ASIA PACIFIC JOURNAL of MEDICAL TOXICOLOGY
APJMT 13;3 http://apjmt.mums.ac.ir September 2024

CASE REPORT

The next gen poison- a case series of amlodipine overdose

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Abstract

Introduction: Amlodipine is a commonly prescribed anti-hypertensive drug. Its inadvertent exposure and intentional overdose is the leading cause of drug overdose seen in the practice of cardiovascular medicine. It can lead to profound hypotension, refractory shock, acute renal failure and end organ damage.
Case reports: A case series of three patients with serious calcium channel blocker (CCBs) overdose, out of which two survived and one succumbed despite aggressive treatment is presented here.
Discussion: Our three patients presented with giddiness caused by hypotension attributable to generalized vasodilatation due to direct effect on vascular smooth muscle; and negative effect on the cardiac pacemaker and myocardial contractility. Hyperglycemia due to reduced insulin release and lactic acidosis also contributes to reduced dromotropic effect. Abdominal pain and vomiting seen in our patients has been ascribed to reduced gastrointestinal motility and stasis of gastric contents. Oliguric renal failure with features of fluid overload seen is attributable to prolonged hypotension and reduced effective circulatory volume. An unusual finding in our cases was non-cardiogenic pulmonary edema. We attribute this to capillary leak syndrome as a result of generalized vasodilatation, resulting in excessive pulmonary capillary transudation.
Conclusion: Thus, management of CCB poisoning can be challenging. Outcome can be improved by early and aggressive intensive care, fluid resuscitation, inotropic support, calcium infusion, glucagon infusion, hyperinsulinemia-euglycemia therapy and other supportive measures. The pulmonary edema can complicate fluid resuscitation, and one might need to stop IV fluids and give diuretics, ventilatory support and increase inotropes in such a scenario.

Keywords: Amlodipine, Non-cardiogenic pulmonary edema, IV calcium therapy, Hyperinsulinemia-euglycemia therapy, Glucagon infusion

How to cite this article: Shah M, Kulkarni A, Ghiya M, Malik A, Gill N. The next gen poison- a case series of amlodipine overdose. *Asia Pac J Med Toxicol* 2024; 13(3): 125-130.

INTRODUCTION

Calcium plays a pivotal role in cardiovascular function. The flow of calcium across cell membranes is necessary for cardiac automaticity, conduction, contraction, and for maintenance of vascular tone. CCBs (calcium channel blockers) interfere with calcium fluxes across cell membranes. CCBs directly block calcium flow through L-type calcium channels found in the heart, vasculature and pancreas. The major toxic effect of overdose is refractory hypotension, due to both vasodilation and impaired cardiac metabolism and contractility. Tissue ischemia and lactic acidosis ensue. Blockade of calcium channels in other tissues, such as pancreatic beta cells lead to reduced insulin release.

CCBs are one of the most widely used group of anti-hypertensives. Amlodipine is a dihydropyridines CCB with longer half-life (30-58 hours), than other CCBs [2]. Its toxicity is seen in doses 5-10 times the therapeutic dose and symptoms occur within 30-60 minutes following ingestion [3]. Amlodipine has a large volume of distribution Vd (21 L/Kg) [4] and unlike non-dihydropyridine CCBs l, dihydropyridines have predominant effect on vascular smooth muscle cells rather than cardiac pacemaker cells or contractility [4].

The longer (up to 72 hours) duration of action, relative lack of negative inotropy, and once-daily dosing has made amlodipine preferred over other CCBs.

We present a series of three cases of poisoning with amlodipine, of which only two survived.

Case 1

A 30-year-old male came to emergency department (ED) with ingestion of 30 tablets of 5mg of amlodipine on 30/12/22 at 7:30pm. Since 8pm he started complaining of dizziness, perspiration, chest pain and cold extremities. He received gastric lavage at 8:30pm at a local hospital and was shifted to our hospital for further management.

At presentation his blood pressure (BP) was 100/60mmhg, pulse rate of 110/min and spo2 of 95 % with GCS score of 15. Patient was shifted to ICU. All routine blood reports were done- liver function test (LFT) and renal function test (RFT)

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were normal. Erythrocyte sedimentation rate (ESR) was 15. Complete blood count was normal except mild leukocytosisr, ABG: ph-7.43, bicarbonate-23.2.

