Case Report

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Calcium Channel Blocker Toxicity- A Case Report with Treatment Overview

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Abstract

A 75 years old male presented to the Emergency Department (ED) with an unexplained hypotension. With a wide differential diagnosis we concluded it could be attributed to an unusually high antihypertensives dosage the patient was receiving, we started treating it as a calcium channel blocker (CCB) toxicity with success. The case report reviews the case with measured levels of medications and reviews treatment of CCB toxicity with current guidelines for treatment.

Keywords: Calcium channel blockers, drug induced bradicardia, drug induced hypotension, drug overdose, toxicity

Introduction

Calcium channel blockers (CCBs) are among the most commonly prescribed antihypertensive agents, yet their toxicity — whether intentional or unintentional — remains one of the most potentially lethal prescription drug poisonings encountered in the emergency department. Elderly patients on complex antihypertensive regimens are particularly vulnerable, as reduced renal clearance, polypharmacy, and unreliable medication adherence can precipitate toxicity even within apparent therapeutic dose ranges. The case report will describe an interesting case with a pharmacological background, and review the standard of care for treatment.

Case Report

Consent to participate has been granted by the patient. A 75 years old male presented to the Emergency Department (ED) with chief complaint of collapse and generalized fatigue. He explained that he felt unwell for the last couple of weeks, he tired quickly, felt energy depleted and dyspneic more than usual. The day of the presentation he got up from the couch to go to the bathroom, his field of vision got black-out and he collapsed. He denied any injury to the body and he did not remember whether he lost consciousness or not, because it all happened too fast. He vomited once, mixture of ingested food with no traces of blood or hematine mass. He did not remember when he threw up and thought it was probably during the collapse. He denied dyspnoea, chest or abdominal pain, fever, changes in urine and stool, coughing or recent weight loss. We contacted the relatives, who gave us additional information. They had a pulse oximeter at home and his measured value at home was 70%.

His regular medication included rosuvastatin (20 mg q.d.), perindopril and indapamide (4 mg/1.25 mg q.d.), enalapril (20 mg q.d.), amlodipin (5 mg q.d.), verapamil (240 mg q.d.) and finasteride (5 mg q.d.). He denied allergies.

In physical examination he appeared pale, hypotensive (81/58 mmHg), normocardic (65 min -1). He was in a hypoxic respiratory failure with the SpO2 of 88%. His CRT was prolonged (5s), there was a loss of turgor, the skin had no signs of mottling. The rest of the physical examination was mostly within normal ranges.

ECG showed junctional rhythm with ventricula frequency of around 60 per minute with a right bundle branch block.

Point of Care Ultrasound (POCUS) has shown prominent B lines with minimal subpleural consolidations in posterior basal parts of the lungs, no signs of fluidothorax and A lung profile in the remainder. His heart had no visible pericardial

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effusion, the function of left ventricle was only slightly affected, no right ventricle strain, normal TAPSE, vena cava inferior (VCI) has a respiratory modulation of 50%, his atria were larger. The RUSH exam has shown no obvious reason for hypotension, his bladder was empty. The two-regional compression test for DVT was negative.

Chest roentgenogram has shown no abnormalities, abdominal RTG has shown mildly dilated small intestinal lumen up to 32mm, the bowel was full of faecal matter.

Laboratory results have shown a slight leukocytosis (12,8), a known normocytic anemia (hemoglobin 114 g L-1), acute kidney injury (315 µmol L–1 creatinine, 17,8 µmol/L urea, oGF 16), hyperglycemia (10.6 mmol/L) with normal electrolytes, low markers of infection (CRP and procalcitonin), normal liver tests and lipase, and slightly elevated blood lactate (2.3 mmol L–1). ABG has shown acute respiratory failure (8.0 kPa pO2), lower bicarbonate (16.7 mmol L-1) and BE (-6.6). His urine sample did not show signs of infection, it was however slightly positive for proteins, higher urobilinogen and signs of microhematuria.

