Reminder of important clinical lesson

Life-threatening calcium channel blocker overdose and its management

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Summary

A young woman presented to the emergency department with complaints of nausea, vomiting, pain in the abdomen and difficulty in breathing after ingestion of 56 tablets of amlodipine 5 mg each (total 280 mg of amlodipine). She was managed using hyperinsulinaemia/euglycaemia therapy and other measures like calcium gluconate, glucagon and vasopressors. She was discharged from hospital in a stable condition after 5 days.

BACKGROUND

Calcium channel blockers (CCBs) are among the most frequently prescribed cardiovascular medications. The management of their overdose is often complicated due to their profound haemodynamic effects. Clinical features of CCB poisoning include hypotension, bradycardias, conduction blocks, pulmonary oedema, hyperglycaemia and metabolic acidosis. Hyperinsulinaemia/euglycaemia therapy is used nowadays to manage CCB overdose. We present a case of a young woman who ingested 56 tablets of amlodipine (5 mg each) and briefly discuss the management of CCB overdose with hyperinsulinaemia/euglycaemia therapy.

CASE PRESENTATION

A 24 year-old woman presented to the emergency department after ingestion of 56 tablets of amlodipine 5 mg each (total 280 mg) with suicidal intent. She developed nausea, vomiting, abdominal pain and difficulty in breathing. The patient had ingested this large dose of amlodipine about 3 h before reporting to our hospital. She had no previously diagnosed psychiatric condition, nor significant chronic medical condition. Her pulse rate was 120/min, systolic blood pressure was 80 mm Hg and respiratory rate was 36/min. Respiratory system examination revealed crepitations bilaterally. Cardiovascular examination was normal apart from tachycardia. The patient was conscious and oriented but anxious. Her abdomen was normal.

INVESTIGATIONS

At the time of admission the patient's haemoglobin was 10.5 g/dl, total leucocyte count was 11 000/ μ l, and differential leucocyte count was neutrophils 80% and lymphocytes 20%. Oxygen saturation by pulse oximetry was 87%, and arterial blood gas analysis showed pO_2 62 mm Hg (8.3 kPa), pCO_2 17.4 mm Hg (2.3 kPa), pH 7.30, and HCO_3^- 8.4 mmol/l. Blood glucose was 11.4 mmol/l (205 mg/dl), blood urea was 22.1 mmol/l

(62 mg/dl) and serum creatinine was 141.4 μ mol/l (1.6 mg/dl). Serum sodium, potassium and calcium were 136 mmol/l (136 meq/l), 4.2 mmol/l (4.2 meq/l) and 2.2 mmol/l (8.8 mg/dl), respectively. ECG was suggestive of sinus tachycardia. Chest x-ray showed bilateral fluffy radio-opaque shadows in a bat wing pattern; however cardiac size was normal. Bedside echocardiography was within normal limits.

TREATMENT

We started standard resuscitative measures urgently in the form of oxygen inhalation, crystalloid bolus and gastric lavage with 75 g activated charcoal. When the patient's blood pressure did not respond to fluid challenge, a central venous catheter was inserted through the right subclavian vein. At that time, her central venous pressure (CVP) was 12 cm H_2O . Two litres of normal saline were further infused over 1 h but blood pressure failed to improve, falling to 68 mm Hg systolic, and the CVP was 16 cm H_2O . An infusion of dopamine was begun and that too failed to elevate blood pressure. Norepinephrine was added. After continuous infusion of dopamine and norepinephrine for a further 1 h, the blood pressure was 72 mm Hg systolic. The patient became drowsy and oxygen saturation as determined by pulse oximetry dipped to 84%.

The patient was intubated and put on mechanical ventilation. A bolus of 30 ml of 10% calcium gluconate was given followed by infusion at 10 ml/h. Serum calcium monitoring was done every 2 h. During the next hour, the blood pressure fluctuated between 60 and 70 mm Hg. Glucagon in a dose of 3 mg was given followed by infusion at 3 mg/h. Five hours elapsed and the patient was still on mechanical ventilation, dopamine, norepinephrine, calcium gluconate and glucagon while her blood pressure was between 60 and 70 mm Hg. The urine output over these 5 h was 60 ml. Intravenous insulin 25 IU was given as a bolus followed by an infusion of 20 IU/h together

with a glucose bolus of 25 g intravenous and a dextrose infusion was started. Blood glucose was monitored every half hour and the insulin/dextrose drip was titrated to maintain euglycaemia. After 1 h of the insulin/dextrose infusion, her blood pressure was 80 mm Hg. This was the first instance when the blood pressure increased. The insulin infusion and vasopressors were further up-titrated and after 2 h her blood pressure was 98 mm Hg, which became 104 mm Hg after the next 2 h. During the further 2 h the patient's blood pressure was between 100 and 110 mm Hg and her urine output also improved. After 8 h at the same rate of insulin and vasopressors, her blood pressure was 110/70 mm Hg, urine output was adequate and CVP was 16 cm H₂O. The doses of vasopressors, calcium gluconate and glucagon were tapered with no fall in BP and she was also weaned off ventilatory support. She was extubated after a further 10 h but the insulin infusion was continued for a further 12 h during which the patient was normotensive and her urine output became normal. The patient was transferred to the medical floor and discharged 5 days later after psychiatric assessment.

