

Allergy to heparins and anticoagulants with a similar pharmacological profile: an update

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Heparins are widely used as anticoagulants. Immunologically-mediated side effects raise the question as to whether other substances with heparin-like pharmacological effects can be safely applied. Hypersensitivity reactions to heparin consist of heparin-induced immune thrombocytopenia, allergic vasculitis, hypereosinophilia, immediate hypersensitivity as well as delayed-type skin reactions. Hypersensitivity to unfractionated and low-molecular-weight heparins and semisynthetic heparinoids is increasingly common, and the pathogenesis, however, is still not fully understood. Clinically, this phenomenon is of relevance because of its increasing incidence and the resulting therapeutic difficulties that arise because several cross-reactions between unfractionated and low-molecular-weight heparins as well as between various heparins and heparinoids have been observed. In some patients with cross-reactivity between various heparins and semisynthetic heparinoids, recombinant hirudins, may be

safe and effective. Combined allergy to recombinant hirudins and heparins, however, has been reported. Therefore, there is an urgent need for therapeutic alternatives. *Blood Coagul Fibrinolysis* 17:605–613 © 2006 Lippincott Williams & Wilkins.

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Introduction

Heparins are potent anticoagulants and are commonly used for the prevention and treatment of thromboembolic diseases, during haemodialysis, and in cardiac as well as arterial surgery to avoid clotting in extracorporeal blood. Heparin is effective, relatively inexpensive, and readily available. The generally accepted hypothesis concerning the mode of action is that heparins accelerate the inhibitory effect of antithrombin III on various serine proteases involved in the blood clotting. The group of heparins is diverse in their molecular structure and mass. The molecular weight ranges from 4000–6000 Da to 20 000 Da. High molecular weight (unfractionated) heparins (12–20 kD) are extracted from either porcine intestinal mucosa or bovine lung. Low molecular weight (LMW) heparins (4–6 kD) are obtained from high molecular weight heparins by fractionation. This fractionation process results in pharmacologically different LMW heparins (enoxaparin, reviparin, dalteparin, nadroparin, tinzaparin, certoparin). LMW heparins substitute for unfractionated heparins in several indications because of their safety and their increased bioavailability and the fact they seem to be less often associated with adverse reactions such as major bleeding [1–3]. Common complications of heparin therapy are bleeding and non-immune heparin-induced thrombocytopenia. Long treatment courses may result in less common complications including skin reactions, eosinophilia, alopecia, osteoporosis, hyperpotassemia, hypoaldosteronism,

priapism, skeletal defects, lipodystrophy and liver dysfunction, the latter being reversible [4].

Recently, LMW heparins have been reported to induce nodules in the anterior abdominal wall fat as detected by computer tomography in 3% of cancer patients treated with LMW heparins, and thereby mimicking metastatic disease [5]. In 2003, Eich and associates [6] reported that calcinosis of the cutis and subcutis occurred as a non-immunologic adverse event to subcutaneous application of LMW calcium-containing heparins to patients suffering from acute or intermittent chronic renal failure with elevated calcium–phosphorus products.

Hypersensitivity reactions to heparin consist of heparin-induced immune thrombocytopenia, hypereosinophilia, allergic vasculitis, immediate hypersensitivity as well as delayed-type skin reactions, such as infiltrated eczematous plaques at injection sites and generalized eczematous reactions (Table 1). Out of these, delayed-type reactions are the most common immune reactions. Heparins are mucopolysaccharides with a strong protein binding potency, which plays an important role in the pathomechanism of heparin allergy. The dermal or subcutaneous protein involved in adherence of the heparin molecule is still unknown. The sensitizing period is weeks and up to several months. After sensitization has taken place re-exposition may induce an allergic reaction after only 2–3 days. The allergic potential is

