

Delayed hypersensitivity at the injection sites of a low-molecular-weight heparin

A. MOREAU, A. DOMPMARTIN, P. ESNAULT, M. MICHEL AND D. LEROY

Department of Dermatology of Caen, France

We report a case of delayed hypersensitivity to a low-molecular-weight heparin. The patient presented with eczema at the site of subcutaneous injections and allergy tests confirmed the clinical diagnosis. There were positive tests with 3 low-molecular-weight heparins and unfractionated subcutaneous calcium heparin but negative with intravenous sodium heparin. Although delayed hypersensitivity to low-molecular-weight heparins is rare, the possibility of cross-allergy to unfractionated heparin could be a therapeutic problem for some patients.

Key words: heparin; delayed hypersensitivity; eczema; drug reaction; cutaneous side-effects; intradermal tests; subcutaneous tests; patch testing technique. © Munksgaard, 1996.

Accepted for publication 2 May 1995

For over 50 years, heparin has been widely used to treat or prevent venous thromboembolism; its molecular weight varies from 3000 to 30,000 daltons. Heparins are all composed of a heterogeneous mixture of polysaccharide molecules extracted from bovine and porcine lung or intestine. Low-molecular-weight heparins are harvested from standard heparin by chemical hydrolysis. Various adverse reactions have been reported, including haemorrhages, thrombopenia, cutaneous necrosis, acute allergic reactions and delayed hypersensitivity at injection sites. We report a case of delayed hypersensitivity at the injection sites of low-molecular-weight heparin.

injections were stopped. Because of local infection with staphylococcus, she was treated with oral pristinamycin (Pyostacine[®], Laboratory Spécia). 2 days later, generalized erythema appeared. Skin biopsy of the eczematous plaques at the sites of injections showed eczema without vasculitis and micro-thrombi. There was no thrombopenia. Eczematous plaques on the thighs responded well to topical corticosteroid, complete clearing requiring 2 weeks. The erythematous rash cleared spontaneously within 10 days. Skin tests were performed 3 months later.

Case Report

Patient

A 47-year-old obese woman underwent ovariectomy; she had hypercholesterolemia, and high blood pressure. She was given postoperatively calcium nadroparin (Fraxiparine[®], Laboratory Choay) subcutaneously. Within 4 days, at the sites of injection on the anterior thighs, inflammatory eczematous plaques appeared, becoming vesicular, bullous and crusted (Fig. 1). The patient recalled that she had had comparable lesions 8 years before, after subcutaneous injections of calcium heparin (Calciparine[®], Laboratory Choay). Therefore, we suspected hypersensitivity to heparin. Heparin



Fig. 1. Eczematous plaques at the injection sites of calcium nadroparin on the thighs.

Table 1. Heparin skin test results

Tests		Unfractionated heparins		Low-molecular-weight heparins		
		Intravenous sodium heparin Héparine sodique Léo® Laboratory Léo	Subcutaneous calcium heparin Héparine calcique Panpharma® Laboratory Panpharma	Calcium nadroparin Fraxiparine® Laboratory Choay	Sodium enoxaparin Lovenox® Laboratory Bellon	Sodium tedelparin Fragmine® Laboratory Pharmacia
prick	20 min	—	—	—	—	—
patch	2 days	—	—	—	—	—
patch	6 days	—	++	++	++	++
intradermal	2 days	—	+	+	+	+
intradermal	6 days	—	++	++	++	++
subcutaneous	2 days	—	—	—	—	—
subcutaneous	6 days	?+	+++	+++	+++	+++

— negative reaction
 ?+ doubtful reaction
 + erythema with infiltration
 ++ erythema with infiltration and vesicles
 +++ erythema with infiltration and bullae

Testing procedure

We tested 3 low-molecular-weight heparins (Fraxiparine®, Lovenox®, Fragmine®), an unfractionated intravenous heparin (Héparine sodique Léo®), an unfractionated subcutaneous heparin (Héparine calcique Panpharma®), the European

standard series and pristinamycin. Heparins were tested as is; pristinamycin tablets were crushed and diluted in saline. We performed prick, patch, subcutaneous and intradermal tests with heparins, patch tests only with the European standard series and pristinamycin. Heparins were injected 0.05 ml intradermally and 0.1 ml subcutaneously. Heparin preparations were preservative-free. Control tests were performed with saline. Tests were read after 20 min, 2 days and 6 days.

