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Case Report

Successful Treatment of Propafenone Intoxication with Intravenous Lipid Emulsion and Review of the Literature

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Abstract

Propafenone is Class Ic antiarrhythmic medication widely used for treating arrhythmias. Propafenone is commonly used for treating atrial fibrillation in patients with no structural heart disease. Intake of an excessive amount of propafenone can lead to cardiotoxic symptoms, such as hypotension, arrhythmias, and death. We report on the case of a 22-year-old female presenting to the Dumlupınar University Evliya Çelebi Training and Research Hospital emergency department after trying to commit suicide by ingesting 6750 mg of propafenon. The patient was initially treated with intravenous fluids, bicarbonate, and atropine. The patient's clinical condition improved quickly and dramatically on the 15th min of intravenous lipid emulsion therapy. For cases that do not respond to initial treatment with intravenous fluids, bicarbonate, and atropine treatment, intravenous lipid emulsion should be primarily considered among treatment choices.

Keywords: Propafenone, intoxication, lipid emulsion

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Introduction

Propafenone is a Class IC antiarrhythmic agent, which has no effect on potassium channels, suppresses beta-adrenergic activity by blocking sodium channels in a velocity-based manner, and blocks the calcium channel (1). Toxic side effects occur in intakes of over 900 milligrams and may lead to fatal consequences by causing myocardial depression, refractory epileptic seizure and ventricular dysrhythmia. Upon examining the literature, it is observed that survival is very rare especially after intakes of over 6 grams. Various treatments such as insulin-dextrose, glucagon, sodium bicarbonate, intravenous lipid emulsion (ILE) therapy and pacemaker were administered in the treatment of intoxication, but a standard treatment protocol could not be developed (2).

It was aimed to present a case of intoxication after suicidal ingestion of forty-five 150-milligram tablets of propafenone (6750 mg) successfully treated with ILE therapy.

Case Report

A 22-year-old female patient who was unconscious was brought to the emergency department by ambulance services after intake of propafenone (forty-five 150-mg tablets) to commit suicide. Upon physical examination performed in the emergency department, the Glasgow Coma Scale was 7, heart rate was 40/min, blood pressure was 60/40 mmHg, and respiratory rate was 20/min. First-degree atrioventricular block, right bundle branch block, QRS enlargement, sinus bradycardia were detected in the ECG (Figure 1). Venous blood gas examination revealed pH: 7.13 PCO_2: 43 PO_2: 35 HCO_3: 13 SO_2: 56

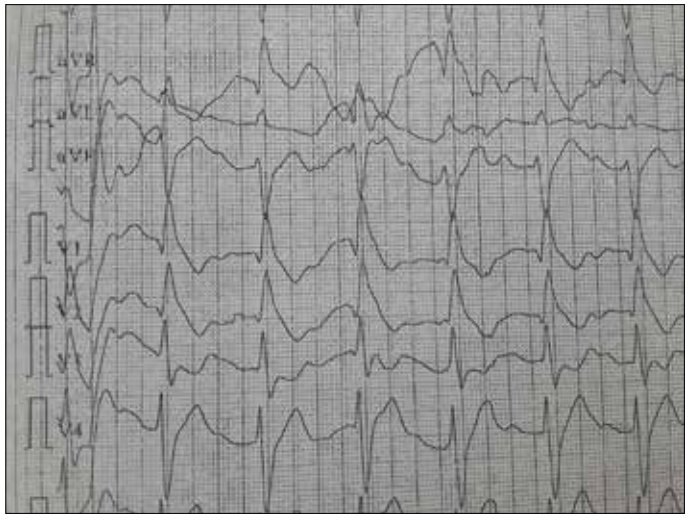

Figure 1. ECG of the patient on admission, first-degree atrioventricular block, right bundle branch block, QRS enlargement, sinus bradycardia.

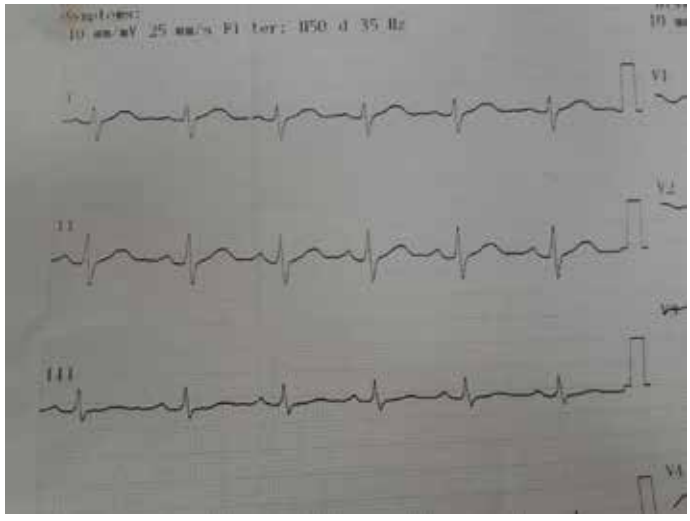

Figure 2. Normal ECG after treatment.