DISCUSSION

CCBs are one of the leading causes of overdose-related deaths among cardiovascular medicines.^{1 2} Amlodipine is a CCB that belongs to the dihydropyridine group. It is well absorbed orally and has a half-life of 30–50 h.³ All CCBs act by blocking the movement of calcium into the cell membrane through the inhibition of voltage-sensitive L-type calcium channels.⁴ In doing so CCBs affect vascular smooth muscle tone, myocardial contractility, automaticity and atrioventricular conduction. Amlodipine (a member of the dihydropyridine class) is unique as it has greater selectivity for vascular smooth muscle as compared with myocardium.⁴ But in a significant overdose of amlodipine some of this selectivity may be lost.³

The clinical manifestations of CCB toxicity are mainly due to peripheral vasodilation and myocardial depression resulting in profound hypotension, shock, bradycardias and conduction blocks.⁵ Bradycardias and conduction blocks are not commonly seen in poisoning with the dihydropyridine (amlodipine) group because of their limited myocardial binding; therefore, poisoning with amlodipine can present with tachycardia or normal heart rate.⁵ Gastrointestinal symptoms like nausea and vomiting and neurological symptoms like coma and respiratory depression are uncommon.⁵ Hyperglycaemia has been documented in numerous reports as another important clinical feature of severe CCB poisoning.⁵ Hyperglycaemia is due to impaired insulin release from β islet cells of the pancreas as insulin release is also dependent on calcium movement via L-type calcium channels. Metabolic acidosis and acute lung injury are also seen in CCB poisoning. The patient presented above had hypotension, nausea, vomiting and metabolic acidosis, her blood sugar was on the high side (11.39 mmol/l, 205 mg/dl), and she also had pulmonary injury as evident from shortness of breath, bilateral crepitations and fluffy infiltrates in a bat wing distribution on a chest radiograph. She had a tachycardia: as discussed above, bradycardias are not commonly seen in toxicity with dihydropyridine CCBs.

The initial treatment of CCB toxicity should begin with airway protection and the administration of oxygen. Appropriate intravascular volume must be established with the use of intravenous fluids (normal saline); in the setting of amlodipine poisoning, marked peripheral vasodilation will require large amounts of intravenous fluid for volume repletion. Gastric lavage can be beneficial if the patient presents within 1–2 h of ingestion but should be used cautiously due to the potential for causing vagal stimulation and exacerbating bradycardias. If the patient has ingested extended-release formulations, whole bowel irrigation is another gut decontamination option. We also managed our patient giving her oxygen inhalation, boluses of intravenous fluids and gastric lavage.

The use of calcium salts for the treatment of CCB overdose is physiologically reasonable and clinically indicated.⁶ Boluses of calcium increase the extracellular Ca²⁺ concentration, which increases the trans cellular concentration gradient, driving Ca²⁺ intracellularly. Calcium can be given 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). Calcium can also be given as 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).⁵ Calcium is not always effective in improving haemodynamic parameters.⁷ Moreover, calcium boluses can cause various adverse effects such as nausea, vomiting, confusion, thrombophlebitis, lethargy, cardiac conduction defects with bradycardias and increased oxygen consumption resulting in angina. Severe hypercalcaemia, although rare, has been reported.⁸ Calcium concentrations should be determined every 2 h to monitor for hypercalcaemia. Our patient was also given a bolus of calcium gluconate followed by infusion along with serum calcium monitoring, but her blood pressure did not respond much to the administration of calcium.

In various case series, vasopressors such as epinephrine, norepinephrine, phenylephrine, isoproterenol, dobutamine and dopamine have been used with varied effect.^{9 10} If dopamine fails to improve blood pressure, direct-acting adrenergic agonists like norepinephrine or phenylephrine should be considered.¹¹ The exact dosing of vasopressors in CCB overdose has not been firmly established; if hypotension persists, the rate of administration should be increased and additional adrenergic agonists should be added.¹² In accordance with this approach, our patient was started on a dopamine infusion but she remained hypotensive despite increasing the dose, so norepinephrine was also added.