Results

All prick tests were negative (Table 1). Patch, intradermal and subcutaneous tests were negative after 20 min. Patch, intradermal (Fig. 2) and subcutaneous tests with subcutaneous calcium heparin and the 3 low-molecular-weight heparins were positive at day 6, reproducing the lesions. Patch and intradermal tests with intravenous sodium heparin were negative. The subcutaneous test with intravenous sodium heparin was doubtful. Control tests were negative. Histology of the intradermal test with subcutaneous calcium heparin was identical to the initial cutaneous lesions.

Discussion

Delayed hypersensitivity at the site of injection of heparin is rare and was first reported in 1952 (1). It was first often mistaken for cutaneous necrosis, but is now well differentiated (2–4). The skin reaction is due to heparin itself and not to preservatives (5–7). The exact antigen has not been identified.

57 cases of delayed hypersensitivity reaction to heparin have been published, mainly in obese



Fig. 2. Intradermal tests at day 6.

women (54 female, 3 male). Lesions developed at the site of subcutaneous injection, around 10 days after initiation of treatment (3 to 15 days) (8). 1 case developed at the site of intravenous injection (9). The reaction depends on the anatomical level of injection: an infiltrated plaque after deep injection and an eczematous lesion after superficial injection (9). Other skin reactions have been published: nodules (10) or inflammatory plaques associated with superficial peeling of the skin (11). General reactions, such as fever, have also been reported (8). 2 patients presented with generalized maculopapular eruptions associated with inflammatory plaques at the site of injection, but the authors could not exclude a Type I allergic reaction (12, 13). Generalized exanthema and "baboon syndrome" have been reported when treatment was continued with subcutaneous injections of unfractionated heparin (14). Histopathology shows eczema with spongiosis and exocytosis. Immunohistochemistry reveals increase of HLA-DR-bearing keratinocytes and predominance of helper/inducer T cells in the perivascular infiltrate. There are no microthrombi or signs of vasculitis (8, 15). Routine patch tests are not adequate to reveal heparin sensitivity. Negative patch tests do not exclude allergy. Subcutaneous and intradermal allergy tests are highly reliable (16, 17). This is probably due to a better antigen penetration. To avoid false-negative reaction at 2 days, it is important to do a delayed reading after day 5.

Delayed hypersensitivity to low-molecular-weight heparin was first reported in 1990; the patient had already had the same lesion with an unfractionated heparin (15). Since then, around 10 cases have been published in the literature (18–22). Our patient had delayed hypersensitivity to low-molecular-weight heparin, confirmed by histology and allergy tests. The erythema that she had could have been a generalization of the initial allergic reaction; however, though patch tests with pristinamycin were negative, it could also have been an exanthematous drug eruption from pristinamycin.

Cross-sensitivities between unfractionated and low-molecular-weight heparin are frequent (4, 8, 15, 23–25). However, some patients can tolerate low-molecular-weight heparins or heparinoid, even though they present with allergy to unfractionated heparin (16, 18). De Boer (26) reported the case of a pregnant woman who was treated with a low-molecular-weight heparin, although she showed allergy to unfractionated heparins and heparinoid. After an eczematous reaction to subcutaneous heparin, another patient (24) was put on intravenous low-molecular-weight heparin, corticosteroids and antihistamines without any side-effects. In this case, we do not know if the tolerance

was induced by the associated corticosteroids antihistamines, or by changing to intravenous administration. Many authors (16, 27) have proposed introducing another heparin molecule if a subcutaneous test is negative. Thus, if necessary, our patient could be treated with intravenous sodium heparin. Because our patient does not have cross-sensitivity between all heparin preparations, we presume that the allergenic potential of heparin is not due to the size of the molecule.

