

Heparin Allergy: Delayed-Type Non– IgE-Mediated Allergic Hypersensitivity to Subcutaneous Heparin Injection

Axel Trautmann, MD^{a,*}, Cornelia S. Seitz, MD^b

KEYWORDS

- Adverse drug reaction • Delayed-type hypersensitivity
- Heparin • Heparinoid • Intravenous challenge

Pathologic immune reactions during ongoing anticoagulation with heparins may present as heparin-induced thrombocytopenia (HIT), erythematous or eczematous lesions around injection sites, or, in extremely rare cases, IgE-mediated urticaria or anaphylaxis.^{1–3} From an allergologist's perspective, however, delayed-type non-IgE-mediated allergic hypersensitivity (DTH) to subcutaneously injected heparin is the most common and clinically relevant issue.^{4–6} Frequently, changing the subcutaneous therapy from unfractionated heparin (UFH) to low molecular weight heparin (LMWH) or treatment with heparinoids does not provide improvement because of extensive cross-reactivity of these anionic polysaccharides. DTH may be verified by skin testing (intradermal and patch tests) or, in cases of false-negative skin test results, by subcutaneous challenge tests.⁷

For the treating physician and patient, diagnosis of allergy to subcutaneously applied heparins usually implies discontinuation of subcutaneously and intravenously applied heparins because, at least theoretically, intravenously applied heparin in sensitized individuals (ie, patients with DTH to subcutaneously injected heparins) may reach the skin by way of blood circulation and may trigger a hematogenous generalized eczematous or exanthematic eruption. Data in the literature^{8,9} and in

^a Allergy Unit, Department of Dermatology, Venereology, and Allergology, University of Würzburg, Josef Schneider Strasse 2, 97080 Würzburg, Germany

^b Department of Dermatology, Venereology, and Allergology, University of Göttingen, Von Siebold Strasse 3, 37075 Göttingen, Germany

* Corresponding author.

E-mail address: trautmann_a@klinik.uni-wuerzburg.de (A. Trautmann).

the authors' studies^{10–13} show that patients with DTH to heparins tolerate intravenous heparin application, however.

PHARMACOLOGY

Heparins are anionic polysaccharides extracted from porcine intestinal mucosa; during the processing process, they are fractionated and depolymerized.¹⁴ Therefore, heparin preparations are not pure substances but a composite of heterogeneous molecules varying in size and chemical structure. For this reason, heparin dose is not recorded in milligrams but in international units (IU). Depending on the average molecular weight, unfractionated high molecular weight heparins (UFH; 12–15 kDa) and LMWHs (4–6 kDa) are distinguished.^{15–17} Anticoagulation capacity depends on anionic charge of carboxy and sulfate groups of the heparin molecule (Fig. 1A). UFH binding to antithrombin leads to inactivation of thrombin and factor Xa, whereas LMWH inhibits factor Xa activity. Like other anionic polysaccharides, UFH unspecifically binds to plasma and tissue macromolecules, resulting in bioavailability of 15% to 30% after subcutaneous application. In contrast, LMWH, such as enoxaparin, reviparin, dalteparin, nadroparin, tinzaparin, and certoparin, has a significantly decreased unspecific binding capacity, resulting in almost 100% bioavailability. Heparins are

