Case Report

Amlodipine and Losartan Overdose Presenting with Refractory Vasodilatory Shock and Acute Kidney Injury: A Case Report

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Abstract

Toxicity due to calcium channel blocker overdose presents as vasodilatory shock that may be refractory to vasopressors and inotropes. Serious toxicities have also been reported with angiotensin II receptor blocker overdose, which may present as persistent refractory hypotension. The treatment options to reverse vasoplegic shock in such cases include conventional vasopressors, high dose insulin, intravenous calcium, terlipressin, and methylene blue. We report a case of a 60-year-old man who presented with decreased responsiveness following intentional ingestion of 85 mg of amlodipine and 350 mg of losartan. He was hypotensive, dyspneic and had bilateral basal crepitations at presentation. He was anuric for six hours following presentation. He was resuscitated with noradrenaline and vasopressin infusion, intravenous calcium, and high-dose insulin euglycemia therapy, highlighting the possible role of such therapies in such cases.

Introduction

Amlodipine is a dihydropyridine calcium channel blocker (CCB) widely used for the treatment of systemic hypertension. Amlodipine overdose accounts for a large proportion of morbidity and mortality due to cardiovascular drugs.[1] Amlodipine was the most common cardiovascular drug overdose in the U.S. in 2022.[2]

On the other hand, overdose due to irbesartan, an angiotensin II receptor blocker (ARB) has been reported to cause vasodilatory shock, refractory to conventional high-dose vasopressors.[3] Chronic use of angiotensin II receptor blockers exhibits inhibitory actions on the central and peripheral sympathetic nervous system and the renin-angiotensin system, thereby augmenting persistent hypotension refractory to vasopressors in such patients who present with calcium channel blocker toxicity.[4,5]

Our patient presented with overdose due to amlodipine and losartan. The patient developed vasodilatory shock, acute cardiogenic pulmonary oedema, and acute kidney injury secondary to drug overdose and sepsis. Appropriate therapies with noradrenaline and vasopressin to counteract vasodilatory shock, empirical antibiotics to combat sepsis, and high-dose insulin euglycemia therapy (HIET) and intravenous calcium therapy to improve cardiac contractility were crucial in treating our patient, highlighting the potential role of such therapies in these patients.

Case Presentation

A 60-year-old hypertensive male, with a history of ischemic stroke 12 years ago, presented to the emergency department with decreased responsiveness following intentional ingestion of 7 tablets of amlodipine and 10 combined tablets of amlodipine and losartan (i.e. 85 mg of amlodipine and 350 mg of losartan), under the influence of alcohol.

In the emergency department, he was found to have a decreased level of consciousness with a Glasgow coma scale (GCS) of 9/15 and a blood pressure of 60/40 mmHg. His pulse rate was 64 beats per

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minute, respiratory rate was 12 cycles per minute, SpO2 was 96% on room air, and he was afebrile. Upon examination, the patient had bilateral crepitations over the lung bases. Crystalloids infusion was initiated in the emergency department. Hypotension was refractory to fluid therapy, so he was started on noradrenaline infusion. Calcium gluconate was administered intravenously.

Investigations showed a leukocytosis with predominant neutrophils and acute kidney injury (AKI) with an elevated serum creatinine level of 2.07 mg/dl. Arterial blood gas analysis revealed high-anion gap metabolic acidosis with respiratory alkalosis. Chest X-ray was done, which showed bilateral lower zone infiltrates.

The patient was transferred to the intensive care unit, where vasopressin infusion was started, and noradrenaline infusion was titrated to maintain a mean arterial pressure (MAP) of≥ 65 mmHg. He was anuric during the first six hours following admission.

On the first day of admission, he was started on HIET at approximately 0945 in the morning. Regular insulin 0.5 unit/kg was administered intravenously, followed by infusion at 0.1 unit/kg/hour, and intravenous dextrose infusion was started to counteract hypoglycemia. At approximately 1200 midday, his urine output improved.

He was started on bolus methylene blue 120 mg intravenously, followed by a maintenance dose at a rate of 30 mg/hour by intravenous infusion. MAP was maintained above 65 mmHg with dual vasopressors, intravenous insulin infusion, and methylene blue infusion.

On the third day, following the resolution of vasoplegic shock, vasopressin infusion was discontinued, and noradrenaline infusion was tapered and discontinued. Regular insulin infusion was stopped, and methylene blue infusion was discontinued on the third day following the improvement in hemodynamic parameters.

His serum creatinine improved to 1.30 mg/dL on day seven, and he was transferred to the medical ward after psychiatry consultation.

His daily investigations and daily urine output have been given in Table 1.

