Amlodipine overdose: what is the role of Intralipid?

Clinical problem and domain
I chose this case because it was the first time I had seen intravenous lipid emulsion (ILE, often referred to by its brand name Intralipid) used for an indication other than local anaesthetic toxicity. I was interested to find out more about the evidence associated with its use in the management of drug overdoses, particularly calcium channel blocker overdose.

A 57 year-old heavy goods vehicle (HGV) driver with a background of hypertension, type 2 diabetes and heavy alcohol intake was admitted to hospital following an intentional overdose of up to 560mg amlodipine the previous evening. On arrival in the Emergency Department he was vomiting and hypotensive (BP 66/43). He was transferred to the medical high dependency unit (HDU) and treated with intravenous (IV) fluids, IV calcium gluconate and glucagon. A central line was inserted and he was commenced on an adrenaline infusion. Antibiotics were started for possible aspiration pneumonia. Acute kidney injury was noted (creatinine 217 micromol/l on admission). Over the next 2 days he had approximately 8000ml IV fluid administered with little improvement in mean arterial pressure (MAP) and worsening renal function. He developed type 1 respiratory failure on day 3 of admission (H+ 35, PCO2 3.5kPa, PO2 8.4kPa, HCO3 18 on 15 litres of oxygen via non-rebreath mask) but was unable to tolerate continuous positive airway pressure (CPAP) via face mask and was transferred to the intensive care unit (ICU), where he was intubated and ventilated.

Management
In ICU, he was commenced on noradrenaline to add vasopressor support. High-dose insulin and dextrose infusion was added. He had a Pulse Contour Cardiac Output (PiCCO) line inserted and was given Intralipid, as per TOXBASE recommendations. By the next day, his adrenaline was weaned off and he became pyrexial. Transthoracic echocardiography showed a small rim of pericardial fluid with reduced left ventricular septal wall motion and an ejection fraction of 64%. There was possible mild right heart dilatation with an estimated pulmonary artery pressure of 35mmHg.

On day 4 in ICU (day 6 in hospital) he developed worsening oxygenation not responding to diuretics or recruitment manoeuvres. The subsequent day he had a dialysis line inserted and was commenced on continuous veno-venous haemofiltration (CVVH) for worsening acute kidney injury. His oxygenation continued to deteriorate and he was commenced on high frequency oscillatory ventilation (HFOV) on day 6 of ICU admission. Chest X-ray showed bilateral opacification in keeping with acute respiratory distress syndrome (ARDS). Bronchoscopy revealed large mucus plugs. There was no positive microbiology. He was discussed with the extracorporeal membrane oxygenation (ECMO) team in Leicester in view of his refractory hypoxia, who agreed he was a suitable candidate for ECMO. He was commenced on ECMO in our ICU and transported on ECMO to Manchester on day 8 of hospital admission. He remained on ECMO for 18 days but eventually suffered an intra-abdominal perforation and died.
Discussion
Amlodipine overdose
Amlodipine is a dihydropyridine calcium channel blocker which is used in the management of angina and hypertension. The peak plasma concentration is reached after 6-12 hours following ingestion and the elimination half-life is 35-50 hours.1,2 Poisoning with calcium channel blockers is relatively common and may be fatal.3 The response to poisoning with amlodipine is variable, with death reported after 140mg, and survival reported following 600mg.2 In overdose, amlodipine causes significant peripheral vasodilation resulting in profound hypotension. There may also be a reflex tachycardia, bradycardia, atroventricular block or myocardial depression. Non-cardiovascular features include nausea, vomiting, agitation, confusion, hyperglycaemia, coma, metabolic acidosis, hyperkalaemia, hypocalcaemia, and coma. Less commonly, seizures, pulmonary oedema, paralytic ileus, mesenteric infarction and hepatotoxicity may occur.2

High quality evidence for the management of calcium channel blocker overdose is lacking. Many reports are from case reports and the literature is heavily biased.3

Immediate management
The immediate management of amlodipine overdose is to maintain a clear airway and adequate ventilation in unconscious patients. Prolonged (at least 1 hour) cardiopulmonary resuscitation (CPR) is required in the event of cardiac arrest. Good neurological outcome has been reported following cardiac arrest due to amlodipine poisoning. Activated charcoal and gastric lavage should be considered in patients presenting within 1 hour of ingestion, although there is no evidence to support this practice. Serial 12-lead electrocardiogram (ECG) s are recommended, particularly following modified-release preparations of the drug. QT prolongation secondary to potassium channel blockade may precipitate torsades de points ventricular tachycardia, which should be treated with magnesium sulphate.2

Blood biochemistry, including urea and electrolytes, calcium and glucose should be checked, along with arterial blood gases in symptomatic patients. Patients should be observed in a healthcare facility for at least 12 hours following ingestion of a standard preparation and at least 24 hours following a modified-release preparation.2

Specific management
Bradycardia should be managed initially with intravenous atropine. In the event of associated hypotension, dobutamine, isoprenaline and external or temporary pacing may be required. Intravenous calcium should be given and an infusion of this may be required. High-dose insulin (bolus of 1 unit/kg followed by an infusion of 0.5-2 units/kg/h) and dextrose infusion is especially useful in the presence of metabolic acidosis and improves cardiac contractility, thus increasing systemic perfusion.2 It has been shown to reduce mortality in calcium channel blocker overdose, but risks hypoglycaemia and hypokalaemia.3 Glucagon can be used for profound hypotension or cardiogenic shock.