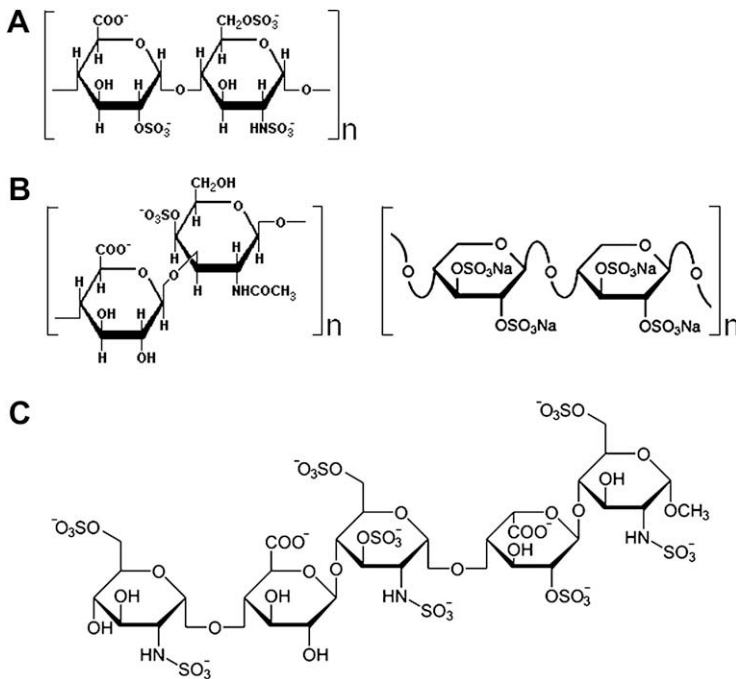


Fig. 1. Chemical structures of anionic polysaccharides. (A) Heparins consist of disaccharide (α -1,4-glycosidic-linked glucosamine and glucuronic acid) subunits that are themselves connected by a α -1,4-glycosidic linkage. Some glucuronic acid components of the polymer are sulfatized. The position of sulfate groups may vary, and a tetrasaccharide unit consists of four to six sulfate moieties. (B) Chondroitin sulfate units are shown on the left, and pentosan polysulfate units are shown on the right. (C) Pentasaccharide fondaparinux differs from heparins by its short saccharide chain selectively blocking factor Xa.

indicated for prophylaxis of thrombosis and for treatment of thromboembolic complications.

Heparinoids are sulfated polysaccharides with antithrombotic effects similar to heparins. Danaparoid (average molecular weight of 6 kDa) is a mixture of heparan sulfate, dermatan sulfate, and chondroitin sulfate (see **Fig. 1B**). Pentosan polysulfate (average molecular weight of 6 kDa) is a semisynthetically produced polysaccharide, derived from pentosan extracted from the bark of the beech tree (see **Fig. 1B**). Although pentosan polysulfate is approved for thrombosis prophylaxis, it is not mentioned in international treatment guidelines.¹⁷

Fondaparinux (average molecular weight of 1.7 kDa) is a chemically synthesized sulfatized pentasaccharide specifically inhibiting factor Xa after binding to anti-thrombin (see **Fig. 1C**).¹⁸ In contrast to heparins and heparinoids, fondaparinux is a chemically defined molecule without unspecific binding characteristics and with fast and complete resorption after subcutaneous injection (100% bioavailability).

Hirudins are polypeptides originally extracted from the leech *Hirudo medicinalis* that function as direct thrombin inhibitors without affecting antithrombin.¹⁹ There are multiple hirudin variants (average molecular weight of 7 kDa). Recently, recombinant hirudins and hirudin variants, such as lepirudin, desirudin, and bivalirudin, were approved as antithrombotic substances.

SYMPTOMS

In case of DTH to subcutaneously applied heparins, itchy erythematous or eczematous plaques develop around injection sites (**Fig. 2A**).^{4-6,20,21} The usual latency for development of characteristic lesions during ongoing therapy is 7 to 10 days; in case of prior sensitization and re-exposure, skin lesions appear within 1 to 3 days.

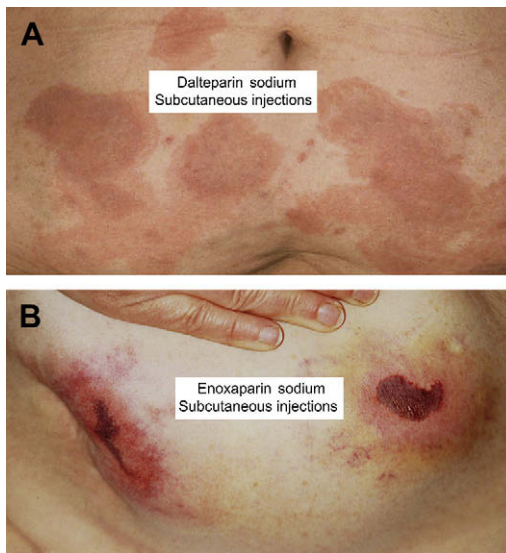


Fig. 2. DTH to subcutaneously applied heparins and heparin-induced skin necrosis. (A) Itchy erythematous and eczematous plaques 12 days after initiation of subcutaneously applied dalteparin. (B) Painful heparin-induced skin necrosis at injection sites 10 days after initiation of subcutaneous enoxaparin injections. (From Gaigl Z, Klein CE, Großmann R, et al. [Managing allergy to heparins]. Dtsch Arztebl 2006;103:2878; with permission.)

The spectrum of skin lesions ranges from mild erythema with little infiltration to typical eczematous plaques with papulovesicles located on an infiltrated erythematous ground. Less frequently, in cases with continuation of subcutaneous injections despite local reactions, a generalized eczema or exanthema with accentuation around injection sites may be observed.^{12,22–25} In early erythematous lesions, histopathologic examination reveals a dense mononuclear infiltrate of predominantly CD4+ lymphocytes with scattered eosinophils. Eczematous lesions additionally show epidermal spongiosis.^{5,6,12,26} These findings are consistent with a DTH reaction of the skin. Potential antigenic determinants of the heparin molecule have not yet been determined, however.

