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AMLODIPINE-ATENOLOL OVERDOSE MANAGEMENT : A CASE REPORT

Clinical Research

MADIHA NOOREEN DEAPRTMENT OF PHARMACY PRACTICE, DECCAN SCHOOL OF PHARMACY, HYDERABAD, TELANGANA, INDIA.

MARYAM DEAPRTMENT OF PHARMACY PRACTICE, DECCAN SCHOOL OF PHARMACY, HYDERABAD, TELANGANA, INDIA.

AYESHA HABEEB DEAPRTMENT OF PHARMACY PRACTICE, DECCAN SCHOOL OF PHARMACY, HYDERABAD, TELANGANA, INDIA.

SYED AAMIR ALI DEAPRTMENT OF PHARMACY PRACTICE, DECCAN SCHOOL OF PHARMACY, HYDERABAD, TELANGANA, INDIA.

ABSTRACT

Fixed dose drug combination (FDC) of amlodipine and atenolol are being prescribed extensively for the management of hypertension and chronic stable angina. The poisoning of calcium channel blocker along with a beta blocker is a nightmare in clinical settings due to potentially life threatening complications, especially, profound refractory bradycardia and persistent hypotension. Lack of treatment guidelines further adds to already challenging clinical scenario. Treatment can be done with fluid, calcium, and beta adrenoceptor agonists or with hyperinsulinemia and euglycemic as adjunctive therapy. The literature available on management of Amlodipine plus atenolol overdose is scarce. The authors present a case of 50 year old female patient who was presented in the emergency department after she had allegedly consumed a bottle of FDC tablets of amlodipine and atenolol. The authors reviews the literature and discusses treatment options available for the management.

KEYWORDS:

Amlodipine overdose, atenolol overdose, calcium channel blocker, beta blocker, inotropes,vasopressor

INTRODUCTION:

Beta adrenergic blockers and calcium channel blockers represent one of the most traditional classes of cardiovascular drugs. According to the American Association of Poison Centers, they are estimated to be 102,170 number of all substance cardiovascular drug exposures and about 45,466 number of single substance exposure. And cardiovascular drug exposures ranked second in case of causing largest number of fatalities due to poisoning.[1]

The basic principle for successful management of chronic conditions is medication compliance. Fixed drug combinations (FDC) are formulated to simplify the medication regimens and thereby helps in improving the drug compliance. FDC formulated drugs are especially effective in hypertension to reduce the blood pressure. The FDC therapy of amlodipine and atenolol is widely accepted for managing the hypertension and chronic stable angina.[2] Hypotension, bradycardia, decreased systemic vascular resistance (SVR), and cardiogenic shock are most distinguishing features of beta-blocker and calcium-channel blocker poisoning. The overdose of these drugs is bête noire for physicians due to their ability to cause refractory bradycardia and hypotension.[3]

Amlodipine used in daily dose of 5-10 mg, is a dihydropyridine calcium channel blocking agent that is commonly used for hypertension and angina. Unlike other CCBs they have low metabolic clearance rate and hence they can be used in the dose of once a day which can have near constant plasma concentration.[4]

Atenolol is beta-1 selective blocker that is used for managing hypertension, ischemic heart disease and cardiac dysrhythmias. It has the advantage of being cardioselective and lack of both membrane depressant activity and intrinsic sympathomimetic activity. These characters makes it productive choice of drug for long term treatment in hypertensive patients.[5]

Overdose of both amlodipine and atenolol in combination is a nightmare. The management strategy includes administration of vasopressors, calcium, beta agonists, glucagon, phosphodiesterase inhibitors and supportive therapy.[6]

We present a case of amlodipine and atenolol FDC poisoning with review of literature.

CASE REPORT:

A 50 year old female patient with no history of psychiatric illness was brought to the tertiary care hospital, following ingestion of 6-7 tablets of fixed dose combination amlodipine and atenolol (50mg/5mg) with suicidal intent. At the time of presentation, giddiness, unconsc iousness, visual disturbances, profuse sweating and irrelevant talking was reported. She also had 2 episodes of emesis.

On taking personal history, it was revealed that the patient was non-alcoholic, non-smoker and gutka chewer. The patient has history of hypertension but not diabetes.

