Seizures and Irreversible Cardiogenic Shock Following Propranolol Poisoning: Report of 2 Cases and Literature Review

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ABSTRACT: Propranolol, a β-blocker (BB), is one of the drugs that can be misused for suicide. The clinical manifestations of overdose can range from asymptomatic to neurological symptoms such as seizures and loss of consciousness, cardiac shock, and even death. Herein, we describe 2 cases that were referred to our hospital's emergency department in northern Iran: The first case was a 37-year-old woman who suffered from a decreased level of consciousness, bradycardia, and hypotension after ingesting 4 g of propranolol tablets. In the second case, a 32-year-old woman was admitted with complete cardiac arrest and a suspected history of ingesting 4.8 g of propranolol pills a few hours before admission. Therefore, the time interval between pill intake and treatment initiation seems to be one of the most important factors in prognosis, in addition to the number and dosage of pills ingested.

KEYWORDS: Propranolol, suicide, seizures, cardiac arrest

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Introduction

Propranolol is a beta-adrenergic antagonist, also known as a β-blocker (BB). Propranolol non-selectively binds to both beta-1 and beta-2 adrenergic receptors and competitively inhibits the binding of epinephrine and nor-epinephrine to these receptors, thus impairing conduction and contraction.[1] It is used to treat a variety of diseases, such as thyrotoxicosis, essential tremor, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, hypertension, angina pectoris, and migraine prevention.[2,3] It is also known as the initiator of the use of BBs in the treatment of cardiovascular diseases.[4] In the field of psychiatry, propranolol is used to treat panic disorders, fear of social situations, and other types of anxiety disorders,[2,3] and in many cases, it is misused for self-treatment due to stage fright and fear of social situations.[5] In addition, there are reports of its misuse for suicide, including by healthcare workers.[6]

The effects of a BB overdose might include hypotension, bradycardia, decreased myocardial contractility, hemodynamic instability, cardiac shock, and hypoglycemia due to the inhibition of glycogenolysis and gluconeogenesis.[7,8] The most lipophilic β-blockers, particularly propranolol, may also easily cross the blood-brain barrier and may cause seizures in overdose situations. Psychological side effects have also been reported with propranolol therapy, and it may also be associated with depression, at least in susceptible patients.[9]

Very little is known about the toxicological characteristics of propranolol regarding the cause of death. However, the most common deaths resulting from BBs are related to propranolol, which can result in cardiac sodium channel blockage, which can widen the QRS and cause monomorphic ventricular tachycardia (VT), or cause the Brugada pattern on electrocardiography (ECG). Death may also result from a severe hemodynamic abnormality that is resistant to treatment. It also contributes to convulsions since it can penetrate the blood-brain barrier.[8,10]

Treatment for overdose is primarily supportive, but in severe cases, in addition to standard conventional treatments such as glucagon, vasopressors, high-dose insulin euglycaemia therapy (HIET), and extracorporeal cardiopulmonary resuscitation (ECPR), extracorporeal membrane oxygenation (ECMO) can be used.[8,11] Herein, we describe 2 cases of propranolol overdose that were referred to the emergency department (ED) in northern Iran, one with 4 g and the other with 4.8 g of propranolol, with 2 different clinical outcomes.

Case Presentation

Case 1

A 37-year-old woman with drowsiness and loss of consciousness was brought to the ED of our hospital in northern Iran half an hour after consuming 100 propranolol (40 mg) tablets to commit suicide. Her vital signs were as follows: blood pressure (BP), 80/50 mm Hg; heart rate (HR), 45 beats/minute; respiratory rate (RR), 18/minute; and temperature, 36.8°C. Her level of consciousness was at the stupor level, which responded only to painful stimulation. In the ED, the patient

was immediately treated with serum dextrose saline at a rate of 20 cc/minute, as well as atropine (1 mg) and nor-epinephrine at a rate of 5 μg/min. She suffered generalized tonic-clonic seizures half an hour after arriving, which were managed by a single dosage of diazepam ampoule (10 mg).

The patient was intubated due to a loss of consciousness, and after a nasogastric tube (NGT) was inserted, gastric lavage was performed, and charcoal powder (60 g) and sorbitol (40 cc) were administered.The results of the initial laboratory testing revealed no electrolyte abnormalities and were normal. The patient's blood sugar was initially 60 mg/dL, but following serum and vasopressor infusion, it increased to more than 100 mg/dL. Except for bradycardia, the ECG revealed no abnormal findings. Due to bradycardia and hypotension, the patient was transferred to the intensive care unit (ICU) and given intravenous (IV) dopamine at a rate of 10 μg/min, calcium gluconate at a dose of 1 g of 10% solution every 8 hours (IV), and glucagon (50 μg/kg over 1 minute, followed by an IV infusion of 1-5 mg/hour), with the goal of adequate perfusion and raising the heart rate above 50 beats/minute.

The patient's husband reported that the patient had a history of major depressive disorder (MDD) and that she was being treated with sertraline (100 mg, tablets) once a day with no previous attempts of suicide. She also had a history of iron deficiency anemia and mitral valve prolapse (MVP), which was treated with propranolol.

The brain computed tomography scan (CT scan) was normal, and the lung CT scan showed evidence of pneumonia aspiration; treatment with ceftriaxone 1 g twice daily (BID) by IV infusion and clindamycin 900 mg 3 times daily (TID) via IV infusion was begun. The sodium-valproate was administered at a dosage of 400 mg stat and then 200 mg BID by IV infusion for up to 48 hours to manage and prevent the patient's seizures. We removed the endotracheal tube 72 hours after the patient's seizures were entirely controlled and did not recur, and after her level of consciousness had increased. She was transferred to the toxicology ward after 4 days in the ICU, when the patient's vital signs had stabilized, and psychotherapy sessions were initiated. After a week, she was discharged in excellent general condition with the recommendation that she continue her counseling at a psychiatric clinic.Written informed consent was obtained from the patient for the publication of this case report.