Our clinical approach to the patient was focused on his hypotension. He was pale, but relatively stable and did not appear shocked and with all the examination mentioned above we could not explain his clinical condition. There was no signs of obstructive or cardiac shock, no signs of sepsis, massive volume depletion, bleeding, nor neurogenic or anaphylactic shock. He received an arterial line for invasive blood pressure measuring. After 1 liter of crystalloids he remained hypotensive and needed an infusion of a vasopressor (norepinephrine, 0.10 mcg kg–1 min–1) to maintain adequate mean arterial pressure (MAP). On suspicion of small bowel obstruction (SBO) a nasogastric tube was inserted, which sucked out a dark-brown fluid.

Because of an unclear underlying reason for hypotension the range of the possible differential diagnostics was widened. In the presence of acute renal failure we did not want to conduct exams that would potentially worsen kidney injury by applying contrast with computed tomography (CT). In addition there was no clear indication of massive gastrointestinal bleeding that would explain the hypotension.

Upon further examination we discovered that he was operated on 2 years before due to SBO attributed to volvulus of the small intestine with hypotension. He also presented to our ED with hypotension 3 months prior to this event. The reason for hypotension was unclear as well, there was a high suspicion of a septic shock because of a CT-identified transient volvulus of small intestine. He was then hospitalized in the ICU, where he did not need any vasopressor after 2 days, the reason for hypotension remained unclear.

We noticed that he had a lot of antihypertensive therapy. In one of the previous admissions it was written that his relatives stated that he occasionally forgot to take his medication or took it repeatedly, for which they said that it could be possible now as well.

We now started to suspect a combined toxicity of angiotensin-converting enzyme inhibitors and calcium channel blockers. In lieu of possible toxicity, a trial of antidote - calcium gluconate (1000 mg) was administered, to which he immediately responded with a raise of systolic blood pressure to 130 mmHg without vasopressor support and a raise of heart rate to 70 min–1. In ECG he had a clear appearance of the p-wave. Because of the success of the trial therapy we decided to administer the full dose of calcium gluconate (additional 2000 mg) and glucagon (4 mg).

The Slovenian Center of toxicology and clinical pharmacology was contacted. They advised us to administer a continuous infusion of glucagon in case of persistent hypotension, which we applied and to send samples for a toxicology report of blood levels of antihypertensive therapy. He was then admitted to internal medicine ward, with a fixed level of norepinephrine infusion. He had an unexplained respiratory failure, for which we could not find a clear culprit.

During his hospital stay he had a CT thorax and abdomen conducted in order to identify any other possible reasons for hypotension and acute respiratory failure. The examinations identified a large 9 x 9 cm hiatal hernia, which was known from previous examinations and atelectatic lung tissue adjacent to it, no sign of pulmonary embolism, a possible adenoma of the right suprarenal gland and a concrement in the gallbladder with a small amount of liquid around it. The esophagogastroduodenoscopy has shown a passage difficulty from the proximal to distal part of the stomach because of the large herniation; about half of the corpus was present proximal to the herniation. The roentgen passage with barium swallow has shown a herniation with no passage obstructions at the time of the examinations.

He needed crystalloid infusion and low dose norepinephrine infusion in first 2 days of his hospital stay.

The analysis of 24 hour ECG Holter showed no malignant rhythm disturbances that would explain his collapse. Echocardiography and cycle ergometer revealed no pathology that would show a possible myocardial dysfunction or exertional angina pectoris or collapse. His pulmonary function was normal.

He was evaluated by a psychiatrist to assess for dementia. He identified a slight cognitive decline with absent suicidal tendencies.

In the time of hospital stay laboratory results have shown no rise in markers of infection and no fall of hemoglobin. His acute kidney injury eventually resolved and he was released home.

Serum levels of antihypertensive therapy were known after the hospital stay. The time of sample collection was approximately 1 to 2 hours after therapy administration and the results have shown a level of amlodipin of 0.08 mg L–1, a level of verapamil of 0.05 mg L–1 and an undetectable level of perindopril (below 0.01 mg L–1). Laboratory results of

adrenocorticotropic hormone levels excluded a hormonally active adenoma.

We concluded that hypotension was attributed to CCB toxicity with an unclear but still possible increased medication intake. We speculated that the absorption could have been delayed because of the present hiatal hernia. He was referred to the thoracic surgeon for the surgical repair.

