A Case of High Dose Metoprolol Poisoning; Case Report and Literature Review

Yüksek Doz Metoprolol Zehirlenme Vakası; Case Report ve Literatürün Gözden Geçirilmesi

Metin Ocağ MD, Halil Çetinkaya MD, Hüseyin Kesim MD
1Gazi State Hospital, Emergency Clinic Samsun, Turkey

Abstract
β-blockers are prescribed by physicians for many medical reasons (hypertension, long-term prophylaxis of angina pectoris, myocardial infarction, stable heart failure treatment, cardiac arrhythmias, etc.). Although cases of β-blocker poisoning have a low rate of 0.9% among all poisoning cases, they have a high mortality rate. Metoprolol, a type of β-blocker, is a selective β1-adrenoceptor antagonist with sympathomimetic effect. This article aims to present a case who took high-dose metoprolol for suicidal purposes and to examine metoprolol poisoning and its treatment in the light of current literature.

Öz
β-blockerler hekimler tarafından birçok tıbbi nedenle reçete edilmektedir (hipertansiyon, anjina pektorisun uzun süreli profilaksi, myokard infarktüsü, stabil kalp yetmezliği tedavisi, kardiyak arıtmalar, vb.). β-blocker zehirlenmeleri tüm zehirlenmeler içerisinde % 0.9 gibi düşük bir orana sahip olsa da mortalite oranı yüksek seyretmektedir. Bir β-blocker çeşit olan metoprolol sempatomimetik etkisi olan selektif β1-adrenozeptör antagonistidir. Bu makalede suişid amaçlı yüksek doz metoprolol alan bir olgunun sunumu ve metoprolol zehirlenmelerinin ve tedavisinin güncel literatür ışığında incelenmesi amaçlanmıştır.
Introduction
Beta-adreno receptor antagonists, more commonly known as β-blockers, are prescribed by physicians for many medical reasons (hypertension, long-term prophylaxis of angina pectoris, myocardial infarction, stable heart failure treatment, cardiac arrhythmias, etc.) (1). Although cases of β-blocker poisoning have a low rate of 0.9% among all poisoning cases, they have a high mortality rate (2). According to the data of the American Poison Control Center published in 2019, β-blocker poisoning is reported to be in the 7th place among 25 deadly substances (3). In β-blocker poisoning with high lipid solubility; serious central nervous system findings such as seizures, respiratory depression, and coma may be encountered (2). In β-blocker poisoning with high lipid solubility; serious central nervous system findings such as seizures, respiratory depression, and coma may be encountered. In addition, resistant bradycardia-hypotension and shock may occur due to cardiac involvement (2). Metoprolol, a type of β-blocker, is a selective β1-adrenoceptor antagonist with sympathomimetic effect (4). In addition, it has been reported that metoprolol is the second most commonly prescribed β-blocker after bisoprolol worldwide (5). This article aims to present a case who took high-dose metoprolol for suicidal purposes and to discuss metoprolol poisonings in the light of current literature.

Case Report
The patient, who had a previously known diagnosis of diabetes mellitus, coronary artery disease and schizophrenia, was found unconscious at home by his relatives. The patient was brought to the emergency room by the emergency medical call center (112) teams. In the physical examination findings of the patient; his general condition was poor, he was unconscious, his respiration was superficial, arterial blood pressure: 60/40 mmHg, heart rate: 46/min, and glasgow coma score: 5. Elective endotracheal intubation was applied to the patient to ensure airway safety. Bolus IV fluid therapy, dopamine and nor-epinephrine infusion were administered for blood pressure regulation. In the first anamnesis taken from the relatives of the patient, it was learned that the patient did not have any previous medical disorders and the inability to measure the blood metoprolol level in our own medicine, which contains 50 mg of metoprolol. Therefore, gastric lavage with nasogastric tube and 50 gr activated charcoal were applied to the patient. It was observed that drug particles came from the lavage fluid. Since the arterial blood pressure values of the patient were 60/30 mmHg, the patient was administered 3*1 mg of atropine. In addition, calcium gluconate 30 ml slow IV infusion was applied to the patient. Since there was no response to atropine and calcium treatment, 2*5 mg glucagon treatment was administered to the patient with an interval of 15 minutes. Since there was no adequate response to this treatment, the patient was started on 5 mg/hour IV infusion therapy. The patient was admitted to the intensive care unit for continued treatment and follow-up. The patient, who did not respond to all supportive treatments in the intensive care unit, was requested to be referred to the upper center for further treatment. However, the patient whose hemodynamics was unstable could not be referred. Despite all the interventions, the patient died approximately 36 hours after hospitalization.