lactate: 11.7. The patient was admitted to the general intensive care unit for a for further examination and treatment. After the nasogastric tube was placed and the stomach lavage was performed, the patient was administered activated charcoal four times within the first 24 hours in a dose of 1 gr/kg every six hours. Sodium bicarbonate infusion in a dose of 1.5 mEq/kg was initiated for deepening metabolic acidosis. For treatment of hypotension, fluid infusion treatment was started after fluid boluses with 0.9 isotonic, 1 milligram of atropine was administered three times for bradycardia, and dopamine infusion was increased up to a dose of 20 mcg/kg/min. The patient suffering tonic-clonic seizure during the first hour of follow-up was administered two milligrams of midazolam to ensure seizure control. The blood propafenone level could not be presented because the propafenone level could not be measured in our hospital.

Patient was administered 20% ILE at a dose of 1.5 mL/kg in 3 minutes, than infusion was started at a rate of 0.25 mL/kg/min for one hour since the patient had seizures, bradycardia, and hypotension. After ILE infusion, dopamine need gradually decreased, ECG returned to normal sinus rhythm (Figure 2), no second seizure activity was observed and the patient's consciousness recovered, the blood pressure returned to normal without vasopressor support, the heart rate and ECG changes and other vital signs also improved. On the second day of the hospitalization, patient had full orientation and was cooperative; oral feeding was initated ; intravenous fluids were ceased, and psychiatry and cardiology departments were consulted. The patient who was discharged to the cardiology department on the third day of hospitalization was discharged without any complications.

Discussion

Propafenone is a Class IC antiarrhythmic agent that inhibits beta-receptor activity by blocking sodium and calcium channels. It is used as second step in the treatment of resistant supraventricular and ventricular arrhythmia (1). Its oral bioavailability varies between 3 and 10%. It can be used in two or three divided doses per day in a dose range of 150 milligrams and 900 milligrams for an antiarrhythmic treatment effect in patients with normal liver and kidney functions (2). After intake, it shows its essential effect by splitting into major metabolites by the cytochrome P450 2D6 (CYP2D6) enzyme in the liver (3). Many fatal toxic side effects of it can be observed due to the intake of over 900 milligrams. These are mainly tonic-clonic seizures, bradycardia, atrioventricular or intraventricular block, ventricular fibrillation. Toxicity treatment is not standard, and it is recommended to administer dopamine, epinephrine and norepinephrine for hypotension as supportive care after the ventilatory support is first provided, and to start sodium bicarbonate solution in patients with deepening metabolic acidosis. Pacemaker application can also be used for bradycardia that does not improve despite these treatments. Glucagon, magnesium, insulin-dextrose, ILE therapy to reduce the toxic drug effect are also among the recommended treatment options (4). Upon examining the literature, it is observed that two studies were conducted on the removal of propafenone metabolites from the body by peritoneal dialysis, intermittent hemodialysis and continuous hemodiafiltration. In these studies, it was observed that propafenone could not be removed from the body by intermittent hemodialysis or continuous hemodiafiltration (5, 6). In their report, Jacob et al. (7) used ILE therapy in two cases for propafenone intoxication treatment. While one of the two cases was successfully treated, it was reported that the other case died. In another report of Tusscher et al. (8), ILE therapy was used for intoxication that developed after the use of propafenone together with enalapril, dabigatran and sildenafilin to commit suicide. It was reported that the vital signs improved in the early period in the treated case, but extubation was performed late. Our patient is also important because she is one of the rare cases treated successfully with ILE therapy along with supportive care after propafenone intoxication.

The first study showing the effectiveness of ILE therapy was conducted on rats in 1998. In the treatment of bupivacaine-induced asystolia, saline, 10%, 20% and 30% lipid emulsion infusion were administered, and plasma bupivacaine levels were compared. It was determined that the plasma bupivacaine level of patients administered with 30% lipid emulsion was significantly higher compared to saline, and the bupivacaine need for animals to die was 50% higher compared to the others treated. As a result of the study, it was reported that lipid infusion could be used in the treatment of bupivacaine-induced cardiotoxicity (7). The first successful treatment with ILE after cardiac arrest due to local anesthesia was reported in 2006, and ILE therapy was started to be used in cases with cardiovascular collapse within the following years (7).

