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A Case Report on Heparin Desensitization after an Enoxaparin Allergy

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Abstract: *Heparin hypersensitivity is rare, but it has been observed in some patients. In this case, a 54-year-old Indian woman with valvular disease and atrial fibrillation underwent heart valve replacement surgery. Enoxaparin was initially used for perioperative bridging, but the patient developed itching shortly after administration. To confirm the absence of a heparin allergy, heparin desensitization was conducted, along with the administration of an antihistamine. The desensitization process went smoothly without any adverse effects. Full-dose heparin was safely used during the surgery. After the operation, the patient was treated with fondaparinux and warfarin. Upon discharge, she was prescribed lifelong warfarin therapy.*

Keywords: *enoxaparin allergy, heparin desensitization, fondaparinux, bridging therapy, anticoagulant*

Abbreviations: *UFH: unfractionated heparin, CPB: cardiopulmonary bypass, LMWH: low molecular weight heparin, HIT: heparin-induced thrombocytopenia, MHVR: mechanical heart valve replacement, AF: atrial fibrillation, LAA: left atrial appendage, INR: international normalized ratio*

1. Introduction

Unfractionated heparin (UFH) is the drug of choice in the prevention of thrombosis in the cardiopulmonary bypass (CPB) circuit due to its rapid onset of action after intravenous administration, relative ease of monitoring, and prompt reversal with protamine sulphate. Enoxaparin, a type of low molecular weight heparin (LMWH), is widely used as a perioperative anticoagulant for surgery as opposed to UFH due to its practicality and user-friendly whereas fondaparinux, a pentasaccharide anticoagulant, is not recommended due to an extended half-life (17–21 hour) and the lack of an adequate antidote, although it may have a role in patients with a history of heparin-induced thrombocytopenia (HIT) (1).

However, hypersensitivity to heparins may hinder its use in cardiac surgery(2,3). We report a case of heparin desensitization following a Type I hypersensitivity reaction towards enoxaparin in a setting where allergy testing was deemed unfeasible, and the use of fondaparinux as an alternative for bridging therapy following the mechanical heart valve replacement (MHVR) surgery.

2. Case Presentation

A 54-year-old Indian woman weighing 62 kg was admitted to Serdang Hospital for double heart valve surgery (aortic valve replacement and mitral valve replacement) and left atrial appendage ligation. She had severe mitral stenosis, severe aortic stenosis with moderate aortic regurgitation, and valvular atrial fibrillation. Prior to the surgery, she was taking warfarin for atrial fibrillation. The last dose of warfarin, 2mg once daily from Mondays to Saturdays and 1.5mg once daily on Sundays, was taken on the admission day. The target international normalized ratio (INR) range for her treatment was 2 to 3.

Due to the high INR level of 2.65 upon admission, perioperative bridging was delayed until the 5th day. Enoxaparin 60mg was given on the 6th day, but the patient experienced itching, starting from the injection site and spreading to various body parts. Enoxaparin administration was immediately stopped. The patient had a history of a similar reaction during a previous hospitalization in 2019, although it was not documented properly. The surgery was further delayed due to fast atrial fibrillation, making the planned angiogram impossible.

No anticoagulants were given as the INR was above the acceptable range.

Considering the patient's allergic history and the unavailability of allergy tests at our facility, we consulted with the cardiologist and cardiothoracic surgeon. Heparin desensitization (2) was started on the 11th (Table 1) day along with oral antihistamines for three days. After completing desensitization on the 14th day, the patient underwent an angiogram and then double heart valve surgery without any allergic reactions to heparin. Post-surgery, the patient's platelet count dropped significantly from a baseline of 284 x 10^3 mcg/L to 83 x 10^3 mcg/L on day 2 post-surgery (Table 2), but heparin induced thrombocytopenia (HIT) was ruled out. Heparin products were avoided due to the platelet drop, and anticoagulation therapy started on day 7 with fondaparinux and warfarin. After 7 days of bridging, the patient continued with oral warfarin to prevent valve thrombosis. She was discharged after 23 days with lifelong warfarin treatment. Subsequent anticoagulant care was managed in the referring facility due to logistical challenges.

