Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

A survival case of high-dose amlodipine intoxication with non-cardiogenic pulmonary edema: a case report

Pankaj Pant, MD[a,*], Sangam Shah, MBBS[a], Ganesh Bhattarai, MBBS[a], Krishna Dahal, MBBS[a], Navindra Raj Bista, MD[a], Sahil Bade, MBBS[b], Kshitij Chapagain, MBBS[c], Sohail Bade, MBBS[b], Sagar Pant, MBBS[b]

Introduction: Dihydropyridines calcium channel blockers at high dose can have conduction abnormalities, reduced inotropism, and non-cardiogenic pulmonary oedema (NCPE) which otherwise, at standard dosage have only vascular selectivity. They remain one of the commonly used anti-hypertensive exhibiting very lethal outcomes (50% mortality rates) in its overdose.

Case presentation: The authors present a case of a 21-year-old male with amlodipine intoxication with 43 tabs of 10 mg (total of 430 mg) ingestion manifested by loss of consciousness, hypotension, tachycardia, and respiratory distress.

Discussion: An amlodipine overdose causes refractory hypotension due to vasodilation and impaired cardiac metabolism and contractility. Further amlodipine toxicity can result in NCPE that manifests clinically as respiratory distress and low oxygen levels due to lung injury caused by inflammation and increased vascular permeability.

Conclusion: This case report emphasizes the significance of early recognition and prompt treatment of amlodipine intoxication, which can result in serious complications like fluid overload and respiratory distress.

Keywords: amlodipine, calcium channel blockers, intoxication, non-cardiogenic pulmonary oedema

Introduction

Amlodipine is commonly prescribed drug for the treatment of hypertension and angina pectoris. Amlodipine dilates arterioles and arteries by blocking calcium influx through L-gated calcium channels in both cardiac and vascular smooth muscle cells. Unlike non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, amlodipine is a dihydropyridine that has little effect on cardiac pacemaker cells or contractility at recommended doses[1]. Amlodipine at its toxic doses can cause, hypotension. Amlodipine is the most common drug overdose that causes cardiovascular problems and has been linked to multiple overdose deaths[2,3]. It has a long half-life of 30–50 h, a large volume of distribution (21 l/kg), and a lo metabolic clearance, all of which result in a slower and longer duration of action[4]. This extended duration of action increases the risk of morbidity and mortality associated with amlodipine overdose. Amlodipine at high doses can cause severe symptoms such as refractory hypotension, myocardial depression, bradycardia, atrio-ventricular node blockade, decreased insulin release leading to hypoglycemia, tissue hypoperfusion, non-cardiogenic pulmonary oedema (NCPE) and signs of heart failure[5]. NCPE is a rare complication of amlodipine overdose and it can be difficult to treat.

We report a rare case of high-dose amlodipine toxicity causing non-cardiogenic pulmonary oedema with full recovery. We have reported this case as per the SCARE guidelines[6].

HIGHLIGHTS

- Dihydropyridines calcium channel blockers at high dose can have conduction abnormalities, reduced inotropism, and non-cardiogenic pulmonary oedema.
- Amlodipine toxicity can result in non-cardiogenic pulmonary oedema that manifests clinically as respiratory distress and low oxygen levels.
- It is the significant to early recognize and promptly treat the amlodipine intoxication.

Case presentation

A 21-years-old male patient with unknown psychiatric disorder was brought to the emergency department (ED) within four hours of ingestion of 43 tablets of amlodipine 10 mg (a total of 430 mg) which he attributed to a panic attack he experienced while surfing internet. He denied concomitant intake of alcohol or any other drugs. Half hour prior to reaching ED, he had an episode of loss of consciousness for around 5 min. On arriving ED, the patient

[a]Tribhuvan University, Institute of Medicine, Maharajgunj, [b]Venus Hospital, Kathmandu and [c]Star Hospital, Lalitpur, Nepal

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Department of Pulmonology, Tribhuvan University, Institute of Medicine, Maharajgunj, Kathmandu 44600, Nepal. Tel.: +977 985 111 0939. E-mail: drpant2015@gmail.com (P. Pant).

Annals of Medicine & Surgery (2024) 86:6689–6692

Received 21 September 2023; Accepted 4 January 2024

Published online 18 January 2024

http://dx.doi.org/10.1097/MS9.0000000000001720

was conscious and oriented to time, place and person. At the time of arrival, he was having tachycardia (123 beats/min), low blood pressure of 80/60 mm Hg along with low oxygen saturation of 86% on room air. However, he was afebrile.

