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ARAŞTIRMA RESEARCH ARTICLE

Delayed-type heparin hypersensitivity: subcutaneous allergy and intravenous tolerance

Gecikmiş tipte heparin aşırı duyarlılığı: Subkütanöz allerji ve intravenöz tolerans

Axel TRAUTMANN[1]

[1] **Allergy Unit, Department of Dermatology, Venereology, and Allergology, Würzburg University, Würzburg, Germany**
Würzburg Üniversitesi, Dermatoloji, Verenoloji ve Allergoloji Bölümü, Allerji Ünitesi, Würzburg, Almanya

ABSTRACT

Objective: Itching erythematous or eczematous plaques around injection sites are fairly frequent side effects of subcutaneous (SC) heparin therapy. This allergic delayed-type hypersensitivity (DTH) to heparin can be diagnosed by skin tests (intradermal, patch) or, in cases where the skin tests are falsely negative, by a SC provocation test. After diagnosis, allergy to SC injected heparin raises the clinically important question of whether or not an intravenous (IV) heparin therapy would be tolerated.

Materials and Methods: Therefore, in recent years, all patients presenting to our allergy unit with suspected heparin allergy underwent a standardized stepwise allergologic work-up including diagnostic tests and IV provocation tests.

Results: The diagnosis of heparin DTH was made in approximately 70% of patients on the basis of skin tests alone, whereas in the remaining 30%, diagnosis could be confirmed only after subcutaneous provocation tests. Most importantly, all patients tolerated an IV provocation test.

Conclusion: Intravenous heparin therapy is well tolerated despite heparin DTH after subcutaneous injection, and the risk of a generalized reaction fol-

ÖZET

Giriş: Enjeksiyon bölgeleri çevresinde kaşıntılı eritematöz ya da ekzematöz plaklar subkütanöz heparin tedavisinin oldukça sık yan etkileridir. Heparine karşı bu allerjik gecikmiş-tipte aşırı duyarlılık (GTD), deri testleri (intradermal, yama) ya da deri testlerinin yanlış negatif olduğu durumlarda, subkütanöz provokasyon testleri ile tanınabilir. Tanı sonrasında, subkütanöz enjekte edilen heparine karşı allerji, intravenöz (IV) heparin tedavisinin tolere edilip edilemeyeceği şeklindeki önemli soruyu ortaya çıkarır.

Gereç ve Yöntem: Bu nedenle, son yıllarda allerji ünitemize şüpheli heparin allerjisi ile başvuran tüm hastalarda tanısal testler ve IV provokasyon testlerini içeren standart kademeli bir şekilde allerji incelemesi yaptık.

Bulgular: Heparin GTD tanısı, hastaların yaklaşık %70'inde sadece deri testleri ile doğrulanırken geriye kalan %30 hastada sadece subkütanöz provokasyon testleri sonrasında belirlendi. En önemlisi, tüm hastalar IV provokasyon testini tolere etti.

Sonuç: Heparinin subkütanöz uygulaması sonrasında ortaya çıkan GTD'ye karşın IV heparin teda-

Yazışma Adresi/Address for Correspondence
Axel TRAUTMANN, MD
Department of Dermatology, Venereology, and Allergology, Würzburg University, Josef Schneider Strasse 2, 97080 Würzburg, Germany
e-posta: trautmann_a@klinik.uni-wuerzburg.de

lowing IV treatment in patients with heparin DTH appears to be minimal. In an emergency situation, the simple switch from subcutaneous to IV heparin therapy without prior allergologic testing may be justified according to the current data.

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Key words: Heparin, skin, necrosis, heparinoids, bronchial provocation tests, hypersensitivity

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visi iyi tolere edilir ve heparin GTD'si olan hastalarda IV tedavi sonrasında sistemik reaksiyon riski düşüktür. Bu bulgular ile acil durumlarda basitçe allerjik testler yapılmadan subkütanözden IV heparin tedavisine geçilmesi kabul edilebilir.

