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CASE REPORT

Intoxication with massive doses of amlodipine and candesartan requiring venoarterial extracorporeal membrane oxygenation

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Abstract

Background: Calcium channel blockers and angiotensin II receptor blockers are commonly prescribed to treat hypertension. Massive overdoses can cause both distributive and cardiogenic shock because of their effects on vascular smooth muscles and severe myocardial depression.

Case Presentation: We present the case of a 46-year-old man who was brought to our emergency department after ingesting 1210 mg amlodipine and 936 mg candesartan. The patient's hemodynamic status deteriorated despite treatment with vasopressors, calcium gluconate, and hyperinsulinemia-euglycemia therapy with mechanical ventilation. Venoarterial extracorporeal membrane oxygenation was initiated for refractory shock. The patient was weaned off extracorporeal membrane oxygenation on day 5 and discharged on day 18 of hospitalization.

Conclusion: When medical therapies are ineffective, aggressive venoarterial extracorporeal membrane oxygenation should be considered for the management of refractory shock in the setting of calcium channel blocker with angiotensin II receptor blocker overdose.

KEYWORDS
amlodipine, candesartan, drug overdose, ECMO, toxicity

INTRODUCTION

An overdose of calcium channel blockers (CCBs) can cause life-threatening hypotension, for which vasopressors might not be effective. Here, we present a case of drug-refractory hypotension caused by a massive overdose of CCBs and angiotensin II receptor blockers (ARBs). The patient was successfully managed with venoarterial extracorporeal membrane oxygenation (VA-ECMO).

CASE PRESENTATION

A 46-year-old man was brought to our emergency department with general malaise 14 h after ingesting 1210 mg amlodipine besylate (amlodipine) and 936 mg candesartan cilexetil (candesartan) in a suicide attempt. He had a history of hypertension, but no known history of mental illness. Upon arrival at the emergency department, his vital signs were as follows: Glasgow Coma Scale score, 13 (E3V4M6); blood pressure, 60/39 mmHg; heart rate, 95 b.p.m. (sinus rhythm); respiratory rate, 30 breaths/min; and blood oxygen saturation, 93% on a reservoir oxygen mask at 10 L/min. Blood tests revealed elevated lactate concentration and metabolic acidosis (Table 1). The 12-lead electrocardiogram findings were as follows: heart rate, 91 b.p.m.; normal sinus rhythm; right bundle branch block; and no QTc prolongation. The transthoracic echocardiogram findings were as follows: visually estimated ejection fraction, 20%; no asynergy; and no valvular disease.

TABLE 1 Laboratory findings on day 1 of hospitalization of a 46-year-old man with intoxication with massive doses of amlodipine and candesartan

Hematology			**Coagulation**		
WBC	18,100/μL	(3,500–8,500)	PT-INR	0.98	(0.9–1.1)
RBC	490 × 10/μL	(430–570)	APTT	25.9 s	(28.0–42.0)
Hb	14.7 g/dL	(11.5–15.0)	Fbg	575 mg/dL	(150–400)
Plt	27.0×10^4/μL	(15.0–35.0)	D-dimer	0.8 μg/mL	(<1.0)
Biochemistry			**Arterial blood gas (Oxygen 10 L/min)**		
T-Bil	0.7 mg/dL	(0.3–1.2)	pH	7.299	(7.35–7.45)
AST	32 U/L	(10–40)	pCO_2	31.6 mmHg	(35–45)
ALT	48 U/L	(5–40)	pO_2	98.6 mmHg	(80–100)
γ-GTP	55 U/L	(15.0–35.0)	HCO_3^-	15.2 mmol/L	(20–26)
BUN	92.6 mg/dL	(8–22)	BE	−9.9 mmol/L	(−3 to 3)
Cre	2.60 mg/dL	(0.47–0.79)	Na	139 mEq/L	(135–148)
CK	80 U/L	(62–287)	K	4.0 mEq/L	(3.5–5.3)
CRP	0.05 mg/dL	(<0.3)	Cl	103 mEq/L	(98–106)
Na	138 mmol/L	(138–145)	Ca	1.24 mmol/L	(1.13–1.32)
K	4.1 mmol/L	(3.6–4.8)	AnGap	25 mmol/L	(10–18)
Cl	106 mmol/L	(101–108)	Glucose	238 mg/dL	(70–110)
Ca	9.9 mg/dL	(8.8–10.1)	Lactate	7.8 mmol/L	(0.5–2.0)

Note: Normal range of values shown in parentheses.