Physical examination showed that patient to be unconscious, with altered sensorium and blood pressure of 80/50 mmHg. On Cardiac auscultation regular heartbeat with no murmur was heard and a heart rate of 49/min was recorded. Respiratory auscultation revealed symmetrical breath sounds, bibasilar inspiratory rales with a respiratory rate of 20 breaths/min. Her abdomen was soft, regular with normal bowel sounds.

Initial laboratory investigations showed <1.5 ng/L of troponin I and 137, 4.8 and 99 meq/L of serum Sodium, potassium and chloride respectively. ECG showed sinus bradycardia with heart rate 42 beats/min. On day 2, 2D echocardiography concluded that patient was in bradycardia, no RWMA, good LV function, mild MR, sclerotic and moderate AR, mild TR with good RV function was reported.

Her vitals for three consecutive days in hospital were as follows:

VITALS	DAY 1	DAY 2	DAY 3	UNITS
BP	80/50	100/60	90/60	mmHg
HR	42	40	66	Beats /min
R/R	18	20	22	Breaths /min
CVS	S1 S2 +	S1 S2 +	S1 S2 +	-
GRBS	198	150	138	mg/dl
P/A	Soft, tender	Soft, tender	Soft, tender	-
SPO2	76%	80%	88%	-

She was given Inj. Atropine IV stat along with the inotropic support through drugs like Inj. Dopamine 5mcg/kg/min. Tab. Orciprenaline 10mg OD was also administered in view of bradycardia. On day 4, her blood pressure improved and she was weaned off inotropes after 3 days. On 5th day she was referred for psychiatric consultation.

The patient was discharged on 6th day with the following medications:

tab. Clopitab A 75/150 mg OD, tab. Pantop 40 mg OD and tab. Aztor 40 mg OD.

DISCUSSION:

Calcium levels are pivotal for maintaining the cellular functions of cardiovascular system. Toxicity due to drugs altering serum calcium levels can have deleterious effects on vascular tone, cardiac muscle contractility and conduction system.[7] According to American Association of Poison Control Centers consensus of 2011, 20% of poisoning deaths occurs due to amlodipine overdose.[8] Amlodipine is a dihydropyridine calcium channel blocking agent that is commonly used for hypertension and angina in the daily dose of 5-10 mg. In case of immediate release and prolonged release CCBs, if the patient doesn't develop hemodynamic disorders for a period of ~6 hours and ~8 hours respectively from the time of intake then the risk of severe repercussion of poisoning is minimal.[9]

Atenolol is widely used beta blocker for critical appraisal for its anti-hypertensive effects in clinical trials (approximately >75%). Other beta blockers such as propranolol, pindolol, metoprolol and third generation of this class of drugs which comprises of carvedilol, labetalol, and nebivolol has not been assessed for long term use in primary hypertension.[10] The vital factor resulting in cardiovascular mortality in beta blocker toxicity is the congestion of cardioactive agents, most commonly calcium channel blockers. The agents with membrane stabilizing activity have been associated with higher rates of mortality in cases that lacks co ingestion of cardiac active drugs. If the patient is asymptomatic for >6 hours then its highly likely that the patient will develop any symptoms.[11]

Calcium levels are pivotal for maintaining the cellular functions of cardiovascular system. Toxicity due to drugs altering serum calcium levels can have deleterious effects on vascular tone, cardiac muscle contractility and conduction system.[7] CCBs and beta blockers inhibits the calcium influx across the cell membrane by different mechanisms. CCBs acts directly by blocking Ca+2 influx through L-type Ca+2 channels which are found in smooth muscles, heart and pancreas. Thus, they have negative inotropic action on heart. BBs alters the calcium channels via secondary messenger cAMP that causes beta stimulation. This leads to decreased intracellular calcium levels which results in cardiac dysfunction, and in severe cases may cause cardiovascular collapse.[4]

Depending upon the intensity of poisoning patient's consciousness may vary from dozing to deep coma.[12] Despite having different mechanism of action and pharmacological profiles CCBs and BBs overdose has similar clinical presentation such as bradycardia and hypotension.[13]