DTH reactions to subcutaneously injected heparin are mostly described in obese women, which is in agreement with findings in the authors' patients.^{11,27} Therefore, gender and obesity seem to be risk factors for the development of DTH to heparin. It is tempting to speculate that hormonal and metabolic influences may play a role in the pathogenesis.²⁸

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of erythematous and eczematous plaques after subcutaneous heparin administration includes hematomas, local infections, and eczema attributable to skin disinfectants.^{7,29} The most important differential diagnosis is heparin-induced skin necrosis, however.

HIT is the most common serious side effect of heparin treatment.³⁰ Patients undergoing hip arthroplasty, thoracic surgery, or coronary artery bypass surgery have a risk of 1% to 5% for developing HIT. Interestingly, UFH has a 10-fold risk for HIT compared with LMWH.³¹ Immune complexes composed of heparin, platelet factor 4, and specific antibodies activate thrombocytes and induce the characteristic decline of thrombocytes of more than 50% or a decrease to a total less than 100,000 thrombocytes/ μ L. In case of HIT, thromboembolic complications occur despite thrombocytopenia (deep vein thrombosis or pulmonary embolism) and arterial thrombosis, leading to ischemia of extremities, cerebrovascular insult, or myocardial infarction (the so-called "white-clot syndrome"). Arterial embolisms are often the result of the false diagnosis of "thrombosis despite anticoagulation," with a subsequent increase in heparin dosage. The usual latency for development of characteristic lesions during ongoing therapy is 5 to 14 days; in case of prior sensitization (exposure to heparins within the past 100 days) and re-exposure, skin lesions appear within 3 to 5 days. Functional assays (serotonin-release test or platelet activation test) and antigen assays (ELISA) may confirm the clinical diagnosis of HIT.³²

Heparin-induced skin necrosis is the cutaneous manifestation of HIT.^{33–36} Typically, painful and mildly infiltrated erythema is followed by a central bullous and necrotic area surrounded by a hemorrhagic rim (see [Fig. 2B](#)). Skin necrosis as a symptom of HIT is not always restricted to heparin application sites but may also occur at distant sites, with a predilection for locations with increased subcutaneous fat tissue, such as mammae, abdomen, buttocks, and thighs. Skin biopsy of typical lesions shows thrombosis of skin vessels without signs of vasculitis. In case of suspected HIT, immediate discontinuation of heparin treatment is required and alternative compounds, such as danaparoid or hirudins, are indicated for treatment of thromboembolic complications.^{37,38} Re-exposure to heparins has to be strictly avoided in the future. Similar clinical and histologic features may be observed for coumarin-induced skin necrosis.^{39–41}

In the beginning of 2008, the Centers for Disease Control and Prevention (CDC) registered a cluster of heparin-associated allergy-like reactions. Among patients

receiving UFH during hemodialysis, reactions included dyspnea, facial edema, urticaria, nausea or vomiting, tachycardia and hypotension, and life-threatening shock. In addition to dermatan sulfate, a known contaminant of heparin, spectroscopy identified oversulfated chondroitin sulfate (OSCS) in tested samples of one heparin manufacturer.⁴² Although chondroitin sulfate is a natural substance derived from animal cartilage, its oversulfated form (ie, OSCS) does not occur naturally. OSCS exerts its effects by activation of the kinin-kallikrein system, leading to generation of bradykinin, and by activation of C3a and C5a, which are potent anaphylatoxins.^{43,44} The contaminated heparin could be traced back to China, where heparins are regularly processed by small and often unregistered plants. Until now, however, it has not been clearly elucidated where the contamination had occurred.

ALLERGOLOGIC WORKUP

Patients referred to the authors' department with suspected DTH to heparins are consecutively subjected to an allergologic workup, including skin tests and subcutaneous challenge tests. In cases in which DTH to heparins is verified, intravenous challenge tests are performed (Fig. 3). As part of the standard practice in the authors' allergy clinic, all patients are informed of any risks involved with the testing and written informed consent for allergologic workup (skin tests and challenge tests) is obtained.

