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Case Report

Anaphylaxis following unfractionated heparin administration: How safe is this drug in the treatment of thromboembolism?

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ABSTRACT

Heparin, a naturally occurring polysaccharide belonging to the glycosaminoglycans (GAG) family, is ubiquitously found in mast cells. Unfractionated heparin is the least processed form of natural GAG, purified from animal tissue. In a 67-year-old female patient diagnosed with hypertension and asthma, who suffered a femoral fracture due to a fall, intravenous heparin sodium was administered for thromboembolic treatment in the postoperative period following closed reduction. Subsequently, respiratory distress, loss of consciousness, and cardiac arrest occured following profound hypotension. The patient, whose clinical findings were evaluated as anaphylaxis, was successfully resuscitated with prompt intervention. Despite immune-mediated reactions and Heparin-Induced Thrombocytopenia (HIT) being commonly encountered side effects in clinical practice, it is crucial for all healthcare professionals to recognize that widely used anticoagulant agents such as heparin sodium can lead to fatal complications.

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1. Introduction

Heparin has found widespread application as an anticoagulant for patients with thromboembolic disorders, those undergoing hemodialysis, as well as individuals undergoing cardiac and arterial surgeries. While bleeding represents the most prevalent side effect, immune-mediated reactions such as thrombocytopenia, skin necrosis, and eczema are also frequently observed [1]. Acute hypersensitivity reactions such as urticaria, angioedema, and bronchospasm, as well as anaphylaxis due to heparin, are seldom reported [2,3].

Anaphylaxis incidents have been documented in the literature, particularly following repeated exposure to heparin sodium sourced from bovine intestines. This case report is presented as unique due to the anaphylaxis episode occurring upon initial exposure to heparin sodium derived from porcine intestines. The current case report was meticulously prepared following the CARE case report guidelines. Informed consent was obtained from the patient for this case presentation in accordance with the Declaration of Helsinki.

2. Case Report

A 67-year-old female patient, with a body mass index (BMI) of 34 (161 cm tall and weighs 89 kg), presented to the Orthopedics department for consultation. She had a medical history of hypertension and asthma. The consultation was regarding a closed reduction procedure, necessitated by the inability to palpate distal peripheral pulses in her left lower extremity. This condition followed a knee prosthesis dislocation resulting from a fall during ambulation.

Upon review of the patient's medical records, it was noted that she did not regularly use medication for asthma. Furthermore, there was no documented history

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of immune-mediated diseases or drug allergies in either the patient or her family. A thorough evaluation of the respiratory system, including lung auscultation, revealed no pathological findings. The patient's peripheral oxygen saturation was measured as 94% while breathing room air, and arterial blood gas values were within normal limits. An electrocardiogram performed in the emergency department indicated sinus rhythm, and subsequent monitoring showed the patient to be normotensive and maintaining a normal heart rate. Based on the blood tests taken in the emergency department, the patient's hematocrit level, electrolyte values, and coagulation parameters were within normal limits.

Following a preoperative assessment, a successful closed reduction procedure was performed under sedoanalgesia (by administering 2 mg midazolam and 50 mcg fentanly) in the operating theatre without complications. The patient, whose postoperative Numeric Rating Scale (NRS) score was evaluated as 1–2 during the postoperative period, was planned to receive an analgesic regimen consisting of 1 gram of paracetamol three times a day. Subsequent postoperative evaluation via contrast-enhanced computed tomography of the lower extremity revealed a 2.5 cm segmental thromboembolism in the proximal left tibialis posterior artery. Consequently, consultation with the Cardiovascular Surgery Department led to the initiation of intravenous unfractionated heparin (UFH) therapy at a dose of 5000 IU (Poliparin®, Polifarma, İstanbul/Türkiye).

