Journal of The Cardiovascular Thoracic Anaesthesia and Intensive Care Society

GKDA Derg 2024;30(4):157-160
Doi: 10.14744/GKDAD.2024.68725

CASE REPORT

Protamine Sulfate Infusion's Rare Side Effect: Severe Hypertension, Tachycardia

Buket Özyaprak,[1] Gürcan Güler,[1] Tuğba Onur,[1] Filiz Ata,[1] İbrahim Burak Şeker,[2] Hande Gürbüz,[3] Nail Kahraman[4]

[1]Department of Anesthesiology and Reanimation, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Türkiye
[2]Department of Cardiovascular Surgery, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Türkiye
[3]Department of Anesthesiology and Reanimation, University of Health Sciences, Bursa City Hospital, Bursa, Türkiye
[4]Department of Cardiovascular Surgery, University of Health Sciences, Bursa City Hospital, Bursa, Türkiye

ABSTRACT

Protamine sulfate is an agent used to antagonize the anticoagulant effect of heparin. Some side effects may occur during the administration of this agent. The most common side effects are hypotension, bradycardia, pulmonary vasoconstriction, and hypoxemia. However, hypertension and tachycardia may also occur, albeit rarely. Here, we present a case in which hypertension and tachycardia developed during protamine sulfate infusion in open-heart surgery.

Keywords: Hypertension, protamine sulfate, side effect, tachycardia

Please cite this article as: "Özyaprak B, Güler G, Onur T, Ata F, Şeker İB, Gürbüz H, Kahraman N. Protamine Sulfate Infusion's Rare Side Effect: Severe Hypertension, Tachycardia. GKDA Derg 2024;30(4):157-160".

Introduction

Protamine sulfate is a drug routinely used to reverse the systemic anticoagulation effects of heparin. However, some side effects may occur due to anaphylactic reactions during the application of protamine sulfate. The most frequently reported side effects in the literature are hypotension, bradycardia, pulmonary vasoconstriction, and hypoxemia.[1] Other rare side effects of protamine sulfate are hypertension and tachycardia. These side effects of protamine sulfate were also reported in a case report by Andersen et al.[2] Information about these side effects in the literature is limited and outdated.[2–5] We aimed to contribute to the literature by sharing our case in which sudden hypertension and tachycardia developed during protamine sulfate infusion after cardiopulmonary bypass in open-heart surgery.

Case Report

A 75-year-old female patient was scheduled for coronary artery bypass graft (CABG) surgery with comorbidities of essential hypertension and type-2 diabetes mellitus regulated with oral antidiabetics. She had no history of allergies. The patient underwent a routine CABG procedure with cardiopulmonary bypass, and extracorporeal circulation (ECC) was terminated when the surgical procedures were completed. Before ECC was terminated, anesthesia was maintained by applying anesthetic agents to the patient. The protamine sulfate dose (Promin, Vem İlaç Sanayi, Türkiye) to be applied for the neutralization of heparin (Koparin vial, Koçak Farma İlaç Sanayi, Türkiye) was calculated as 1.3 mg of protamine sulfate for every 100 Units of heparin. Protamine sulfate was administered to the patient

Address for correspondence: Buket Özyaprak, MD. Sağlık Bilimleri Üniversitesi, Bursa Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, Bursa, Türkiye
Phone: +90 224 275 64 00 **E-mail:** b.ozyaprak@hotmail.com

Submitted: October 21, 2024 **Accepted:** December 03, 2024 **Available Online:** December 31, 2024
The Cardiovascular Thoracic Anaesthesia and Intensive Care - Available online at www.gkdaybd.org

intravenously (IV) through a different peripheral venous route where inotropic and vasopressor agents were not given. However, during our application of protamine sulfate, hypertension and tachycardia developed, and the patient became hemodynamically unstable. When the patient became hemodynamically stable with medical treatments, the aortic cannula was removed from the aorta. The hemodynamic findings that developed in the patient and the medications administered to the patient in the stages immediately before and after the termination of the ECC phase are summarized in Table 1. The patient, who had no other problems during the intraoperative and postoperative periods, was discharged on the 7th postoperative day.

