Case Report

Iatrogenic hypercalcemia induced acute pancreatitis following verapamil overdose: A case report

Krishna Ranatunga[1*], Krishantha Jayasekera[1]
[1]Teaching Hospital, Karapitiya, Sri Lanka

Abstract

Calcium channel blockers (CCBs) are a widely prescribed group of medications. CCB overdose results in profound haemodynamic effects, which could lead to rapid deterioration. It often requires a multitude of pharmacological agents to achieve a favourable outcome. Herein, we report a case of a 56-year-old female who presented after verapamil overdose and was treated with intensive medical therapy including an intravenous infusion of calcium. She subsequently developed iatrogenic hypercalcemia-induced acute pancreatitis. She was successfully managed with supportive care.

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*✉ **Correspondence:** krishr099@gmail.com https://orcid.org/0000-0002-8768-6230

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Introduction

Calcium channel blocker overdose is usually lethal and challenging to manage [1]. The majority of reported fatal cases of verapamil poisoning are due to large intentional overdoses. Patients may present to the first medical contact asymptomatic but could deteriorate very rapidly. Aggressive management with fluid resuscitation and supportive therapy is highly important. Severe hypercalcemia and associated complications are rare consequences of therapeutic intravenous calcium infusion [2-4].

Case description

A 56-year-old female presented to the emergency department (ED) four hours after intentional ingestion of 9 tablets of 240 mg sustained-release verapamil, following a family dispute. At the time of presentation, she had diffuse nonspecific headache without sinister symptoms, dizziness and nausea. She had no chest pain, palpitations, abdominal pain or shortness of breath. She had a history of Wolf-Parkinson-White syndrome and had undergone radio-frequency ablation in 2019. She also had right ventricular outflow tract obstruction with ventricular ectopics and was on oral sustained-release verapamil 240mg daily. Upon arrival at the ED, her Glasgow Coma Scale was 15/15. Her blood pressure (BP) was 65/30 mm Hg. She had regular low-volume pulse and the rate was 62 beats/ min (bpm). Heart sounds were normal without murmurs. Respiratory, neurological and abdominal examinations were unremarkable.

Fluid resuscitation was initiated immediately with 500 millilitres of intravenous 0.9% rapid saline bolus

followed by 1 litre over the next 1 hour. Although she presented four hours after ingestion, as it was a slow-release preparation, gastric decontamination was done with 50 g of activated charcoal. One hour after fluid resuscitation, her vitals remained unstable with a BP of 66/32 mmHg and pulse rate (PR) of 56 bpm. Bedside echocardiography revealed a collapsed inferior vena cava with globally impaired cardiac contractility. Aggressive fluid resuscitation was continued with another litre of intravenous 0.9% saline. Meanwhile, she was initiated on high insulin euglycemic therapy (HIET) with a bolus of regular short acting insulin given intravenously. Euglycemia was maintained with a 10% dextrose infusion. Patient remained persistently bradycardic and hypotensive with heart rate fluctuating between 50 to 60 beats per minute & systolic blood pressure (SBP) around 70 mmHg, despite intravenous fluid resuscitation with 2.5 litres. Hence, inotropic support was established with intravenous noradrenaline 0.2 mcg/kg/min via a peripheral line while central access was obtained. In addition, 1 mg of intravenous glucagon was administered. She was given 30 mL of 10% calcium gluconate intravenously followed by an infusion of 0.5 mL/kg/hour.

Her initial serum biochemistry and haematology were as tabulated below (Table 1). Venous blood gas revealed a pH of 7.39, bicarbonate of 23.2 mmol/L. Electrocardiogram showed sinus bradycardia.

Despite up-titration of the infusion rate of intravenous noradrenaline, the patient remained hemodynamically unstable warranting the support of a second inotrope. Thus intravenous dopamine was initiated. The patient was transferred to the intensive care unit for further management. With the support of the two inotropes and other supportive therapy, her SBP remained between 90 to 100 mmHg and PR between 60 to 70 bpm. On day 2 (D2) of admission, HIET and inotropes were gradually tapered, maintaining a stable SBP 90-110 mmHg.

By evening on the second day, she complained of severe central abdominal pain with mild abdominal distension. Mesenteric ischemia was suspected. But investigations including serum amylase, abdominal ultrasonography were suggestive of acute pancreatitis. She had no features of gallstone disease or autoimmune pancreatitis. She denied alcohol use. The cause for acute pancreatitis was revealed as iatrogenic hypercalcemia. Her initial serum calcium level checked nearly 10 hours post initiation of calcium infusion was 3.41 mmol/L (reference range 2.1 – 2.57 mmol/L) This was despite calcium being infused at a rate recommended by the expert consensus. Calcium infusion was omitted. Hypercalcemia slowly resolved with meticulous fluid resuscitation. Repeated serum calcium on the next day was 2.8 mmol/L. She was gradually weaned off inotropes, managed symptomatically and her clinical course gradually improved.