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Anahtar kelimeler: Heparin, deri, nekroz, heparinoid, bronşiyal provokasyon testi, duyarlılık

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INTRODUCTION

Heparins injected by subcutaneous (SC) or intravenous (IV) route enable easily controllable anticoagulation for inpatients and outpatients[1]. Heparins are sulphated, anionic polysaccharides extracted from porcine intestinal mucosa and vary in size and composition. According to the mean molecular weight, a distinction is made between unfractionated, high molecular weight heparins [unfractionated heparin (UFH), molecular weight 10 to 20 kDa] and fractionated, low molecular weight heparins (LMWH, molecular weight 4 to 6 kDa).

A delayed-type hypersensitivity (DTH) reaction against SC injected heparin implies the final diagnosis "heparin allergy" for physician

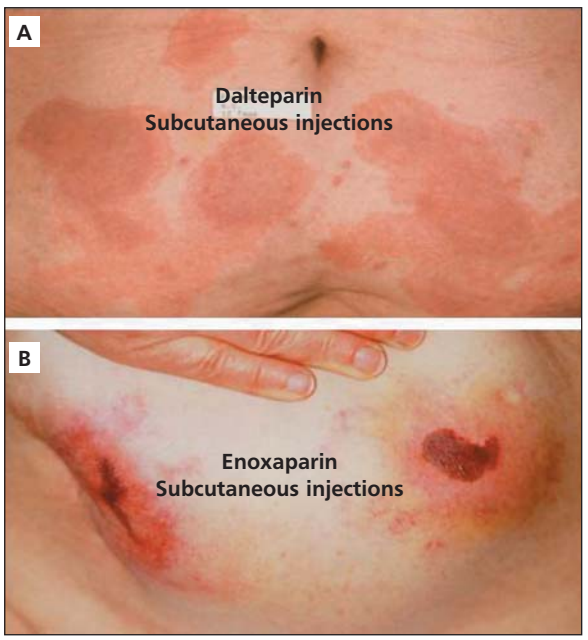

Figure 1. DTH to subcutaneous injected heparins and heparin-induced skin necrosis. (A) Itchy erythematous and eczematous plaques 12 days after initiation of subcutaneous applied dalteparin. (B) Painful heparin-induced skin necrosis at injection sites 10 days after initiation of subcutaneous enoxaparin injections.

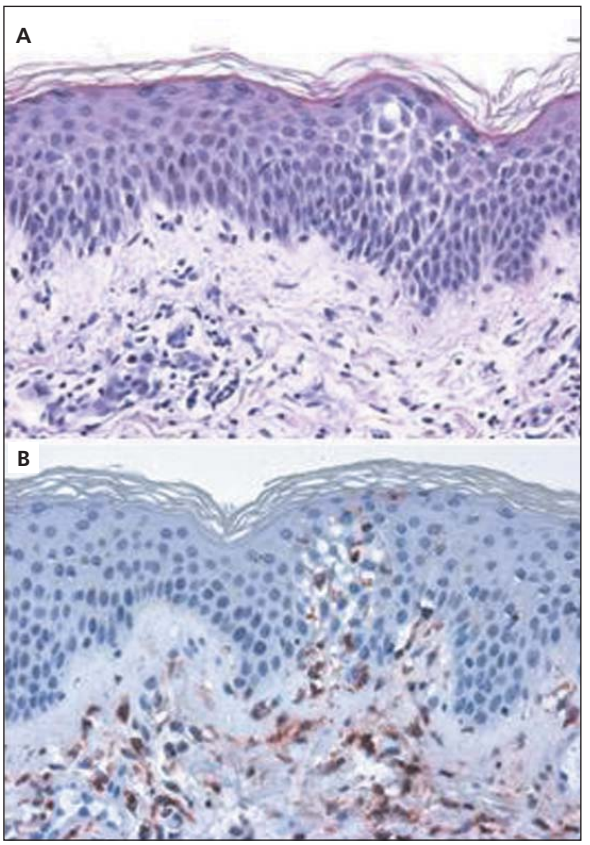

Figure 2. Histopathology shows dermal CD4+ T cells infiltrating the spongiotic epidermis, giving rise to the eczematous clinical appearance. (A) Hematoxylin-eosin staining. (B) Immunohistology staining of CD4+ cells.

and patient, and at least some patients are given an allergy document stating simply "heparin allergy". As a consequence, these patients may not receive any further heparin treatment, and because of the theoretical risk of a generalized reaction, no IV heparin is administered either.

