

Acute generalized exanthematous pustulosis induced by enoxaparin: 2 cases

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Delayed-type hypersensitivity skin reactions to heparins are frequent (7.5% of patients treated), occurring mainly as eczematous lesions at injection sites and very rarely as severe

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cutaneous adverse reactions (1). We report 2 cases of enoxaparin-induced acute generalized exanthematous pustulosis (AGEP) and discuss cross-reactivity between heparins.

CASE REPORTS

Case 1: A 74-year-old woman was referred to our emergency dermatology department for a sudden, diffuse febrile rash followed by a superficial post-pustular desquamation as shown by the patient's own pictures. The diagnosis was strongly suggestive of AGEP at Day 3 after a colonic surgery and pantoprazole, paracetamol, neovofam, phloroglucinol, ketoprofen and enoxaparin were the suspected drugs. *Case 2:* A 74-year-old woman hospitalized in neurology, presented a diffuse febrile erythematous rash with non-follicular pinhead-sized pustules reinforced in the large folds and associated with leukocytosis at 12700/ μ L. The diagnosis of AGEP was assessed; bisoprolol and enoxaparin, started 2 days previously, were suspected and stopped. Allergologic explorations were performed at 5 and 3 months after skin recovery, respectively, according to international recommendations (2). For the two patients, patch tests (PTs) were performed with the commercialized pills of the suspected drugs diluted at 30% in petrolatum and with several undiluted heparins (Table). They were applied on the upper back by using IQ ultra chambers (Chemotechnique Diagnostics, Vellinge, Sweden), with readings on Day 2 (D2) and D4. Intradermal tests (IDTs) were also performed, with heparins diluted from 10^{-3} to 10^{-1} with reading on D3. In both cases, all PTs were negative, and only delayed reading of enoxaparin-IDT was positive, associated with polysensitization to other heparins (Table, Figure). Neither patient reported onset or reinforcement of the eruption at the site of the enoxaparin injection. Patient 1 reported a similar previous diffuse

desquamative rash occurring 13 years earlier after surgery, in which heparin administration was probable, and patient 2, a rash occurring 3 years earlier, when enoxaparin was among the offending drugs, but no test had been performed.

Discussion

We report 2 cases of AGEP due to enoxaparin proven by positivity on delayed reading of IDT associated with several heparin cross-reactions and a history evoking a similar previous episode. Only 2 cases of severe cutaneous adverse reactions related to heparins have been published: one of drug reaction with eosinophilia and systemic symptoms induced by enoxaparin (no skin tests performed) and one of AGEP induced by dalteparin, with polysensitization that relapsed during the subcutaneous tests (Table) (3,4). Two cases of acute localized exanthematous pustulosis, a variant of AGEP, have also been reported: one induced by bemiparin with positivity of PT and rechallenge but without cross-reactivity, and one induced by calcium heparin with previous similar episodes with enoxaparin and nadroparin (5,6). Allergologic exploration is also needed to find safe alternatives in case of eczema localized at the injection site. Indeed, despite topical steroids and a switch to another heparin, eczema can persist or even spread due to cross-reactivities (7). As in our cases, the literature shows that cross-reactions between heparins are frequent in delayed-type hypersensitivity (93% of tested patients, median number of positive drugs per patient = 3) and do not depend on the molecular weight of the molecules (Table) (1,3, 6-8). Pentasaccharide fondaparinux is often proposed as the best alternative, but tests remain necessary because of possible cross-reactivity (1,3,8). Heparin sodium is another safe proven alternative, even when skin tests are

positive, but its intravenous route is less convenient (8,9). Despite or because of their wide use, heparins can be overlooked in drug allergy investigations, especially if the lesions do not start at the injection site. Extensive allergologic exploration is advised to provide a suitable alternative.