Table 1: Summary of Investigations and Urine Output During Hospital Stay

Investigations	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Hemoglobin (g/dl)	14.5	14.2	13.5	13.7	13.0	14.1	13.8	14.5	14.2	
White blood cell count (per µl)	17420	15470	13040	11830	12980	9270	7730	8680	9440	
Blood Urea (mg/dl)	36	72	84	85	90	114	116	113	106	87
Serum Creatinine (mg/dl)	2.07	4.18	4.81	4.42	2.00	1.83	1.59	1.30	1.21	1.16
Sodium (mmol/l)	141.9	142	143.4	146	144	143	143	140	136.3	138.1
Potassium (mmol/l)	3.5	4.2	4.8	3.3	3.8	3.2	3	4	3.3	3.3
Calcium (mg/dl)	10.2		8.8							
Serum Lactate (mmol/l)	4.8		1.30		1.38	1.2				
CPK (mcg/l)			1913						228	
LDH (U/l)			522						871	
Urine output (ml per 24 hours)		315	2470	2150	1442	1485	1470	1800	1750	1100

Discussion

Amlodipine is a long acting dihydropyridine CCB that blocks the transmembrane flow of calcium ions through voltage-gated L-type (slowly inactivating) calcium channels in the myocardium and vascular smooth muscle cells, reducing peripheral vascular resistance. Calcium influx initiates excitation–contraction coupling, sinoatrial node depolarization in the myocardium and the maintenance of vascular and gastrointestinal smooth muscle tone. CCBs inhibit L-type calcium channels in pancreatic islet cells, reducing insulin secretion and resulting in hyperglycemia and reduced cardiac glucose utilization. Amlodipine causes potent vasodilation by stimulating nitric oxide release and increasing cyclic guanosine monophosphate (cGMP) production. Methylene blue, which is a scavenger of nitric oxide and an inhibitor of nitric oxide synthase, has been used for refractory shock in patients with amlodipine toxicity.[6]

Losartan is a selective angiotensin II receptor blocker that inhibits the vasoconstrictive properties of angiotensin II. It is widely used in the

treatment of essential hypertension, hypertension in patients with left ventricular hypertrophy, heart failure, and diabetic nephropathy.

A consensus statement has been published on the recommendations for the management of CCB toxicity. Various modalities have been used to counteract the vasoplegic properties of CCBs, which cause vasodilatory shock that mimics anaphylactic shock and septic shock. Some of these treatment modalities include high-dose insulin euglycemia therapy, noradrenaline, adrenaline, vasopressin, lipid-emulsion therapy, intravenous calcium, methylene blue, and venoarterial extracorporeal membrane oxygenation (VA-ECMO).[7]

In contrast, there have been no consensus statement recommendations for the management of ARB toxicity. Toxicity due to Irbesartan, an ARB has been reported to cause life-threatening persistent hypotension. Chronic ARB use at conventional dosages augments the inhibition of the central and peripheral sympathetic nervous system and the renin-angiotensin systems. Hypotension due to CCB toxicity in patients on long-term ARB may be refractory to conventional vasopressor therapy.

The consensus statement recommends the use of HIET as the first-line treatment for CCB toxicity. High-dose insulin allows myocardial cells to take up glucose and has direct concentration-dependent inotropic effects on myocardial cells. The proposed dose regimen of high-dose regular insulin is 1 unit/kg, followed by infusion of 1 unit/kg/hour with maintenance of euglycemia with dextrose infusion as needed and close monitoring of serum potassium.[7] Observational studies[8,9] and case series[10-12] have documented an improvement in cardiac contractility, blood pressure, and potential increase in survival with the use of high-dose insulin in CCB-poisoned patients.

Intravenous calcium is recommended as a first-line therapy alongside HIET in symptomatic patients with CCB overdose.[7] Intravenous calcium administration increases extracellular calcium concentration and improves cardiac contractility and blood pressure.[15,16] CCBs can produce clinical effects, such as hypocalcemia, with significant cardiac depression and hypotension. The use of intravenous calcium in such settings reverses the toxicity due to CCB overdose. Noradrenaline is a vasopressor that is used in vasodilatory shock due to CCB toxicity.[15] The use of adrenaline is also recommended in CCB-poisoned patients in shock to increase contractility and heart rate. Lipid emulsion therapy is reserved for cases refractory to first line therapy.[16] There are case reports showing the use of methylene blue in the treatment of refractory vasodilatory shock due to CCB overdose.[17,18]

Our patient developed AKI due to sepsis and multiorgan dysfunction, which resolved after adequate restoration of systemic perfusion and resolution of sepsis. AKI can also be attributed to acute cardiorenal syndrome, in which the rapid worsening of cardiac function leads to AKI.[19]

Conclusion

Poisoning due to amlodipine and losartan can be a therapeutic challenge if the vasoplegic shock is refractory to conventional therapies. Drugs that improve cardiac contractility and increase systemic vascular resistance by reversing the vasodilatory effects on the vascular smooth muscles, are crucial in reversing vasodilatory shock in such patients.

Ethical Approval

The authors have nothing to report.

Consent

Written informed consent was obtained from the patient for publication.

Authors' Contribution

Conceptualization, investigation, project administration, and writing of the original draft was done by UKS. Supervision and validation was done by MJS. Conceptualization, reviewing and editing was done by RBS.

Conflicts of Interest

The authors declare no conflict of interest.

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