

CARDIODEPRESSIVE SYNDROME AFTER DILTIAZEM OVERDOSE

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REZUMAT

Sindromul cardiodepresiv secundar intoxicației acute cu blocați de calciu este destul de rar întâlnit în practica medicală, dar are o mortalitate crescută comparativ cu alte tipuri de intoxicații. Tratatamentul intoxicației acute cu blocați calcici trebuie să fie agresiv și aplicat cât mai rapid din momentul prezentării la medic, pentru a reduce cât mai mult mortalitatea. Prezentăm cazul unui pacient de 64 ani, care a luat o supradoză de 4,2 g diltiazem cu eliberare imediată. A fost adus la spital la 3 ore de la ingestie, de către soție, prezentând hipotensiune, bradicardie și alterarea stării de conștiență. S-a instituit imediat umplere volemică, s-a administrat gluconat de calciu intravenos, atropină și dopamină în perfuzie, fără redresarea tensiunii arteriale și a frecvenței cardiace. A necesitat cardiostimulare temporară pentru o perioadă de 48 de ore, cu o evoluție ulterioară favorabilă.

Cuvinte cheie: diltiazem, blocați calcici, supradoză, sindrom cardiodepresiv, cardiostimulare externă

ABSTRACT

Cardiodepressive syndrome caused by calcium channel blocker overdose is rare in practical medicine but has a higher mortality compared with other drug overdoses. The treatment in calcium channel blocker overdose should be aggressive and started at the time of presentation, in order to prevent death of patients. We present a 64 year old man with an overdose of diltiazem 4.2 g (immediate release preparation). He was brought by his wife 4 hours after ingestion with hypotension, bradycardia and altered mental status. He was treated with intravenous fluids, intravenous calcium gluconate, atropine and intravenous dopamine infusion without resetting of arterial pressure and heart rate. He required temporary cardiac pacing over the next 48 hours with favorable evolution.

Key Words: diltiazem, calcium channel blocker, overdose, cardiodepressive syndrome, external cardiac pacing

CASE REPORT

We present the case of a 64 years old male patient who was brought into the emergency department of hospital by ambulance, accompanied by his wife, 4 hours after an suicidal attempt by ingestion of 70 tablets of 60 mg diltiazem (4.2 grams). His wife told us that the patient was taking daily diltiazem for arterial hypertension and angina pectoris. He ingested the above mentioned medicines after a family dispute. Previously, he consumed alcoholic drinks. He refused to go to hospital until he entered in a state of lethargy, confusion and impossibility to walk, that determined his wife to call an ambulance and accompany him to the hospital.

The first clinical examination revealed: arterial hypotension - 60/40 mm Hg, heart rate 62/min, lethargy, confusion. Examination of other systems was normal. The admission electrocardiogram showed the presence of a sinus bradycardia.

Volume expansion fluid therapy was started with crystalloid solutions. He received 0.9% sodium chloride and Ringer lactate solution till 3000 ml. Initially, intravenous 30 mg of 10% calcium gluconate, was administered followed by two more doses of 30 mg in a 20-30 minute interval, without resetting of the arterial pressure. Hence, on a second intravenous line we started administration of vasopressor agents – dopamine hydrochloride 15 µg/kg/min. On ECG a junctional rhythm of 53 beats/min was observed, for which we associated 1 mg atropine administrations, repeated up to 2 mg.

Taking into account the presence of arterial hypotension and bradycardia, despite the ingestion of a calcium channel blocker with immediate release – diltiazem – in a large quantity (4.2 grams) and late presentation at hospital (over 4 hours after ingestion), it was decided to quickly set up a temporary transvenous cardiac pacing. Later on the evolution was favorable

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with arterial pressure and heart rate normalization. The patient was monitored in the intensive care unit for 48 hours, being discharged from hospital after four days of hospitalization.

DISCUSSION

Calcium channel blockers are cardiovascular drugs in current usage since '80 for treating arterial hypertension, cardiac arrhythmias, and hypertrophic cardiomyopathy.^{1,2}

There are three large classes of calcium channel blocker that differ by their chemical structure and by their binding site of slow calcium channels in cardiac and vascular smooth muscle: dihydropyridines, phenylalkylamines and benzothiazepines.^{1,3}

As for the pharmacokinetics of calcium channel blockers, they are rapidly absorbed after ingestion reaching the plasmatic peak in 20-45 minutes for immediate release preparations and in 4-12 hours for sustained or slow release preparations.^{1,3} The calcium channel blockers are well bound to the plasmatic proteins, in proportion of 70-98% and consequently the hemodialysis is not efficient in calcium channel blockers overdose.^{1,3} Their metabolization is carried out mainly by the liver by oxidative pathways.^{1,2} Calcium channel blockers elimination is mainly renal and in a small proportion through bile and faeces and it varies depending on calcium channel blockers type and on the ingested dose.^{1,3}

Calcium channel blocker overdose, although rarely encountered in practice compared with other types, bares a high lethal potential.^{1,3} The data in the literature shows a mortality of 60% of these patients in USA.^{1,2} Based on this reasons we consider it is necessary to know both the clinical manifestations and specific therapeutic measures for this poisoning in order to save as many lives as possible.

