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# COMBINED CALCIUM CHANNEL BLOCKER AND ANGIOTENSIN-CONVERTING ENZYME INHIBITOR OVERDOSE

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## ABSTRACT

*Introduction:* Combined overdoses of angiotensin-converting enzyme inhibitors and calcium channel blockers are rare but associated with more severe toxicity than either agent alone.

*Case description:* A 48-year-old woman presented to the emergency department nine hours after intentionally ingesting 40 tablets of amlodipine (10 mg) and 40 tablets of ramipril (10 mg). On arrival, she was hypotensive and tachycardic. Initial management included fluids, intravenous calcium and insulin bolus followed by high-dose insulin euglycaemic therapy (HIET). Despite escalating vasopressor support, she developed mixed vasoplegic and cardiogenic shock complicated by acute kidney injury, fluid overload, respiratory failure and metabolic acidosis, necessitating intubation and continuous renal replacement therapy. Improvement in haemodynamics was only achieved by day 9. She was transferred from the intensive care unit (ICU) on day 20 with residual weakness from ICU-acquired myopathy and was ultimately discharged after 66 days, with a prolonged hospitalisation attributed to delirium and deconditioning.

*Discussion:* Severe combined angiotensin-converting enzyme inhibitors (ACEI) and calcium channel blockers (CCB) overdose may cause prolonged, refractory haemodynamic instability requiring extended high-dose insulin euglycaemic therapy (HIET), vasoactive support and fluid administration. Concentrated insulin, dextrose and vasopressor preparations may help mitigate fluid overload. Angiotensin II may be a potential treatment for refractory vasoplegia, although evidence and availability remain limited. Secondary complications can prolong recovery beyond the duration of drug toxicity.

*Conclusion:* This case highlights the need for individualised, multidisciplinary management, early HIET, vasoactive support and fluid-sparing strategies in severe combined ACEI and CCB overdose.

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## KEYWORDS

Amlodipine, ramipril, calcium channel blocker and angiotensin-converting enzyme inhibitor overdose, refractory vasoplegia, high-dose insulin euglycaemic therapy

## LEARNING POINTS

- Management of severe combined calcium channel blocker and angiotensin-converting enzyme inhibitor overdose may require prolonged resuscitation with high-dose insulin euglycaemic therapy, vasoactive support and fluid administration. The cumulative fluid requirements of these therapies, combined with complications such as acute kidney injury, can contribute to severe fluid overload. The use of concentrated insulin, dextrose and vasopressor preparations may help limit the iatrogenic fluid accumulation.
- Clinicians should anticipate and proactively manage secondary complications, including acute kidney injury, volume overload, respiratory failure and infection, as these complications may independently prolong recovery beyond the expected duration of drug toxicity.
- Combined angiotensin-converting enzyme inhibitor and calcium channel blocker overdose lacks established management guidelines and requires individualised, multidisciplinary care based on clinical severity and response to therapy.

## INTRODUCTION

Antihypertensive drug overdoses are serious emergencies with potentially fatal outcomes[1]. Although reports of combined angiotensin-converting enzyme inhibitors (ACEI) and calcium channel blockers (CCB) overdose are rare, existing literature suggests that co-ingestion can result in a more severe toxicity than either drug alone[2,3]. This report presents a 48-year-old woman who developed profound refractory vasoplegia after intentionally ingesting high doses of amlodipine and ramipril, underlining the challenges in managing such complex overdoses. This report was prepared following the CARE case report guidelines.

## CASE DESCRIPTION

A 48-year-old, 80 kilograms, female with a history of hypertension, dyslipidaemia, type 2 diabetes, depression, alcohol and cocaine use disorder, and prior suicide attempts, presented to the emergency department following the ingestion of 40 tablets of amlodipine 10 mg and 40 tablets of ramipril 10 mg, approximately 9 hours prior to arrival. She had also consumed 12 large beers.

