

# Amlodipine -Atenolol Overdose Management: A Physician's Nightmare

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## ABSTRACT

The author reports a case of a 22-year-old female, daughter of a known hypertensive patient, who happened to consume her mother's medicine. Her mother was on a fixed drug combination (FDC) of amlodipine and atenolol. The patient was brought to the emergency department with drowsiness following ingestion of 15 tablets of amlodipine-atenolol FDC (5+ 50 mg). On evaluation, she had refractory bradycardia and hypotension along with hyperkalemia. She was managed initially with gastric lavage with activated charcoal, and subsequently with supplementation of atropine, inotropes, anti-hyperkalaemic measures, pacemaker and levosimendan.

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## INTRODUCTION

Fixed drug combination (FDC) of amlodipine and atenolol is widely prescribed for the management of hypertension and chronic stable angina but very few reports are available for the management of amlodipine-atenolol overdose. Treating patients with overdose of amlodipine-atenolol is challenging even to the most experienced physicians, due to the onset of refractory bradycardia and hypotension. Intravenous calcium chloride, calcium gluconate along with atropine, high dose insulin with supplemental dextrose and potassium, with inotropic support are proved to be beneficial in the management of such cases. Temporary pacemaker insertion can be considered for the patient with refractory bradycardia. As atenolol is dialysable, hemodialysis can be done to remove the drug if the patient presents early, i.e., within 24hrs of poisoning (Patel *et al.*, 2007; Frishman *et al.*, 1979; Delima *et al.*, 1995). Amlodipine is a dihydropyridine calcium channel blocker (CCB) that blocks the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle, with a predominant effect on

vascular smooth muscle cells than on cardiac pacemaker cells. But with significant overdose, this pharmacologic selectivity may be lost (DeWitt and Walkman, 2004).

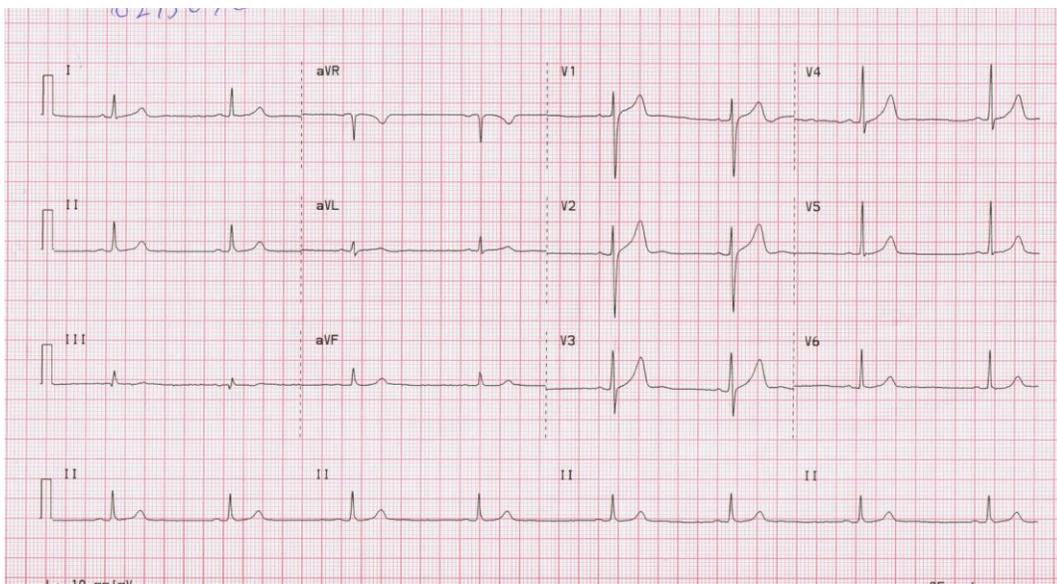
Atenolol is a cardio-selective beta-blocker (beta<sub>1</sub>-adrenergic antagonist) that lacks intrinsic sympathomimetic activity (Hoffmann and Lefkowitz, 1996).

Combination of the two drugs results in additive antihypertensive action. Atenolol has a long elimination half-life and a delayed onset of action, whereas amlodipine has a slow rate of absorption and also, low metabolic clearance (Stanek *et al.*, 1997). Atenolol is removed mainly via renal elimination, whereas 60% of an oral dose of amlodipine is excreted in the urine as inactive metabolites with less than 10% excreted unchanged (Beresford *et al.*, 1988). Overdose of FDC of amlodipine and atenolol is associated with high mortality, and only a few case reports have been documented about the treatment of overdose. A new inotropic drug, levosimendan could be beneficial in treating the hemodynamic compromise of severe CCB overdose and literature search reveals only one article about the use of levosimendan in the treatment of CCB overdose (Varpula *et al.*, 2009). We report one such case of overdose of amlodipine-atenolol treated with traditional treatment measures along with levosimendan.

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**Fig. 1:** ECG showing sinus bradycardia.