Routine investigations showed haemoglobin (Hb 11.4 gm/dl) [Ref: 12–16 gm/dl], white blood cells (WBC) (11 400/cu.mm) [Ref: 4000–11 000/cu.mm]. Comprehensive toxicology analysis of urine was negative for opioids, morphine, alcohols, amphetamines, and so forth. serum urea (BUN) 19 mg/dl) [Ref: 6–24 mg/dl] ; creatinine (Cr) 1.2 mg/dl) [Ref: 0.7–1.3 mg/dl]; serum calcium 8.1 mg/dl [Ref: 8.6–10.3 mg/dl]; phosphorus 4.9 mg/dl [Ref: 2.5–4.5 mg/dl] sodium (138 mEq/l) [Ref: 135–145 mEq/l] ; potassium (3.9 mEq/l) [Ref: 3.5–5.2 mEq/l] and glucose plasma level 144 mg/dl [Ref: 70–140 mg/dl]. Liver function tests, sedimentation rate (ESR), and C-reactive protein (CRP) were within the normal limits.

The oxygen saturation was increased to 96% with the help of a face mask delivering 8 l of oxygen. Gastric lavage was performed in the ED with two liters normal saline (NS) followed by fluid resuscitation with 3 l NS intravenously. However, here was no improvement in the blood pressure, hence the patient was shifted to ICU and started on nor-adrenaline at the rate of 3 mcg/min and in increasing titration. Intravenous (IV) calcium gluconate bolus was also given in every 4 h.

On the second day of admission, the patient developed fever (maximum recorded temperature being 101° F)and burning micturition, with routine urine examination showing plenty of pus cells attributed to urinary tract infection. Therefore, IV cefepime + Sulbactam were added. The patient also developed shortness of breath and productive cough with reddish/pinkish frothy sputum. On bilateral chest auscultation crackles over entire lung fields were heard and portable chest x-ray revealed bilateral haziness in the lung parenchyma. Arterial blood gas test was done which showed type I respiratory failure (pH = 7.48, pCO_2 = 24 mm hg, pO_2 = 49 mm Hg, HCO_3-16 mmol/l). The patient had developed diffuse non-pitting oedema in all four limbs causing difficulty in peripheral access so central line insertion was done. Echocardiography revealed ejection fraction of 60%. Considering the findings of all these investigations, diagnosis of non-cardiogenic pulmonary oedema was made. The patient also developed oliguria despite fluid challenge with urine output of 150 ml over 12 h (0.19 ml/kg/h). The patient was kept on Continuous positive airway pressure ventilation (CPAP) with PEEP 10 cm of water; however, CPAP was not tolerated, hence he was switched back to reservoir mask with flow of 15 l/min which improved theO_2 saturation to 92–94%. A second inotrope, dopamine was started at 5 mcg/min and nor-adrenaline was increased to 7 mcg/min. Insulin infusion was also started at rate of 10 U/h and General random blood sugar (GRBS) was monitored hourly. Along with these, IV infusion of 10% dextrose and 20 mEq potassium was given every four hourly to the patient followed by regular monitoring of serum potassium two hourly and its supplementation accordingly. IV torsemide 40-40-20 mg along with bolus doses in between was commenced in the patient which resulted in the gradual improvement of respiratory distress. Urine output also improved to 1.03 ml/kg/h.

Despite the treatment, the respiratory distress worsened, fever was persistent and the sputum production increased on the third day of admission. Hence the patient was kept on CPAP four hourly throughout the day and continuously overnight. Antibiotics was changed to meropenem. The inotropic support and insulin infusion were titrated according to hourly GRBS and serum potassium levels at 8–10 U/h.

By fourth day, the respiratory distress subsided, frequency of cough and sputum production reduced, oxygen requirement gradually decreased and was gradually weaned off of oxygen over next 2 days, inotropic support was gradually tapered and the insulin infusion was stopped by sixth day of admission. The patient was then shifted to ward on sixth day of admission and observed for next few days. Psychiatry consultation was done. His vitals were stable in the ward and the patient was discharged on the 10th day.

Discussion

We have a presented a case which shows the complexity of treating severe amlodipine overdoses. We managed the patient with aggressive fluid resuscitation, calcium gluconate infusion, vasopressors and inotropes, regular insulin with dextrose, non-invasive ventilation, diuretics and antibiotics.

