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Review

HIGH-DOSE INSULIN EUGLYCEMIC THERAPY

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SUMMARY – Calcium channel blockers and beta-blockers toxicity/poisoning are one of the most common causes of poisoning. More importantly, they are among the deadliest types of poisoning caused by cardiac drugs that emergency physicians can encounter. Common toxidrome caused by these medications includes the following symptoms: hypotension, bradycardia, hypoglycemia/hyperglycemia, hypothermia, arrhythmia, and seizures. Treatment is usually complex, It consists of administration of various medications, such as crystalloids, intravenous calcium, glucagon, vasopressors/inotropes, and especially high-dose insulin euglycemic therapy. In this paper, we will review the mechanism for this type of treatment, propose a potential protocol for its application and address possible adverse effects. High-dose insulin euglycemic therapy should be an integral part of the treatment protocol for calcium channel blockers and beta-blockers toxicity.

Key words: *calcium channel blockers, beta-blockers, toxicity, high-dose insulin euglycemic therapy*

Introduction

Cardiovascular drug poisoning is the second leading cause of death by drug poisoning, according to the U.S. Poisoning Network/National Poison Data System (NPDS). Among all cardiovascular drugs, most deaths were caused by beta-blockers and calcium channel blockers[1], a trend has been increasing for years. On the other hand, hyperinsulinemia-euglycemia therapy of cardiovascular drug toxicity has been unfairly neglected. In some scientific papers it has been mentioned as a last line of treatment, which should not be the case because treatment with high doses of insulin while maintaining euglycemia is an excellent way to treat the toxicity of cardiovascular drugs. There are not many articles or randomized studies on this topic in the literature, but it is known that the success rate of treatment of calcium blockers and beta-blockers toxicity with this protocol is between 84 and 100%. In this review, we will discuss the protocol, and its indications and safety, focusing on its use and effectiveness in an emergency department.

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Discussion

Symptoms of poisoning

The most common symptoms of poisoning with calcium channel blockers and beta-blockers are hypotension, bradycardia, and shock. The onset of symptoms depends on the formulation of the drug. In most cases of typical poisoning the symptoms will develop within eight hours, while drugs with a prolonged action period may take 24 hours. In cases of poisoning with unknown cardiovascular drugs and in which typical toxidromes occur, measuring blood sugar levels may be a key factor, since poisoning with calcium channel blockers usually results in hyperglycemia, while poisoning with beta-blockers results in hypoglycemia. Among other symptoms, it is important to mention the occurrence of nausea and vomiting, arrhythmias, as well as neurological symptoms, such as delirium, epileptic seizures, and coma.

The emergence of different symptoms caused by calcium channel blockers poisoning also depends on the characteristics of the drug itself. Thus, non-dihydropyridine blockers, such as verapamil, usually lead to deep myocardial suppression and less noticeable vasodilation. These patients are commonly presented with severe bradycardia. In contrast, patients with dihydro-

pyridine drug poisoning, such as amlodipine, usually present with more pronounced vasodilation and therefore predominantly with vasodilatory shock and reflex tachycardia, and only in high doses with bradycardia. Furthermore, there are differences in beta-blocker poisoning depending on the subgroup of the drug. Lipophilic drugs, such as propranolol, due to their characteristics, will lead to frequent CNS symptoms, such as delirium and epileptic seizures. Drugs that predominantly affect myocardial sodium channels (propranolol, carvedilol) may lead to the development of arrhythmias, especially with the widening of the QRS complex and development of monomorphic ventricular tachycardias, as well as the development of profound hypotension. Peripheral vasodilators (nebivolol) usually lead to profound hypotension due to their primary action.[2]

