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Efficacy of insulin therapy in severe poisoning with calcium channel blockers

A.Yu. Simonova[✉1,2,3], K.K. Ilyashenko[1,3], M.M. Potskhveriya[1,2], T.T. Tkeshelashvili[1], S.S. Petrikov[1]

[1]N.V. Sklifosovsky Research Institute for Emergency Medicine, 3 Bolshaya Sukharevskaya Sq., Moscow 129090 Russia;

[2]Russian Medical Academy of Continuous Professional Education, 2/1 Bldg.1 Barrikadnaya St., Moscow 125993 Russia;

[3]Lopukhin Federal Research and Clinical Center of Physical-Chemical Medicine of Federal Medical Biological Agency, 1A Malaya Pirogovskaya St., Moscow 119435 Russia

✉Corresponding author: Anastasiya Yu. Simonova, Cand. Sci. (Med.), Leading Researcher, Scientific Department of Acute Poisonings and Somatopsychiatric Disorders, N.V. Sklifosovsky Research Institute for Emergency Medicine; Assistant at the Department of Clinical Toxicology, Russian Medical Academy of Continuous Professional Education; Senior Researcher, Lopukhin Federal Research and Clinical Center of Physical-Chemical Medicine of Federal Medical Biological Agency, SimonovaAU@sklif.mos.ru

Abstract

Background. *In recent years, there has been an increased number of poisoning with drugs that mainly affect the cardiovascular system, including calcium channel blockers. According to foreign literature, insulin therapy is an effective and safe method of treating patients with severe poisoning with calcium channel blockers.*

Objective. *To demonstrate the efficacy of high-dose insulin in severe poisoning with calcium channel blockers.*

Results. *Patient T., 37 years old, took 1000 tablets of nifedipine for suicide 4-6 hours before admission to the hospital. In connection with the development of refractory shock and the ineffectiveness of basic therapy (the intravenous administration of 0.9% sodium chloride solution, calcium chloride (saturated dose), vasopressor/inotropic agents), a decision was made to administer high doses of insulin. After a bolus intravenous injection of insulin, the rate of its intravenous administration was 0.5 U/kg/h and, due to the lack of hemodynamic effect, it was gradually increased in increments of 1–2 U/kg/h at every 15–30 minutes up to a maximum of 8 U/kg/h with constant monitoring of glucose and potassium levels in the blood. As a result, the target hemodynamic parameters were achieved. Then the insulin infusion rate was gradually reduced and, upon achieving hemodynamic stabilization, its administration was stopped 2 days after the start. On the 9th day from the moment of hospital admission the patient was transferred from the Intensive Care Unit to the Acute Poisoning Department.*

Conclusions. *The presented case report shows the efficacy and expediency of using the insulin therapy in the developed refractory shock due to severe poisoning with calcium channel blockers.*

Keywords: poisoning with calcium channel blockers, acute chemical poisoning, calcium channel blockers, insulin therapy, cardiogenic shock

Conflict of interests Authors declare no conflict of interest

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ABS, acid-base status
BP, blood pressure
CCB, calcium channel blocker
ECG, electrocardiography
EchoCG, echocardiography
GCS, Glasgow Coma Scale
HR, heart rate
i/v, intravenous
ICU, intensive care unit
IL, intestinal lavage
MLV, mechanical lung ventilation
RMV, respiratory minute volume

Rationale

In recent years, there has been an increase in the case number of poisoning with drugs that are primarily used for cardiovascular indications, including calcium channel blockers (CCBs) [1–4]. In clinical practice, CCBs have a wide range of pharmacological effects: hypotensive, antianginal, antiarrhythmic, antithrombotic, antiatherogenic, being one of the maingroups of drugs in the treatment of arterial hypertension; indications for their use may include strokes, acute coronary syndrome, myocardial infarction and other diseases [5, 6]. Currently, CCBs are among the most frequently prescribed drugs for the cardiovascular system diseases [7]. Their widespread use for medicinal purposes and over-the-counter sales lead to accidental and suicidal poisonings, often accompanied by the development of severe complications and deaths [8].

Currently, there are no standard treatments that could be effective in all cases of severe CCB poisoning. Some authors note that the management tactics for patients presented with poisoning with drugs of this group should be chosen individually, based on a thorough assessment of the patient response to treatment [7].