Amlodipine overdose results in refractory hypotension due to vasodilation and impaired cardiac metabolism and contractility. This causes tissue ischaemia and lactic acidosis, while other tissues, such as pancreatic beta cells, are affected by calcium channel blockade, resulting in decreased insulin release[4]. On the third day, non-cardiogenic pulmonary oedema developed in our patient. Patients who take amlodipine, a dihydropyridine, may exhibit cardiogenic pulmonary oedema because it preferentially inhibits L-type calcium channels in smooth muscle and myocardial depressant action at hazardous doses[7,8]. Additionally, incidences of non-cardiogenic pulmonary oedema and catastrophic shock were observed in few studies[9–11]. Uncertainty surrounds the cause of non-cardiogenic pulmonary oedema in CCB overdose patients. Interstitial oedema eventually results from an increase in transcapillary hydrostatic pressure brought on by excessive pulmonary capillary transudation brought on by selective precapillary vasodilatation[12,13]. In our case, severe hypotension was observed, this could be also reason for the development of NCPE.

The treatment of critically ill patients with amlodipine overdose necessitates gastric decontamination and supportive care, including airway protection, adequate breathing, and circulation. To maintain adequate circulation, multiple simultaneous therapies are often required, such as IV fluids, vasopressors, inotropes, calcium, glucagon, high-dose insulin with supplemental glucose therapy, phosphodiesterase inhibitors, pacemakers, and even extracorporeal membrane oxygenation in refractory shock. The treatment of non-cardiogenic pulmonary oedema is largely supportive and aims to ensure adequate ventilation and oxygenation[14].

There is mounting evidence that the preferred first-line treatment for calcium channel blocker poisoning is the use of insulin to maintain normal blood glucose levels [known as hyperinsulinemia-euglycemia therapy (HIE)]. It has been hypothesized that insulin enhances the way that carbohydrates are broken down in cardiac muscle cells, raises blood levels of ionized calcium, or directly enhances inotropy[11]. However, there are no established guidelines on the dose of insulin to use in amlodipine toxicity. In our patient's case, we had started with a low dose of insulin due to low serum potassium levels and normal cardiac contractility based on echocardiogram findings.

Another challenge to amlodipine toxicity was development of NCPE, which is characterized by respiratory distress and low oxygen levels due to lung injury caused by inflammation and increased vascular permeability. As a result, protein-rich fluid builds up in the alveoli, which reduces the production of surfactants and causes respiratory failure. NCPE typically manifests within 24 h of onset but may present a few days later[14]. The most widely accepted theory for its occurrence in CCB poisoning is selective precapillary dilatation leading to pulmonary capillary transudation. While NCPE has been observed in other CCB overdose cases, it is rarely reported with amlodipine[11,15,16]. To manage NCPE, it is important to closely monitor the balance of fluids and carefully administer diuretics to maintain hemodynamic stability and adequate oxygenation. In more severe cases, non-invasive or mechanical ventilation may be necessary[14]. In our case torsemide was started with CPAP, which showed significant decreased bilateral chest crackles and resulted improvement of oxygen saturation. Low-dose insulin (diluted) being used with significant volume of normal saline may have worsened clinical symptoms of pulmonary oedema in this case placing the patients at risk of volume overload. Some studies suggest use of concentrated insulin in setting of calcium channel blockers to reduce the effects with fluid overload[17].

If the symptoms persist, lipid emulsion or glucagon infusion may be administered. Glucagon activates myocardial adenylate cyclase, increasing cardiac cyclic adenosine monophosphate levels, resulting in inotropic effect. It is useful in patients with severe hypotension that is unresponsive to other interventions. IV lipid infusions have been recently used to treat lipid-soluble drug overdoses. Increasing serum lipid levels can significantly increase the drug's volume of distribution, thus reducing its effective plasma level. It decrease the concentration of free active drug, improving myocardial activity and function[11].

Extracorporeal membrane oxygenation (ECMO) has emerged as a preferred treatment approach in major academic medical centres for seriously ill individuals who have been poisoned and have not responded to standard resuscitation therapies or antidotes[15]. There have been instances where patients were effectively treated using veno-arterial ECMO[5,18,19]. Total plasma exchange involves replacing a patient's plasma with albumin or fresh frozen plasma to remove drugs from the system[5]. Rarely methylene blue is indicated in relation to amlodipine poisoning; however, it reduces intracellular cGMP, scavenges nitric oxide, and prevents nitric oxide synthesis to reverse vasoplegia[8]. Amlodipine's high protein binding of 98% makes it difficult to remove via haemodialysis[5].

Conclusion

Although the mortality rate due to CCB overdose in cardiovascular medicine is relatively high, no formal guidelines exist with respect to in-hospital management. Even though the management of amlodipine is quite challenging , the prompt and aggressive treatments can improve outcome of the patient. Furthermore researches are needed to define a clear treatment approach including the role of mechanical circulatory devices in these critically sick patients in the days to come.