## CASE REPORT

A 22 year old female was brought to the emergency triage with drowsiness, following ingestion of 15 FDC tablets of amlodipine-atenolol (5+ 50 mg). She was initially taken to a local hospital and was treated with a gastric lavage with activated charcoal. Atropine was also given in view of bradycardia, and then she was referred to our hospital for further management. At the time of presentation, she was drowsy, with a heart rate of 48 beats per min, systolic blood pressure of 80 mm of Hg, oxygen saturation of 88% at room air, electrocardiogram showing sinus bradycardia (Fig 1). Atropine was given, and inotropic support was provided with noradrenaline and dopamine. Echocardiography was normal. Her laboratory investigations showed random blood sugar of 277mg/dL, serum creatinine of 1.2 mg/dL and serum potassium of 5.6 mEq/L. She was started on IV fluids, 50% dextrose with insulin and calcium gluconate. As atenolol is dialysable and since the patient had bradycardia and hyperkalemia, sustained low efficiency dialysis (SLED) was done for 6 hours. Patient had 25 mL of urine output during the first 12 hrs after overdose.

Urine output increased to 650 mL on the 2<sup>nd</sup> day, and improved further on the subsequent days. In view of bradycardia, a temporary pacemaker was inserted. She was also given levosimendan for 36hrs for positive chronotropic action on the heart. Her blood pressure gradually improved, and she was weaned off inotropes after 3 days. The temporary pacemaker was also removed on the 6<sup>th</sup> day of admission. Psychiatry consultation was sought on day 7, and she was diagnosed to have an adjustment disorder. She was discharged on day 8.

## DISCUSSION

The cardiovascular side effects of amlodipine are assumed to be due to decreased insulin levels. Decreased secretion

of insulin and increased insulin resistance result in hyperglycemia and metabolic acidosis that are commonly observed with amlodipine overdose (Melander *et al.*, 1979). Amlodipine overdose predominantly causes hypotension, conduction disturbances like sinus bradycardia and varying degrees of atrio-ventricular block and less commonly, non-cardiogenic pulmonary edema (Stanek *et al.*, 1997; Sanaei-Zadeh, 2012).

The cardiotoxicity due to atenolol is mainly due to ion imbalance, membrane stabilization and cardiac hyperpolarization. This results in bradycardia, low cardiac output, cardiac failure, hypotension, cardiogenic shock and rarely, bronchospasm, ventilatory depression and hypoglycemia (Frishman *et al.*, 1979).

The patient developed bradycardia and hypotension that were initially treated with atropine and inotropic agents like dopamine and noradrenaline, along with IV fluids. In view of persistent hypotension, intravenous insulin along with dextrose solution was also administered. Insulin increases plasma levels of ionized calcium, improves hyperglycemic acidotic state and myocardial utilization of carbohydrates, and also exerts an inotropic action. Hyperinsulinemic euglycemia therapy should be considered for patients with calcium channel blocker overdose who are refractory to supportive therapy (Patel *et al.*, 2007). Intravenous calcium supplementation in the forms of calcium gluconate and calcium chloride are also proved to be beneficial as augmenting extracellular calcium overcomes competitive antagonism. Intravenous glucagon as an inotropic agent has been the treatment of choice for massive beta-blocker overdose (Frishman *et al.*, 1979). But, as glucagon was not available, we have not administered it for our patient. Other treatment options for beta-blocker overdose include atropine, beta1 agonists, phosphodiesterase inhibitors (like aminophylline, amrinone and milrinone), cardiac pacing and hemodialysis. Hemodialysis should be reserved for removal of renally excreted beta-blockers like atenolol, as these patients may be refractory to pharmacologic

therapy (Delima *et al.*, 1995). Transvenous pacing may be indicated in cases of severe symptomatic bradycardia not responding to atropine or isoprenaline infusion (Kenny, 1994). In our patient, transvenous pacing and hemodialysis were done. Intravenous infusion of levosimendan, a calcium sensitizer was also administered for its positive chronotropic action on the heart. Levosimendan is a myocardial calcium sensitizer, which binds to cardiac troponin-C and improves the availability of calcium to actin and myosin fibers. Levosimendan acts as a cardioprotective drug and also reverses myocardial stunning (Varpula *et al.*, 2009). The patient had oliguria during initial 24hrs, which is common with amlodipine overdose. She gradually improved, with inotropes being tapered off; temporary pacemaker removed and was discharged from the hospital on the 7<sup>th</sup> day.

## CONCLUSION

Combination of amlodipine-atenolol overdose is potentially lethal and prompt treatment should be initiated without delay. Amlodipine overdose can be treated with early gastric decontamination, intravenous calcium and glucagon, judicious use of inotropic agents, and hyperinsulinemic euglycemia therapy; whereas atenolol overdose is treated with glucagon, atropine, hemodialysis, and in refractory cases, cardiac pacing can be done. Also, levosimendan, a calcium sensitizer, is tried for its positive chronotropic action.

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