Translated by E.V. Trushina

**Review**

**https://doi.org/10.23934/2223-9022-2024-13-2-269-279**

# A Modern View on the Treatment for Acute Calcium Channel Blocker Poisoning

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**BACKGROUND** At the beginning of the 21st century, the structure of acute exotoxicoses changed, in particular, an increase in poisoning by drugs that mainly affect the cardiovascular system, including calcium channel blockers, was noted. Currently, there is no clear treatment algorithm for this group of patients.

**AIM OF STUDY** To evaluate the effectiveness of methods for the treatment of acute calcium channel blocker (CCB) poisoning according to the literature.

**MATERIAL AND METHODS** The search for domestic publications was carried out in the eLibrary database, foreign ones - in the MEDLINE/PubMed, Google Scholar databases for the period from 2010 to February 2022, as well as among previously published works that have no modern analogues. The terms used as a search query were according to the official MeSH terms: “calcium channel blockers” OR “Blockers, Calcium Channel” OR “Calcium Channel Antagonists” AND “poisoning”.

**RESULTS** This review contains information about the mechanism of action, clinical picture, diagnosis of calcium channel blocker poisoning, as well as the results of using various methods of treatment for this pathology.

**CONCLUSIONS** Summarizing the data obtained, it is possible to schematically present an algorithm for the treatment of patients with acute CCB poisoning. After cleansing the gastrointestinal tract and starting infusion therapy, pathogenetic treatment with the use of calcium preparations should be carried out, subsequently, in case of unstable hemodynamics, the prescription of vasopressors and inotropic drugs is indicated; and if there is no positive dynamics, insulin therapy must be added. However, it should be noted that such a scheme is indicative, reflecting the key points. In general, this problem remains open and requires further multicenter studies.

**Keywords:** calcium channel blocker poisoning, toxicology, acute poisoning, calcium channel blockers, insulin therapy
**For citation** Simonova AYu, Ilyashenko KK, Potskhveriya MM, Belova MV, Asanova LR. A Modern View on the Treatment for Acute Calcium Channel Blocker Poisoning. *Russian Sklifosovsky Journal of Emergency Medical Care.* 2024;13(2):269–279. https://doi.org/10.23934/2223-9022-2024-13-2-269-279 (in Russ.)
**Conflict of interest** Authors declare lack of the conflicts of interests
**Acknowledgments, sponsorship** The study had no sponsorship

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AV block – atrioventricular block
BP – blood pressure
CCBs – calcium channel blockers
ECG – electrocardiogram
EchoCG – echocardiography
ECMO – extracorporeal membrane oxygenation
MAP – mean arterial pressure
MB – methylene blue
cAMP – cyclic adenosine monophosphate
CTT – chemical toxicity test
CVA –- central venous access
VA ECMO – veno-arterial extracorporeal membrane oxygenation

## RELEVANCE

At the beginning of the 21st century, the structure of acute exotoxicoses changed, in particular, an increase in the number of poisonings by drugs that primarily affect the cardiovascular system, including calcium channel blockers (CCBs) was noted [1–5]. Due to their mechanisms of action, CCBs are used as antiarrhythmic, hypotensive and antianginal agents for various diseases of the cardiovascular system [6]. Over the years, they have shown high hypotensive and preventive effectiveness against cerebral strokes, acute coronary syndrome, myocardial infarction, etc. [7]. The widespread, often uncontrolled, use of CCBs for therapeutic purposes, as well as their availability for purchase without a prescription lead to accidental and suicidal poisoning, often accompanied by the development of severe complications, in some cases with fatal outcome [8].

Despite a sufficient amount of information regarding the diagnosis and treatment of patients with acute CCB poisoning, there is currently no clear algorithm for treating this group of patients in domestic and foreign literature. In this regard, we decided to analyze and systematize literature data to substantiate an integrated approach to the treatment of patients with CCB poisoning.

**Aim:** to evaluate the effectiveness of treatment methods for acute CCB poisoning according to literature data.

## MATERIAL AND METHODS

The search for domestic publications was carried out in the eLibrary database, foreign - in the MEDLINE/PubMed, Google Scholar databases for the period from 2010 to February 2022, as well as among previously published works that have no modern analogues. As a search query, we used official MeSH terms: “calcium channel blockers” OR “Blockers, Calcium Channel” OR “Calcium Channel Antagonists” AND “poisoning”. We analyzed publications describing the mechanism of action, clinical picture, diagnosis of CCB poisoning, as well as works assessing the effectiveness of various treatment methods.

### PHARMACOKINETICS AND MECHANISM OF ACTION

Drugs of the CCB group inhibit the transmembrane calcium flux by blocking L-type calcium channels. Along with this, they competitively irritate beta-adrenergic receptors, which further reduces the transmembrane flux of calcium ions by inhibiting cAMP (cyclic adenosine monophosphate) synthesis [9-11]. CCBs are divided into three groups depending on the structure and degree of affinity for a certain part of the channels.

Thus, dihydropyridines (nifedipine, amlodipine, etc.) have a high affinity for L-type channels of the vascular smooth muscles, whereas phenylalkylamines (verapamil, etc.) and benzothiazepines (diltiazem, etc.) (non-dihydropyridines) act mainly on myocardial cells [12,13]. In this regard, dihydropyridines in therapeutic doses cause vasodilation, minor myocardial depression, and may actually increase cardiac output due to reflex tachycardia [14]. Phenylalkylamines block myocardial and smooth muscle L-type calcium channels, leading to depression of the heart muscle and inhibition of electrical activity of the sinus node. Benzothiazepines have a more pronounced chronotropic effect than a vasoactive one. In case of poisoning, loss of this pharmacological selectivity may occur [15, 16]. CCBs in toxic doses block sodium channels, causing prolongation of the QRS complex on the electrocardiogram (ECG) [17].

CCBs also have a toxic effect on L-type calcium channels in pancreatic β-cells, interfering with the release of insulin. This leads to hypoinsulinemia and insulin resistance, causing hyperglycemia and ketoacidosis. The hypoinsulinemic state caused by CCBs prevents the uptake of glucose by cardiomyocytes, depriving them of the energy substrate, which further impairs cardiac contractility [14].