Table 1 Hypersensitivity reactions to heparins and alternative treatments

Immunological adverse events	Heparins	Low molecular weight heparins	Semisynthetic heparinoids	Synthetic heparin: fondaparinux	Recombinant hirudins
Immediate-type reactions (type I reactions)	Anaphylactic shock Urticaria, angio-oedema Hypotension, urticaria and bronchospasm, erythema, facial and pharyngeal oedema.	Urticaria, angio-oedema, dyspnoea, wheezing	<i>Danaparoid</i> : none so far <i>Pentosan polysulphate</i> : None so far	None so far	Urticaria, angio-oedema, hypotension, anaphylactic shock, cardiovascular arrest, urticaria and bronchospasm, erythema, pruritus of palms and soles, nausea, vomiting, fever, facial and pharyngeal oedema, particularly after previous exposition
Type II reactions	HIT-II, Heparin-induced skin necrosis	HIT-II, Heparin-induced skin necrosis	<i>Danaparoid</i> : HIT-II <i>Pentosan polysulphate</i> : HIT-II Heparin-induced skin necrosis	None so far	None so far
Type III reactions Delayed-type (type IV reactions) (DTHR)	Vasculitis, Arthus reaction Drug rash, Hypersensitivity syndrome, Lyell's syndrome Localized and generalized DTHR; Baboon's syndrome; Localized itchy plaques combined with hypereosinophilia	Arthus reaction, Vasculitis Localized and generalized DTHR	None so far Localized DTHR	None so far Localized DTHR	Arthus-reaction Localized DTHR, Exanthema

not lost by processing unfractionated heparin to obtain LMW heparins. With the fractionation method, allergens may persist so that only molecular weight discriminates unfractionated heparins from LMW heparins and all variants of allergic reactions that develop to unfractionated heparins may also occur after administration of LMW heparins because of antigen sharing [7]. Heparin is most probably a mixture of allergen components. Different patterns of cross-reactions between different heparins and heparins and heparinoids suggest that there are several epitopes responsible for allergic reactions to this drug [8,9]. The allergens, however, have not been identified and characterized. Bovine and porcine elements do not play a role, because sensitized patients experienced allergic reactions even after exchange of the heparin preparation [10]. Heparin sensitization can be induced by any variant of the application, even topical application [11], either after previous sensitization or after direct topical application (Jappe, unpublished observations). According to Stüttgen a cutaneous uptake of heparin takes place [12]. Its form of application and its influence on the development of immune reactions is still not fully understood. Heparin-induced thrombocytopenia (HIT) type II occurs predominantly after intravenous application [13]. The application pathway alone, however, does not seem to be responsible: an allergic vasculitis occurred after topical treatment with heparin after previous subcutaneous sensitization to the drug [14].

Sometimes, however, sensitization is dependent on the form of application: patients who have been sensitized to subcutaneous heparin may tolerate intravenous heparin treatment, a phenomenon known as compartment allergy

[15] and relevant for the choice of a treatment with alternative heparin-like drugs.

Immediate type reactions (type I reactions)

Heparin-related, immediate-type reactions such as generalized urticaria, angio-oedema, allergic rhino-conjunctivitis, bronchospasm and severe anaphylaxis are very rare [16–19]. The mechanisms underlying these immune reactions have not, however, been elucidated. Recently, Bottio and co-workers [20] observed a systemic reaction with circulatory collapse and airway blockage following intravenous administration of porcine gut heparin in a patient undergoing a mitral valve repair. The immunological nature of this reaction was proven by skin prick test after complete resolution. The patient was positive for even the highest dilution of the suspected drug, whereas nine control subjects were not. Anaphylactic reactions to LMW heparins (enoxaparin, reviparin, dalteparin) during haemodialysis rarely occur [21–23] and have to be distinguished from infrequent anaphylactic or anaphylactoid reactions during haemodialysis, which can be due to ethylene oxide hypersensitivity or toxicity, reactions induced by dialyser membrane, toxic effects of formaldehyde or glutaraldehyde and idiopathic responses [24,25]. In 2005, Bircher and Harr described a 30-year-old female patient with Muckle-Wells syndrome who had used dalteparin subcutaneously for more than 10 years and who developed severe urticaria, nausea, mild dyspnoea and swollen hands after re-administration. Intradermal test with all LMW heparins was positive and accompanied by a flare of urticaria. Intravenous challenge with unfractionated heparins and subcutaneous provocation with fondaparinux was tolerated [26].

