

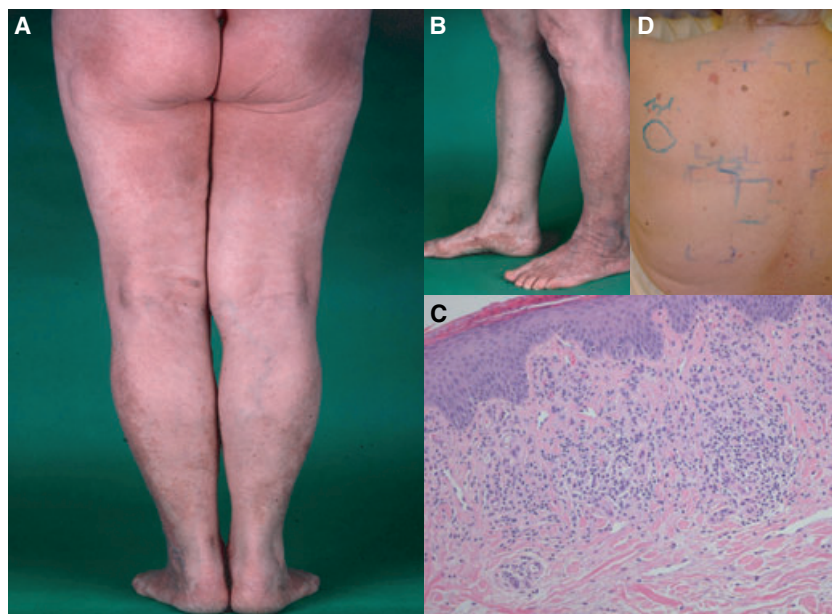


Figure 1. A and B: Clinical picture at presentation. C: Dermatopathology showing orthohyperkeratosis, focal hypergranulosis, and in sections hydropic degeneration of the basement membrane zone; sub-epidermally a band-shaped lymphohistiocytic infiltrate; haematoxylin-eosin stain. Original magnification $\times 10$. D: Patch test revealing positive reaction to combined preparation IH and bufexamac.

plus® are interpreted as 'compound' allergy and might be explained by an accumulating, or a neoantigenic effect of the substances when combined (5, 6).

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Immediate type hypersensitivity to low molecular weight heparins and tolerance of unfractionated heparin and fondaparinux

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Key words: drug allergy; fondaparinux; heparin; immediate type hypersensitivity.

Delayed-type hypersensitivity to not only high but also low molecular weight heparins (LMWH) and recently to fondaparinux (1, 2) is occasionally observed as localized infiltrated plaques at

the injection sites. By contrast, immediate-type hypersensitivity to heparins is an extremely rare event if one takes into consideration that these compounds have been administered to a very large number of patients during the past 50 years. Consequently, literature concerning immediate-type hypersensitivity is sparse (3–6).

We report a 30-year-old female patient with Muckle-Wells syndrome (autoinflammatory, autosomal disease with cold urticaria and sensorineural deafness) and factor V Leiden thrombophilia, who has repeatedly used dalteparin (LMWH) subcutaneously (sc) over the past 10 years. During the last year mild local swelling was observed after use of dalteparin.

Upon the latest readministration of dalteparin, within 15 min, severe pruritic urticaria, nausea, mild dyspnea and swollen hands occurred, which responded to antiallergic treatment.

To test the working hypothesis of an immediate-type reaction to dalteparin (LMWH) an initial diagnostic work up with skin prick (SPT) and intracutaneous tests (ICT) with a series of LMWH (dalteparin, nadroparin, enoxaparin), glycosaminoglycan (danaparoid), unfractionated heparin, fondaparinux (a pentasaccharide) and the hirudin lepirudin was performed. To rule out a type I reaction to the preservatives, these specific substances were also tested.

Positive SPT were only observed with dalteparin and nadroparin, whereas positive ICT were seen with respect to all LMWH (dalteparin, nadroparin, enoxaparin) and to danaparoid, but not to unfractionated heparin, fondaparinux, and lepirudin (Table 1). Also, all preservatives (chlorocresol, sodium disulfite) tested were negative. Thirty minutes after the ICT series a mild flare of urticaria was observed which responded to oral antihistamines. After having obtained informed consent, a provocation test was performed with the skin test-negative unfractionated heparin and fondaparinux to identify an alternative drug for im-

A female patient with immediate hypersensitivity to LMWH and tolerance of unfractionated heparin and fondaparinux.

Table 1. Results of diagnostic tests

Drug	Prick test	Intracutaneous test	Provocation
	1 : 1		
Liquemin® (heparin)	–	Negative (1 : 1)	Negative (intravenous)
Fragmin® (dalteparin)	+	Positive (1 : 100)	n.d.
Fraxiparin® (nadroparin)	++	Positive (1 : 100)	n.d.
Clexane® (enoxaparin)	–	Positive (1 : 10)	n.d.
Orgaran® (danaparoid)	–	Positive (1 : 10)	n.d.
Refludan® (lepirudin)	–	Negative (1 : 1)	n.d.
Arixtra® (fondaparinux)	–	Negative (1 : 1)	Negative (subcutaneous)

n.d., not done.

diate anticoagulation. Intravenous unfractionated heparin as well as subcutaneous fondaparinux was tolerated at full doses.

We were able to demonstrate a specific type I sensitivity to dalteparin with an extensive cross-reactivity to other LMWH (nadroparin, enoxaparin) and to the glycosaminoglycan danaparoid, whereas no sensitization to unfractionated heparin, the pentasaccharide fondaparinux and the hirudin lepirudin was found. Unfractionated heparin and fondaparinux were not only skin test negative but were also well tolerated upon reexposure. Interestingly, fondaparinux was also tolerated in some patients with delayed plaques from LMWH (2), but not in others (1).

Only few case reports of immediate hypersensitivity exist in which appropriate skin testing with unfractionated heparin and LMWH has been performed (3–6). In contrast to our case, these cases showed co- or cross-reactivity between the unfractionated heparin and the tested LMWH leading to the conclusion that all

types of unfractionated and LMWH should be avoided in these patients, although not all types of LMWH have been tested. As a therapeutic alternative, Patriarca et al. were able to desensitize or at least to tolerize a patient with unfractionated heparin (5).

In conclusion, we recommend that skin tests (SPT, ICT) be performed with all types of heparins, pentasaccharides, hirudin and danaparoid in order to identify a safe alternative anticoagulant. As a second step, a provocation test should be performed with skin test-negative agents. In our case we were able to demonstrate the safety and efficacy of this method.

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