CCBs are well absorbed after oral administration, and are metabolized in the liver by the P450 enzyme with endogenous clearance of more than 400 ml/min [12]. All CCBs are highly bound to plasma proteins and are fat soluble drugs. The volume of distribution of verapamil is 5.5 l/kg, diltiazem - 5.3 l/kg, nifedipine - 0.8 l/kg [18].

### CLINICAL PICTURE AND DIAGNOSIS OF ACUTE CCB POISONING

The first symptoms of CCB poisoning may be nonspecific: dizziness, fatigue, weakness. The main clinical signs of intoxication are hypotension and the presence of bradycardia, as a result of decreased myocardial contractility and automatism of the sinus node, and vasodilation [14, 19]. The time of onset and duration of symptoms of poisoning depends on the CCB drug. The toxicity of CCBs when taking the regular dosage form manifests itself 20 minutes - 2-3 hours after taking the drug, and when using a prolonged release dosage form - up to 16 hours [15, 18]. It is noted that the timing of the appearance of the first symptoms of poisoning also depends on the pharmacokinetics of specific medicines. For example, in case of nifedipine, verapamil and diltiazem administration, symptoms appear after 0.5–2 hours, the half-life being from 2 to 7 hours; and when taking a second generation CCB (amlodipine), symptoms can be observed after 6–12 hours, since their half-life is 30–50 hours [18, 20]. For most drugs from the CCB group, only therapeutic concentrations are given in the available literature, and the exact toxic and lethal concentrations in blood plasma are not established. When using some CCBs for therapeutic purposes, significant interindividual differences are found associated with the age, genetic and other characteristics of patients, which may be accompanied by manifestations of toxicity [20, 21]. Thus, in elderly and senile patients, poisoning can develop when taking therapeutic doses. If there is an evidence of taking increased doses of the drug and no symptoms of poisoning, the patients should be monitored for at least 24 hours [22]. Some authors focus on the development of rapid negative dynamics, even death, in some initially stable patients [1].

It is established that phenylalkylamines (verapamil) have the most pronounced effect on cardiac conduction. Benzothiazepines (diltiazem, etc.) have a less pronounced effect in this regard; at the same time, their chronotropic and inotropic effects, capability to lower blood pressure (BP), and cause cardiogenic shock were discovered [18, 23]. Toxic doses of drugs from the dihydropyridine group are often accompanied by bradycardia instead of reflex tachycardia due to the loss of their preferential selectivity for peripheral smooth muscles [18]. Despite the decrease in blood pressure, the patients may maintain clear consciousness for a long time; however, a sharp deterioration in neurological status may also occur due to critically reduced cerebral perfusion.

In diagnostic terms, the dynamic twelve-lead ECG is of paramount importance [1, 18, 24].

Poisoning by non-dihydropyridine CCBs is usually manifested by atrioventricular block, bundle branch block, prolongation of the QT interval on the ECG; by dihydropyridines - reflex sinus tachycardia. There are indications that sodium channel blockade, causing prolongation of QRS on the ECG, increases the risk of developing dysrhythmia up to asystole [18]. Initially, sinus bradycardia is recorded on the ECG, followed by varying degrees of atrioventricular block

(AV block), as well as nodal and ventricular bradydysrhythmias; and then sinus tachycardia (nifedipine), atrial arrhythmias and transient rhythms, prolongation of the QT interval on the ECG [1].

Along with this, it is recommended to use pulse oximetry, echocardiography, hemodynamic monitoring – non-invasive or invasive (invasive blood pressure measurement, central venous access (CVA), PiCCO, etc. in severe CCB poisoning) [25]. Standard laboratory tests are indicated: determination of the gas composition and acid-base state of arterial and venous blood, electrolyte composition, general and biochemical blood tests [26]. Some authors draw attention to the advisability of determining the concentration of lactate in the blood, which also serves as a prognostic factor for death [27].

Since, as mentioned earlier, CCBs have a toxic effect on L-type calcium channels in the pancreatic beta cells, interfering with the release of insulin, this leads to hyperglycemia, ketoacidosis; and therefore it is recommended to monitor blood glucose levels [28, 29]. There are indications that the degree of hyperglycemia correlates with the severity of poisoning [30]. Moreover, some authors note that it is more pronounced in case of poisoning by diltiazem and verapamil compared to amlodipine [22, 23, 29]. The presence of hyperglycemia is a factor in the differential diagnosis of CCB poisoning and β-blocker poisoning [18].

Chemical toxicity test (CTT) of CCB level in the blood is carried out extremely rarely. Hoffman R.I. et al. note that CTT of serum concentrations of CCBs is not performed due to the complexity of this procedure [18]. According to some studies, there is a correlation between the concentration of the drug in the blood and fatal outcome [30]. Considering the above-mentioned interindividual differences in the manifestation of CCB toxicity and the increasing incidence of acute CCB poisoning, the development of methods for their chemical and toxicological detection in the biological environments of the body seems relevant. This is the subject of recent research, the results of which are used both for the diagnosis of acute poisonings, including fatal ones, and for therapeutic drug monitoring [5, 31–33].

## TREATMENT

Treatment of patients with CCB poisoning must begin with ensuring airway patency, stabilizing hemodynamics, and central venous catheter (CVC) insertion [18]. In the presence of hypotension and bradycardia, treatment should begin with the administration of atropine and infusion therapy [26].

A mandatory condition for the treatment of patients with CCB poisoning is gastric lavage, if no more than 2 hours have passed since administration of conventional forms of the drugs [15, 18]. A number of sources indicate that when lavaging the stomach, it is necessary to remember about the possible aggravation of hypotension and bradycardia due to stimulation of the vagus nerve [34]. The introduction of activated carbon (1 g/kg) is especially effective in the first hours after CCB taking, however, it is noted that its use is advisable even later [35, 36]. When taking long-acting CCBs, repeated administration of activated carbon is indicated [18]. Some authors note the need for “orogastric” lavage (administration of polyethylene glycol at a rate of 2 liters per hour for an adult until clear lavage water appears) in order to achieve bulky stool when taking long-acting CCBs [29, 37, 38]. However, this method is not recommended in cases of unstable hemodynamics [39, 40]. According to recent data, it is more appropriate to use saline enteral solution for intestinal lavage [41].

