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CASE REPORT

Case of fixed-dose combination antihypertensive medications, amlodipine and losartan, intoxication

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Abstract

Background: Fixed-dose combination (FDC) medications are increasingly utilized in clinical practice due to their convenience and potential benefits in improving adherence. However, reports on FDC intoxication remain uncommon, and management strategies for such cases are not well established. **Case**: A 19-year-old female presented to the emergency department (ED) six hours after intentionally ingesting 400 mg of amlodipine and 4000 mg of losartan, components of the combination drug Amosartan-Q, which also contains rosuvastatin. Despite intensive treatment, including inotropic agents, calcium gluconate, glucagon, hyperinsulinemic-hypoglycemic therapy, and continuous renal replacement therapy, her hemodynamic status continued to deteriorate. Approximately 54 hours after arrival, she suffered pulseless electrical activity (PEA) arrest and subsequently died. **Conclusions**: The management of FDC drug overdose remains poorly defined, and conventional therapies are often insufficient. This case highlights a significant gap in clinical understanding and underscores the need for further research and standardized treatment protocols for FDC intoxication.

Keywords

Emergency department; Fixed-dose combination medications; Poisoning; Suicide

1. Introduction

Fixed-dose combination (FDC) medications are increasingly utilized in clinical practice [1]. These medications offer several benefits, including enhanced therapeutic efficacy, reduced side effects, and simplified drug regimens, which collectively improve patient compliance [2]. However, the management of FDC drug overdose remains poorly understood, and conventional treatment strategies often fail to produce favorable outcomes [3].

This case report describes the toxicological presentation and management of an antihypertensive overdose involving Amosartan-Q, a combination drug containing the calcium channel blocker (CCB) amlodipine, the angiotensin II receptor blocker (ARB) losartan, and the lipid-lowering agent rosuvastatin. As the prevalence of combination drugs continues to increase, this case provides important insights into the challenges faced by emergency physicians in managing similar overdoses effectively.

2. Case report

A 19-year-old female (weight: 95 kg, height: 174 cm, body mass index: 31.38 kg/m^2) presented to the emergency department (ED) of our institution after self-reported intentional ingestion of 80 tablets of her father's prescription medication, Amosartan-Q (5 mg amlodipine/50 mg losartan/10 mg rosuvastatin per tablet), approximately 6 hours prior, at around 1 PM. Her medical history included depression and panic disorder. One month earlier, she had been hospitalized after a suicide attempt involving the ingestion of 24 Amosartan-Q tablets and was discharged following treatment with norepinephrine (NE) infusion at a rate of 25 mcg/min.

Upon arrival at the ED at 6 PM, her vital signs were blood pressure: 98/58 mmHg; heart rate: 110/min; temperature: 36 °C; respiratory rate: 18 breaths/min; and Glasgow Coma Scale (GCS) score: E3V4M6. Physical examination revealed generalized weakness but was otherwise unremarkable. Laboratory tests indicated elevated lactate levels and metabolic acidosis (Table 1). A 12-lead electrocardiogram (ECG) revealed sinus tachycardia at 109 beats per minute, with findings suggestive of right ventricular hypertrophy and inferior Q-waves, likely a normal variant. Transthoracic echocardiography demonstrated normal left ventricular cavity size and systolic function (ejection fraction: 56%), with no valvular abnormalities or regional wall motion defects.

Initial management included intravenous administration of 0.9% normal saline. A right jugular central line and Foley catheter were placed. Despite adequate hydration, her blood pressure declined to 64/32 mmHg at 7:40 PM, with a heart rate of 110/min and respiratory rate of 17 breaths/min, necessitating the initiation of NE infusion. Intravenous calcium gluconate (400 mg) was administered, and hyperinsulinemia/euglycemia therapy (HIET) was initiated, which included a bolus of 50

TABLE 1. Initial laboratory data of the patient.

Variables	Value
Hemoglobin (g/dL)	13.0
Hematocrit (%)	38.3
White blood cell (10^9/L)	16.7
Platelet (10^9/L)	327
C-reactive protein (mg/dL)	0.4
Aspartate aminotransferase (IU/L)	33
Alanine aminotransferase (IU/L)	32
Blood urea nitrogen (mg/dL)	12
Creatinine (mg/dL)	1.2
Sodium (mmol/L)	134
Potassium (mmol/L)	3.6
Prothrombin time (INR)	0.9
Partial thromboplastin time (sec)	10.5
pH, arterial	7.377
pCO_2, arterial	28.7
pO_2, arterial	60.2
Bicarbonate, arterial	15.0
Base excess, arterial	−10.8
Lactate, arterial	33.6

INR: International Normalized Ratio; pCO_2: Partial pressure of carbon dioxide; pO_2: Partial pressure of oxygen.

mL dextrose 50% and 90 units of regular insulin, followed by continuous insulin infusion at 90 units/hour. Blood glucose levels were monitored, and the infusion rate was adjusted as needed.