The treatment of poisoning

The treatment of poisoning caused by these drugs is complex and requires action using multiple mechanisms. Among the non-specific drugs that are used in the treatment, decontamination is worth mentioning. Activated charcoal can be applied if it one to two hours has passed since the ingestion of the drug. Irrigation of the entire intestine with polyethylene glycol should be considered when ingesting a large amount of a slow-releasing drug or amlodipine, which has a long action. Further treatment depends on the assessment of the patient's hemodynamic status, which can be made with ultrasound. This step is crucial because it is important to distinguish whether the cardiotoxic effect of the drug is predominant, which may manifest itself with reduced cardiac output, or whether the main problem is peripheral vasodilation. The recommended vasopressors are adrenaline and noradrenaline.[3] Adrenaline is the drug of choice because it can affect both hypotension and bradycardia. Noradrenaline is recommended in patients who predominantly present with symptoms of vasodilation, such as in cases of ingestion of dihydropyridine calcium channel blockers and beta-blockers with vasodilatory effect. Glucagon is also used in the first-line treatment. Glucagon acts by increasing intracellular levels of cAMP and has a positive inotropic and chronotropic effect, independent of beta-receptor activation, hence glucagon is superior in the treatment of beta-blockers poisoning, especially in patients presenting with reduced ejection fraction and bradycardia. On the other hand, glucagon has no effect on calcium channel blockers poisoning that have a dominant vasodilating effect. Application of intravenous calcium is indicated for calcium channel blockers poisoning as well as beta-blockers poisoning. Atropine may also be considered but is unlikely to affect bradycardia caused by poisoning with these drugs. As a second-line treatment, the use of methylene blue, ECMO, hemodialysis, and the application of lipid emulsions may be considered.

Hyperinsulinemia-euglycemia therapy

Part of the first-line treatment of calcium channel blockers and beta-blockers poisoning is certainly hyperinsulinemia-euglycemia therapy.[4] Hyperinsulinemia-euglycemia therapy (HIET) is primarily used in treating severe overdoses of calcium channel blockers, although it can also be used to treat beta-blockers poisonings that require inotropic support.

The mechanism of action is simple because this method of treatment supports the "metabolic hunger" of the heart, which is caused by the toxicity of calcium channel blockers or beta-blockers and which has a direct cardio-toxic effect. Poisoning with calcium channel blockers alone leads to several metabolic effects that must be emphasized:

- Hyperinsulinemia (insulin release is dependent on calcium uptake into the pancreatic beta cells via L-type calcium channels)
- Insulin resistance, which is caused by the toxicity of calcium channel blockers
- Calcium channel blockers act on the heart muscle cells by reducing the utilization of free fatty acids, increasing myocardial dependence on carbohydrates by reducing the intake of free fatty acids and glucose into muscle cells and by reducing the activity of mitochondria, which are essential for carbohydrate catabolism.

Insulin itself has several effects related to the repair of toxic effects:

- It increases the uptake of glucose and lactate into myocardial cells.
- It improves myocardial function without the need to increase oxygen demand.
- It increases pyruvate dehydrogenase activity, which improves lactate oxidation and the "cleansing" of cytosols from glycolysis byproducts that may affect calcium turnover and lead to diastolic dysfunction.

- It improves myocardial contraction due to greater glucose availability.
- It increases the activity of calcium-dependent ATPase in the sarcoplasmic reticulum.
- It increases the concentration of calcium in the cytoplasm.
- It improves calcium inflow into mitochondria.

In animal models of beta-blockers and calcium channel blockers poisonings, this treatment has led to better hemodynamic stability and survival compared to the treatment with vasopressors and glucagon.[5] In clinical studies, hyperinsulinemia-euglycemia therapy leads to a significant normalization of blood pressure and hemodynamic parameters in poisoning with various drugs from groups such as verapamil, diltiazem, amlodipine, propranolol, and other beta-blockers.[6,7,8]

Hyperinsulinemia-euglycemia therapy can be used together with catecholamines (as part of inotropic support) since they act favorably on each other. Insulin inotropy itself is not related to catecholamines and it is not affected by beta-blockade, thus an additive effect is expected. Furthermore, insulin itself has a beneficial effect on myocardial contraction, but without chronotropic effect, and in high doses it can lead to vasodilation.

The treatment of calcium channel blockers or beta-blockers toxicity with this method is particularly important in patients with predominantly myocardial disjunction (bradycardia and reduced ejection fraction) and the effect of this treatment is usually lower in patients with a clinical picture of vasodilatory shock.

