References

1. Breathnach S M. Drug reactions. In: Champion R H, Burton J L, Ebling F J G (eds): Rook/Wilkinson/Ebling: *Textbook of dermatology*, 5th edition. Oxford: Blackwell Scientific Publications, 1992: 2961–3035.
2. Peppercorn M A. Sulfasalazine: pharmacology, clinical use, toxicity and related new drug development. *Ann Intern Med* 1984: *101:* 377–386.
3. Pullar T, Hunter J A, Capell H A. Sulfasalazine in rheumatoid arthritis: a double blind comparison of sulfasalazine with placebo and sodium aurothiomalate. *Br Med J* 1983: *287:* 1102–1104.
4. Das K M, Eastwood M A, McManus J P A, Sircus W. Adverse reactions during salicylazosulfapyridine therapy and the relation with drug metabolism and acetylator phenotype. *N Engl J Med* 1973: *289:* 491–495.
5. Kanwar A J, Singh M, Yunus M, Belhaj M S. Fixed eruption to sulphasalazine. *Dermatologica* 1987: *174:* 104.
6. Udono M, Murayama F, Tanioka H. Fixed drug eruption due to salazosulfapyridine and fixed drug eruption due to mefenamic acid. *Medical Achievements of Sasebo City Hospital* (in Japanese) 1991: *17:* 57–61.
7. Hertl M, Jugert F, Merk H F. $CD8^+$ dermal T cells from a sulphamethoxazole-induced bullous exanthem proliferate in response to drug-modified liver microsomes. *Br J Dermatol* 1995: *132:* 215–220.
8. Hayllar J, Bjarnason I. Sulphasalazine in ulcerative colitis: in memoriam? *Gut* 1991: *32:* 462–463.

Delayed allergic skin reactions due to subcutaneous heparin-calcium, enoxaparin-sodium, pentosan polysulfate and acute skin lesions from systemic sodium-heparin

PATRICK KOCH, SOHAD HINDI AND DIRK LANDWEHR

Hautklinik der Universität des Saarlandes, D-66421 Homburg/Saar, Germany

Key words: heparin; low-molecular-weight heparin; heparinoids; pentosan polysulfate; adverse reactions; delayed hypersensitivity; medicaments; tolerance; systemic contact dermatitis.

Heparin-induced delayed allergic skin reactions due to subcutaneously (s.c.) administered unfractionated (UH) or low molecular weight heparins (LMWH) are well documented (1–5) and distinct from heparin-induced skin necrosis (6), or urticaria with angioedema induced by preservative-free LMWH (7).

Case Report

A 45-year-old-woman, immobilized after fracture of the right ankle, was treated with 7500 IU heparin-calcium (Calciparin®) s.c. 3× a day. 14 days after beginning therapy, she developed erythematous, infiltrated, pruritic, painful plaques at injection sites on the lower abdomen and left thigh. Switching to enoxaparin-sodium (Clexane 40®), 1 ampoule daily, had similar effects 3 days after the 1st injection. 12,500 IU heparin-sodium were then administered intravenously (i.v.). On the following day, the patient developed a maculopapular rash predominantly on the trunk. Urgently needed anticoagulation was then achieved with an s.c. heparinoid (pentosan polysulfate; Fibrezym®, Bene, München, Germany), well-tolerated in 10 previously tested patients (8). The maculopapular rash cleared within a few days on topical corticosteroids. However, after 2 weeks treatment with pentosan polysulfate 50 mg 2× daily, erythematous but not pruritic or painful lesions developed at the s.c. injection sites on the right thigh.

Both classical patch tests and patch tests using the skin stripping method (9), as well as intradermal (i.d.) tests with different heparin preparations, were performed 2 weeks after discontinuing therapy with UH and LMWH, to identify a safe heparin preparation for anticoagulation. During testing, and despite the lesions induced, anticoagulation had to be continued with s.c. pentosan polysulfate, because her surgeons considered coumarin therapy inadequate. Topical corticosteroids simultaneoulsy applied on the injection sites resulted in good tolerance of the injections. No flare of dermatitis at previously affected sites was observed.

Despite extensive allergological investigations, including recent heparin preparations, cross-reactions were observed for all the UH, LMWH and heparinoids tested (Table 1). Patch tests with the DKG standard series, as well as a preservatives series including benzyl alcohol, showed sensitizations to fragrance mix 8% pet., balsam of Peru 25% pet. and 5-chloro-2-methyl-4-isothiazolin-3-one/2-methyl-4-isothiazolin-3-one (100 ppm aq.).