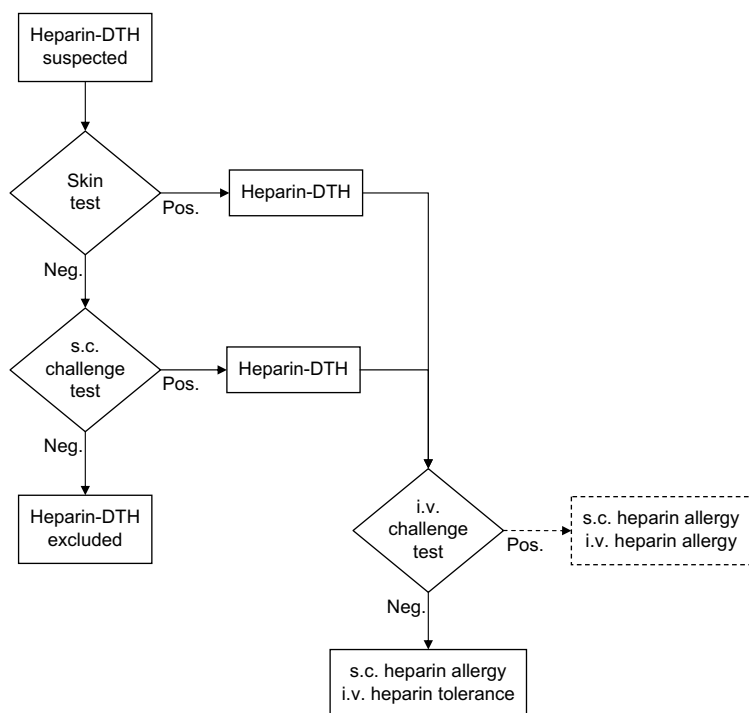


Fig. 3. Recommended steps of the allergologic workup in patients with a history of DTH to subcutaneously injected heparins. The diagnosis in case of a positive intravenous challenge test result is depicted in dotted lines because this has not occurred in our studies, in which all patients tolerated intravenous challenge tests. i.v., intravenous; Pos., positive; Neg., negative; s.c., subcutaneous.

Skin Tests

The authors perform intradermal tests on the volar forearm and patch tests on the back with a panel of heparin and heparinoid preparations, including UFH and the LMWHs nadroparin, dalteparin, and enoxaparin; the heparinoids danaparoid and pentosan polysulfate; and fondaparinux (**Table 1**). For intradermal tests, heparin preparations are used in a 1:10 dilution (using sodium chloride 0.9% solution). Patch tests are performed after tape stripping for better antigen penetration with pure heparin solutions.⁴⁵ Allergologic testing of patients with a panel of different heparin preparations can reveal cross-reactivity among heparins and exclude a causal role of preservatives sometimes added to heparin multidose products, such as sodium metabisulfite, benzyl alcohol, or chlorocresol. Most single-dose heparin products contain salts, acids, or bases for pH adjustment but no preservatives (see **Table 1**). Skin tests are read on days 2, 3, and 4 according to the 1+ to 3+ scoring system recommended by the International Contact Dermatitis Research Group. The 2+ to 3+ reactions can be considered unequivocally positive. In approximately 60% of all cases, crescendo reactions to skin tests develop only after 3 to 4 days. Therefore, skin tests should be read for at least 4 days. In 70% to 80% of all patients, allergy to heparins may be diagnosed by skin tests alone. Frequently, several positive test reactions throughout the panel of UFH and LMWH may be observed. Single negative skin test reactions are usually false-negative, and subsequent subcutaneous challenge usually proves cross-reactivity. Overall, correctly performed skin tests with heparins are safe, and generalized reactions usually do not occur.

Immediate-type reactions may be observed in approximately 10% of intradermal tests despite the 1:10 dilution of testing solutions; in most cases, they are attributable to histamine liberation of heparin, and therefore should not be interpreted naively as proof of an IgE-mediated allergy. Anaphylactic reactions or immediate-type skin test reactions may also be caused by accidental or deliberate contaminants (eg, histamine, OSCS) during the processing of heparins.^{42,43,46}

Subcutaneous Challenge

All challenge tests should be performed and interpreted according to international standards by experienced allergologists.^{47,48} Mandatory is strict adherence to contraindications, side effects, and drug interactions of heparins. In case of negative skin test results, subcutaneous challenge tests of heparins at a therapeutic dosage are indicated. The subcutaneous challenge procedure in the authors' department is performed in an outpatient setting. Reading of the skin injection site is performed on days 2, 3, 4, and 7. In 20% to 30% of patients, diagnosis of DTH to subcutaneously applied heparins can only be established by positive challenge test results.

Allergic hypersensitivity reactions are not "all or none" responses but, instead, present as a spectrum of symptoms depending on the degree of sensitization. This is also the case for heparin allergy, which may be clinically present within a spectrum of symptoms. Patients with a rather low degree of sensitization only develop erythematous plaques around injection sites. In these cases, the results of skin tests may be false-negative, and diagnosis of heparin allergy can only be achieved by positive subcutaneous challenge test results. Strong sensitization presents clinically as a pronounced local eczematous reaction, and continuation of heparin injections in such cases may lead to development of a generalized eczema. Skin tests in these cases usually show at least 2+, and sometimes 3+, reactions.