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LEGENDS OF THE FIGURE

Results of the delayed intradermal reactions on day 3:

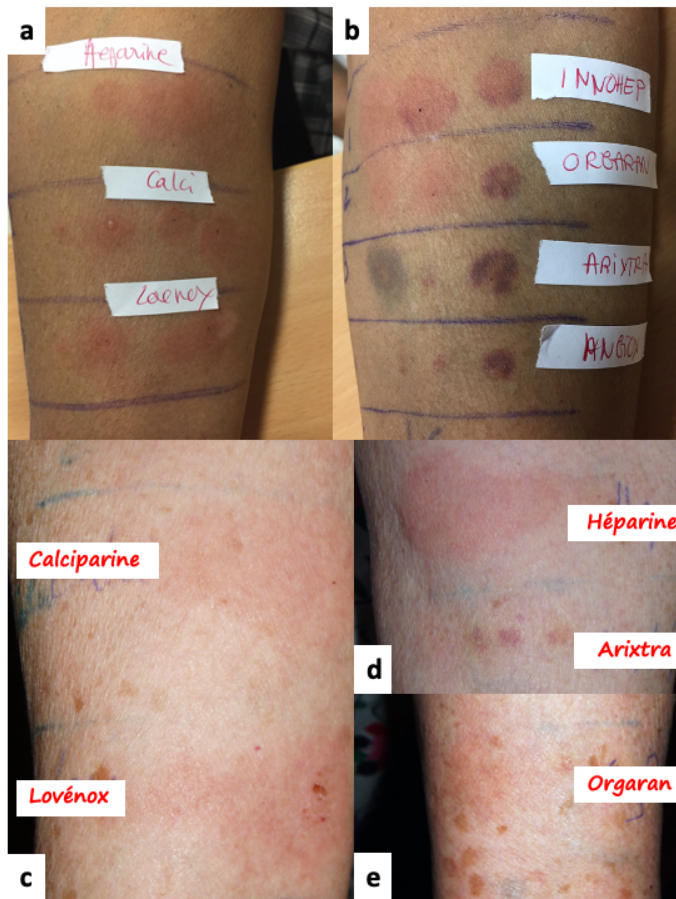
Patient no. 1: **a)** Positive tests for heparin sodium (Héparine®), heparin calcium (Calciparine®) and enoxaparin (Lovenox®); **b)** Positive test for tinzaparin (Innohep®) and danaparoid (Orgaran®) and negative tests for fondaparinux (Arixtra®) and bivalirudin (Angiox®).

Patient no. 2: **c)** Positive tests for heparin calcium (Calciparine®) and enoxaparin (Lovenox®); **d)** positive test for heparin sodium (Héparine®) and negative tests for fondaparinux (Arixtra®); **e)** positive test for danaparoid (Orgaran®)

Table: Cross-reactivity between heparins in delayed hypersensitivity: results of allergologic explorations in the two cases and the literature (1,3)

Substance Class	Anticoagulant	Case 1 induced by enoxaparin (D-IDT)	Case 2 induced by enoxaparin (D-IDT)	AGEP induced by dalteparin (D-SC) (3)	Systematic review : overall cross reactivity with other classes in % regardless of suspected heparin (tested by PT, IDT or D-SC) (1)	
Unfractionated heparins	Heparin calcium	++	++	ND	NE	67.5%
	Heparin sodium	++	++	ND	NE	
Low-molecular- weight-heparins (LMWH)	Enoxaparin	++	++	++	80.6%	73.2%
	Tinzaparin	++	ND	++	56.9%	
	Dalteparin	ND	ND	ND (denial)	69.9%	
	Other LMWH	ND	ND	++ or +++	65– 80.9%	
Heparinoids	Danaparoid	++	++	+++	65.7%	55.6%
	Pentosan polysulfate	ND	ND	-	36.4%	
Synthetic pentasaccharide	Fondaparinux	-	-	++	10.4%	
Hirudins	Bivalirudin	-	ND	ND	NE	

DHSR: delayed-type hypersensitivity skin reactions; D-IDT: delayed reading of intradermal test, D-SC: delayed reading of subcutaneous injection; PT: patch-test; ND: not tested ; NE: not evaluated for overall cross-reactivity



190x254mm (96 x 96 DPI)