In view of hypotension after trial of IV fluid bolus with normal saline at 100ml per hour, he was started on noradrenaline support. Bolus of calcium gluconate given (10mg in 100ml NS) and then as infusion at 1mg/hr. The patient maintained bp of 110/70mmhg and urine output 50ml/hr at the end of day 1. The patient's bp rose to 128/80mmhg after 3 days of ICU stay and inotropes were tapered off. Patient was then discharged on fluoxetine 20mg OD by psychiatry team from the ward.

Case 2

A 20 year female, came to the ED with alleged history of consumption of 40 tablets of amlodipine 5mg on 16/3/23 at 4pm. 2 hours later, patient started to have giddiness and went to nearby clinic where her BP was 70/40mmHg. Gastric lavage given immediately and patient transferred to our center with multiple episodes of vomiting.

Patient was immediately shifted to ICU where IV fluids started (normal saline at 100 ml/hr). Injection calcium gluconate 10mg given as bolus and repeated twice after which infusion started at 1mg/hr. In view of persistent hypotension and oliguria, inotropic support (noradrenaline & eventually vasopressin) was added. The hyperinsulinemia euglycemia drip (human regular insulin infusion at 20 U/hr under cover of dextrose infusion as per sugar levels, being monitored 1 hourly) and antibiotic (cefoperazone + sulbactam 1.5gm BD) was initiated. At the end of day 1 the BP rose to 90/60mmhg.

Her initial laboratory data (table 1) was: hemoglobin:9.9g/dl, WBC:21300cumm, platelets 426000cumm, creatinine 3.4mg/dl, routine urine showed 10 to

Table 1. Day wise labs of case 2

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Hemoglobin (gm/dl)	9.9	10.1	10.1	8.5	9.2	8.8	8.2	8 8.7
Total leucocyte count (10^3/µl)	21.3	23.7	21.76	15.87	17.01	19.17	15.15	14.97
Platelet (10^3/µl)	426	389	319	281	290	301	299	261
Erythrocyte sedimentation rate (sec)	15							
Sr. Bilirubin – total (mg/dl)							0.5	
Sr. Bilirubin – direct (mg/dl)							0.3	
Sr. Bilirubin – indirect (mg/dl)							0.2	
Sr. Aspartate transaminase [ast]/ got (iu/l)							27	
Sr. Alanine transaminase [alt]/ gpt (iu/l)							24	
Sr. Alkaline phosphatase (iu/l)							64	
Total sr. Protein (gm/dl)							5.7	
Sr. Globulin (gm/dl)							2.8	
Sr. Albumin (gm/dl)							2.9	
Sr. Creatinine (mg/dl)	3.4	3.5	2.1	1.4	1.3	1.0	0.6	0.5
Sr. Calcium (mg/dl)	6.4		6.9		6.9	6.7	7.2	
Sr. Sodium (meq/l)		127	123	119		116	137	134
Sr. Potassium (meq/l)		3.3	3.9	4.2		3.8	3.6	3.2
Sr. Chloride (meq/l)		96	95	94		92	100	96
Urine routine	Pus cells - 10-12/hpf granular cast present							
Abg [ph arterial blood/ pc02 arterial blood (mmhg) / p02 arterial blood (mmhg) / hc03 arterial blood (mmol/l)/ o2 saturation arterial blood (%)]	7.445/ 24.1/ 86.1/ 16.2/ 97.1	7.403/ 20.7/ 75.7/ 12.6/ 95.6		7.351/ 19.5/ 73.2/ 10.6/ 94.5		7.441/ 19.4/ 60.9/ 12.9/ 92.9		
Vbg [ph venous blood/ pc02 venous blood (mmhg) / p02 venous blood (mmhg) / hc03 venous blood (mmol/l) / o2 saturation venous blood (%)]								7.492/ 34.4/ 46.1/ 25.8/ 85.9
Culture and sensitivity							Central line – acinetobacter baumanii Urine – klebsiella pnumoniae Blood- no growth	

12 pus cells/hpf, s. Calcium 6.4mg/dl, electrolytes (Na:127meq/l, K:3.3meq/l, Cl:96meq/l.), LFT was normal-(bilirubin total/direct (mg/dl) 0.5/0.3, AST/ALT (IU/L) 27/24)

Inj glucagon was given (10mg S/C) on day 2, infusion of glucagon could not be continued due to financial constraints.

On day 3, patient had persistent oliguria (urine output around 10-15ml/hr) and developed fluid overload as suspected on auscultation and confirmed on X-ray and HRCT chest (figure 1); (2D echo-no abnormality). Non-invasive ventilatory (NIV) support with 40% FiO2 and furosemide infusion at 30 mg/hr started. IV fluids were stopped. The insulin and dextrose infusion was continued, along with inotrope and calcium infusions.