Table 1
Panel of heparins and heparinoids tested in the authors' allergy clinic

Heparins/Heparinoids	Product	Preservatives, Additives for pH Adjustment
Heparin sodium (UFH)	Heparin-natrium-5000 ratiopharm (ratiopharm, Ulm, Germany)	None
Nadroparin calcium	Fraxiparin-0.3 (GlaxoSmithKline, München, Germany)	Calcium hydroxide, hydrochloric acid
Dalteparin sodium	Fragmin/D (Pharmacia, Karlsruhe, Germany)	Sodium chloride
Enoxaparin sodium	Clexane-40 mg (Sanofi-Aventis, Frankfurt, Germany)	None
Danaparoid sodium	Orgaran (Organon, Oberschleissheim, Germany)	Sodium metabisulfite, sodium chloride, hydrochloric acid
Pentosan polysulfate sodium	Fibrezym (bene Arzneimittel, München, Germany)	Levulinic acid, sodium chloride
Fondaparinux sodium	Arixtra-2.5 mg (GlaxoSmithKline, München, Germany)	Sodium chloride, hydrochloric acid, sodium hydroxide

Intravenous Challenge

In the authors' department, intravenous challenge is a standardized procedure using UFH (5000 IU heparin-natrium/0.5 mL). On day 1, patients receive an intravenously administered bolus of 2500 IU. On day 2, another bolus of 2500 IU is administered, followed by intravenous administration of 7500 IU over a period of 6 hours. A time interval of at least 6 weeks between positive skin test results or positive subcutaneous challenge test results and intravenous challenge tests should be strictly adhered to.

HEPARIN ALLERGY: SUBCUTANEOUS ALLERGY AND INTRAVENOUS TOLERANCE

In case of DTH to subcutaneously injected heparin, intravenous application of this drug theoretically implies the risk for a generalized eczematous reaction. Evidence that intravenous administration of heparin is tolerated despite DTH was previously observed in single patients, however.^{8,10,49,50} In two prospective studies, the authors demonstrated that intravenous administration of heparin was well tolerated without side effects in 64 patients who developed eczema-like infiltrated plaques after subcutaneous injection of heparin.^{11,13} Therefore, intravenous application of heparin is a safe alternative for anticoagulation in these patients. Furthermore, in case of therapeutic necessity, the shift from subcutaneous to intravenous heparin administration without prior tests may be justified even in cases with generalized eczema.¹²

Currently it is unknown, why some patients initialize an immune reaction after subcutaneous application of UFH and LMWH, whereas intravenous administration of heparin is well tolerated. Eczematous plaques after subcutaneously injected heparins are likely real DTH caused by heparin-specific T lymphocytes. Subtle differences in the absorption of heparin from the skin and differential processing or presentation of antigens depending on the route of application may be the responsible factors. In addition to its traditional anticoagulant activity, anti-inflammatory effects of heparin have been described.⁵¹ It has been shown that UFH and, to a lesser extent, LMWH down-regulate L-selectin.⁵² Because L-selectin has a crucial role in lymphocyte homing, this effect may therefore inhibit the migration of activated T cells, preventing clinically obvious inflammation.

In case of premature intravenous challenge tests performed less than 4 to 6 weeks after positive skin testing results, flare-up reactions at previously positive skin testing sites may develop. A single reported case of generalized eczema after intravenous heparin challenge tests may have been attributable to a too short interval between a positive skin test or positive subcutaneous challenge test result and intravenous challenge.⁵³ This observation supports the hypothesis that depot effects may play an important pathogenic role. Alternatively, intravenous heparin administration may activate residual specific T lymphocytes in skin test areas, similar to mechanisms discussed for fixed drug eruptions.

CROSS-REACTIVITY AND ALTERNATIVE ANTICOAGULATION

Typical for DTH against subcutaneously administered heparins is the extensive cross-reactivity between all UFH and LMWH. Potential alternative antithrombotic compounds are the heparinoids danaparoid and pentosan polysulfate.⁵⁴ Heparinoids were initially developed as alternatives in case of antibody-mediated HIT. Although danaparoid indeed shows low cross-reactivity with heparin in terms of heparin-induced antibody binding, it may cross-react with heparin in case of DTH. Heparinoids sometimes have negative skin test results. Most of these test results are false-negative,

however, and in subcutaneous challenge tests, skin lesions also develop after heparinoid application because of cross-reactivity. Tolerance of a single challenge test should also not be overinterpreted. Several of the authors' patients also developed eczematous plaques around injection sites despite an initial negative subcutaneous challenge test result to heparinoids after a longer anticoagulation period and increasing number of heparinoid injections. As already suggested by the chemical structure, cross-reactivity between heparinoids and heparins is quite common.²⁶

Previously, fondaparinux was considered another potential alternative anticoagulant compound.^{55,56} In one of the authors' studies,¹¹ however, positive skin test results with fondaparinux were observed in 6 of 16 patients with DTH to subcutaneously applied heparins. Meanwhile, several studies confirmed that only up to 50% of patients with DTH to subcutaneous heparins tolerate fondaparinux.^{57–60} This is not surprising because fondaparinux is an anionic polysaccharide like heparin; therefore, cross-reactivity develops after continued anticoagulation for a longer period despite initial tolerance of the compound in skin and subcutaneous challenge tests.

