Case Report

HYPERSENSITIVITY REACTIONS TO LOW MOLECULAR WEIGHT HEPARIN IN A PREGNANT WOMAN

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Itchy, erythematous or eczematous plaques occurring at the site of low molecular weight heparin (LMWH) injection are generally attributed to delayed-type hypersensitivity reactions (DHR) and are reported in the 10% of patients[1]. An even higher risk of reactions to these compounds is described during pregnancy, with an estimated incidence of 19.8%[1]. Nadroparin is the LMWH with the highest incidence of DHR, as compared, for instance, to dalteparin or enoxaparin[1]. Skin tests, epicutaneous tests and subcutaneous challenge with these compounds have shown an adequate sensitivity and specificity for diagnostic purposes[2], but we still lack standardised guidelines for selecting safe alternative LMWHs. Cross-reactivity among different LMWHs has been reported in literature in 33-73% of patients[3,4]. Potential alternative antithrombotic compounds are the heparinoids danaparoid and pentosan polysulfate[5,6]. Fondaparinux (a chemically synthesised sulfatised pentasaccharide) is actually considered the alternative of choice in cases of allergic reactions to LMWHs, but the experience with this drug during pregnancy is limited to a small cohort of patients, with safety and economical issues yet to be completely addressed[7]. Skin tests with LMWHs have proven to have quite a high negative predictive value, and might be reliably suggested for the identification of safe alternative heparins[8].

We report the case of a 38 year old pregnant woman who was referred because of recurrent skin lesions localised at the injection site of enoxaparin and nadroparin. The patient was on treatment with LMWH due to a previous intrauterine foetal death (IFD) and to a heterozygous protrombin mutation. A thorough screening for inherited thrombophilic disorders (presence of Factor V Leiden, methylenetetrahydrofolate reductase mutations, antithrombin III, protein C and S deficiency) and acquired thrombophilia (lupus like anticoagulant, IgG and IgM anticardiolipin and antibeta2-glycoprotein-I-antibodies was negative. Past medical history was unrevealing and no other allergies were referred. Written informed consent was obtained. Skin prick tests with undiluted drugs, intradermal tests at dilutions of 1:100 and 1:10 and epicutaneous tests with undiluted enoxaparin (2,000 UI/0,2 ml), nadroparin (2,850 IU/0,3 ml), dalteparin (2,500 IU/0,2 ml), parnaparin (3,200 IU/0,3 ml) and fondaparinux (2,5 mg/0,5 ml) were performed as previously described[2,8]. Results of immediate and delayed reading are shown in Table I.

Based on the skin test results, subcutaneous challenge with dalteparin at the dosage of 2,500 IU/0,2 ml was performed[9]. A week later, given the absence of immediate and delayed hypersensitivity reactions, dalteparin was increased to the therapeutic dosage of 5,000 IU without experiencing any adverse event. At the 38th gestational week she underwent a caesarean delivery (because of a previous caesarean section) of an healthy baby of 3240 g. She continued with LMWH prophylaxis for 6 weeks after delivery. Overall the patient has been treated 7 months with daily subcutaneous dalteparin and no hypersensitivity reactions had occurred.

This case suggests that cross-reactivity does not necessarily concern all molecules and skin tests, with all available LMWHs, reliably identify sensitisation to these molecules and might be considered for the selection of safe alternative LMWH, before switching to fondaparinux or to other non-heparin anticoagulants. In particular, we observed a good tolerance to dalteparin in a pregnant woman already sensitised to enoxaparin, nadroparin and parnaparin. These results are of relevance because the diagnostic approach has been obtained during pregnancy, a clinical setting where therapeutic or prophylactic LMWHs are increasingly prescribed by Gynaecologists, but standardised guidelines for the management of hypersensitivity reactions to these compounds are lacking. Whether dalteparin has a better safety profile in pregnant women as compared to other LMWHs definitely needs to be assessed in a larger study.

TABLE I: RESULTS OF THE SPT AND IDT PERFORMED WITH LMWH

TEST LMWH	SPT	IDT 1:100	IDT 1:10	PATCH 48-96H	48H LECTURE IDT	96H LECTURE IDT
Enoxaparin	-	-	-	-	4mm	5mm
Nadroparin	-	-	7mm	-	5mm	5mm
Dalteparin	-	-	-	-	-	-
Parnaparin	-	-	-	-	-	4mm
Fondaparinux	-	-	-	-	-	-

- Positive control with histamine: 5 mm; positive test if >= 3 mm

DECLARATION OF CONFLICT OF INTEREST

The authors do not have a conflict of interest.

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