On day 4, the insulin and dextrose infusion were stopped once her urine output started to increase (around 100ml/hr) and BP was maintained >100/70mmhg. Furosemide, calcium and inotropes were tapered and stopped. Patient was maintained on negative balance till pulmonary edema settled. Patient was weaned off from NIV. Her creatinine reduced to 1.4 and serum sodium level normalized to 136.

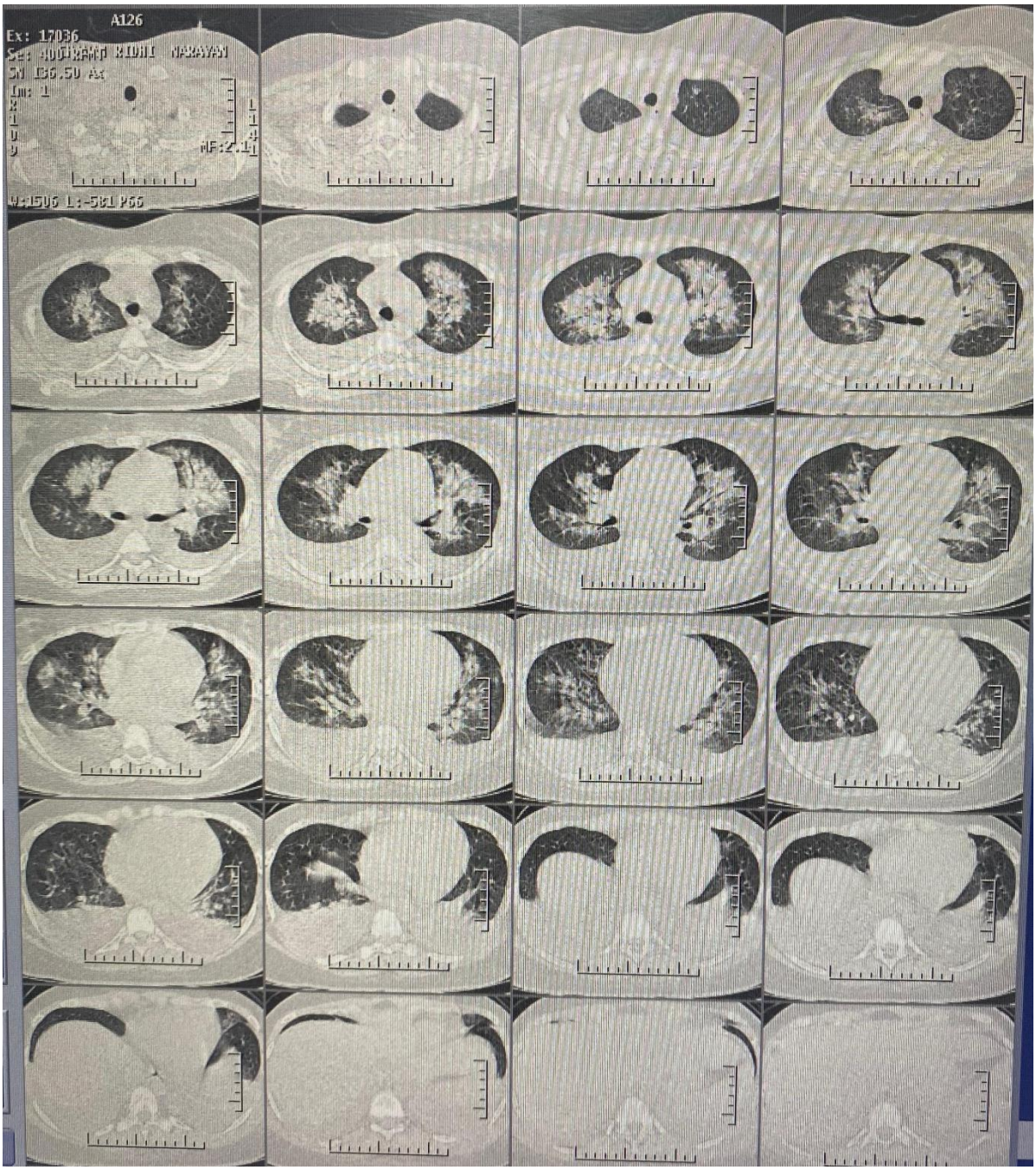

Figure 1. HRCT chest denoting pulmonary edema and pleural effusion in case 2

Patient started to develop fever on day 5. Central line and foleys were removed. Urine culture showed E.coli and central line culture showed Acinetobacter baumanii; sensitive antibiotics were initiated. Patient was shifted to ward.

