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Venoarterial extracorporeal membrane oxygenation for the management of massive amlodipine overdose

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Abstract

A 50-year-old man was admitted to the intensive care unit with respiratory failure and shock after suffering a massive overdose of amlodipine, lisinopril and hydrochlorothiazide. Despite mechanical ventilation, vasopressors, calcium gluconate, hyperinsulinemia-euglycemia therapy, methylene blue and intravenous fat emulsion, the patient's respiratory and hemodynamic status deteriorated. Venoarterial extracorporeal membrane oxygenation (ECMO) was initiated to provide cardiopulmonary support in the setting of profound respiratory failure and refractory shock. The patient was placed on ECMO 19 hours after arrival to the hospital, after which vasopressor and ventilatory requirements decreased significantly. The patient was decannulated from ECMO after 8 days and was discharged home after a 56-day hospitalization. Early institution of ECMO should be considered for the management of respiratory failure and refractory shock in the setting of calcium channel blocker overdose when medical therapies are insufficient.

Keywords

ECMO; amlodipine; overdose; shock; respiratory failure

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Introduction

Calcium channel blockers (CCBs) accounted for 34% of cardiovascular drug-related deaths and 3.2% of all deaths due to pharmaceutical exposures reported to poison control centers in 2011.[1] Amlodipine is often favored over other CCBs due to its selectivity for peripheral vasculature and once-daily dosing. However, with a half-life of approximately 34 hours and a loss of vascular selectivity at high doses, the management of amlodipine overdose is challenging.[2] We describe the successful use of venoarterial extracorporeal membrane oxygenation (ECMO) for severe hypoxemic respiratory failure and refractory shock due to amlodipine overdose after the failure of conventional medical management.

Case History

A 50-year-old man with a history of depression and alcohol abuse was brought to the hospital after the ingestion of 500 mg of amlodipine, 1000 mg of lisinopril, and 625 mg of hydrochlorothiazide, in a suicide attempt. Upon arrival, the patient was normotensive and tachycardic, with normal oxygen saturation. Neurologic status was intact and an electrocardiogram showed normal conduction. Within 1 hour, the patient developed hypotension to a blood pressure nadir of 50/34 mmHg and became obtunded. He was intubated, started on dopamine, norepinephrine, normal saline, calcium gluconate and glucagon and was transferred to the intensive care unit (ICU). Given the concern that amlodipine toxicity was the etiology of his shock, hyperinsulinemia-euglycemia therapy was initiated with insulin. After fluid resuscitation, the central venous pressure was 22 mmHg; however, he remained in shock. Phenylephrine, vasopressin and epinephrine were added and maximized without hemodynamic improvement (Figure 1). Severe hypoxemic respiratory failure developed, with a ratio of the partial pressure of oxygen in arterial blood (PaO_2) to the fraction of inspired oxygen (FiO_2) of 79. A transthoracic echocardiogram revealed a left ventricular ejection fraction of 70%. Laboratory analysis demonstrated severe hypokalemia, hypophosphatemia and renal failure.

In the setting of severe hypoxemia and ongoing shock, with blood pressures ranging from 69/39 to 92/31 mmHg despite maximal therapy, including the addition of methylene blue and intravenous fat emulsion, he was started on venoarterial ECMO. The circuit consisted of a Rotaflow centrifugal pump (Maquet Cardiovascular, Hirrlingen, Germany), a Quadrox D oxygenator (Maquet), a 24 Fr elongated one-piece arterial cannula (Medtronic, Minneapolis, MN) grafted to the right axillary artery and a 24 Fr multi-port venous cannula (Avalon Laboratories, LLC, Rancho Dominguez, CA) in the left femoral vein.[3] The blood flow rate was 5.6 L/min, the sweep gas flow rate was 3.0 L/min and the fraction of delivered oxygen was 1.0. Heparin was administered for anticoagulation, with a goal activated partial thrombo-plastin time of 40 to 60 seconds. The FiO_2 on the ventilator was reduced to 0.4 with a PaO_2 of 212 mmHg.

