

Association of Hamburg Stock Exchange, and B. Paulus). European frog's legs are never used. Usage of chemicals of any kind is strictly prohibited and regularly controlled in Germany. As reported (D. Wöhner, Personal Communication, 10 January 1984, Public Veterinary Institute, Saarbrücken, Germany), chemicals were never found in imported frog's legs, and *Salmonella* contamination only in very rare cases. Fresh frog's legs are imported only occasionally, via Paris, for a few gourmet restaurants (B. Paulus).

Only one case of food poisoning from frogs has been reported: schizophrenia-like symptoms culminating in the motiveless murder of relatives among native Africans after consumption of bullfrogs (2). Possible causes include the ingestion of bufotonin, a schizophrenogenic substance found in the tissue of some species of frogs, or an allergic reaction to food.

Key words: food allergy; frog's legs allergy; professional dermatosis.

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Delayed hypersensitivity skin reaction to enoxaparin

DEDELAYED hypersensitivity skin reactions have been described as erythematous, infiltrated plaques at injection sites, after administration of heparin and low-molecular-weight heparin (LMWH) preparations. We report one case of erythematous infiltrated plaques at enoxaparin injection sites. This case provides evidence of a delayed-type hypersensitivity reaction. The allergic study demonstrated that a subcutaneous challenge test is the most reliable diagnostic measure.

■ A 73-year-old woman was admitted to our hospital because of increasing thoracic pain and dyspnea after a fall, and she was diagnosed as



FIGURE 1 Erythematous infiltrated plaques on abdomen of patient.

having thoracic traumatism on admission. To prevent thrombosis, she was initially treated with enoxaparin (Clexane®) 40 mg once a day, injected subcutaneously in the abdominal wall for 10 days. Thirteen days after admission, 3-6 cm of well-defined, pruritic, erythematous infiltrated plaques developed at previous enoxaparin injection sites; some of them showed partial ecchymosis (Fig. 1). The platelet count was always normal. The patient refused to undergo biopsy. After treatment with antihistamines and topic corticosteroids, the lesions disappeared in 15 days.

The results of patch tests with the standard contact antigen panel of the International Contact Dermatitis Research Group (ICDRG) were negative. Patch tests with sodium heparin, calcium enoxaparin, and calcium nadroparin (as is) were negative.

Subcutaneous challenge test with 7500 UI calcium heparin induced an erythematous infiltrated plaque at the injection site at 96 h. After previous warning of the risk of these tests and consent having been obtained for them to be done, intravenous challenge tests with sodium heparin at 1000 and 5000 UI were negative. Erythematous infiltrated plaques to enoxaparin were diagnosed.

A case of erythematous infiltrated plaques at enoxaparin injection sites.

■ Erythematous infiltrated plaques appear to be a common but neglected cutaneous reaction to heparin. The reported cases of this reaction are shown in Table 1. The underlying pathophysiologic mechanism is unknown; but two possibilities, a mild

Table 1. Reported cases of erythematous infiltrated plaques to heparin

Substance	Pathologic mechanism	No. of cases	Authors
Calcium heparin	Delayed hypersensitivity	1	de Kort et al.
Calcium heparin	Delayed hypersensitivity	1	Guillet et al.
Calcium heparin	Heparin necrosis	1	Tosti et al.
Sodium heparin	Delayed hypersensitivity	1	Korstanjie et al.
Calcium heparin	Delayed hypersensitivity	1	Valsecchi et al.
Calcium heparin	Heparin necrosis	6	Tuneu et al.
Calcium heparin	Delayed hypersensitivity	15	Klein et al.
Calcium heparin	Delayed hypersensitivity	2	Bircher et al.
Calcium heparin	Delayed hypersensitivity	1	Dupin et al.

form of heparin necrosis and a probable delayed hypersensitivity reaction, have been suggested. Delayed hypersensitivity skin reactions always occur at the site of injection, often 10–20 days after the start of treatment, usually in obese and diabetic women (1, 2) like our patient. These findings could suggest that hormonal influences and a 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.

Phillips et al. (3) described for the first time a skin reaction after treatment with enoxaparin, and they postulated in the pathogenesis a localized Arthus reaction. Our data support the view that erythematous infiltrated plaques are a delayed-type hypersensitivity reaction: lesions developed 13 days after the start of prophylactic heparin administration, subcutaneous provocation test with calcium heparin was positive at 96 h and no necrosis was observed. In several reports (2, 4), delayed hypersensitivity reactions have been diagnosed without histologic confirmation; unfortunately, we could not obtain a biopsy, and a mild form of heparin necrosis cannot be excluded.

Ingber et al. (5) mention that low dosis of LMWH 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, in our case, the conditions were different for two reasons: our patient received subcutaneous injections of enoxaparin at the usual dosis of 40 mg (0.4 ml), and not at the low dosis of 3 mg (0.03 ml) used by Ingber et al.; moreover, they patch-tested every patient 1 week after the injection while we patch-tested our patient 1 month after the first injection and previous challenge test with calcium heparin.

It has been previously suggested that skin reaction may be due to preservatives present in heparin preparations rather than to the heparins themselves, but Clexane does not contain preservatives.

This case demonstrates the possibility of cross-reactivity between unfractionated heparin (calcium heparin) and LMWH (enoxaparin). This is a problem if one must use heparin to prevent thrombosis, but it is important to emphasize that our patient was free to use sodium heparin because the intravenous challenge test with this drug was negative.

Finally, when the patch test is negative, a subcutaneous challenge is necessary. This is the most reliable test modality. In order to identify discrete and late positive results, it should be read at 30 min and 2 and 4 days.

Key words: allergy; delayed hypersensitivity; enoxaparin; heparin.

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