Patient was discharged on 3rd day of ward stay, after psychiatric evaluation which revealed major depressive disorder with impulsive deliberate self-harm. Oral fluoxetine and etizolam was started. BP at the time of discharge 120/80mmhg. CBC at the time of discharge 10.3/5850/300000.

Case 3

A 50 years hypertensive female, came with ingestion of 30 tablets of amlodipine 5 mg at around 4pm on 24/3/23. After four hours, patient complained of giddiness, perspiration and tingling and numbness on both upper and lower limbs. She was brought to ED after 6hrs of consumption of tablets in confused state, where she had 2-3 episodes of vomiting.

At presentation the pulse was 120/min and bp was 70/40mmhg. IV fluid bolus and infusion started immediately (normal saline at 100 ml/hr). Inotropes (noradrenaline and vasopressin) started. Two boluses dose of calcium gluconate 10mg given immediately and infusion started at 1mg/hr. The hyperinsulinemia euglycemia drip was started with insulin (regular) at 24 U/hr and dextrose infusion as per blood sugar levels. Broad spectrum antibiotic was started empirically.

Her initial laboratory data showed, creatinine: 2.0mg/dl, serum sodium: 142meq/l, potassium: 4.0meq/l, chloride: 104meq/l and serum calcium: 9 mg/dl, CBC-11.4/20100/539,000. In view of refractory shock, adrenaline infusion added at 2 mg/hr.

In spite of triple inotropic support, at end of day 2 her blood pressure was 84/44mm/Hg and oliguria was persistent. She developed pulmonary edema on 3rd day (figure 2). IV fluids stopped and NIV support along with furosemide infusion started. Her laboratory parameters worsened, serum creat: 2.6mg/dl, CBC 11.4/28.02/606. S. Calcium of 6.9 electrolyte 138/4.2/105.

Patient eventually went into metabolic acidosis (ABG-pH/pco2/po2/hco3 7.312/29.5mmhg/206.9mmhg/14.6mmol/dl) and was electively intubated. Nephrologist advised low efficiency dialysis (SLED) once BP rises to 100mmhg. Relatives did not consent for dialysis (and glucagon injection) as they had financial constraints. Patient had 2 fever spikes with WBC

