

Delayed-type hypersensitivity to heparins: different patterns of cross-reactivity

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Adverse reactions to high and low-molecular-weight heparins (LMWH) are well-known clinical problems. Immediate-type allergic reactions to heparins, including urticaria and asthma, have been reported rarely. However, delayed-type hypersensi-

tivity (DTH) reactions are common (1–3). Administration of unfractionated heparin (UFH) or LMWH may induce a non-necrotic eczematous reaction at the site of injection, which is mediated by a delayed hypersensitivity mechanism. An eczematous process may be observed on involved skin within the first 4 days after injection. This eczema may become generalized if treatment is continued. Different patterns of response to skin testing with heparins and cross-reactivity have been described (4).

Fondaparinux, a synthetic pentasaccharide, is included in the group of ultra-low-molecular-weight heparins (ULMWH). It is considered as the first heparin that selectively inhibits the coagulation factor Xa (5, 6). Recently, there have been several reports in the literature suggesting that this drug is a safe alternative in patients with DTH to heparins (7–9). We report our recent experience.

Patients and Methods

Case no. 1

A 68-year-old female was treated with calcium heparin during an episode of venous thrombosis. After 8 weeks, she complained of localized itchy plaques at the injection sites, which then became sheeted over the abdominal area after a few days. Histological examination was consistent with acute eczema.

Case no. 2

Following osteosynthesis surgery, a 44-year-old female received nadroparin prophylactically, 0.6 ml, twice a day. After 2 weeks, she developed itchy infiltrated plaques at the injection sites. Skin biopsy was consistent with subacute eczema.

Case no. 3

A 44-year-old female received nadroparin, 0.4 ml, twice a day in the post-operative period of an intervertebral herniated disc surgery. Seven days later, an infiltrated itchy erythematous plaque developed at the injection sites. No skin biopsy was performed.

Case no. 4

A 68-year-old female was treated with enoxaparin 60 mg, twice a day, due to a deep vein thrombosis. After 3 days, itchy infiltrates eczematous plaques

Table 1. Results of prick test (1/1), intradermal (1/10), patch test (1/1), and subcutaneous challenge (1/1) with heparins and fondaparinux (different patterns of cross-reactivity)

	Hep.Na ⁺	Bemiparin	Enoxaparin	Nadroparin	Dalteparin	Fondaparinux
Case 1						
Prick test	—	—	—	—	—	—
ID	D2	D4	D2	D2	D4	—
Patch test	—	D4	—	—	D4	—
s.c.	NT	NT	NT	NT	NT	+36 hr
Case 2						
Prick test	—	—	—	—	—	—
ID	D2	D2	D2	D2	D4	—
Patch test	—	—	—	—	—	—
s.c.	NT	NT	NT	NT	NT	Tolerated
Case 3						
Prick test	—	—	—	—	—	—
ID	D2	—	—	D2	D2	—
Patch test	—	—	—	—	—	—
s.c.	NT	NT	NT	NT	NT	Tolerated
Case 4						
Prick test	—	—	—	—	—	—
ID	—	—	D2	—	D4	—
Patch test	—	—	—	—	—	—
s.c.	NT	D2	NT	NT	NT	Tolerated

Hep.Na⁺, sodium heparin; ID, intradermal test; NT, not tested; s.c., subcutaneous; tolerated, no adverse reaction.

appeared on her abdominal wall at the injection site. Histological study was consistent with acute eczema once again.

Prick tests, intradermal tests, and patch testing were performed with UFH (sodium heparin), LMWH (nadroparin, enoxaparin, bemiparin, and dalteparin), and an ULMWH (fondaparinux) as summarized in Table 1. Informed consent was obtained from all patients.

Prick and intradermal tests were performed on the volar aspect of their forearms (1/10–1/1 dilutions) with readings at 15 minutes (at D0), D2, and D4. Patch tests (Curatest[®]; Lohman & Rauscher GmbH, Neuwied, Germany) were carried out on their backs (2-D occlusion) with undiluted preparations with readings at 30 minutes (at D0), D2, and D4 including tests with petrolatum as a negative control. Ten controls were included for all skin testing. Negative skin tests were followed by drug provocation subcutaneously with increasing doses up to therapeutic dosage.

Results

Summarized in Table 1.

Conclusions

We obtained different patterns of reactivity. These cases show the wide variability of heparin cross-reactivity, among LMWH, between LMWH and UFH, and among LMWH, UFH, and

ULMWH. These results are consistent with those in the literature.