In case of DTH to heparins, itching or burning, erythematous and sometimes eczematous plaques develop around the injection sites one or two weeks after beginning the SC injections (Figure 1a)[2,3]. In rare cases, generalized eczema or exanthema may be observed with a still visible punctum maximum at the injection sites[4]. Histopathologic examination reveals a dense infiltrate of predominantly CD4+ T cells consistent with a T cell-mediated DTH reaction (Figure 2). However, the exact antigenic determinants of the heparin molecule are thus far not known precisely.

Differential diagnoses to erythematous or eczematous plaques around heparin injection sites may include hematomas, local infections, and irritant or allergic contact dermatitis due to skin disinfectants. The most important differential diagnosis is heparin-induced skin necrosis, the skin manifestation of heparin-induced thrombocytopenia (HIT), since in the majority of cases, the allergologist does not see the lesions himself and presumptive diagnosis relies on the description by the referring physicians or patients[5]. Moreover, non-dermatologists and/or non-allergologists may confuse the clinically distinct signs of HIT, i.e. redness of the skin is assumed as one and the same as eczema or dermatitis.

In HIT, after a time interval of one or two weeks, initial erythema appears at the injection sites-or during IV heparin therapy, it is disseminated with a predilection for locations with increased subcutaneous fat tissue-which is followed by sharply circumscribed, painful necrosis (Figure 1b)[6]. Through HIT, activation of thrombocytes occurs due to IgG antibodies directed against the complex of heparin and platelet factor 4, with the consequence of venous and arterial thromboembolism. In case of heparin-induced skin necrosis, further administration of UFH or LMWH and even allergy testing with heparins is contraindicated. Therapeutic alternatives include danaparoid, lepirudin or argatroban[7].

MATERIALS and METHODS

In this article, we describe the diagnostic procedure of DTH against SC injected heparins on the one hand, while on the other hand, we point to our most important result: these patients nevertheless tolerate IV heparin therapy.

In our allergy unit, all patients in whom heparin DTH is suspected receive standardized, stepwise allergy testing including skin tests (intradermal, patch) and SC provocation tests (Figure 3)[8]. In patients with confirmed heparin DTH, we proceed to IV provocation tests with heparin, after patients are thoroughly informed about the benefits and risks and provide a written informed consent.

Skin test; intradermal tests on the volar forearm (0.02 to 0.05 mL/injection) are done using heparin preparations diluted 10% in physiological saline solution (NaCl 0.9%). Without such a dilution, falsely positive immediate wheal-and-flare reactions are a consequence of the

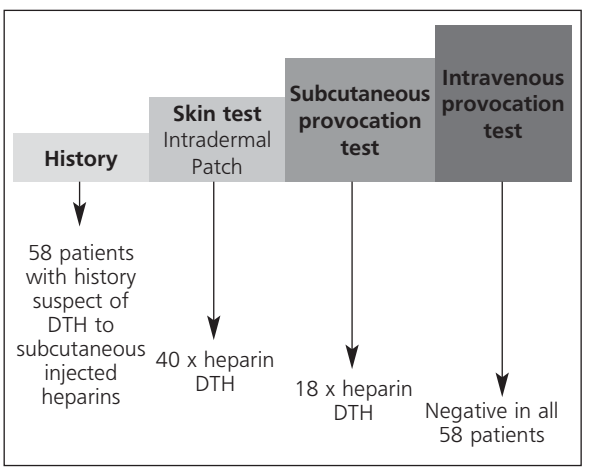

Figure 3. Stepwise testing and results.

well- known histamine-liberating properties of heparin preparations. For the patch tests on the upper back, which are modified by tape stripping of the epidermal horny layer, undiluted heparin preparations are used[9]. The test areas are read after two, three, and four days, in accordance with international recommendations[10]. The individual heparin preparations are a UFH; the LMWHs nadroparin, dalteparin, and enoxaparin; and the heparinoids danaparoid and pentosan polysulfate and, since 2002, fondaparinux.