Comment

Delayed-type hypersensitivity reactions to heparins are common. The clinical appearance in all cases previously described is almost identical to that in our patient. Skin biopsies showed eczematous changes when taken from active lesions (1, 3, 4) or positive i.d. test reactions at D3 (4). In some patients, histological changes were compatible with acute dermatitis (2, 3, 5). Both UH and LMWH may induce the lesions. When i.d. and s.c. provocation tests are performed, most patients react to

Table 1. Test results

	Test	30′	D1	D2	D3	D4	D5	D6	D7
Unfractionated heparins									
'pure' heparin-sodium (8800 IU/ml)	PT		−	−	−	−	−	−	−
(in crystalline form, introduced in a sterile 0.9% NaCl solution a few min before testing)[a]	ID	−	+	+	+	+	+	+	+
heparin-sodium (5000 IU/ml)	PT		−	−	−	−	−	−	−
(Heparin-Natrium Braun®)[b]	ID	−	+	+	+	+	+	+	+
heparin-sodium (5000 IU/ml)	PT		−	−	?+	−	−	−	−
(Upjohn®)[c]	ID	−	−	−	−	−	−	+	+
heparin-calcium (25000 IU/ml)	PT		−	−	−	−	−	−	−
(Calciparin®)[d]	ID	−	+	+	+	+	+	+	+
Low-molecular-weight heparins									
heparin-sodium (Fraxiparin®)[d]	PT		−	+	++	++	?+	?+	−
MM: 4000–5000	ID	−	+	+	+	+	+	+	+
dalteparin-sodium (Fragmin D®)[e]	PT		−	−	−	−	−	−	−
MM: 4000–6000	ID	−	−	−	−	−	−	+	+
enoxaparin-sodium (Clexane 20®)[f]	PT		−	−	+	+	?+	?+	−
MM: 4000–6000	ID	−	−	−	+	+	+	+	+
reviparin-sodium (Clivarin®)[a]	PT		−	−	?+	?+	?+	?+	−
MM: 3500–4000	ID	−	−	+	+	+	+	+	+
Heparinoids									
danaparoid-sodium (Orgaran®)[g]	PT		−	−	?+	?+	?+	?+	−
	ID	−	+	+	+	+	+	+	+

+: erythema and papules; −: negative test; ++: erythema, papules and vesicles; MM: medium molecular weight

PT: patch test using the skin stripping method (9), with undiluted heparin and heparinoid applied for 24 h on the upper back and read after 24 h (D1) and then each day until D7. Conventional patch tests were negative for different types of heparin and heparinoids.

ID: intradermal tests with 0.05 ml of the undiluted heparin or heparinoid preparation.

[a] Nordmark, Uetersen, Germany. [b] Braun, Melsungen, Germany. [c] Upjohn, Kalamazoo, USA. [d] Sanofi-Winthrop, München, Germany. [e] Pharmacia, Erlangen, Germany. [f] Rhône-Poulenc, Köln, Germany. [g] Organon, Oss, The Netherlands

All the heparins and danaparoid-sodium are derived from porcine intestinal mucosa. Heparin-sodium Upjohn® is derived from bovine lung and pentosan polysulfate from beech wood. Only heparing-sodium Upjohn® contains benzyl alcohol as a preservative. The other heparin preparations are preservative-free.

both the fractionated and unfractionated heparin molecule itself, but the LMWH dalteparin-sodium (Fragmin®) has been proposed as a possible alternative (10).

To our knowledge, lesions induced by i.v. UH in delayed hypersensitivity to subcutaneous heparins (UH and LMWH) and heparinoids have not been described before. As reported previously by us (4, 8, 11) and others (12), s.c. heparinoids may be a safe alternative in these patients. However, a delayed skin reaction to s.c. UH, LMWH and the heparinoid, danaparoid, occurred in 1 patient (13). In a further case, danaparoid (Org. 10172, Orgaran®) also gave a positive i.d. test reaction in a patient with a Type IV skin reaction following s.c. injections of unfractionated sodium-heparin (14). Since this heparinoid is a mucopolysaccharide derived from porcine intestinal mucosa, it may share identical allergens with heparin (14). However, an allergic reaction to pentosan polysulfate, derived from beech wood, was unexpected in our patient. According to the manufacturer of this heparinoid, no changes in manufacturing have occurred in recent years.

Patients with delayed skin reactions to heparin should be investigated by patch, i.d. and s.c. provocation tests before continuing therapy with another heparin preparation or heparinoids, not overlooking combined sensitizations to UH and LMWH nearly always present in these patients. Allergological investigations, including new LMWH, should nevertheless be performed after healing of the lesions, to try to identify a heparin for i.v. therapy. In our case, no alternative heparin, not even the new LMWH sodium-reviparin (Clivarin®), could be found for the patient. To our knowledge, a delayed allergic reaction to this new LMWH, most likely explained as a cross-reaction with other LMWH and UH, has not previously been reported. These cross-reactions are, in our experience, habitually observed when testing patients with eczematous plaques from s.c. heparin. However, even when allergological investigations are negative to dalteparin-sodium (10, 11), urgently needed i.v. coagulation with this LMWH should only be given accompanied by corticosteroids and antihistamines (11). In our experience, false-negative test reactions cannot yet be totally excluded.

References

1. Guillet G, Plantin P, Delaire P. Placards inflammatoires aux points d'injection d'héparine calcique témoignant d'un eczéma à l'héparine. *Presse Méd* 1988: *17:* 1154.
2. Klein G F, Kofler H, Wolf H, Frisch P O. Eczema-like, erythematous, infiltrated plaques: a common side effect of subcutaneous heparin therapy. *J Am Acad Dermatol* 1989: *21:* 703–707.

