

## Life-threatening amlodipine and irbesartan poisoning in two adolescents: Extracorporeal life support is life-saving

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### ABSTRACT

Calcium channel blockers (CCBs) and angiotensin receptor blockers (ARBs) are widely used in clinical practice and are easily available. Intoxication with these drugs results in life-threatening deep vasoplegic shock, making them particularly dangerous, especially for children. Here, we report two patients who ingested amlodipine and irbesartan for suicidal attempts and were unresponsive to all conventional treatments. They were placed on venoarterial extracorporeal membrane oxygenation (VA-ECMO) and hemodynamically stable immediately after extracorporeal life support (ECLS). Patients were successfully decannulated and extubated. CCB and ARB poisoning that are resistant to medical therapy can be treated by ECLS successfully.

**Keywords:** Amlodipine poisoning, irbesartan poisoning, vasoplegic shock, extracorporeal life support, children

### INTRODUCTION

Amlodipine is a dihydropyridine calcium channel blocker (CCB) that blockades slow L-type calcium channels in vascular smooth muscle and pancreatic beta cells. Intoxication with amlodipine results in vasoplegic shock and myocardial depression. Sartans are antagonists of angiotensin-1 (AT1) receptors of angiotensin II (AII). Angiotensin receptor blocker (ARB) toxicity is associated with hypotension, acute renal failure, and deep hypokalemia. The elimination half-life of both drugs (31-46 hours for amlodipine and 11-15 hours for irbesartan) is prolonged in case of poisoning.<sup>1,2</sup>

Especially CCB overdoses are associated with high morbidity and mortality secondary to multiorgan dysfunction and

catecholamine-refractory hypotension. The current medical treatments based on expert opinion and case reports aim to provide organ support. In patients with cardiogenic and distributive shock caused by massive overdoses of CCBs and ARBs, venoarterial extracorporeal membrane oxygenation (VA-ECMO) has the potential to improve the patient's hemodynamic status.<sup>1-3</sup>

### CASE 1

A fifteen-year-old girl ingested amlodipine and irbesartan combined preparation 325 mg of amlodipine (6.5 mg/kg) and 9750 mg of irbesartan (195 mg/kg) for a suicidal attempt. She was lethargic and hypotensive on admission (60/40 mmHg). Mean arterial pressure was (MAP) 46 mmHg. She was limp with



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filiform pulses, hypothermic (35°C), and a capillary refill time of 4 seconds. Heart rate was 110 beats/min; respiratory rate was 25/min. The patient was intubated for increased work of breathing.

Despite she was started on high doses of norepinephrine (1.2 mcg/kg/min), epinephrine (1.2 mcg/kg/min), dopamine (15 mcg/kg/min), and terlipressin (25 mcg/kg/dose) remained hypotensive. Hyperinsulinemia/euglycemia therapy (infusion rate titrated up to 1 IU/kg/hour with target glucose level 100-200 mg/dL), calcium gluconate (1 mEq/kg/hour, target  $iCa^{++}$  level  $>1.5$  mmol/L), 20% lipid emulsion (1.5 mL/kg bolus, then an infusion of 0.25 mL/kg/min for 30–60 minutes), and methylene blue (MB) (1mg/kg/hour infusion after 2 mg/kg loading dose) were started. A transthoracic echocardiograph showed left ventricular ejection fraction (LVEF) was 40%.

The patient was placed on VA-ECMO 10 hours after pediatric intensive care unit (PICU) admission. An arterial cannula (17 fr) was placed in the left femoral artery with a 12 fr distal perfusion cannula. The venous side of the circuit was inserted in the right femoral vein (21 fr). Heparin infusion started at 10 IU/kg/hour after a single 30 IU/kg bolus with a target activated clotting time (ACT) of 180-220 seconds. At 2nd hour of therapy, rapid improvement was observed in hypotension, and lactic acidosis resolved on the second day. Vasopressors were weaned on the second day of ECLS.

An acute ischemia developed at the arterial cannulation side (left foot) on the 3rd ECLS day. Doppler ultrasonography showed arterial thrombosis (left main and external iliac artery), the patient's hemodynamics were stable, and ECLS was terminated with thrombectomy at the 76th hour. The patient was extubated on day 4. Systemic heparinization continued with low molecular weight heparin (LMWH) 40 mg/day for ten days. The patient received arterial thrombosis prophylaxis with aspirin (3mg/kg/dose once daily). Enteral nutrition with a nasogastric tube is tolerated on the third day, and she started oral feeding on the seventh day. She was discharged from the PICU to an inpatient psychiatry unit 14 days later.

## CASE 2

A 16-year-old girl with a history of depression attempted suicide with approximately 280mg of amlodipine (4,7 mg/kg), 16800mg of irbesartan (280 mg/kg), and 700mg of hydrochlorothiazide (11,67mg/kg). Upon presentation to the PICU at the 6th hour of ingestion, she had hypotension with a blood pressure of 75/40 mmHg (MAP 51 mmHg). The heart rate was 138 beats/min, and the respiratory rate was 28 /min. Laboratory tests revealed elevated serum creatinine of 2.3 mg/dL and lactic acidosis (pH 7.24, lactic acid 8.4mmol/L).