Discussion
Blockade of β-receptors results in decreased production of intracellular cyclic adenosine monophosphate (cAMP). As a result, the multiple metabolic and cardiovascular effects of circulating catecholamines are reduced (6). The most important predictive factor in β-blocker toxicity is whether the drug has membrane stabilizing activity. It is known that metoprolol has low membrane stabilizing activity only at high doses (7). It is reported that the therapeutic plasma concentration range of metoprolol in the treatment of cardiovascular diseases is 0.035-0.50 mg/L (8). Metoprolol is metabolized by the liver and excreted by the kidneys. The half-life is 3-7 hours. It has moderate lipid solubility and blocks β1 adrenergic receptors. It is reported that the threshold value is 400 mg in adults and 5mg/kg in children (9). Metoprolol overdose, depending on the dose taken in the clinic, may lead to symptoms such as bradycardia, hypotension, cardiogenic shock, hypoglycemia, hypothermia, seizure, altered consciousness, QT prolongation and QRS enlargement (10). In this case, the dose taken by the patient was not clear due to the unreliability of the anamnesis and the inability to measure the blood metoprolol level in our hospital. Our patient had signs of hypotension, cardiogenic shock, bradycardia, first-degree AV block, and altered consciousness.

Due to its lipophilic properties, the drug crosses the blood-brain barrier in β-blocker poisoning and central nervous system effects may be observed. Therefore, rapid airway management is important in such patients (9). In literature, majority of the publications recommend gastric lavage and the administration of activated charcoal in β-blocker poisoning (11,12). However, cases that died despite gastric lavage and administration of activated charcoal were also reported (13). Removal of drug particles by lavage after high-dose drug intake may have a positive effect on prognosis. However, in this case, it was thought that the lavage procedure limited its possible positive effect. In case of seizures in β-blocker poisoning, the first choice is benzodiazepines. If there is QTc prolongation, magnesium sulfate is given; if QRS widening is present, sodium bicarbonate is given in the treatment (9). In the treatment of hypotension and shock, IV fluids and ketocalone and/or high-dose insulin euglycemic treatments are recommended. The mechanism of action of high-dose insulin therapy in β-blocker poisoning is not clear. In the literature, it is unclear whether high-dose euglycemic insulin therapy or ketocalone therapy is superior. However, case series in which high-dose insulin euglycemic therapy is more effective constitute the majority (1,14,15). In another study, it was reported that the combined use of ketocalone and high-dose insulin euglycemic therapy is more effective (16). Such patients may also benefit from the treatment of calcium salts (7). In this case, the patient was administered ketocalone and...
calcium therapy, but no adequate response was obtained. The effect of IV glucagon therapy in patients with hypotensive and cardiogenic shock is also unclear when compared to other agents. Glucagon activates adenylate cyclase independently of beta-adrenergic agents and causes an increase in cAMP. Increased cAMP: Increases the amount of intracellular calcium required for depolarization by increasing contractility. In a previous study, it was reported that high-dose glucagon treatment increased mean arterial pressure and mean heart rate (17). In another study, it was reported that glucagon therapy was not superior to high-dose insulin euglycemic therapy and lipid emulsion therapy (18). In previous studies on animals studies, it has been reported that IV glucagon treatment increases heart rate but does not have a positive effect on mean arterial pressure, cardiac output and mortality (14,20). In this case, the patient was administered IV glucagon bolus and infusion therapy, but no response was obtained. There are limited publications in the literature supporting the efficacy of atropine therapy in bradycardia for beta-blocker poisoning. In a previous case report, it was reported that 0.5 mg of atropine treatment increased heart rate and mean arterial pressure in a 15-year-old female patient who received 500 mg of atenolol (20). In a previous study on animal, it was reported that IV atropine was effective in correcting bradycardia due to propranolol overdose (21). The patient in this presentation was also administered IV atropine treatment, but no response was obtained. There are many case reports and animal studies investigating the effectiveness of IV lipid emulsion therapy in the treatment of beta-blocker poisoning. However, there is no clear evidence supporting the effectiveness of this treatment. In a previous study with 36 patients, 10 patients were given IV lipid emulsion therapy and it was found to be ineffective (22). However, in some case reports, it has been reported that IV lipid emulsion therapy increases heart rate and blood pressure (11,12,23). An experimental study showed that high-dose insulin therapy was more effective than IV lipid emulsion therapy (24). More extensive studies are needed to investigate the efficacy of this treatment. Since metoprolol is not a water-soluble drug, hemodialysis treatment has no efficacy on it (9). Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) therapy also plays an active role in beta-blocker poisoning in cardiogenic shock resistant to all pharmacotherapy. In a previous comparative observational study, V-A ECMO treatment was shown to be effective in eliminating hemodynamic instability (25). There are case reports reporting that cardiac pacemaker application is also effective to eliminate hemodynamic instability in beta-blocker poisoning cases (26). As a result, treatment of beta-blocker poisoning is complex and difficult for physicians. Despite all treatment efforts, mortality is high in such patients. If possible, these patients should be treated and followed up in fully equipped hospitals with toxicology centers. In treatment, catecholamines, vasopressors, fluid therapy, high-dose insulin euglycemic therapy and V-A ECMO applications have a mortality-lowering effect. However, the mortality-reducing effect of glucagon, lipid emulsion therapy, calcium and atropine is not clear (1)

Conflict of Interest: None declared

References

5. (http://www.whocc.no/actcddd_index/).
Model of Severe Propranolol Toxicity: A Pilot Study.