Because of their completely different chemical structure, hirudins are the only safe alternative for subcutaneously applied anticoagulation. Available for clinical use are recombinant hirudins, including lepirudin, desirudin, bivalirudin, and other direct thrombin inhibitors, such as argatroban. Because of the lack of antidotes for neutralization, application of these compounds is always associated with increased risk for bleeding complications. Lepirudin is indicated for treatment of thromboembolic complications and HIT.⁶¹ In Germany, desirudin, bivalirudin, and argatroban are only approved for limited indications: desirudin is approved for prophylaxis of deep vein thrombosis after hip and knee replacement surgery, whereas bivalirudin is indicated as an anticoagulant in patients undergoing percutaneous coronary intervention. Argatroban is approved for anticoagulation in patients who have HIT. Despite approval of these new anticoagulants (direct thrombin inhibitors, Xa-inhibitors), heparin remains the medication of first choice, especially for intravenous anticoagulation.¹⁶

CONCLUDING REMARKS

- DTH reactions to subcutaneously injected heparins are relatively common and clinically present as erythematous or eczematous plaques restricted to the injection site. In case of continuation of heparin injections, there is a risk for generalized eczema or exanthema.
- The most important differential diagnosis of DTH to subcutaneous heparins is heparin-induced skin necrosis, the leading cutaneous symptom of HIT.
- For diagnosis of DTH to subcutaneous heparins, a step-by-step allergologic workup, including skin and subcutaneous challenge tests, is a safe procedure with a high predictive value when performed and interpreted by experienced allergologists.
- Extensive cross-reactivity among different heparins is the rule, including all UFH and LMWH preparations of all manufacturers.
- Heparinoids (eg, danaparoid, pentosan polysulfate) or fondaparinux, as anionic polysaccharides, are not suitable alternative substances in most cases. Because of their similar chemical structure, cross-reactivity is likely, especially if prolonged treatment periods are necessary.
- The only safe alternative compounds are thrombin inhibitors (eg, lepirudin, desirudin, bivalirudin). In case of DTH reactions to subcutaneously injected heparin, diagnostic testing of these compounds before application is not necessary.

- In patients with hypersensitivity reactions to subcutaneously injected heparin, intravenous challenge tests usually demonstrate intravenous tolerance. The risk for a generalized reaction after intravenous application appears to be minimal. However, substantial uncertainty still exists as to whether intravenous administration is really safe in all these patients.
- In clinical practice, there is frequently no time for the recommended complex and time-consuming allergologic workup. In case of therapeutic necessity, the shift from subcutaneous to intravenous heparin administration without prior allergologic tests may be justified according to current data.