Transthoracic echocardiogram on ECMO day 2 showed a newly reduced left ventricular ejection fraction of 10%. Despite the reduced cardiac function, vasopressors and inotropes were successfully weaned in the setting of ongoing venoarterial extracorporeal support. He was decannulated from ECMO after 8 days and remained hemodynamically stable. On ICU

day 17 he was liberated from mechanical ventilation without the need for supplemental oxygen.

The ICU course was notable for renal failure that required temporary continuous venovenous hemodialysis, *S. epidermidis* bacteremia, and drainage of a loculated pericardial effusion. Left ventricular function improved to 45% during his hospitalization. He was discharged from the hospital with an intact mental status on hospital day 56 and returned to functional independence.

Discussion

CCB overdose may cause significant morbidity and mortality.[1] Although dihydropyridine CCBs generally have been thought to be less lethal in overdose due to their selectivity for the peripheral vasculature and lesser effect on the conduction system, they have been documented to cause profound hypotension, bradyarrhythmias and shock.[4,5] Amlodipine is extensively protein bound with a large volume of distribution and, therefore, not dialyzable. Thus, the treatment of CCB overdose focuses on overcoming its effects on vascular smooth muscle, cardiac myocytes and conduction tissue, and pancreatic beta cells.[4-6] The combination of dihydropyridine CCBs and angiotensin converting enzyme inhibitors or angiotensin receptor blockers may blunt vasoconstrictive and sympathetic responses and worsen CCB toxicity.[7] The ingestion of an excessive dose of lisinopril, in addition to the overdose of amlodipine, may help to explain the refractory nature of this patient's vasodilatory shock. The etiology of the patient's hypoxemic respiratory failure could not be definitively elucidated in this case, though non-cardiogenic pulmonary edema has been described as a complication of CCB overdose and may explain our patient's hypoxemia.[1,8-10] Invasive mechanical ventilation is usually sufficient to manage such sequelae. The use of ECMO has been reported for the management of overdose-related respiratory failure that has failed conventional management, though not specifically in the setting of CCBs.[11-13] This case report illustrates the use of ECMO for both mechanical circulatory and respiratory support when medical therapy alone was insufficient.

The patient was volume resuscitated and a calcium infusion was started in an attempt to overcome calcium channel antagonism, despite which he required adrenergic agonists and vasopressors for hypotension. Case reports indicate that adrenergic agents have had some success in treating CCB overdose;[4,5,7] however, our patient remained in refractory vasodilatory shock. Glucagon was administered in an attempt to activate adenylate cyclase independent of beta adrenergic receptors, but was unsuccessful.[14] Other medical therapies were attempted, including hyperinsulinemia-euglycemia therapy, methylene blue and intravenous fat emulsion. Insulin's property as a positive inotrope and its ability to improve carbohydrate metabolism may provide a benefit in CCB overdose.[15,16] Methylene blue, by scavenging nitric oxide, may have a role in refractory septic shock, cardiopulmonary bypass-induced vasodilation and anaphylaxis; however, it had no effect in our patient.[17-20] Emulsion infusion, which creates an expanded lipid phase in the blood that leads to a redistribution and trapping of tissue-bound drug, has been used in medication overdoses, but did not have any benefit here.[21-23] Given his rapidly deteriorating oxygenation and refractory shock, the decision was made to initiate venoarterial ECMO. The infusion of

intravenous fat emulsion in patients on ECMO has been reported to cause agglutination in the ECMO circuit, though none was noted in this case.[24]

There is a growing body of literature on extracorporeal support for refractory shock or cardiotoxicity due to poisoning.[13,25-29] Our use of venoarterial ECMO was prompted by severe hypoxemia superimposed on refractory vasodilatory shock. A venoarterial configuration proved additionally helpful when the patient developed a severe cardiomyopathy. The use of an arterial reinfusion cannula grafted to an axillary artery, as opposed to a femoral artery, provided the added benefit of delivering oxygenated blood more directly to the aortic arch, maximizing oxygen delivery to the coronary and cerebral vascular beds.[3] During the eight days of ECMO support, there were no alterations to the configuration, replacement of circuit components or complications related to the circuit. Given the patient's potentially reversible cause of shock and respiratory failure, the goal of ECMO was to provide temporary respiratory and hemodynamic support until his body was able to metabolize the amlodipine, lisinopril and hydrochlorothiazide.

