

Arthus reaction to lepirudin, a new recombinant hirudin, and delayed-type hypersensitivity to several heparins and heparinoids, with tolerance to its intravenous administration

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The pathogenesis of allergic reactions to heparin is poorly understood. Clinically, this phenomenon is relevant because of its increasing incidence and the resulting therapeutic challenges due to various cross-reactions between unfractionated and low-molecular weight heparins as well as between heparins and heparinoids. A 44-year-old female patient had developed a delayed-type hypersensitivity to certoparin-sodium. Diagnostic allergy testing revealed various cross-reactions between different heparins as well as an intolerance to heparinoids. After subcutaneous challenge with the recombinant hirudin lepirudin (Refludan®) the patient developed a local Arthus reaction at the injection site. In general, recombinant hirudins do not cross-react with high- or low-molecular weight heparins and heparinoids because of a different molecular structure and are therefore an alternative in case of adverse reactions to heparins and heparinoids. Whereas a local Arthus reaction has already been described twice for low-molecular weight heparins, this is to the best of our knowledge the first observation of a superficial leukocytoclastic vasculitis due to s.c. applied lepirudin. Intravenous administration of heparins and heparinoids in case of hypersensitivity to these drugs following topical application risks a generalized eczematous reaction in patients with delayed-type allergy to both groups of substances. In our patient with delayed-type hypersensitivity to heparins and heparinoids and superficial vasculitis due to lepirudin, the intravenous challenge with heparin and a heparinoid was justified as an ultima ratio measure and proved to be the useful therapeutical alternative.

Key words: Arthus reaction; delayed-type allergy; heparin; recombinant hirudin. © Munksgaard, 2002.

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Heparins are widely used as anticoagulants. Hypersensitivity reactions to heparin comprise a spectrum of heparin-induced immune thrombocytopenia, allergic vasculitis, hypereosinophilia, immediate hypersensitivity as well as delayed-type skin reactions, such as infiltrated eczematous plaques at injection sites and generalized eczematous reaction (1–5). The pathogenesis of allergic reactions to heparin is poorly understood (6). Clinically, this phenomenon is relevant because of its increasing incidence and the resulting therapeutic challenges due to various cross-reactions between unfractionated and low-molecular weight heparins as well as between heparins and heparinoids (7).

Case Report

A 44-year-old female patient received certoparin-sodium (monoembolex®/Novartis Pharma) once daily subcutaneously (s.c.) for prevention of thromboembolic disease after surgery. After 3 weeks of treatment she developed erythematous, pruritic and infiltrated plaques at the s.c. certoparin injection sites on the thighs. Thrombocytopenia could not be detected during follow-up. Patch testing with the standard series of the German Contact Dermatitis Group and the preservatives used in different brands of heparins (chlorocresol, benzalkonium chloride, thimerosal (Hermal, Trolab/

Table 1. Synopsis of the results from skin, in vitro and provocation testing

Drug	Patch test late phase reaction	Intradermal test read at	Subcutaneous provocation test	Lymphocyte transformation test	Intravenous provocation test
	6 h	20 min, 6 h, 1D, 2D, 3D, 4D			
Certoparin-sodium	Positive	Positive at D3, D4	Not done	Negative	Not done
Reviparin-sodium	Positive	Negative	Not done	Negative	Not done
Dalteparin-sodium	Positive	Negative	Not done	Negative	Not done
Enoxaparin-sodium	Positive	Negative	Not done	Negative	Not done
Nadroparin-calcium	Positive	Negative	Not done	Negative	Not done
Heparin-sodium	Positive	Negative	Not done	Negative	Negative
Danaparoid	Positive	Negative	Not done	Negative	Not done
Pentosan-polysulphate	Positive	Positive at D3, D4	Not done	Negative	Negative
Lepirudin 15 min:	Negative	Negative	Positive at 15 min: superficial leukocytoelastic vasculitis	Negative	Not done