Provocation test; the SC provocation test with skin test-negative heparin preparations is performed by injection of a single therapeutic dose into the skin of the lower abdomen. For the IV provocation test, patients receive a UFH preparation. On day one, heparin-sodium is given as a bolus injection, at a dosage of 2500 international units (I.U.). On day 2, 5000 I.U. is given as a bolus injection, followed by 7500 I.U. over 6 hours. The observation period is 3 days, and all patients are instructed to present again at the hospital if they develop symptoms at a later stage.

RESULTS

Results of a series of 58 patients are summarized in Figure 3. Stepwise testing was done to confirm the diagnosis of heparin DTH and thus ended at step 2 or step 3, before the IV provocation test in all patients was done in step 4. Diagnosis of heparin DTH was made in 40 patients in which skin tests yielded unequivocally positive results. In the remaining 18 patients, heparin DTH was diagnosed only after positive SC heparin provocation tests. Most importantly, all 58 patients tolerated the subsequent IV provocation test with heparin without side effects. In 57 patients, the interval between positive skin tests or SC provocation test and IV provocation was more than 6 weeks; in one patient it was only 4 weeks. In this patient, we observed flare-up reactions at the formerly positive skin test sites during the second day of IV provocation.

DISCUSSION

In recent years, we and other authors were able to demonstrate that patients with DTH to SC injected heparin could tolerate IV administration of heparin[11-16]. It is important that such patients not be informed only that they have a heparin allergy and that they not be given an allergy document indicating only "heparin allergy". A provocation test demonstrates that IV-administered heparin is tolerated, and such a supplement in the allergy document enables straightforward IV anticoagulation in the future. In urgent cases (e.g., in surgical procedures in which extracorporeal circulation is necessary), anticoagulation with IV heparin is justified in case of known heparin allergy manifesting as erythematous or eczematous plaques around injection sites, even without prior allergy testing.

Female sex and obesity are risk factors for developing a DTH to SC heparin injections; it is therefore tempting to speculate that hormonal or metabolic factors play a pathogenic role[17,18]. In the series of Figure 3, 52 out of 58 patients were women; body mass index (BMI) was normal in 4 patients only (18.5 to 24.9), 20 were overweight (25 to 29.9), and 34 were obese (> 30.0)[11]. The question of why patients develop allergic hypersensitivity to SC injected heparin but tolerate IV administration does not yet have a definitive answer. The crucial factor is probably unspecific binding of the anionic heparin polysaccharides to proteins or other macromolecules after SC injection on the one hand, and differences in the presentation or processing of heparin antigens according to the mode of administration (IV or SC) on the other. The difference between sensitization of the immune system, i.e. immunization to heparins (detectable through positive skin tests, heparin-specific T cells or antibodies) and a clinically relevant disease (an allergy with specific symptoms) becomes particularly obvious in this scenario of heparin allergy and IV heparin tolerance (Figure 4).

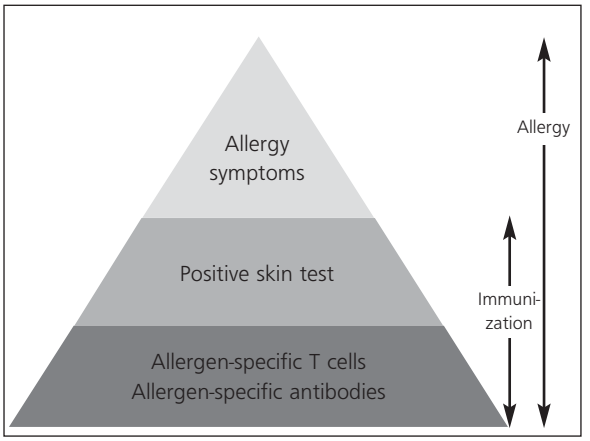

Figure 4. The "iceberg" model illustrates the difference between sensitization of the immune system (or immunization, alternatively) and clinically relevant allergy disease.

