

A very rare side effect of amlodipine: non-cardiogenic pulmonary edema

*Amlodipinin çok nadir bir yan etkisi:
Kardiyojenik olmayan pulmoner ödem*

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ABSTRACT

Calcium channel blockers are among the most widely used drugs in cardiovascular medicine. Amlodipine, which is both cost-effective and taken once daily, is one of the most commonly prescribed agents. Although peripheral edema is a well-known side effect of amlodipine, non-cardiogenic pulmonary edema associated with amlodipine is very rare. Herein, we describe a 24-year-old female case of non-cardiogenic pulmonary edema after ingestion of 300 milligram of amlodipine orally for a suicide attempt. The patient was successfully treated with fluid replacement, inotropic drugs, and mechanically ventilation. To the best of our knowledge, this is the first case reported in Turkey.

Keywords: Amlodipine; drug overdose; pulmonary edema; suicide attempt.

Amlodipine is a commonly used long-acting dihydropyridine calcium channel blocker, which inhibits calcium influx through the L-type calcium channels. In regular doses, it mainly affects peripheral arterial vascular smooth muscle cells with mild effects on the myocardial cells. Although peripheral edema is a well-known side effect of amlodipine, pulmonary edema associated with amlodipine is very rare.^[1-6] Herein, we present a case of non-cardiogenic pulmonary edema associated with amlodipine overdose.

ÖZ

Kalsiyum kanal blokerleri kardiyovasküler tıpta en çok kullanılan ilaçlar arasındadır. Hem düşük maliyetli, hem de günde bir kez kullanılan amlodipin, en sık reçete edilen ilaçlardan biridir. Periferik ödem amlodipinin iyi bilinen bir yan etkisi ise de amlodipin ile ilişkili kardiyojenik olmayan pulmoner ödem çok nadirdir. Bu yazıda, intihar amacıyla 300 mg amlodipini oral yoldan alan, kardiyojenik olmayan pulmoner ödemli 24 yaşında bir kadın olgu sunuldu. Hasta sıvı replasmanı, inotropik ajanlar ve mekanik ventilasyon ile başarı ile tedavi edildi. Bildiğimiz kadarı ile bu Türkiye’de sunulan ilk olgudur.

Anahtar sözcükler: Amlodipin; ilaç; aşırı doz; pulmoner ödem; intihar teşebbüsü.

CASE REPORT

A 24-year-old woman presented to our emergency department with hypotension, vomiting, and deterioration of general condition three to four hours after taking 300 mg of amlodipine orally for a suicide attempt. She had no known disease. On her physical examination, she was conscious and pale. Her body temperature was 36.3 °C, arterial blood pressure was 70/40 mmHg, pulse rate was 115 bpm, and respiratory rate was 24 breaths per minute. The other



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physical examination findings were unremarkable. On admission, white blood cell count was $20,110 \times 10^3/\mu\text{L}$, aspartate transaminase was 47 U/L (upper limit: 35 U/L), and blood glucose level was 238 mg/dL. No other abnormality was noted on routine blood tests.

Following nasogastric irrigation, 1 mg/kg activated charcoal was administered through the tube in the emergency department. The patient was admitted to the intensive care unit and 150 mL/h fluid replacement therapy and calcium infusion were initiated to control serum calcium levels. Intravenous dopamine and dobutamine infusions, both at a rate of 10 $\mu\text{g}/\text{kg}/\text{min}$, were initiated for ongoing hypotension. The administration of activated charcoal and gastric protection by pantoprazole treatment was continued. Urine output started eight hours following admission. On the second day of admission, her oxygen saturation declined. Chest auscultation revealed bilateral inspiratory crackles at the base and mid-zones of the lungs. Radiological findings on chest X-ray were compatible with pulmonary edema (Figure 1). Twelve-lead electrocardiography was normal except mild sinus tachycardia (120 bpm). Left ventricular systolic functions, wall motions, cardiac chamber sizes, wall thicknesses, and cardiac valve morphology and functions were all normal on transthoracic echocardiographic examination. Despite oxygen and continuous positive airway pressure (CPAP) administration, the patient was intubated and mechanically ventilated on Day 3 of admission due to ongoing hypoxia. Fluid resuscitation, dopamine,

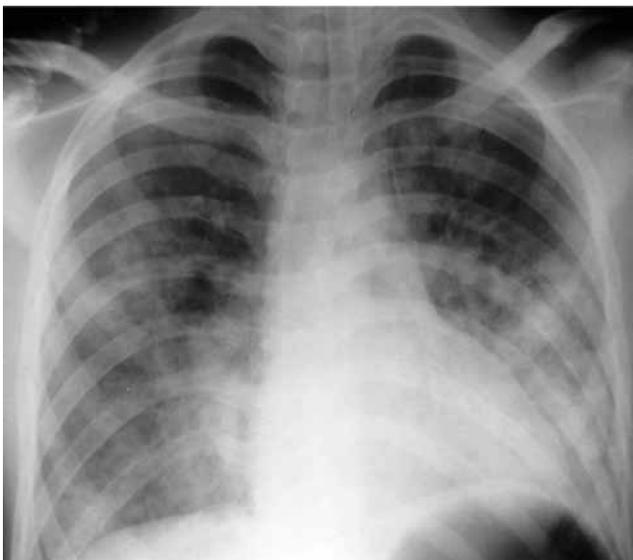


Figure 1. Chest X-ray showing that confluent alveolar infiltrates in the perihilar areas and lower lobe.

