Contact Dermatitis, 1998, 39, 43–44
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CONTACT DERMATITIS
ISSN 0105-1873

Short Communication

Intravenous challenge with heparins in patients with delayed-type skin reactions after subcutaneous administration of the drug

Axel Trautmann, Eva-B. Bröcker and C. Eberhard Klein

Department of Dermatology, University of Würzburg, Josef Schneider Strasse 2, D-97080 Würzburg, Germany

Key words: heparin; heparinoid; delayed-type skin reaction; medicaments; intravenous challenge. © Munksgaard, 1998.

Delayed-phase reactions after subcutaneous (s.c.) injection of high- or low-molecular-weight heparins are not rare. They present as indurated s.c. swelling with overlying erythema/eczema, causing burning or itching (1). Occasionally, an exanthematous reaction supervenes. If further anticoagulation is necessary, cross-reactivity with other anticoagulants (heparinoids), such as dermatan sulfate (Orgaran™) or sodium pentosan polysulfate (Fibrezym™), is common (2). Even after the introduction of the new anticoagulant lepirudin (Refludan™), heparins remain the drugs of choice, particularly for intravenous (i.v.) anticoagulation. The most important differential diagnosis from delayed-type reactions after s.c. heparin is the initial stage of heparin-induced skin necrosis, which may be a sign of heparin-induced thrombocytopenia (HIT). Cutaneous necrosis is characterized by a well-defined eschar surrounded by an inflammatory halo, and can occur either at the injection site or at distant sites.

Patients and Methods

Based on case reports in the literature (3) and our own previous case (2), we challenged 8 patients with proven delayed-type hypersensitivity reactions after s.c. administration of heparins by i.v. provocation. All 8 patients tolerated the challenge with Liquemin N 25000™ uneventfully and without any antiallergic medication. Prior to the i.v. challenge, all patients received patch tests after stratum corneum stripping and intracutaneous tests with readings at 20 min, 6, 24, 48, 72 and 96 h. Drugs tested were the suspected heparin and the high-molecular-weight heparins Liquemin N 25000™ and Thrombophob 25000™, as well as the low-molecular-weight heparins Fragmin P™ and Fraxiparin 0.3™, and the substitute drugs dermatan sulfate (Orgaran™) and sodium pentosan polysulfate (Fibrezym™). Moreover, to exclude hypersensitivity to the preservative chlorocresol, it was included in the patch test series at 1% pet.

7/8 patients reacted positively to low- and high-molecular-weight heparin, 5/8 to Orgaran™ and Fibrezym™, on epicutaneous or intracutaneous tests, showing eczematous lesions at the test site. Characteristically, the reactions occurred after 72–96 h. 1/8 patients reacted positively to heparins, 3/8 to Orgaran™ and Fibrezym™, only on s.c. provocation. No patients reacted to chlorocresol. None of the patients showed thrombocytopenia or other clinical signs of HIT.

Discussion

Our results indicate that i.v. administration of heparins is possible without side-effects in a considerable number, if not in all, patients who react with localized eczema after s.c. injection of the drug. This is particularly important if the patients require short-term i.v. anticoagulation during cardiovascular surgery. In other cases, it may be an option simply to shift from s.c. to i.v. administration. Our observations also raise questions with regard to the immunological mechanism underlying the localized eczematous reaction.

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