As glucagon was unavailable at the facility, arrangements were made with a neighboring hospital to procure it. Glucagon (5 mg) was administered intravenously at 9:41 PM, approximately 3 hours and 40 minutes after the patient's arrival. During this time, the patient experienced one episode of vomiting, which was controlled with metoclopramide. Her vital signs were recorded as blood pressure: 80/36 mmHg; pulse: 100 beats/min; respiratory rate: 26 breaths/min; and oxygen saturation: 96%.

The patient was then admitted to the ICU (Intensive Care Unit) at 11 PM due to persistent hypotension (blood pressure: 66/38 mmHg), a heart rate of 100/min, and a respiratory rate of 26 breaths/min. NE infusion was increased to a maximum dose of 0.281 mcg/kg/min, and fluid intake was maintained at 180 mL/hour, but her urine output remained low at 6 mL/hour. On the second day of hospitalization, she was given additional glucagon (20 mg over 4 hours) due to persistent hypotension, bringing the cumulative dose to 26 mg. Then, we had another episode of vomiting occurred, and antiemetics was prescribed. At 8 AM, her blood pressure was recorded as 58/43 mmHg, heart rate as 95/min and respiratory rate as 22 breaths/min, due to which dopamine infusion at 5 mcg/kg/min and epinephrine infusion at 3 cc/hour (0.053 mcg/kg/min) were initiated. One hour after increasing the epinephrine dose to 5 cc/hour, her blood pressure improved to 83/41 mmHg, with a heart rate of 110/min and respiratory rate of 27 breaths/min. Due to oliguria (<20 mL/hour), continuous renal replacement therapy (CRRT) was initiated following the insertion of a left jugular temporary hemodialysis catheter.

Approximately 50 hours after arrival, her respiratory rate increased to 40 breaths/min, and she began experiencing dyspnea. One hour later, she developed pulseless electrical activity (PEA) arrest with loss of consciousness. Return of spontaneous circulation (ROSC) was achieved after 18 minutes of cardiopulmonary resuscitation (CPR); however, she remained comatose. Four hours later, she experienced another PEA arrest, and despite over 30 minutes of CPR, ROSC was not achieved, and she succumbed to her condition.

3. Discussion

In South Korea, cardiovascular drugs contribute to only 1.2% of all intentional poisoning cases related to suicide [4]. Overdoses due to antihypertensive medications are uncommon, and their management is often limited to conventional or conservative treatments. However, the increasing prescription of FDCs highlights the need for better understanding of their overdose management. For example, prescriptions for amlodipine-valsartan combinations in South Korea increased from 1.7% in 2013 to 5.5% in 2018, according to data from the Korea Health Insurance Review and Assessment Service [5]. Despite this trend, no study has yet reported on FDC intoxication in South Korea. This report discusses an overdose involving a combination of CCBs and ARBs.

Amlodipine, a third-generation dihydropyridine calcium antagonist, is widely used for treating angina pectoris and supraventricular tachycardia. Its primary action as a peripheral vasodilator makes it selective for calcium channels in smooth muscles over the myocardium. However, in overdose situations, this selectivity diminishes, leading to potential myocardial effects and negative relaxant outcomes. Furthermore, in extended-release formulations, peak blood levels may be delayed by 22–24 hours, complicating overdose management [6–8].

Conventional treatments for CCB overdose include airway management, oxygen supplementation, gastrointestinal decontamination, fluid resuscitation, and the use of calcium salts, vasopressors, hyperinsulinemia/euglycemia therapy (HIET), and atropine for bradycardia. Glucagon has shown efficacy in reducing myocardial toxicity caused by CCBs [9]. For cases resistant to first-line treatments, intravenous lipid emulsions (ILE) and higher doses of HIET are recommended [10–13]. In addition, methylene blue has been used to manage refractory vasodilatory shock [14].