After assessing the hemodynamic profile, targeted therapy should be carried out taking into account hemodynamic parameters. If the administration of vasopressors is ineffective, infusion therapy (crystalloids) under the control of volume status and mean blood pressure is indicated [23, 26]. At the same time, a number of researchers recommend avoiding hyperinfusion due to the high risk of developing pulmonary edema; crystalloid solutions should be administered in a volume of 20 ml/kg [1, 2, 22, 42]. Although other works emphasize that the volume of infusion therapy should be individualized, taking into account the volume status [1, 43].

For bradycardia, atropine is administered at a dose of 0.5–1 mg intravenously every 2–3 minutes to a maximum dose of 3 mg [18, 44]. However, in some cases, a lack of effect was noted [43].

### CALCIUM SUPPLEMENTS

The use of calcium supplements in this pathology is pathogenetic in nature, increasing the extracellular concentration of this ion, and, consequently, the concentration gradient facilitating the entry of calcium into the cell. This leads to increased contractility and improved cardiac conductivity, and increased blood pressure [18].

There are various recommendations for the administration of calcium supplements in this group of patients. Calcium gluconate should be administered through central or peripheral venous access, calcium chloride – through central venous access if there are no restrictions [45]. According to the literature, it is advisable to administer 10–20 ml of 10% calcium chloride over 10–20 minutes in adults [1, 2, 28]. If no effect is observed, this dose must be repeated up to 4 times every 20 minutes [46]. Calcium gluconate - 10%, 30–60 ml [1]. Yatsinyuk B.B. et al. recommend to administer calcium chloride intravenously as a bolus of 100 mg over 15 minutes, followed by infusion of 0.1–0.2 mg/kg in case of compensated version of hemodynamic disturbances based on mean arterial pressure (MAP) and cardiac index (CI). In decompensated version, calcium chloride is to be administered intravenously as a bolus of 200 mg over 15 minutes, followed by infusion of 0.1–0.2 mg/kg [47].

There are reports in the literature about the development of hypercalcemia after the administration of calcium preparations [48]. Thus, Sim M.T. et al. described a case of iatrogenic hypercalcemia that resulted in death [49]. Often, due to the risk of developing this side effect, clinicians choose other methods of treatment for CCB poisoning. When administering calcium preparations, it is necessary to monitor (every 20 minutes) serum concentrations of calcium and phosphate to detect hypercalcemia and hypophosphatemia, as well as to perform ECG before and after the administration of calcium preparations [2, 18]. Nausea, vomiting, and confusion may also occur with calcium administration.

### VASOPRESSOR/INOTROPIC AGENTS

In the literature, there is still no consensus on the priority of using insulin or vasopressor/inotropic drugs when infusion therapy and calcium supplementation are ineffective [48].

However, most literature sources indicate that in the case of shock, a decrease in MAP below 65 mmHg, the development of lactic acidosis, and if previous therapy (infusion, calcium supplements) is ineffective, the administration of vasopressor/inotropic drugs should be started. To patients requiring vasopressor support, it is advisable to initially insert an arterial catheter for invasive blood pressure monitoring [1].

Omar A. Alshaya et al. indicate that the choice of drug should be guided by the type of shock. Epinephrine increases heart rate (HR), contractility, blood pressure by stimulating ß1 and α1 receptors; norepinephrine increases blood pressure by acting on α1 receptors; dobutamine increases heart rate and contractility by stimulating ß1 receptors. Epinephrine and dobutamine are recommended for cardiogenic shock, norepinephrine – for vasogenic shock [50]. However, most recommendations indicate that in case of CCB poisoning, norepinephrine is the drug of choice [1, 2]. According to the literature, the initial dose range for norepinephrine infusion is 0.02 to 1 mcg/kg/min to

improve hemodynamics and hemoperfusion, titrated to achieve a MAP of 65 mmHg [1]. If one vasopressor is ineffective, a second one should be added depending on the results of hemodynamic monitoring. PiCCO monitoring and echocardiography (EchoCG) will help carry out targeted hemodynamic therapy [51].

### INSULIN THERAPY

Most researchers point out that only if the administration of vasopressors is ineffective, it is necessary to start insulin therapy while continuing to administer vasopressors [2]. However, Bruno Mégarbane recommends insulin therapy in the first line before the administration of vasopressors [52].

Insulin in large doses is an inotropic drug, causing vasodilation, improving microcirculation and systemic hemoperfusion [53]. Insulin also ensures that cardiomyocytes absorb glucose, which is the preferred energy substrate of the heart during stress. In addition, the administration of exogenous insulin corrects insulin deficiency in CCB poisoning [53]. However, a complete understanding of the mechanisms of its action in this pathology is currently missing.

Numerous studies were conducted to demonstrate the effectiveness and safety of hyperinsulinemic-euglycemic therapy, subject to careful monitoring [30, 54]. A number of authors recommend starting insulin therapy 15 minutes after the start of vasopressor administration if they do not yield the desired effect [55]. However, there are no randomized controlled trials in humans comparing the effectiveness of insulin therapy and vasopressor administration. Some clinical observations and experimental studies showed that insulin therapy restores hemodynamic stability more quickly [56]. The effect of high doses of insulin appears 1 hour after the start of administration, so administration of vasopressors should not be stopped until hemodynamic parameters stabilize [54].