If hypotension does not respond to initial treatment, inotropic support should be instituted, with either adrenaline or dobutamine and/or noradrenaline, depending on whether hypotension is the result of both cardiac dysfunction and reduced systemic vascular resistance (SVR), mainly reduced SVR, or the negative inotropic and chronotropic effects of amlodipine.2
TOXBASE recommends that ILE should be considered if cardiotoxicity does not respond to the measures detailed above. Its use is discussed further in the next section.

Seizures should be managed with benzodiazepines, with barbiturates as second-line treatment. Phenytoin should be avoided due to its cardiotoxic effects. Pulmonary oedema should be managed supportively with CPAP or positive-pressure ventilation and positive end-expiratory pressure (PEEP). In the event of ongoing metabolic acidosis despite adequate fluid resuscitation, sodium bicarbonate should be considered.

There are case reports detailing the use of methylene blue, levosimendan, metaraminol, vasopressin and plasmapheresis for the management of profound cardiovascular compromise, but their routine use is not recommended. Intra-aortic balloon pumping, cardiac bypass, and veno-arterial extracorporeal membrane oxygenation have been used successfully in a few cases. Extracorporeal life support is associated with improved survival in patients with cardiac arrest or severe shock, however risks include thrombosis, limb ischaemia and haemorrhage. There is no role for haemodialysis in the management of amlodipine due to its high volume of distribution.

The role of Intralipid
Weinberg et al demonstrated a reversal of bupivicaine-induced cardiotoxicity in rats in 1998 as a chance finding following resuscitation with a soybean oil emulsion normally used as a parenteral nutrition solution. This finding was later confirmed using dogs as subjects. Since then, case reports have shown neurologically intact recovery in humans following cardiac arrest secondary to local anaesthetic agents and ILE is now included in the guidelines of professional bodies for severe local anaesthetic toxicity poisoning. Its use was then studied in animal models of other drugs commonly implicated in poisoning. Its successful use has been reported in a variety of classes of drugs, including calcium channel blockers, beta blockers, and tricyclic antidepressants.

Mechanism of action
There are multiple proposed mechanisms of action, including:
- “Lipid sink” theory - lipid binds toxin to pull the drug from the target tissue, thereby reducing the free concentration of the active drug which reverses toxic effects
- “Fatty acid metabolism” theory - large lipid load offsets inhibition of fatty acid metabolism caused by toxin
- Direct cardiotonic effect, improving myocardial function
- “Ion channel modulation” theory - lipid causes modulation of cardiac sodium channels

Use in calcium channel blocker overdose
Return of spontaneous circulation was reported 5 minutes after administration of ILE 80 minutes after cardiac arrest from a suspected co-ingestion of verapamil and atenolol. However, neither toxin was confirmed analytically and the patient was also receiving high does insulin infusion, so it is not possible to say whether the ILE had a beneficial effect and if so, which poison it worked on. The patient subsequently became shocked and, despite a further infusion of ILE and insertion of an intra-aortic balloon pump, died.

Dose of ILE
Most studies use 20% ILE, of varying doses. TOXBASE recommends a dose of 1.5ml/kg Intralipid as an intravenous bolus followed by an infusion of 0.25-0.5ml/kg/min for 30-60 minutes, to an initial maximum of 500ml. This is based on a systematic review by Jamaty.
et al, can be repeated 1-2 times in the event of ongoing cardiovascular collapse or asystole and should be titrated to response.9

Timing of ILE
There are no studies looking at optimal timing of ILE in calcium channel blocker overdose. Benefits have been reported up to 80 minutes after verapamil-mediated cardiac arrest.10 We gave it to our patient on admission to ICU, however this was 3 days after ingestion and so probably too late.

Adverse effects
The use of ILE in parenteral nutrition is associated with hypersensitivity, pancreatitis, fat embolism and myocardial failure, and so it is likely that it may cause these problems when given in poisoning.7 Adverse effects of ILE include hypertriglyceridaemia, hypoxaemia, hyponatraemia, inability to obtain accurate full blood count, arterial blood gas and electrolyte levels, ARDS, hypersensitivity, fat embolism syndrome and phlebitis.3,7,9 It is not clear whether our patient’s respiratory distress was exacerbated by the administration of ILE, although it is possible.

Research limitations
Much of the evidence for the use of ILE in calcium channel-blocker overdose is extrapolated from animal studies and case reports. There is a publication bias in case studies involving the use of ILE, as cases where it did not work are reported less frequently than those where it does. It has been shown to improve haemodynamic parameters and survival in animal models in intravenous poisoning with verapamil.3 This is difficult to extrapolate to humans ingesting oral preparations. A human case series involving 5 patients reported a mortality of 60% when using ILE.3 This is higher than previously reported studies of calcium channel blockers, however the studies are difficult to compare as the case series used only severe cases, whereas previous studies include varying severities of poisoning.3 Death following administration of ILE in case reports does not necessarily imply failure of ILE therapy, as the cause of death in these cases may be due to a multitude of causes.4

Future research
Future research should look at interactions between ILE and other antidotes, optimal timing of ILE therapy, whether dose adjustment is required in particular patient groups, and longterm outcomes following ILE infusion.9

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Lessons learnt
I witnessed possible problems associated with the use of ILE, including respiratory distress and the inability to measure serum electrolytes. I also learned that the evidence for the use of ILE in calcium channel blocker overdose is weak, coming mainly from animal studies and human case reports. Studies are heterogenous and so are difficult to compare. It is therefore vital to ensure systematic reporting of ILE use in poisoning and cases should be reported to the lipid registry to inform further recommendations.4 I believe that ILE has a role as an adjunctive therapy in calcium channel blocker overdose, but only after general supportive management and recognised specific treatment has been unsuccessful.

112 words

Total 1941 words
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