Discussion

Protamine sulfate is used to antagonize the anticoagulant effect of heparin in open-heart surgery with cardiopulmonary bypass, but it may cause serious side effects. Hypertension, which may develop suddenly as a protamine sulfate reaction, is one of these side effects and may result in mortality in open-heart surgery. Severe hypertension that develops before aortic decannulation from the aorta may cause aortic dissection. Therefore, our approach to the sudden attacks of hypertension and tachycardia during protamine sulfate administration was aggressive medical treatment in this case (Table 1). During the last of these hypertension and tachycardia attacks, we considered that it might be an allergic

Table 1. Hemodynamic findings and medications administered at the end of the patient's ECC period and in the subsequent periods

Periods	Hemodynamic findings and administered medications
Before ECC terminated period	Mean arterial blood pressure: 70 mm Hg - Pulse: 95 beats / minute CVP: 11 mmHg Maintenance of anesthesia was applied (IV) • Midazolom 0.02 mg/kg (Zolamid, Vem İlaç Sanayi, Türkiye) • Fentanyl 2 mcg/kg (Talinat, Vem İlaç Sanayi, Türkiye), • Rocuronium 0.3 mg/kg (Myokron, Vem İlaç Sanayi, Türkiye) Inotropic agent therapy (IV) • Dobutamine 5 mcg/kg/minute (Dobcard, Vem İlaç Sanayi, Türkiye) Vasodilator agent treatment (IV) • Nitroglycerin 0.1 mcg/kg/minute (Perlinganit, Adeka İlaç Sanayi, Türkiye)
Protamine sulfate test dose application period	Systemic arterial blood pressure: 185/95 mmHg - Pulse rate: 103 beats/minute CVP: 11 mmHg Volatile Anesthetic Agent was started • Sevoflurane 0.5 MAC (Sevorane,Abbott, USA) Inotropic agent therapy (IV) • Dobutamine 1 mcg/kg/minute Vasodilator agent administered as a bolus (IV) • Nitroglycerin 0.3 mg/minute Vasodilator agent infusion therapy is increased (IV) • Nitroglycerin 0.3 mcg/kg/minute
In the 50% of protamine sulfate application period	Systemic arterial blood pressure: 212/105 mmHg - Pulse: 124 beats/minute CVP: 12 mmHg Anesthesia maintenance was repeated and the MAC value of the volatile anesthetic agent was increased. • Midazolom 0.02 mg/kg • Fentanyl 2 mcg/kg • Rocuronium 0.3 mg/kg • Sevoflurane 1 MAC Beta blocker and vasodilator agent were administered as bolus (IV) • Metoprolol 2mg/minute (Mepolex, Menta Pharma İlaç Sanayi, Türkiye), • Nitroglycerin 0.3 mg/minute Inotropic agent therapy (IV) • Dobutamine infusion was stopped. Vasodilator agent infusion treatment dose increased (IV) • Nitroglycerin 0.5 mcg/kg/minute

Table 1. Cont.

During the total dosage of protamine sulfate completion period	Systemic arterial blood pressure: 235/122 mmHg - Pulse: 132 beats/minute CVP: 11 mmHg Different intravenous anesthetic agent was administered (IV) and volatile anesthetic agent was continued • Propofol (Propofol, Polifarma İlaç Sanayi, Türkiye) • Sevoflurane 1 MAC Beta blocker and vasodilator agent were re-administered as bolus (IV) • Metoprolol 2mg/minute • Nitroglycerin 0.3 mg/minute Vasodilator agent infusion therapy was continued (IV) • Nitroglycerin 0.5 mcg/kg/minute Antiallergic agent and steroid agent were administered (IV) • Pheniramine 0.5 mg/kg (Avil, Sandoz İlaç Sanayi, Türkiye) • Dexamethasone 0.5 mg/kg ((Dekort, Deva İlaç Sanayi, Türkiye)

ECC: Extracorporeal circulation; CVP: Central venous pressure; IV: Intravenous; MAC: Minimum alveolar concentration.

reaction due to protamine sulfate infusion and administered an antiallergic agent and steroid as IV treatment (Table 1).