Discussion

The patient presented to the emergency department with hypotension, which was not explained by usual signs and symptoms. We approached the patient with a wide differential diagnosis as explained in the presentation of the case.

At home the patient was receiving an unusual antihypertensive pharmacotherapy combination with two angiotensin-converting enzyme (ACE) inhibitors enalapril and perindopril concomitant. This pharmacotherapy medicine combination was not the same to the one provided at discharge 3 months ago from our hospital. We also can't predict which medicine he was taking considering that his relatives stated he occasionally forgot or took medicines repeatedly. Using Slovenian prescription history records online base (named "e-recept") we can only say that the patient has all perindopril and enalapril as well as amlodipine and verapamil available at home.

Perindopril erbumin and enalapril maleate are both ACE inhibitors. Oral enalapril is a prodrug, rapidly absorbed. The peak concentration in serum occurs in 1 hour. Following absorption, enalapril is rapidly and extensively hydrolyzed to enalaprilat, which has a pharmacologic effect. Peak serum concentrations of enalaprilat occur about 4 hours after an oral dose of enalapril tablet, and the effective half-life is 11 hours. Excretion of enalaprilat is primarily renal. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril. Exposure to enalapril and enalaprilat is increased in patients with impaired renal function, the dose should be adjusted (1,2).

Oral perindopril is also a prodrug. It is rapidly absorbed, the peak concentration in serum occurs in 1 hour. It is extensively metabolized, mainly in the liver, to the active perindoprilat and inactive metabolites including glucuronides. Perindopril is excreted mainly in the urine, as an unchanged drug, as perindoprilat, and as other metabolites. Perindoprilat is excreted more slowly in the elderly and patients with heart or renal failure. In patients with renal insufficiency, the dose should be adjusted (1,2).

Amlodipine and verapamil are both CCB. They belong to two main chemical classes, phenylalkylamines (verapamil) and dihydropyridines (nifedipine, amlodipine, felodipine, isradipine, nicardipine, nimodipine). Each subclass presents different affinities for cardiac tissue and vascular smooth muscle. A strong affinity for both myocardium and vascular smooth muscle is presented with verapamil. It also suppresses cardiac contractility, SA nodal automaticity, AV nodal conduction and causes potent vasodilation. On the other side dihydropyridines (amlodipine) are very effective vasodilators with less influence on cardiac tissue (3).

Oral amlodipine is well absorbed. Peak concentration in serum occurs from 6 to 12h after ingestion. Amlodipine is extensively metabolized by the liver to inactive metabolites. Ten percent of the parent compound and 60% of metabolites are excreted in the urine (1,2). Kidney function does not alter drug metabolism.

80-90% of oral verapamil is absorbed from the small intestine. Peak concentration in serum occurs in 1 to 2h after ingestion. It undergoes considerable first-pass loss and is extensively metabolized in the liver. Bioavailability is only about 20%. Twelve metabolites have been identified. Of these only norverapamil has any significant activity. Norverapamil represents about 6% of the dose eliminated in urine and reaches steady-state plasma concentrations approximately equal to those of verapamil. About 70% of a dose is excreted by the kidneys in the form of its metabolites, but about 16% is excreted in the bile into the feces. Less than 4% is excreted unchanged. Verapamil metabolism does not depend on the renal function (1,2).

Our patient was taking verapamil in prolonged-release tablets form. Potential symptoms of toxicity may be delayed up to 12 h. The measured level of verapamil was 0.05 µg mL-1. A nonlinear correlation between the verapamil dose administered and the verapamil plasma level does exist. Chronic oral administration of 120 mg of verapamil HCl every 6 hours results in plasma levels of verapamil ranging from 0.125 to 0.4 µg mL-1. Usual therapeutic plasma concentration is 0.05 to 0.25 (-0.5) µg mL-1, toxic plasma levels are above 1 µg mL-1 and described lethal concentrations above 2.5 µg mL-1 (4).

Measured amlodipine level in our patient was 0.08 µg mL-1. Usual therapeutic plasma concentration is 0.005 - 0.018 µg mL-1. Toxic plasma levels are above 0.088 µg mL-1. Described lethal concentrations are 0.1 – 0.2 µg mL-1 (5).