3. Bircher A J, Fliickiger, Buchner S A. Eczematous infiltrated plaques to subcutaneous heparin: a type IV allergic reaction. *Br J Dermatol* 1990; *123:* 507–514.
4. Koch P, Schäfer H, Bahmer F A. Allergische Hautreaktionen gegen Standard- und niedermolekulare Heparine. Gute Verträglichkeit von Heparin-Analogen. *Z Hautkr* 1991: *66:* 428–435.
5. O'Donnell B F, Tan C Y. Delayed hypersensitivity reaction to heparin. *Br J Dermatol* 1993: *129:* 507–514.
6. Koch P, Wagner S, Baum H P. Nécroses cutanées à l'héparine et déficit en protéine C? *Ann Dermatol Vénéréol* 1994: *121:* Suppl I, S 122.
7. Odeh M, Oliven A. Urticaria and angioedema induced by low-molecular-weight heparin. *Lancet* 1992: *340:* 972–973.
8. Koch P. Dermites eczématiformes à l'héparine. A propos de 10 cas. *Journées Dermatologiques de Paris* 1993: *17–20 March:* C29.
9. Klaschka F. Tesafilmabrissmethode: Empfindlichkeitssteigerung von Epikutantests. *Hautarzt* 1985: *36:* 250.
10. Schey S A. Hypersensitivity reactions to heparin and the use of new low molecular weight heparins. *Eur J Haematol* 1989: *42:* 107.
11. 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.
12. Zimmermann R J, Harenberg J, Weber E, De Vries J X, Jarass W, Schmidt W. Behandlung bei Heparin-induzierter kutaner Reaktion mit einem niedermolekularen Heaparin-Analog. *Dtsch Med Wschr* 1984: *109:* 1326–1328.
13. Sivakumaran M, Ghosh K, Munks R, Gelsthorpe K, Tan L, Wood J K. Delayed cutaneous reaction to unfractioned heparin, low molecular weight heparin and danaparoid. *Br J Haematol* 1994: *86:* 893–894.
14. Korstanje M J, Bessems P J M, Hardy E, Van De Staak W J B M. Delayed-type hypersensitivity to heparin. *Contact Dermatitis* 1988: *20:* 383–384.

Allergic contact dermatitis from Dragophos S, a new emulsifier

J. J. Goday Buján, I. Yanguas Bayona, M. González Güemes, R. Ilardia Lorentzen and R. Soldeta Arechavala

Servicio de Dermatología, Hospital Santiago Apóstol, C/ Olaguibel 29, 01004 Vitoria, Pais Vasco, Spain

Key words: Dragophos S; emulsifiers; cosmetics; allergic contact dermatitis; sodium dihydroxyacetyl phosphate isopropyl hydroxycetyl ether.

Case Report

A 49-year-old man started applying a 12% ammonium lactate lotion (Algorex®) 2× a day for xerosis on the anterior left leg. 5 days later, he developed a very pruriginous erythema, which then became eczematous, in the affected area. After discontinuing application of the lotion, and with the administration of topical corticosteroids, the process remitted in a few days.

Patch test were carried out with the GEIDC standard series and the lotion, as is, using Al-test® and Mefix®, readings being made at 2 and 4 days, according to ICDRG guidelines. Patch tests were then done with the components of the lotion (kindly supplied by Reig Jofré Lab.) in various concentrations and vehicles (ammonium lactate, Arlacel 165, Dragophos S (pure), Dragoxat EH, cetyl alcohol, Cutina GMS, sorbitol, allantoin, Nipastat, Nipantiox (BHA), essence). Positivity was found to the lotion, as is, and 1 component, Dragophos S (Table 1). 15 controls carried out with the lotion and Dragophos S 5% aq. were all negative.

Table 1. Patch test results

Allergen	D2	D4
GEIDC standard series	–	–
Algorex® as is	–	++
Dragohpos S 5% aq.	+	++
Dragophos S 1% aq.	?+	++
other constituents	–	–

Discussion

Dragophos S (sodium dihydroxycetyl phosphate isopropyl hydroxycetyl ether) is a yellowish waxy substance that is used as an emulsifier in cosmetic creams, hand creams, body milks, make-up removers, aftershave lotions, sunscreens, aftersun lotions and fluid make-ups. It can be incorporated in both fatty and aqueous phases, its total incorportion being assured between 80–85°C.

A study carried out by the laboratory that manufactures Dragophos S described it as non-irritating, both in a skin irritation test on guinea pigs and in an epicutaneous test on humans, at concentrations of 10%. Furthermore, according to the method of Magnusson and Kligman, it was considered not to cause hypersensitivity in guinea pigs.

In the case we report, both the clinical course and the patch tests confirmed the diagnosis of allergic contact dermatitis due to Dragophos S emulsifier. To our knowledge, this is the 1st case described in the literature. Although we found positivity to it down to 1% aq., it might perhaps be preferable to patch test it at 5% aq.