Heparins injected subcutaneously or intravenously enable easily controllable anticoagulation for inpatients and outpatients. Heparins are sulfated, anionic polysaccharides that vary in their structure and composition. According to their mean molecular mass, a distinction is made between unfractionated, high molecular weight heparins (molecular weight 10-20 kDa) and fractionated, low molecular weight heparins (molecular weight 4-6 kDa). In case of a delayed-type hypersensitivity reaction against subcutaneously injected heparins, itching or burning, erythematous and sometimes eczematous plaques develop at the injection sites one or two weeks after the injection (1, 2) (figure a). In rare cases, generalized eczema or exanthema with a discernible punctum maximum may be observed at the injection sites (3, 4). These erythematous and eczematous plaques are symptomatic of a T-lymphocyte mediated delayed-type hypersensitivity reaction, whose antigenic determinants in the heparin molecule are thus far not precisely known. This delayed hypersensitivity reaction can be diagnosed through allergy skin tests (intracutaneously and epicutaneously), or, in cases where the skin tests are false negatives, through a subcutaneous provocation test.

The most important differential diagnosis to delayed-type hypersensitivity reaction against subcutaneously injected heparins is rarer, heparin-induced skin necrosis, a clinical manifestation of heparin-induced thrombocytopenia (HIT) (5). After a latent period of one or two weeks, initial erythema appears at the injection sites – and in rare cases, more widely disseminated – which is followed by clearly circumscribed, painful necroses (figure b). Through immunoglobulin G antibodies against the complex of heparin and platelet factor 4, thrombocyte activation occurs, with the associated risk of venous and arterial thromboembolism (6). In case of heparin-induced skin necrosis, further administration of unfractionated or low molecular weight heparins is contraindicated, as is allergy testing with heparins. Therapeutic alternatives include lepirudin, danaparoid, or argatroban. Further differential diagnoses to erythematous or eczematous plaques are hematoma, infections, or contact allergy to skin disinfectants.

**SUMMARY**

Introduction: The occurrence of an allergic reaction to subcutaneous heparin raises the clinically important question as to whether intravenous heparin would be tolerated, but few data are available to date. Itchy erythematous or eczematous plaques at the injection site are side effects of heparin administration, and denote a delayed-type hypersensitivity reaction. Methods: Case series of 38 patients with heparin allergy. All patients received standardized stepwise allergy testing including skin tests and provocation tests. Results: The diagnosis of delayed-type hypersensitivity to heparin was made in 27 patients on the basis of skin tests alone and in a further 11 after subcutaneous provocation tests. All 38 patients tolerated an intravenous provocation test. Discussion: Intravenous heparin therapy is in general well tolerated even where there is a delayed hypersensitivity type allergy against heparin injection. The risk of generalized reaction following intravenous treatment appears to be minimal. In an emergency situation, a switch from subcutaneous to intravenous heparin is both acceptable and advisable even prior to formal immunological investigation and diagnosis. The reason why patients allergic to subcutaneous heparin tolerate intravenous administration is uncertain. Dtsch Arztebl 2006; 103(43): A 2877–81.

Key words: heparin, heparin induced skin necrosis, heparinoid, provocation test, delayed hypersensitivity reaction

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The delayed-type hypersensitivity reaction against subcutaneously injected heparins implies a diagnosis of heparin allergy for doctor and patient, and at least a proportion of patients is given an allergy passport. These patients do not receive any further treatment with heparins; because of the risk of a hematogenic generalized reaction, no intravenous heparin is administered either. We describe the diagnosis of a delayed-type hypersensitivity reaction against subcutaneous heparins on the one hand, and on the other hand, we describe our most important result: such patients tolerate intravenous heparin none the less (7-10).

Method
From 1998 to 2005, patients in whom delayed-type hypersensitivity reaction against subcutaneous heparins was suspected, received standardized, stepwise allergy testing at the authors' hospital, using skin tests (intracutaneous test and epicutaneous test) and subcutaneous provocation tests (diagram 1). In all patients with a confirmed delayed-type hypersensitivity reaction against heparins, an intravenous provocation test with heparin was conducted, after patients had been thoroughly informed about risks and had given written consent.

Skin tests
The intracutaneous tests on the volar forearm (0.02 to 0.05 ml/injection) were conducted by using heparin preparations diluted in 0.9% NaCl (1 part heparin : 10 parts NaCl). For the epicutaneous tests on the back, which were modified by tape stripping of the horny layer of the epidermis, undiluted heparin preparations were used. The test areas were read after two, three, and four days, in accordance with international recommendations (11). The individual test substances were unfractionated heparin; the low molecular weight heparins nadroparin, dalteparin, and enoxaparin; the heparinoids danaparoid and pentosan polysulfate and, since 2002, fondaparinux.

