizures.

Sotalol is a class 3 (prolongs repolarization) antiarrhythmic with some class 2 (beta adrenoceptor antagonist) properties. Sotalol has been shown to be an effective agent in the treatment of complex and refractory ventricular arrhythmias. Sotalol at therapeutic doses produces minimal QTc interval prolongation; however there are theoretical concerns regarding its use as an antiarrhythmic in TCA poisoning where the baseline QTc is already prolonged. In common with other class 3 agents, sotalol may produce torsades de pointes that can deteriorate into ventricular fibrillation, a risk that is increased with a prolonged baseline QT interval. Because of these concerns, lignocaine may be a better first line antiarrhythmic in TCA overdose when QT is prolonged. Despite this potential risk, sotalol appeared to be an effective antiarrhythmic in this case, restoring sinus rhythm.

TCAs have been shown to have cerebroprotective properties when given prior to ischaemic episodes in animal models. The good neurological recovery in this case is most likely because of immediate commencement of resuscitation which was continued throughout the period of cardiorespiratory collapse. Any cerebral protection provided by the high plasma concentration of TCA remains open to speculation.

REFERENCES
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