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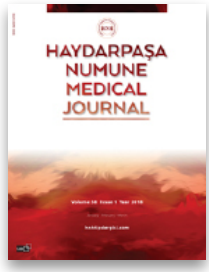

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CASE REPORT

Intravenous Lipid Emulsion Therapy in a Case of Multiple Drug Intoxication: Case Report*

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Abstract

Intake of cardiovascular drugs is frequently observed among the patients brought to emergency departments with an intoxication clinic. In those patients who are treated for intoxication, actual therapy is mainly supportive in most of the cases if there isn't any special antidote for the agent. This case report is about a patient who intended to commit suicide with oral intake of metoprolol, perindopril, atorvastati and isosorbide monohydrate. Upon worsening of her general condition in spite of supportive therapy, she was given intravenous lipid therapy. In this manuscript, application of intravenous lipid therapy is presented in a patient who intended to commit suicide, She was unresponsive to supportive therapy after ingestion of multiple cardiovascular drugs including metoprolol, perindopril, isosorbide monohydrate and atorvastatin.

Keywords: Intravenous lipid; intoxication; isosorbide monohydrate; metoprolol; perindopril.

In the United States every day approximately 2000 cases of intoxication apply to emergency services. Drug intoxication is the most important cause of mortality in adults aged 35-54 years [1]. Cardiovascular drugs are frequently used to commit suicide, and they are at the top of the list of deaths due to poisoning [2].

Standard resuscitation algorithms are often inadequate in intoxications and it is important to consider adjuvant treatments with appropriate antidotes for intoxicated patients. Current treatment algorithms often priorly suggest supportive and symptomatic treatments in the absence of specific therapeutic interventions. Specific antidotes are not available in the majority of intoxications [3].

Metoprolol is a selective β1 adrenergic antagonist. It is the only β1 adrenergic antagonist with official approval by the FDA (Food and Drug Administration) for the treatment of angina pectoris and complications after acute myocardial infarction. It may be used to control ventricular rate, to prevent tachycardia and hypertension in supraventricular tachycardias, atrial fibrillation or flutter occurring in response to perioperative stimuli. When used through IV route, its effect starts within 5-10 minutes and lasts for 2-4 hours [4].

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In case of intoxication with metoprolol, clinical findings vary depending on lipid-solubility of the drug, its partial agonistic effect and dose. Hypotension and bradycardia are the most common cardiac findings. Other clinical features include varying degrees of heart blocks, pulmonary edema, hypoglycemia, and central nervous system symptoms [5].

Perindopril is a new generation angiotensin-converting enzyme inhibitor [6]. In case of poisoning with perindopril, hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitation, bradycardia may be seen [6].

Isosorbide dinitrate causes relaxation in vascular smooth muscle. Its mechanism of action can be summarized as increase in cGMP that activates guanyl cyclase, decrease in intracellular calcium, and the metabolism of nitric oxide that causes vasoconstriction. High doses may cause hypotension [4].

In this case report, in the light of the literature, we aimed to present intravenous lipid therapy in the treatment of patient who ingested metoprolol, perindopril, atovastatin and isosorbide monohydrate for suicidal purposes, in whom we couldn't achieve desired success.

Case Report

A 17-year-old female patient was admitted to the emergency department of our hospital 6 hours after ingesting multiple drugs for the purpose of suicide. From her anamnesis, we learnt that she had applied to an emergency service of an external center 5 hours after drug intake, Gastric lavage was applied to her in this center and activated carbon treatment was started before she was referred to our center (Bülent Ecevit University Medical Faculty Hospital).

At the first evaluation of the patient in the emergency service, it was seen that her general health state was moderately well, and she had somnolence. The Glascow coma score was assessed as 10 points. Her arterial blood pressure was 100/60 mmHg, and heart rate 89 bpm, and the cardiac and respiratory system examinations were not remarkable. She had not any neurological deficit. In the ECG examination, QT and QTc intervals were not prolonged.

Blood count, liver function tests, BUN, creatinine and electrolyte values were within normal limits. As learnt from patient's relatives she ingested 1000 mg metoprolol, 150 mg perindopril, 1800 mg isosorbide monohydrate and 200 mg atorvastatin.

The National Poison Counseling Center was consulted, and close monitoring for her hypotension, bradycardia, A-V block, and glucagon infusion for her hemodynamic stabilization were recommended.

In the treatment of the patient, insulin-dextrose infusion, which ranked on the top of beta-blocker poisoning treatment algorithm, was started and activated carbon treatment was continued. During monitorization of the patient in the intensive care unit, heart rate decreased within the first hour despite insulin-glucose therapy down to 55 bpm. During her intensive care unit follow-up, her heart rate was 40-50 bpm and blood pressure 90/30-110/40 mmHg. A total of 3 mg intravenous atropine was used intermittently. Inotropic treatment was initiated in the patient who could not respond to treatment. Glucagon could not be used because it could not be provided.

Based on risk/benefit ratios, the efficacy of intravenous lipid emulsions in beta-blocker poisonings in experimental studies, and past case presentation, we decided to use intravenous lipid emulsion as described in the literature. The patient was given 100 mL of 20% lipid solution within 15 minutes as an infusion at a rate of 1.5 mL/kg-1. The heart rate before the infusion was 45 bpm and the blood pressure 91/31 mmHg. In ECG evaluation, sinus bradycardia was present and QT interval was 441 ms and QTc interval 392 ms. During lipid infusion, heart rate was 44-46 bpm, blood pressure changed between 93/41-91/38 mmHg. After lipid infusion, heart rate was 43-54 bpm, and sinus bradycardia was achieved. QT duration was 457 ms, and QTc duration 390 ms.

