CASE REPORT

Serum alkalinisation is the cornerstone of treatment for amitriptyline poisoning

Benjamin Ramasubbu,¹ David James,² Andrew Scurr,¹ Euan A Sandilands³¹Intensive Care Unit, Ealing Hospital, London, UK²Regional Drug and Therapeutics Centre, NPIS Newcastle, Newcastle upon Tyne, UK³National Poisons Information Service Edinburgh, NHS Lothian, Edinburgh, UK**Correspondence to**Dr Euan A Sandilands,
euan.sandilands@nhslothian.
scot.nhs.uk

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SUMMARY

A 28-year-old woman was admitted in a comatose state following ingestion of 5 g of amitriptyline. On arrival, there was intermittent seizure activity and a broad complex tachycardia on the ECG. Immediate resuscitation included 8 mg lorazepam, 2 L crystalloid fluid, 100 mL 8.4% sodium bicarbonate, 2 g of magnesium sulphate and lipid emulsion infusion. Despite this, the broad complex tachycardia persisted with haemodynamic instability. The case was discussed with the National Poisons Information Service, which advised further 8.4% sodium bicarbonate to achieve serum alkalinisation. Following this, the QRS duration reduced and haemodynamic stability was achieved. Serum alkalinisation continued in the intensive treatment unit before the patient was successfully extubated on day 5 and discharged on day 7 with no neurological sequelae. To our knowledge, this case is the largest recorded overdose of amitriptyline to have survived to discharge. The importance of serum alkalinisation in the management of tricyclic antidepressant poisoning is highlighted.

BACKGROUND

Amitriptyline, a tricyclic antidepressant (TCA) used in the treatment of mood disorders and neuropathic pain,¹ is a common cause of fatal self-poisoning, primarily as a result of cardiovascular toxicity.² In 2012, TCAs were associated with 233 drug-related deaths in England and Wales, 67% of which were due to amitriptyline.³ The treatment of amitriptyline poisoning is well described, and focuses on serum alkalinisation with sodium bicarbonate to achieve cardiovascular stability and prevent life-threatening arrhythmias. Treatment guidelines are available on TOXBASE®,⁴ the online toxicology database provided by the National Poisons Information Service (NPIS). In recent years, newer treatments such as intravenous lipid emulsion (ILE) (intralipid) have emerged and, despite limited evidence, are increasingly being used in cases of severe drug-induced cardiotoxicity.^{5 6} However, it is critical for physicians treating TCA-poisoned patients to be aware of the importance of serum alkalinisation in the prevention of life-threatening arrhythmias. To our knowledge, this is the largest reported overdose of amitriptyline to have survived to discharge and highlights this treatment modality as the cornerstone of management.

CASE PRESENTATION

A 28-year-old woman (80 kg) was admitted to the emergency department in a convulsive state

following ingestion of 5 g of amitriptyline (62.5 mg/kg). Initial treatment included intravenous lorazepam (4 mg), which was repeated 10 min later due to ongoing convulsions. This terminated the convulsions although the patient was now in a comatose state (Glasgow Coma Scale (GCS) 3/15). She was intubated and ventilated with propofol (40 mg), fentanyl (75 µg) and rocuronium (50 mg). An ECG performed at the time demonstrated a broad complex tachycardia with no obvious p wave activity (figure 1). The blood pressure (BP) was 95/55 mm Hg and the pulse 130 bpm. The blood sugar and temperature were normal. A venous blood gas analysis demonstrated a pH of 6.86, base excess (BE) of -14.2 and lactate 19.2.

TREATMENT

Immediate resuscitative treatment was provided as per TOXBASE® guidelines. This included 2 L of crystalloid, 100 mL 8.4% sodium bicarbonate and 2 g of magnesium sulfate. An infusion of ILE was also administered. Despite an initial improvement in acid-base status (pH 7.37, BE -5.6 and lactate 3.6), cardiovascular instability persisted with a broad complex tachycardia and hypotension. Following discussion with the NPIS, further alkalinisation with 200 mL 8.4% sodium bicarbonate was instituted to achieve a pH of 7.5. Following this treatment, the QRS duration reduced (figure 2), hypotension resolved and haemodynamic stability was achieved.

OUTCOME AND FOLLOW-UP

The patient was transferred to intensive care where her admission was complicated by an intercurrent chest infection. The QRS duration remained prolonged (120–130 ms) for 72 h during which time she received ongoing serum alkalinisation with sodium bicarbonate. Serum amitriptyline levels, and those of its major metabolite nortriptyline, were measured on admission and at 72 h, and are shown in table 1. The patient was safely extubated on day 5 and discharged with no neurological sequelae on day 7.