Glucose monitoring is necessary before initiating insulin administration. An insulin dose of 1 to 10 U/kg/h is considered effective; in some cases, in order to stabilize hemodynamics, it was successfully used at a dose of 22 U/kg/h as well [53, 57]. The standard insulin administration regimen is as follows: its initial bolus dose is 1 U/kg intravenously, followed by regular infusion of 0.5 U/kg per hour, the rate of which can be increased due to the lack of effect within 60 minutes from the start of therapy. Titration is necessary until hypotension is eliminated or the maximum dose - 10 U/kg per hour - is reached. If necessary, to maintain normoglycemia throughout insulin therapy and for 24 hours after its completion, a 5–10% glucose solution should be administered [53]. But often in patients with CCB poisoning due to hyperglycemia, additional glucose administration is not required. Yatsinyuk B.B. et al. propose the following regimen for administering insulin and glucose in case of verapamil poisoning: bolus insulin - 1 unit/kg for 15 minutes, followed by infusion - 1 unit/kg/hour; bolus glucose - 0.5 g/kg over 15 minutes, followed by infusion - 0.25 g/kg/h [47].

Target hemodynamic parameters are as follows: MAP of more than 65 mmHg, systolic blood pressure of more than 90 mmHg. It is necessary to determine the level of glucose and potassium in the blood 30 minutes after the start of insulin therapy, then every hour, and during the first day after completion of insulin therapy. Blood gases should be monitored at least 4–6 times per hour during the first 24–48 hours of therapy. If the potassium concentration decreases below 3.5 mmol/l, it is necessary to administer potassium supplements. Engebretsen K.M. points out that it is necessary to adjust the blood potassium level if it is below 2.8–3.0 mEq/L in the blood [58]. Hypokalemia develops as a result of the movement of potassium into the cellular space, and not due to a decrease in potassium concentration in the body. In the largest review of clinical observations, mild to severe hypoglycemia without neurological sequelae and mild hypokalemia without cardiac arrhythmia were reported in 73% and 82% of cases, respectively. The disorders were quickly stopped [59]. Another review observed no complications associated with insulin administration [46].

According to the literature, insulin therapy should not be terminated until hemodynamic stability not requiring the administration of

vasopressor drugs is achieved. The effect usually appears within 30–60 minutes. The issue of stopping insulin therapy among clinicians is controversial, and there is no consensus on it. Insulin should be withdrawn slowly under the following parameters: MAP is more than 65 mm Hg, elimination of lactic acidosis, and improvement in the level of consciousness [2, 48]. A number of reports state that the target indicators are as follows: heart rate = 50 beats/min or more, systolic blood pressure – 100 mmHg. Insulin therapy should be discontinued slowly (up to several days), since hemodynamic instability may return [55].

Stephen V.S. et al. 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 [2].

Cole J.B. et al. suggested that it is advisable to begin insulin therapy during the prehospital stage at a dose of up to 8 U/kg/h after consultation with the toxicologist [48].

As a result of their research, the authors found that patients with amlodipine poisoning, whose treatment included insulin therapy, required greater amounts of vasopressor agents and methylene blue than patients with verapamil or diltiazem poisoning. This is due to the fact that, unlike other CCBs, amlodipine, like insulin, stimulates endothelial nitric oxide synthase, resulting in synergistic vasodilation [60].

#### GLUCAGON

Glucagon is an endogenous polypeptide hormone secreted by pancreatic cells. It stimulates adenylate cyclase and has an inotropic and chronotropic effect. Information on the use of glucagon in case of CCB poisoning is contradictory. Some authors did not see convincing evidence of its effectiveness in these exotoxicoses [2]. However, a number of studies have established a positive effect of glucagon [61, 62]. The studies were either experimental in nature or based on case series, which is considered to have a low level of evidence.

#### FAT EMULSIONS (FE)

There are many reports in the literature on the effectiveness of fat emulsions in poisoning by lipophilic drugs, including CCBs. It is believed that FE “absorb” fat-soluble drugs and are excreted from the body due to a concentration gradient; FE also provide the myocardium with a ready source of energy, improving cardiac function [63].

Currently, some researchers recommend the following regimen for FE administration: a loading dose of 1.5 ml/kg of 20% lipid emulsion over one minute, followed by an infusion of 0.025 ml/kg per minute over 30–60 minutes [53].

In general, the mechanism of FE action is not completely clear, and optimal doses have not been established [64]. There is no information on prospective randomized studies proving the effectiveness of FE administration in case of CCB poisoning.

#### METHYLENE BLUE (MB)

The effectiveness of MB in CCB poisoning began to be studied not so long ago. CCBs are known to enhance the activity of endothelial nitric oxide synthase, resulting in the production of large amounts of nitric oxide. Nitric oxide activates guanylate cyclase and the formation of cyclic guanylate monophosphate, which leads to smooth muscle relaxation and vasoplegia. MB is an inhibitor of guanylate cyclase, causes vasoconstriction, and also improves sensitivity to catecholamines [22]. Biplab K. Saha et al. argue that early use of MB will lead to a reduction in vasopressor requirements and complication rates [54].

Other researchers did not recommend the use of MB due to insufficient evidence base [22].

The optimal dose of MB for refractory shock has not been established [65, 66]. The effect is observed 5 minutes after infusion and lasts 4 hours. Side effects (dizziness, headache, nausea, cyanosis) are rarely observed at doses below 2 mg/kg. MB is an easily accessible, inexpensive and safe drug [54].

#### OTHER DRUGS

Some researchers recommend the inotropic agent of Levosimendan in CCB poisoning [67]. It

increases the strength of the heart's contraction, has a vasodilating effect on blood vessels, and is a selective phosphodiesterase inhibitor. The effectiveness of this drug for CCB poisoning has not been proven. There are isolated reports in the literature on the use of phosphodiesterase inhibitors in this pathology [68]. Drugs of this group increase the level of cAMP, the level of calcium in the cell, and myocardial contractility. However, their use can lead to severe vasodilation and arterial hypotension. Data from experimental studies are contradictory [18].

Despite the fact that there are isolated reports of the effectiveness of these drugs in case of CCB poisoning, researchers do not recommend their use due to the possible aggravation of hypotension [18].

### EXTRACORPOREAL METHODS

Hemodialysis. After analyzing 83 publications (1 systematic review, 1 cohort study, 19 pharmacokinetic studies, 55 clinical observations, 7 experimental studies; a total of 210 patients), the Extracorporeal Treatments in Poisoning (EXTRIP) workgroup does not recommend the use of hemodialysis in complex treatment for severe poisoning by CCBs (verapamil, amlodipine, diltiazem), which is explained by the pharmacokinetic properties of the drugs (high degree of plasma protein binding) [12].