Lepirudin, a recombinant hirudin with no structural similarity to heparins and heparinoids, which has been introduced as a treatment alternative to heparins in cases of severe allergic reactions also induces severe type I reactions occurring within minutes after treatment initiation, such as hypotension, hypotension-induced cardiac infarction, cardiorespiratory arrests, anaphylactic shock, urticaria and bronchospasm, erythema, pruritus of palms and soles, nausea, vomiting, fever, facial and pharyngeal oedema. These severe reactions can occur particularly in patients who are treated within 3 months of a previous lepirudin exposure [27].

Allergic type II and type III reactions to heparins

Heparin-induced thrombocytopenia (type II)

The most serious adverse event of heparin treatment is the immune HIT. It is characterized by a reduction of thrombocyte counts by at least 50% between day 5 and day 10 of treatment. In parallel, a thrombotic complication such as arterial thrombosis, venous thrombosis, or disseminated intravascular coagulation develop in 50% of cases. Immunologically, HIT represents a type II reaction [28]. An immune reaction develops with the production of polyclonal IgG-antibodies (HIT-antibodies), usually directed against the heparin-platelet factor 4 complex, followed by the activation of platelets with the subsequent generation of thrombin and hence producing a procoagulatory state. The HIT-antibodies activate platelets via their Fc ϵ RIIa-receptor leading to platelet aggregation, thereby inducing thrombocytopenia. Platelets collected from HIT patients are characterized by increased numbers of Fc-receptors on their surface and an increased activation in the presence of the antibodies [29]. These antibodies, however, are not heparin-specific [30] and may pre-exist in patients who have never been exposed to heparins previously [31]. Another pathomechanism is based on the development of an endothelial lesion due to an interaction between HIT-antibodies directed against the heparin-platelet factor 4 complex. HIT-antibodies react with endothelial cells to which platelet factor 4 and heparin sulphate are bound, thereby causing endothelial damage [32]. All stages of this pathomechanism depend on the patient's individual characteristics: multimolecular platelet factor 4/heparin complexes represent the major antigen in HIT [32,33]. They might present several epitopes and form immune complexes after HIT antibody binding which activate platelets via their Fc ϵ receptor RII. There is evidence that molecules involved in this process might be different in some individuals. In some patients, not only HIT-IgG but also HIT-IgM antibodies were detected. Other patients' sera contained specific antibodies to only platelet factor 4 alone. HIT may occur with all methods of administration of heparin. The risk of developing HIT increases with porcine and bovine heparins, however, compared with LMW heparins and in individuals with

preexisting cardiovascular disease. The reaction may develop within hours in previously treated patients. Early diagnosis whenever symptoms like skin lesions, thrombocytopenia or thrombosis occur is vital as treatment discontinuation may prevent life-threatening complications in other organ systems. Heparin-dependent platelet-activating IgG, which in subsequent publications are named 'HIT-antibodies', can be detected in patients with heparin-induced painful or necrotic plaques irrespective of whether or not thrombocytopenia is existent [34]. As confirmed by Folwaczny and Stürmer [35], however, thrombocytopenia is not a valuable tool to predict the development of characteristic complications of a HIT.

According to Warkentin and co-authors [36], HIT type II is more common in patients with unfractionated heparin than in those treated with LMW heparins. This may not be true anymore, however, since the LMW heparins are widely used and the reports on LMW heparin associated HIT increased in number during the last years. Based on observations on cross-reactivity, Tonn and co-workers [37] strongly advise against the use of enoxaparin or other LMW heparins in patients with a previous history of heparin-associated thrombocytopenia or heparin-induced dermal necrosis.