Ethical approval

Ethical approval is not required for the case report in our institution, Tribhuvan University Teaching Hospital.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Source of funding

Not applicable.

Author contribution

P.P., S.S., G.B. wrote the original manuscript, reviewed, and edited the original manuscript. K.D., N.R.B., S.B., K.C., S.B., S.P. reviewed and edited the original manuscript.

Conflicts of interest disclosure

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Research registration unique identifying number (UIN)

1. Name of the registry: None.
2. Unique Identifying number or registration ID: None.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): None.

Guarantor

Dr. Pankaj Pant.

Data availability statement

All the relevant data have been included in the manuscript itself.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

[1] Basile J. The role of existing and newer calcium channel blockers in the treatment of hypertension. J Clin Hypertens (Greenwich). 2004;6:621–29.
[2] Watson WA, Litovitz TL, Klein Schwartz W, *et al*. 2003 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med. 2004;22:335–404.
[3] Stanek EJ, Nelson CE, Denofrio D, *et al*. Amlodipine overdose. Ann Pharmacother. 1997;31:853–6
[4] Agarwal MA, Flatt D, Khouzam RN, *et al*. The potential detrimental effects of calcium channel blockers' overdose and current available management. Ann Transl Med 2018;6:1616.
[5] Ramanathan K, Mohanty B, Tang S, *et al*. Extracorporeal therapy for amlodipine poisoning. J Artific Organs 2020;23:183–6.

[6] Agha RA, Franchi T, Sohrabi C, *et al*. SCARE Group. The SCARE 2020 Guideline: Updating Consensus Surgical CAse REport (SCARE) Guidelines. Int J Surg 2020;84:226–30.
[7] Shah SK, Goswami SK, Babu RV, *et al*. Management of calcium channel antagonist overdose with hyperinsulinemia-euglycemia therapy: case series and review of the literature. Case Rep Crit Care 2012;2012:1–5.
[8] Vogt S, Mehlig A, Hunziker P, *et al*. Survival of severe amlodipine intoxication due to medical intensive care. Forensic Sci Int 2006;161: 216–20.
[9] Naha K, Suryanarayana J, Aziz RA, *et al*. Amlodipine poisoning revisited: acidosis, acute kidney injury and acute respiratory distress syndrome. Indian J Crit Care Med 2014;18:467–9.
[10] Kute V, Shah P, Goplani K, *et al*. Successful treatment of refractory hypotension, noncardiogenic pulmonary edema and acute kidney injury after an overdose of amlodipine. Indian J Crit Care Med 2011;15:182–4.
[11] Hasson R, Mulcahy V, Tahir H. Amlodipine poisioning complicated with acute non-cardiogenic pulmonary oedema. BMJ Case Rep 2011;2011: bcr0720114467.
[12] Humbert VH Jr, Munn NJ, Hawkins RF. Noncardiogenic pulmonary edema complicating massive diltiazem overdose. Chest 1991;99:258–9.
[13] Siddiqui AF, Alsabaani AA, Abouelyazid AY, *et al*. Risk factors of multiple sclerosis in aseer region, Kingdom of Saudi Arabia. Neurosciences 2021;26:69–76.
[14] Shetty K, Sherif L, Babu R, *et al*. Noninvasive ventilation in a patient with noncardiogenic pulmonary edema following amlodipine poisoning. J Anaesthesiol Clin Pharmacol 2015;31:264–6.
[15] Saravu K, Balasubramanian R. Near-fatal amlodipine poisoning. J Assoc Physicians India 2004;52:156–7.
[16] Hedaiaty M, Eizadi-Mood N, Sabzghabaee AM. Noncardiogenic pulmonary edema after amlodipine overdose without refractory hypotension and bradycardia. Case Rep Emerg Med 2015;2015:1–4.
[17] Rafeq R, Salzman M. Use of concentrated insulin in the management of calcium channel blocker overdose: a case report. J Pharm Pract 2023;36: 1519–22.
[18] Weinberg RL, Bouchard NC, Abrams DC, *et al*. Venoarterial extracorporeal membrane oxygenation for the management of massive amlodipine overdose. Perfusion (United Kingdom) 2014;29:53–6.
[19] Maskell KF, Ferguson NM, Bain J, *et al*. Survival after cardiac arrest: ECMO rescue therapy after amlodipine and metoprolol overdose. Cardiovasc Toxicol 2017;17:223–5.