

Dabigatran offers the simplest solution for thromboprophylaxis after orthopaedic surgery in patients allergic to low-molecular-weight heparins

Heparins, particularly low-molecular-weight heparins (LMWH), are drugs that are used worldwide and are the first choice for prevention of deep vein thrombosis in many clinical settings. Heparin allergy is rare; in most cases it presents as Gell and Coombs type IV local delayed reaction, with onset only hours or days after administration of the drug and consisting of itchy eczema-like lesions surrounding the administration sites. Nevertheless, the rash may spread to several areas of the body (generalized contact dermatitis). When heparin allergy is suspected, a comprehensive allergy work-up is recommended, both to establish the diagnosis of hypersensitivity to a particular heparin and identify other heparins without cross-reactivity to replace the culprit drug at the time or in the future. LMWH are known to show extensive cross-reactivity; thus, in many cases, classic heparinoids (danaparoid), indirect anti-Xa factors (fondaparinux) (Grims *et al*, 2007) or even unfractionated heparin (intravenous sodium heparin), have been recommended and administered without reactions (Seitz *et al*, 2008; Trautmann & Seitz, 2009). Nevertheless, there remain patients in whom heparin allergy extends to all kinds of heparins.

An 82-year-old woman, with a history of breast cancer, treated at the age of 62 years and currently disease-free, hypertension treated with barnidipin, valsartan, doxazosin and torasemide, stable renal failure grade 3 and generalized osteoarthritis, was scheduled for right-knee replacement. When questioned about drug allergies, she recalled that 10 years previously, 7 d after starting enoxaparin for a minor orthopaedic operation on her right foot, she suffered a

generalized maculopapular pruriginous rash with no angioedema or systemic symptoms that lasted 1 week, necessitating withdrawal of the drug and treatment with antihistamines and corticosteroids. Furthermore, 6 months previously, 5 d after starting enoxaparin for a left-knee replacement she suffered a similar episode.

An allergologic work-up was performed. Patch tests with all available heparins (bemiparin, dalteparin, enoxaparin, nadroxiparin, fondaparinux and sodium heparin) were performed with commercial heparins *as is* with readings at 48 h, 96 h and 7 d, being positive for enoxaparin (++) at 96 h and for enoxaparin and bemiparin (++) at day 7. Prick tests at full concentrations of the same heparins were negative; therefore, intradermoreactions were scheduled at weekly intervals, beginning with a 1:100 concentration until reaching a full-strength concentration (Bircher *et al*, 2006), showing strong delayed positive results (Table I), with itchy vesicles and/or blisters with all LMWH (Fig 1). Lymphoblastic transformation tests to enoxaparin and bemiparin were negative. As the only heparin to prove negative in the skin test was sodium heparin, which has also been claimed to be safe in patients with LMWH allergy (Trautmann & Seitz, 2009), we performed a provocation test with the intravenous administration of 1000 iu of sodium heparin followed one hour later by 4000 iu of the drug. No immediate reactions were detected; however, five days later, the patient presented a widespread pruriginous, eczematous rash on forearms, chest, abdomen and thighs, which required treatment with antihistamines and corticosteroids and scaled off after 1 week. A diagnosis of delayed-type

Table I. Results of skin tests (prick and intradermoreactions) to heparins.

Time	Week 1					Week 2				Week 3			
	Prick	ID 1:100				ID 1:10				ID 1:1			
Heparin		I	48 h	96 h	7 d	I	48 h	96 h	7 d	I	48 h	96 h	7 d
Bemiparin	–	–	+	+++	+++								
Dalteparin	–	–	–	++	+++								
Enoxaparin	–	–	+	+++	+++								
Nadroxiparin	–	–	?	++	++								
Fondaparinux	–	–	–	–	?	–	–	–	?	–	–	+	+
Natrium heparin 5%	–	–	–	–	–	–	–	–	–	–	–	–	–

IDR, intradermoreactions; I, immediate reading (20 min); ?, doubtful; +, indurate red papule >5 mm; ++, indurate red papule >5 mm plus vesicles; +++, blisters.



Fig 1. Intradermoreactions to heparins (fifth day). 1: saline (negative); 2: bemiparin (blister); 3: dalteparin (blister); 4: enoxaparin (blister); 5: nadroxiparin (blistering); 6: fondaparinux (starting microvesicles); 7: unfractionated heparin (negative).

allergy to all heparins was established and a decision was made to give anticoagulant prophylaxis for deep vein thrombosis with a direct thrombin inhibitor (dabigatran). The patient underwent uneventful right-knee replacement under dabigatran 110 mg twice daily, which was maintained for 6 weeks with no side effects.

Cross-reactivity among heparins is very common in patients with delayed hypersensitivity to heparins and involves all possible combinations, although it seems to be particularly coincidental between bemiparin and enoxaparin (Grims *et al*, 2007), as observed in the present patient. Nevertheless, tolerance to intravenous unfractionated sodium heparin has been demonstrated in patients with allergy to several LMWH; furthermore, it has been affirmed that sodium heparin can be safely administered without an allergologic study in these situations (Seitz *et al*, 2008; Trautmann & Seitz, 2009). However, the present case showed that this is not always so and that, although it may be time-consuming, an allergologic work-up is warranted in such situations prior to the administration of any kind of heparin in order to avoid severe generalized reactions.

In emergency cases, or in those with demonstrated allergy to all available heparins or in which an allergologic study would

not be available, dabigatran, a selective, reversible, direct thrombin inhibitor with similar anticoagulant efficacy and side effects to enoxaparin is the drug of choice and the simplest pragmatic solution for deep vein thrombosis prophylaxis in hip or knee replacement (Wolowacz *et al*, 2009), although fondaparinux may also be considered for cost-effectiveness, as long as the allergy work-up was negative. Furthermore, oral administration, early onset of action and facilitation of clot lysis render dabigatran an attractive drug for the prevention of deep vein thromboembolism in the early post-operative period of arthroplasty (Ammollo *et al*, 2010).

Disclosure of conflict of interest

Authors have nothing to disclose.

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