

Case report

Delayed-type hypersensitivity to subcutaneous enoxaparin

Méndez J, Sanchís ME, de la Fuente R, Stolle R, Vega JM, Martínez C, Armentia A, Sánchez P, Fernández A. Delayed-type hypersensitivity to subcutaneous enoxaparin.

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Background Enoxaparin and other low-molecular-weight heparins are widely used to prevent and treat thromboembolic disorders. Cutaneous reactions secondary to enoxaparin injections include delayed hypersensitivity skin reactions described as erythematous, infiltrated plaques at injection sites. We studied three cases of erythematous infiltrated plaques after enoxaparin injection in order to establish the allergenic importance of this low-molecular-weight heparin.

Methods Patch tests were performed with sodium heparin, calcium heparin, calcium enoxaparin, and calcium nadroparin. A subcutaneous test with calcium heparin and an intravenous challenge test with sodium heparin were done. A punch biopsy was obtained from an erythematous plaque in one patient.

Results Patch tests were negative to calcium heparin in all patients, positive to enoxaparin and nadroparin in two patients, and positive to sodium heparin in one patient. In two patients, the subcutaneous challenge test was positive, the intravenous challenge test was negative, and the histopathologic appearance of the biopsy resembled a delayed-type hypersensitivity reaction.

Conclusions These cases provide evidence of type IV hypersensitivity and the possibility of crossed-allergenicity among unfractionated heparin and low-molecular-weight heparins. We show that the subcutaneous challenge test is the most reliable diagnostic measure.

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The clinical use of prophylactic doses of heparin to prevent pulmonary or venous thrombosis is widely accepted. Nowadays, unfractionated heparins are being replaced by low-molecular-weight heparins because of the improved pharmacodynamic properties and better safety profile (1). Adverse reactions to heparins include immunologically mediated hypersensitivity reactions: heparin-induced immune thrombocytopenia (2); immediate hypersensitivity reactions (3); and delayed (type IV) hypersensitivity skin reactions such as large, symptomatic, erythematous infiltrated plaques at injection sites (4).

Material and methods

Three patients showing cutaneous reactions after enoxaparin injections were studied.

Case reports

Patient 1. A 73-year-old woman was admitted to our hospital because of increasing thoracic pain and dyspnea after she had suffered a fall. She was diagnosed as having thoracic traumatism on admission. For prevention of thrombosis, she was initially treated with enoxaparin 40 mg once a day, injected subcutaneously in the abdominal wall for 10 days. By 13 days after admission, well-defined, pruritic, erythematous infiltrated plaques had developed at previous enoxaparin injection sites on the abdomen and arms (Fig. 1). After treatment with antihistamines and topical corticosteroids, the lesions healed in 15 days.

Patient 2. A 46-year-old woman suffering from rheumatoid arthritis was admitted to our hospital because of increasing leg pain, and she was initially

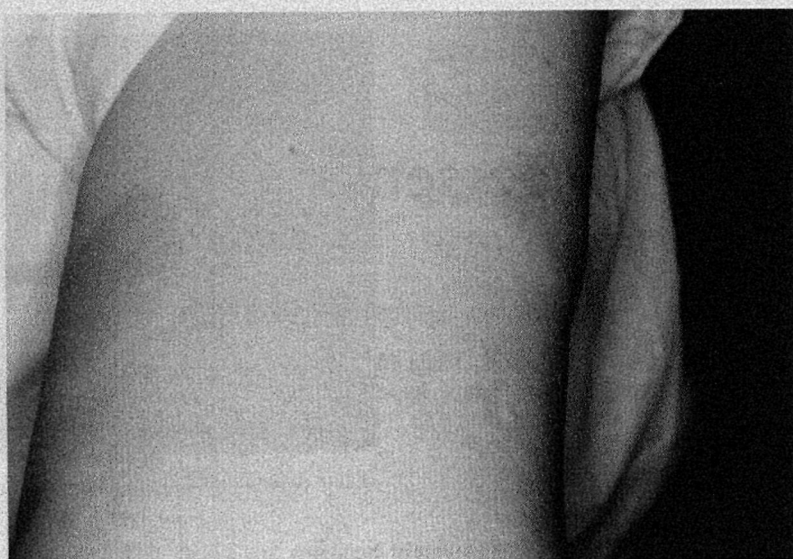


Fig. 1. Erythematous infiltrated plaques on arm of patient 1.

treated with subcutaneous enoxaparin 40 mg once a day. Two days later, the patient developed clinical symptoms of pulmonary embolism confirmed by pulmonary scintigraphy. Six days later, pruritic, erythematous infiltrated plaques developed at previous enoxaparin injection sites, and enoxaparin was replaced by sodium heparin with good tolerance. The lesions healed in 1 month after treatment with antihistamines and topical corticosteroids.

