Noninvasive ventilation in a patient with noncardiogenic pulmonary edema following amlodipine poisoning

To the Editor,

Calcium channel blockers (CCB) are antihypertensives and atrioventricular nodal blocking agents that are commonly prescribed. While CCB overdose is rare, it is often lethal and optimal therapy remains unclear. In 2011, the American Association of Poison Control Centers reported 5408 single exposures to CCB, resulting in 25 deaths.[1] Amlodipine belongs to the dihydropyridine class of CCB. Dihydropyridines primarily affect the peripheral vasculature, but cardiac toxicity may be observed in overdose. Amlodipine's long duration of action increases the risk of morbidity and mortality from overdose. Complications of overdose include stroke, hyperglycemia, bowel ischemia, noncardiogenic pulmonary edema and cardiovascular collapse.

Noncardiogenic pulmonary edema is due to changes in permeability of the pulmonary capillary membrane as a result of either a direct or an indirect pathologic process. It is identified by the presence of radiographic evidence of alveolar fluid accumulation without hemodynamic evidence to suggest a cardiogenic etiology. Medication overdose, mainly salicylates and opiates are known to cause noncardiogenic pulmonary edema. It is also an uncommon complication of CCB toxicity. Among the various proposed theories for noncardiogenic pulmonary edema in CCB poisoning, the most popular is the selective precapillary dilatation resulting in pulmonary capillary transudation.[2] Although noncardiogenic pulmonary edema has been reported with other CCB overdose, it has been rarely reported with amlodipine;[2,3] and none of the reported literature that we reviewed mentioned the use of noninvasive ventilation (NIV) as a treatment option.

We describe a case of noncardiogenic pulmonary edema following intoxication with amlodipine, successfully managed with NIV. Marked improvement in all hemodynamic parameters were noted with a combination of fluids, inotropes and calcium.

A 31-year-old female presented to our emergency department with complaints of recurrent vomiting 6 h after an intentional intake of 40 tablets of amlodipine besylate 5 mg. On admission, she was conscious, oriented and cooperative. Her pulse rate was 130/min, blood pressure was 100/70 mmHg and saturation was 97%. Arterial blood gas (ABG) analysis in room air showed pH of 7.52, pO_2 of 85 and pCO_2 of 26 with a bicarbonate of 21.6. Electrocardiogram showed sinus tachycardia. Chest X-ray and echocardiogram revealed no abnormalities. Within 12 h of admission she developed hypotension, for which she received nor adrenaline infusion (at a rate of 0.1 μg/kg/min, which was later tapered) along with intravenous fluids (crystalloids) and 10 mL of 10% calcium gluconate. She subsequently developed breathlessness with a saturation of 95%. ABG showed pH of 7.35, pCO_2 of 24 and a pO_2 of 70 with FiO_2 of 0.4. A repeat chest X-ray revealed bilateral haziness, but a repeat echocardiogram remained normal. Her central venous pressures were also normal. A provisional diagnosis of noncardiogenic pulmonary edema was made, and it was decided to mechanically ventilate her. As she was cooperative and conscious, she was put on NIV using continuous positive airway pressure mode with a pressure of 10 and FiO_2 of 0.6. She also received antibiotics and furosemide injection. Over the next few days, she showed gradual improvement in her symptoms, ABG and chest X-ray. On the 3rd day of admission, she was weaned off NIV and inotropes were tapered. She was finally discharged on the 6th day after psychiatry counseling.

Amlodipine is a dihydropyridine CCB. Peripheral edema is a documented adverse effect of amlodipine medication. An overdose causing noncardiogenic pulmonary edema has rarely been reported. Amlodipine inhibits calcium influx into the cardiac and vascular smooth muscle cells through L-gated calcium channels, causing dilatation of both arterioles and arteries with reflex tachycardia. Unlike the nondihydropyridine CCB, dihydropyridines have little effect on cardiac pacemaker cells or contractility. In poisoning, this selectivity may be lost. Amlodipine is slowly absorbed, with peak plasma concentrations observed after 6-9 h, and a half-life at first dose of roughly 45 h.[4] This long life increases the risk of morbidity due to refractory hypotension. Our patient developed severe hypotension within 12 h unresponsive to intravenous fluids or calcium and required noradrenaline infusion for nearly 72 h. She later showed clinical signs of respiratory distress. Drug overdose is one of the causes of noncardiogenic pulmonary edema. It represents a wide spectrum of lung injury with progressive respiratory distress and refractory hypoxemia. The indirect injury to the lung results in an inflammatory cascade causing parenchymal cellular damage leading to increased vascular permeability to proteins and accumulation of protein rich fluid in the alveolar air sacs. Oxygenation is further hampered by decreased surfactant production secondary to cellular damage. Ultimately, alveolar collapse results, producing decreased pulmonary compliance and eventually respiratory failure. Noncardiogenic pulmonary edema usually develops within 24 h of onset but can even