Arthus reaction

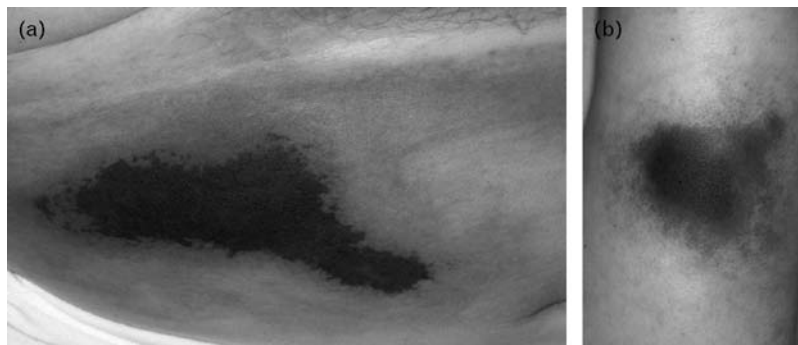
The Arthus reaction is characterized by inflammatory lesions with an erythematous induration, oedema, haemorrhage and subsequent necrosis, which develops during a few hours after intradermal injection of an antigen in previously sensitized individuals with precipitating antibodies directed to the antigen in question. Localized Arthus reactions have been observed after subcutaneous application of unfractionated heparin and the LMW heparin enoxaparin [38,39] as well as after subcutaneous administration of lepirudin, a recombinant hirudin [40].

Heparin-induced skin necrosis

Heparin-induced skin necrosis is a rare but potentially devastating complication of heparins and LMW heparins and typically affects middle-aged women with a history of thrombotic disease. Clinically it is not distinguishable from cumarine necrosis [41]. In general, it develops after subcutaneous injection of heparin. Occurrence after intravenous application and in areas distant to the sites of injection is, however, possible [13,42–45] indicating that the development of heparin-induced skin necrosis does not seem to depend on the administration route.

The cause of heparin-associated skin necrosis is still not fully understood. Some authors believe that immunologically it is an Arthus reaction [15], whereas others suggest a primarily thrombotic condition, mediated by a heparin-dependent antibody reacting with platelets to

Fig. 1



Heparin-induced skin necrosis at the injection sites after 7 days of subcutaneous treatment with nadroparin in a 74-year old woman. (a) Abdominal skin. (b) Thigh.

form a thrombus [46]. Warkentin [34] identified heparin-dependent, platelet-activating, IgG-antibodies which activate platelets via Fc-receptor in sera of six patients with heparin-induced skin lesions leading to thrombocyte aggregation, which supports the hypothesis that thrombosis of perforating vessels supplying the skin produces ischaemia and infarction progressing to inflammation and necrosis is the mechanism and represents a cutaneous heparin-induced thrombocytopenia [34]. Symptoms may develop at the injection site, which is relatively common, but also may occur far away from the application site within 1–2 weeks after treatment initiation and presents as erythematous, itching or burning induration with subsequent necrosis (Fig. 1), followed by resolution after treatment discontinuation [47]. Heparin-induced skin necrosis may be accompanied with thrombocytopenia and lethal thrombotic complications. Sometimes a diffuse skin necrosis may occur. In previously treated patients symptoms may develop earlier than after 2 weeks of treatment.

In 1979, Ranft and Klöß [14] reported an allergic vasculitis due to cutaneous resorption of topically applied heparin after previous sensitization to heparins due to subcutaneous injection. Gibson and co-workers [48] reported a heparin-induced skin necrosis, which began as urticaria far from the injection site followed by thrombocytopenia without an immune reaction involving thrombocytes. After discontinuation of treatment, the lesions resolve. Sometimes, however, surgical intervention is necessary. It is recommended that because of the high incidence of cross-reactivity between various heparins, all forms of heparin exposure should be avoided after such skin necrosis episodes [49].