Treatment protocol

The following treatment protocol is recommended. Begin the treatment with an insulin bolus at a dose of 1 unit/kg intravenously (IV). If the glucose level is lower than 11,1 mmol/L, administer 25g of glucose intravenously (IV). Next, start to administer insulin as a continuous infusion at a dose of 0.5-1 units/kg/h (in adults this does is usually between 35 and 100 units/h). It is recommended that insulin be administrated via an infusion pump to a separate intravenous route. If the response after 20 minutes is not adequate, the insulin dose should be increased by 0.5 units/kg/h every 15 minutes up to a maximum dose of a 4 units/kg/h (although there are scientific papers in which dosing went up to a maximum of a 14 units/kg/h). A favorable response is considered to be a hemodynamic stabilization of the patient. In addition, it is necessary to give glucose and maintain its range between 6 and 12 mmol/L. Start the infusion at 0.5 mg/kg/h (in any formulation - 5%, 10%, 25% glucose). Five percent glucose can lead to hyponatremia. Therefore it is necessary to monitor sodium levels every two hours. In addition, when administering 25% or 50% glucose, it is important to establish a central venous pathway to prevent the development of peripheral venous thrombophlebitis. At the beginning of the treatment, glycemia should be monitored every 15 to 30 minutes. The usual dose of glucose maintenance in patients treated with this protocol is 10 to 70 g of glucose per hour. After the hemodynamic stabilization of patients and improvement of organ perfusion, it is expected that the need for glucose to maintain normoglycemia will increase. After four hours of treatment with the maintenance of euglycemia, monitoring can be less frequent. It is recommended to monitor glucose every four hours. Potassium and acid-base status are initially monitored every 30 minutes, less frequently at a later stage of treatment. Patients should be hemodynamically monitored with blood pressure measurements every half hour and with frequent assessments of cardiac ejection fraction and myocardial contractility.[9]

Adverse effects

The adverse effects of this treatment are predictable and easy to treat. Even in extreme cases, when 1,000 units of insulin were accidentally given as loading doses in case of verapamil poisoning, there were no adverse events. Common side effects of this treatment are hypoglycemia (in 16% of cases), hypokalemia, hypomagnesemia, and hypophosphatemia. Hypoglycemia is paradoxically more common in cases of milder clinical toxicity presentations with hypotension. Glucose usually does not need to be given initially in patients with calcium channel blocker poisoning. Hypokalemia is a less common side effect and correction of hypokalemia should be avoided, as hypokalemia itself is the result of intracellular displacement of potassium from the extracellular space due to insulin rather than kaliopenia itself. Hypokalemia in this method of treatment also has positive effects, since it leads to improved myocardial contractibility due to increased calcium inflow into systole, and elevated intracellular potassium levels have a stabilizing effect on cardiac muscle cell membranes during excessive excitation (as in catecholamine treatment). Potassium levels should

be monitored every hour at the beginning of treatment and every two hours thereafter.[10] Regarding other electrolytes, it seems reasonable to monitor magnesium and phosphate levels every six hours, because during treatment, hypophosphatemia and hypomagnesemia may occur, primarily due to fluid loading. For all of these reasons and the need for constant monitoring, patients with beta-blockers or calcium channel blockers poisoning should be treated in the intensive care units.

Conclusion

Although there is a wealth of data in the literature on the safe treatment with hyperinsulinemia-euglycemia protocol, there are still many questions that can only be answered by randomized clinical trials, which are still lacking. However, since it is known in literature that the success of this treatment is very high, between 84 and 100%, this method of treatment is effective and safe in patients who have poisoning with calcium channel blockers or beta-blockers. The protocol can be started in parallel with other first-line treatment modalities. In cases where patients do not respond well to volume therapy, therapy with intravenous calcium or glucagon can be conducted. Hyperinsulinemia-euglycemia therapy is cheap, effective, and readily available. It has had excellent therapeutic responses with a small number of side effects that can be treated quickly and adequately.

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Sažetak

HIPERINZULINEMIJA-EUGLIKEMIJA LIJEČENJE

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Otrovanja sa blokatorima kalcijevih kanala i sa beta-blokatorima spadaju u jedne od češćih uzroka trovanja, ali još i važnije, jedne od najsmrtonosnijih trovanja sa kardiološkim lijekovima sa kojima se liječnici u hitnoj medicini mogu susresti. Tipičan toksidrom uključuje simptome poput hipotenzije, bradikardije, aritmije, hipoglikemije/hiperglikemije, hipotermije i epileptičkih napada. Liječenje je kompleksno, a samo specifično liječenje uključuje primjenu kalcija, volumena, vazopresora/intropa, glukagona, te osobiti naglasak stavlja na primjenu hiperinzulinemija-euglikemija liječenja. U ovom preglednom radu osvrnuti ću se na mehanizam ovog načina liječenja, protokol primjene te nuspojave koje se mogu javiti. Hiperinzulinemija-euglikemija liječenje trebao bi biti integralni dio protokola liječenja trovanja sa beta-blokatorima i blokatorima kalcijevih kanala.

Ključne riječi: *blokatori kalcijevih kanala, beta-blokatori, toksičnost, hiperinzulinemija-euglikemija, liječenje*