A CASE OF SEVERE VERAPAMIL INTOXICATION

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ABSTRACT

Introduction: Verapamil is a potent calcium channel blocker (CCB) used to treat a variety of common cardiovascular abnormalities including hypertension, angina pectoris and supraventricular arrhythmias. The principal effects of verapamil are on the cardiovascular system where it decreases atrioventricular conduction and has a negative inotropic effect.

Case report: A 33-year-old woman was admitted to the emergency department due to an intentional overdose of verapamil. She appeared to be lethargic and developed hypotension, A-V dissociation and circulatory failure. She recovered with the appropriate use of symptomatic and supportive therapy.

The patient received a total of 24 g of calcium gluconate within 24 hours. Smaller amounts of calcium gluconate (1 to 2 g) or larger doses over prolonged periods of time (24 g in 44 hrs) have been administered in other cases described in the literature.

Conclusions: Large doses of calcium are effective and safe in the treatment of verapamil intoxication when given continuously with adequate monitoring.

Key words: intoxication, verapamil, calcium gluconate

SAŽETAK

Uvod: Verapamil kao lek iz grupe blokatora kalcijumskih kanala, blokira ulazak kalcijuma u čeliju. U akutnom trovanju verapamilom se potenciraju njegovi farmakološki efekti na kontraktilnost i sprovođenje u miokardu.

Prikaz slučaja: Pacijentkinja stara 33 godine, primljena je u Centar za urgentnu medicinu somnolentna, hipotenzivna, bradikardična sa atrioventrikularnom disocijacijom. Uspešan medikamentozni tretman doveo je do povoljnog ishoda.

Zaključak: Navedeni prikaz slučaja smatramo važnim jer u nama dostupnoj literaturi nije opisana primena tako visoke doze kalcijuma u kratkom vremenskom periodu, koja je dala povoljan efekat u trovanju verapamilom.

Ključne reči: trovanje, verapamil, kalcijum-glukonat.

Abbreviations

A-V – Atrio-ventricular
CCB – Calcium channel blocker

Skracenice

A-V – Atrio-ventrikularni
CCB – Blokatori kalcijumovih kanala

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INTRODUCTION

Verapamil belongs to the group of calcium channel blockers. These drugs lock the entry of calcium into cells through slow L-type calcium channels during the excitation-contraction phase in smooth muscles and have inhibitory actions on smooth muscles in the heart, blood vessels and the entire heart conducting system. In a normal cell, the concentration of free calcium ion is rather low compared to the concentration in extracellular liquid.

Verapamil is well-absorbed after oral intake, but its bioavailability is only 10-20% because of intense metabolism after its first passage through the liver. With liver insufficiency, the bioavailability goes up to 90%. Approximately 90% of the injected dose is bound to plasma protein. The elimination half time of verapamil is 3 to 8 hours. Norverapamil, a verapamil metabolite, has 20% of the pharmacological activity of verapamil \(^1,2\) and is eliminated primarily through the kidneys. The main effect of verapamil is on conduction in the heart, causing a depression of sinoatrial node and a decrease in atrioventricular conduction. The effect on myocardium and peripheral blood vessels is less pronounced.

With acute verapamil intoxication, the pharmacological effects on contraction and conduction in myocardium are highly emphasised. There is also an effect on the central nervous system. Ingestion of 3 or more grams of verapamil causes serious disorders: conduction disorders in A-V node progressing to A-V dissociation, hypotension, impairment of consciousness, convulsions and breathing disorders. Hyperglycaemia often occurs as a result of decreased insulin release from beta cells in the pancreas, a process dependent on calcium input through slow calcium channels \(^1\). In treating oral poisonings, gastric lavage is process dependent on calcium input through slow calcium channel blockers. These drugs lock the entry of calcium into cells through slow L-type calcium channels during the excitation-contraction phase in smooth muscles and have inhibitory actions on smooth muscles in the heart, blood vessels and the entire heart conducting system. In a normal cell, the concentration of free calcium ion is rather low compared to the concentration in extracellular liquid.

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CASE REPORT

A 33-years-old female patient was admitted to the Emergency Department due to verapamil intoxication. The precise circumstances of poisoning are unknown, but family members confirmed an oral intake of verapamil a few hours prior to admittance. She was drowsy, hypotensive (60/40 mmHg), bradycardic (32 beats per minute) and eupneic, with normal appearance and weight. Cardiac action was rhythmic with low tones. Physical examination did not reveal other abnormalities. ECG showed AV block of the third degree with ventricular frequency 32/min. After admission, the patient’s stomach was lavaged and activated charcoal was administered. The laboratory analyses showed hyperglycaemia (13.9 mmol/l), leukocytosis (13.0x 10^9 /l), hypokalemia (3.4 mmol/l) and metabolic acidosis (pH 7.32, HCO3 14.9 mmol/l, BE -11.2 mmol/l). The chest x-ray was normal. The patient was transferred to the intensive care unit and constantly monitored for vital functions.

An hour after admittance, the patient’s blood pressure rapidly dropped due to asystole, cardiac shock and respiratory arrest. An aggressive therapy, including cardiopulmonary resuscitation, intubation and multiple pharmacological agents, resulted in a positive outcome. In the next two hours, repeated administration sets of calcium gluconate, atropine, adrenaline and dopamine infusions, resulted in normalisation of blood pressure (80/30 mmHg to 100/45 mmHg). Heart frequency varied from 55/min to 60/min.

