Case Report

Amlodipine overdose complicated by non-cardiogenic pulmonary edema and diffuse alveolar hemorrhage: A case report

ABSTRACT

A young adult female presented with hypotension and depressed mental status after intentional overdose of Amlodipine. After intubation and institution of lung-protective mechanical ventilation, initial management focused on maintenance of a mean arterial blood pressure over 65 mmHg and included fluid resuscitation (eight liters of crystalloid), Insulin and dextrose, intravenous calcium and, finally, vasopressor support. Her course was complicated by hypoxia due to non-cardiogenic pulmonary edema requiring diuresis. She was extubated soon thereafter but developed severe hypoxia within 72 hours requiring re-intubation. A subsequent bronchoscopy demonstrated diffuse alveolar hemorrhage (DAH). This is the first report of DAH complicating amlodipine overdose.

Key words: Amlodipine; DAH; overdose

Introduction

Amlodipine, a calcium channel blocker (CCB), is a commonly prescribed antihypertensive agent.[1] Overdose with Amlodipine is relatively rare[2] but can lead to bradycardia, hypotension, non-cardiogenic pulmonary edema (NCPE) and death if not identified and treated aggressively.[3-6] Management of acute overdose includes intravenous (IV) crystalloid resuscitation and vasopressor infusions to counter amlodipine-induced vasodilation and maintain mean arterial blood pressure (MAP), glucagon to promote cardiac contractility, and IV calcium to overcome blocked calcium channels in the myocardium and vasculature.[7] Intravenous lipid emulsion therapy can bind excess CCB and promote clearance while combined insulin-dextrose infusions (hyperinsulinemia-euglycemia) can counter CCB-induced insulin resistance thereby increasing glucose uptake and promoting improved peripheral vascular resistance and cardiac contractility.[8] Finally, extracorporeal membrane oxygenation can support patients with refractory cardiogenic shock.[7] NCPE is caused by pulmonary vasodilation and overflow, exacerbated by fluid resuscitation, and diuretics typically yield benefit.[7,8]

We present a case of Amlodipine overdose complicated by hypotension and NCPE, with later development of diffuse alveolar hemorrhage (DAH). To date, there have been no

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Will R Bringgold, Micah T Long[1]

Department of Medicine, Division of Pulmonary and Critical Care, University of Wisconsin Hospitals and Clinics, Madison, WI, [1]Department of Anesthesiology, Division of Critical Care, University of Wisconsin Hospitals and Clinics, Madison, WI, USA

Address for correspondence: Dr. Will R Bringgold, UW CSC, Department of Medicine, 600 Highland Ave, Madison, WI 53792, USA. E-mail: wbringgold@uwhealth.org

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reported cases of DAH due to Amlodipine overdose when searching using the mesh terms 'calcium channel blocker', 'Amlodipine' and 'diffuse alveolar hemorrhage'. Written health insurance portability and accountability act authorization was obtained from the patient and this manuscript adheres to the applicable EQUATOR guidelines and adds to the literature by describing a case of amlodipine overdose resulting in NCPE complicated by DAH.

Case Description

A 39-year-old female with a history of hypertension, migraine headaches and depression was admitted to the intensive care unit (ICU) of a referring hospital after an intentional Amlodipine overdose of at least 300 mg. Her blood alcohol content on arrival was 210 mg/dL; the remainder of her drug screen was negative. On arrival she exhibited tachycardia (110 beats per minute) and hypertension (140/100 mmHg), with a normal respiratory rate and oxygen saturation on room air. Initial management included three grams of calcium gluconate and eight liters of intravenous crystalloid. Unfortunately, within 12-hours she developed chest pain, tachypnea and hypotension to 97/63 mmHg for which she received three additional liters of crystalloid. Chest radiography revealed pulmonary edema and she was intubated for hypoxia, with an oxygen saturation nadir of 83% [Figure 1]. She had worsening hypotension after intubation requiring initiation of a norepinephrine infusion to maintain a MAP above 65 mmHg prior to transfer to our ICU.

On arrival to our ICU, the patient was intubated and sedated with course bilateral breath sounds, a normal cardiac exam and well perfused but edematous lower extremities. Point-of-care echocardiography revealed normal biventricular function without valvular abnormalities or pericardial effusion. Labs revealed a creatinine of 1.35 mg/dL (KDIGO Stage 2 AKI), low albumin of 2.9 g/dL, leukocytosis to 25.5 K/uL, and a normal hemoglobin and platelet count. A troponin was elevated, later peaking at 0.31 ng/mL. Repeat chest radiography again showed pulmonary edema and an electrocardiogram demonstrated nonspecific T-wave abnormalities without ST changes. Her initial ventilator settings were pressure regulated volume control with a goal tidal volume of 450, a positive end-expiratory pressure (PEEP) of 12 with a driving pressure of 15. Over the next 12 hours, ventilation was weaned to pressure support of 5 and PEEP of 8. Norepinephrine was similarly weaned and discontinued. Furosemide was initiated for hypervolemia; serum calcium was replenished with additional supplementation and a high-dose insulin and dextrose infusion instituted.

