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MANAGEMENT OF INTOXICATION WITH THE CA-CHANNEL BLOCKER – LERCANIDIPINE

Kolevska I[1], Gavrilovska Brzanov A[2], Agushi A[2], Donev Lj[2] , Paruleska S[3]

[1]General Hospital Kumanovo, Republic of North Macedonia
[2]University Clinic for Traumatology, Orthopedic Disease, Anesthesiology, Reanimation and Intensive Care Medicine and Emergency Department, Faculty of Medicine, "Ss. Cyril and Methodius" University, Skopje, Republic of North Macedonia
[3] General Hospital Ohird, Republic of North Macedonia

Abstract

Lercanidipine is a dihydropyridine calcium channel blocker that works by relaxing and opening the blood vessels, allowing the blood to circulate more freely around the body. This lowers the blood pressure and allows the heart to work more efficiently. An overdose of calcium channel blockers results in toxicity along with profound hypotension and shock. We present a case of a 27-years-old woman who was admitted to the ICU, after the intentional ingestion of large amounts of the calcium channel blocker, Lercanidipine. She was presented with refractory hypotension and non-cardiogenic pulmonary edema, which was treated successfully with the guidance of invasive hemodynamic parameters. The treatment included high-dose insulin infusions in combination with dextrose (10%), calcium, norepinephrine and dobutamine infusions. When supportive and specific pharmacological measures fail to adequately reverse refractory conditions in a calcium channel blocker overdose, the use of extracorporeal life support should be considered. The efficacy of these pharmacological and non-pharmacological interventions generally advocated in calcium channel blocker poisoning that needs further in-depth mechanistic foundation, in order to improve individualized treatment of calcium channel blocker overdosed patients.

Key Words: *Calcium-channel blocker, Intoxication, Lercanidipine, Overdose.*

Introduction

Calcium channel blockers are widely prescribed for the management of hypertension, arrhythmias and angina pectoris (1-2). They can be divided into dihydropyridines and non-dihydropyridines based on expected physiologic effects. The dihydropyridines are potent vasodilators but have a minimal effect on myocardium contractility and conduction pathways, whereas the non-dihydropyridines have a greater effect on myocardium contractility and conduction pathways, but a minimal effect on vasodilatation. However, at the higher doses seen, especially in massive overdose cases, such selectivity is usually lost (3).

Lercanidipine, a dihydropyridine (CCB), is commonly used as an antihypertensive drug. He works by relaxing and opening the blood vessels allowing the blood to circulate more freely around the body. This mechanism lowers the blood pressure and allows the heart to work more efficiently. It is completely metabolized in the liver. The elimination half-life is 8 to 10 hours, and the drug does not accumulate. Because of the depot effect, the antihypertensive action lasts for at least 24 hours and 50% is excreted via the urine. In the case of severe toxicity, good outcomes can be achieved through aggressive treatment and the provision of circulatory support (4). American Poison Control Centers (APCC) have reported cardiovascular drugs as the third fastest-growing category of substance exposures. According to a 2021 report, by APCC there are 6,162 exposures to CCBs, resulting in 37 deaths and 1,228 exposures occurred in children younger than 6 years old (5).

Case Report

A 27-years-old woman who had been hospitalized to the Department of Toxicology was moved to the Intensive Care Unit. She was conscious, contactable, and oriented in time, place, and people at the time of admission. She acknowledged taking all CCBs, including lercanidipine, at the same time. She was tachycardic and hypotensive and on oxygen mask. The patient's vital signs upon arrival were 100% peripheral oxygen saturation (SaO2), 115/min heart rate, and 53/23mmHg blood pressure. Antibiotic, antiemetic, gastroprotective, anticoagulant, diuretic, catecholamine support and hyperinsulinemic euglycemic therapy were all started right away. In order to test for the blood type, full blood counts, electrolytes, liver and kidney function, blood glycose, C-reactive protein, and coagulation, we collected samples. We also obtained lung X-rays, implanted a nasogastric tube, and coordinated the monitoring of the acid-base state. Potassium was 3.02mmol/L, glucose was 22.8mmol/L, lactate was 12.82mmol/L, and BE was 20.3mmol/L in her initial serum electrolyte panel. A tachycardia of 160 beats per minute was detected on her ECG.

The patient was initially admitted to the Department of Toxicology, where she was treated with 3.5 liters of IV fluids, including 60ml of calcium glutamate injection, a titrated insulin drip, an uptitrated dopamine drip, 30ml of KCL 7.4% injection, and 250ml of lipofundin injection.

However, noradrenaline (0.04mcg/kg/min) and dobutamine (2mcg/kg/min) infusions were started in the ICU due to persistently low blood pressure, as well as vasogenic and cardiogenic shock. Actrapid 1–10 I.U./kg/hr. hyperinsulinemia euglycemia therapy was started at the same time. Abruptly, the patient's condition began to worsen, exhibiting non-cardiogenic pulmonary edema and mental disintegration. It was decided to place the patient on mechanical ventilation and intubate her. On day two, we administered an infusion of amiocordin (600mg/ 50ml; 2.2ml/h) and glyceryl trinitrate (0.1mcg/kg/hr). Blood pressure was consistently low, and we were attempting to keep it within a moderate range of at least 60mmHg MAP. A low dose of nitroglycerin (0.025 micrograms/kg/min) was started for coronary dilatation due to the patient's continuous tachycardia. On the third day, amiocordin was used to manage the tachycardia and GTN was discontinued. We also closely monitored the arterial blood gas analyses (ABG) and we had linear decline of the lactates by the third day (7.25mmol/L after 24h; 4.03mmol/L after 48h; 1.75mmol/L after 72 hours). After the glucose level returned to normal on the fourth post-admission day, the glyceryl trinitrate infusion was stopped. Following a week, the amiocordin infusion was discontinued, and weaning off catecholamines was initiated, with a gradual

reduction, based on hemodynamic stability. By the time the patient's ABG returned to normal on nineth day (lactates-0.70 mmol/L), they met the requirements to be weaned off from mechanical ventilation. After the choice to wean was made, the sedation was discontinued. After a whole day, she was successfully and painlessly extubated the following day. On the fourteenth day of stay, the patient was released from the Department of Toxicology, exhibiting no neurological deficits.