Immune responses are not "all or none" reactions. Even an immune response to heparins does not always take the same intensity but manifests in a spectrum, with substantial qualitative differences. Patients with low-grade immune reactions to heparins develop only discrete erythematous plaques around the injection sites, their skin tests are sometimes negative, and the diagnosis can be made only after a positive SC provocation test. Patients with a high-grade immune response show a strong local reaction clinically with an infiltrated eczematous plaque, on which densely clustered papulovesicles may confluence into larger blisters. Then, at least two-fold positive reactions during skin tests to most tested heparin preparations are the rule. These highly sensitive patients may also show so-called flare-up reactions on formerly eczematous plaques or positive skin test sites during IV provocation, especially if less than 4 weeks have passed between plaque healing and provocation testing. One possible explanation for flare-up reactions is activation of allergen-specific T cells that have remained in the formerly positive skin test areas after IV administration of heparin, similar to what is being discussed for fixed drug eruption. A single case report of such a generalized eczema after heparin administration may be due to the too-short of a time interval between positive skin tests or positive SC provocation tests and IV heparin administration[19].

Generally, there is extensive cross-reactivity between all preparations of UFH and LMWH in cases of heparin DTH. Potential heparin-like alternatives include the heparinoids danaparoid and pentosan polysulfate, which are both semisynthetically produced anionic polysaccharides[20]. Heparinoids, especially pentosan polysulfate, actually often yield negative results in skin tests. However, most of these skin tests are falsely negative, because the DTH and thus cross-reactivity clinically manifests during SC provocation tests. The tolerability of a single SC provocation test should also not be overestimated. Several of our patients developed erythematous and eczematous plaques after an increasing number of heparinoid injections during long-term therapy despite a previously negative single SC provocation test with a heparinoid. In summary, cross-reactivity between heparins and heparinoids is common, as may be expected in light of their similar chemical structures[21].

Fondaparinux, a synthetic heparin analogue, which consists of one defined pentasaccharide unit (molecular weight 1.7 kDa) and which inhibits specifically factor Xa, has been licensed in Germany since 2002[22]. Fondaparinux has been studied as an alternative preparation to SC injected heparin[23,24]. We observed positive skin test reactions to fondaparinux in 15 out of 37 patients with a heparin DTH. In the meantime, several publications have shown that maximally 50% of patients with a heparin DTH tolerate fondaparinux without developing symptoms[25-27].

Consequently, hirudins-which as proteins have a completely different chemical structure-are the only safe alternative preparations available for SC applied anticoagulation. Recombinant hirudins (lepirudin, desirudin, bivalirudin) and other direct thrombin inhibitors, such as argatroban, are also possible therapeutic alternatives for IV anticoagulation with heparin.

In administering these substances, the major concern is that these drugs cannot be neutralized as easily as heparins; no antidote exists. Lepirudin is licensed for the treatment of thromboembolic disorders and in HIT. It has a relatively narrow therapeutic window, and treatment monitoring using thrombin time and prothrombin time is not reliable; ideally, the treatment should be monitored with a specific test-e.g. the ecarin clotting time[28]. Up to 40% of patients develop lepirudin-specific IgG antibodies. Desirudin, bivalirudin and argatroban have a narrow range of indications. Desirudin is licensed for the prophylaxis of deep venous thromboses of the leg after total hip replacement and knee replacement operations. Bivalirudin is licensed as an anticoagulant for percutaneous coronary angiography, and argatroban as an anticoagulant in patients with HIT. It is therefore obvious that heparins remain the drug of choice even after new anticoagulants have been licensed (such as direct thrombin inhibitors or inhibitors of factor Xa), especially for IV anticoagulation[20].

Erythematous and eczematous plaques after SC injection are symptoms of a heparin DTH.

What to do if SC anticoagulation is the treatment of choice?

• For SC injection, extensive cross-reactivity exists between all UFH and LMWH heparin preparations. If the SC heparin injections are continued despite local reactions, there is a risk of a generalized eczema or exanthema.

• The heparinoids danaparoid or pentosan polysulfate show cross-reactivity to heparins in more than 80% and are not suitable treatment alternatives.

• Fondaparinux SC injections could be tried. Because of its similar chemical structure, however, cross-reactivity is possible, especially after long-term treatment.

• SC injected hirudins are tolerated.

What to do if IV anticoagulation is necessary?

• IV administered heparin is usually well tolerated despite heparin DTH. The risk of a generalized reaction after IV administration seems to be very low.

• In urgent cases, the simple shift from SC to IV heparin administration is possible and justified, even without prior allergologic testing.

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