Glucagon is used in the management of CCB poisoning because of its significant chronotropic and inotropic effects. It acts by stimulating adenylyl cyclase, thereby causing an increase in intracellular concentrations of cyclic AMP (cAMP). The initial dose is a 2–5 mg intravenous bolus followed by continuous infusion at a dose of 2–5 mg/h. Glucagon is especially useful in CCB overdose if there is a suspicion of concomitant poisoning with β -adrenergic blockers.¹³ Our patient was also given glucagon but her blood pressure did not respond much to glucagon administration.

Various clinical observations support the use of the hyperinsulinaemia/euglycaemia technique (HIET) in the management of CCB overdose and circulatory

compromise.^{12 14–18} These clinical observations also suggest that this technique should probably be used early in the management of CCB overdose.

CCBs inhibit the calcium channels of β cells of the pancreas, leading to hypoinsulinaemia and hyperglycaemia.¹⁹ Hypoinsulinaemia and insulin resistance could be cornerstones in the pathophysiology of CCB cardiovascular toxicity. Under normal aerobic conditions, myocardial cells oxidise free fatty acids (non-esterified fatty acids) as the main energy substrate. Conversely, in poor haemodynamic conditions (such as those induced by CCB toxicity), myocardial cells switch to glucose as the main fuel. However, the decreased perfusion impairs glucose delivery to tissues. Furthermore, hypoinsulinaemia and insulin resistance inhibit the uptake of glucose, especially by myocardial and vascular muscle cells, thereby preventing its adequate use as a main energy substrate. The lack of fuel and energy stores further compromise the cardiovascular condition already impaired by the blockade of calcium channels. These mechanisms give rise to the hypothesis that high-dose insulin therapy could be beneficial in the management of CCB overdose by overcoming hypoinsulinaemia and insulin resistance and thereby breaking the vicious circle of haemodynamic deterioration leading to shock and death.²⁰ Increasing amounts of data from studies in animals also support the administration of insulin while maintaining normal blood glucose as a first-line therapy in CCB poisoning.²¹ The proposed dosing of insulin in CCB toxicity is to give a regular insulin 1 IU/kg intravenous bolus followed by insulin infusion at the rate of 0.5 IU/kg/h.^{20 22} Blood glucose should be checked every half hour and hypertonic glucose must be infused to maintain blood sugar in the upper normal range. Supplemental potassium is required only to prevent severe hypokalaemia.^{20 22} Such a treatment technique is often referred to as the hyperinsulinaemia/euglycaemia technique (HIET) in the management of CCB overdose. HIET improves inotropy and peripheral vascular resistance and reverses acidosis, possibly by improving the uptake of carbohydrates by myocytes and smooth muscle cells.¹⁴ Our patient was also given a regular insulin bolus followed by infusion and it was only after initiation of this therapy that her blood pressure showed an improving trend.

Another class of drugs that can be used in the management of CCB poisoning are phosphodiesterase inhibitors like amrinone, milrinone and enoximone. They inhibit the breakdown of cAMP by phosphodiesterase, thereby increasing cAMP levels. These noncatecholamine inotropes increase intracellular calcium and improve inotropy.⁵

The possible role of levosimendan in a verapamil overdose using a rodent model has been investigated recently.²³ Human experiences have also proposed the beneficial effect of levosimendan in CCB overdose.²⁴ Levosimendan is a myocardial calcium stabiliser that binds to cardiac troponin-C and improves the availability of calcium to actin and myosin fibres, thereby improving cardiac contractility.²⁵

The use of intralipid infusion to trap lipid-soluble CCB in the plasma and prevent it from penetrating cardiac tissue has been used in some case reports.²⁶ The suggested antidotal mechanism of intralipids is that they sequester lipophilic toxins in a newly created intravascular lipid

pool. This lipid pool 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.²⁷

In refractory cases, transthoracic or intravenous cardiac pacing may improve the heart rate. Intra-aortic balloon counter pulsation can also be considered in patients refractory to pharmacotherapy.⁵

Learning points

- Poisoning with calcium channel blockers is often challenging for the emergency physician.
- Hyperinsulinaemia/euglycaemia therapy, when initiated promptly and aggressively, is very useful in the management of calcium channel blocker (CCB) overdose.
- Other useful strategies to manage CCB overdose include glucagon, calcium, inotropes and phosphodiesterase inhibitors.
- Temporary cardiac pacing and intra-aortic balloon pump counter pulsation can be tried in refractory cases.

Competing interests None.

Patient consent Obtained.

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