A transthoracic echocardiograph showed normal biventricular function. Three liters of crystalloid were given, and she was started on high doses of norepinephrine (1.5 mcg/kg/min), epinephrine (1.2 mcg/kg/min), and terlipressin (25 mcg/kg/dose). She received a twice bolus of 20% lipid emulsion (1.5 mL/kg). Hyperinsulinemia/euglycemia therapy (HIET), calcium gluconate (1 mEq/kg/hour, target  $iCa^{++}$  level  $>1.5$  mmol/L), and MB (1mg/kg/hour infusion after 2 mg/kg loading dose) were started. Shortly the patient was intubated for increased work of breathing and a decrease in Glasgow Coma Scale (GCS). Despite high-dose vasopressors, urine output and lactic acidosis were worsening, and we initiated VA-ECMO approximately eight hours after arrival. The patient was placed on VA-ECMO at the bedside, with a 21 Fr right femoral vein and a 19 Fr left femoral artery with a distal perfusion cannula. Heparin infusion started at 10 IU/kg/hour after a single 30 IU/kg bolus with a target ACT of 180-220 seconds. 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, and lipid emulsion.

An acute ischemia developed at the arterial cannulation side (left foot) on the second ECLS day. Doppler ultrasonography showed arterial thrombosis, and the patient underwent a thrombectomy. The patient was decannulated on day three and extubated on day 4. His vasopressor requirement improved steadily after admission, and by day 6, she was weaned off all vasopressors. He was discharged to an acute rehab facility on day 18.

## DISCUSSION

CCB and ARB overdose can be fatal due to refractory peripheral vasodilation, myocardial depression, acute renal failure, and deep hypokalemia. Initial stabilization consists of providing systemic management, including airway, respiratory, and circulatory control. A recent review about symptomatic CCB poisoning recommends fluid repletion, IV calcium, HIET, adrenergic agents according to the type of shock, and atropine for adult patients. In patients who are refractory to the first-line treatments, second-line therapies are incremental doses of HIET, IV lipid-emulsion therapy (ILE), and VA-ECMO in case of refractory shock.<sup>4</sup>

Calcium replacement is the most important step in CCB poisoning. Administration of 10% calcium gluconate 30–60 mL every 10–20 minutes or an infusion at 0.6–1.2 mL/kg/hour is generally effective. CCB poisoning leads to insulin resistance, so insulin therapy is recommended with 0.5–2 U/kg/hour as an initial dose. Doses up to 10/U/kg/hour are supported only

by case series. It is supposed that ILE provides an energy source to myocytes and compartmentalizes xenobiotics into the lipid phase. A twice bolus of lipid emulsion 20% 1.5 mL/kg, then an infusion of 0.25 mL/kg/min for 30–60 minutes is suggested. MB resolves vasoplegia by reversing CCBs' effects, decreasing intracellular cyclic guanosine monophosphate (cGMP), scavenging nitric oxide (NO), and inhibiting NO synthesis. Currently, there is not enough evidence to recommend the routine administration of MB in vasodilatory shock.<sup>4</sup>

In studies conducted in our country with patients admitted to PICU due to drug poisoning, the frequency of CCB poisoning was reported as %1.2-1.7.<sup>5,6</sup> Among these patients, mortality was reported in one patient who presented with CCB and ARB combined overdose. Combined overdoses of dihydropyridines with ARBs/ACEIs caused more significant hypotension and required more hemodynamic support than overdoses of dihydropyridines alone.<sup>7</sup> In these scenarios, there is a notable increase in cardiac output due to the extensive drug-induced vasodilation and the requirement of massive doses of vasoactive medications to sustain adequate end-organ perfusion pressure.

Several centers have reported the use of ECLS to treat distributive shock following CCB overdose and a combined amlodipine, lisinopril, and hydrochlorothiazide overdose with good results.<sup>8-10</sup> ECMO has been shown to have reasonable outcomes for advanced CCB poisoning, mostly in the adult population. However, high-flow ECMO applications can be quite challenging, especially in pediatric patients, due to the small diameters of arteries and veins.

A systemic review that aimed to describe the mortality and the complications observed with ECMO use in patients with CCB overdose reported that 26 patients (11.4%) had extremity complications secondary to ischemia.<sup>11</sup> Sorabella et al. reported four pediatric CCB cases who underwent central ECMO cannulation.<sup>12</sup> These patients aged between 12 and 17 years had a rising lactate level and profoundly elevated VIS score at the time of ECMO cannulation. Similar to our cases, they initiated VA-ECMO within 8 hours of admission in three patients. In the pediatric population, providing high-flow ECMO support with peripheral cannulation is technically difficult because of the smaller vein diameter. They concluded that central ECMO support in cases of massive vasodilatory shock following CCB overdose is safe and effective. Both of our cases had leg ischemia due to peripheral cannulation. Although it did not cause morbidity in long-term follow-up, it caused early ECMO termination in one patient. In these patients, the choice of peripheral or central ECMO should be made by making a patient-specific benefit-loss calculation.

In conclusion, VA-ECMO can be a life-saving treatment modality for individuals experiencing severe cardiogenic and distributive shock resulting from substantial overdoses of CCBs and ARBs. Patients with CCB and ARB overdose should be referred to ECMO centers after first-line medical management. Although complications related to peripheral cannulation are frequently observed, it is possible to reduce the rate of undesirable outcomes with close monitoring and appropriate treatments.

### Informed consent

Written informed consent was obtained from the patients for the publication of the case report.

### Author contribution

Surgical and Medical Practices: GK, İE, KC, ONT; Concept: GK, PYÖ; Design: PYÖ, BK; Data Collection or Processing: GK, SÇ; Analysis or Interpretation: GK, PYÖ; Literature Search: GK, KC, SÇ ; Writing: GK, PYÖ. All authors reviewed the results and approved the final version of the article.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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