References

1. Plancherel P. Klinische und gerinnungsphysiologische untersuchungen mit einem neuen heparindepotpräparat. *Z Klin Med* 1952; 150: 213–259.
2. Ulrick P J, Manoharan A. Heparin-induced skin reaction. *Med J Aust* 1984; 140: 287–289.
3. Tosti A, De Padova M P, Patrizi A, Minghetti G, Veronesi S. Unusual reaction to subcutaneous heparin. *Contact Dermatitis* 1985; 13: 190.
4. Tuncu A, Moreno A, De Moragas J M. Cutaneous reactions secondary to heparin injections. *J Am Acad Dermatol* 1985; 12: 1072–1077.
5. Hancock B W, Naysmith A. Hypersensitivity to chlorocresol-preserved heparin. *Br Med J* 1975; 3: 746–747.
6. Ainley E J, Mackie I G, MacArthur D. Adverse reaction to chlorocresol-preserved heparin. *Lancet* 1977; 8013: 705.
7. Dux S, Pitlik S, Perry G, Rosenfeld J B. Hypersensitivity reaction to chlorbutol-preserved heparin. *Lancet* 1981; 8212: 149.
8. Klein G F, Kofler H, Wolf H, Fritsch P O. Eczema-like, erythematous, infiltrated plaques. A common side effect of subcutaneous heparin therapy. *J Am Acad Dermatol* 1989; 21: 703–707.
9. Delaval Y, Nogues I, Logeais B, Pibouin M, Chevrant-Breton J. Un cas de toxidermie vésiculo-pustuleuse induit par l'héparine. *Rev Fr Allergol* 1993; 4: 338.
10. Schey S A. Hypersensitivity reactions to heparin and the use of new low-molecular-weight heparins. *Eur J Haematol* 1989; 42: 107.
11. Durst J, Inglis R. Toxische epidermiolyse als lokal-kutane reaktion bei heparin-low-dose-therapie. *Med Welt* 1986; 37: 654–655.
12. Young E. Allergy to subcutaneous heparin. *Contact Dermatitis* 1988; 19: 152–153.
13. Patrizi A, Di Lernia V, Patrone P. Generalized reaction to subcutaneous heparin. *Contact Dermatitis* 1989; 20: 309–310.
14. Pfeiff B, Pullmann H. Baboon-artiges arzneiexanthem auf heparin. *Deutsche Dermatologie* 1991; 39: 559–560.
15. Bircher A J, Flückiger R, Buchner S A. Eczematous infiltrate plaques to subcutaneous heparin: a type IV allergic reaction. *Br J Dermatol* 1990; 123: 507–514.
16. Bircher A J. Allergische reaktionen vom spättyp auf heparine. *Allergologie* 1993; 16: 268–274.
17. O'Donnell B F, Tan C Y. Delayed hypersensitivity reaction to heparin. *Br J Dermatol* 1993; 129: 634–636.
18. Koch P, Schäfer H, Bahmer F A. Allergische hautreaktionen gegen standard und niedermolekulare heparine: gute verträglichkeit von heparin-analogen. *Z Hautkrankh* 1991; 66: 428–435.
19. Manoharan A. Heparin-induced skin reaction with low-molecular-weight heparin. *Eur J Dermatol* 1992; 48: 234.
20. Phillips J K, Majumdar G, Hunt B J, Savidge G E. Heparin-induced skin reaction due to two different prepara-

- tions of low-molecular-weight heparin. *Br J Haematol* 1993; 84: 349-350.
21. Rassmussen C, Skov L, Da Cunha Bang F. Delayed-type hypersensitivity to low-molecular-weight heparin. *Am J Contact Dermatitis* 1993; 4: 118-119.
22. Bircher A J, Itin P H, Tsakiris D A, Surber C. Delayed hypersensitivity to one low-molecular-weight heparin with tolerance of other low-molecular-weight heparins. *Br J Dermatol* 1995; 132: 461-463.
23. Guillet G, Delaire P, Plantin P, Guillet M H. Eczema as a complication of heparin therapy. *J Am Acad Dermatol* 1989; 20: 1130-1132.
24. Koch P, Bahmer F A, Schäfer H. Tolerance of low-molecular-weight heparin after eczematous reaction to subcutaneous heparin. *Contact Dermatitis* 1991; 25: 205-206.
25. Korstanje M J, Bessems M J, Hardy E, Van de Staak B M. Delayed-type hypersensitivity to heparin. *Contact Dermatitis* 1989; 20: 383-384.
26. De Boer K, Heyboer H, Ten Cate J W, Borm J J J, Van Ginkel C J W. Low-molecular-weight heparin treatment in a pregnant woman with allergy to standard heparins and heparinoid. *Thromb Haemost* 1989; 61: 148.
27. Bircher A J. Diagnostic tests for delayed type hypersensitivity reactions to heparins and safety of intravenous heparin. *Am J Contact Dermatitis* 1994; 5: 56-57.

Address:

Dominique Leroy
Service de Dermatologie
Centre Hospitalier Universitaire
Avenue Georges Clemenceau
14033 Caen Cedex
France

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.