

Delayed-type hypersensitivity skin reactions due to heparins and heparinoids. Tolerance of recombinant hirudins and of the new synthetic anticoagulant fondaparinux

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Eczema-like, infiltrated plaques at subcutaneous heparin-injection sites are well-documented side effects of these anticoagulants. They are due to delayed-type hypersensitivity. In 4 patients, patch, intradermal and subcutaneous tests were performed with a panel of unfractionated heparins (UFHs), low-molecular-weight heparins (LMWHs), heparinoids, recombinant hirudins and a new synthetic pentasaccharide anticoagulant fondaparinux sodium, to find safe alternatives. 3 patients were sensitized to all the UFHs and LMWHs. The LMWH tinzaparin sodium and the heparinoid pentosan polysulfate were found to be a possible substitute in patient no. 1 and 2, respectively. The recombinant hirudins and fondaparinux sodium were tolerated without any side effects in all patients tested. Fondaparinux is a synthetic copy of a pentasaccharide sequence in the heparin molecule. It is the first in a new class of antithrombotic agents. Our study suggests that it is a new safe alternative in patients with eczema-like, infiltrated plaques at subcutaneous heparin-injection sites.

Key words: delayed-type hypersensitivity; fondaparinux sodium; heparinoids; heparins; low-molecular-weight heparins; recombinant hirudins. © Blackwell Munksgaard, 2004.

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Heparin-induced non-necrotic skin reactions caused by subcutaneous administration of unfractionated heparins (UFHs) or low-molecular-weight heparins (LMWHs) are due to delayed hypersensitivity (1–3).

Between January and June 2003, 4 patients presented themselves or were referred to our dermatology department with typical painful lesions at the injection sites of different brands of heparins. In these patients, tolerance to a new synthetic heparin, fondaparinux sodium as well as to recombinant hirudins (r-hirudins) was demonstrated while allergy testing.

Patients and Methods

Patients

All patients complained of painful, infiltrated plaques at the subcutaneous injection sites on the abdominal wall or the thighs, compatible with a delayed-type allergy to heparins, as previously reported (2, 3).

Patient no. 1, a 73-year-old woman, had received fraxiparin subcutaneously once a day to prevent thromboembolic disease after abdominal surgery. 3 days after beginning the treatment, she complained of typical skin lesions of delayed-type heparin allergy and was referred to our dermatology department for allergological investigations. Clinical examination showed typical lesions on the abdominal wall. There was no thrombocytopenia.

Because she needed anticoagulation medication, the r-hirudin desirudin (15 mg $\times$ 2 daily), which was considered to be a safe alternative in these patients (4), was administered subcutaneously and tolerated without any side effects. In order to identify the entire spectrum of sensitization to heparins, patch, intradermal and subcutaneous tests were performed with a panel of UFHs, LMWHs, heparinoids, r-hirudins and fondaparinux sodium (Tables 1 and 2) after clearing of the skin lesions.

Patient no. 2, a 61-year-old woman, was referred for allergological investigations before

Table 1. Anticoagulants tested

Heparins, heparinoids, hirudins and fondaparinux	Origin	Abbreviation	Preservatives
Unfractionated heparins			
Heparin calcium 25 000 IU/ml	Porcine	U1	—
Heparin sodium 5000 IU/ml	Porcine	U2	Benzyl alcohol
Low-molecular-weight heparins			
Nadroparin calcium	Porcine	L1	—
Dalteparin sodium	Porcine	L2	—
Enoxaparin sodium	Porcine	L3	—
Reviparin sodium	Porcine	L4	—
Certoparin sodium	Porcine	L5	Chlorocresol
Tinzaparin sodium	Porcine	L6	Benzyl alcohol
Heparinoids			
Danaparoid	Porcine	D	—
Pentosan polysulfate	Beechwood	H	—
Recombinant hirudins			
Desirudin	Yeasts		—
Lepirudin	Yeasts		—
Fondaparinux	Synthetic		—

undergoing abdominal surgery. In 1995, she complained of erythematous and infiltrated plaques on the abdominal wall several days after subcutaneous anticoagulation with heparin calcium, then with dalteparin sodium. The patient could

not remember the therapeutic doses of the heparins. Allergy testing was then performed (Tables 1 and 2).