On arrival, she was alert but complained of generalised weakness and blurred vision. She had profound hypotension and tachycardia (53/37 mmHg, 107 beats/minute), a normal respiratory rate and an oxygen saturation of 93%. The physical examination was unremarkable. Initial laboratory tests showed glucose 19.5 mmol/l, creatinine 78 µmol/l (baseline 45 µmol/l), pH 7.4, lactate 4.4 mmol/l, ionised calcium 1.07 mmol/l, albumin 34 g/l, ethanol level 27 mmol/l and a urine toxicology screen positive for cocaine and amphetamines.

She received 2 litres of crystalloids and 1 gram IV of calcium chloride; the local poison control centre was consulted. Although her point-of-care ultrasound showed normal left ventricular function, high-dose insulin euglycaemic therapy (HIET) was initiated empirically due to severe hypotension with inappropriate normocardia (60 beats/minute). She received a 1 unit/kg bolus of IV regular insulin followed by a continuous infusion at 1 unit/kg/h.

Approximately 1 hour after presentation (day 1, 18:40), a norepinephrine infusion was started at 5 mcg/min and rapidly escalated. She was transferred to the intensive care unit (ICU) at 20:40, where her mean arterial pressure remained low (53 mmHg via brachial arterial line) on norepinephrine 54 mcg/min. Over the following 24 hours, vasopressin (up to 0.08 units/min) and epinephrine (up to 5 mcg/min) were added to target a mean arterial pressure of 65 *(Fig. 1)*. Calcium chloride 1 g IV every 8 hours was administered for 3 days, bringing the cumulative dose since admission to 10 g by day 3.

On day 2, she developed hyperactive delirium, which required boluses of intravenous diazepam, haloperidol and ketamine. Vasopressor support was escalated (norepinephrine 72 mcg/min, epinephrine 5 mcg/min, vasopressin 0.08 units/min) and a 10% dextrose infusion was initiated at 100 ml/hr to support HIET. Despite these measures, the patient progressed to mixed vasoplegic and cardiogenic shock, complicated by worsening oliguric acute kidney injury (AKI), significant volume overload and probable acute lung injury. The low urine output further declined from 12.5 ml/hr on day 1 to 4.1 ml/hr on day 3, resulting in a cumulative positive fluid balance of 8 litres. A high-dose furosemide bolus (240 mg IV) yielded minimal diuresis. The patient subsequently developed worsening hypoxemic respiratory failure and metabolic acidosis, prompting initiation of continuous renal replacement therapy (CRRT) and intubation. After intubation, sedation was maintained with high-dose continuous propofol infusion. On day 5, a fentanyl infusion was started for sedation and analgaesia, followed by paralysis with rocuronium on day 6 to optimise mechanical ventilation

