

Case report

Rush desensitization in heparin hypersensitivity: a case report

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Among all the known drug intolerances, adverse reactions to heparin are not very common. No desensitization in patients with heparin hypersensitivity has ever been attempted. We report the case of a 55-year-old female patient with mitral stenosis and insufficiency, and tricuspid and aortic insufficiency. The patient underwent heparin treatment, and urticaria occurred with either s.c. calcium heparin or i.v. sodium heparin. Allergy testing (skin tests and patch tests) was negative. A pseudoallergic intolerance was diagnosed. Mitral valve replacement with the extracorporeal circulation method was necessary; therefore, heparin treatment was administered. A heparin rush desensitization together with antihistamine drugs (4 mg chlorpheniramine maleate for 3 d) was started: 50 UI (0.5 mg) s.c. sodium heparin were first administered; within 4 d, 5000 UI (50 mg) sodium heparin was administered i.v. with no side-effects. A full-dosage heparin treatment was then administered and heart surgery was easily performed. During the postsurgical course, i.v. sodium heparin was smoothly replaced with s.c. calcium heparin (25 000 UI s.c. per day) and with oral anticoagulants (sodium warfarin).

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Hypersensitivity adverse reactions during heparin treatment are not common. Usually, local urticarioid reactions are observed. Systemic urticaria-angioedema reactions and even anaphylactic shock have been described (2, 5, 6). These anaphylactic reactions are now very rare thanks to improved heparin cleansing.

We report a case of successful desensitization in a heparin-sensitive patient with systemic urticarioid reactions in whom no other anticoagulant could be used. In the literature, no desensitization was ever attempted in patients with heparin hypersensitivity (either allergic (immunologically mediated) or pseudoallergic).

Material and methods

Case report

A 55-year-old female patient was admitted to hospital with calcified mitral stenosis (area 0.8 cm²), mitral insufficiency (1 + / 2 +), slight tricuspid insufficiency,

aortic insufficiency (2 +), ejection fraction (57%), II NYHA class, and atrial fibrillation.

This patient had been symptom-free until April 1990, when she was hospitalized for an acute pulmonary edema. During that admission, the diagnosis of mitral and aortic disease was established, and a twice daily s.c. 0.5 ml calcium heparin treatment was started. This treatment was continued for a week and interrupted after the occurrence of diffuse urticaria. Therefore, an oral anticoagulant treatment with warfarin (Coumadin) was started. In September 1990, the patient was hospitalized to undergo heart surgery. After the hemodynamic testing, sodium heparin i.v. infusion treatment was started, but it was interrupted 3 d later after the occurrence of diffuse urticaria. In the patient's history, no allergy to drugs, food, or atmospheric agents was reported. Oral anticoagulants (Coumadin) were administered again, and heart surgery was postponed.

In February 1991, the patient was again admitted to the Perugia University Hospital, and urticaria oc-

curred once more after s.c. and i.v. administration of sodium heparin. In September 1991, the patient was admitted to the Gemelli Hospital, Rome, for further tests. The patient underwent an allergy testing again: prick test, skin test, and patch test with sodium heparin and calcium heparin were negative (these reactions were, therefore, pseudoallergic). In January 1992, the patient suffered from tachyarrhythmia and was again admitted to the Gemelli Hospital to undergo mitral valve replacement. After an allergology consultation, the treatment with clorpheniramine maleate (one 4-mg tablet three times a day) was started on 31 January. Four days later, a rush desensitization with sodium heparin (5000 UI = 50 mg/ml) was started (Table 1).

Results

Progressively increasing doses of the drug were well tolerated, and no side-effects (local or systemic) occurred. A dose of 5000 UI (50 mg) of i.v. sodium heparin was administered for another 4 d together with 12 mg/d clorpheniramine maleate: no allergic reaction occurred. Subsequently, the patient underwent surgery by the extracorporeal circulation (ECC) method. A premedication of 10 more i.v. mg of clorpheniramine maleate was added. After heparinization of the patient with 3 mg/kg of sodium heparin injected in the pulmonary artery soon after sternotomy and 100 mg added to the machine, surgery was performed at -30°C . Doses of 400 mg refracted protamine sulfate were administered at the end of the ECC system. Basal activated coagulation time (ACT) was 148 s. After the first heparin dose, it increased to 699 s, decreased to 546 s at the beginning of ECC, increased to 646 s at the end of ECC, and finally decreased to 118 s after protamine administration. No drug-induced skin or systemic reaction occurred during surgery. No important complicating disease was observed during the post-surgical course in the intensive care unit. The patient was extubated 12 h after operation, and she left the intensive care unit on day 2. After removal of the drains, calcium heparin was administered, starting from day 2: 12 500 UI s.c. twice a day, the same dose

on day 3, interrupted on day 4 after the morning dose. Oral anticoagulants (sodium warfarin) were administered simultaneously. At length, no urticaria was exhibited after the last calcium heparin dose. The patient was discharged from the heart surgery ward after 9 d.

Discussion

Hypersensitivity reactions to heparin are seldom observed. The pathogenesis of these reactions is mainly extraimmunologic or pseudoallergic (negative immune and allergy testing). *Sensu stricto* allergic reactions have rarely been reported: there are reports of type I immunoreactions (IgE-mediated) (11), type IV immunoreactions (cell-mediated) (10–12), or combined immunoreactions (types I and IV) (13).

Patients allergic or pseudoallergic to heparin were often treated with low-mol.-mass heparin without any reaction occurring (4). Low-mol.-mass heparin (2500–6000 Da), inhibiting factor Xa, but with little effect on thrombin activation (3), was obtained by chemical depolymerization of classical heparin (medium mol. mass 15 000 Da). These molecules have two distinct effects: antithrombotic and anticoagulant (1). On the other hand, their administration during ECC is still experimental because some trials (7) have shown low manageability of these molecules. Our patient, undergoing surgery with ECC, could therefore not be treated with low mol.-mass heparin. For this reason, we started a desensitizing treatment, following the procedures we applied in similar intolerance of other drugs (8–9). We report good results from this treatment: the patient was able to undergo surgery with ECC, and a 400-mg heparinization with sodium heparin was performed without hypersensitivity reactions.

This method is quick, easy to apply, and free from side-effects. We believe that it is suitable for patients with heparin hypersensitivity in whom heparin treatment is necessary.

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Table 1. Rush desensitization protocol with sodium heparin

Day 1	– 50 UI (0.5 mg) s.c. – After 40 min, 250 UI (2.5 mg) s.c.
Day 2	– After 40 min, 500 UI (5 mg) s.c. – 500 UI (5 mg) s.c. – After 40 min, 1500 UI (15 mg) s.c.
Day 3	– After 40 min, 3000 UI (30 mg) s.c. – 500 UI (5 mg) i.v. – After 40 min, 1500 UI (15 mg) i.v.
Day 4	– After 40 min, 3000 UI (30 mg) i.v. – 5000 UI (50 mg) i.v.

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