

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/6716806>

Management of cutaneous type IV hypersensitivity reactions induced by heparin

Article in *Thrombosis and Haemostasis* · December 2006

DOI: 10.1160/TH06-04-0210 · Source: PubMed

CITATIONS

35

READS

451

5 authors, including:



Ralf Joachim Ludwig

Universitätsklinikum Schleswig - Holstein

345 PUBLICATIONS 4,912 CITATIONS

[SEE PROFILE](#)



Marc Schindewolf

University Hospital Frankfurt

62 PUBLICATIONS 696 CITATIONS

[SEE PROFILE](#)



Jochen Utikal

German Cancer Research Center

365 PUBLICATIONS 11,265 CITATIONS

[SEE PROFILE](#)



Edelgard Lindhoff-Last

Goethe-Universität Frankfurt am Main

144 PUBLICATIONS 2,958 CITATIONS

[SEE PROFILE](#)

Some of the authors of this publication are also working on these related projects:



Lipids and PAD [View project](#)



Inducing pluripotency by small molecules [View project](#)

Review Article

Management of cutaneous type IV hypersensitivity reactions induced by heparin

Ralf J. Ludwig^{1,2}, Marc Schindewolf³, Jochen Utikal⁴, Edelgard Lindhoff-Last³, Wolf-Henning Boehncke¹

¹Department of Dermatology, Clinic of the J. W. Goethe University, Frankfurt am Main, Germany; ²pharmazentrum frankfurt / ZAFES, Clinic of the J. W. Goethe University, Frankfurt am Main, Germany; ³Department of Internal Medicine (Division of Vascular Medicine), Clinic of the J. W. Goethe University, Frankfurt am Main, Germany; ⁴Department of Dermatology, Venerology and Allergology, University Medical Center Mannheim, Ruprecht-Karl University Heidelberg, Mannheim, Germany

Summary

Localized hypersensitivity reactions to subcutaneous heparin injections have been described since 1952. Yet, the incidence of these reactions, which are distinct from skin lesions associated with heparin-induced thrombocytopenia type II (HIT II), remains uncertain. However, in the last 10 years an increasing number of patients have been reported, leading to the assumption that cutaneous hypersensitivity reactions towards heparin are underreported. Clinically patients present with itching, sometimes infiltrated, and blistering erythemas at the injection sites of heparins. The diagnosis of cutaneous heparin allergy may, on the one hand, lead to delay of required medical or surgical treatment. On the other hand, delayed initiation of treatment may lead to a gen-

eralized eczematous reaction. Hence, from review of 223 cases of patients with cutaneous hypersensitivity reactions to heparin, we here summarize the clinical picture of cutaneous type IV allergic reactions, define risk factors on both the patient- and drug-side, and give an overview of principle therapeutic alternatives, as well as recommendations for treatment options for emergency and elective patients. As the proposed management of patients with cutaneous hypersensitivity reactions to heparin may have fatal consequences when applied in patients with HIT type II, diagnosis of skin lesions in heparin-treated patients needs to be precise.

Keywords

Heparin, inflammation, pharmacology, allergy

Thromb Haemost 2006; 96: ■■■■

Introduction

Heparin¹ was introduced into clinical practice as an anticoagulant over 60 years ago, and has a long history for treatment / prophylaxis of thromboembolic diseases (1). It belongs to the class of glycosaminoglycans, which are polysaccharides widespread in vertebrates, including humans. Heparin itself is not antigenic and thus not capable of leading to sensitization – and subsequent cutaneous type IV allergic reactions. However, polyvalent anions such as heparin bind to proteins (2). As known from heparin-induced thrombocytopenia type II (HIT II), heparin-protein-complexes can lead to the formation of neoepitopes, whereby the

chain length of the heparin molecule plays an important role (2, 3). Cutaneous hypersensitivity (CHS) reactions have been noticed as early as in 1952 by Plancherel (4). However, for the next 20 years no new cases were reported. In contrast, over the last 10 years an increasing number of reports on patients with type IV CHS reactions were published. Still, the incidence of heparin-induced CHS reactions is currently not known but believed to be underreported (5–10). This assumption may be sustained by the increasing numbers of patients with CHS reactions towards heparin being reported in the literature (Fig. 1). To address this issue more concisely, a PubMed search with the keywords “heparin”, “allergy” and “skin” was performed on January 17th, 2006. From

Correspondence to:
Ralf J. Ludwig, MD
Department of Dermatology
Clinic of the Johann Wolfgang Goethe-University
Theodor-Stern-Kai 7, D-60590 Frankfurt am Main, Germany
Tel.: +49 69 6301 6162, Fax +49 69 6301 7139
E-mail: r.ludwig@em.uni-frankfurt.de

Footnotes:
¹In this manuscript the term “heparin” refers to both unfractionated heparin (UFH) and low-molecular-weight heparins (LMWH).