MARS therapy. Beyls C. et al. conducted a retrospective cohort study that included 7 patients with severe CCB poisoning who were admitted to the hospital with cardiogenic shock. The complex of treatment for the patients included the use of MARS therapy. An increase in MAP from 56 (43–58) to 65 (61–78) mmHg (p =0.005) was detected. The dose of norepinephrine decreased statistically significantly from 3.2 (0.8–10) μg/kg/min to 1.2 (0.1–1.9) μg/kg/min (p = 0.008); and the lactate level decreased from 3.2 (2.4–3.4) mmol/L-1 to 1.6 (0.9–2.2) mmol/L-1 (p = 0.008). All the patients were discharged in satisfactory condition [69]. Two more clinical cases were described by Martinez Garcia J.J. et al. [70]. Connor-Schuler R.L., having received positive results after using MARS therapy, concluded that this treatment method is effective [71].

Osman Yeşilbaş et al. suggested that single-pass albumin dialysis (SPAD) would be effective in case of CCB poisoning. The authors described a clinical observation in which a 15-year-old patient showed positive dynamics after albumin dialysis [72]. Essink J. et al. demonstrated successful treatment of a patient with CCB poisoning, which included the use of SPAD and extracorporeal membrane oxygenation (ECMO) [73]. Clinicians observed a positive effect in a patient with amlodipine poisoning after plasmapheresis [74].

Veno-arterial extracorporeal membrane oxygenation (VA ECMO). VA ECMO provides temporary hemodynamic support. VA ECMO should be used as a last-line option. The indication for VA ECMO in case of CCB poisoning is refractory shock, despite intensive therapy (infusion therapy, calcium supplements, vasopressor/inotropic drugs, high doses of insulin, fat emulsions, in some cases, intra-aortic balloon counterpulsation) [75, 76].

## CONCLUSION

Summarizing the data obtained, we can schematically present an algorithm for the treatment of patients with acute poisoning by calcium channel blockers. After cleansing the gastrointestinal tract and starting infusion therapy, pathogenetic treatment should be carried out using calcium preparations; subsequently, in case of unstable hemodynamics, the prescription of vasopressors and inotropic drugs is indicated; and if there is no positive dynamics, it is recommended to add insulin therapy. However, it should be noted that the given scheme is indicative in nature, reflecting key points. In general, this problem remains open and requires further multicenter studies.