The pathogenesis of heparin hypersensitivity is not fully understood. Heparins may act as haptens by binding to dermal and/or subcutaneous structural proteins. Different patterns of cross-reactions among different heparins show the presence of several antigenic epitopes. The role of local proteins is further underlined by the observation that intravenous treatment with heparin does not lead to an allergic reaction in patients with DTH (10, 11). Possible reasons for intravenous tolerance might be the difference in antigen processing and presentation of selectively sensitized lymphocytes in the dermis (12).

There are several cases reported where fondaparinux seems to be a safe alternative for these patients. In these studies, the molecular size is proposed as one of the key elements in the occurrence of adverse events. As in our series, we have found several cases published where fondaparinux, for unclear reasons, was not well tolerated (13, 14). Recent literature suggests that molecular weight is not the determining factor of tolerance and cross-reactivity between heparins (15). Consequently, we recommend including this drug when testing patients with delayed hypersensitivity to heparins before using it as an alternative.

Even though subcutaneous testing is considered the gold standard, the intradermal test is possibly the best method. Whichever is used, both

require a second reading to avoid false negatives.

We emphasize that therapy discontinuation is recommended in order to prevent a generalized reaction.

References

- Koch P, Hindi S, Landwehr D. Delayed allergic skin reactions due to subcutaneous heparin-calcium, enoxaparin-sodium, pentosan polysulfate and acute skin lesions from systemic sodium-heparin. *Contact Dermatitis* 1996; 34: 156–158.
- Bircher A J, Fluckiger R, Buchner S A. Eczematous infiltrated plaques to subcutaneous heparin: a type IV allergic reaction. *Br J Dermatol* 1990; 123: 507–514.
- Bircher A J, Harr T, Hohenstein L, Tsakiris D A. Hypersensitivity reactions to anticoagulant drugs: diagnosis and management options. *Allergy* 2006; 61: 1432–1440.
- Poza-Guedes P, Gonzalez-Perez R, Canto G. Different patterns of cross-reactivity in non-immediate hypersensitivity to heparins: from localized to systemic reactions. *Contact Dermatitis* 2002; 47: 244–245.
- Petitou M, Duchaussoy P, Herbert J M et al. The synthetic pentasaccharide fondaparinux: first in the class of antithrombotic agents that selectively inhibit coagulation factor Xa. *Semin Thromb Hemost* 2002; 28: 393–402.
- Keam S J, Goa K L. Fondaparinux sodium. *Drugs* 2002; 62: 1673–1685.
- Maetzke J, Hinrichs R, Staib G et al. Fondaparinux as a novel therapeutic alternative in a patient with heparin allergy. *Allergy* 2004; 59: 237–238.

8. Sacher C, Hunzelmann N. Tolerance to the synthetic pentasaccharide fondaparinux in heparin sensitization. *Allergy* 2003; 58: 1318–1319.
9. Ludwig R J, Beier C, Lindhoff-Last E, Kaufmann R, Boehncke W H. Tolerance of fondaparinux in a patient allergic to heparins and other glycosaminoglycans. *Contact Dermatitis* 2003; 49: 158–159.
10. Jappe U, Juschka U, Kuner N et al. Fondaparinux: a suitable alternative in cases of delayed-type allergy to heparins and semisynthetic heparinoids? A study of 7 cases. *Contact Dermatitis* 2004; 51: 67–72.
11. Fields R M, Peppo W. The use of intravenous recombinant hirudin in the treatment of deep vein thrombosis in a patient with an acute heparin allergy. *Ann Emerg Med* 2002; 40: 155–158.
12. Grassegger A, Fritsch P, Reider N. Delayed-type hypersensitivity and cross-reactivity to heparins and danaparoid: a prospective study. *Dermatol Surg* 2001; 27: 4752.
13. Maetzke J, Hinrichs R, Schneider L A, Scharffetter-Kochanek K. Unexpected delayed-type hypersensitivity skin reactions to the ultra-low-molecular-weight heparin fondaparinux. *Allergy* 2005; 60: 413–415.
14. Hirsch K, Ludwig R J, Lindhoff-Last E, Kaufmann R, Boehncke W H. Intolerance of fondaparinux in a patient allergic to heparins. *Contact Dermatitis* 2004; 50: 383–384.
15. Grims R H, Weger W, Reiter H, Arbab E, Kranke B, Aberer W. Delayed-type hypersensitivity to low molecular weight heparins and heparinoids: cross-reactivity does not depend on molecular weight. *Br J Dermatol* 2007; 157: 514–517.

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