²Only those publications which clearly documented sensitization towards heparin by prick- patch- or i.c. in-vivo tests, or histological verification of CHS were included. Those, merely describing “skin lesions” after heparin administration or reporting “skin lesions” in the setting of immune heparin-induced thrombocytopenia were excluded from the analysis.

Received April 14, 2006
Accepted after resubmission September 6, 2006

Republished online ■■ doi:10.1160/TH06-084-0210

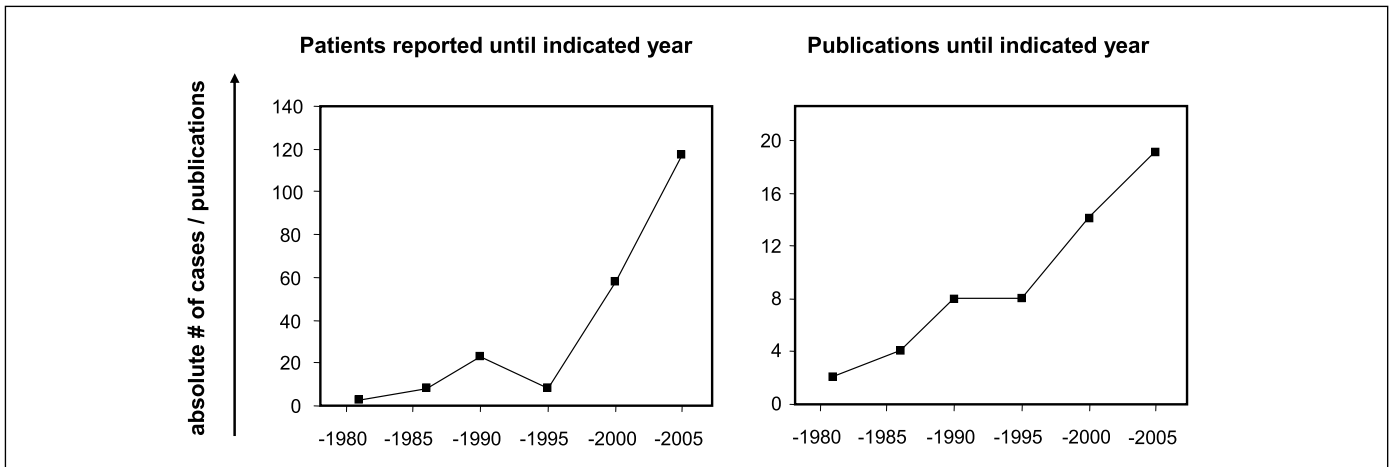


Figure 1: Patients with cutaneous hypersensitivity (CHS) reactions towards heparin reported in the literature. On January 17th, 2006, a PubMed search with the keywords “heparin”, “allergy” and “skin” was performed. From 181 publications those dealing with heparin induced cutaneous type IV allergic reactions were selected. In addition, references from selected publications were screened for additional publications. Overall, 56 papers were selected. In summary, 223 patients with CHS reactions towards heparin have been published. As shown, the number of reported patients, as well as the number of publications have dramatically increased over the last years. However, it remains uncertain, whether this is due to an increased awareness or a true raise in incidence.

181 publications, those dealing with heparin-induced cutaneous type IV allergic reactions² were selected. In addition, references from selected publications were screened for additional publications. Overall, 56 papers were selected. In total, 223 patients with heparin induced CHS reactions have been published (Fig. 1, see Supplementary Table online at www.thrombosis-online.com). The fact that known or newly diagnosed cutaneous heparin allergy may lead to a delay of required medical or surgical treatment is a challenging difficulty. Proper management of patients with cutaneous allergic reactions towards heparin will aid to avoid these obstacles. Hence, in this review we summarize the clinical presentation of cutaneous type IV allergic reactions, de-

fine risk factors on both the patient- and drug-side, give an overview of principle therapeutic alternatives, as well as recommendations for treatment options for emergency and elective patients.