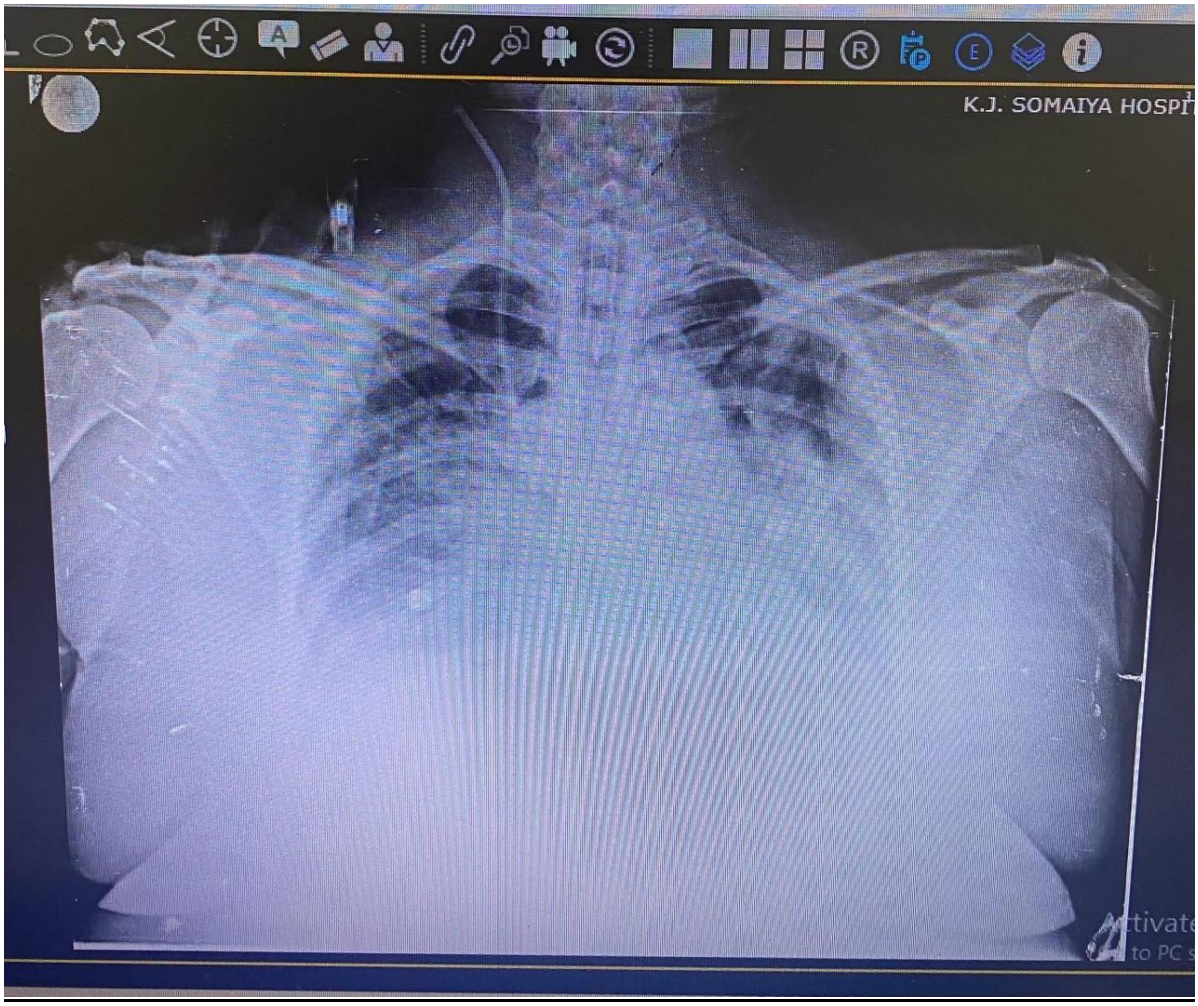

Figure 2. CXR denoting pulmonary edema in case 3

counts increased from 28,000 to 32,000. Urine and blood cultures sent, which later showed no growth. Patient's acidosis was worsening (pH = 7.197) and still had oliguria (output 10 ml/hr). Sodium bicarbonate infusion started at 10 mEq/hr. Patient developed a cardiac arrest at night and succumbed at night on 3:36 am on 28/3/23 (4th day of admission).

DISCUSSION

CCBs directly block L-type calcium channels causing relaxation of the vascular smooth muscle with subsequent vasodilation. Calcium channel blockade concurrently triggers the heart to switch to preferential carbohydrate metabolism as opposed to the free fatty acid oxidation that occurs in the myocardium in non-stressed state [5]. In the beta-islet cells of the pancreas, calcium channel antagonism inhibits insulin secretion, producing insulin resistance and hyperglycemia [5].

The giddiness in our 3 patients is caused by hypotension, which we attribute to generalized vasodilatation due to direct effect on vascular smooth muscle; worsened by negative effect on the cardiac pacemaker and myocardial contractility. Hyperglycemia and lactic acidosis also contributes to reduced dromotropic effect. Abdominal pain and vomiting is ascribed to reduced GI motility. Oliguric renal failure seen in our patient is attributable to prolonged hypotension and reduced effective circulatory volume [6]. Our patients had pulmonary edema (noncardiogenic) with bilateral pleural effusion, which is believed to be due to selective precapillary vasodilation (and excessive fluid resuscitation for treatment of hypotension) [7] leading to the so called 'systemic capillary leak syndrome' (SCLS).

Treatment includes supportive care including maintenance of ABCs (airway, breathing, and circulation) [8]. Gastric lavage, activated charcoal or whole bowel irrigation are not routinely indicated but may be useful if the patient presents within 1 to 2 hours of a life-threatening ingestion [9].

Hypotension is initially managed with volume loading; however, as our patient developed signs of fluid overload (SCLS), we did not continue IV fluids. Vasopressors (noradrenaline, adrenaline, dopamine) are routinely initiated, but this treatment is often ineffective as the primary mechanism of hypotension is arterial muscle relaxation and not hypovolemia. Correction of acid-base disturbances and electrolyte abnormalities optimizes cardiac function.

Calcium gluconate/chloride is the specific antidote [2], given in continuous infusion (Ca chloride 0.2 ml/kg/hr) or IV boluses (10 ml of 10% calcium chloride/20-30 ml of calcium gluconate, every 15-20 minutes; maximum: 30 g over 12 hours) which is given to overcome the competitive blockade of calcium channels [2].