Discussion

Cardiac arrhythmias, angina pectoris, hypertension and other conditions are treated using CCBs. There are two forms of these drugs available: immediate-release and extended-release. Conventionally used CCBs fall into one of three primary chemical classes: dihydropyridines (i.e. lercanidipine), benzothiazepines (i.e. diltiazem), or phenylalkylamines (i.e. verapamil). Each subclass has a different affinity for cardiac tissue and vascular smooth muscle.

The majority of experts' consensus recommendations for therapies for CCB toxicity are based on poor levels of evidence. Hemodialysis and hemofiltration fail to remove CCBs due to their large distribution volume (2-6). In the example we've given, hemofiltration was not started.

Every CCB subclass suppresses the synthesis of pancreatic insulin and results in end-organ insulin resistance, which raises blood sugar levels. One clinical sign of the severity of poisoning is hyperglycemia. In our instance, hyperinsulinemia euglycemic medication was used to treat glycemia (9). Moreover, CCBs prevent glucose catabolism and calcium-stimulated mitochondrial activity, which leads to the production of lactate and ATP hydrolysis and ultimately, metabolic acidosis (8). In the situation we presented, bicarbonates were administered when blood pressure returned to normal and satisfactory urine production was maintained.

Severe hypoperfusion and end-organ ischemia resulting from a severe dosage can cause seizures, myocardial infarction, ARDS, renal failure, intestinal infarction and stroke (8). Many methods can be used to treat CCB poisoning: Within one to two hours of consumption, gastric lavage or 1g/kg of activated charcoal may be administered for intestinal purification. Calcium administration is justified by the fact that raising the extracellular calcium concentration promotes calcium influx through open L-type calcium channels. However, reactions to severe poisoning are inconsistent and subpar. Severe CCB poisoning can be effectively treated with hyperinsulinemia euglycemia. Monitoring of potassium and blood glucose levels is necessary prior to starting with insulin therapy. The current recommendation for insulin dosage is 1 I.U./kg for a regular intravenous bolus followed by 1–10 I.U./kg/hr for continuous infusion, which we successfully used in our case (10-13).

In severe cases of CCB poisoning, patients may experience profound cardiovascular collapse due to the loss of peripheral vascular resistance and cardiac depression. This refractory hypotension requires aggressive intervention, often involving the use of vasopressors such as dopamine, noradrenaline, epinephrine or dobutamine. However, selecting the most appropriate agent can be challenging and requires careful consideration of the patient's hemodynamic status and underlying cardiac function. Our situation was well treated with dobutamin and norepinephrine (10).

Furthermore, the management of CCB poisoning extends beyond pharmacological interventions. Patients may require supportive measures such as mechanical ventilation to address respiratory failure secondary to severe hypoperfusion or metabolic acidosis (10). On admission our patient

was not intubated and placed on mechanical ventilation, but after situation deteriorated mechanical ventilation was started for 10 days. Additionally, close monitoring of electrolyte levels, particularly potassium, is essential as hypokalemia can exacerbate cardiovascular instability and arrhythmias.

In cases where conventional therapies fail to adequately manage CCB toxicity, extracorporeal life support (ECLS) may be considered as a rescue therapy. ECLS techniques, such as veno-arterial extracorporeal membrane oxygenation (VA-ECMO), can provide circulatory and respiratory support while allowing for the removal of toxins from the bloodstream. Due to limited resources in our center unfortunately ECMO is not available (14-16).

Despite advancements in treatment modalities, the prognosis of severe CCB poisoning remains guarded, particularly in cases of delayed presentation or profound cardiovascular collapse. Early recognition of toxicity, prompt initiation of appropriate therapies, and close monitoring of the patient's response are crucial for optimizing outcomes in these challenging cases (14).

Overall, the management of severe CCB poisoning requires a multidisciplinary approach involving emergency physicians, toxicologists, intensivists, and pharmacists working collaboratively to provide comprehensive care to affected patients. Continued research and education in this field are essential to further refine treatment strategies and improve patients' outcomes(14). In our presented case, colleagues were not able to stabilize the patient, and she was transferred to the ICU, where profound treatment was taken with mechanical ventilation and intensive therapy guided by invasive hemodynamic monitoring and repeated arterial blood gas analysis, laboratory investigation and a coagulation test.

Conclusion

CCBs overdoses are challenging to treat, and the usual management can fail in cases with significant overdoses. It is important to have taken a careful history, to do a physical examination, and to do close invasive hemodynamic monitoring, to anticipate complications and treat them as they occur. Urgent administration of fluids, calcium, vasopressors and hyperinsulinemic euglycemic therapy seem to be the most validated initial approaches to treatment. Our successful management strategy should serve as a good learning experience for how to manage this kind of patient.

Abbreviations

CCBs: Calcium channel blockers; MAP: Mean arterial pressure; GTN: glyceryl trinitrate.

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