

Correspondence

Recall urticaria induced by skin tests with heparin

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SIR, We describe a patient with recall urticaria (RU) at previous dalteparin injection sites elicited 1 year later by intracutaneous skin tests at the forearms with dalteparin and certoparin. This points to an unknown mechanism of long-lasting 'tissue type I memory'.

A 42-year-old woman with a history of vein thrombosis and heterozygous activated protein C resistance was treated with dalteparin during her second pregnancy. One year later she underwent radioactive iodine therapy and again was treated with dalteparin. One hour after the first subcutaneous injection at the right lower quadrant, she developed weals at the injection site. In addition, she developed weals on her left lower quadrant where she had been treated with dalteparin previously.

Twelve months later, standard prick (as is) and intracutaneous tests (1 : 10) were performed on the forearms with heparins, low molecular weight heparins (LMWH) (such as enoxaparin, dalteparin, nadroparin, tinzaparin and certoparin), heparinoids and hirudins. While there was no reaction at the test sites, 20 min later the patient developed weals at both lower quadrants of her abdomen (Fig. 1). Histological examination of punch biopsies from these sites demonstrated oedema within the papillary dermis and a mostly perivascular infiltrate of neutrophils and eosinophils (Fig. 2a). Immunohistochemistry revealed the absence of B and T cells in the specimen using the markers CD3, CD4, CD20, CD79a and MUM1. In a second intracutaneous test with dalteparin alone (1 : 10), a 3-mm immediate reaction to dalteparin (+) was elicited at the injection site. Based on history and test results, the diagnosis of RU to dalteparin was established.



Fig 1. Weals on the lower left and right quadrants of the abdomen 20 min after skin tests with dalteparin at the forearm.

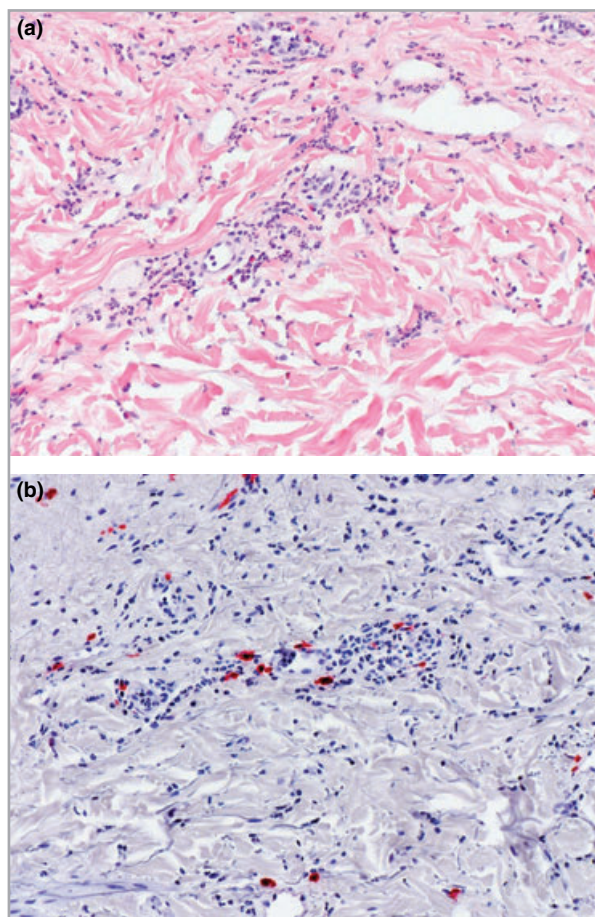


Fig 2. Histological examination of punch biopsies from the abdominal skin. (a) Oedema within the papillary dermis and a mostly perivascular infiltrate of neutrophils and eosinophilic granulocytes. No B or T cells were detectable (haematoxylin and eosin). (b) No apparent increase in mast cell numbers (tryptase stain).

In order to analyse whether heparin allergy in our patient occurred also with other LMWH, intracutaneous tests with enoxaparin, tinzaparin, certoparin and heparin (excluding dalteparin) were performed. Only injection of certoparin elicited RU at the same location of her abdomen again without eliciting a test reaction at the forearm. Subcutaneous provocation tests with lepirudin, danaparoid, fondaparinux and nadroparin were well tolerated.

Allergies to heparins are frequent but present mainly as delayed-type hypersensitivity reactions at the injection sites and less commonly as immediate-type hypersensitivity reactions.^{1,2} RU was described for the first time by Kelso *et al.* in patients

undergoing subcutaneous immunotherapy.³ Another case was described by Karaayvaz and Ozanguc.⁴ RU can be induced also under other circumstances, including aerosol exposure,⁵ heparin injection,⁶ cancer immunotherapy with HER-2/neu peptide-based vaccines,⁷ and intravenous injection of levofloxacin.⁸ However, isolated RU following very limited antigen exposure during skin tests has never been described.

In our patient, almost 1 year after RU was induced by subcutaneous injection with dalteparin, intracutaneous tests with either dalteparin or certoparin elicited RU at former injection sites—even in the absence of a reaction at the test site. The 3-mm weal detected in the second intracutaneous skin test with dalteparin (1 : 10) may have been a false-positive irritation reaction. The RU response, however, suggests cross-reactivity between dalteparin and certoparin. Dalteparin and certoparin both belong to the group of LMWH, generated by depolymerization via deaminative cleavage.⁹ However, cross-reactivity between certain LMWH is difficult to predict from structure and investigations were limited to delayed-type hypersensitivity responses.¹⁰

Even though RU is well characterized clinically, its underlying mechanisms remain elusive. However, as RU could still be induced almost 1 year after the last heparin injection, one has to postulate long-lasting memory for this type of hypersensitivity. As mast cells are crucial for immediate hypersensitivity reactions, they are the most obvious candidate for mediating this type of localized 'tissue memory'. At sites of previous mast cell activation there may be an increase in mast cell number that persists over time. However, histological examination of punch biopsies from RU sites in our patient did not reveal an increase in mast cell numbers (tryptase staining) compared with healthy controls¹¹ although subtle differences in cell numbers may be overlooked (Fig. 2b). Another possibility is that mast cells at RU sites may be more sensitive to reactivation due to hitherto unknown mechanisms, and analysis of the activation marker CD63 in mast cells may help to define RU better in the future. Alternatively, effector cells downstream of mast cell activation, such as endothelial cells, may be involved.

In patients with RU, skin and provocation tests should be performed routinely to detect the responsible allergens and to

characterize possible cross-reactions to other related allergens as in our patient.

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Conflicts of interest: none declared.