ARBs are rapidly absorbed after oral administration, with peak blood concentrations occurring within one hour and a short half-life of 1.5–2.5 hours. The related toxicity symptoms primarily include hypotension and tachycardia, although bradycardia may occur due to parasympathetic stimulation, and treatment typically involves gastrointestinal decontamination and supportive care, as ARB toxicity symptoms are not reversed by hemodialysis [15].

While ARBs rarely cause life-threatening symptoms alone,

their combination with dihydropyridines has been associated with severe hypotension requiring aggressive hemodynamic support [16].

Studies have demonstrated improved survival rates in patients with refractory cardiovascular shock due to drug toxicity when extracorporeal membrane oxygenation (ECMO) is initiated early [17, 18]. ECMO provides hemodynamic support, allowing for the safe administration of drugs with hypotensive and negative inotropic effects, such as intravenous verapamil, a CCB. By maintaining systemic circulation, ECMO facilitates the controlled use of such medications during critical periods. In addition to providing circulatory support, ECMO is particularly effective in managing catecholamine-driven electrical storms, which are often resistant to conventional therapies. It enables the gradual weaning off catecholamine infusions while stabilizing hemodynamics and restoring systemic circulation [19]. This dual functionality makes ECMO a valuable tool in cases where traditional treatments fail to achieve hemodynamic stability. Furthermore, ECMO's ability to sustain circulation offers a critical window for the redistribution and metabolism of toxic substances, particularly in cases of reversible intoxications, which can enable the restoration of cardiac function in otherwise healthy hearts, highlighting the importance of early ECMO intervention in severe cases of drug toxicity [20, 21].

In previous studies, ECMO has demonstrated significant efficacy in managing severe drug overdoses. For example, a 46-year-old man who ingested 1210 mg of amlodipine and 936 mg of an ARB was weaned off ECMO after 5 days and discharged after 18 days [22]. Similarly, a 50-year-old man who ingested 500 mg of amlodipine, 1000 mg of lisinopril, and 625 mg of hydrochlorothiazide was placed on ECMO 19 hours after admission, weaned after eight days, and discharged after 56 days [23]. In another case involving a 28-year-old woman who ingested 400 mg of amlodipine, ECMO was initiated 1 day after admission due to persistent hypotension refractory to dietary therapy and was discharged on day 8 [24].

In our case, the patient had ingested 24 tablets of Amosartan-Q, equivalent to 120 mg of amlodipine and 1200 mg of losartan, 2 months before the fatal event. On that occasion, the patient recovered after three days of vasopressor therapy, including norepinephrine. However, in the present event, she ingested significantly higher doses (400 mg of amlodipine and 4000 mg of losartan), and despite aggressive treatment, including the administration of glucagon and inotropics, persistent hemodynamic instability was observed.

Although no critical dose thresholds for initiating ECMO in CCB overdoses have been established, early ECMO initiation should be considered in patients who ingest high doses of CCBs. For instance, a 55-year-old woman who ingested 180 mg of olmesartan and 140 mg of amlodipine was successfully managed with calcium gluconate and inotropic agents without ECMO, achieving discharge after five days [25]. In our case, ECMO was not initiated due to the parents' decision to decline ECMO on account of its cost and to discontinue aggressive treatment during the second cardiac arrest.

In this case, the patient succumbed despite the use of established therapeutic interventions. The combination of multiple drugs in overdoses may result in greater hemodynamic compromise than single-drug overdoses, highlighting the need for earlier consideration of ECMO in such cases. We believe this case underscores the importance of timely trials of ECMO in managing severe multiple -drug overdoses, particularly when initial signs of stabilization are absent.

However, this report is limited by its nature as a single case study, which inherently restricts the generalizability of its findings. Furthermore, due to the lack of serum drug concentration data and the rapid clinical deterioration of the patient, it was not possible to fully elucidate the pharmacokinetic behavior and time-dependent toxicity of the fixed-dose combination. Further research and accumulation of similar cases are necessary to guide clinical decision-making in such intoxications.

4. Conclusion

Venoarterial extracorporeal membrane oxygenation can be considered early in the management of patients who overdose on fixed-dose combination medicines and do not achieve hemodynamic stabilization with initial therapy.

AVAILABILITY OF DATA AND MATERIALS

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

AUTHOR CONTRIBUTIONS

JYC—designed the research study. YHC—performed the research. JYL, JYC—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ewha Womans University Seoul Hospital (IRB No.: 2024-12-033). Since the patient had passed away, informed consent was obtained from the parents.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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