Conclusion

ECMO may be considered in cases of hypoxemic respiratory failure and refractory shock in the setting of CCB overdose when medical therapy is ineffective.

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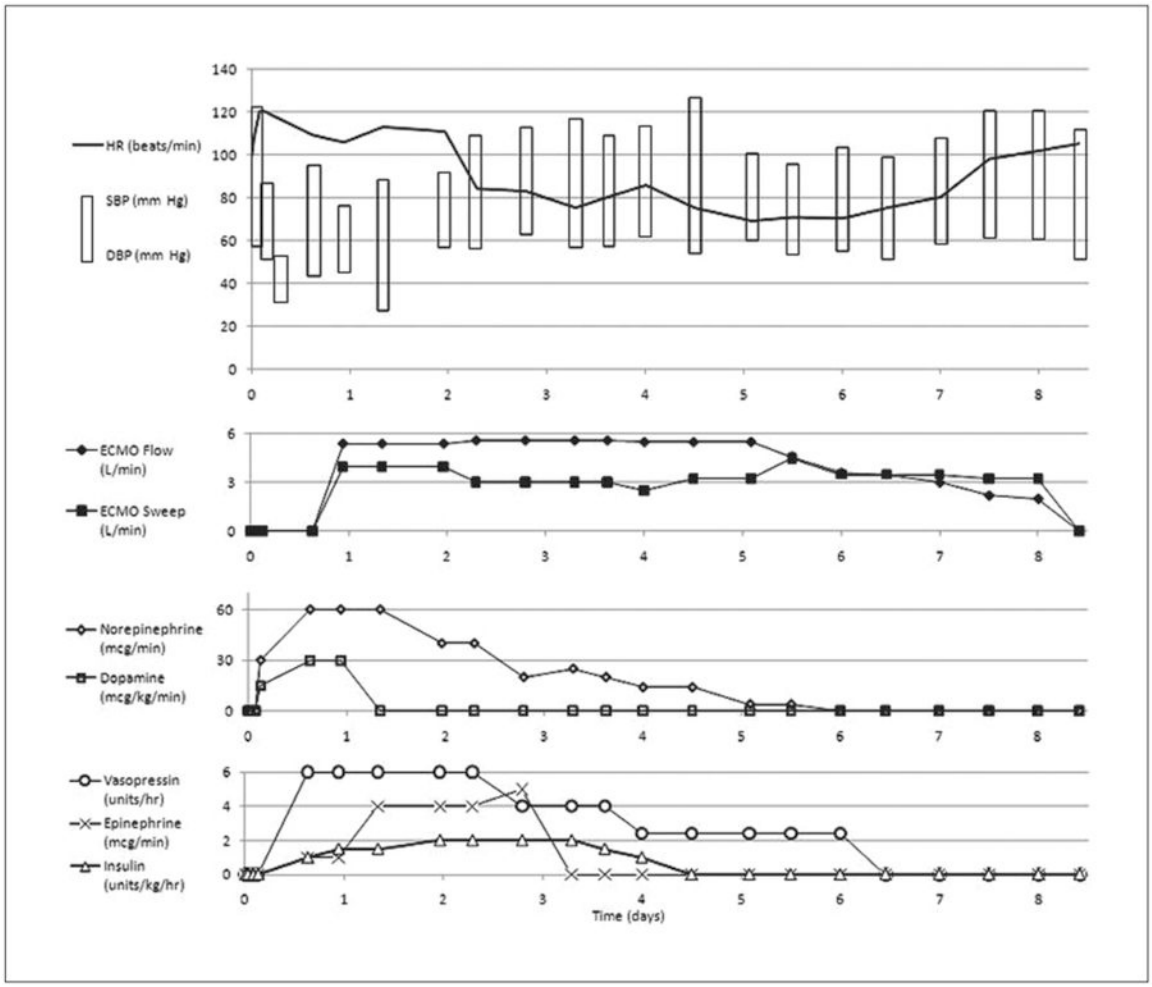

Figure 1.

Vital signs, venoarterial ECMO settings and vasopressor requirements during the patient's intensive care unit course. Vasopressor infusion rates were significantly reduced while maintaining a mean arterial pressure ≥60 mmHg after initiation of venoarterial ECMO. ECMO: extracorporeal membrane oxygenation.