Drug rash

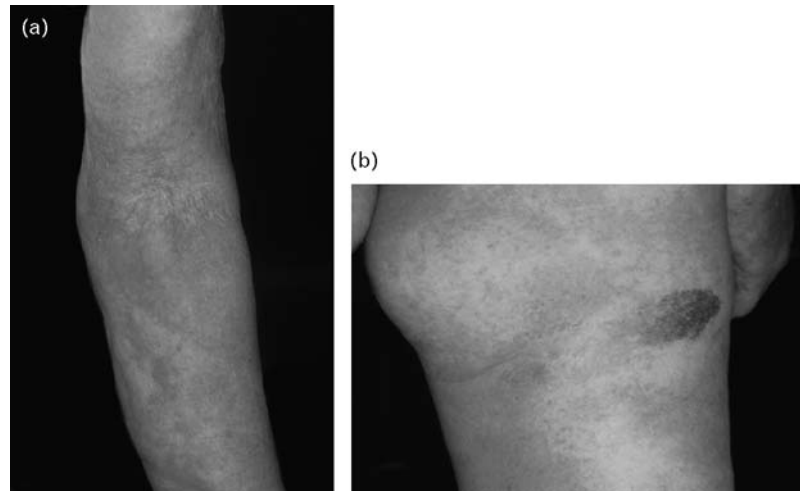
Unfractionated as well as LMW heparins may also induce generalized maculo-papular drug rashes (Fig. 2), partly with blisters, sometimes associated with fever and

thereby representing a hypersensitivity syndrome [50–53]. These reactions are considered to be delayed-type reactions although not always mediated by CD4+ T-cells. There are different entities of drug rashes with different degrees of seriousness to the patient. Palmo-plantar itching after heparin therapy was described [54]. Leung and co-workers [55] reported a toxic epidermal necrolysis in a male neonate following the maternal use of heparin in a dosage of 1000 units of heparin per hour intravenously. Forty-eight hours after birth, the neonate had exfoliation of the skin, skin culture being negative for bacteria and fungi, viral study findings normal [55].

Type IV allergic reactions and the phenomenon of cross-reactivity

Heparin-induced non-necrotic reactions caused by subcutaneous administration of unfractionated heparins and LMW heparins are due to a delayed type hypersensitivity reaction (DTHR) (type IV allergic reaction) [56–58].

In 1952, Plancherel first described skin lesions developing at the injection site of heparin. Since then, DTHR proved to be the most common variant of allergic reaction to heparins which initially may not easily be distinguished from the more severe heparin-induced necrosis. During an interval of 10 to more than 20 days after treatment initiation with both unfractionated and LMW heparins DTHR occur as indurated subcutaneous oedema at the site of injection with additional erythema, later transforming into eczema accompanied by itching (Fig. 3). Re-exposure induces the development of skin lesions in only 2–3 days. Histology reveals a dense lymphocytic infiltrate and a spongiotic dermatitis. Immunohistochemistry shows CD4-positive T-cells dominating, which is expected for a type IV reaction [57]. In 1993, Giustolisi and co-workers reported a collection of cases with itchy erythematous plaques at the injection sites of subcutaneous heparins who in parallel developed blood

Fig. 2

Generalized rash after 5 days of treatment with dalteparin in a 75-year-old woman.

hypereosinophilia [59]. Bircher and co-workers had observed a similar phenomenon and additionally had investigated a skin biopsy from the patient. This revealed eosinophils in the tissue as well. From this observation, the authors hypothesized that CD4-activation associated with enhanced granulocyte–macrophage colony-stimulating factor, IL-3 and IL-5-secretion induced growth and activation of eosinophils [60].

In cases where heparin treatment was not interrupted, DTHRs localized at the injection sites developed into a generalized eczematous reaction [61]. In order to prevent systemic reactions it is, therefore, strongly recommended to discontinue the therapy after clinically apparent heparin sensitization has been initiated. Originally, preservatives were thought to be the most important allergens for delayed-type reactions to heparin preparations

