Calcium channel blocker poisoning

(Zatrucie blokerami kanału wapniowego)

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Abstract – Calcium channel blocker poisoning is relatively frequent and it is life-threatening. The study presents epidemiological data concerning calcium channel blocker poisoning, the clinical symptoms of such a poisoning, basic methods of treating patients with calcium channel blockers available to emergency response teams. The treatment involves the elimination of the unabsorbed drug, by a specific antidote (calcium chloride in large doses of up to 10 or 20 ampoules, intravenously). The use of volume expanders, administering catecholamines during the shock, cardiac stimulation, intubation and mechanical ventilation in the case of respiratory failure play important role in the treatment.

Key words - poisoning, calcium channel blockers.

Authors’ contributions to the article:
A. The idea and the planning of the study
B. Gathering and listing data
C. The data analysis and interpretation
D. Writing the article
E. Critical review of the article
F. Final approval of the article

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I. INTRODUCTION

Calcium channel blocker poisoning is frequent and it can be life-threatening. It is the most prevalent reason of death due to vascular drug poisoning. According to the records of the American Association of Poison Control Centers, 20% of all deaths due to a drug poisoning involved an amlodipine poisoning [1].

In the case of a single-dose poisoning in children, the study by Hetterich et al. did not observe severe poisonings [2] but other authors reported lethal poisoning of children with a single dose of a drug [3]. However, the assessment of the numbers of the tablets taken can be difficult and what has initially been considered one dose of a drug can result in death [4]. Calcium channel blocker poisoning is often unintentional [3], which makes the diagnosis difficult.

In the case of adults, some cases have been reported that the poisoning had been caused by taking 1 tablet more than the standard daily dose set for the patient [3].

Calcium channel blockers can be divided into 2 groups according to their target: bipyridine derivatives (they mainly expand vessels) and non-bihydropyridine derivatives (they mainly slow down cardiac activity and atrioventricu-
lar conduction and they reduce cardiac muscle contraction). However, it should be noted that in the case of large doses, the drugs lose their selectivity [5].

II. THE REASONS OF UNINTENTIONAL CALCIUM CHANNEL DRUG POISONING AND THE DIFFICULTIES RELATED TO THE DIAGNOSIS

Many drugs are manufactured under different names. Nowadays in particular, a change of the drug by a pharmacist at a pharmacy involves the risk of double dosing by the patient. For this reason, information concerning the drug poisoning can be difficult to obtain. Calcium channel blockers belong to 2 groups with different targets:
- bipyridine derivatives: amloppynine (preparations: Amlozex, Amlodip, Aldan, Norvasc, Normodypine);
- nifedipine (Plendil), lacidipine (Lacipil);
- nitrendipine (Nitrendipine), niphedipine (Cordafen), lecardipine (Primacor, Lecalpin)
- non-bipyridine derivatives: verapamil (Isoptin, Staveran), diltiazem (Dilzem, Oxycardil).

Calcium channel blockers are also present in many combination drugs used in arterial hypertension treatment. Toxic dose of calcium channel blockers can be small, particularly in elderly persons, persons drinking regularly large quantities of grapefruit juice, and in patients with kidney and liver diseases [6]. Publications describe cases of a calcium channel blocker poisoning due to the intake of 1 additional dose of a drug by a patient chronically treated with such drugs. The poisoning can also be caused by drinking a large quantity of grapefruit juice, which hinders the metabolism of enzymes participating in the elimination of calcium channel blockers, which results in the increase of the concentration of these drugs in plasma [6].

In each case when there is a suspicion of a calcium channel blocker poisoning, even if it is thought that only a small dose has been taken, the patient must be transported to an emergency department and then possibly to an acute poisoning centre [3,7].

If 6 hours have elapsed from the intake of immediate-release drugs, or 18 hours in the case of prolonged release calcium channel blockers other than verapamil, or 24 hours in the case of verapamil preparations with prolonged action, and the patient does not have haemodynamic disorders, the risk of severe consequences of the poisoning is negligible. In publications, however, there are descriptions of cases of much-delayed beginning of severe haemodynamic disorders in the case of prolonged-release drug forms [9]. Therefore, with no haemodynamic disorders, every patient has to be observed – for at least for 24 hours or longer – if he or she has taken prolonged-release drug forms.