Table 1: Investigation findings

Investigation	D1	D2	D4	D8
haemoglobin (g/dL)	11.5	11.2	11.9	12.2
white cells (× 109 /l)	14.75	15.6	12.8	11.8
platelets (x 109/L)	168	208	196	252
Random blood sugar (mg/dL)	238	190	156	148
Serum potassium (mmol/L)	3.8	3.6	4.2	4.1
Serum sodium (mmol/L)	129	145	138	140
Serum creatinine (umol/L)	99	112		96
Serum corrected calcium (mmol/L)	3.41*	2.80		2.14
Serum amylase (U/L)		3400	2208	168
Aspartate transaminase (U/L)		40		
Alanine transaminase (U/L)		46		
Alkaline phosphatase (U/L)		168		
Total Bilirubin (mg/dL)		0.8		
Direct Bilirubin (mg/dL)		0.4		
Non fasting total cholesterol (mg/dL)			170	
C-reactive protein (mg/L)		28		7
Urine full report		Normal		
Stool for occult blood		Negative		
USS abdomen	Prominent hypoechoic pancreas with a thin layer of peri-pancreatic fluid collection suggestive of acute pancreatitis. Intraperitoneal free fluid was noted in right sub diaphragmatic and hepatorenal pouch of Douglas			
Chest radiograph	B/L pleural effusions			

*10 hours after admission

Discussion

Management of CCB overdose can be challenging as unexpected complications may occur. Intravenous calcium used in the management could lead to hypercalcemia-associated acute pancreatitis, a dire complication if not identified and managed appropriately.

Verapamil a nondihydropyridine CCB has a greater effect on myocardial contractility, automaticity and atrioventricular conduction with minor effect on

peripheral vasculature [1]. CCB overdose is associated with a high incidence of morbidity and mortality. According to a review by Lisette B et al, reported toxic doses of verapamil, including both fatal and nonfatal cases have ranged from 800 mg to 24,000 mg, while the lowest definitive fatal dose of verapamil was 2280 mg [5]. Symptoms due to sustained-release formulations may not manifest until more than 12 hours post-ingestion and may persist for 48–72 hours [5]. Cardiovascular effects of note are profound hypotension, bradycardia and conduction blocks. Mesenteric infarction, hyperglycaemia, noncardiogenic pulmonary oedema, metabolic acidosis, stroke are also reported complications of CCB toxicity [4].

There is no antidote for CCB overdose to date. Management is mainly supportive. Orogastric lavage and gastrointestinal decontamination with activated charcoal may benefit selected patients. The cornerstone of management is to achieve hemodynamic stability by optimizing intravascular volume and restoring cardiac output. Therefore, intravenous fluid resuscitation plays a major role. It is recommended to use norepinephrine to raise BP in vasoplegic shock [6]. Epinephrine is also an option. Clinicians may use dobutamine, in the presence of confirmed myocardial dysfunction [4]. HIET is believed to improve inotropy, peripheral vascular resistance and reverse acidosis [4,7].

Use of calcium salts is logical to overcome intracellular hypocalcaemia. Boluses of calcium increase extracellular calcium concentration, which increases the trans cellular concentration gradient and maximize calcium entry through unblocked channels [2,6]. Intravenous calcium has shown transient improvements in cardiac output and BP with minimal effect on heart rate in animal studies [1]. Observational human studies are more variable. Severe hypercalcemia is a rare complication of intravenous calcium infusion. Calcium can be administered as an intravenous bolus (10–20 mL of 10% calcium chloride or 30–60 mL of 10% calcium gluconate, to be repeated every 15–20 min, up to four doses, followed by a continuous infusion (0.2–0.4 mL/kg/h of 10% calcium chloride or 0.6–1.2 mL/ kg/h of 10% calcium gluconate) [7]. The exact endpoint is unclear. This could be either observed hemodynamic stability or double the normal value of serum calcium levels.

Despite intravenous calcium being administered according to the recommended doses, our patient developed hypercalcemia. Past records revealed normocalcemia six months ago. Hypercalcemia as a cause of pancreatitis is very rarely reported. Michael T. Sim et al reported a case of amlodipine overdose treated with intravenous calcium that led to iatrogenic pancreatitis and anuric kidney injury with a total serum calcium level of 32.3 mg/dL [3]. Khan et al. also documented a similar case of iatrogenic hypercalcemia which induced pancreatitis with a serum calcium level of 22.7 mg/dL [3].

In our patient, the highest level of calcium was 3.41 mmol/L, which induced pancreatitis. This was measured approximately 10 hours after the initiation of calcium infusion. Had serum calcium levels been measured earlier, the calcium dose could have been adjusted, minimising the risk of occurrence of pancreatitis. Thus, we would like to stress upon frequent monitoring of serum calcium levels and goal-directed adjustment of the infusion rate.

Conclusion

The management of CCB overdose could be a challenge. Overdose of CCBs results in profound hemodynamic effects and fluid resuscitation, calcium, vasopressors and HIET therapy are well validated approaches to treatment. Intravenous calcium infusion must be used cautiously and with close monitoring anticipating complications.

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