Patient 3. A 69-year-old woman developed generalized eczema 24 h after intravenous administration of sodium heparin during arterial bypass surgery. Two years later, this patient was admitted to our hospital because of thoracic pain, and daily subcutaneous 40 mg enoxaparin treatment was started, but it was interrupted 3 days later after pruritic, erythematous infiltrated plaques developed at previous enoxaparin injection sites. She was treated with oral and topical corticosteroids, and the lesions healed in 21 days.

Allergologic study

Patch tests were performed in all patients on the back with the following drugs: sodium heparin, calcium heparin, calcium enoxaparin, and calcium nadroparin (as is). The patch tests were read at 48 and 96 h. At the time of patch test reading, we used the 1+ to 3+ scoring system recommended by the International Contact Dermatitis Research Group. Five subjects who had received subcutaneous enoxaparin previously without any history of adverse reactions to this drug were used as controls.

A subcutaneous challenge test with 0.3 ml (7500 IU) of calcium heparin was carried out on the abdomen in all patients. Test results were considered positive if slightly infiltrated and erythematous areas larger than 1 cm in diameter developed at the injection site.

Intravenous challenge tests with sodium heparin at 1000 and 5000 IU were done in patient 1. These challenge tests were not done in patient 2 because she had tolerated sodium heparin administered in the treatment of a pulmonary embolism when she was in the hospital. We did not do a challenge test

Table 1. Results of studies performed

Patient no.	Patch tests				Subcutaneous challenge test	Intravenous challenge test
	Sodium heparin	Calcium heparin	Calcium enoxaparin	Calcium nadroparin		
1	—	—	—	— ^{a)}	+ ^{b)}	—
2	—	—	+	+	—	—
3	+	—	+	+	+	ND

^{a)} Negative test.

^{b)} Positive test.

ND: not done.

Table 2. Reported cases of delayed hypersensitivity reactions to heparin and low-molecular-weight heparins

Substance	No. of cases	Authors	Reference
Calcium heparin	15	Klein et al.	4
Calcium heparin	1	Guillet et al.	8
Sodium heparin	1	Korstanje et al.	9
Calcium heparin	2	Bircher et al.	10
Calcium heparin	1	Valsecchi et al.	11
Calcium heparin	1	de Kort et al.	12
Calcium heparin	1	Dupin et al.	13
Sodium heparin	1	O'Donnell et al.	14
Sandoparin	1	Bircher et al.	15
Calcium enoxaparin	1	Moreau et al.	21
Calcium heparin	1	Koch et al.	22
Calcium enoxaparin	1	Méndez et al.	23
Calcium nadroparin	1	Gonzalo & Revenga	27

with sodium heparin in patient 3 because she had had generalized eczema 24 h after administration of sodium heparin and her patch test with sodium heparin was positive.

Written informed consent was obtained before challenge in all patients.

One spontaneous lesion was removed for biopsy and processed for routine histologic examination in patient 3. Patients 1 and 2 refused to allow a biopsy to be performed.

Results

The results of the studies performed are described in Table 1. Patch tests were positive to calcium enoxaparin and calcium nadroparin at 96 h in patient 2 and were positive to sodium heparin, calcium enoxaparin, and calcium nadroparin at 96 h in patient 3. The controls did not react to any of these tests, proving the absence of irritant effect at the concentrations used.

A subcutaneous challenge test with calcium heparin induced an erythematous infiltrated plaque at the injection site at 48 h in patient 1 and at 96 h in patient 3.

An intravenous challenge test with sodium heparin in patient 1 was negative.

The lesion removed for biopsy in patient 3 showed marked dermal edema and perivascular lymphocytic infiltrates with eosinophils. The epidermis exhibited pronounced focal spongiosis and exocytosis of lymphocytes.