dobutamine infusions, and calcium replacement therapies were continued. Forty-eight hours after intubation, hypoxia and chest radiography findings improved, and the patient was extubated. On Day 5 of admission, arterial blood pressure was normal and dopamine/dobutamine infusions were discontinued. On Day 8 of admission, the patient was transferred to the ward. Following complete clinical and laboratory recovery, the patient was discharged on Day 13.

DISCUSSION

Calcium channel blockers are among the most commonly used anti-hypertensive agents. Half-life and tissue distribution of amlodipine are high. Amlodipine toxicity starts 30 to 60 min after taking 5 to 10 times of normal dose of amlodipine.^[7,8]

The consequences of amlodipine intoxication include fundamental problems such as hypotension and arrhythmias. Hypoperfusion due to hypotension may lead to acute kidney injury. Non-cardiogenic pulmonary edema associated with amlodipine overdose is very rare. To date, seven cases of amlodipine associated non-cardiogenic pulmonary edema have been reported (Table 1).^[1-6] Similar to our case, most of the reported cases were young females and had hypotension at presentation. Of these, four needed short-term intubation without reported mortality.^[1-6] Intravenous fluids, inotropes, and calcium gluconate were the most commonly used treatments in reported cases of amlodipine associated pulmonary edema. Increased pulmonary capillary transudation secondary to precapillary vasodilation is probably the main mechanism responsible for amlodipine associated non-cardiogenic pulmonary edema.^[1-6]

In calcium channel blocker intoxications, activated charcoal administration or intestinal lavage with polyethylene glycol are recommended within 24 hours after drug intake. In addition to intravenous fluids, if necessary, inotropic drugs should be used for hypotension.^[1-6,9] In certain cases, calcium infusions may improve contractility and hypotension.^[10] In our case, we used activated charcoal for intestinal lavage, intravenous fluid, positive inotropic drugs, and intravenous calcium infusion. Insulin has been reported to increase serum ionized calcium levels and to improve myocardial carbohydrate utilization and has been suggested in treatment.^[11]

In addition, although methylene blue (Jang *et al.*^[12]) and plasma exchange^[13] have been reported to be beneficial in severe intoxication, it was not necessary in our case. Lipid emulsion was reported to be beneficial in lipophilic drugs intoxications,

Table 1. Reported cases of amlodipine associated pulmonary edema

References	Age/Gender	Dose (mg)	BP (mmHg)	Heart rate	Heart rhythm	Treatment	Outcome
Hasson et al. ^[3]	22/F	Amlodipine: 280	71/30	60	Sinus rhythm	Intravenous fluid, Calcium gluconate Inotropes	Discharged on Day 5
Naha et al. ^[4]	18//F	Amlodipine: 85 Atenolol: 850	70/50	130	Sinus rhythm	Intravenous fluid Inotropes Calcium gluconate	Discharged on Day 8
Selej and Farber ^[2]	49/M	Amlodipine: 600 Clonazepam: 60 Tramadol: 500	Hypotensive	Bradycardia	Junctional rhythm	Intravenous fluid, Lipid emulsion Inotropes Insulin and dextrose solution Intubation (48 hours)	Unknown
Ghosh and Sircar ^[6]	25/F	Amlodipine: 100	Systolic 60	80	Sinus rhythm	Intravenous fluid Inotropes Calcium gluconate Diuretics Glucagon	Discharged on Day 5
Ghosh and Sircar ^[6]	65/F	Amlodipine: 50 Atenolol: 50	112/76	62	Sinus rhythm	Intravenous fluid Calcium gluconate Glucagon Inotropes Hemodialysis Intubation (48 hours)	Discharged on Day 10
Kute et al. ^[1]	28/F	Amlodipine: 250	70/50	130	Sinus rhythm	Intravenous fluid Inotropes Calcium gluconate Insulin/dextrose solution Glucagon Intubation (3 days)	Discharged on Day 8
Upreti et al. ^[5]	28/F	250	60/40	128	Sinus rhythm	Intravenous fluid Inotropes Calcium gluconate Intubation (48 hour)	Discharged on Day 8

BP: Blood pressure.

such as calcium channel blockers in two studies.^[14] In our case, we administered intralipid emulsion after intubation. Although significant clinical improvement was observed 24 hours later, it is still unclear how much intralipid emulsion contributed to this improvement.

In conclusion, although rare, amlodipine overdose may lead to non-cardiogenic pulmonary edema. Early gastric irrigation, fluid replacement therapy, positive inotropic agents, and calcium may be required. Due to non-cardiogenic pulmonary edema and related complications, some patients may also need mechanical ventilation.

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