In the patient whose laboratory parametres did not change, the blood pressure was 90/30 mmHg and the heart rate 40-45 bpm. Therapy was continued with close follow-up. Glucagon was procured from outside the province, and its infusion was initiated, which led to normalization of heart rate and blood pressure values with inotropic support. After the hemodynamic stability of the patient was achieved, psychiatric consultation was made and the patient was discharged with the recommendation to apply to the psychiatric outpatient clinic.

Discussion

Cardiovascular drugs are often used for committing suicide and at the same time they are among the top causes of death due to poisoning. In the annual report of American Association of Poison Control Centers for the year 201210.77% of deaths due to poisoning were related to abuse of cardiovascular drugs [2]. Clinical findings in beta blocker poisoning can vary according to the type of drug. The main clinical manifestations that can be seen in beta blocker poisoning include hypotension, bradycardia, prolongation of QRS interval, nausea and/or vomiting, delirium, convulsions and coma [5]. As noted in the literature, bradycardia and hypotension were observed in our patients, resistant to atropine, insulin glucose and inotropic therapy.

In the treatment of beta blocker drug poisoning, activated carbon treatment administered within the first two hours may be beneficial in order to reduce drug absorption and accelerate excretion [5]. In our present case, activated carbon treatment was applied at the center to which he applied after drug intake. Beta blocker poisoning; step therapy in hypotension and shock therapy is recommended. Intravenous fluid therapy should be given as the first step, and if no response is obtained the first choice in the second step should be administration of glucagon [5].

We have planned to use glucagon therapy for bradycardia and hypotension refractory to fluid therapy, atropine and inotropic support, but insulin glucose therapy was used since glucagon was not available in our center, and city, insulin-glucose therapy was used. If the first two steps in the treatment of hypotension in beta blocker poisoning fail, calcium is given at the third step. Treatment with catecholamines, high dose insulin therapy, lipid emulsion therapy and mechanical support (pace-maker, ECMO, intraaortic balloon pump) can be applied at the fourth step if no response is available yet [5]. In our case, intravenous lipid therapy, which was reported to be effective in betabloker poisonings in previous studies and case reports, was used at this step because we couldn't get effective response with previous treatment regimens.

The efficacy of intravenous lipid emulsion therapy (IVLE) has been demonstrated previously in the treatment of cardiac arrest developed with the use of local anesthetic bupivacaine with high lipid solubility [7]. Currently, intravenous lipid administration has become a method of treatment included in treatment guidelines for systemic toxicity developed due to local anesthetics [8]. The first case of successful cardiac arrest following the administration of intravenous lipid emulsion in a case of bupropion and lamotrigine intoxication resulting in cardiac arrest was reported in 2008 [9]. This report was followed by publications that reported successful results of intravenous lipid administrations in the treatment of cardiac arrest developed due to haloperidol [10], amitriptyline [11], and endosulfan use [12] in the following years [10-12].

IVLE has also been found to be effective in the treatment of intoxications with various cardiovascular drugs [13-18]. In previous studies, successful results with lipid emulsion have been reported in cases with verapamil intoxication [13-18]. In an experimental study conducted, it was determined that among cases with verapamil toxicity in the intralipid-treated group, the mean verapamil lethal dose was higher than the control group (25.7 mg/kg vs 13.6 mg/kg) [16].

In another experimental study, the efficacy of different lipid doses (0, 6.2, 12.4, 18.6, 24.8 and 37.6 mL/kg lipid doses) in the treatment of verapamil toxicity was investigated and it was found that lipid administration at high doses prolonged survival times when compared with lower doses (0, 6.2, and 12.4 mL/kg) but doses higher than 18.6 ml/kg did not add any additional survival benefit [17].

Besides, in this study, as a secondary outcome, lipid administration at a dose of 24.8 mL/kg was found to be more effective on heart rate and mean arterial pressure [17]. In another toxicity study, standard resuscitation with atropine, saline, and calcium was compared with lipid therapy, and it has been found that the lipid treatment prolonged the mean arterial pressure and life span relative to standard resuscitation [18].

IVLE treatment is included in the treatment algorithms of beta blocker poisoning [5]. Previous studies have shown the beneficial effects of IVLE administration on propranolol, atenolol and nebivolol toxicities [19-29]. The common point of these events and experimental studies is the reversal of cardiovascular changes resulting from intoxication with highly lipid soluble drugs thanks to intravenous lipid administration.

In a recent randomized controlled trial, 15 patients with non-fatal intoxication manifestations were treated with intravenous lipid treatment and patients in the control group with standard therapy. As a result, Glascow Coma Scale Score was statistically significantly higher in the intravenous lipid group compared to the control group [29]. Nevertheless, IVE treatment did demonstrate a beneficial effect in our case with multidrug intoxication including metoprolol.

In an experimental study conducted after our experience with unfavourable result, it was emphasized that hemodynamically beneficial effects of IVLE therapy were not observed in metoprolol intoxication [30]. The results of this experimental study are consistent with the results we have observed in our case [30].

The number of controlled trials in this area is limited and the majority of information we have, is derived from case reports and trials conducted in animals, as the conduction of randomized controlled prospective studies on the cases with intoxication are challenging for ethical reasons. Today, the main reason why intravenous lipid therapy is not widely used in toxicity algorithms is the lack of sufficient knowledge about the possible side effects of intravenous lipid therapy and the lack of sufficient randomized controlled trials. For this reason, we have found it important to share

the negative consequences of intravenous lipid therapy in our case with multidrug intoxication. Intravenous lipid administration is a method that has been used for a long time in the treatment of parenteral nutrition, so unexpected, very different side effects are unlikely to be encountered.

Intravenous lipid therapy has unfortunately not shown the expected effects in our case with multiple drug intoxication. We believe that it will be useful to continue the experimental studies and case presentations on this subject at an increasing rate.

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