According to world literature, insulin therapy is an effective and safe method of treating patients with severe poisoning with calcium channel blockers [2, 9–11]. However, at present there are no clear recommendations on the technique of using hyperinsulinemic-euglycemic therapy in this group of patients.

Aim. To present the example of a clinical case report demonstrating the efficacy of using high doses of insulin for severe poisoning with calcium channel blockers.

Clinical case report

Patient T., 37 years old, was admitted at the N.V. Sklifosovsky Research Institute for Emergency Medicine with a diagnosis of "Poisoning with calcium channel blockers" (T46.1 according to ICD-10). From the patient history it was known that the patient (with body weight of 100 kg) had taken 1000 nifedipine tablets (10 mg each) for the purpose of suicide 4-6 hours before admission at the hospital. At the prehospital stage, gastric lavage using a tube, and fluid therapy were performed. Blood pressure (BP) was recorded at 90/60 mm Hg, heart rate (HR) was 105 per minute. During transportation, a decrease in blood pressure to 75/40 mm Hg was noted, for which the administration of norepinephrine was started at a dose of 0.3 mcg/kg/min.

At 15:35, the patient was admitted to the intensive care unit (ICU) of the Toxicology Center of the N.V. Sklifosovsky Research Institute for Emergency Medicine in an extremely severe condition: coma, mydriasis, severe acrocyanosis, absent pulsation in the main and peripheral arteries. According to the cardiac monitor, there was bradycardia with transition to idioventricular rhythm and asystole. Cardiopulmonary life support measures were initiated. The patient was intubated, and mechanical lung ventilation (MLV) was started. Continuous chest compressions were

maintained. Epinephrine (0.1%) was administered initially at a dose of 1 ml, and then 1 ml every 3 minutes (total 10 ml). Cardiopulmonary life support measures for 27 minutes led to a positive effect.

At 16:05, the patient's extremely serious condition was observed: consciousness level by the Glasgow Coma Scale (GCS) was scored as 5, SOFA score was 12, mechanical ventilation: assist control intermittent positive-pressure ventilation, inspiratory volume 600 ml, PEEP 5 mbar, respiratory minute volume (RMV) 11 L/min. Blood pressure 60/30 mm Hg, heart rate 119 beats/min, blood oxygen saturation when measured transcutaneously (SpO_2) was 93%. Norepinephrine administration was started at 2mcg/kg/min, dobutamine at 10 mcg/kg/min. There was anuria. Echocardiography (EchoCG) results were the following: dilatation of the left chambers; left ventricular global systolic function was reduced due to diffuse hypokinesis with ejection fraction 23%; signs of moderate pulmonary hypertension (pulmonary artery systolic pressure (PASP) was 37 mm Hg). Electrocardiography (ECG) showed the following: sinus tachycardia; load on the left ventricle; the ST segment elevation in chest leads V1–2, the ST segment depression in standard leads I, II, III, as well as signs of myocardial damage in enhanced avF lead and chest leads V4–6. Blood test results were as follows: pH 7.09; base excess (BE) -8.5; blood lactate 14.8 mmol/L; Hb 117 g/L; leukocytes 13.3 109/L; troponin 0.110 ng/mL. Other parameters were within reference values.

Due to the development of refractory shock and the inefficacy of basic therapy (intravenous [IV] administration of 0.9% sodium chloride solution, calcium chloride (saturated dose), vasopressor/inotropic agents), a decision was made to administer high doses of insulin. The blood glucose level was initially measured to be 32 mmol/L. Next, a bolus insulin solution was administered intravenously at a dose of 1 U/kg (100 U). After this, intravenous administration of insulin 0.5 U/kg/hour diluted

in 0.9% sodium chloride solution was started (Figure). The administration of calcium chloride was continued under the control of the blood level of ionized calcium and vasopressor/inotropic agents. Meanwhile, there was no improvement in hemodynamic parameters: blood pressure was 60/30 mm Hg. Due to the lack of effect and the extremely serious condition of the patient, after 15 minutes it was decided to increase the dose of insulin to 1 U/kg/hour.