Discussion

Erythematous infiltrated plaques appear to be a common but neglected cutaneous reaction to heparin. The underlying pathophysiologic mechanism is unknown; but two possibilities have been

suggested: a mild form of heparin necrosis (5–7) and a probably delayed hypersensitivity reaction (8–15). The allergen has not been identified, but it is probably associated with, or is part of, the heparin molecule; heparin binds strongly to proteins, a prerequisite for a complete antigen. Delayed hypersensitivity skin reactions always occur at the site of injection, often 10–20 days after the start of the treatment, and this disorder appears usually in obese and diabetic women (4, 6, 15); our three patients were obese women and one of them was diabetic, too. These findings suggest that hormonal influences and metabolic disturbance may play a role in the pathogenesis of this reaction, perhaps modulating the local irritative effect of the heparin. Therefore, female sex, obesity, and diabetes may be risk factors for the development of sensitization to subcutaneous heparin and low-molecular-weight heparins.

Enoxaparin is the first low-molecular-weight heparin to be marketed in the USA (16). The adverse reactions reported with enoxaparin have been hematoma, urticaria, angioedema, and cutaneous necrosis (17–19). Phillips et al. (20) described for the first time a skin reaction after treatment with enoxaparin, and they postulated in the pathogenesis a localized Arthus reaction. Since then, three cases of cutaneous reaction secondary to enoxaparin injections have been reported (21–23). Our data support the view that erythematous infiltrated plaques are a delayed-type hypersensitivity reaction: the development of lesions 3–13 days after the start of prophylactic heparin administration, delayed hypersensitivity reactions to patch testing and subcutaneous challenge in two patients, the absence of signs of skin necrosis, and the histopathologic appearance in the biopsy obtained in patient 3. The reported cases described as delayed hypersensitivity reactions to heparin and low-molecular-weight heparins are shown in Table 2.

Ingber et al. (24) mention that a low dose of low-molecular-weight heparins inhibits the elicitation of allergic contact dermatitis and showed that enoxaparin could modify a positive patch test. This possibility could explain why patch tests were negative in our study, but we think that the conditions were different in our cases for two reasons: our patients received subcutaneous injections of enoxaparin at the usual dose of 40 mg (0.4 ml), and not at the low dose of 3 mg (0.03 ml) that Ingber et al. used; moreover, these authors patch-tested every patient 1 week after the injection while we patch-tested our patients 1 month after the first injection and previous challenge test with calcium heparin.

It has been previously suggested that the skin

reaction may be due to preservatives present in heparin preparations rather than to the heparins themselves (25), but enoxaparin does not contain preservatives.

These cases demonstrate the possibility of cross-reactivity between unfractionated heparin (calcium and sodium heparin) and low-molecular-weight heparins (enoxaparin and nadroparin), as previously reported (2, 14, 20–23, 26, 27). All the patients were sensitized to enoxaparin, patients 2 and 3 had a patch test positive to nadroparin, and patients 1 and 3 had a challenge test positive to calcium heparin; but it is important to emphasize that patients 1 and 2 could use sodium heparin any time if they needed it. Patient 3 is a particular case because she suffered from generalized eczema, a very rare reaction (2), 24 h after intravenous administration of sodium heparin. She had a patch test positive to sodium heparin; therefore, alternative anticoagulants should have been used in this patient.

The subcutaneous challenge test was an important diagnostic method in our study because two patients with negative patch test to calcium heparin had a positive subcutaneous challenge test to calcium heparin.

If a patient develops a reaction to heparin and it seems to be an erythematous infiltrated plaque, several techniques should be used to confirm the diagnosis and to discover a heparin which does not provoke a reaction. For safety reasons, a patch test should be performed initially. When the patch test is negative, a subcutaneous test and sometimes an intravenous challenge test are necessary. For identification of discrete and late positive results, the subcutaneous test should be read at 30 min, 2 days, and 4 days.

In conclusion, we can say that clinicians should be aware of the possibility of the appearance of erythematous infiltrated plaques in patients receiving subcutaneous prophylactic enoxaparin, probably as a type IV hypersensitivity reaction. The allergic study demonstrates that a patient may also develop this complication after administration of other heparin preparations, sodium heparin included, and that the subcutaneous challenge test is the most reliable test modality.

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