Clinical aspects of heparin induced cutaneous type IV allergic reactions

Clinical picture

Clinically patients present with itching, sometimes infiltrated, and blistering erythemas at the injection sites of heparins (5–7, 11, 12). The size of individual lesions may vary, ranging from



Figure 2: Clinical presentation of cutaneous heparin-hypersensitivity reactions. a) Single, small erythematous plaque with few papulovesicles at the lower abdomen after subcutaneous challenge with a therapeutic dose of fondaparinux four days before. b) Multiple large and diffusely demarcated erythematous plaques with papulovesicles and scaling on the leg of a patient after repeated exposure to danaparoid. (Image is taken from 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)

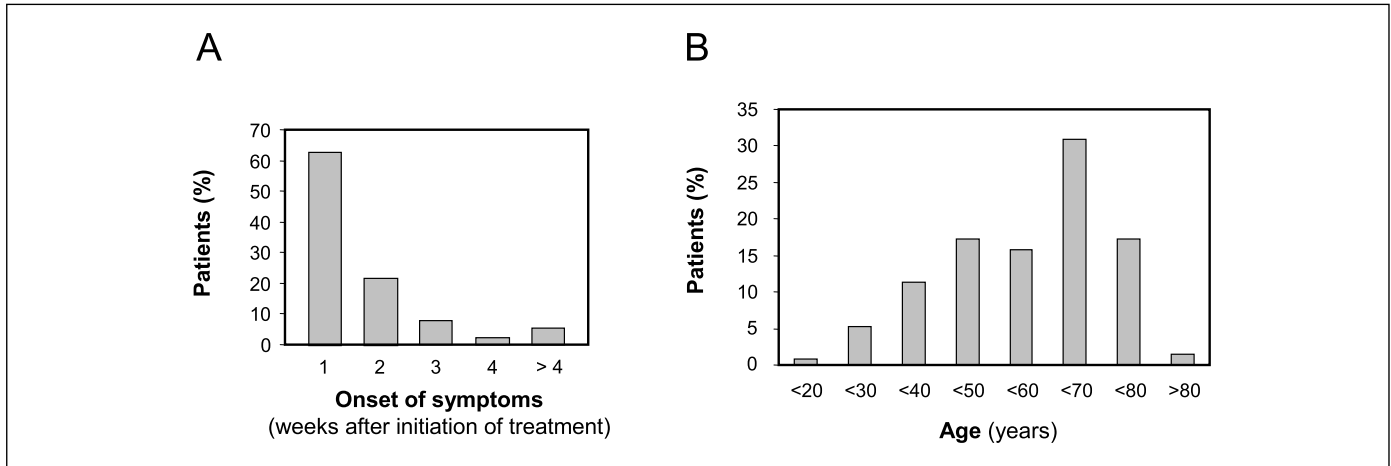


Figure 3: Onset of symptoms after initiation of heparin therapy and age distribution at diagnosis. A) Data on the onset of symptoms was available for 114 patients. In the vast majority, cutaneous hypersensitivity (CHS) responses were observed within the first week after initiation of subcutaneous anticoagulant treatment. Among these patients symptoms usually occurred between days 2 and 4 of heparin application (see Supplementary Table online at www.thrombosis-online.com). Hence, most of patients presenting with CHS responses towards heparin are already sensitized. In the remaining patients, sensitization is achieved rather rapidly: Of all patients presenting with cutaneous hyper-

sensitivity reactions to heparin after the first week of treatment, the majority of eczematous lesions was observed two weeks after initiation of anticoagulant treatment. Seldom, lesions are observed at later time points; with one patient developing itchy plaques at injection sites five months after continuous sandoparin therapy (24). B) In the evaluated publications, age was specified for 133 patients. In these, the average age at diagnosis was 56 ± 15 years (mean $\pm$ SD). The majority of patients was aged between 60 and 69 years. In addition, heparin cutaneous hypersensitivity is only seldom observed before the age of 40.

very small to rather large lesions (Fig. 2). Seldom, generalized eczematous reactions may result (13–15). If a biopsy is obtained, histological examination reveals epidermal spongiosis and edema with a lymphocytic infiltrate, accompanied by numerous eosinophils in the papillary dermis (6). However, obtaining a punch biopsy for diagnosis is not routinely required – usually CHS reactions toward heparin are diagnosed based on the history and clinical presentation of the patient. In some occasions, especially those where lesions are present as erythemas only and not localized at the injection sites, obtaining a biopsy may be helpful to distinguish between CHS reactions and heparin-induced skin reactions (e.g. erythemas and/or necrosis), which can be associated with HIT II (16). To differentiate between those two different diseases is of utmost importance, as treatment options (see below) for heparin-induced CHS are of potential great risk for patients with HIT-associated cutaneous reactions.