Amlodipine in toxic doses blocks calcium influx in the pancreatic islets thereby inhibiting the release of insulin and causing hyperglycemia. Amlodipine can lead to metabolic acidosis with compensatory hypocapnia that occurs due to hyperventilation. In case of acute respiratory failure, acidosis can be attributed to both metabolic and respiratory in origin.[14] Its cardiac effects includes sinus bradycardia, atrioventricular block, and right bundle branch block.[12]

Atenolol in toxic doses causes ion imbalance and cardiac hyperpolarization that leads to low cardiac output, hypotension, sinus bradycardia, heart failure, cardiogenic shock. It also causes bronchospasm, ventilatory depression and hypoglycemia due to lack of beta selectivity in higher doses.[15] Central nervous system depression can also occur with lipophilic beta blocker agents such as carvedilol and propranolol that are highly lipophilic where as metoprolol and pindolol are moderately lipophilic.[13] Due to sodium channel blockade, in certain cases of BB toxicity prolonged QRS can also be observed.[16]

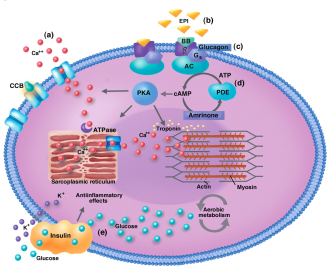


FIGURE 1: The above image illustrates the involvement of calcium, epinephrine (EPI), glucagon, amrinone, and insulin in the treatment of β-blocker (BB) and calcium-channel blocker (CCB) toxicity.[13]

Aggressive therapy is the call of the hour in case of toxicity. In case of extended release CCBs, gut decontamination by administering activated charcoal or whole bowel irrigation or multiple-dose charcoal therapy is indicated.But the likely risks related with the gut decontamination procedures should be taken into account, for example, gastric lavage should not be given to the patients with bradycardia or conduction abnormalities. Cases with sustained release preparations toxicity should be monitored closely for at least 24 hours and those with non-sustained release preparations should be monitored for about 12 hours.[16] CCB overdose antidotes includes calcium salts, glucagon and insulin therapy. Calcium when given in the dose of 0.2ml/kg up to a total of 10ml, usually improves myocardial contractility and may also help to improve sinus rate and atrioventricular conduction. When calcium gluconate is given, the dose can be increased to 20 to 30 ml. The doses can be repeated for every 15-20 minutes for up to a total of four doses. Continuous infusion of calcium chloride at the rate of 0.2ml/kg up to a total dose of 10ml/hr. can also be administered as an alternative. Glucagon 10mg given via intravenous route stimulates the adenyl cyclase which increases the cAMP levels that results in positive inotropic and chronotropic effects.[17] Phosphodiesterase inhibitors (e.g., aminophylline, amrinone and milrinone), adrenergic agents, cardiac pacing, balloon pump or extracorporeal bypass are often used as supportive therapy.[16] Recently, the promising effects of hyper insulinemic euglycemic therapy has been evolving in the literature through case reports and case series.[18]This intervention has the strongest evidence but of lower quality.[19] For beta adrenergic blocking agents overdose, glucagon has been the treatment of choice. Other treatment options include beta agonists, atropine, phosphodiesterase inhibitors, cardiac pacing and hemodialysis.[20]

In our patient the effect of amlodipine on vascular smooth muscle is strikingly obvious due to the presence of profound hypotension, requiring administration of intravenous fluid i.e., 0.9% normal saline stat and inotropic support with injection dopamine. Symptomatic bradycardia was managed with the administration of atropine and orciprenaline.The altered sensorium of the patient can be fairly attributed to the decreased perfusion to the brain tissue due to hypotension rather than atenolol, a beta blocker, since it is not a lipophilic drug.

CONCLUSION:

The calcium channel blocker overdose along with beta blocker toxicity is a potentially life threatening combination and hence demands immediate therapeutic intervention. In case of non-dialyzable drugs, correction of electrolyte abnormalities, metabolic acidosis and hypotension helps to improve the clinical outcomes. We conclude that amlodipine plus atenolol overdose can be managed with atropine, orciprenaline, dopamine along with the intravenous administration of normal saline.

CONFLICT OF INTEREST:

Authors have no conflict of interest.

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