## REFERENCES


1. DeRoos F. Calcium channel blockers. In: Hoffman R. (ed.) *Goldfrank's Toxicologic Emergencies.* 10th ed. New York: McGraw-Hill; 2015:884–892.
2. Stephen VS, Pluymers NA, Gauton SJ. Emergency management of calcium channel blocker overdose. *S Afr Med J*. 2019;109(9):635–638. PMID: 31635586 https://doi.org/10.7196/SAMJ.2019.v109i9.13704
3. Simonova AYu, Rozhkov PG, Belova MV, Ilyashenko KK, Potskhveriya MM, Ostapenko YuN, et al. Analysis of the toxicological situation in Moscow in the first three months of the COVID-19 pandemic. *Toxicological Review*. 2021;29(5):49–57. (In Russ.) https://doi.org/10.36946/0869-7922-2021-29-5-49-57
4. Ilyashenko KK, Simonova AYu, Belova MV. A structural analysis of acute exotoxicoses in people of elderly and senile age. *Toxicological Review*. 2017;(1):10–14. (In Russ.) https://doi.org/10.36946/0869-7922-2017-1-10-14
5. Kvachakhiya LL. *Razrabotka metodologii sudebno-khimicheskogo analiza lekarstvennykh veshchestv iz gruppy blokatorov kal'tsievykh kanalov: dr. med. sci. diss. synopsis.* Moscow; 2021. (In Russ.) Available at: https://www.sechenov.ru/upload/iblock/41b/Avtoreferat-Kvachakhiya-L.L.pdf [Accessed May 13, 2024]
6. Kukes VG, Starodubtsev AK (eds.). *Klinicheskaya farmakologiya i farmakoterapiya*. Moscow: GEOTAR-Media Publ.; 2006. (In Russ.)
7. Shilov AM. Third-generation calcium channel blockers in the treatment of arterial hypertension. *Systemic Hypertension*. 2013;3:38–43. (In Russ.)
8. Mowry JB, Spyker DA, Cantilena LR Jr, McMillan N, Ford M. 2013 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st Annual Report. *Clin Toxicol (Phila)*. 2014;52(10):1032–1283. PMID: 25559822 https://doi.org/10.3109/15563650.2014.987397
9. Gupta B., Kerai S. Amlodipine toxicity complicated by concurrent madications. *Korean J Anesthesiol*. 2018;71(6):489–490. PMID: 26990756 https://doi.org/10.4097/kja.d17.00071
10. Shenoy S, Lankala S, Adigopula S. Management of calcium channel blocker overdoses. *J Hosp Med*. 2014;9(10):663–668. PMID: 25066023 https://doi.org/10.1002/jhm.2241.
11. St-Onge M, Dubé PA, Gosselin S, Guimont C, Godwin J, Archambault PM, et al. Treatment for calcium channel blocker poisoning: a systematic review. *Clin Toxicol (Phila)*. 2014;52(9):926–944. PMID: 25283255 https://doi.org/10.3109/15563650.2014.965827.
12. Wong A, Hoffman RS, Walsh SJ, Roberts DM, Gosselin S, Bunchman TE, et al. Extracorporeal treatment for calcium channel blocker poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicology (Phila)*. 2021;59(5):361–375. PMID: 33555964 https://doi.org/10.1080/15563650.2020.1870123
13. Chakraborty RK Calcium channel blocker toxicity. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2022. Available at: https://www.statpearls.com/nursepractitioner/ce/activity/65968/?specialty=specialty [Accessed May 13, 2024].
14. DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and β-blocker toxicity. *Toxicol Rev*. 2004;23(4):223–238. https://doi.org/10.2165/00139709-200423040-00003
15. Graudins A, Lee HM, Druda D. Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies. *Br J Cin Pharmacol*. 2016;81(3):453–461. PMID: 26344579 https://doi.org/10.1111/bcp.12763
16. Shepherd G, Klein-Schwartz W. High-dose insulin therapy for calcium-channel blocker overdose. *Ann Pharmacother*. 2005;39(5):923–930. PMID: 15811898 https://doi.org/10.1345/aph.1E436
17. Spasova AP, Loginov AV, Yurovickij VL, Barysheva OYu, Strategopulo VA. A Case of Severe Amlodipine Poisoning. *Russian Journal of Anesthesiology and Reanimatology*. 2015;60(6):61–64. (in Russ.)
18. Hoffman RS, Nelson LS, Howland MA, Lewis NA, Flomenbaum NE, Goldfrank LR. (eds.) *Goldfrank's Manual of Toxicologic Emergencies*. New York: McGraw-Hill Medical; 2007. (Russ. ed.: Khoffman R, Nel'son L, Khauland M-E, L'yuin N, Flomenbaum N, Goldfrank L. *Ekstrennaya meditsinskaya pomoshch' pri otravleniyakh*. Moscow: Praktika Publ.; 2010.)
19. Yatsinyuk BB, Brusin KM, Sentsov VG. Klinicheskaya diagnostika pervichnogo kardiotoksicheskogo effekta pri ostrykh otravleniyakh blokatorami β-adrenergicheskikh retseptorov i ingibitorami medlennykh kal'tsievykh kanalov. *Rossiyskie meditsinskie vesti*. 2010;15(3):56–62. (In Russ.)
20. Baselt RC. *Disposition of toxic drugs and chemicals in man*. 9th ed. Seal Beach, CA, USA: Biomed Publications; 2011.
21. Breimer DD, Schelens JHM Nifedipine: variability in its kinetics and metabolism in man. Pharmacology &Therapeutics. 1989;44(3):445–454
22. St-Onge M, Anseeuw K, Cantrell FL, Gilchrist IC, Hantson P, Bailey B, et al. Experts consensus recommendations for the management of calcium channel blocker poisoning in adults. *Crit Care Med*. 2017;45(3):e306–e315. PMID: 27749343 https://doi.org/10.1097/CCM.0000000000002087
23. Lindeman E, Ålebring J, Johansson A, Ahlner J, Kugelberg FC, Grass JN. The unknown known: non-cardiogenic pulmonary edema in amlodipine poisoning, a cohort study. *Clin Toxicol (Phila)*. 2020;58(11):1042–1049. PMID: 32114860 https://doi.org/10.1080/15563650.2020.1725034
24. Rietjens SJ, de Lange DW, Donker DW, Meulenbelt J. Practical recommendations for calcium channel antagonist poisoning. *Neth J Med*. 2016;74(2):60–67. PMID: 26951350
25. Eisenberg MJ, Brox A, Bestawros AN. Calcium channel blockers: an update. *Am J Med*. 2004;116(1):35–43. PMID: 14706664 https://doi.org/10.1016/j.amjmed.2003.08.027
26. Kerns W2nd. Management of β-adrenergic blocker and calcium channel antagonist toxicity. *Emerg Med Clin North Am*. 2007;25(2):309–331. PMID: 17482022 https://doi.org/10.1016/j.emc.2007.02.001
27. Chen C, Voicu S, Diallo A. The severity and mortality prediction of calcium-channel blocker poisoning in the intensive care unit. *Clin Toxicol*. 2020;58(6):508. https://doi.org/10.1080/15563650.2020.1741981
28. Kumar K, Biyyam M, Bajantri B, Nayudu S. Critical management of severe hypotension caused by amlodipine toxicity managed with hyperinsulinemia/euglycemia therapy supplemented with calcium gluconate, intravenous glucagon and other vasopressor support: Review of literature. *Cardiol Res*. 2018;9(1):46–49. PMID: 29479386 https://doi.org/10.14740/cr646w
29. Levine M, Boyer EW, Pozner CN, Geib AJ, Thomsen T, Mick N, et al. Assessment of hyperglycemia after calcium channel blocker overdoses involving diltiazem or verapamil. *Crit Care Med*. 2007;35(9):2071–2075. PMID: 17855820 https://doi.org/10.1097/01.ccm.0000278916.04569.23
30. Krenz JR, Kaakeh Y. An Overview of Hyperinsulinemic-Euglycemic Therapy in Calcium Channel Blocker and β-blocker Overdose. *Pharmacotherapy*. 2018;38(11):1130–1142. PMID: 30141827 https://doi.org/10.1002/phar.2177