Case 2

A 32-year-old woman who was found unconscious in her home was brought to our hospital by her husband, who mentioned that 12 empty packets of propranolol had been found next to her (each pack containing 10 tablets, 40 mg). He didn't know the exact time of taking the pills, but mentioned that she had been alone at home for at least 6 hours prior to admission. The patient, a healthcare worker, had no previous psychological disorders or suicide attempts, although her husband had reported a verbal argument that morning. She was in complete cardiopulmonary arrest at the time of admission, so we attempted CPR on her immediately, but it was unsuccessful. The serum level of propranolol was reported to be 3.5 μg/mL after the autopsy, which was in the toxic and lethal range, confirming the diagnosis of propranolol intoxication. Written informed consent was obtained from the patient's parents for the publication of this case report. This study was conducted according to the Declaration of Helsinki Principles. Also, CARE guidelines and methodology were followed in this study.

Discussion

After oral intake, propranolol is well absorbed, having a 30% bioavailability. It has a half-life of 3 to 5 hours but has high fat solubility and high protein binding (90%).[11] However, in overdose, toxin-induced impairment of blood flow to organs, saturation of the enzymatic biotransformation, and a long-term absorption phase may lead to a prolonged apparent elimination half-life.[12] Its therapeutic range is commonly defined as a plasma concentration of 0.05 to 0.10 μg/mL,[11] and its peak effect occurs 1.0 to 1.5 hours after ingestion. According to the literature, propranolol toxicity occurs at plasma concentrations of more than 2 μg/mL and mortality occurs at levels greater than 3 μg/mL.[11,13]

Manifestations of BB overdose can range from asymptomatic bradycardia to cardiac shock and death. Although there is no clear information on the mechanism of death in propranolol poisoning, cardiac depression, which is thought to be an important mechanism of death, usually appears within 2 hours after consumption, and will not occur if it does not happen within 6 hours of ingestion.[14,15]

Treatment of propranolol overdose is primarily supportive and includes measures to accelerate removal of the drug (ie, gastric lavage, activated charcoal, magnesium citrate), as well as treatment to reverse the drug's severe hemodynamic effects. Epinephrine, atropine, isoproterenol, dopamine, and glucagon have all been recommended as therapeutic interventions.[16,17]

In the face of BBs toxicity, glucagon has been advertised as one of the most effective treatment agents because it stimulates the enzyme adenylyl cyclase, resulting in the formation of cyclic adenosine monophosphate (cAMP), which is required for myocardial cell function, thus exerting positive inotropic and chronotropic effects on the myocardium, increasing heart rate, contractility, and improving cardiac conduction.[11] Although the mechanism of action of insulin is still unknown, currently hyper-insulinemic euglycemia is used in the treatment and management of cardiac drug-induced shock, especially with overdose of BBs and calcium channel blockers.[18]

Lauterbach[19] investigated the differential toxicity of BBs (beta1-selective and beta1-nonselective) in adults regardless of exposure intention. It has been shown that medications that are beta1-selective do not cause complications. Patients who have been intoxicated with non-selective beta-1 drugs such as

propranolol seem to have a greater rate of seizures than selective beta-1 drugs (atenolol and asbutolol).

Reith et al[20] showed that 29% of individuals who received a propranolol overdose suffered seizures, indicating that the chemical is lipophilic and has a membrane-stabilizing effect. They also revealed that if patients had QRS >100 ms were more likely to have a seizure. Furthermore, dosages greater than 1.5 g have been associated with seizures.

According to Graudins et al[21] BB overdose is commonly accompanied by shock, which includes significant myocardial collapse, bradycardia, hypotension, and decreased contractility. In overdose, some BBs, such as propranolol and labetalol, antagonize voltage-gated sodium channels and may be associated with a higher mortality risk than other BBs. To improve myocardial contractility, HIET is recommended not only in cases of calcium channel blocker (CCB) overdose but also in cases of BB overdose or a combination of BBs and CCBs. It should be initiated as soon as myocardial dysfunction is suspected. Inotropic and chronotropic support can be provided by catecholamine infusions in addition to this treatment. In BB overdose, high-dose glucagon infusions produced moderate chronotropic and inotropic effects.

Additionally, as the inotropic effects of HIET may be delayed by up to 15 to 60 minutes, supportive treatment using vasopressors may be required. Phosphodiesterase, found in substances like amrinone and milrinone, elevates cAMP and may be beneficial for increasing inotropy. Until the drug effect subsides, prompt initiation of ECPR, ECMO, and continuation of mechanical life support may be required.[8]

Conclusion

In addition to the total dosage, the time interval between ingesting the tablets and beginning the appropriate treatment seems to be one of the most important factors in determining the prognosis of propranolol overdose. Therefore, due to the high mortality of propranolol overdose, clinicians should initiate glucagon immediately in patients with hypotension and bradycardia who are resistant to standard therapy. According to the importance of ECPR and ECMO treatment based on evidence, it is suggested that in severe cases of beta blocker poisoning, ECPR and ECMO should be used in addition to standard conventional treatment to reduce mortality.

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Authorships

ASh involved in the collecting of samples and data. MS and ZZ comprised in the interpretation writing, editing of the manuscript. MS preparing the draft and submitted of the manuscript. All authors reviewed and approved the final version of the manuscript.

Data Availability Statement

The data are available with the correspondence author and can be achieved on request.

Ethical Approval

The study was approved by our local ethics committee.

Informed Consent

Written informed consent was obtained of case 1 from the patient and for case 2, was obtained from the patient's parents for the publication.

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