It has been reported that ILE therapy, which is widely accepted as the standard treatment in local anesthetic toxicity, can also have therapeutic effectiveness for the toxicity of many other lipophilic drugs such as antipsychotics, antidepressants and calcium channel blockers (9). Although the effect of ILE therapy on how to provide this benefit has not yet been fully understood, many theories have been proposed to explain its effect mechanism. One of them is the "lipid sink" theory. According to this theory, the lipid emulsion forms a concentration gradient in the plasma for a toxic drug in the tissue, takes the toxic drug from tissue to the lipid phase and ensures that it moves away from target receptors (7, 10). A second mechanism is that ILE infusion provides a continuous source of energy for myocytes under toxic conditions (11). Another proposed mechanism is that it provides an increase in contractility in the cardiac myocyte cells by affecting the voltage-gated sodium channels and sodium channels. According to other mechanisms proposed, it increases the positive inotropic effect as a metabolic stimulant through the G proteins, which are the second messenger, and shows its effect by ensuring that pH moves to alkaline side (12, 13).

Although there is no consensus on the timing and dose of ILE therapy in various intoxications, especially in case of the development of cardiovascular complications associated with local anesthetics, the guide's recommendation is to repeat the second dose according to clinical requirement after giving bolus in a dose of 1.5 mL/kg or 100 mL from 20% intralipid solution, and to administer infusion at a rate of 0.25-0.50 mL/kg 30-60 minutes (13). In our patient, the infusion was administered at a rate of 0.25 mL/kg for approximately one hour through the peripheral route after giving bolus in a dose of 1.5 mL/kg from 20% lipid solution. Although there is no recommendation or priority in terms of the route of administration (central/peripheral) in the literature, it has been mentioned that the peripheral route may lead to the development of deep vein thrombosis. There is no specified ILE therapy regimen algorithm recommended for propafenone intoxication, and the treatment regimens used in the literature are different from each other. Since clinical recommendations regarding the use of ILE therapy in poisonings and intoxications have low level of evidence, there is a need for further studies to determine the effectiveness, indication, side effects, limitations and the best treatment regimen.

Although the use of ILE as an antidote has extensive effectiveness in terms of rapid clinical improvement and seems life-saving its side effects such as pancreatitis, respiratory distress syndrome, fat overload syndrome, hepatosplenomegaly, hepatitis, seizure, fat embolism and coagulopathy have been reported (7). Levine et al. (7) used ILE therapy in the toxication caused by the ingestion of overdose tricyclic antidepressant in a 13-year-old female patient and reported that pancreatitis and acute respiratory distress syndrome developed as side effects as a result of this treatment. Meaney et al. (14) successfully treated the patient by using 2300 mL 20% ILE therapy as a first-line treatment in the treatment of unresponsive shock due to amlodipine and ethanol usage for four and a half hours (total infusion dose 20.9 mL/kg) and discharged the patient without any sequela. They reported rapid improving lipaemia and hypoxia as a side effect of ILE therapy. In our patient, no side effects were faced during the treatment in the intensive care unit, transfer to the cardiology service and at discharge.

Although there are studies (7) showing that ILE therapy is useful in cardiovascular collapse due to the excessive use of lipophilic drug, there are also opposing studies (15, 16). Especially in life-threatening situations such as cardiac arrest and refractory shock, it is recommended that treatment can be administered by considering that the benefit and potential risk are equal. The reason why there is no recommendation on its definite administration is the inconsistent results reported in literature and studies and the possibility that ILE therapy may increase the absorption of toxins and also may interact negatively with the treatments that are considered to be useful, such as vasopressor and insulin, glucagon (17). Since ILE therapy was administered towards the end of the supportive care given, it is difficult to distinguish whether the benefits that are considered to belong to ILE therapy are due to previous treatments or synergistic effects. Furthermore, treatment failures are rarely reported. When it is considered from this point of view, ILE therapy was applied as the initial treatment regimen because it is rapid-acting due to the fact that the general condition of our patient was getting worse and she was about to go into refractory shock despite hemodynamic support. It may be important in terms of showing that treatment is effective. ILE therapy was administered alone in our case as in the case reported by Young et al. (18) and Wilson et al. (19). In our case, the need for dopamine gradually decreased approximately fifteen minutes after the bolus dose of ILE therapy, and the dopamine infusion was stopped in the first hour of treatment. In other cases reported, ILE therapy and other support treatments such as insulin-dextrose, glucagon were administered together. In the case reported by Doepker et al. (20), ILE therapy was administered together with insulin-glucose treatment, and the patient was discharged without sequela on the fourth day. The use of ILE therapy in this way should be kept in mind as a life-saving treatment option for many patients by leading to a new effect mechanism for the treatment of toxications resulting from the ingestion of excessive doses of lipophilic agents.

Conclusion

The fact that ILE therapy, which has been used for nutrition therapy for many years, has therapeutic effectiveness for the toxicity of many other lipophilic drugs such as antipsychotics, antidepressants and calcium channel blockers for suicide or at overdose, apart from its known use in local anesthetic toxicity, may provide a new treatment modality that should be kept in mind when other treatment options do not work or can be used with other treatment options. As information on ILE treatment and its characteristics continues to increase, its safe usage rate in toxications will also continue to increase.

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