Patient no. 3, a 54-year-old woman, developed, 10 years ago, large and extensive infiltrated erythematous and painful plaques at the subcutaneous

Table 2. Results of allergological investigations

Number	Sex	Age	Anticoagulants tested	Patch tests	Intradermal tests	Subcutaneous tests
1	Female	73	Unfractionated heparins (UFHs)	—	+	Not done
			L1, L2, L3, L5	+	+	Not done
			L4	—	+	Not done
			L6	—	—	—
			D	—	+	Not done
			H	—	—	—
			Lepirudin	—	—	Not done
			Desirudin	—	—	—
			Fondaparinux	—	—	—
			UFHs	—	+	Not done
2	Female	61	L2, L3, L5	+	+	Not done
			L1, L4	—	+	Not done
			L6	—	—	+
			D	+	+	Not done
			H	—	—	?
			Lepirudin	—	—	Not done
			Desirudin	—	—	—
			Fondaparinux	—	—	—
			UFHs	—	+	Not done
			L1→L5	+	+	Not done
3	Female	54	L6	—	—	+
			D	+	+	Not done
			H	—	—	+
			Lepirudin	—	—	—
			Desirudin	—	—	—
			Fondaparinux	—	—	—
			UFHs	—	—	+
			L1→L4	—	—	+
			L5	+	+	Not done
			L6	—	—	+
4	Female	59	D	—	—	+
			H	—	—	+
			Lepirudin	—	—	—
			Desirudin	—	—	—
			Fondaparinux	—	—	—
			UFHs	—	—	+
			L1→L4	—	—	+
			L5	+	+	Not done
			L6	—	—	+
			D	—	—	+

injection sites of UFHs and LMWHs used to prevent thromboembolic disease. She could not indicate the anticoagulants used and presented herself for allergy testing (Tables 1 and 2).

Patient no. 4, a 59-year-old woman, was treated in June 2002 with certoparin sodium (3000 IU anti-Xa/d) to prevent thromboembolic disease after orthopaedic surgery. This treatment was tolerated without any side effects for 6 weeks. In August 2002, she developed large erythematous skin lesions at the subcutaneous injection sites of certoparin. The therapy was then switched to tinzaparin sodium. However, this also resulted in erythematous and infiltrated lesions at the injection sites. Further therapy with danaparoid resulted in large haematomas of the abdominal wall. The anticoagulants were then stopped and the patient was referred in June 2003 for allergy testing (Tables 1 and 2).

Allergological investigations

Patch testing was performed with the standard series of the German Contact Dermatitis Group (DKG) and the preservatives used in different brands of heparins (Table 1). Guidelines recommended by the DKG for this testing were used (5). The test substances of the standard series (Hermal, Reinbek, Germany) as well as the heparins, heparinoids, r-hirudins, fondaparinux and preservatives in heparin brands were applied to the patients' upper back for 24 h using Leukotest[®] (Beiersdorf, Germany) and fixed with Mefix[®] (Mölnlycke, Hilden, Germany). Readings were taken after 24, 48 and 72 h. A patch test reaction was considered allergic when a score of +, ++ or +++ was given at 48 and 72 h or only at 72 h.

Intradermal (i.d.) tests were performed on the flexural side of the forearm with 0.05 ml of undiluted brands of UFHs, LMWHs, heparinoids, r-hirudins and fondaparinux. Readings were taken after 20 min to exclude immediate hypersensitivity, and after 24, 48, 72 and 96 h. The test was considered positive when an infiltrated eczematous reaction was noted at 48, 72 or 96 h.

Subcutaneous (s.c.) tests were performed on the abdominal wall with 0.1 ml of similar undiluted brands of heparins, heparinoids, r-hirudins and fondaparinux which had produced negative results in the i.d. test. The tests were read up to 96 h. When s.c. testing was performed, a maximal dose of 0.3 ml of heparins, heparinoids, hirudins and fondaparinux sodium were injected daily (3 s.c. tests). A therapeutic dose of pentosan polysulfate (1 ampoule), desirudin (15 mg, 0.5 ml), lepirudin (1 ml of a solution of 50 mg/ml in the 3rd and 4th patients) and fondaparinux sodium (2.5 mg, 0.5 ml) was injected subcutaneously in

the abdominal wall or in the thighs when the s.c. test was negative. Only 1 of these therapeutic tests was performed on the same day.

