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Unexpected outcome (positive or negative) including adverse drug reactions

# Amlodipine poisioning complicated with acute non-cardiogenic pulmonary oedema

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## Summary

Amlodipine poisoning is an uncommon presentation with potentially life threatening complications. As there are few cases of severe poisoning documented, management guidelines are limited. The authors present the case of a 22-year-old female who presented to hospital 6 h after ingesting 280 mg of amlodipine. She was treated with aggressive fluid resuscitation and calcium gluconate infusion. She went on to develop acute non-cardiogenic pulmonary odema for which she needed a frusemide infusion. She stayed in hospital for 5 days and was discharged after a psychiatric review with no long-term complications. The authors discuss the other management options available for patients presenting with amlodipine overdose.

## BACKGROUND

Calcium channel blockers are the leading cause of cardiovascular drug overdose and are responsible for 65% of deaths related to cardiovascular drugs.[1] Amlodipine is a dihydropyridine calcium channel blocker used to treat essential hypertension. Amlodipine inhibits calcium influx into cardiac and vascular smooth muscle cells through L-gated calcium channels, which leads to dilation of both arterioles and arteries.[2] Unlike the non-dihydropyridine calcium channel blockers, dihydropyridines mainly affect smooth muscle cells with little effect on cardiac pacemaker cells or contractility,[3] however in the clinical setting of significant overdoses, this selectivity may be lost.[1] Amlodipine is slowly absorbed, with peak plasma concentrations observed after 6 to 9 h,[4] and a half life at first dose of roughly 45 h.[5] Amlodipine seems to have a linear pharmacokinetic profile, with dose ingested correlating with mean peak plasma concentration.[6]

Significant overdose of calcium channel blockers can lead to profound hypotension and bradycardia which is often refractory to standard resuscitation methods.[1 7] These overdoses can challenge even the most experienced physician, especially as there is limited clinical experience with amlodpine overdose.

## CASE PRESENTATION

A 22-year-old female was admitted to the acute medical admissions unit via the accident and emergency department 6 h after she had deliberately ingested 280 mg of amlodipine. She was previously fit and well with no medical history and no previous self harm attempts.

On admission, she had a heart rate of 60 beats per min and blood pressure of 71/30 mm Hg. She showed no signs of cardiac or respiratory distress. ECG on admission showed normal sinus rhythm and no pathological changes. Her laboratory tests on admission were normal and initial chest x-ray was unremarkable. Patient was fluid resuscitated with Hartmann's solution and for accurate monitoring, a urinary catheter was inserted.

Patient systolic blood pressure remained low, and a repeat ECG showed T-wave inversion in the lateral leads. Her repeat blood results showed a hypocalcaemia of 2.08 mmol/l. She was immediately commenced on an infusion of calcium gluconate; 30 ml of 10% calcium gluconate over 5 min followed by an infusion of 10 ml/h of 10% calcium gluconate as advised by the national poisons information service. Fluid resuscitation with Hartmann's solution was continued to maintain adequate blood pressure and by the end of day one patient had a positive fluid balance of 4750 ml. As urine output was adequate we decided against inotropic support.

On day 2, the patient became acutely short of breath and developed signs of congestive heart failure; on auscultation there were crackles to the mid-zones bilaterally, her jugular venous pressure was raised at 5 cm, and she had a systolic murmur and a gallop rhythm. Arterial blood gas on room air showed that the patient was hypoxic with a $pO_2$ 7.02 kpa. A repeat chest x-ray showed signs of gross heart failure by means of upper lobe diversion and fluid in the horizontal fissure. Upon these results the patient was commenced on mid flow oxygen 8 litres via non-re-breathing mask and a furosemide infusion started at 80 mg over 6 h, which was then increased to 120 mg over 6 h. At the same time, the fluid administration was restricted. A 12 h troponin was elevated. Due to the hypoxia, gross pulmonary odema and raised troponin we arranged for an ECG to assess cardiac function, a CT pulmonary angiogram (CTPA) to rule out a pulmonary embolus and an urgent cardiology review.

On day 3, the patient had the ECG which showed large bilateral pleural effusions. The heart itself showed a normal left and right ventricular size, normal systolic function and no obvious regional wall abnormalities noted at rest. The CTPA confirmed presence of large bilateral pleural effusions but showed no evidence of a pulmonary embolus. The patient was reviewed by the cardiologists who felt that the raised troponin was not clinically significant. The fluid balance on days 3 and 4 was negative 2270 ml and 2200 ml, respectively.