The clinical symptomatology of calcium channel blockers overdose is dominated by the presence of the cardiodepressive syndrome (bradycardia and arterial hypotension) associated with neurological (lethargy, confusion, convulsions, coma), respiratory (acute pulmonary edema, respiratory depression), metabolic (hyperglycemia, lactic acidosis) and gastro-intestinal (nausea, vomits) manifestations.

Cardiovascular toxicity is the main manifestation of calcium channel blockers overdose being represented by cardiodepressive syndrome.^{1,3} However, more often in the presence of a cardiodepressive syndrome, it is worth to consider other poisonings too: beta-blockers, digitalis or clonidine.^{1,3}

Considering all these mentioned aspects, the treatment of calcium channel blocker poisoning should be aggressive and immediately initiated at the time of presentation in order to save as many patients as possible.

In the case of asymptomatic patients, who ingested calcium channel blockers with immediate release, their hospitalization and monitoring both hemodynamically and electrocardiographic in the first 8-12 hours since ingestion is imperative.^{1,3} Some authors recommend a 24 hours supervision.^{1,2} For all the patients who ingested slow release calcium channel blocker the monitoring should be extended till 36 hours.² Many patients who are asymptomatic at presentation develop cardiodepressive syndrome shortly after their admission.^{1,3} For the asymptomatic patients the recommendations suggested by most authors are to admit all of these patients in hospital and to monitor them in the intensive care units.^{1,3}

The treatment of calcium channel blocker overdose is aiming to improve the cardiac contractility, to increase the heart rate and consequently to improve tissue perfusion.^{1,5} There is no drug administration considered safe and efficient in severe forms of calcium channel blocker poisoning. For these cases the most important thing to do is an emergency application of supportive measures for preserving vital functions.^{1,3}

The pharmacological therapy of calcium channel blockers overdose is a "step" therapy that usually starts by intravenous calcium administration, considering that the calcium entering the cells could improve the myocardial contraction. Most authors recommend calcium doses of 1-2 g, but there are cases in the literature where huge quantities were administrated reaching 13-14 g of calcium.^{1,5} However, calcium administration doesn't always determine improvement of hemodynamic parameters. Before intravenous calcium administration, it is mandatory to exclude digitalis overdose that could determine the appearance of certain fatal arrhythmias.^{1,3}

The next pharmacological step in therapy is represented by vasopressors administration, most used being dopamine hydrochloride by intravenous infusion (10-20 µg/kg/min) that increases arterial pressure as well as heart rate.^{1,3}

If no hemodynamic improvement is observed, glucagon is another therapeutic agent that could increase cardiac contractility and dromotropism by stimulating adenilatcyclase, increasing the quantity of intracellular cAMP. The starting dose is 3 mg of glucagon, in slow intravenous administration. The dose can be increased till no more than 15 mg, if no

response is obtained.¹⁻³

Another pharmacological agent recommended is amrinona, a positive noncatecholaminergic inotropic agent that inhibits phosphodiesterase.¹⁻³

Recently, some authors showed that a good effect on the arterial hypotension determined by calcium channel blockers overdose could be obtained by large doses of intravenous insulin administration in doses of 0,1 U/kg with glucose, aiming to increase the carbohydrate metabolism in the heart and increase the cardiac contractility.^{2,3,6} The mechanism by which intravenous insulin administration in large doses can influence the cardiodepressive syndrome in calcium channel blockers overdose is not completely understood. It is known only that calcium channel blockers inhibit insulin release from pancreatic cells.^{1-3,6}

Among the decontamination measures, gastric lavage is recommended if the patient reaches the hospital in the first two hours from the ingestion or whole bowel irrigation for the patients who ingested slow release calcium channel blockers.¹⁻³

Usually, pharmacologic measures are not efficient in severe poisoning cases and the setting of a temporary cardiac pacing or even the insertion of an intraaortic balloon pump device is mandatory in order to save the patient's life.¹⁻³

Our patient was admitted three hours after immediate release diltiazem preparation ingestion with cardiovascular toxicity manifestations (arterial hypotension, bradycardia and later on junctional

rhythm). In the first step pharmacological therapy with intravenous calcium administration, volume expansion fluids and later on dopamine and atropine was tried, without resetting of the arterial pressure and heart rate. Taking into account the high mortality rate determined by calcium channel blockers overdose, the involvement of an immediate release preparation, the large time span from the ingestion moment and the alcohol consumption which enhanced drug absorption, we considered suitable to set up a temporary cardiac pacing in due time to save the patient's life. In our opinion, this represents the only method that could improve the prognostic of these patients, and is worth using as early as possible, in cases where the cardiodepressive syndrome manifestations are not rapidly remitted under pharmacological therapy.

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