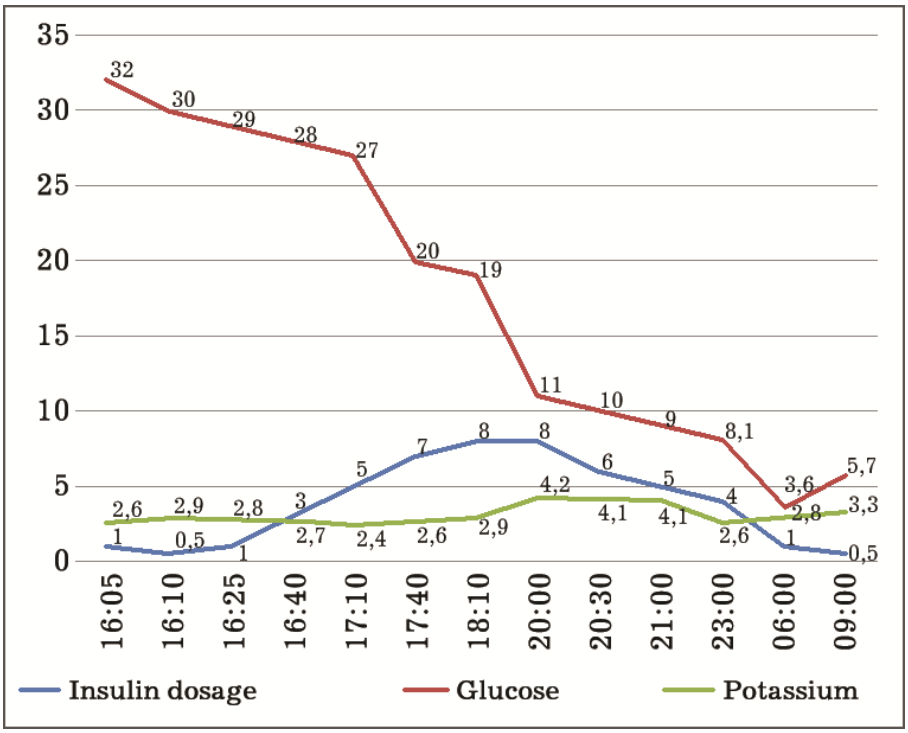

Figure. Dynamics of insulin dosage, blood levels of glucose and potassium

Continuous hemodynamic monitoring was carried out, as well as monitoring of the blood levels of glucose, potassium, and calcium (every 30 minutes). Due to the lack of effect, the insulin infusion rate was increased to 3 U/kg/hour after 15 minutes, and to 5 U/kg/hour after another 30 minutes. In this case, the glucose solution was not administered due to hyperglycemia. The administration of calcium

chloride, norepinephrine, dobutamine, and potassium chloride was continued. Anuria was noted. Hemodynamic stability was not achieved. After 30 minutes, it was decided to increase the insulin infusion rate to 7 U/kg/hour, and to 8 U/kg/hour after another 30 minutes. After 15–30 minutes, blood pressure became 95/55 mm Hg, heart rate was 109 beats/min. The volume of urine was 200 mL. Acid-base status (ABS) in blood showed pH 7.27, BE -5, blood lactate level 8.1 mmol/L, potassium 4.2 mmol/L. After hemodynamics stabilization, ABS monitoring continued every hour. After reaching blood pressure of 110/60 mm Hg (mean arterial pressure 77 mm Hg), we began to gradually reduce the rate of insulin infusion, while simultaneously reducing the doses of norepinephrine and dobutamine. At 21:00, the insulin infusion rate was 5 U/kg/hour, blood glucose was 9 mmol/L, and potassium was 4.1 mmol/L. We continued to reduce the infusion rate of insulin and cardiotonics. At the same time, a solution of 10% glucose was administered at a rate of 100 ml/h under the control of blood glucose levels. Intestinal lavage (IL) was started for detoxification purposes. At 23:30, the ABS was as follows: pH 7.36, BE -1, blood lactate 5.5 mmol/L, potassium 2.6 mmol/L, blood glucose 8.1 mmol/L.

