

Low Doses of Low Molecular Weight Heparin *In vivo* Inhibits the Elicitation of Contact Hypersensitivity

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Low-dose low molecular heparin inhibits T lymphocyte-mediated autoimmune disease and allograft reactions in mice *in vivo* and *in vitro*. High doses of heparin are not effective. The purpose of this preliminary study was to analyze the effect of low-dose, low molecular weight heparin (Enoxaparin, Clexane[®]) on the expression of patch testing in patients with contact dermatitis. Eleven patients with allergic contact dermatitis, and positive patch tests reactions, were given a single subcutaneous injection of Clexane[®] 3 mg (0.03 ml) and were reevaluated for positive reactions after the injection. Eight out of 21 positive reactions (38%) became negative after the injection and 4 out of 21 reactions (19%) changed from ++ before the injection to + after. An impressive improvement was observed in 3 patients with chronic allergic contact dermatitis. Low-dose low molecular weight heparin inhibits the elicitation of allergic contact dermatitis.

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Previously one of us reported that administration of relatively low doses of heparin to mice *in vivo* (5 µg/day) or *in vitro* (0.1 µg/ml) inhibits T lymphocyte-mediated autoimmune disease and allograft reactions (1).

High doses of heparin were not as effective as low doses.

This study was undertaken to analyze the effect of low-dose low molecular weight heparin (Enoxaparin, Clexane[®]) on the expression of positive patch tests in patients with contact dermatitis.

MATERIAL AND METHODS

Eleven patients, 6 females and 5 males, with allergic contact dermatitis and positive reactions in standard patch tests (Standard European Patch Tests, Trolab-Hermal) formed the study group.

All the patients refrained from taking any medication for at least one month entering the study and also during the study.

Table I lists details concerning the patients: gender, age, allergic contact dermatitis, location, duration, and reaction before and after injections.

The patients were patch-tested with the European standard series using Finn Chambers and Micropore[®] tape applied to the back.

The tests were removed after 2 days and evaluated after at least 2 h.

The positive allergic reactions were defined as +, ++ and +++. (+ = erythema or infiltration, ++ = small vesicles, +++ = bulla).

Two weeks after the first patch tests we gave the patients a subcutaneous injection of 3 mg of low-dose low molecular weight heparin - Enoxaparin, Clexane[®] (Rhone Poulenc - France). One week later, we patch-tested again every patient with the allergens that gave a positive reaction in the first patch tests (we used the same allergens (Trolab-Hermal, Germany), the same Finn chambers, the same Micropore[®] tape

and applied them on the back on the same places. Two days later we again read the reactions defined as +, ++ and +++.

The reactions before the injection were compared to those after the injection. Additionally, we evaluated the clinical changes following the injection.

Twenty patients who undertook the same method and schedule, but without injections, formed the control group. The control group consisted of 16 females and 4 males aged 17-60 years, with allergic contact dermatitis confirmed by patch tests. The duration of the contact dermatitis was 1-4 years. Eleven patients had hand eczema, 4 facial eczema, 2 hand with facial eczema, and 3 disseminated allergic contact dermatitis. In this group, 2 patients showed a positive reaction to the first patch test and a negative reaction to the second patch test (the positive reactions to the first patch tests were to nickel and potassium dichromate).

RESULTS

The results are shown in Table I. Eight of the 21 positive reactions (38%) disappeared after the injection; 4 reactions changed from ++ before the injection to + after the injection (19%). In 3 patients (nos. 3, 9, 10) with chronic allergic contact dermatitis, an impressive improvement was observed.

In patient no. 3, who had suffered from a chronic disseminated allergic contact dermatitis for 2 years, the dermatosis disappeared 5 weeks after the heparin injection. He received three additional injections (one injection every 2 weeks) and now, 2 years after the last injection, he only has a very mild eruption.

Patient no. 9 is a baker. He had had severe hand eczema for 3 years. One week following the injection he experienced a remarkable improvement. Two years after this single injection, he only had dry skin and some mild fissures on his palms. He did not change his profession or work conditions.

Patient no. 10 is a housewife. She had had blistering hand eczema (nickel dermatitis) for 3 years. Following four heparin injections, one every 2 weeks, the incommensurate dermatitis completely disappeared. After a follow-up of more than 2 years, no eruption has been noticed. She has continued to do the same house duties as before. The control group comprises 31 positive reactions in the first patch testing. In the second patch testing, two positive reactions became negative (patients nos. 3 and 5); the reproducibility of the patch tests was 93.5%.

