

## Different patterns of cross-reactivity in non-immediate hypersensitivity to heparins: from localized to systemic reactions

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**Key words:** heparin; low-molecular-weight heparin; drug allergy; non-immediate hypersensitivity; patch test method; cross-reactivity.

Unfractionated heparin (UH) has been replaced by low-molecular-weight heparin (LMWH) in thrombosis therapy. Several adverse reactions to heparin are often described, but immunologically mediated reactions are rare.

### Patients and Methods

We describe 4 patients showing non-immediate allergic reactions to LMWH with different patterns of response to skin testing and cross-reactivity.

#### Case no. 1

Male, 41 years old; around acute ischaemic cardiopathy he received 0.6 mL of nadroparin (Fraxiparina®, Sanofi-Synthelabo) twice daily. Infiltrated itchy erythematous plaques on the abdominal wall appeared 3 days later, and 24 h after that the lesions spread all over his trunk.

#### Case no. 2

Female, 54 years old; she was treated with nadroparin (Fraxiparina®), 0.6 mL, twice a day during a venous thrombosis. From the very first dose 4 cm plaques developed at the injection sites. After 4 days nadroparin was changed to enoxaparin (Clexane®, Rhone-Poulenc Rorer), but the same plaques appeared again.

Therapy was stopped 96 h later, due to a diffuse maculopapular rash.

#### Case no. 3

Female, 41 years old; a pregnant woman with antiphospholipid syndrome was prophylactically treated with enoxaparin (Clexane®) 40 mg a day, and after a week she complained of localized itchy plaques. As her symptoms persisted, therapy was discontinued on the 4th day.

#### Case no. 4

Female, 62 years old; following an osteosynthesis procedure she received prophylactically enoxaparin (Clexane®) 40 mg a day, and 2 weeks later itchy infiltrated plaques appeared on the lower abdomen, persisting for 7 days. Heparin was interrupted on the 8th day due to an itchy rash spreading over the whole abdomen.

Informed consent was obtained from all patients. Patch tests were carried out on their backs with undiluted preparations of 3 types of LMWH and UH (1000 IU/mL), with readings at 30 min [day (D)0], 48 and 96 h (D2 and D4). After a week, prick and intradermal (ID) tests were performed on their volar forearms (1/10–1/1 dilutions). 10 controls were included for all skin testing. Negative

cutaneous tests were followed by drug provocation test with increasing doses up to therapeutic dosage. Biopsy was made of all positive results.

### Results

We obtained different patterns of positive patch tests (Table 1); one was positive to all heparins, another to all LMWHs, and another was positive to only the implicated LMWH. Prick testing was negative in all patients. ID testing was positive in 2 patients (with undiluted solution): one had an immediate positive reaction that persisted to D2, and the other began to become positive at D2 (lasting till D4). All controls were negative. Only in case no. 4 did we need to perform a provocation test with the relevant LMWH, when a 3-cm itchy plaque appeared at D2. All biopsies showed epidermal spongiosis and a perivascular lymphocytic infiltrate in the upper dermis; no necrotic changes were found.

### Discussion

These cases show the wide variability of heparin cross-reactivity, among LMWHs themselves and also between LMWHs and UHs. Based on our results, we believe that different

Table 1. Results of skin testing and subcutaneous provocation test

|            | Enoxaparin | Nadroparin | Dalteparin | Sodium heparin |
|------------|------------|------------|------------|----------------|
| Case no. 1 |            |            |            |                |
| Patch      | +(D4)      | +(D4)      | +(D4)      | +(D4)          |
| Prick      | –          | –          | –          | –              |
| ID         | –          | –          | –          | –              |
| s.c.       |            |            |            |                |
| Case no. 2 |            |            |            |                |
| Patch      | +(D2)      | +(D2)      | +(D2)      | –              |
| Prick      | –          | –          | –          | –              |
| ID         | –          | –          | –          | +(D0)          |
| s.c.       |            |            |            |                |
| Case no. 3 |            |            |            |                |
| Patch      | +(D2)      | –          | –          | –              |
| Prick      | –          | –          | –          | –              |
| ID         | +(D0)      | +(D0)      | +(D0)      | +(D2)          |
| s.c.       |            |            |            |                |
| Case no. 4 |            |            |            |                |
| Patch      | –          | –          | –          | –              |
| Prick      | –          | –          | –          | –              |
| ID         | –          | –          | –          | –              |
| s.c.       | +(D2)      | –          | –          | –              |

derivatives of heparin should be included in the diagnostic procedure (1, 2). Only one patient had negative results to all skin testing, so we encourage their use as a diagnostic tool in suspected allergic reactions to heparin. Non-immediate localized hypersensitivity reactions have previously been described (3, 4), but secondary rashes are exceptional (2,5). We describe three cases where LMWH was not interrupted and plaques were followed by itchy exanthema. Therefore, discontinuation of therapy is strongly recommended in such cases to prevent systemic reactions.

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## Allergic contact dermatitis due to hydrophilized ceramide

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**Key words:** allergic contact dermatitis; cosmetics; ceramide (hydrophilized ceramide).

### Case Report

A 22-year-old woman presented with itchy erythema on her face. She had used 3 types of moisturizing creams on the same site for 10 days, but it had become worse. Clinical examination showed oedematous erythema on her cheeks and neck.

Betamethasone valerate ointment was applied for 5 days and the lesion disappeared. Each medicament and cosmetic that the patient had used was patch tested (as is). She responded positively only to Sebum Control Emulsion™ (made in Japan: containing 0.5% hydrophilized ceramide, modified synthetic ceramide). Then, of every ingredient of Sebum Control Emulsion™, only 0.5% and 0.25% hydrophilized ceram-

ide in pet. was positive (Table 1). Patch testing with 0.5% hydrophilized ceramide in pet. in 5 controls was negative. Based on these findings, a diagnosis of allergic contact dermatitis due to hydrophilized ceramide was made.

### Discussion

This hydrophilized ceramide resembles type 2 ceramide and is synthesized chemically. The material contains some impurities besides the main structure. A literature search (PubMed) resulted in 1 related article (1), but there was no case report on allergic contact dermatitis due to ceramide or any similar substances.

### References

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Table 1. Patch test results

| Substance                              | D2  | D3  | D4 | D7  |
|----------------------------------------|-----|-----|----|-----|
| Sebum Control Emulsion™ (as is)        | ? + |     |    | ? + |
| Ingredients of Sebum Control Emulsion™ |     |     |    |     |
| Hydrophilized ceramide 0.5% pet.       | –   | ? + | +  | +   |
| Hydrophilized ceramide 0.25% pet.      | –   | ? + | +  | +   |
| Others                                 | –   | –   | –  | –   |
| Lipophilic ceramide A 0.5% pet.        | –   | –   | –  | –   |
| Lipophilic ceramide B 0.5% pet.        | –   | –   | –  | –   |
| Petrolatum                             | –   | –   | –  | –   |