Abbreviations: ALT, alanine transaminase; AnGap, anion gap; APTT, activated partial thromboplastin clotting time; AST, aspartate aminotransferase; BE, base excess; BUN, blood urea nitrogen; Ca, calcium; CK, creatine kinase; Cl, chloride; Cre, creatinine; CRP, C-reactive protein; Fbg, fibrinogen; Hb, hemoglobin; HCO_3^-, bicarbonate; K, potassium; Na, sodium; pCO_2, partial pressure of carbon dioxide; Plt, platelet; pO_2, partial pressure of oxygen; PT-INR, prothrombin time international normalized ratio; RBC, red blood cell; T-Bil, total bilirubin; WBC, white blood cell; γ-GTP, gamma-glutamyl transferase.

Based on the patient's medical history, we suspected acute amlodipine and candesartan intoxication that led to shock. However, despite our attempts to improve his condition with fluid resuscitation and the administration of high-dose noradrenaline and vasopressin, there was no improvement in the patient's blood pressure or lactic acidosis. To maintain the patient's blood calcium levels, we administered calcium gluconate and regularly monitored the levels using arterial blood gas tests. Hyperinsulinemia-euglycemia therapy was initiated at a rate of 0.5 U/kg/h, without a bolus to avoid hypoglycemia and hypokalemia. Additionally, we administered lipid emulsion and glucagon. Unfortunately, the patient's vital signs, ejection fraction, and left ventricular outflow tract velocity time integral showed no improvement. We considered using methylene blue, but it was unavailable at our hospital.

In addition to distributive shock, we suspected impaired cardiac function contributing to the catecholamine-refractory hypotension, suggesting cardiogenic shock. Consequently, we decided to intubate the patient and initiate VA-ECMO approximately 4 h after arrival. Following the initiation of VA-ECMO, we observed a gradual improvement in blood lactate concentration and metabolic acidosis, and we simplified our management approach by discontinuing hyperinsulinemia-euglycemia therapy, lipid emulsion, and glucagon.

Despite the improvement observed with VA-ECMO, the patient still required catecholamines for several days to maintain mean arterial pressure, indicating persisting refractory distributive shock. Over time, the patient's requirement for catecholamines decreased, and cardiac function gradually improved, ultimately leading to successful weaning from VA-ECMO on day 5 of hospitalization. Although the patient experienced renal failure due to the intoxication, renal replacement therapy was not deemed necessary. Finally, the patient was extubated on day 9 and discharged on day 18 without experiencing any complications related to VA-ECMO. Blood levels of amlodipine and candesartan were determined. The maximum blood concentrations of amlodipine and candesartan were 536.9 and 8.1 mg/mL, respectively, on day 1 (Figure 1).

DISCUSSION

We encountered a patient with hypotension refractory to drug therapy, due to the co-ingestion of massive doses of amlodipine and candesartan, in whom VA-ECMO played a life-saving role.

Amlodipine is a CCB belonging to the class of dihydropyridines that exerts antihypertensive effects by acting on vascular smooth muscles. It is characterized by a long duration of action, taking 7.6 ± 1.8 h to reach maximum blood concentration, and has an elimination half-life of 34 ± 5 h.[1] Dihydropyridines are highly selective for vascular smooth muscles; however, when administered excessively, they may lose their selectivity and act on the myocardium, resulting in a negative inotropic effect.[2] In addition, the extent of amlodipine's antihypertensive effects is based on its serum concentrations.[3] Fatal cases have been reported at doses of 70 mg