Reinbek, Germany) was negative. Further diagnostic allergy tests were performed with the following heparins: reviparin-sodium (Clivarin®/Knoll, Ludwigshafen, Deutschland), enoxaparin-sodium (Clexane®, Aventis Pharma, Bad Soden, Germany), dalteparin-sodium (Fragmin®, Pharmacia, Erlangen, Germany), nadroparin-calcium (Fraxiparin®, Sanofi-Synthelabo, Berlin, Germany) and heparin-sodium (Heparin-Natrium Braun®, Braun, Melsungen, Germany), the semisynthetic heparinoids danaparoid (Orgaran®, Thiemann, Waltrop, Germany) and pentosanpolysulphate (Fibrezym®, bene-Arzneimittel, Munich, Germany) as well as lepirudin, a new recombinant hirudin, syn. leucine-threonine-desulfohirudin (Refludan®, Aventis Pharma). Intradermal tests with all substances were performed on the flexural side of the forearm with 0.05 mL. Only certoparin-sodium and pentosanpolysulphate were positive after 3Ds (Table 1). No immediate-type hypersensitivity occurred. Patch tests revealed positive results for unfractionated and low-molecular weight heparins and the heparinoids pentosanpolysulphate and danaparoid sodium, whereas lepirudin did not provoke any positive reaction. Lymphocyte transformation assay was carried out with non-heparinized but EDTA substituted blood according to standard procedures with different dilutions of heparins, heparinoids and lepirudin. Pokeweed mitogen served as positive control. The patients' lymphocytes reacted comparably to those of healthy control individuals. To find a safe anticoagulant for our patient, the s.c. provocation test was performed with lepirudin, which had been negative for all tests. Fifteen minutes after s.c. application of 0.1 mL lepirudin (= 0.2 mg) a progressing erythema and oedema developed at the site of injection. A biopsy was taken 2 h after s.c.

provocation. Histopathology revealed focal fibrin deposition and extensive extravasation of erythrocytes and oedema of vessel walls. The latter showed infiltration by a neutrophilic infiltrate and leukocytoclasia, also present in the surroundings of the vessels. These findings were representative of a superficial leukocytoclastic vasculitis. Skin testing with the additive of lepirudin, i.e. mannitol, only induced mild transient erythema. We hospitalized the patient for an intravenous challenge with heparin-sodium 15,000 IE a day and pentosanpolysulphate 100 mg a day. The substances were given for 3 days each and were well tolerated without additional application of glucocorticosteroids or antihistamines.

Discussion

Delayed-type hypersensitivity to heparins is probably more common than might be expected from the literature. It seems to be related to the heparin molecule itself. Different patterns of cross-reactions between different heparins, and heparinoids and heparins as well, indicate the existence of more than one antigenic epitope (6–8). However, the heparin epitopes responsible for sensitization have not yet been fully characterized. In the case of delayed-type hypersensitivity to heparins and heparinoids following topical application, intravenous administration of these drugs risks a generalized eczematous reaction. The investigation of peripheral blood lymphocytes in a lymphocyte transformation assay is not generally helpful to distinguish between substances that can safely be used and those which should be avoided because the *in vitro* test results may be discordant with skin test reactions and clinical symptoms (1). This is a well known phenomenon and was suggested to be de-

