CASE REPORT

Dramatic resuscitation with Intralipid in an epinephrine unresponsive cardiac arrest following overdose of amitriptyline and propranolol

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SUMMARY

Amitriptyline and propranolol are life threatening in overdose. The efficacy of intravenous lipid emulsion (ILE) in tricyclic antidepressant and propranolol overdose is unclear. We report a dramatic response to ILE following pulseless electrical activity arrest due to mixed amitriptyline and propranolol overdose.

BACKGROUND

Following a life-threatening overdose of amitriptyline and propranolol which culminated in pulseless electrical activity (PEA) cardiac arrest, intravenous lipid emulsion (ILE) produced a dramatic resolution of cardiovascular instability which was unresponsive to standard medical therapy. We also report an abrupt relapse of coma and apnoea 16 hours following resuscitation, and a dramatic return of conscious level and respiration following a repeated dose of ILE. This adds further evidence for a genuine effect of ILE.

CASE PRESENTATION

A 50 kg woman aged 25 years was discovered unresponsive in her bed by her partner. She was surrounded by open empty amitriptyline, propranolol and pregabalin tablet containers; the exact dose was unknown, but it had been consumed sometime in the preceding 3 hours. She later confirmed to a mental health nurse that she had taken a multiple packet overdose of these drugs with the intention of self-harm.

She was found to be in respiratory arrest by paramedics. She was centrally cyanosed and very poorly perfused. A supraglottic airway was inserted and she was easily hand ventilated. Pulse oximetry could not be measured due to poor peripheral perfusion. She was in sinus rhythm at a rate of 70 bpm and her blood pressure was 80/60 mm Hg. Her Glasgow Coma Score (GCS) was 3. Her pupils were fixed and dilated with an estimated diameter of 6 mm. There was no evidence of seizures. She arrived to hospital 62 min after being found unresponsive.

On arrival in the emergency department, she was tolerating the supraglottic airway without drugs and was apnoeic without manual ventilation. She remained GCS 3 with unreactive, 6 mm pupils and her initial blood glucose was 7.1 mmol/L. She was white/mottled and stony cold to touch, despite only a mild hypothermia (35.7°).

Her trachea was intubated and an arterial line was inserted. She subsequently became progressively more bradycardic and hypotensive, despite initial boluses of metaraminol (1–5 mg), ephedrine (6–12 mg) and then epinephrine (100–500 µg, with a total of 2 mg given). Given the history, glucagon (5 mg) was administered, but to no effect. Progressive cardiovascular collapse resulted in a narrow complex PEA arrest with a rate of 50–70. CPR was performed for 3 min and a further 1 mg epinephrine was administered. Following return of spontaneous circulation, she continued to be profoundly vasoconstricted and hypotensive (88/62 mm Hg). Over the following 10 min, she was given: 10 mL of calcium chloride, 10 units of actrapid in 50 mL of 50% glucose, 200 mL of 8.4% sodium bicarbonate and epinephrine boluses in increments up to a further 2 mg. Despite this, she did not develop tachycardia and she remained white/mottled and in persistent toxicological cardiogenic shock with a blood pressure persistently <80 mm Hg systolic. A second cardiac arrest looked imminent.

Seventy-five millilitres of 20% intravenous Intralipid (1.5 mL/kg, total dose 15 g) were infused over 1 min. Over the subsequent 10 min, the patient's clinical status improved dramatically: her blood pressure recovered to 110/70 mm Hg on a weaning dose of epinephrine (0.1 µg/kg/min at that time) and her peripheral perfusion improved dramatically—she became warm and pink with a capillary refill time of 2–3 s. She remained unresponsive on propofol 3 mg/kg/hour, but her pupils reduced in size to a diameter of 3 mm and became reactive. She was given activated charcoal via nasogastric tube and required a total of 75 g of intravenous glucose to treat hypoglycaemic episodes over the next 10 hours. She was sedated with 1% propofol (1–4 mg/kg/hour; total dose 1.4 g) and alfentanil (10–40 µg/kg/hour) for 16 hours to establish stability, allow intravenous access and allow for drug metabolism.

Sixteen hours later, she appeared to have completely recovered. She was haemodynamically unsupported off sedation, was neurologically alert, appropriate and obeying commands, with pupils that were reacting normally. With good gas exchange on minimal ventilatory support, she was uneventfully extubated to nasal high-flow cannulae 50 L/min flow and 50% inspired oxygen. Following extubation, her cardiovascular system remained unsupported and her neurological state remained