DISCUSSION

T lymphocytes express a heparanase enzyme that degrades the heparan sulfate moiety of the proteoglycan of the extracellular matrix (2, 3). The ability of activated T lymphocytes to penetrate the extracellular matrix and migrate to target tissues was found to be related to the expression of this heparanase enzyme (3, 4).

Heparin molecules inhibit the expression of T lymphocytes

Table I. Patient details and reactions before and after injections
ACD = allergic contact dermatitis; F = female; M = male.

Patient No	Age/ Sex	ACD duration	ACD location	Positive reaction before the injection	Reaction after the injection
1	30/F	1 yr	Hand eczema	Nickel +2	Nickel +1
2	34/M	3 yrs	Hand eczema	Mercaptomix +2 MBT +2	Mercaptomix +2 MBT +2
3	60/M	2 yrs	Disseminated	Epoxy resin +2	Epoxy resin +1
4	40/M	1.5 yrs	Facial eczema	Fragrance +2	Negative
5	25/F	2 yrs	Hand eczema	Nickel +2	Nickel +1
6	42/M	5 yrs	Hand eczema	Potassium dichromate +1 Thiuram mix +2	Negative Thiuram mix +1
7	38/F	2 yrs	Hand & limb eczema	Colophony +2 Potassium dichromate +2	Negative Potassium dichromate +2
8	40/F	2.5 yrs	Hand & facial eczema	Thiuram mix +3 Fragrance +1	Thiuram mix +3 Fragrance +1
9	38/M	3 yrs	Hand eczema	Nickel +1 Colophony +1	Negative Negative
10	60/F	3 yrs	Hand eczema	Cinamic aldehyde +2 Cinamic alcohol +2	Cinamic aldehyde +2 Cinamic alcohol +2
11	28/F	1 yr	Facial eczema	Potassium dichromate +1 Cobalt +1 Paraphenylenediamine +3 Formaldehyde +2 Nickel +2	Negative Negative Paraphenylenediamine +3 Negative Nickel +2

heparanase activity *in vitro* and *in vivo*, and administration of a low dose of heparin in mice inhibited lymphocyte traffic and delayed-type hypersensitivity (5).

Low-dose heparin, once daily, was found to prolong allograft survival and inhibited experimental autoimmune diseases adjuvant arthritis and experimental autoimmune encephalomyelitis (5).

Enoxaparin (Clexane®) is a low molecular weight heparin. A number of low molecular weight heparins have been developed commercially and have been shown to be safe and effective (6). Enoxaparin shows less ability to prolong the activated partial thromboplastin time, while possessing the same ability as other low molecular weight heparins to inhibit an activated factor. It produces less bleeding in experimental models than standard commercial grade heparin (6).

The administration of an ultramini dose of 3 mg Enoxaparin in a subcutaneous injection, as shown in the present study, is safe and harmless. The observation that low-dose heparin (but not a high dose) is effective in the regulation of T lymphocytes and inhibits migration of T lymphocytes to delayed-type hypersensitivity sites in laboratory animals led us to investigate the effect of heparin on allergic contact dermatitis in humans. The results of the present study are impressive and promising. Thirty-eight percent (8/21) of the positive reactions became negative after a single administration of 3 mg Enoxaparin, and 19% (4/21) of the reactions changed from ++ to +. Three patients with a long-standing chronic allergic contact dermatitis improved dramatically after a single (or more in two cases) injection, and the improvement is still a fact, approximately two years after treatment. We inquired about these patients' health many times, and they did not have to change their occupation or daily duties. Since the reproducibility of patch tests in the

control group is high (93.5%), we do not think the results were influenced by the reproducibility problem.

The treatment with 3 mg of subcutaneous Enoxaparin injections was found to be safe, without any side-effects or effect on the blood clotting system. It is of interest that in a recent study (7) delayed-type hypersensitivity to low molecular weight heparin was observed. In our study a pregnant woman received a daily subcutaneous injection of 5,000 IU of Fragmin (low molecular weight heparin preparation). After 8 to 9 days of treatment, the patient developed an eczematous eruption on the abdominal wall at the sites of injection. Patch tests to two types of low molecular weight heparin (Fragman and Clexane®) gave a +1 positive reaction after one week. Undiluted Clexane®, 100 mg/ml, was applied. This case stressed once again the importance of injecting the precise dose of subcutaneous Enoxaparin (Clexane®) (3 mg) to achieve good results without side-effects.

Is an ultramini dose of low molecular weight heparin a new effective and safe treatment for contact dermatitis? This question is now being investigated in a number of studies at our department.

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