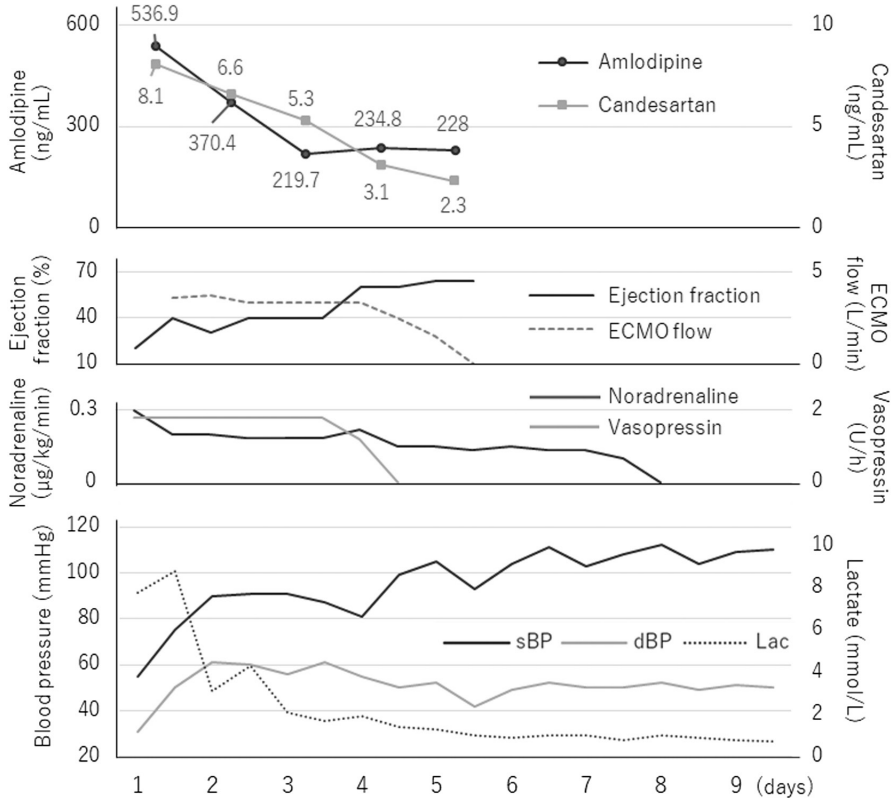

FIGURE 1 Blood concentrations of amlodipine and candesartan during the clinical course of a 46-year-old man with intoxication with massive doses of amlodipine and candesartan. dBP, diastolic blood pressure; ECMO, extracorporeal membrane oxygenation; Lac, lactate; sBP, systolic blood pressure.

and serum drug concentrations of 185 μg/L.[4] In this case, the serum drug concentration (536.9 μg/L) was extremely high compared to that in previous reports. Therefore, the patient may have experienced both cardiogenic and distributive shock. Worldwide, cases of survival and discharge after oral ingestion of doses exceeding 1000 mg are extremely rare,[5] and a PubMed search found no case report in the past 30 years of a patient discharged alive after taking more than 1200 mg amlodipine. Therefore, to the best of our knowledge, the oral dose of amlodipine (1250 mg) ingested by our patient is the highest among all reported survival cases.

Angiotensin II receptor blockers inhibit vasoconstriction and reduce peripheral vascular resistance and blood pressure by directly blocking the angiotensin II type 1 receptor, the primary target of angiotensin II. Symptoms of ARB intoxication include hypotension, nausea/vomiting, dizziness, fatigue, and somnolence. Severe symptoms are uncommon, and according to a case series of 206 ARB overdoses, only one pediatric patient required intravenous fluids for treatment.[6] Moreover, long-term use of ARBs can lead to decreased sensitivity to hormones that regulate blood pressure, resulting in catecholamine-refractory hypotension.[7]

In addition, regarding the interaction between CCBs and ARBs, the vasodilating effect of CCBs is compensated for by the activity of the renin-angiotensin system, but suppression of this compensatory effect by ARBs contributes to severe hypotension.[8] Indeed, as previously reported by Huang et al.[8] the combined overdose of dihydropyridines and ARBs resulted in more severe hypotension and required greater hemodynamic support compared with overdosing on dihydropyridines alone.

The treatment of acute poisoning with amlodipine is based on systemic management, including airway, respiratory, and circulatory control. There are several specific treatment methods to cope with distributive shock due to vasodilation, such as calcium and glucagon administration, high-dose insulin therapy, and lipid emulsion therapy. However, as in this case, if the patient develops refractory shock, VA-ECMO has the potential to improve the patient's hemodynamic and metabolic status. In 2021, Upchurch et al.[9] recommended the consideration of VA-ECMO in the absence of contraindications for all patients with acute poisoning and refractory cardiogenic shock. In fact, the use of VA-ECMO for treating drug intoxication, including several cases of amlodipine intoxication, has increased in recent years.[9]

Similar to drug-induced refractory shock, septic shock causes a condition that can result in simultaneous cardiogenic and distributive shock. In recent years, VA-ECMO has been found to be effective for distributive shock. Falk et al.[10] reported that VA-ECMO may be beneficial for both the hospital and long-term survival of patients with distributive septic shock. They argued that VA-ECMO supports the failing heart but does not directly impact other parts causing hypotension; however, improving tissue oxygenation may

play a role in stabilizing circulation and limiting the negative impact of generalized poor oxygenation.

Consequently, the active management of patients with drug-refractory hypotension using VA-ECMO appears to be a reasonable strategy.

CONCLUSION

Venoarterial extracorporeal membrane oxygenation can be used in patients with severe cardiogenic and distributive shock caused by massive overdoses of CCBs and ARBs.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of Interest.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Approval of the research protocol: N/A.
Informed consent: Informed consent for the publication of this case report was obtained from the patient.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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