Approximately 5 minutes after the commencement of heparin infusion, the patient experienced severe respiratory distress and wheezing consistent with laryngeal edema. Additionally, there was a loss of consciousness (Glasgow Coma Score decreased from 15 to 7) and profound hypotension (systolic arterial pressure was measured as 64/36 mmHg). Subsequently, ventricular tachycardia from sinus rhythm was observed. Based on these findings, a diagnosis of anaphylactic shock was considered. Cardiac arrest due to asystole occurred roughly 1 minute after the onset of shock symptoms and clinical intervention, occurring simultaneously. Immediate interventions included administration of 1 mg adrenaline and 80 mg prednisolone via 20 G peripheral venous access, along with oxygen support using a bag valve mask. Cardiopulmonary resuscitation was initiated, leading to the restoration of spontaneous rhythm after 2–3 minutes. Following that, there was no requirement for an additional adrenaline bolus or positive inotrope.

Although initially considered for intubation, the patient exhibited rapid improvement in consciousness and vital signs. There were no signs of laryngeal edema, and the patient showed full cooperation with normal vital parameters. Consequently, the decision to proceed with intubation was deferred. Subsequent electrocardiography revealed atrial fibrillation, which was managed with amiodarone infusion according to protocol.

Further evaluation via echocardiography post-anaphylaxis revealed multiple cardiac abnormalities including sclerotic aortic valve, ascending aortic dilatation, aortic insufficiency, mitral and tricuspid insufficiency, left atrial dilatation, left ventricular hypertrophy, and diastolic dysfunction, with an ejection fraction of 65%. Consultation with the Immunology department confirmed the diagnosis of acute anaphylaxis to UFH based on clinical evaluation and exclusion of alternative causes. Given the risk of re-anaphylaxis with allergy testing due to ongoing low molecular weight heparin use, testing was not recommended at that time. Instead, a plan for future testing during a period of heparin abstinence was proposed. The decision was made to discontinue UFH therapy and initiate treatment with fondaparinux (7.5 mg subcutaneously once a day) to manage thrombophlebitis The patient was monitored in the intensive care unit for two days to ensure airway safety and monitor for late signs of anaphylaxis. No complications were observed during this period. Subsequently, due to the absence of indications for continued intensive care, the patient was discharged to the Orthopedics service without complication.

3. Discussion

As detailed in the case presentation, the patient's unexpected reaction to unfractionated heparin was promptly and effectively managed with intervention. This drug is commonly utilized in various surgical procedures for different medical indications in our clinic. The timely intervention averted potentially severe consequences. Heparin, a medication with broad indications across various medical specialties and global utilization, exhibits a side effect spectrum encompassing simple hypersensitivity responses to potentially fatal anaphylactoid reactions [1–3].

The rationale behind initiating intravenous unfractionated heparin therapy instead of other alternatives like low molecular weight heparin (LMWH) products or non-vitamin K antagonist oral anticoagulants (NOACs) based on several factors including immediate anticoagulation (rapid onset of aciton), reversible anticoagulation (shorter half-life), monitoring (monitoring of activated partial thromboplastin time (aPTT) to adjust the dose and maintain therapeutic levels) and renal impairment [4].

Anaphylactic symptoms and anaphylactic shock represent serious, swiftly progressing, and potentially lethal systemic reactions that manifest subsequent to exposure to a triggering agent The diagnosis of anaphylaxis is established based on clinical criteria, emphasizing the urgency to promptly initiate treatment in life-threatening situations. Adrenaline stands as the primary pharmacological intervention for anaphylaxis, and there are no absolute contraindications to its administration. Swift intravenous administration of adrenaline in anaphylaxis treatment is crucial to avert the onset of profound hypotension, which can lead to fatal outcomes [5].