Andersen et al.[2] published an article regarding the protamine sulfate side effects of hypertension and tachycardia in a patient who was on a hemodialysis program. After the protamine sulfate infusion administered at the end of the hemodialysis procedure, the patient developed hypertension and tachycardia, and this event occurred a total of three times on different dates. In the same publication, it was reported that, according to the files of the Medication Experience Unit at The Upjohn Company, five patients on a chronic dialysis program also developed hypertension with protamine sulfate administration after dialysis. The common feature of these reported patients is that they were undergoing hemodialysis. Additionally, two patients had a history of allergy. In our case, there was no history of hemodialysis or allergy. However, it is frequently emphasized in publications that side effects during protamine sulfate administration may be due to anaphylactic reasons.[1,2]

Gourin et al.[3] observed a slight increase in blood pressure after protamine administration in normovolemic dogs. However, this effect was thought to be due to excessive volume replacement following an impact of volume pooling in the splanchnic area rather than a decrease in systemic vascular resistance.[3] In a later study by Coulon et al.,[4] it was stated that the hemodynamic response following protamine sulfate was closely related to the patient's volume status. Additionally, the authors suggested that protamine sulfate may increase blood pressure in patients with optimal volume replacement. In our case, the normal CVP values suggested that our patient was normovolemic during protamine sulfate application. This may be one of the factors causing protamine hypertension (Table 1). When protamine is administered intravenously from a peripheral route, it first reaches the pulmonary circulation. With the hypothesis that side effects of protamine sulfate in the pulmonary vascular area can be avoided by bypassing the pulmonary circulation, Pauca et al.[5] administered protamine sulfate through the aorta to 79 patients in their study. According to the results of this study, a slight but significant increase in systemic arterial blood pressure and heart rate, as well as a significant increase in cardiac output ($p<0.001$), were observed. They thought these results might be due to protamine sulfate's systemic arterial vasoconstrictive effect, which is similar to the effect on pulmonary circulation after its intravenous application.[5]

In conclusion, it should not be forgotten that there may be an increase in blood pressure and heart rate in patients during protamine sulfate administration. This outcome can be caused by both immune and non-immune factors. We think that the first condition for the clinician to prevent negative consequences in such a side effect is to make the diagnosis immediately and apply the treatment urgently.

Disclosures

Informed Consent: The authors stated that written consent was obtained from the patient in the study.

Authorship Contributions: Concept – B.Ö., G.G.; Design – B.Ö., G.G., N.K.; Supervision – B.Ö., T.O., F.A.; Fundings – B.Ö., G.G., H.G.; Materials – B.Ö., G.G., İ.B.Ş.; Data collection &/or processing – B.Ö., G.G., İ.B.Ş., N.K.; Analysis and/or interpretation – B.Ö., G.G., H.G.; Literature search – B.Ö., G.G., H.G., N.K.; Writing – B.Ö., G.G.; Critical review – B.Ö., T.O., F.A.

Conflict of Interest: All authors declared no conflict of interest.

Use of AI for Writing Assistance: No AI technologies utilized.

Financial Disclosure: The authors declared that this study has received no financial support.

Peer-review: Externally peer-reviewed.

References

1. Nybo M, Madsen JS. Serious anaphylactic reactions due to protamine sulfate: A systematic literature review. Basic Clin Pharmacol Toxicol 2008;103:192–6.
2. Andersen JM, Johnson TA. Hypertension associated with protamine sulfate administration. Am J Hosp Pharm 1981;38:701–3.
3. Gourin A, Streisand RL, Stuckey JH. Total cardiopulmonary bypass, myocardial contractility, and the administration of protamine sulfate. J Thorac Cardiovasc Surg 1971;61:160–6.
4. Coulon C, Freysz M, Jaboeuf R, David M. Appreciation of optimal loading at the end of cardiopulmonary bypass: "The protamine sulfate test". Int J Artif Organs 1982;5:387.
5. Pauca AL, Graham JE, Hudspeth AS. Hemodynamic effects of intraaortic administration of protamine. Ann Thorac Surg 1983;35:637–42.