Provocation test
The subcutaneous provocation tests were performed by abdominal injections with heparin preparations that were skin test-negative in therapeutic dosages. For the intravenous provocation tests, patients received an unfractionated heparin preparation. On the first day, heparin-sodium was given as a bolus injection, at a dosage of 2 500 international units (IU). On the second day, 5 000 IU were given as a bolus injection, followed by 7 500 IU over six
hours. The observation period was three days, and all patients were instructed to present again at the hospital, even if they developed symptoms at a later stage.

**Results**

**History**

The 36 women and 2 men were 36 to 94 years of age (median 63 years). 24 patients were treated with low molecular weight heparins, 11 with unfractionated heparins. In 3 patients, the type of heparin used could not be established, but all three had received subcutaneous injections by way of preventing thrombosis. Erythematous or eczematous plaques had developed within a week (n = 31) or two weeks (n = 6) after the subcutaneous injections had started. In one of the patients, this time interval was not known. The body mass index (BMI) was normal in one patient only (18.5 to 24.9), 13 were overweight (25 to 29.9), and 24 were obese (≥ 30.0).

**Allergy testing**

The results of the allergy tests are summarized in diagrams 1 and 2. The tests concentrated on the tolerability of intravenously administered heparin; not all theoretically possible skin and provocation tests were conducted in all patients. Stepwise testing was done primarily to confirm a diagnosis of delayed hypersensitivity to heparins and thus ended at step 2 or step 3, before the provocation test was done in step 4 (diagram 1). A diagnosis of delayed-type hypersensitivity to subcutaneous heparins was made in 27 patients after the skin test yielded positive results. In the remaining 11 patients, delayed-type hypersensitivity was diagnosed only after positive subcutaneous provocation tests. All 38 patients tolerated the subsequent intravenous provocation test with heparin without developing side effects. In 37 patients, the interval between the skin test and intravenous provocation was more than 6 weeks; in one patient, it was only 4 weeks. In this patient, the authors observed flare-up reactions at the former skin test sites on the second day of intravenous provocation.

**Discussion**

The authors showed that patients with delayed-type hypersensitivity reaction to subcutaneously injected heparin tolerate intravenous administration of heparin; something that is confirmed by the literature (7–10). Such patients should therefore not only receive the information that they have a heparin allergy or an allergy passport, which indicates that they have “heparin allergy”. A provocation test shows that intravenously administered heparin is tolerated, and an entry to that effect in the allergy passport enables straightforward intravenous anticoagulation in the future. In urgent cases (e.g., in surgical procedures in which extra-corporeal circulation is used), anticoagulation with intravenous heparin is justified in case of known heparin allergy with erythematous or eczematous plaques, even without prior allergy testing.

Female sex and obesity are risk factors for developing a delayed-type hypersensitivity to subcutaneous heparins; a possible influence of hormonal or metabolic factors cannot be ruled out (12, 13). The question why such patients develop allergic reactions to
subcutaneously injected heparin but tolerate intravenous administration, does not have a
definitive answer. The crucial factor is probably unspecific binding of the heparins to
proteins or other macromolecules after subcutaneous injection on the one hand, and
differences in the presentation or the processing of heparin antigens according to the mode
of administration (intravenous or subcutaneous) on the other hand. The difference between
sensitization of the immune system/immunization to heparins (detectable through skin tests,
T-lymphocytes, antibodies) and an allergy (a disorder with specific symptoms) becomes
particularly obvious in this scenario of heparin allergy and intravenous administration of
heparin (diagram 3).

Immune responses are not "all or nothing" reactions. Even an immune response to
heparins does not always take the same shape but manifests in a spectrum, with substantial
qualitative differences. Patients with low-grade immunity to heparins have only discrete erythematous plaques at the injection sites, their skin tests are often negative, and a diagnosis can be made only after a positive subcutaneous provocation. High-grade immunity shows up clinically as a distinctive local reaction with infiltrated eczematous plaques, on which densely clustered papulovesicles may undergo confluence into larger blisters. The positive reactions to all heparins in the skin tests are then at least twofold positive as a rule – often even threefold. Patients may show so-called flare-up reactions on former eczematous plaques or positive skin test sites during intravenous provocation, especially if less than 4 weeks have passed between plaque healing and provocation. One possible explanation is activation of specific T-lymphocytes that have remained in the formerly positive skin areas after intravenous administration of heparin, similar to what is being discussed for the fixed drug exanthema. A single case report of a generalized eczema after heparin administration may, however, be due to too short a time interval between positive skin tests/positive subcutaneous provocation tests and intravenous administration of heparin (14).