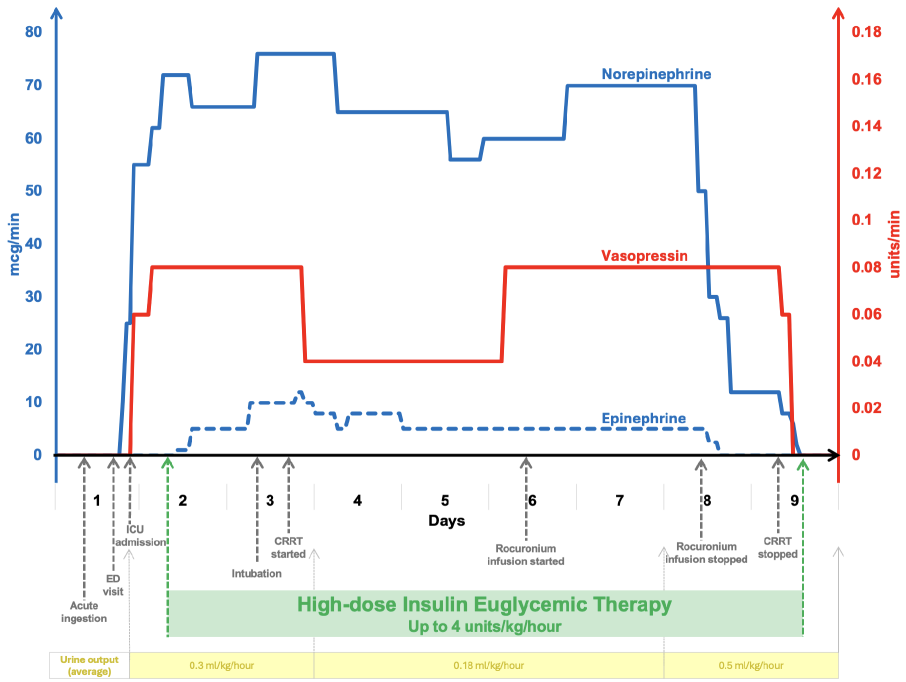



*Figure 1. Clinical course after acute overdose with 40 tablets of amlodipine 10 mg and 40 tablets of ramipril 10 mg in a 48-year-old female of 80 kilograms.*

in the context of severe hypoxia, metabolic acidosis and patient-ventilator dyssynchrony.

Vasopressor requirements peaked at day 3 (norepinephrine 76 mcg/min, epinephrine 12 mcg/min) and HIET was titrated up to 4 units/kg/hr using high-concentration insulin preparations (10 units/ml) as well as a dextrose 50% preparation to minimise fluid burden. The glycaemia target was 5 to 12 mmol/l during the patient's course of treatment; the target was achieved using a dextrose 50% nursing titration algorithm with glycaemia checks every hour.

By day 8, a transthoracic echocardiogram demonstrated hyperdynamic right and left ventricles allowing epinephrine to be tapered and stopped. Norepinephrine and vasopressin were subsequently weaned then stopped; CRRT and insulin were also discontinued on day 9. The dextrose infusion was discontinued by day 10. A tracheostomy was performed on day 13 due to profound weakness and ventilator dependence despite having achieved haemodynamic stability. A computed tomography (CT) head was unremarkable, and an electromyography confirmed ICU-acquired myopathy. The patient was weaned off mechanical ventilation on day 16 and transferred to the internal medicine unit on day 20; she was discharged after 66 days, after being delayed by both delirium and deconditioning.

## DISCUSSION

A severe overdose resulted in eight days of haemodynamic instability, with rapid resolution during the final 24 hours. This duration exceeds that previously reported in the literature, typically persisting for 4 to 9 days, although durations of up to 18 days have also been reported. The patient's prolonged ICU admission may be attributed to the ingestion of two cardiovascular medications at an exceptionally high dose with possible synergistic effects, exceeding those previously reported in the literature[1–4]. The presence of additional factors that exacerbate hypotension, including pneumosepsis, the use of neuromuscular blocking agents and high-dose sedative use, likely further contributed to the severity of the patient's haemodynamic instability, and their resolution and cessation may account for the rapid improvement of vasoplegia observed during the final 24 hours of day 8.

Ramipril is rapidly absorbed and is converted to its active metabolite, ramiprilat, with approximately 60% of the parent drug and its metabolites eliminated in the urine. Ramiprilat is moderately bound to albumin and is only partially removed by dialysis. It exhibits biphasic elimination kinetics: an initial elimination half-life of 13–17 hours, which is prolonged in renal impairment, and a terminal half-life, related to the slow dissociation of the ramiprilat–ACE complex, exceeding 50 hours[5]. In this patient, AKI and the prolonged terminal half-life of ramiprilat likely worsened the observed profound and prolonged vasoplegia.