3. Discussion

The most common hypersensitivity reaction to Low Molecular Weight Heparin (LMWH) is the Type IV hypersensitivity (4) reaction, with Type I hypersensitivity reactions occurring sporadically (4,5). Conducting a skin prick test may not definitively prove an IgE-mediated allergy, as reactions could be due to unspecific heparin-induced histamine liberation (5). Although Heparin-induced IgE-mediated hypersensitivity and anaphylactoid reactions are rare but serious concerns, especially for patients requiring Cardiopulmonary Bypass (CPB). In our case, we observed a probable hypersensitivity reaction (pruritus) at the injection site, radiating throughout the body, which subsided upon discontinuation of enoxaparin. There have been reports (2,3) of attempted heparin desensitization before CPB, highlighting its importance. Until more data is available on alternative anticoagulants for CPB, we recommend heparin desensitization, as successfully demonstrated in this case. Therapeutic alternatives for LMWH sensitization include Unfractionated Heparin (UFH) with an average risk and the structurally unrelated pentasaccharide fondaparinux, which has the lowest risk for cross-reactivity (6).

The use of fondaparinux for postoperative bridging lacks strong supporting evidence, although a few case reports have shown successful outcomes. While fondaparinux is not officially indicated for Heparin-Induced Thrombocytopenia (HIT), there have been instances where it was employed effectively (7–10). Despite its safe administration in this patient, there are several considerations supporting its use as postoperative bridging after Mitral Valve Heart Replacement (MHVR).

While there is no established standard for the postoperative dosage of fondaparinux in patients with MHVR, the typical therapeutic dose is 7.5 mg daily owing to the high risk of thrombosis in these patients. In this case, we chose a more cautious approach, prescribing a prophylactic dose of 2.5 mg. This decision was guided by the patient's elevated risk of postoperative bleeding and the lack of a specific reversal agent for fondaparinux. Furthermore, the extended half-life of fondaparinux necessitates careful timing of its initiation after surgery. Although the manufacturer’s prescribing information suggests fondaparinux can be safely administ- ered 6 to 8 hours postoperatively, in this patient, we delayed the initiation until 7 days after surgery. This cautious approach was taken due to concerns about the patient's platelet levels and increased bleeding risk.

4. Conclusion

We present a successful case of postoperative bridging with fondaparinux in a patient with MHVR and a history of LMWH allergy with postoperative thrombocytopenia. Fondapari-nux may provide an option for bridging for such patients, but further clinical investigations are warranted to identify the role of this agent for prophylaxis of thrombus formation in patients with MHVR.

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Table1. *Heparin desensitization regimen*

Day	Regimen	Remark
1	s.c. UFH 50 U (undiluted); rest 40 minutes	0.05 ml from 1000 U/ml vial
	s.c. UFH 250 U (undiluted); rest 40 minutes	0.25 ml from 1000 U/ml vial
	s.c. UFH 500 U (undiluted)	0.50 ml from 1000 U/ml vial

2	s.c. UFH 500 U (undiluted); rest 40 minutes	0.50 ml from 1000 U/ml vial
	s.c. UFH 1500 U (undiluted); rest 40 minutes	1.50 ml from 1000 U/ml vial
	s.c. UFH 3000 U (undiluted)	3.0 ml from 1000 U/ml vial
3	IVI Heparin (as per dilution) 500 U; rest 40 minutes	To run 2 ml/hour for 30 minutes
	IVI Heparin (as per dilution) 1500 U; rest 40 minutes	To run 2 ml/hour for 90 minutes
	IVI Heparin (as per dilution) 3000 U	To run 2 ml/hour for 3 hours
4	IVI Heparin (as per dilution) 5000 U	To run 2 ml/hour for 5 hours

IVI: Intravenous infusion; s.c.: subcutaneous; UFH: Unfractionated heparin

IVI Heparin dilution:

1 ampoule UFH (25000 U/5 ml) + 45 ml of normal saline (NS) to make up to total volume 50 ml

Final concentration: 500 U/ml

Maximum administration rate: 1000 U/ hour = 2 ml/hour

Adapted from: Patriarcha et al.

Table2. *Platelet level trend during ward stay*

Day of ward stay	Platelet level (x 10^3 mcg/L)	Remark
Day 0	284	Admission
Day 10 of admission	227	One day before heparin desensitization
Day 15 of admission	207	Day 1 post heparin desensitization; angiogram
Day 17	130	Day of surgery
Day 19	83	Day 2 post-surgery
Day 24	118	Day 7 post-surgery

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