By 10:00 o'clock the next day, the patient’s level of consciousness had recovered to score 14 by GCS; the mechanical ventilation continued (FiO_2 60%, SPO_2 98%, in SIMV mode, VC + PS (volume control + pressure support); inspiratory volume: 575 mL, forced inspirations rate was 8/min, pressure support level (PS, ASB) 10 mbar, PEEP 6 mbar, respiration rate 15 breaths per minute, RMV 9 L/min). Norepinephrine was administered at 0.45 mcg/kg/min, dobutamine at 5.0 mcg/kg/min, insulin at 0.5 U /kg/hour. Blood pressure was 114/70 mm Hg, heart rate was 93 beats/min, ECG showed sinus tachycardia. Ejection fraction at echocardiography was 57%. The IL procedure was completed, bulky

loose stool was obtained. One day later, the administration of insulin and vasopressor/inotropic drugs was discontinued once the hemodynamics stability had been achieved. After completion of insulin therapy, monitoring of blood glucose and potassium levels was continued. The level of glucose in the blood varied during the day within the range of 4.5–8.4 mmol/L, that of potassium between 3.3–5.2 mmol/L. Due to the development of complications (purulent tracheobronchitis, bilateral polysegmental pneumonia), the patient continued treatment in the ICU. On the 9th day from hospital admission, the patient was transferred to the Acute Poisoning Department for further treatment. The patient was then discharged home from hospital in satisfactory condition.

Discussion

The efficacy of insulin therapy in cardiogenic shock can be accounted to several mechanisms. Insulin in large doses is an inotropic drug, causing vasodilation, improving microcirculation and systemic hemoperfusion [7, 12]. Insulin acts as a vasodilator enhancing the function of endothelial nitric oxide synthase; its administration corrects microvascular disorders and leads to an increase in cardiac output [9]. Insulin also ensures the glucose absorption by cardiomyocytes, which is the preferred energy substrate for the heart during stress. In addition, the administration of exogenous insulin compensates for its deficiency in case of CCB poisoning [12]. An overdose of CCBs leads to hyperglycemia and ketoacidosis due to their toxic effect on L-type calcium channels in the pancreas beta cells, preventing the release of insulin [13, 14]. There are data that the degree of hyperglycemia correlates with the severity of poisoning [10]. The presence of hyperglycemia is a factor of differentiated diagnosis between the CCB poisoning and β-blocker poisoning [7].

Currently, there is no consensus on when to start administering high doses of insulin, and there is no clear algorithm for insulin therapy with regard to the severity. Most investigators state that only if the administration of calcium supplements and vasopressor/inotropic agents is ineffective, it is necessary to initiate the administration of high doses of insulin [1]. A number of experts note that it is advisable to administer insulin before vasopressor therapy due to the significant efficacy of this method [9, 15]. There are no randomized controlled trials in humans comparing the efficacy of insulin therapy with that of vasopressors. Some clinical observations and experimental studies have shown that insulin therapy controls hemodynamic instability faster than the administration of cardiotonics [16]. An insulin dose of 1 to 10 U/kg/hour is considered effective; in some cases, in order to stabilize hemodynamics, it was successfully used at a dose of 22 U/kg/hour [12]. The standard insulin therapy regimen is its administration in an initial i/v bolus dose of 1 U/kg followed by i/v infusion of the drug at a rate of 0.5 U/kg/hour, which can be increased due to the lack of effect, according to some authors, during 15–60 minutes from the start of therapy [2, 9, 11]. It must be titrated until hypotension is coped with or until the maximum dose of 10 U/kg/hour is reached. If necessary, in order to maintain normoglycemia throughout insulin therapy and for 24 hours after its completion, a 5–10% glucose solution should be administered [12]. The target values are: the mean arterial pressure more than 65 mm Hg, systolic blood pressure more than 90 mm Hg, diuresis 1–2 mL/kg [1].

In our clinical case, the patient sustained poisoning with a drug nifedipine from the CCB class of dihydropyridines. It is known that nifedipine is rapidly absorbed from the gastrointestinal tract, its binding to proteins is 92–98%, its half-life is about 2 hours, and clinical symptoms of poisoning appear after 0.5–2 hours [7, 17]. Upon hospital

admission, the patient was in refractory shock: the blood pressure was 60/30 mm Hg.