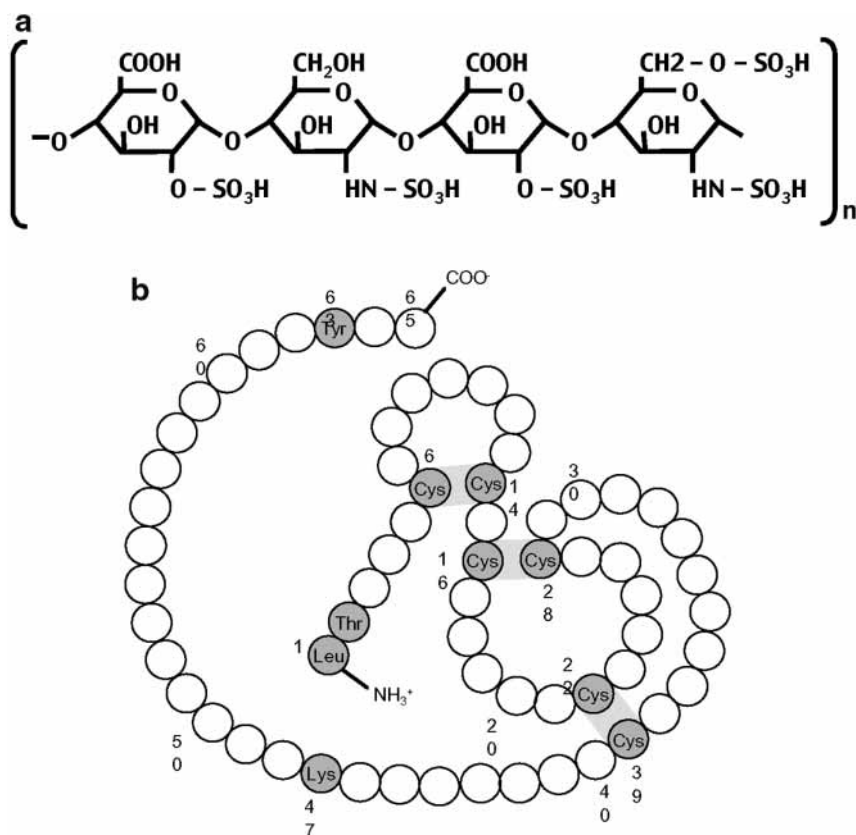


Fig. 1. a. Structure of heparin (22). b. Structure of lepirudin.

pendent on, for example, impaired antigen-presentation, low number of antigen-reactive cells in blood samples as well as antigen-specific cells homing to the site of local reaction. Recombinant hirudin (r-hirudin) is a polypeptide and therefore has a chemical structure different to heparin (Figs 1a, 1b). It has, however, similar pharmacological characteristics. In general, r-hirudins do not cross-react with high- or low-molecular weight heparins and heparinoids and are therefore an alternative in case of adverse reactions to heparins and heparinoids (9–11). Two r-hirudin variants have been approved for clinical use recently: desirudin (Revasc®) and lepirudin (Refludan®). Nevertheless, immediate- and delayed-type hypersensitivity has also been described for r-hirudins (11, 12). Local skin reactions at injection sites have been observed for lepirudin in about 0.5% of the patients. According to their recently published data, r-hirudins are safe and effective when applied over an intravenous (i.v.) or s.c. route (13, 14). Close et al. investigated 200 volunteers, exposing them to r-hirudin (CGP 39393 = desirudin) (15). Three volunteers developed allergic reactions, three others a positive skin test after a second course of desirudin; and one developed a positive skin test after the third course of s.c. r-hirudin (15). Four patients were re-exposed to 2×25 mg of s.c. r-hirudin for

8–27 d after they had previously undergone r-hirudin i.v. treatment, one of them four times. None of the patients developed IgE antibodies and none had any clinical side-effects during re-exposure to r-hirudin (16). Huhle et al. investigated 14 patients; none showed allergic skin reactions after s.c. application of 25 mg of lepirudin twice daily (17). Whereas a local Arthus reaction has already been described twice for low-molecular weight heparins (18, 19), this is to the best of our knowledge the first report of a superficial leukocytoclastic vasculitis due to s.c. applied lepirudin. A toxic vasculitis can be excluded for our patient because of the fact that a dose 250 times higher than that used by us for s.c. provocation has been well tolerated by other individuals (17). It is possible, however, that our patient was sensitized during the skin tests that were performed before s.c. provocation. Compared to the number of cases that tolerated s.c. application of r-hirudin without complications, a local Arthus reaction as uniquely observed by us may prove to be an extremely rare pattern of an allergic reaction. Although there are few publications on i.v. tolerance of heparins and heparinoids in patients with delayed-type local reactions upon s.c. application, the question of i.v. compatibility of heparin in such patients remains debatable (20). Possible reasons for i.v. tolerance

might be the difference in antigen processing and presentation and preferential homing of selectively sensitized lymphocytes in the dermis (21). In our patient with delayed-type hypersensitivity to heparins and heparinoids and superficial vasculitis due to lepirudin, the i.v. provocation with heparin and a heparinoid was justified as an ultima ratio measure and proved to be the useful therapeutical alternative.

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