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fully intact. Forty-five minutes later, without warning, she deteriorated dramatically. She became apnoeic, and her GCS fell to 3. Her pupils dilated to 7 mm bilaterally and became unresponsive to light. Her pulse fell from 110 to 64 bpm (with normal ECG morphology) and her blood pressure fell to 85/54 mm Hg, but her skin perfusion remained intact. Her blood sugar level remained normal. A Guedel airway was inserted and she was mask ventilated. While preparing for reintubation, 100 mL of 8.4% sodium bicarbonate was given with no effect. Seventy-five millilitres of 20% intravenous Intralipid (1.5 mL/kg) were again infused. There was a rapid and dramatic response in neurological function. Within 2 min, the patient's GCS rose to 15 with higher functions fully intact and her pupils returned to normal size and reactivity. Blood pressure and pulse improved to normal without cardiovascular support. The subsequent ECG was unremarkable. She expelled the Guedel airway and tracheal intubation was no longer required. An infusion of 20% Intralipid was started at 75 mL/hour for 2 hours, which was then reduced to 25 mL/hour and continued for a further 14 hours. She was discharged home 4 days later with no discernible neurological or myocardial injury.

INVESTIGATIONS

She had no impediment to gas exchange at any time and serial arterial blood gases showed only a very mild metabolic acidosis (most acidemic base excess: -3.6 mmol/L). The highest lactate recorded was 4.1 mmol/L. The initial ECG (see [figure 1](#)) showed sinus rhythm with heart rate of 66; first-degree heart block (PR interval: 216 ms); widened QRS (136 ms); dominant terminal R wave in aVR; prolonged QT interval (QTc: 503 ms). Her admission blood tests including FBC, U&Es, LFTs, paracetamol and salicylate levels were all normal. The ECG following infusion of Intralipid shows no abnormalities and is shown in [figure 2](#).

DIFFERENTIAL DIAGNOSIS

The clinical picture showed toxicological features of all three drugs. Features of amitriptyline overdose included a prolonged QRS duration and QT interval and a QRS pattern in aVR, as a consequence of fast sodium channel blockade. Features of β blocker overdose included first-degree heart block, with bradycardia and hypotension that was refractory to epinephrine and PEA cardiac arrest. The reduction in conscious level can be attributed to the central nervous system depressant effects of pregabalin, amitriptyline and potentially propranolol, due to the ease with which it crosses the blood-brain barrier.

Her fixed and dilated pupils were likely due to the antimuscarinic effects of amitriptyline. The absence of a significant metabolic acidosis was unusual for a significant amitriptyline overdose and we do not have an explanation for this. The peak lactate was remarkably low, given the degree of haemodynamic compromise, but this is an observed phenomenon of β blocker overdose which fits with the current understanding on the role of adrenergic stimulation in generating hyperlactataemia.^{1 2} The episodes of hypoglycaemia are typical with excess β blockade and relate to inhibition of glycogenolysis and gluconeogenesis.

TREATMENT

After supportive care on the intensive care unit and the pharmacological interventions outlined above, she was reviewed by the inpatient psychiatric team.

OUTCOME AND FOLLOW-UP

The patient was discharged home 5 days after admission with no discernible neurological or myocardial injury. Follow-up with community psychiatric services was arranged.

DISCUSSION

We report a case of life-threatening amitriptyline, propranolol and pregabalin overdose which was refractory to standard medical supportive therapy. We report dramatic cardiovascular recovery following the administration of 20% Intralipid and subsequently dramatic neurological recovery following a second dose of 20% Intralipid, administered following an apparent relapse in the toxic neurological effects of these drugs.

Amitriptyline is a tricyclic antidepressant. It elicits competitive blockade of neuronal uptake of norepinephrine and serotonin. It exhibits powerful anticholinergic, antihistaminergic as well as α_1 blocking effects; and it is non-specifically sedating. Amitriptyline is also lipophilic and blocks membrane sodium channels, exhibiting a class Ia effect on the heart. Its half-life in overdose is variable, between 13 and 81 hours.³ Propranolol is a highly lipophilic, non-selective β blocker without intrinsic sympathomimetic activity. In high doses, it exhibits membrane-stabilising effects by blockade of voltage-gated sodium channels, akin to the actions of local anaesthetic agents. The duration of action is longer than the elimination half-life (4 hours) would suggest. Pregabalin blocks the $\alpha_2 \delta 1$ subunit of the voltage-gated calcium channels in the central nervous system. It is excreted unchanged in the urine.

While the mechanism of action of these drugs is different, they display similarities in their lipophilic physicochemical properties and their avidity for sodium channels, particularly in high dose, both of which lend themselves to the proposed mechanisms of action of ILE.