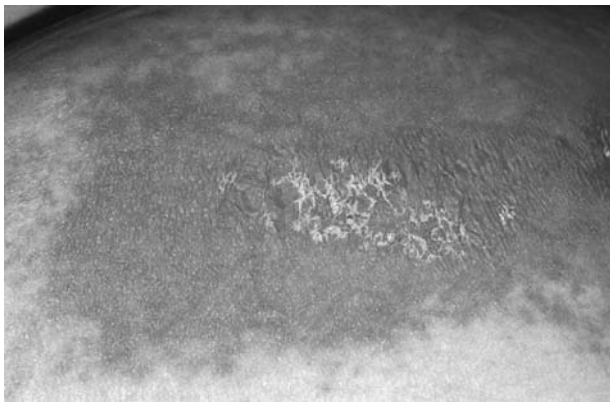
(thimerosal, chlorocresol, chlorbutanol, benzalkonium chloride). In fact, these substances are a rare cause of sensitization [62–64]. Sensitization and subsequent development of a DTHR is predominantly associated with a strong protein-binding capacity of heparins, since the mucopolysaccharide structure alone cannot be made responsible for the immune reaction.

A particular variant of systemically induced allergic contact dermatitis is the baboon's syndrome which was reported after subcutaneously administered unfractionated heparin [65]. The baboon's syndrome is a drug rash that predominantly involves axillae, groin, genitalia and elbows and is considered to be a haematogenous DTHR.

DTHRs are not only observed to unfractionated and LMW heparins but also to the semisynthetic heparinoids danaparoid and pentosanpolysulphate. Danaparoid is a mucopolysaccharide derived from porcine intestinal mucosa, it may share identical allergens with heparins [66]. Pentosanpolysulphate is derived from beech wood, indicating that a possible epitope sharing cannot be due to a fractionation process. DTHRs to this heparinoid also occur, however, even following sensitization to heparins, as described below.

A phenomenon which became evident with DTHRs to heparins, although it also occurs in the rare HIT type II, is cross-reactivity between unfractionated heparins, heparins and LMW heparins and sometimes additionally with semisynthetic heparinoids [67].

Trautmann and co-workers [51] observed in 81.1% of patients with heparin allergy cross-reactions with danaparoid and in 45.5% with pentosanpolysulphate [51].

Fig. 3

Indurated itching plaque at the injection site after 20 days of treatment with heparin sodium.

There are, however, case reports on different patterns of cross-reactions and tolerance of LMW heparins and heparinoids in patients with heparin allergy [8,9,68,69]. There are cases for which complete cross-reactivity exists between several heparins and heparinoids [70,71]. Since the intensity of cross-reactivity is not predictable, differentiated allergy diagnostic tests should be performed before an alternative heparin, LMW heparin or a heparinoid is applied.

Diagnostic tests in cases of suspected heparin hypersensitivity

In cases of suspected heparin allergy treatment has to be discontinued immediately. A heparin-induced skin necrosis or HIT type II should be excluded by clinical investigation, thrombocyte count and immunological tests (see below, *In-vitro diagnostic tests*). Clinically apparent skin necrosis should be confirmed histologically. Since thrombocyte counts are not the indicative symptom of a HIT type II but thrombosis and the detection of HIT-antibodies, patients with heparin treatment should be investigated for clinical signs of a thrombosis regularly in short intervals. Those individuals who developed a thrombosis under heparin treatment should be tested for HIT-antibodies to detect a HIT type II in progress [35].

Diagnostic allergy testing

Skin tests

Diagnostic allergy tests include skin-prick test, intradermal, and patch test as well as subsequent subcutaneous and sometimes intravenous challenge.

Immediate-type reactions 20 min after skin-prick or intradermal tests seldom indicate a true type I allergy but are mostly due to histamine-releasing effects of heparins. Skin prick and intradermal tests are performed on the volar forearm with 0.05 ml of each substance (heparins, heparinoids and other alternative substances) with readings at 20 min and 24, 48, 72 and 96 h (Fig. 4). In cases of suspected rare immediate type reactions to heparins the skin prick test should include several titration steps: 0.05 ml of 1:1000, 1:100, and 1:10 dilutions.

