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Delayed hypersensitivity challenged by subcutaneous Bemiparin

Bemiparin delayed type hypersensitivity

To the Editor:

Low-molecular-weight heparins (LMWHs) are now routinely used in protocols for the treatment of suspected myocardial infarction, unstable angina, deep vein thrombosis and pulmonary embolus.

A 65-year-old woman with contact dermatitis to nickel developed infiltrated itchy and big eczematous plaques at the subcutaneous injection sites on the lower abdomen, one week after beginning treatment with Bemiparin due to an orthopaedic surgery. This drug was changed for Enoxaparin, tolerated during her admission, but days later she complained of the same lesions.

In order to identify an alternative heparin and once informed consent had been obtained, patch, intradermal, and subcutaneous tests were performed with a panel of unfractioned heparin (UFH), LMWHs and Fondaparinux.

Patch tests performed with Sodic Heparin, Bemiparin, Enoxaparin, Dalteparin, Nadroparin, Tinzaparin and Fondaparinux were negative, except for Bemiparin which was positive at 96 hours (eczematous plaque in application area) and less clear for Enoxaparin. Intradermal tests with Sodic Heparin, Enoxaparin, Dalteparin, Nadroparin, Tinzaparin and Fondaparinux were negative except for Enoxaparin which was positive at 24 hours.

Due to the necessity of anticoagulant treatment, subcutaneous challenge test was developed with Nadroparin, Dalteparin, Tinzaparin and Sodic Heparin, which were positive (itchy infiltrates and erythematous plaques hours later). However, subcutaneous challenge test with Fondaparinux was negative.

Heparins are complex mixtures of mucopolysaccharides produced from porcine or bovine intestines and lungs. Molecular weight differentiates UFHs (10-20 KDa) from LMWHs (4-6 KDa)[1].

Heparin eczema-like plaques result due to the binding of the heparin molecule to dermal protein, triggering a delayed-type hypersensitivity (DTH) reaction.[2]

The consulted bibliography shows the wide variability of heparin cross-reactivity, among LMWHs themselves and also between LMWHs and UFHs,[1,3–6] so all heparins should be avoided in such individuals.

According to what Ludwig published[7], a substance with a very low molecular weight is believed to reduce the frequency of DTH reactions to LMWH. Bemiparin (3.7 Kda) is supposed to be a suitable alternative when there is DTH reaction[5]. In our patient Bemiparin probably caused DTH reaction.

The study by Grims[5] did not show a correlation between molecular weight and the frequency of cross-reactivity, and reported the first cases of cross-reactivity of Bemiparin with other LMWHs. In this study Fondaparinux was well tolerated, as happened to our patient.

Grims[5] also found a particularly high cross-reactivity between Enoxaparin and Bemiparin. He explains this cross-reactivity because all patients had primarily been sensitized to Enoxaparin and cross-reactivity to Bemiparin was highest with Enoxaparin probably due to a similar chemical structure. We think our patient was sensitized first to Bemiparin and later, due to the cross-reactivity between them, she developed the eczematous plaques with Enoxaparin.

The use of a substance with an entirely different chemical structure such as recombinant hirudin (Lepidurin) or Fondaparinux (17 KDa) nearly excludes cross-reactivity with LMWHs,[5,6] but they must be probed because there are described cases in the literature of type IV reaction to Fondaparinux[2,8] and anaphylactic reactions to Lepirudin.[9]

We challenged with other LMWHs that had negative patch or intradermal tests to get an alternative and sure treatment and, with the exception of Fondaparinux, all proved positive. So patch and intradermal tests were partially useful to find an alternative drug, with subcutaneous challenge test being the best means of detecting the entire spectrum of sensitisation.[4,5]

We have found in the literature some reports about the intravenous heparin tolerance in patients with DTH reaction.[10,11,12] Gaigl et al.[12] published a prospective study in 2004 in which 28 patients with a proven delayed-type hypersensitivity to subcutaneous heparin were challenged with intravenous heparin, being well tolerated for all of them. So, in case of therapeutic necessity, the shift from subcutaneous to intravenous heparin would be justified[12]. A possible reason for intravenous tolerance may be the difference in antigen processing and presentation of selectively sensitized lymphocytes in the dermis.[11,12] Trautman and Seitz[13] in their report, consider that, although there are some prospective studies supporting the use of intravenous administration of heparin in patients with DTH reaction, substantial doubt still

exists as to whether the use of intravenous administration of heparin is really safe for all these patients.

In conclusion, we report a rare case of delayed-type hypersensitivity reaction to Bemiparin. We have demonstrated cross-reactivity between Bemiparin and Enoxaparin by patch test. Due to the possibility of cross-reactivity between heparins, before recommending an alternative heparin, an allergic study with patch, intradermal and subcutaneous challenge tests must be performed. We think that subcutaneous challenge test is necessary to confirm the tolerance of the alternative drug.

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Case report: specific immunotherapy with dust mite allergens in a child with severe atopic dermatitis

To the Editor,

Atopic dermatitis is a chronic inflammatory skin condition that appears to involve a genetic defect in the proteins supporting the epidermal barrier. The goals of treatment are to reduce symptoms, prevent exacerbations, and to minimise therapeutic risks. This includes general measures, antihistamines, topical or systemic corticosteroids, topical calcineurin inhibitors and management of infections. In severe cases, systemic immunosuppressive agents like cyclosporine may be useful, but are not exempt of important adverse effects. Although there has been some controversy regarding the role of allergy in atopic dermatitis, the bulk of the data indicate that allergy plays a role in selected patients. Dust mites are consistently the most common positive aeroallergen, and also appear to be the most clinically relevant. However, specific immunotherapy is not generally taken into account as a therapeutic tool for atopic dermatitis.

A 10-year-old male patient with a history of persistent rhinitis and mild asthma was referred to our unit with severe atopic dermatitis, presenting intense pruritus, lichenified plaques, scaly and excoriated papules with huge affectation of quality of life (bad sleep, impossibility to practice sports). SCORAD at first visit was 106.6. Laboratory tests showed IgE levels of 12457 UI/ml with dust mite specific levels >100 kU/ml (*Dermatophagoides pteronyssinus*, *Blomia tropicalis*). He was not sensitised to other environmental or food allergens. Unfortunately, the severity of eczema did not allow the performing of skin prick test or atopy patch test. Treatment with antihistamines, topical and systemic corticosteroids showed only partial response.

We started specific subcutaneous immunotherapy (ALK-ABELLO, *Dermatophagoides pteronyssinus* 60%, *Blomia tropicalis* 40%) in addition to sustained treatment with antihistamines (hydroxyzine 50 mg/D and levocetirizine