Patients with an intoxication with CCB may present with hypotension, bradycardia and also with heart failure signs. Despite hypotension, they retain their mental status, possibly due to the neuroprotective effects of CCB, though this may decline when cerebral perfusion becomes critically diminished. The ECG may show a prolonged PR and any bradydysrhythmia (6).

The fact that both the blood pressure has risen and heart rate normalised after calcium gluconate serves as the strongest clinical evidence for CCBT, as well as a lack of need for additional therapy as the medication effect resolved in the following days.

Even though the levels were not enough to claim to be toxic (verapamil level was within therapeutic range and amplodipine on borderline toxic), the clinical picture,

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the combination of the multiple antihypertensive therapy, the amplification of the drug's effect by the renal failure, possible repeated dosing (with an unintentional overdose) and the age of the patient were all important factors that strongly support the claim of the effect of the CCB and the clinical picture that supported CCBT.

Thus we would like to emphasise that the proposed starting treatment in the case of CCBT is *i.v.* fluids for hypotension and atropine for bradycardia (7,8). Atropine may be ineffective in CCBT (9). Calcium salts are used to overcome the cardiovascular effects of CCB; 10% CaCl2 (or Ca gluconate as a 3 times higher dose) in a 10-20ml slow bolus (preferably through a central line), repeated up to 4 times over 20 min. A continuous high dose administration has been used successfully, with 0.5 mEq calcium kg-1 h-1 (0.2 ml kg-1 h-1 of the aforementioned calcium chloride), where one must be careful not to induce hypercalcemia. Treatment may not be effective as CCB interfere with both the serum concentration and with intracellular handling of calcium (10-12).

Glucagon is used to increase heart rate in CCB toxicity through an increase in intracellular cyclic adenosine monophosphate, but has no effect on MAP. A 5 mg *i.v.* bolus is advised with a possible repetition twice, every 10 minutes (13-15).

Vasopressors should be used after the fluid bolus, with norepinephrine being the prefered choice and the addition of a secondary vasopressor is often required. The doses may be higher than those we are used to see in septic shocks (16). High-dose insulin (bolus bolus of 1 unit kg-1, followed by continuous infusion of 0.5 unit kg-1 h-1 and titrated - raise of 50 % until either target is met or a maximum dose of 10 unit kg-1 h-1 is reached), with a hemodynamic response delayed by 30-60 min (17-20).

Possible adjuncts to consider in treatment, with no high-quality studies to support them, are lipid emulsion therapy with the emulsion acting as a lipid sink and inactivating the molecules (21-23), phosphodiesterase inhibitors (inamrinone), levosimendan, invasive treatments, such as transvenous pacing and extracorporeal membrane oxygenation (ECMO), but they should not be used routinely as there are only case reports of use (24-29).

In addition to that, in our patient we considered the effect of the large hiatal hernia on absorption and slower drug release because of a slower digestive rate and a possible factor in the patient's CCB toxicity. But upon extensive research, no case reports or literature reviews on the topic have been found, thus opening the room for discussion on a possible factor that has not been speculated until now. There is some existing literature on the effect of gastric stasis (in this case by the hiatal hernia) that could support this causal relationship, and some on the direct effect of the hiatal hernia and the delayed effect of drugs (because they reached the small intestine, where the drugs are absorbed, later than intended), but no literature supports this argument directly (30,31), which leaves the argument on only the speculative level.

Conclusion

This case highlights the diagnostic challenge of unintentional CCB toxicity in an elderly patient, where the absence of classic bradycardia, near-therapeutic serum drug levels, and a multifactorial clinical picture obscured the diagnosis until empirical calcium gluconate administration produced an immediate and definitive hemodynamic response. The co-prescription of antihypertensive drugs, compounded by acute kidney injury, advanced age, and possible repeated dosing, illustrates how cumulative pharmacological burden can produce toxicity that standard dosing thresholds fail to predict. Additionally, we speculate on a novel hypothesis that the patient's large hiatal hernia — by altering gastric transit and delaying drug delivery to the small intestine — may have contributed to a delayed and prolonged toxic effect, an interaction not previously described in the literature and warranting further investigation.

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