In the case of elderly persons, an unintentional calcium channel blocker poisoning [taking the drug due to negligence, taking an additional dose due to feeling unwell] is often misdiagnosed [3].

III. CLINICAL SYMPTOMS OF CALCIUM CHANNEL BLOCKER POISONING

Calcium channel blocker poisoning can lead to the occurrence of a number of clinical symptoms from severe weakness, a collapse, sweating, nausea and vomiting, hypotension, up to a hock and acute cardiopulmonary arrest in the pulseless electrical activity [7,10,11]. The lack of symptom does not mean the lack of poisoning if the intake of the drugs took place recently, since in the case of the prolonged-action preparations, the symptoms of an acute poisoning can occur even 24 hours after the drug intake.

Hypotension is the most frequent symptom of calcium channel blocker poisoning and, depending on its level, a collapse, disturbance of consciousness, seizure, apoplectic stroke, intestinal ischemia, renal failure, coma, and death can occur in its course.

IV. PHYSICAL EXAMINATION

During physical examination of a patient with a calcium channel blocker poisoning, disturbances of consciousness of various degrees can be observed: from dozing to a deep coma. The patient's breathing is accelerated, the heart rate can be accelerated or slowed down, arterial pressure is reduced. A typical situation involves well-perceptible peripheral pulse despite low arterial pressure.

Clinical symptoms in the initial phase of a poisoning depend on the type of drugs; at the later stage, with larger doses, the specificity of the drug action in relation to the types of calcium channels is decaying, which can result in a bradycardia in the course of an amlodipine poisoning [13].

In the course of a verapamil poisoning, a non-cardiogenic lung oedema can occur, whose mechanism is unclear [14].

V. ELECTROCARDIOGRAPHIC TEST

An electrocardiographic test can display a sinus tachycardia, a junctional rhythm, a low atrial rhythm, a junctional rhythm, an atrioventricular rhythm, a right bundle branch block [13,15].
VI. LABORATORY TESTS

Gasometry
A gasometrical test can display metabolic acidosis with compensatory hypocapnia due to hyperventilation [16]. In the states of acute respiratory failure, the acidosis can be of mixed origin: metabolic and respiratory, with the increase of carbon dioxide pressure.

Calcium level
Hypocalcaemia is rarely diagnosed in the case of a calcium channel blocker poisoning; however, its occurrence can make one suspect a poisoning with the said drugs in the case of unclear medical history and the lack of other causes leading to hypocalcaemia [17].

Glycaemia
As a result of a calcium channel blocker poisoning, hyperglycaemia can occur due to the blocking of insulin release from the pancreatic islets by the drugs in question [5].

VII. THERAPEUTIC TREATMENT

Monitoring and maintaining the patient's vital function is the fundamental task of the emergency response team. Other important tasks involve gathering information significant for the determination of the further procedure and the ways of treatment. In the case of a drug poisoning, the possible or accurate dose of the drug taken should be determined, as well as its type and other drugs taken. If earlier electrocardiograms are available, they should be brought with the patient.

The patient should be monitored throughout the transport.

The patient poisoned with calcium channel blockers should be evaluated not only in terms of the occurrence of the poisoning and the need of treatment but also in terms of possible psychical disorders and the necessity to prevent another suicidal attempt.

Therapeutic treatment in patients with calcium antagonists poisoning
Removal of the unabsorbed substance, administering specific antidotes and symptomatic treatment counteracting the effects of the poisoning comprise the main treatment directions in the case of a patient with a calcium channel blocker poisoning (Table 1) [16,19]. Before gastric lavage, the unconscious patient should be intubated so as to secure him/her against aspiration [3,7,10,11].

Table 1. Therapeutic treatment

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>the removal of the poison eaten</td>
<td>gastric lavage</td>
</tr>
<tr>
<td>the reduction of the poison absorption</td>
<td>activated carbon</td>
</tr>
<tr>
<td>the use specific antidotes</td>
<td>calcium chloride</td>
</tr>
<tr>
<td>symptomatic treatment</td>
<td>intubation and ventilation fluid</td>
</tr>
<tr>
<td></td>
<td>therapy</td>
</tr>
<tr>
<td></td>
<td>catecholamines</td>
</tr>
<tr>
<td></td>
<td>glucagon</td>
</tr>
<tr>
<td></td>
<td>cardiac stimulation</td>
</tr>
<tr>
<td></td>
<td>sodium carbonate</td>
</tr>
</tbody>
</table>

Table 2 presents the rules of dosing the drugs used in the treatment of a calcium channel blocker poisoning.