Glucagon may be given because it activates myocardial adenylate cyclase and thus increases cyclic adenosine monophosphate, which results in inotropic and chronotropic effect [9]. The initial dose of glucagon is 50 to 150 mg/kg [9]. Glucagon bolus may be repeated in 3 to 5 minutes up to 30 mg cumulative dose or alternatively, infusion can be given following the initial bolus [9]. Glucagon was administered in the initial hours to our patients but could not be continued due to their financial constraints.

Hyperinsulinaemia/euglycaemia therapy (HIET) consists of the infusion of high-dose regular insulin (HDI) (usually 0.5 to 1 IU/kg per hour) combined with glucose to maintain euglycaemia. Experimental and clinical experience suggest that it is superior to conventional pharmacological treatments (calcium salts, adrenaline or glucagon.) [10]. It is postulated that HDI has strong positive inotropic properties [5]. Insulin allows the switch of the cell metabolism from fatty acids to carbohydrates, required in stress conditions, especially in the myocardium and vascular smooth muscle, causing improvement in cardiac contractility and restored peripheral resistances [10]. Moreover, exogenous insulin can overcome insulin deficiency that occurs due to CCB toxicity [5]. HDI improves systemic perfusion and also improves catecholamine response [5]. Studies show accelerated oxidation of myocardial lactate and reversal of metabolic acidosis with HDI [5].

Unlike dialysable toxins (methanol, ethylene glycol, and aspirin), CCBs have large Vd and are highly protein-bound, making them poor candidates for removal by hemodialysis [8]. Dialysis however, was needed in our third owing to metabolic acidocis, oliguria and renal shutdown secondary to amlodipine poisoning.

Finally, intravenous lipid infusions have been used to treat lipid-soluble drug overdoses. It decreases the distribution of lipophilic agents into the tissues and may result in the redistribution of the toxic drug from the tissues back into the lipid channel [11]. Cardiac pacing in third degree heart blocks, intra-aortic balloon pump, extracorporeal membrane oxygenation and partial liquid ventilation are in experimental stage [3]. These modalities were not feasible in our resource limited setting and financial constraints in most of the populace we treat.

Only a handful articles have been published yet on amlodipine overdose. Even fewer are those who develop non-cardiogenic pulmonary edema with amlodipine. A 42 year old woman with overdose of amlodipine, came to ED with hypotension and tachycardia was treated with GI decontamination and IV hydration. This patient, like our 2nd case, also developed pulmonary edema which eventually settled. She was monitored with serial serum amlodipine levels, which we could not do due to our resource limited center [12].

Another case where a 20 year male presented with consumption of 40 tablets of 10 mg of amlodipine was managed with IV fluids, calcium and inotropes. He developed pulmonary edema in the course of treatment. Although the authors could not prove the non-cardiogenic nature of pulmonary edema with 2D echocardiography or pulmonary capillary wedge pressure, we were able to do the former investigation [2].

In another case, a 37 year female had ingested amlodipine 6.7 mg/kg, atenolol 33.3 mg/kg, and alprazolam 1 mg/kg in a suicide attempt. She was initially managed with IV fluids, inotropes, glucagon and calcium with only transient and mild improvement in the BP. Insulin infusion was initiated at 35 IU/h with dextrose infusion as per sugars. Within 1 hour, BP

increased and no further hypotension occurred and the patient improved gradually [4].

CONCLUSION

Amlodipine overdose can be potentially fatal owing to non-cardiogenic pulmonary edema, refractory shock, and acute renal failure, and its management can be challenging. Outcome can be improved by hydration, inotropic support, calcium infusion, HIET and other supportive measures.

The course of hospitalization of all our 3 patients was highly variable. The first patient required only IV fluid and noradrenaline support while the course was complicated by SCLS and oliguric acute renal failure in 2nd case that was managed conservatively; although dialysis may be needed, as in the 3rd case. The management of every patient should be individualized. Treatments have to be holistic, yet tailor made based on risk versus benefit analysis while also bearing in mind the patients' financial constraints and the hospitals limited resources. A multi-disciplinary approach involving amicable and frequent communication between the medical and critical care team, can sometimes be the difference in the patients' outcome.

ACKNOWLEDGMENTS

The authors would like to thank Dr Minu Ramakrishnan (Superintendent, KJ Somaiya hospital) and Dr Varsha Phadke (Dean, KJ Somaiya medical college) for their support and encouragement.

Conflict of Interest: The authors have no conflict of interest.

Funding and Support: No sources of funding were used to assist in the preparation of this manuscript.

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