Patch testing should include the standard series of the preservatives sometimes used in different brands of heparins (chorcresol, benzalkonium chloride, thimerosal) as well as different unfractionated heparins, LMW heparins, heparinoid preparations (danaparoid and pentosanpolysulphate after tape stripping). A panel of different LMW heparins should be included in the test because of the high rate of cross-reactions between heparins, LMW heparins and heparinoids [72]. Readings are done on days 3 and 4 according to the guidelines of the German Contact Dermatitis Research Group and the International Contact Dermatitis Research Group, respectively (Fig. 5), and should in cases of suspected delayed-type allergy to heparins also

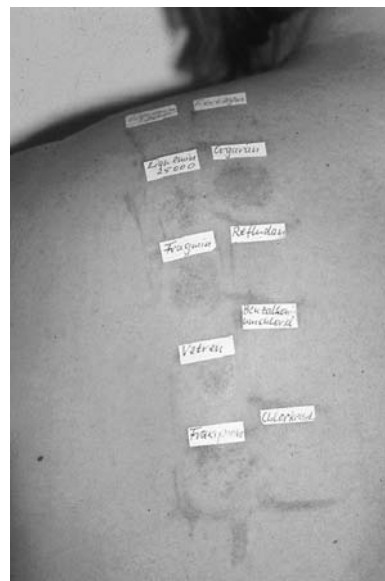
Fig. 4



Positive intradermal test reaction at 48 h on the volar forearm of a patient with delayed-type allergy to certoparin.

be undertaken at days 5 and 6 [73,74]. Whereas the patch test is not positive in all cases of DTHR, probably due to the epidermal barrier to heparins [56,57,68], the intradermal test with subsequent subcutaneous challenge proved to be the most sensitive test to detect DTHRs to heparins. Semisynthetic heparinoids as well as fondaparinux should be included in the testing because they may be tolerated when heparins and LMW heparins are not, thereby representing treatment alternatives [9,71,75–79].

Fig. 5



Patch test results in a patient with delayed-type allergy towards several heparins and heparinoids after 96 h.

Subcutaneous challenge

Subcutaneous challenge is performed either into the volar forearm or the abdominal skin with skin test-negative heparins and heparinoids in a therapeutic dose. Results are obtained 20 min and 24, 48, 72 and 96 h after heparin administration.

Intravenous challenge

There are different methods of intravenous challenges [40,71,80,81]. For an intravenous provocation test with heparins or heparinoids, however, patients should be hospitalized. The substances should be given for at least 3 days. According to several publications and own observations the test substances will most likely be tolerated without additional application of glucocorticosteroids and antihistamines [40,70,81]. Recently, Gaigl and associates [81] performed a prospective study on 28 patients with proven DTHRs to heparins. They applied unfractionated heparin sodium in a dosage of 2500 IU as a bolus on day 1, 5000 IU as a bolus followed by 7500 IU for 6 h on day 2 with a follow-up period of 3 days [81]. No individual experienced a DTHR after intravenous challenge with heparin.

In-vitro diagnostic tests

Patients receiving heparin should be investigated for clinical symptoms of thrombosis [35]. According to Follwaczny [35] thrombocytopenia is not a reliable indicator for HIT type II. Therefore, in cases where HIT is suspected the antibody test (heparin induced thrombocyte activation test) and an enzyme-linked immunosorbent assay for the detection of thrombocyte factor 4, heparin and antibody towards thrombocyte factor 4-complex should be performed immediately [35].

In-vitro tests for the detection of DTHRs to heparin are not commonly used or commercially available. Lymphocyte transformation assays have so far been negative with heparin or showed results discordant to the patient history and skin tests. The hypotheses which could explain the lack of T-cell stimulation are immunomodulating and immunosuppressive effects of heparins as well as the known fact that antigen-specific cells are homing to the site of local reaction and, therefore, are not circulating in the blood [8,40,56,68].

Treatment of hypersensitivity reactions to heparins

Treatment of immediate type allergic reactions consists of antihistamines and in severe cases glucocorticosteroids orally or even intravenously. Whereas in localized DTHR to heparins topical glucocorticosteroids generally are sufficient, in generalized eczema systemic application might be advisable. Surgical debridement may be of advantage in heparin-induced skin necrosis. Since 1997 recombinant hirudins have been available for the treatment of HIT.