31. Mel'nikov ES. *Khimiko-toksikologicheskiy analiz gipotenzivnykh lekarstvennykh sredstv pri ostrykh otravleniyakh: cand. med. sci. diss. synopsis*. Moscow; 2016. Available at: https://www.sechenov.ru/upload/medialibrary/e9c/avtoreferat_final_melnikov.pdf [Accessed May 13, 2024]
32. Gonzalez O, Alonso RM, Ferreirós N, Weinmann W, Zimmermann R, Dresen S. Development of an LC–MS/MS method for the quantitation of 55 compounds prescribed in combined cardiovascular therapy. *J Chromatography B Analyt Technol Biomed Life Sci*. 2011;879(3-4):243–252. PMID: 21190906 https://doi.org/10.1016/j.jchromb.2010.12.007
33. Rodina TA, Melnikov ES, Belkov SA, Danko AA, Sokolov AV, Prokofiev AB. Therapeutic drug monitoring of nifedipine by HPLC-MS/MS in treatment of arterial hypertension. *Journal Biomed*. 2017;(4):53–69. (In Russ.)
34. Thompson AM, Robins JB, Prescott LF. Changes in cardiorespiratory function during gastric lavage for drug overdose. *Hum Toxicol*. 1987;6(3):215–218. PMID: 3596605 https://doi.org/10.1177/096032718700600307
35. Laine K, Kivistö KT, Neuvonen PJ. Effect of delayed administration of activated charcoal on the absorption of conventional and slow-release verapamil. *J Toxicology: Clin Toxicol.* 1997;35(3):263–268. PMID: 9140320 https://doi.org/10.3109/15563659709001210
36. Laine K, Kivistö KT, Laakso I, Neuvonen PJ. Prevention of amlodipine absorption by activated charcoal: effect of delay in charcoal administration. *Br J Clin Pharmacol*. 1997; 43(1):29–33. PMID: 9056049 https://doi.org/10.1111/j.1365-2125.1997.tb00029.x
37. Cumpston KL, Aks SE, Sigg T, Pallasch E. Whole bowel irrigation and the hemodynamically unstable calcium channel blocker overdose: primum non nocere. *J Emerg Med*. 2010; 38(2):171–174. https://doi.org/10.1016/j.jemermed.2007.11.100
38. Buckley N, Dawson AH, Howarth D, Whyte IM. Slow-release verapamil poisoning. *Med journal Aust.* 1993;158(3):202–204. PMID: 8450791
39. Bryant SM, Naples J. Morbidity associated with whole bowel irrigation. *Pediatr Emerg Care*. 2007; 23(11):846. PMID: 18007223 https://doi.org/10.1097/PEC.0b013e31815a0679
40. Albertson TE, Owen KP, Sutter ME, Chan AL. Gastrointestinal decontamination in the acutely poisoned patient. *Int J Emerg Med*. 2011;4:65. PMID: 21992527 https://doi.org/10.1186/1865-1380-4-65
41. Matkevich VA, Potskhveriya MM, Goldfarb YuS, Simonova AYu. Violations of Homeostasis Parameters in Acute Poisonings and Ways of Their Correction. *Toxicological Review*. 2018;(3):18–26. (In Russ.) https://doi.org/10.36946/0869-7922-2018-3-18-26
42. Rizvi I, Ahmad A, Zaman S. Life-threatening calcium channel blocker overdose and its management. *BMJ Case Rep*. 2012:bcr0120125643. PMID: 22669854 https://doi.org/10.1136/bcr.01.2012.5643
43. Ramoska EA, Spiller HA, Myers A. Calcium channel blocker toxicity. *Ann Emerg Med*. 1990;19(6):649–653. PMID: 2344082 https://doi.org/10.1016/s0196-0644(05)82469-2
44. Proano L, Chiang WK, Wang RY. Calcium channel blocker overdose. *Am J Emerg Med.* 1995;13(4):444–450. PMID: 7605536 https://doi.org/10.1016/0735-6757(95)90137-X
45. Kerns W 2nd, Kline J, Ford MD. Beta-blocker and calcium channel blocker toxicity. *Emerg Med Clin North Am*. 1994;12(2):365–390. PMID: 7910555.
46. Cole JB, Arens AM. Cardiotoxic medication poisoning. *Emerg Med Clin North Am.* 2022;40(2):395–416. PMID: 35461630 https://doi.org/10.1016/j.emc.2022.01.014
47. Yatsinyuk BB, Sentsov VG, Laptev AM, Gavrikov PP. Sposob lecheniya kompensirovannogo i dekompensirovannogo narusheniya kardiogemodinamiki pri ostrom otravlenii Verapamilom. Patent RF 2 694 262$^{(13)}$ C1. Khanty-Mansiysk; 2019 (In Russ.). Available at: https://patents.s3.yandex.net/RU2694262C1_20190711.pdf [Accessed May 13, 2024]
48. Cole JB, Arens AM, Laes JR, Klein LR, Bangh SA, Olives TD. High dose insulin for beta-blocker and calcium channel-blocker poisoning. *Am J Emerg Med*. 2018;36(10):1817–1824. PMID: 29452919 https://doi.org/10.1016/j.ajem.2018.02.004
49. Sim MT, Stevenson FT. A fatal case of iatrogenic hypercalcemia after calcium channel blocker overdose. *J Med Toxicol*. 2008;4(1):25–29. PMID: 18338308 https://doi.org/10.1007/BF03160947
50. Alshaya OA, Alhamed A, Althewaibi S, Fetyani L, Alshehri S, Alnashmi F, et al. Calcium Channel Blocker Toxicity: A Practical Approach. *J Multidiscip Healthc*. 2022;15:1851–1862. https://doi.org/10.2147/JMDH.S374887
51. Pinsky MR. Pulmonary artery occlusion pressure. *Intensive Care Med*. 2003;29(1):19–22. PMID: 12528017 https://doi.org/10.1007/s00134-002-1570-5
52. Mégarbane B. High-dose insulin should be used before vasopressors/inotropes in calcium-channel blocker toxicity. *Br J Clin Pharmacol*. 2023;89(4):1269–1274. https://doi.org/10.1111/bcp.15641
53. Walter E, McKinlay J, Corbett J, Kirk-Bayley J. Review of management in cardiotoxic overdose and efficacy of delayed intralipid use. *J Intensive Care Soc*. 2018;19(1):50–55. PMID: 29456602 https://doi.org/10.1177/1751143717705802
54. Saha BK, Bonnier A, Chong W. Rapid reversal of vasoplegia with methylene blue in calcium channel blocker poisoning. *Afr J Emerg Med.* 2020;10(4):284–287. PMID: 33299766 https://doi.org/10.1016/j.afjem.2020.06.014
55. Woodward C, Pourmand A, Mazer-Amirshai M. High-dose insulin therapy, an evidence-based approach to beta-blocker/calcium channel blocker toxicity. *Daru*. 2014;22(1):36. PMID: 24713415 https://doi.org/10.1186/2008-2231-22-36
56. Skoog C, Engebretsen K. Are vasopressors useful in toxin-induced cardiogenic shock? *Clin Toxicol (Phila)*. 2017;55(4):285–304. PMID: 28152638 https://doi.org/10.1080/15563650.2017.1284329
57. Stellpflug SJ, Harris CR, Engebretsen KM, Cole JB, Holger JS. Intentional overdose with cardiac arrest treated with intravenous fat emulsion and high-dose insulin. *Clin Toxicol (Phila).* 2010;48(3):227–229. PMID: 20141425 https://doi.org/10.3109/15563650903555294
58. Engebretsen KM, Kaczmarek KM, Morgan J, Holger JS. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. *Clin Toxicol (Phila).* 2011;49(4):277–283. PMID: 21563902 https://doi.org/10.3109/15563650.2011.582471
59. Page CB, Ryan NM, Isbister GK. The safety of high-dose insulin euglycaemia therapy in toxin-induced cardiac toxicity. *Clin Toxicol (Phila.)*. 2018;56(6):389–396. PMID: 29069937 https://doi.org/10.1080/15563650.2017.1391391
60. Cole JB, Lee SC, Prekker ME, Kunzler NM, Considine KA, Driver BE, et al. Vasodilation in patients with calcium channel blocker poisoning treated with high-dose insulin: a comparison of amlodipine versus non-dihydropyridines. *Clin Toxicol (Phila)*. 2022;60(11):1205–1213. https://doi.org/10.1080/15563650.2022.2131565 PMID: 36282196
61. Mahr NC, Valdes A, Lamas G. Use of glucagon for acute intravenous diltiazem toxicity. *Am J Cardiol.* 1997;79(11):1570–1571. PMID: 9185662 https://doi.org/10.1016/s0002-9149(97)90000-x