REFERENCES

1. Harenberg J, Hoffmann U, Huhle G, et al. Cutaneous reactions to anticoagulants. Recognition and management. *Am J Clin Dermatol* 2001;2:69–75.
2. Harr T, Scherer K, Tsakiris DA, et al. Immediate type hypersensitivity to low molecular weight heparins and tolerance of unfractionated heparin and fondaparinux. *Allergy* 2006;61:787–8.
3. Rajka G, Skog E. On the question of heparin hypersensitivity. *Acta Derm Venereol* 1962;42:27–34.
4. Trautmann A, Hamm K, Bröcker EB, et al. [Delayed hypersensitivity to heparins. Clinical signs, diagnosis, therapeutic alternatives]. *Z Hautkr* 1997;72:447–50 [in German].
5. Bircher AJ, Flückiger R, Buchner SA. Eczematous infiltrated plaques to subcutaneous heparin: a type IV allergic reaction. *Br J Dermatol* 1990;123:507–14.
6. Klein GF, Kofler H, Wolf H, et al. Eczema-like, erythematous, infiltrated plaques: a common side effect of subcutaneous heparin therapy. *J Am Acad Dermatol* 1989;21:703–7.
7. Bircher AJ, Harr T, Hohenstein L, et al. Hypersensitivity reactions to anticoagulant drugs: diagnosis and management options. *Allergy* 2006;61:1432–40.
8. Boehncke WH, Weber L, Gall H. Tolerance to intravenous administration of heparin and heparinoid in a patient with delayed-type hypersensitivity to heparins and heparinoids. *Contact Dermatitis* 1996;35:73–5.
9. Irion R, Gall H, Peter RU. Delayed-type hypersensitivity to heparin with tolerance of its intravenous administration. *Contact Dermatitis* 2000;43:249–50.
10. Trautmann A, Bröcker EB, Klein CE. Intravenous challenge with heparins in patients with delayed-type skin reactions after subcutaneous administration of the drug. *Contact Dermatitis* 1998;39:43–4.
11. Gaigl Z, Klein CE, Großmann R, et al. [Managing allergy to heparins]. *Dtsch Arztebl* 2006;103:2877–81 [in German].
12. Seitz CS, Bröcker EB, Trautmann A. Management of allergy to heparins in post-operative care: subcutaneous allergy and intravenous tolerance. *Dermatol Online J* 2008;14(9):4.
13. Gaigl Z, Pfeuffer P, Raith P, et al. Tolerance to intravenous heparin in patients with delayed-type hypersensitivity to heparins: a prospective study. *Br J Haematol* 2005;128:389–92.
14. Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 2001;119:64–94.
15. Blann AD, Landray MJ, Lip GY. ABC of antithrombotic therapy: an overview of antithrombotic therapy. *BMJ* 2002;325:762–5.
16. Hyers TM. Management of venous thromboembolism: past, present, and future. *Arch Intern Med* 2003;163:759–68.

17. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133:381–453.
18. Keam SJ, Goa KL. Fondaparinux sodium. *Drugs* 2002;62:1673–85.
19. Weitz JI, Crowther M. Direct thrombin inhibitors. *Thromb Res* 2002;106:275–84.
20. Guillet G, Delaire P, Plantin P, et al. Eczema as a complication of heparin therapy. *J Am Acad Dermatol* 1989;20:1130–2.
21. Korstanje MJ, Bessems PJ, Hardy E, et al. Delayed-type hypersensitivity reaction to heparin. *Contact Dermatitis* 1989;20:383–4.
22. Kim KH, Lynfield Y. Enoxaparin-induced generalized exanthem. *Cutis* 2003;72:57–60.
23. Patrizi A, DiLernia V, Patrone P. Generalized reaction to subcutaneous heparin. *Contact Dermatitis* 1989;20:309–10.
24. Greiner D, Schöfer H. [Allergic drug exanthema to heparin. Cutaneous reactions to high molecular and fractionated heparin]. *Hautarzt* 1994;45:569–72 [in German].
25. Estrada Rodriguez JL, Gozalo RF, Ortiz U, et al. Generalized eczema induced by nadroparin. *J Investig Allergol Clin Immunol* 2003;13:69–70.
26. Grassegger A, Fritsch P, Reider N. Delayed-type hypersensitivity and cross-reactivity to heparins and danaparoid: a prospective study. *Dermatol Surg* 2001;27:47–52.
27. Mendez J, Sanchis ME, de la Fuente R, et al. Delayed-type hypersensitivity to subcutaneous enoxaparin. *Allergy* 1998;53:999–1003.
28. Kroon C, de Boer A, Kroon JM, et al. Influence of skinfold thickness on heparin absorption. *Lancet* 1991;337:945–6.
29. James RF. Rectus sheath haematoma. *Lancet* 2005;365:1824.
30. Greinacher A, Warkentin TE. Recognition, treatment, and prevention of heparin-induced thrombocytopenia: review and update. *Thromb Res* 2006;118:165–79.
31. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:311–37.
32. Eichler P, Raschke R, Lubenow N, et al. The new ID-heparin/PF4 antibody test for rapid detection of heparin-induced antibodies in comparison with functional and antigenic assays. *Br J Haematol* 2002;116:887–91.
33. Warkentin TE, Roberts RS, Hirsh J, et al. Heparin-induced skin lesions and other unusual sequelae of the heparin-induced thrombocytopenia syndrome: a nested cohort study. *Chest* 2005;127:1857–61.
34. Yates P, Jones S. Heparin skin necrosis—an important indicator of potentially fatal heparin hypersensitivity. *Clin Exp Dermatol* 1993;18:138–41.
35. Shelley WB, Sayen JJ. Heparin necrosis: an anticoagulant-induced cutaneous infarct. *J Am Acad Dermatol* 1982;7:674–7.
36. Balestra B. [Skin necrosis: a paradoxical complication of anticoagulation]. *Schweiz Med Wochenschr* 1995;125:361–4 [in German].
37. Hirsh J, Heddle N, Kelton JG. Treatment of heparin-induced thrombocytopenia: a critical review. *Arch Intern Med* 2004;164:361–9.
38. Alving BM. How I treat heparin-induced thrombocytopenia and thrombosis. *Blood* 2003;101:31–7.
39. Argaud L, Guerin C, Thomas L, et al. Extensive coumarin-induced skin necrosis in a patient with acquired protein C deficiency. *Intensive Care Med* 2001;27:1555.
40. Wattiaux MJ, Herve R, Robert A, et al. Coumarin-induced skin necrosis associated with acquired protein S deficiency and antiphospholipid antibody syndrome. *Arthritis Rheum* 1994;37:1096–100.