Insulin therapy was started because the treatment with administering calcium chloride and vasopressor/inotropic agents appeared ineffective. After a bolus injection of insulin, the rate of intravenous administration was 0.5 U/kg/hour, and then, due to the lack of hemodynamic effect, it was gradually increased in increments of 1–2 U/kg/h at every 15–30 minutes to a maximum of 8 U/kg/hour. Administration of this dose of insulin made it possible to achieve the target values of hemodynamic parameters. The blood levels of potassium and glucose were monitored every 30 minutes in the first hours. Hypokalemia up to 2.4 mmol/L was noted. It is known that the decrease in the blood level of potassium occurs as a result of its moving into the cellular space, rather than a decrease of its total concentration in the body. In one of the largest review of clinical case reports, mild to severe hypoglycemia without neurological sequelae and mild hypokalemia without cardiac arrhythmia were reported in 73% and 82% of cases, respectively. The impairments were quickly controlled [11]. In our clinical case, the initial glucose level was high 32 mmol/L, which is typical for CCB poisoning. After 4 hours, the blood glucose level dropped to 9 mmol/L, as a result of which the glucose infusion was started simultaneously with the insulin administration. No hypoglycemia was noted.

The issue of insulin therapy discontinuation is controversial among clinicians; there is no consensus on this matter. Some authors believe that insulin should be withdrawn by tapering (within up to several days) with achieving the following parameters: mean arterial pressure more than 65 mm Hg, control of lactic acidosis and improvement in the level of consciousness [1, 9]. A number of reports indicate that the target values

are: a heart rate of 50 beats/min or more, systolic blood pressure 100 mm Hg. [2, 18]. In our case, we began to reduce the insulin infusion rate when hemodynamic stability was achieved, simultaneously with a decrease in the doses of vasopressor/inotropic drugs.

A number of authors emphasize that medical personnel should be informed about the advisability of administering high doses of insulin to severe patients with CCB poisoning in order to avoid premature cessation of therapy and its adverse consequences in the form of re-development of hemodynamic disorders [1].

Conclusion

The clinical case report we have presented shows the efficacy and feasibility of using insulin therapy in the refractory shock developed due to severe poisoning with calcium channel blockers.

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Information about the authors

Anastasia Yu. Simonova, Cand. Sci. (Med.), Leading Researcher, Department of Acute Poisonings and Somatopsychiatric Disorders, N.V. Sklifosovsky Research Institute for Emergency Medicine; Assistant of the Department of Clinical Toxicology, Russian Medical Academy of Continuous Professional Education; Senior Researcher, Lopukhin Federal Research and Clinical Center of Physical-Chemical Medicine of Federal Medical Biological Agency, https://orcid.org/0000-0003-4736-1068, SimonovaAU@sklif.mos.ru

35%, development of the study concept and design, collection and processing of material, data analysis and interpretation, writing the article

Kapitalina K. Ilyashenko, Prof., Dr. Sci. (Med.), Scientific Consultant, Department of Acute Poisonings and Somatopsychiatric Disorders, N.V. Sklifosovsky Research Institute for Emergency Medicine; Leading Researcher, Lopukhin Federal Research and Clinical Center of Physical-Chemical Medicine of Federal Medical Biological Agency, https://orcid.org/0000-0001-6137-8961, IlyashenkoKK@sklif.mos.ru

25%, development of the study concept and design, drafting the manuscript,

Michael M. Potskhveriya, Dr. Sci. (Med.), Head of Scientific Department of Acute Poisonings and Somatopsychiatric Disorders, N.V. Sklifosovsky Research Institute for Emergency Medicine; Associate Professor, Department of Clinical Toxicology, Russian Medical Academy

of Continuous Professional Education, https://orcid.org/0000-0003-0117-8663, PotskhveriyaMM@sklif.mos.ru

15%, data analysis and interpretation, text editing

Tengiz T. Tkeshelashvili, Head of Critical and Intensive Care Unit for Emergency Detoxification, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0003-4990-1363, TkeshelashviliTT@sklif.mos.ru

15%, data analysis and interpretation

Sergey S. Petrikov, Corresponding Member of the Russian Academy of Sciences, Dr. Sci. (Med.), Director of N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0003-3292-8789, PetrikovSS@sklif.mos.ru

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