62. Walter FG, Frye G, Mullen JT, Ekins BR, Khasigian PA. Amelioration of nifedipine poisoning associated with glucagon therapy. *Ann Emerg Med*. 1993;22(7):1234–1237. PMID: 8517581 https://doi.org/10.1016/s0196-0644(05)80998-9
63. Rothschild L, Bern S, Oswald S, Weinberg G. Intravenous lipid emulsion in clinical toxicology. *Scand J Trauma Resusc Emerg Med*. 2010;18:51. PMID: 20923546 https://doi.org/10.1186/1757-7241-18-51
64. Gosselin S, Hoegberg LC, Hoffman RS, Graudins A, Stork CM, Thomas SH, et al. Evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning. *Clin Toxicol (Phila)*. 2016;54(10):899–923. PMID: 27608281 https://doi.org/10.1080/15563650.2016.1214275
65. Jang DH, Nelson LS, Hoffman RS. Methylene blue for distributive shock: a potential new use of an old antidote. *J Med Toxicol*. 2013;9(3):242–249. PMID: 23580172 https://doi.org/10.1007/s13181-013-0298-7
66. Fadhlillah F, Patil S. Pharmacological and mechanical management of calcium channel blocker toxicity. *BMJ Case Rep*. 2018;2018: bcr2018225324. PMID: 30150339 https://doi.org/10.1136/bcr-2018-225324
67. Varpula T, Rapola J, Sallisalmi M, Kurola J. Treatment of serious calcium channel blocker overdose with levosimendan, a calcium sensitizer. *Anesth Analg*. 2009;108(3):790–792. PMID: 19224785 https://doi.org/10.1213/ane.0b013e3181931737
68. Wolf LR, Spadafora MP, Otten EJ. Use of amrinone and glucagon in a case of calcium channel blocker overdose. *Ann Emerg Med*. 1993;22(7):1225–1228. PMID: 8517579 https://doi.org/10.1016/s0196-0644(05)80996-5
69. Beyls C, Malaquin S, Huette P, Mary A, Besserve P, Roger PA, et al. Hemodynamic impact of molecular adsorbent recirculating system in refractory vasoplegic shock due to calcium channel blocker poisoning. *Int J Artif Organs*. 2021;44(12):944–951. PMID: 33818171 https://doi.org/10.1177/03913988211007865
70. Garcia Martinez JJ, Mollard F, Baud FJ, Bendjelid K. Intoxication with calcium channel blockers and other highly protein-bound drugs: why use MARS? Two clinical case reports. *J Clin Toxicol*. 2018;8:3. https://doi.org/10.4172/2161-0495.1000388
71. Connor-Schuler RL, Carr JM, Reaven MS, Bridgman BT, Patel DM, Subramanian RM. The Efficacy of Albumin Dialysis in the Reversal of Refractory Vasoplegic Shock Due to Amlodipine Toxicity. *Crit Care Explor*. 2020;2(6):e0120. PMID: 32695989 https://doi.org/10.1097/CCE.0000000000000120
72. Yeşilbaş O, Ramoğlu MG, Çayan ÖK, Cem E, Seven P. Successful single-pass albumin dialysis in the management of severe calcium channel blocker poisoning. *Turk Pediatri Ars*. 2020;55(1):82–84. PMID: 32231456 https://doi.org/10.14744/TurkPediatriArs.2019.27880
73. Essink J, Berg S, Montange J, Sankey A, Taylor V, Salomon J. Single-Pass Albumin Dialysis as Rescue Therapy for Pediatric Calcium Channel Blocker Overdose. *J Investig Med High Impact Case Rep*. 2022;10:23247096221105251. https://doi.org/10.1177/23247096221105251
74. Ezidiegwu C, Spektor Z, Nasr MR, Kelly KC, Rosales LG. A case report on the role of plasma exchange in the management of a massive amlodipine besylate intoxication. *Ther Apher Dial*. 2008;12(2):180–184. PMID: 18387170 https://doi.org/10.1111/j.1744-9987.2008.00567.x
75. Weiner L, Mazzeffi M, Hines E, Gordon D, Herr DL, Hong K Kim. Clinical utility of venoarterial-extracorporeal membrane oxygenation (VA-ECMO) in patients with drug-induced cardiogenic shock: a retrospective study of the Extracorporeal Life Support Organizations' ECMO case registry. *Clin Tox (Phila)*. 2020;58(7):705–710. PMID: 31617764 https://doi.org/10.1080/15563650.2019.1676896
76. Upchurch C, Blumenberg A, Brodie D, MacLaren G, Zakhary B, Hendrickson RG. Extracorporeal membrane oxygenation use in poisoning: a narrative review with clinical recommendations. *Clin Toxicol (Phila)*. 2021;59(10):877–887. PMID: 34396873 https://doi.org/10.1080/15563650.2021.1945082

**Received on 17/04/2023**
**Review completed on 25/10/2023**
**Accepted on 26/03/2024**