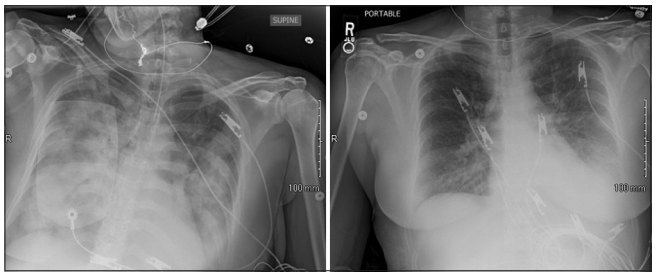

Figure 1: Chest Radiography. Pre and post-intubation radiographs from original outside hospital admission

Over the next 24 hours, the patient responded well to diuresis, her chest radiograph improved and she was extubated. She required high-flow nasal cannula and intermittent non-invasive positive pressure ventilatory support after extubation for continued tachypnea. She remained afebrile and her white count improved but due to her tenuous respiratory status, empiric Ceftriaxone and Azithromycin were initiated to treat possible aspiration pneumonia.

Two days after extubation the patient's radiograph showed worsening of her bilateral lung opacifications. A contrast-enhanced chest computed tomography was negative for pulmonary embolism but demonstrated diffuse ground glass opacities consistent with lung edema [Figure 2]. Her respiratory status declined with severe hypoxia prompting reintubation 72 hours after her initial extubation. Surprisingly, a bronchoscopy after her reintubation demonstrated progressive bloody aliquots consistent with DAH [Figure 3]. Her bronchoalveolar lavage (BAL) differential had 62% neutrophils and 35% macrophages but bacterial and fungal cultures were negative. Autoimmune markers including double stranded DNA, rheumatoid factor and antinuclear antibody screen were benign. Dexamethasone 20 mg IV daily was started empirically and a negative fluid balance

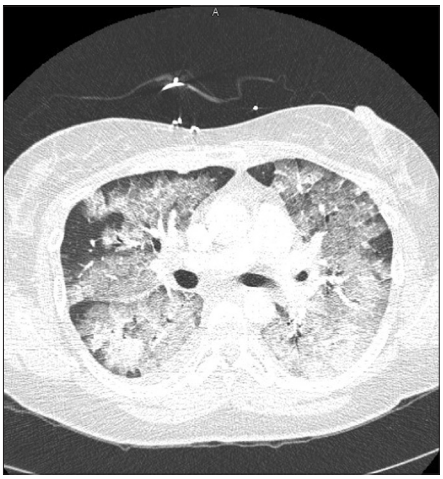

Figure 2: Computed Tomography of the Chest. Diffuse ground glass opacification of bilateral lung fields is apparent, with no pulmonary embolism on this contrast-enhanced study

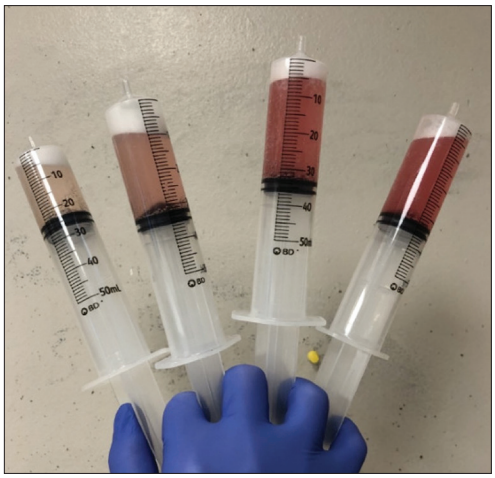

Figure 3: Serial Bronchoalveolar Lavage (BAL) Samples. Progressive hemorrhage on serial BAL samples, diagnostic for diffuse alveolar hemorrhage

was maintained without further diuretic administration. Her respiratory status quickly improved and she was extubated without further difficulty. The patient finished five days of steroid therapy and was discharged home less than 48 hours after transferring out of the ICU. Later follow-up with her primary physician showed only lingering mild fatigue and no pulmonary symptoms.

Discussion

Non-cardiogenic pulmonary edema is a relatively rare complication in CCB overdose but has been documented in several case reports.[3-6] The mechanism is not completely understood but is thought to be due to increased pulmonary blood flow from pulmonary precapillary vasodilation that results in an increased pulmonary trans-capillary gradient and leak.[4-6] This edema is exacerbated by fluid resuscitation and can result in hypoxic respiratory failure.

Diffuse alveolar hemorrhage is a syndrome that results from injury to the alveolar-capillary basement membrane. It is diagnosed on BAL when lavage aliquots are progressively more hemorrhagic. It is a syndrome with a myriad of causative etiologies including systemic vasculitides, rheumatologic disease, infections, prescribed or illicit drugs, connective tissue disease and acute respiratory distress syndrome (ARDS). For our patient, pneumonia was considered, but the clinical picture was not consistent and cultures returned negative. Other workup ruled out vasculitides, rheumatologic disease and connective tissue disease, as did her post-illness course that was uncomplicated and without signs of autoimmune illness unmasked or triggered by her overdose. Additionally, her lack of pre-illness hemoptysis, anemia and post-illness steroid dependence for wellness made pulmonary hemosiderosis unlikely. ARDS was excluded based on underlying pulmonary edema. Further, the time course of progression and recovery is not wholly consistent with a typical ARDS diagnosis.

Instead, we believe DAH was triggered by amlodipine overdose inducing severe precapillary pulmonary vasodilation and resultant pulmonary capillary pressure with further insult from crystalloid-administration induced loss of the glycocalyx.[9,10] The pulmonary glycocalyx helps maintain adequate oncotic balance within the pulmonary vasculature and disruption can decrease endothelial lining thickness and lead to alveolitis manifested as DAH.[9]

This case is the first report of Amlodipine overdose complicated by NCPE and subsequent DAH. In cases of Amlodipine overdose, initial fluid resuscitation should be guided to specific endpoints and vasoactive medications should be considered in lieu of excess fluid resuscitation that may result in NCPE, glycocalyceal disruption and DAH.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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