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Case Report

Lipid emulsion therapy in cardiodepressive syndrome after diltiazem overdose—case report

Abstract

We present a case of diltiazem overdose in which the patient ingested 5.6 g in an apparent suicide attempt. She was admitted in the emergency department 2 hours postingestion with cardiodepressive syndrome. She was treated with gastric lavage, activated charcoal, intravenous fluids, calcium, and epinephrine, without improvement in vital signs. We gave her an infusion of 20% intralipid, leading to a favorable evolution. The patient was stable hemodynamically and metabolic in the following 24 hours. She was alert and oriented and was extubated in the second day. She was discharged after 4 days in a good state and without any neurologic deficits.

Overdoses with cardiovascular drugs are associated with significant morbidity and mortality, thus being in the attention of the practitioners. Calcium-channel blockers and β-blockers represent 2 of the most important classes of cardiovascular drugs involved in producing cardiodepressive syndrome [1–3].

In calcium-channel blocker overdoses, the therapeutic measures must be aggressive and initiated as soon as possible. The first-line antidote treatment is calcium and should be administered initially intravenous in bolus and then in infusion. It is recommended to use calcium gluconate intravenous initial dose of 3 to 5 ampoules, 10% solution, followed by an infusion of 1 mL/kg per hour [1–5]. The second line of antidote treatment is represented by glucagon, which stimulates the adenylate cyclases at cellular level, short circuiting in this way the calcium and the β receptors of the myocardium and determining a positive inotropic and chronotropic effect. The initial recommended glucagon doses is 2 to 10 mg administered intravenous followed by an infusion of 0.05 to 0.1 mg/kg per hour [1–5]. A third line of therapy used, so-called metabolic treatment or hyperinsulinemic euglycemia therapy, is represented by administration of insulin in association with hypertonic glucose. Insulin has the role of a positive inotropic agent, helping the heart to use more efficiently the carbohydrates, which will favorably influence the cardiodepressive syndrome. These patients tolerate high doses of insulin as a consequence of insulin resistance and hyperglycemia produced by this poisoning. Usually, one would start with an intravenous bolus of 1 IU/kg followed by an infusion of 0.5 IU/kg per hour in association with a bolus of 25 g of glucose followed by an infusion of 0.5 g/kg per hour [1–6].

Another metabolic therapy recommended for toxic lipophilic agents is represented by intravenous lipid emulsion administration to reestablish the physiologic and metabolic integrity of myocardium by increasing the transport of fatty acids. The administration protocol implies an initial intravenous dose of 1.5 mL/kg in 1 minute followed by an infusion of 0.25 mL/kg per minute [7–13].

An 81-year-old woman, at the second suicide attempt, was brought to the emergency department by ambulance, with the suspicion of an overdose of cardiovascular medication from her own prescription. The patient was found lying unconscious on the floor in her apartment by her son around 11:00 AM. Her son mentioned that about 1 hour before that he had communicated with his mother and she was in a good overall condition. Her son told that she had a history of hypertension and ischemic heart disease, for which was chronically treated with diltiazem and indapamid. Physical examination at admission showed an unconscious old woman with a Glasgow Coma Scale score of 4, heart rate of 50 beats per minute, respiratory rate of 32 breaths per minute, blood pressure of 80/40 mm Hg. She had bronchial rales on both lungs and an oxygen saturation of 80%. She was admitted in the intensive care unit and promptly received tracheal intubation and mechanical ventilation. At the arrival time, the arterial blood gas revealed metabolic acidosis: pH 7.20, bicarbonate level of 12.6 mmol/L, base excess of 17 mmol/L, lactate level of 10.7 mmol/L, glucose of 366 mg/dL, urea of 41 mg/dL, and creatinine of 1.1 mg/dL. We did not measure the serum diltiazem concentration (not available in our hospital). Chest radiography showed bilateral diffuse infiltrates. Electrocardiogram showed sinus bradycardia. She was treated with 4 L of intravenous crystalloid solution and 4 g of calcium gluconate followed by an infusion of 1 mL/kg per minute. In the same time, an infusion with epinephrine was started in a dose of 1 μg/kg per minute. We also performed gastric lavage, and 50-g activated charcoal was administered on gastric tube. Approximately 4 hours from admission, despite aggressive fluid resuscitation associated with calcium and hyperglycemic euglycemia therapy, her condition remained critical. Electrocardiogram showed Mobitz II of 4/1 second-degree atrioventricular block. We gave 100 mL of 20% intralipid followed by an infusion of 0.5 mL/kg per hour for 12 hours, leading to a favorable evolution. The systolic blood pressure increased at 120/70 mm Hg; heart rate was 72 beats per minute. The patient was stable hemodynamically and metabolic in the following 24 hours. She was alert and oriented and was extubated on the second day. She informed that she had taken 96 tablets of 60 mg diltiazem and 16 tablets of 1.5 mg SR indapamid at 9:00 AM on the day she was admitted. She was discharged after 4 days in a good state and without any neurologic deficits.