After five hours, arterial blood pressure and heart frequency normalised and remained stable until the end of hospitalisation. Sixteen hours later, the endotracheal tube was removed and the patient appeared to be conscious and able to speak. It was revealed later that, in an attempt to kill herself, the patient swallowed 50 tablets of verapamil (80 mg each). During the recovery, ECG showed an AV block of the first degree followed by sinus rhythm with negative T waves in V₁-V₂ and, later, in V₂-V₃.

DISCUSSION

It is always a challenge to treat patients with severe verapamil intoxication. Initial decontamination and supportive measures with intravenous use of calcium and vasoconstrictors are basic principles of treatment. Such a therapy improves haemodynamics and metabolic efficiency. One of the first measures in hypotensive patients is adequate restitution of plasma volume. Gastric lavage and administration of activated charcoal may be considered in patients admitted up to 6 to 8 hours after ingestion \(^1,2\). This particular patient was admitted 5 hours after the intake of 4 g of verapamil. After admittance, gastric lavage was performed and activated charcoal was administered (1 g/kg BW).

The patient was diagnosed with hypotension and bradycardia at admittance; cardiac shock occurred later. Haemodynamic variables change according to verapamil dose. Approximately 45% of patients who swallow 2 g of verapamil develop hypotension and shock, but 100% of patients with an intake over 2 g show these same changes. Patients have died after doses of 1.4, 2.4 and 2.8 g, while a recovery was described in a patient who had taken 6 g \(^3\).

Co-ingestion of verapamil with beta blockers could lead to significant intoxication \(^5\). The lethal and toxic doses of calcium channel blockers in humans have not been defined precisely. Conclusions on a toxic dose have been approximated from descriptions of intoxication cases \(^6\). One case described a patient who had taken 9.6 g of verapamil, developed cardiac shock and third-degree A-V block, but recovered after adequate supportive therapy \(^4\).

Due to bradycardia, atropine was given to the patient in repeated doses of 5 mg. Atropine increased heart rate from 55 to 77 beats per minute. However, other studies have shown that atropine neither increases blood pressure nor improves survival \(^7\).

Recoveries have been described after administration of orciprenalin, calcium gluconate or dopamine without an effect on blood pressure. Conversely, adrenaline infusion
Figure 1. ECG of the patient intoxicated with verapamil
amines are also an effective combination. In the treatment of our patient, total amounts of 17 mg of adrenaline and 24 g of calcium gluconate with dopamine were administered. Some reference books have described that the administration of 18 g of calcium gluconate within three hours resulted in a positive outcome, while others have used significantly lower (1-2 g) or higher doses, but in longer periods of time (e.g. 24 g in 44 hours). Some authors suggest concomitant administration of calcium gluconate and NaCl, because of a better exchange of sodium and calcium ions, and the addition of digoxin to atropine. There is no agreement in the literature about optimal dosage of intravenous calcium. Some surveys recommend a dose of 1 g calcium chloride every 15 to 20 minutes up to a total amount of 4 g. Others suggest 1 g every 2-3 minutes up to the maximum effect. The rest claim that the best effects can be achieved by continuous calcium infusion. Recent studies on verapamil intoxication in dogs have shown that the administration of calcium with digoxin had a useful effect on systolic pressure, but monotherapy with calcium was effective only in intoxications with low doses of verapamil. Calcium and sympathicomimetic amines are also an effective combination.

The atrioventricular block is present in 82% of verapamil intoxication cases, but there is no correlation between ingested dose and the disturbance in atrioventricular conduction. Those could be seen even with ingested doses below 1 g. In 90% of cases, an AV block of the third degree appears, while AV blocks of the first and second degree are present in 10% of cases. A full recovery to the normal sinus rhythm occurs within 5-48 hours. One patient with a severe intoxication experienced hypotension and AV block of the third degree for 48 hours.

Atropine is a potentially useful intervention for bradycardia associated with an overdose of calcium-channel blockers. Initial treatment with doses of 0.5 to 1 mg of atropine, every two to three minutes up to a total of 3 mg, may be given. Use of transthoracic and intravenous cardiac pacing to increase heart rate has been successful in patients with an overdose of a calcium-channel blocker. However, two primary limitations have been noted: 1) the failure to capture, and 2) the failure to increase blood pressure, despite successful increases in heart rate. As a last effort in cases in which other treatments have failed, mechanical support with the use of intra-aortic balloon counterpulsation or even extracorporeal bypass should be considered. Because the inotropic failure resulting from an overdose of calcium-channel blockers is generally transient (lasting less than 72 hours), invasive mechanical support and even extracorporeal bypass can be lifesaving and return a patient to his or her previous level of functioning.

Cases of CCB-poisoned patients who failed to respond to fluids, calcium, or dopamine and dobutamine, but had significant increases in both heart rate and blood pressure after glucagon administration, have been reported. Glucagon has significant inotropic and chronotropic effects.

CONCLUSION

In this case, a favourable effect was reached; a serious acute verapamil poisoning was cured using high doses of calcium gluconate with nonspecific detoxification, symptomatic and supportive therapy. From this case, one can learn that large doses of calcium are an effective and safe treatment of verapamil intoxication when given cautiously and with adequate monitoring.

REFERENCES