Treatment with a heparin-like drug in cases of hypersensitivity to different heparins or heparinoids

Therapeutic alternatives mainly consist of drugs with a different molecular structure revealing pharmacological features different to those of heparin and are, therefore, not discussed in this review. The choice of a heparin-like drug may be difficult. In some cases, where there is no cross-reactivity to heparinoids, danaparoid can be used [23,79]. Among the presently available heparinoids only danaparoid and pentosanpolysulphate show pharmacological features comparable to those of heparins. In both cases the substances are semi-synthetic sulphated mucopolysaccharides, which in contrast to heparins have polysaccharide chains of a different structure. There are cases, however, for which complete cross-reactivity between several heparins and heparinoids exists. This is when treatment options should include intravenous instead of subcutaneous administration of heparins, and recombinant hirudins [70,71]. DTHR to subcutaneously administered heparins does not exclude its tolerance after intravenous application [40,70,71]. Possible reasons for intravenous tolerance might be the difference in antigen processing and presentation and preferential homing of selectively sensitized lymphocytes in the dermis. This phenomenon is called compartment allergy. Despite several publications on the tolerance of intravenous heparins and heparinoids in patients with local DTHR on subcutaneous administration, the safety of intravenous heparin in this clinical setting is still controversial [50], as subcutaneously sensitized patients may develop a widespread eczematous reaction. Gaigl and associates [81], however, recently demonstrated in a prospective study that in patients with verified DTHRs intravenous heparin is well tolerated and in urgent cases can be given intravenously without prior testing. This intravenous challenge test should, however, be performed under medical supervision.

When intravenous heparin treatment is not applicable, direct thrombin inhibitors may be used in patients allergic to heparin [82]. Recombinant hirudins, for example, are a possible alternative. They are polypeptides and, therefore, have a chemical structure different to heparin. Recombinant hirudins do not cross-react with unfractionated or LMW heparins and heparinoids because there is no epitope sharing [83]. They have pharmacological characteristics similar to heparins. A few reports of immune reactions towards recombinant hirudins exist [27,84–87]. Local skin reactions at injection sites have been documented for lepirudin in about 0.5% of patients, including a local Arthus reaction [40] as well as systemic reactions like IgG-mediated urticaria [88], DTHR and maculo-papular rash in 4% of treated patients [89]. According to a recent report, severe anaphylactic reactions during lepirudin treatment occur [27] and re-exposed patients could be at increased risk of severe anaphylactic reactions [27] which seems to be mediated

by IgG- instead of IgE-antibodies. Therefore, a suitable alternative treatment is needed. Fondaparinux is the first of a new class of antithrombotic drugs. It is a sulphated pentasaccharide with antithrombotic properties made in its entirety by chemical synthesis. Its structure is identical to the critical pentasaccharide sequence of heparin. Occasionally, however, there are cross-reactions between various heparins and fondaparinux [78,90]. Nevertheless, fondaparinux still seems to be a valuable alternative in most cases of heparin and hirudin hypersensitivity.

Conclusion

Hypersensitivity to unfractionated, LMW heparins and semisynthetic heparinoids is increasingly common, the delayed-type allergy being the predominant variant. Clinically, this phenomenon is of relevance because of the resulting therapeutic difficulties that arise due to several cross-reactions between unfractionated and LMW heparins as well as between various heparins and heparinoids. Since the intensity of cross-reactivity is not predictable, differentiated allergy diagnostic tests should be performed before an alternative heparin, LMW heparin or a heparinoid is applied. This diagnostic procedure should consist of skin-prick test, intradermal test with readings at days 3 and 4, and if possible at days 5 and 6, including LMW heparins as well as alternative treatments (heparinoids and the synthetic heparin), followed by a subcutaneous challenge with the drug negative in all skin tests. Intravenous application may prove a treatment alternative in rare cases of a wide range of cross-reactions.

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