41. Bauer KA. Coumarin-induced skin necrosis. *Arch Dermatol* 1993;129:766–8.
42. Guerrini M, Beccati D, Shriver Z, et al. Oversulfated chondroitin sulfate is a contaminant in heparin associated with adverse clinical events. *Nat Biotechnol* 2008;26:669–75.
43. Kishimoto TK, Viswanathan K, Ganguly T, et al. Contaminated heparin associated with adverse clinical events and activation of the contact system. *N Engl J Med* 2008;358:2457–67.
44. Blossom DB, Kallen AJ, Patel PR, et al. Outbreak of adverse reactions associated with contaminated heparin. *N Engl J Med* 2008;359:2674–84.
45. Oldhoff JM, Bihari IC, Knol EF, et al. Atopy patch test in patients with atopic eczema/dermatitis syndrome: comparison of petrolatum and aqueous solution as a vehicle. *Allergy* 2004;59:451–6.
46. Hermann K, Frank G, Ring J. Contamination of heparin by histamine: measurement and characterization by high-performance liquid chromatography and radioimmunoassay. *Allergy* 1994;49:569–72.
47. Demoly P, Bousquet J. Drug allergy diagnosis work up. *Allergy* 2002;57:37–40.
48. Aberer W, Bircher A, Romano A, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003;58:854–63.
49. Liew G, Campbell C, Thursby P. Delayed-type hypersensitivity to subcutaneous heparin with tolerance of i.v. administration. *ANZ J Surg* 2004;74:1020–1.
50. Jappe U, Reinhold D, Bonnekoh B. Arthus reaction to lepirudin, a new recombinant hirudin, and delayed-type hypersensitivity to several heparins and heparinoids, with tolerance to its intravenous administration. *Contact Dermatitis* 2002;46:29–32.
51. Tyrrell DJ, Horne AP, Holme KR, et al. Heparin in inflammation: potential therapeutic applications beyond anticoagulation. *Adv Pharmacol* 1999;46:151–208.
52. Derhaschnig U, Pernerstorfer T, Knechtelsdorfer M, et al. Evaluation of antiinflammatory and antiadhesive effects of heparins in human endotoxemia. *Crit Care Med* 2003;31:1108–12.
53. Schiffner R, Glassl A, Landthaler M, et al. Tolerance of desirudin in a patient with generalized eczema after intravenous challenge with heparin and a delayed-type skin reaction to high and low molecular weight heparins and heparinoids. *Contact Dermatitis* 2000;42:49.
54. Lindhoff-Last E, Kreutzenbeck HJ, Magnani HN. Treatment of 51 pregnancies with danaparoid because of heparin intolerance. *Thromb Haemost* 2005;93:63–9.
55. Ludwig RJ, Beier C, Lindhoff-Last E, et al. Tolerance of fondaparinux in a patient allergic to heparins and other glycosaminoglycans. *Contact Dermatitis* 2003;49:158–9.
56. Ludwig RJ, Schindewolf M, Alban S, et al. Molecular weight determines the frequency of delayed type hypersensitivity reactions to heparin and synthetic oligosaccharides. *Thromb Haemost* 2005;94:1265–9.
57. Utikal J, Peitsch WK, Booken D, et al. Hypersensitivity to the pentasaccharide fondaparinux in patients with delayed-type heparin allergy. *Thromb Haemost* 2005;94:895–6.
58. Hirsch K, Ludwig RJ, Lindhoff-Last E, et al. Intolerance of fondaparinux in a patient allergic to heparins. *Contact Dermatitis* 2004;50:383–4.
59. Hohenstein E, Tsakiris D, Bircher AJ. Delayed-type hypersensitivity to the ultra-low-molecular-weight heparin fondaparinux. *Contact Dermatitis* 2004;51:149–51.
60. Maetzke J, Hinrichs R, Staib G, et al. Fondaparinux as a novel therapeutic alternative in a patient with heparin allergy. *Allergy* 2004;59:237–8.
61. Kam PC, Kaur N, Thong CL. Direct thrombin inhibitors: pharmacology and clinical relevance. *Anaesthesia* 2005;60:565–74.