Our data reiterate the cross-reactivity between all preparations of unfractionated and low molecular weight heparins in cases of delayed hypersensitivity against subcutaneous heparins. Heparin-like, potential drug alternatives include the heparinoids danaparoid and pentosan polysulfate. Heparinoids are semisynthetically produced, anionic polysaccharides (15). Heparinoids, especially pentosan polysulfate, actually often yield negative results in skin tests. However, many of such skin tests are false negatives, because the delayed-type hypersensitivity and thus cross-reactivity manifests itself during subcutaneous provocation tests. The tolerability of a single subcutaneous provocation test must not be overestimated. Several of our patients developed erythematous and eczematous plaques after longer-term therapy and an increasing number of heparinoid injections, in spite of negative subcutaneous provocation tests and intravenous administration of heparinoids. Finally, cross-allergies between heparins and heparinoids are common, as may be expected in the light of their chemical structures (16).

Since 2002, fondaparinux has been licensed in Germany, a synthetic heparin analogue, which consists of only one pentasaccharide sequence (molecular weight 1.7 kDa) and which inhibits specifically the factor Xa. Fondaparinux has been studied as an alternative preparation to subcutaneous heparins (17, 18). We observed in 6 of 16 patients (37.5%) with a delayed-type hypersensitivity reaction to heparin injections positive skin tests to fondaparinux and in the meantime, several publications have shown that a maximum of 50% of patients with a delayed-type hypersensitivity reaction to subcutaneous heparin tolerate fondaparinux without developing symptoms (19–22). Consequently, hirudins – which, as proteins, have a completely different chemical structure – are the only safe alternative preparations available for purposes of subcutaneous anticoagulation. Recombinant hirudins

The "iceberg" model shows the difference between sensitization of the immune system/immunization and allergy

DIAGRAM 3

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(lepirudin, desirudin, bivalirudin) and other direct thrombo-inhibitors, such as argatroban, are possible therapeutic alternatives for the purposes of intravenous anticoagulation with heparin. In administering these substances, the fundamental problem is that these preparations cannot be neutralized; no antidote exists. Lepirudin is licensed for the treatment of thromboembolic disorders and in HIT. It has a relatively narrow therapeutic range, and treatment monitoring using thrombin time and prothrombin time is not reliable; ideally, the treatment should be monitored with a specific test – for example, ecarin clotting time (23). Up to 40% of patients develop lepirudin specific IgG antibodies. Desirudin, bivalirudin, and argatroban have a narrow indication range. Desirudin is licensed for the prophylaxis of deep venous thromboses of the leg after total hip replacement operations and knee replacement operations. Bivalirudin is licensed as an anticoagulant for percutaneous coronary angiography, and Argobatran as an anticoagulant in patients with HIT. It is therefore obvious that heparins remain the drug of choice even after newer coagulant substances have been licensed (such as direct thrombo-inhibitors or inhibitors of factor Xa), especially for intravenous anticoagulation (25).

Conclusions

Erythematous and eczematous plaques after subcutaneous injection are symptomatic of a delayed-type hypersensitivity to heparins.

- What to do if subcutaneous anticoagulation is the treatment of choice?
  - For subcutaneous injection, pronounced cross-reactivity exists between all unfractionated heparins and low molecular weight heparin preparations. If the heparin injections are continued none the less, the risk arises of a generalized eczema or exanthema.
  - The heparinoids danaparoid or pentosan polysulfate display cross-reactivity to heparins of more than 80% and are no suitable treatment alternatives.
  - Fondaparinux injections could be tried. Because of its similar chemical structure, however, cross-reactivity is possible, especially after longer-term treatment.
  - Subcutaneously injected hirudins are tolerated.

- What to do if intravenous anticoagulation is necessary?
  - Intravenously administered heparin is usually well tolerated in spite of the delayed hypersensitivity. The risk of a generalized reaction after intravenous administration seems low.
  - In urgent cases, the change from subcutaneous to intravenous heparin administration is possible and sensible, even without prior allergy testing.

Conflict of Interest Statement

The authors declare that no conflict of interest exists according to the Guidelines of the International Committee of Medical Journal Editors.

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