Results

Sensitization to heparins and heparinoids

Delayed-type hypersensitivity reactions to UFHs, LMWHs and danaparoid were observed in all 4 patients tested (Table 2). In the 1st patient, tinzaparin sodium was negative on i.d. and s.c. testing and was thus considered as a possible substitute. However, consecutive therapy was not conducted with this anticoagulant. Desirudin, lepirudin and fondaparinux sodium were tolerated in all patients tested without any side effects. The 3rd and 4th patients did not tolerate pentosan polysulfate. Consecutive therapy conducted outside our department with this heparinoid in the 2nd patient (50 mg $\times$ 2 daily) resulted in erythematous but not infiltrated plaques at the subcutaneous injection sites on the abdominal wall. However, the patient was not referred to our dermatology department again.

Discussion

Erythematous, infiltrated and painful plaques on the sites of subcutaneous heparin injection represent a more common side effect than is generally realized.

Heparins are complex mixtures of mucopolysaccharides produced from porcine or bovine intestines and lungs. Molecular weight differentiates UFHs (10–20 kDa) from LMWHs (4–6 kDa) (6). Heparin, a negatively charged mucopolysaccharide, binds strongly to proteins, a prerequisite for a complete antigen (7). Due to the structural similarities of the UFHs and the LMWHs, all available heparin preparations may thus elicit positive reactions. However, the heparin fractions which induce the sensitization have not been determined. As reported previously (3, 7–9), some patients with delayed hypersensitivity to UFHs or LMWHs may tolerate 1 or 2 LMWHs without any side effects. Time-consuming allergy studies and extensive skin testing are, however, necessary to find such an alternative in only a few patients.

Heparinoids such as pentosan polysulfate, but not danaparoid in our experience, may be an alternative for some groups of patients (10–12) but not for others (12). However, some patients having a positive localized s.c. test with danaparoid may tolerate this heparinoid with the application of local corticosteroids (13).

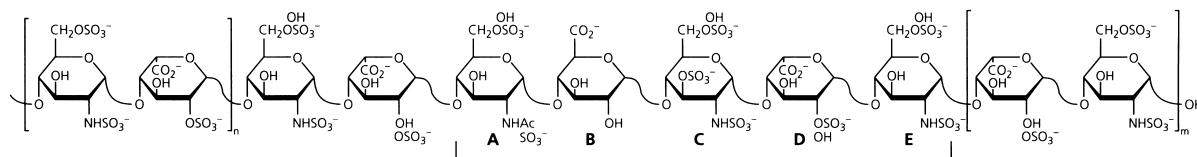


Fig. 1. The heparin molecule. Part A–E represents the synthetic pentasaccharide fondaparinux.

r-Hirudins, such as desirudin and lepirudin used for the treatment of heparin-induced thrombocytopenia type II, may be safe therapeutic alternatives in patients with delayed-type allergy to heparins (3, 4, 13, 14). There are no chemical similarities with UFHs or LMWHs. However, r-hirudins may also induce immediate (15) as well as delayed-type (16, 17) hypersensitivity skin reactions. An Arthus reaction to lepirudin (18) as well as eczematous reactions and maculopapular exanthems in 4% of treated patients has also been described with this anticoagulant (19).

There is no cross-sensitization between heparins and hirudins, but considering the possibility of fatal anaphylactic shock caused by lepirudin (20) and bleeding during intravenous application, the use of hirudins is restricted and requires specific monitoring (13).

In contrast to standard heparin and LMWH, which are heterogeneous compounds derived from animals with the potential to induce antiplatelet antibodies, fondaparinux is a new chemically synthesized selective inhibitor of activated factor X (21, 22). Its structure is the copy of the heparin pentasaccharide sequence, the shortest chain within the heparin molecule required for antithrombin inhibition of activated factor X and without antithrombin effects (Fig. 1). Phase I trials have shown 100% bioavailability after subcutaneous administration. In several studies, it has shown its effectiveness in preventing venous thromboembolism in patients undergoing hip or knee replacement surgery (22). Fondaparinux is the first in a new class of antithrombotic agents expected to play a major role in the prevention and treatment of venous and arterial thrombotic diseases (23). It has not been reported to cause antibody-induced thrombocytopenia (24).

Our results in 4 patients indicate that fondaparinux may also be a safe therapeutic alternative in patients with delayed hypersensitivity to heparins and heparinoids. Cross-reactions with UFHs were not observed in our study, despite the chemical similarities.

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