DISCUSSION

The pharmacology of TCAs is complex and a range of clinical features may be expected following overdose. Amitriptyline is rapidly absorbed following ingestion, reaching peak plasma concentration within 6 h.⁷ It is highly protein bound with a large volume of distribution (10–20 L/kg) and is metabolised by the cytochrome P450 enzyme system to its major metabolite, nortriptyline. Amitriptyline has a

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Figure 1 Admission ECG.

long elimination half-life (up to 25 h), which may be prolonged even further in overdose.⁸

The primary antidepressant effect of amitriptyline is due to blockade of pre-synaptic uptake of amines including serotonin, norepinephrine and dopamine. Secondary pharmacological effects such as anticholinergic effects, blockade of cardiac sodium channels and antagonism of histamine and α 1-adrenergic receptors, give rise to additional clinical features.² The principal mechanism of TCA toxicity is sodium channel blockade resulting in slowing of depolarisation of the cardiac action potential through the myocardium and conducting tissue.⁹ Clinically, this may present as prolongation of the QRS complex on the ECG and as potentially life-threatening arrhythmias. A prolonged QRS duration of >100 ms and a reduced level of consciousness have both been shown to predict severity of TCA toxicity.² Amitriptyline concentration, on the other hand, is not a reliable predictor of toxicity.

The use of sodium bicarbonate in the treatment of TCA-induced cardiotoxicity is well documented.¹⁰ A retrospective review of 91 cases of TCA poisoning where sodium bicarbonate was administered in the acute management to achieve a target plasma pH of 7.5–7.55 demonstrated an increase in systolic BP (>15 mm Hg or to >90 mm Hg) within 1 h in 20 of 21 patients and a narrowing of the QRS interval (by >0.03 s or to <0.11 s) within 30 min in 39 of 49 patients.¹¹ The mechanism by which sodium bicarbonate exerts this effect, however, is unclear. Alkalinisation increases protein binding of TCAs and

consequently reduces the concentration of pharmacologically active free drug, which may cause toxicity.¹² There may also be a direct effect on myocardial contractility through reversal of systemic acidosis, which has been shown to exacerbate TCA-induced cardiotoxicity.¹³ Even in the absence of acidosis, however, sodium bicarbonate reduces TCA-induced cardiotoxicity, suggesting that other mechanisms are involved.^{13–14} Administration of hypertonic sodium chloride to TCA poisoned animals has been shown to be as effective as sodium bicarbonate in reversing QRS prolongation and hypotension suggesting that the beneficial effects of sodium bicarbonate may be more attributable to an increase in sodium concentration than correction of pH.¹³ Overall, a combination of factors are likely to be important while the relative contribution of each is unclear. Current TOXBASE® guidelines advocate serum alkalinisation with sodium bicarbonate (target pH 7.5–7.55) in the presence of a QRS duration greater than 120 ms, arrhythmias, or hypotension resistant to fluid resuscitation.⁴

ILE has emerged as a potential treatment in cases of severe drug cardiotoxicity over recent years. Initial efficacy of ILE was demonstrated in the setting of local anaesthetic systemic toxicity and although the precise mechanism is not fully understood, a commonly postulated theory involves creation of a 'lipid sink' to effectively inactivate lipophilic drug molecules.¹⁵ Despite animal studies¹⁶ and case reports¹⁷ suggesting clinical benefit, the body of evidence supporting the use of ILE in TCA poisoning remains limited.

Figure 2 ECG following treatment with sodium bicarbonate.

Table 1 Amitriptyline and nortriptyline concentration at admission and 72 h after admission

	Admission	At 72 h
Amitriptyline (μg/L)	917	358
Nortriptyline (μg/L)	141	282

Extracorporeal treatments to enhance drug elimination are often considered in cases of severe poisoning where large quantities of a drug have been ingested. In the case of TCA poisoning, however, the large volume of distribution of TCAs means that the benefit of such therapies is limited. A recent review by the Extracorporeal Treatments In Poisoning (EXTRIP) workgroup concluded that TCAs are not effectively removed via haemodialysis and extracorporeal treatments should not be used to treat TCA poisoning.¹⁸

Learning points

- ▶ Tricyclic antidepressant (TCA) overdose is common and clinical features occur as a result of anticholinergic effects, cardiac sodium channel blockade and antagonism of histamine and α 1-adrenergic receptors.
- ▶ The principal mechanism of TCA toxicity is sodium channel blockade resulting in QRS prolongation and life-threatening arrhythmias.
- ▶ Serum alkalisation with sodium bicarbonate is the mainstay of treatment of TCA cardiotoxicity.

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