## OUTCOME AND FOLLOW-UP

The patient remained on intravenous diuretics for the next 3 days, with her kidney function being closely monitored. She continued to improve clinically. Her hypoxia and signs of overload resolved. She was discharged on day 5 post admission after a psychiatric consult had been obtained, with oral diuretics for a short course and review of her symptoms in clinic.

## DISCUSSION

Only a few cases of serious or fatal overdose have been reported.[8] Acute non-cardiogenic pulmonary oedema,[9 10] hypodynamic shock[11 12] and hyperglycaemia[13] are recognised complications of calcium channel blocker overdose.

We have a presented a case which shows the complexity of treating severe amlodipine overdoses. We managed the patient with aggressive fluid resuscitation, calcium gluconate infusion for cardiac protection and later diuretic infusion to treat the non-cardiogenic pulmonary odema. The pathogenesis of non-cardiogenic pulmonary oedema is thought to be due to precapillary vasodilation resulting in excessive pulmonary capillary transudate secondary to pressure effect.[9] As there are few cases of severe poisoning documented, management guidelines are limited and can only advise.

Gastrointestinal decontamination is advocated because of the potential lethal nature of calcium channel blocker (CCB) overdoses and the lack of specific efficacious antidote.[14] The National Poisons Information Service suggests that if a patient presents with in the first h, decontamination should be aggressive with activated charcoal.[15] Whole bowel irrigation may be performed in setting of massive overdose or overdose with modified release CCB. If whole bowel irrigation cannot be performed then multiple doses of charcoal may be given every 4 h.[16] As the patient presented to accident and emergency 6 h post ingestion this was not performed.

As with any patient presenting with profound hypotension, first line management is aggressive fluid resuscitation, then followed by a calcium gluconate bolus and infusion.[9 17] The calcium improves myocardial contractility and systemic perfusion. This is the standard treatment given in the documented literature.

There is increasing evidence for administration of insulin while maintaining normal glucose levels as first line treatment in poisoning with calcium channel blockers.[18] Suggested mechanisms are that insulin improves carbohydrate metabolism in cardiac muscle cells, increases plasma levels of ionised calcium, or that insulin itself has a direct positive inotrophic effect.[14 18] We considered this, however as our patient was clinically improving we opted not to administer.

Some documented cases advocate inotropic support such as epinephrine and dopmanine, in patients with persistent hypotension and/or acidosis.[17] We considered this as an option, however as the patient maintained a good urine output and was not acidotic, inotropic support was withheld. A newer inotropic drug levosimendan has properties which may be more beneficial than other inotropic drugs in managing haemodynaimc compromise in severe calcium channel blocker overdose. It improves cardiac contraction by improving the use of available cytosolic calcium, rather than by flooding the cell with excessive calcium.[19 20] In one case of persistent hypotension and acidosis despite inotropic support with dopamine, levosimendan was shown to dramatically improve cardiac function and acidosis.[7]

If symptoms persist despite the above interventions, a lipid emulsion infusion or glucagon infusion may be given.[15] It is thought that the lipid infusion may decrease the concentration of free active drug and therefore improve myocardial activity and function, while glucagon also improves myocardial function and is useful in patients with severe hypotension unresponsive to other interventions.[15]

### Learning points

- Amlodpine overdoses may currently be a rare presentation, but with an increasing number of people now on calcium channel blockers these cases may become more common place. It is important to have a structured approach to deal with amlodipine overdoses and to be aware of the potentially life threatening complications.
- Gastrointestinal decontamination should be performed if patient presents within the first h due to potential lethal nature of amlodipine, and seek advice immediately from national poisons service.
- Be aware of complications of amlodipine overdose; acute non-cardiogenic pulmonary odema, hypodynamic shock and hyperglycaemia.
- Aggressive fluid resuscitation to maintain blood pressure with accurate urine output monitoring, along with calcium gluconate infusion to improve myocardial contractility and systemic perfusion.
- Consider insulin infusion and/or inotropic support if patient remains hypotensive, becomes acidotic or if becomes clinically unstable.
- Ensure patient has a psychiatric review and adequate follow-up when discharged into the community.

**Competing interests** None.

**Patient consent** Obtained.

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