Table 2. Dosage of the drugs used in the case of a calcium channel blocker poisoning

<table>
<thead>
<tr>
<th>activated carbon</th>
<th>form</th>
<th>dose</th>
<th>Adult person, 80 kg of weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>powder</td>
<td>1 g/kg b.w.</td>
<td>80 g</td>
</tr>
<tr>
<td>Fortrans</td>
<td>74 g sachet</td>
<td>1 litre of solution per 15-20 kg b.w.</td>
<td>4 sachets in 4 litres of water</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>amp. 10 ml</td>
<td>2-4 amp. within 5 minutes, the dose is repeated depending on the clinical status</td>
<td>2-4 amp. to be repeated up to the total dose of 20 amp. during resuscitation up to 13 amp.</td>
</tr>
<tr>
<td>Glucagon</td>
<td>amp. 1 g</td>
<td>adults 5-10 g intravenously and an infusion 2-10 g/h</td>
<td>5-10 amp. intravenously then an infusion 2-10 amp./h</td>
</tr>
<tr>
<td>Dopamine</td>
<td>amp. 200 mg in 5 ml [4%]</td>
<td>15-25 micrograms/kg b.w./min;</td>
<td>after diluting 1 amp. 4% in 50 ml of NaCl in a pump at the rate of 25 ml/h</td>
</tr>
<tr>
<td>Atropine</td>
<td>amp. 1 mg 0.5 mg</td>
<td>up to 3 mg in divided doses</td>
<td>up to 3 mg in divided doses</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>amp. 1 mg</td>
<td>from 0.4 to 5 mg/hour</td>
<td>from 0.4 to 5 mg/hour</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>amp. 1 mg or 1 ml</td>
<td>from 0.4 to 10 mg/hour</td>
<td>from 0.4 to 10 mg/hour</td>
</tr>
<tr>
<td>Glucagon</td>
<td>amp. 1 g</td>
<td>5 g and infusion 1-2 g/h</td>
<td>5 amp. intravenously and an infusion</td>
</tr>
<tr>
<td>Sodium carbonate</td>
<td>amp. 10 ml 8.4% 20 mEq</td>
<td>3-5 amp.</td>
<td>3-5 amp.</td>
</tr>
</tbody>
</table>

Activated carbon – in the case of a poisoning, it is administered orally after adding water to the powder so as to obtain a suspension with the consistence of thick sour cream.
Gastric lavage is carried out using water with activated carbon. Then a full dose of the suspension is administered orally. If there are no recommendations to carry out gastric lavage [too much time has elapsed since the drug intake], the suspended carbon should be only administered orally.

**Noradrenaline** – it is particularly recommended to administer it in the case of a decrease of systolic pressure below 70 mmHg.

**Calcium chloratum** – in the co-occurrence of a digoxin poisoning, calcium salts should be administered only after lowering the digoxin level.

**Glucagon** is used in a very large dose and such a quantity of this drug is normally not available in an ambulance. Children – initial 50-150 micrograms/kg and an infusion 1-5 mg/kg b.w./h

**Sodium carbonate** – a half in bolus, the rest can be diluted in physiological saline and administered in an infusion.

**VIII. ADVANCED TREATMENT METHODS IN HOSPITAL CONDITIONS**

Endocavitary stimulation is used in hospital conditions in the case of patients with a bradycardia. In pre-hospital conditions, percutaneous stimulation is possible. Moreover, in the hospital conditions, large doses of insulin are used along with maintaining correct glycaemia by means of glucose infusions [15].

ECMO is an advanced treatment method available only in certain centres. Publications describe cases of successful application of ECMO in the treatment of a patient with a channel blocker poisoning and acute respiratory failure, in an untreatable shock [18]; however, this method is not effective in all cases and despite managing haemodynamic complications, the death of the patient can occur due to liver damage [19].

Another therapeutic alternative is plasmapheresis, which decreases plasmatic concentration of the drug in blood [20].

**IX. REFERENCES**