Time course of CHS reactions towards heparin

Most CHS reactions to heparin are noticed within one week after initiation of anticoagulant treatment (6, 11, 17, 18). In a second group of patients (19–23), heparin allergy is observed after weeks of repetitive subcutaneous injections of the drugs (Fig. 3A). These two peaks in onset of the disease most likely reflect the fact that patients with prompt reactions are already sensitized to heparin. This assumption is sustained by the fact that symptoms in this cohort of patients mostly developed within three days of subcutaneous (s.c.) heparin treatment. Whereas patients with a late onset of cutaneous allergic reactions to heparin become sensitized during the treatment period. From the data reviewed, sensitization in most patients occurs within the first two weeks of heparin treatment; however, sometimes it may take as long as five months (24). These differences may be due to the he-

parin preparation used. Yet, there is currently not enough data available to sustain this hypothesis. If treated accordingly (omission of the respective heparin preparation and application of topical steroids if desired), lesions usually resolve within a week.

Risk factors for development of type IV heparin allergy

From review of the literature, two groups of risk factors can be identified (Table 1): First, patient-related – and second, risk factors related to the different heparin preparations. On the patient side, the most predominant risk factor for development of an adverse CHS responses towards subcutaneous injected heparin is female sex – 92.5% of all 212 reported patients in which sex was specified were female (see Supplementary Table online at www.thrombosis-online.com). This gender imbalance is far greater compared to the increased female gender in HIT, which is approximately 1.5 – 2.0 : 1 according to a recent publication (25). The disease also develops more often in the elderly (Fig. 3B), with over 65% of patients being older than 50 years and an average age at diagnosis of 56 ± 15 years [mean $\pm$ standard error

Table 1: Risk factors for development of cutaneous hypersensitivity reactions to heparin. Likely, but not proven risk factors are marked with a “?”.

Risk factors on patient's side	Risk factors on the drug's side
Female sex	Increasing molecular weight
Older age	
Pregnancy	
Prolonged exposure to heparin (?)	
Obesity (?)	

(SD)]. Younger patients developing a CHS reaction towards heparin are mostly pregnant – 47.8% of all 23 patients in this age group and 61.1% of all 18 patients, where the indication for heparin treatment was stated, were pregnant (see Supplementary Table online at www.thrombosis-online.com). This fact may indicate that hormonal factors are important for generation of protein-heparin complexes, which are presented as allergens, in the skin. Another explanation for the relatively high prevalence of cutaneous heparin-hypersensitivity reactions in pregnancy might be the long exposure to the drug. However, this issue remains to be investigated in future clinical trials. Obesity has also been implied to be a risk factor. However, only a minority patients with CHS reactions towards heparin have been reported to be overweight (22, 26–30). As obesity was not stated for the remaining majority of patients, it remains uncertain if obesity is a risk factor for development of cutaneous type IV allergic reactions towards heparin.

In addition, the heparin preparation used also has a great influence on the elicitation of cutaneous type IV allergic reactions. A recent study from our group has identified molecular weight as an important determinant for sensitisation towards different heparin preparations. In this study we plotted the molecular weight of anticoagulants (UFH, tinzaparin, nadroparin, certoparin, enoxaparin, dalteparin, danaparoid and fondaparinux) to the cumulative degree of sensitization towards these preparations, as determined by allergologic work-up in 12 patients with CHS reactions toward heparin. A strong correlation of these two parameters was observed. In contrast, the degree of sulfation did not correlate with the cumulative degree of sensitization towards the heparins. Hence, molecular weight determined the frequency of CHS reactions to heparin and synthetic oligosaccharides (5). These findings are in accordance with data published by Lane (2), who showed that heparin binding to proteins increases with

the molecular weight of the heparin, which is a prerequisite for heparin to become a possible allergen (2, 3, 9).

Management of patients with CHS reactions towards heparin

If a cutaneous reaction under heparin is observed, immune heparin-induced thrombocytopenia with associated skin lesions needs to be ruled out clinically (16) and by appropriate laboratory investigations for HIT, which include measurement of platelet count, comparison with recent previous values (to detect new-onset thrombocytopenia that begins five or more days after starting heparin) and detection of pathogenic platelet-activating anti-platelet factor 4/heparin (PF4/heparin) antibodies using either heparin-dependent platelet activation assays or anti-PF4/heparin immunoassays (31, 32). In some patients, obtaining a skin biopsy for differentiation of HIT-associated skin lesions and allergic reactions may be required (especially at the onset of symptoms), which in most cases can clearly distinguish between the two diseases – even between heparin-induced CHS and the erythematous stage of HIT-associated skin lesions (M. Wolter, Department of Dermatology, Clinic of the J. W. Goethe University, Frankfurt, Germany – personal communication). Histopathologically, in heparin-induced skin lesions a dermal vascular occlusion secondary to microvascular platelet–fibrin plugs, or „white clots“ can be observed. In developed lesions the overlying epidermis shows ischemic necrosis. In contrast, histological examination of heparin-hypersensitivity reactions reveals epidermal spongiosis, dermal oedema and a lymphocytic infiltrate, accompanied with numerous eosinophils in the papillary dermis (6). After diagnosis of heparin-induced CHS reaction is established, a number of therapeutic alternatives can be offered to

Table 2: Properties of alternative anticoagulants.