This case was presented because, to the extent of our knowledge, it is the second case of acute diltiazem overdose treated with intravenous lipid emulsion that has survived. The intravenous lipid emulsion was initially designed to treat cardiotoxicity induced by intravascular injection or local anesthetic overdose. The published

cases with intravenous lipid emulsion for treating cardiotoxicity are few in the scientific literature, only 42 cases, 19 of which had local anesthetics overdoses and 23 had nonanesthetic cardiotoxic medication (tricyclic antidepressants, calcium-channel blockers, and β-blockers) [7,8,11–13].

Calcium-channel blockers cause cardiodepressive syndrome through blockage of calcium channels that are found in myocardium and smooth muscle cells [4,5,9]. Diltiazem depress sinoatrial and atrioventricular nodal conduction, decrease myocardial contractility, and decrease peripheral vascular resistance. In myocardial tissue, this results in negative inotropy, chronotropy, and dromotropy. In vascular tissue, this results in arterial smooth muscle relaxation. Calcium-channel blockers are also considered metabolic poisons [4,5]. The heart is dependent on free fatty acids for energy. In calcium-channel blocker overdose, the heart becomes more dependent on carbohydrates for energy, and insulin release from the pancreas is blocked. As a result, the ability of the heart to use the preferred energy substrate efficiently is exacerbated [4–6]. This determines appearance of hyperglycemia and lactic acidosis and further depressing the myocardial contractility [4-6,9].

The mechanism for intravenous lipid emulsion therapy that has been termed *lipid rescue* has not yet been elucidated [10–12]. Myocardial extraction of free fatty acids is decreased in calcium-channel blocker overdose despite maintained plasma levels [10]. The beneficial effect with intravenous lipid emulsion is enhancement of myocardial fatty acids transport, which restores the physiologic and metabolic integrity of the myocardium [10]. Intravenous lipid emulsion therapy determines an expanded intravascular lipid phase named "lipid sink" [8,10,11]. The lipophilic drugs will repartition into this space moving away from affected organs, thereby reducing the amount of drug available to exert its toxic effects. This mechanism of an altered volume of distribution as a result of binding in a "nontoxic space" is similar to the use of digoxin specific antibody fragments or multiple dose of activated charcoal [10].

Our case demonstrates that fat emulsion therapy can be effective in calcium-channel blocker overdose. The optimal dose, timing, and duration of therapy remain unclear. In our case, we based on previous case reports fat emulsion therapy protocols [7,8,10–12]. Our patient has not developed adverse effects of intravenous lipid emulsion such as acute lung injury or hyperamylasemia. For all cases with lipophilic drug overdoses and hemodynamic instability, when standard resuscitation protocols are unsuccessful, clinicians can consider administration of intravenous lipid emulsion [2,8,11,12]. This method of treatment is currently considered one of the standard treatments for calcium-channel blocker and β-blocker overdoses, being used as a monotherapy or in association with hyperinsulinemic euglycemia therapy. Fat emulsion therapy is now recommended in advanced cardiac life support guidelines for cardiac arrest secondary to lipophilic agents. In conclusion, intravenous lipid emulsion therapy might be considered in cardiodepressive syndromes resulting from calcium-channel blockers overdose if this does not respond to standard resuscitation measures [2,8,11–13].

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