present few days later. Pulmonary capillary wedge pressure measurements are generally normal. The initial chest X-ray of our patient was normal; and after 12 h, the repeat chest X-ray revealed bilateral homogenous opacities as seen in Figure 1. Even though we had resuscitated her with intravenous fluids, her central venous pressures never increased more than the expected range and hence we made a provisional diagnosis of noncardiogenic pulmonary edema.

Reports of noncardiogenic pulmonary edema related to overdose of verapamil, have been documented in the literature.[5,6] The exact mechanism of noncardiogenic pulmonary edema is not well known. Leesar *et al.* suggested that verapamil may lead to leaky capillary syndrome attributable to inhibition of prostacyclin release.[7] Dihydropyridines are known to cause precapillary vasodilatation and peripheral edema; a massive dose may cause edema in the lung via the same mechanism. A large dose of CCB may interact with inflammatory cytokines to cause an acute respiratory distress like syndrome. Prolonged hypotension has also been implicated in the development of pulmonary edema. High concentrations of verapamil significantly increase interleukin-1 induced expression of endothelial leucocyte adhesion molecule-1.[6] This mechanism may have a role in the pulmonary edema seen in amlodipine intoxication and needs to be clarified with further studies. Whatever the underlying pathophysiological mechanism, an important contributory factor is the volume overload because of excessive fluid resuscitation, especially during the initial hypotensive period.

Initial management of critically ill patients involves gastric decontamination and supportive care to ensure airway protection, adequate breathing and circulation. Maintenance of adequate circulation may often require a multitude of simultaneous therapies that include intravenous fluids, vasopressors, inotropes, calcium, glucagon, high dose insulin with supplemental glucose therapy, phosphodiesterase inhibitors, mechanical devices such as pacemakers and even extracorporeal membrane oxygenation in refractory shock.[8] Treatment of noncardiogenic pulmonary edema is largely supportive, aimed at ensuring adequate ventilation and oxygenation. We could successfully manage our patient with NIV as she was conscious and cooperative. Randomized studies have shown reductions in mortality if NIV techniques are used early enough in the course of the disease.[9,10] Although the pulmonary edema is not due to fluid overload, elevation in circulating blood volume and subsequent intravascular pressure can result in worsening of alveolar fluid collection and deoxygenation. Small amounts of diuretics can be used judiciously, to produce significant reductions in extracellular alveolar edema thereby enhancing oxygenation as seen in our patient.

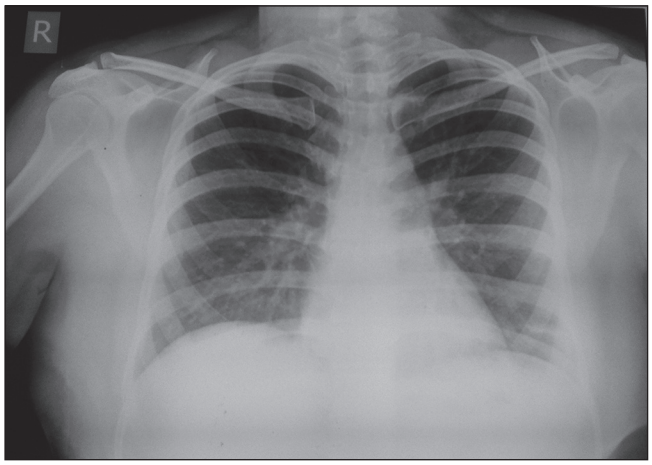

Figure 1: Bilateral nonhomogenous opacities

The recognition of the amlodipine overdose as a cause of noncardiogenic pulmonary edema and the prompt institution of early mechanical ventilation in these patients, along with aggressive management of shock is vital for a better prognosis. Among the treatment modalities, NIV can be successfully used in compliant patients. More research needs to be done to identify the exact mechanism of pulmonary edema in amlodipine poisoning.

Kishan Shetty, Lulu Sherif, Rakesh Babu, Girish Bhatt[1]

Department of Anaesthesiology, Father Muller Medical College, [1]Department of Medicine, Kasturba Medical College, Mangalore, Karnataka, India

Address for correspondence: Dr. Lulu Sherif, Department of Anaesthesiology, Father Muller Medical College, Mangalore, Karnataka, India.
E-mail: lulusherif@gmail.com

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