ILE is established as the recommended antidote in local anaesthetic systemic toxicity which has resulted in alterations in mental state, tonic-clonic convulsions or cardiovascular collapse.⁴

The role of ILE in amitriptyline and propranolol overdose is much less established. The recently published lipid emulsion workgroup, an international collaboration between various international toxicology bodies, recommended ILE only as last line therapy in life-threatening overdose with amitriptyline or lipid-soluble β blockers.⁵

There have been no human randomised controlled trials of ILE to treat either amitriptyline or propranolol overdose. There are many published case reports of the successful use of ILE in amitriptyline overdose.^{6 7} Animal studies are inconclusive. ILE administration to anaesthetised pigs 30 min following a toxic intravenous dose of amitriptyline (10 mg/kg) resulted in lower brain and heart tissue concentrations of the amitriptyline when compared with pigs randomised to receive Ringer's acetate.⁸ In another pig experiment, ILE did not prevent death any more than sodium bicarbonate following a severe amitriptyline overdose.⁹ ILE was more effective at resuscitating rabbits following a severe intravenous clomipramine overdose compared with 8.4% sodium bicarbonate or 0.9% saline solutions. Clomipramine is a tricyclic antidepressant with similar lipid affinity. A rat experiment found that ILE reduced survival when administered 30 min following a very large enteral overdose of amitriptyline (70 mg/kg) compared with either Hartmann's or sodium bicarbonate solutions. An explanation for this finding is that ILE might enhance drug absorption from the gut.¹⁰

Figure 1 ECG prior to Intralipid.

Figure 2 ECG post Intralipid.

With regard to propranolol overdose, there are two published case reports that suggest a clinical response to ILE.^{11 12} In rabbits given an intravenous propranolol overdose, low blood pressure was corrected by 6 mL/kg infusion of 20% ILE.¹³ An experiment on rats failed to show any improvement in hypotension or survival, though there was a reduction in QRS duration.¹⁴

The mechanism of action of ILE remains unclear. A prominent hypothesis is that ILE creates an expanded lipid phase in the blood into which lipophilic drugs accumulate and are removed from their site of action. This is commonly known as the lipid sink hypothesis. Alternative hypotheses for the mechanism of action of ILE include its ability to provide a metabolic substrate for myocardial cells whose usual aerobic requirement for lipid

could not be supplied in the face of poisoning, or a protective effect on sodium channels. All three hypotheses may be applicable in this case, but the lipid sink hypothesis best explains the observed relapse in symptoms of amitriptyline overdose (mydriasis, loss of consciousness, apnoea) and propranolol (reduced heart rate), all of which resolved within minutes of repeat administration of ILE. We conjecture that metabolism of ILE led to the release of amitriptyline and propranolol allowing them to exert toxicity again. Given the prolonged duration of action of propranolol and the extremely long half-life of amitriptyline, and with no elimination half-life data available for ILE, we surmise that ILE was cleared more quickly than the drugs sequestered into the lipid phase. It is not clear why the symptoms manifested so suddenly; we put forward two theories. First, given that an infusion of ILE was not continued following the initial bolus, the total dose of ILE was lower and the clearance from one body compartment was completed abruptly.¹⁵ Second, we theorise that 1% propofol may have delivered a lipid load which may have either sequestered some of the toxins or may have tempered the metabolism of ILE until such time that the infusion was stopped. The 1% propofol solution that was used contained 10% ILE (100 mg/mL soya bean oil, 22.5 mg/mL glycerol, 12 mg/mL egg phospholipid (verbal report—Fresenius Kabi (the manufacturer)). The propofol infusion that this patient received delivered 10–40 mg/kg/hour of ILE for 16 hours. This is in the region of half the recommended dose of 50 mg/kg/hour (or 0.25 mL/kg/hour of 20% ILE).⁵ Following the relapse and repeat bolus, an infusion of ILE was started and continued for 14 hours, after which time the patient remained stable. We would therefore recommend starting an infusion of ILE, even in the absence of ongoing instability, where the half-life or clinical actions of the toxins are long enough to warrant concern. We would also advocate patients

who have received bolus ILE without infusion remain closely monitored on the critical care unit until ILE and/or propofol can assume to have been cleared from the body.

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Contributors AG (Consultant) and PLF (Specialty Doctor) had the initial idea for the case report after managing the patient in the emergency department and the critical care unit, and having made the decision to give the Intralipid as described in the report. PLF and MG carried out literature searches. The article was written by PLF, MG and KA with significant alterations and additions by AG. AG is the guarantor and controlled the decision to publish. The patient was initially looked after by AG (Consultant) and PLF (Specialty Doctor) in the acute phase of their illness. AG continued to oversee the patient's care in the following 48 hours with the help of KA (Specialty Doctor) and MG (SHO). KA (Specialty Doctor) and MG (SHO) sought consent from the patient to publish the report and followed the patient's progress until hospital discharge.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- Consider treatment with intravenous lipid emulsion (ILE) in overdoses of highly lipid-soluble drugs and/or those with significant sodium channel blockade, where a lack of response to conventional therapy is observed.
- Consider an infusion of ILE where the duration of the toxicological effects may be prolonged. Where an infusion of ILE is not started, consider that the lipid dose of propofol may deliver enough emulsion to sequester the toxin, resulting in relapse of symptoms on cessation of the propofol infusion.
- Propranolol is unique among all β blockers in its sodium channel effects and its lipid solubility.

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