Commercial UFH is derived from porcine intestinal mucosa or bovine lung. It comprises a blend of polysaccharides with substantial protein-binding affinity, typically sized between 10 to 20 kDa, and exhibits notable allergenic potential. The precise pathophysiology underlying heparin-induced anaphylactoid reactions remains incompletely understood; nevertheless, their potential for mortality underscores the paramount importance of

prompt and efficacious intervention [2]. It is somewhat remarkable that the number of reported cases of anaphylaxis attributed to heparin is relatively low, with most documented instances dating back several decades [1]. Bernstein [6] has reported the first documentation of anaphylaxis to heparin sodium. It involved a 71- year-old woman who had received heparin after a heart attack but experienced anaphylaxis when given heparin again due to thrombophlebitis. Bernstein reviewed 32 cases of heparin sensitivity, where seven showed anaphylaxis after heparin use. One case showed hypersensitivity to bovine heparin without skin reactions but with antibodies against bovine heparin [7]. Another report documented anaphylactic shock from porcine heparin during heart valve surgery [8].

Heparin-induced anaphylactic and anaphylactoid reactions, especially those linked to oversulfated chondroitin sulfate (OSCS) contamination in the drug, have gained increased attention in recent decades. A critical moment came in 2007 when a surge in anaphylactic reactions tied to unfractionated heparin (UFH) was noted [4]. This discovery followed the FDA receiving 574 reports via the Adverse Event Reporting System related to heparin use. Among these, 94 resulted in deaths, and 68 showed symptoms of allergic reactions like nausea, dyspnea, or hypotension [2,9] These reactions were due to OSCS contamination in specific batches of UFH made in China, which led to a global recall of heparin in 2008.

Heparin-induced thrombocytopenia (HIT) is an immune-driven response caused by platelet-activating IgG antibodies binding to complexes of platelet factor 4 (PF4) and heparin [8]. This reaction can lead to acute cardiovascular collapse, particularly with repeated heparin use [10,11].

The administration of heparin to individuals with heparin-induced antibodies can lead to life-threatening pulmonary or cardiac events. In the medical history of the patient described in our case report, there was no prior use of heparin, heparin-derived medications, or other anticoagulant drugs. Historically, hypersensitivity reactions to heparin were often attributed to impurities. However, this specific case highlights that anaphylactoid reactions triggered by heparin can arise from the substance itself, even in the absence of HIT. Therefore, we propose that the anaphylactic reaction observed in this case occurred due to the acute anaphylaxis process rather than the mediators resulting from previous sensitization. Clinicians research ways to predict hypersensitivity reactions to heparin before administering it due to the high mortality risks involved [12]. Some of them suggest using intradermal skin tests to assess the likelihood of a patient developing such a reaction to heparin or other drugs. A positive result in these tests indicates a higher risk of a severe reaction, helping clinicians consider alternative medications and potentially reducing morbidity and mortality. However, these tests are not widely available in hospitals, emphasizing the need for more research to develop reliable predictive tests and better understand the mechanisms behind heparin-induced reactions [2].

One limitation of this case is the absence of allergy and immunological tests, such as serum tryptase, which is elevated after anaphylaxis and used to confirm the diagnosis in patients with suspected anaphylaxis. This omission makes the diagnosis of anaphylactic shock uncertain. The differential diagnosis includes the possibility of vasovagal shock or cardiac arrest following ventricular fibrillation, given the patient's severe cardiac abnormalities. Additionally, a pulmonary embolism could not be initially ruled out and was considered; however, the patient's subsequent improvement suggests this was less likely. While anaphylaxis remains the most compelling and likely diagnosis to account for the patient's clinical presentation, it cannot be unequivocally confirmed as correct due to the outlined reasons.

4. Conclusions

Heparin, renowned for its widespread usage and diverse therapeutic indications, occupies a crucial role in clinical practice through its unfractionated and synthetic forms. While historically associated with anaphylaxis due to certain preservatives, contemporary knowledge underscores its predominant link to HIT and other immune-mediated responses rather than anaphylactic reactions. The case discussed here contributes to the expanding literature on this rare reaction, emphasizing the imperative for further research aimed at enhancing our understanding of its underlying mechanisms. We advocate for heightened vigilance among healthcare professionals regarding heparin as a potential trigger for anaphylactic reactions.

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Conflict of Interest

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Author Contributions

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Data Availability

The datasets created and/or analyzed during the current study are not publicly available, but are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

None declared.

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