Amlodipine is well absorbed, with an absolute bioavailability of 64–90%. It is extensively metabolised in the liver, with approximately 90% converted to inactive metabolites; about 93% is bound to plasma proteins, and haemodialysis is unlikely to be beneficial. Approximately 10% of the parent compound and 60% of its metabolites are excreted in the urine. The elimination half-life of amlodipine is 30–50 hours[6]. In the context of overdose, hepatic metabolism becomes saturated, leading to a prolonged elimination half-life[7]. The exact duration of vasoplegia is unpredictable.

Combined overdoses of dihydropyridine CCBs, such as amlodipine, and ACEIs, such as ramipril, are infrequently reported but tend to present with more complex and severe clinical manifestations compared to overdoses involving either agent alone. These combined overdoses

typically feature profound hypotension refractory to fluids and requiring haemodynamic support. Altered mental status, AKI, metabolic acidosis, hyperglycaemia, pulmonary oedema and respiratory failure may occur, especially in severe overdose. The resulting multiorgan failure complicates management and often necessitates interventions beyond vasoplegia treatment[2-4,8].

No specific guidelines exist on management of ACEI and CCB co-ingestion. Isolated ACEI overdose has limited complications and is generally managed with supportive measures (e.g. activated charcoal and crystalloids boluses), with catecholamines less frequently used. Administration of naloxone and angiotensin II via IV might have benefits in refractory cases[9]. Dihydropyridine CCBs overdose can be challenging, particularly with large ingestions, which causes a loss of receptor selectivity to smooth muscle cells, resulting in inhibition of myocardial calcium channels and ultimately cardiovascular collapse[7]. Supportive care, vasopressors or inotropes are often required to manage vasoplegia, and additional interventions such as HIET, IV calcium, glucagon and atropine (if bradycardia is present) are typically necessary[1,9].

Given the severity of CCB overdose and overlap with ACEI management, the CCB overdose protocol was followed[1]. The patient required HIET, calcium chloride and high-dose vasopressors. Activated charcoal was withheld due to delayed presentation, vomiting and intubation risk. An insulin bolus was given within the first hour, but HIET started about 24 hours post-ingestion as vasopressor needs rose. Early HIET is important, as its effect on cardiac contractility is observed within 60 mins after initiation[9]. Alternative therapeutic approaches and outcomes have been described in the literature. Gutierrez et al. documented a case of combined CCBs and ACEIs overdose in which angiotensin II initiation at day 2 led to a significant improvement in vasoplegia after maximal support with HIET, multiple vasopressors and lipid emulsion were insufficient[4]. Successful treatment with angiotensin II was also reported by Tovar et al. and Keller et al.[2,3]. Angiotensin II is FDA-approved for vasodilatory shock in the US but was not approved in Canada at the time of the PMPRB assessment.[10]. Its impact on this patient's vasopressor needs is unclear, given the amount ingested was 25–50% higher than those reported in other cases[2-4].

Volume overload is a common complication in combined CCB and ACEI overdose, mainly due to the large fluid volumes needed for resuscitation and drug infusions. Using concentrated vasopressors, inotropes, insulin and dextrose preparations helps limit fluid intake. Despite this approach by days 2 and 3, the patient developed diuretic-resistant volume overload, AKI and metabolic acidosis refractory to bicarbonate, requiring CRRT. Similar cases report the use of haemodiafiltration for these complications[4,8]. In severe cases with associated respiratory failure, veno-venous extracorporeal membrane oxygenation was used, markedly improving the respiratory function[8]. In this patient, mechanical ventilation with sedation alone was inadequate prompting rocuronium paralysis on day 6, which may have further delayed recovery from myopathy.

## CONCLUSION

In summary, this case highlights the complexity of managing combined CCB and ACEI overdose, characterised by profound and prolonged vasoplegia. Complications such as volume overload, nosocomial infection (pneumosepsis) and haemodynamic stressors (high-dose sedatives), can exacerbate hypotension and delay recovery. Clinicians should anticipate a protracted course and consider early initiation of HIET, the use of concentrated vasopressors and fluid-sparing strategies. Angiotensin II may provide additional therapeutic benefit.

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