Anticoagulant	Advantage(s)	Disadvantage(s)	Recommendation
UFH i.v.	– reliable anticoagulation – inexpensive – short half-life	– handling (i.v. infusion) – HIT-antibody testing has to be negative	– First choice in emergency if HIT-associated skin lesions are excluded and HIT-antibodies can not be detected
Lepirudin or Desirudin	– s.c. injection possible (off-label use) – no crossreactivity with heparin – no crossreactivity concerning HIT – short half-life	– antibody formation – fatal anaphylactic reactions possible – expensive – accumulation in renal insufficiency	– emergency patients, esp. if HIT-antibody testing is not possible – alternatively in elective patients
Danaparoid	– s.c. injection possible	– 3% crossreactivity (HIT) – up to over 40% cross-reactivity (CHS) – long half-life – expensive	– emergency patients, esp. if HIT-antibody testing is not possible – Elective patients after negative in i.c. and challenge tests
Argatroban	– no crossreactivity (HIT) – no crossreactivity (CHS) – short half-life	– s.c. injection not possible – expensive – accumulation in liver dysfunction	– Emergency patients, esp. if HIT-antibody testing is not possible – Alternatively in elective patients
Fondaparinux	– save – s.c. injection possible – no crossreactivity (HIT)	– crossreactivity with heparins (CHS) < 10 % – long half-life – no prospective trials in HIT-patients available	– Elective patients after negative in i.c. and challenge tests
Pentosanpolysulfate	– s.c. injection possible	– crossreactivity with heparins	– Elective patients after negative in i.c. and challenge tests

these patients. These options differ with regard to safety and practical issues, which are detailed below (Table 2).

Emergency patients

In emergencies, where continuous anticoagulation is required, intravenous injection of UFH or administration of lepirudin are the only current alternatives which can be offered to patients. The first case of tolerance of intravenous (i.v.) heparin despite eczematous reaction to subcutaneous (s.c.) injected heparin was published in 1991 by Koch et al. (20). The authors describe a 67-year-old patient with proven type IV sensitisation to heparin, who required heparin treatment during surgery for worsening coronary heart disease. The patient tolerated i.v.-heparin treatment without any side effects. As the patient additionally received methylprednisolone and clemastine, it can not be ruled out that a possible cutaneous reaction was suppressed by the later medication. Yet, subsequently evidence has accumulated from several case reports that i.v. heparin treatment is tolerated despite CHS responses towards subcutaneous injected heparin (22–33, 34). A recent prospective clinical trial, which included 28 patients with proven CHS towards a wide range of heparin preparations, has now clearly shown that i.v. heparin is well tolerated by these patients. No systemic or cutaneous reactions were observed after i.v. challenge with UFH during a three-day follow-up period (35). I.v. heparin administration may therefore be the anticoagulant of choice in emergency cases for patients with CHS responses towards heparin. We favor this approach over lepirudin. The thrombin inhibitor lepirudin is a recombinant non-human protein and was the first approved anticoagulant not cross-reacting with HIT antibodies (36). However, for several reasons, we only regard lepirudin as an alternative to i.v. heparin in patients with CHS towards heparin: In contrast to heparin, lepirudin itself may be antigenic. This is reflected by the high incidence of anti-hirudin antibodies in patients receiving lepirudin for longer periods of time (37–39). In addition, type I (40–43) and type IV (44, 45) cutaneous reactions to lepirudin or hirudin have been observed; with even fatal anaphylactic reactions being described (41). However, to put the risk of anaphylaxis caused by lepirudin into perspective, the risk of severe anaphylactic reactions is 0.015% on first treatment and 0.16% in re-exposed patients (41). Therefore, i.v.-heparin application should only be performed when HIT-antibody testing revealed a negative result. If HIT can not be ruled out or if HIT-antibodies are present, lepirudin, danaparoid or argatroban can be used as alternative anticoagulants. Fondaparinux may be a further option (Table 2). However, in contrast to the situation in HIT, in which danaparoid and (likely) fondaparinux can be administered by s.c. or i.v. route with very low risk of inducing in-vivo cross-reactivity, in heparin-induced CHS, cross-reactivity rates resulting from s.c. administration of fondaparinux and danaparoid have been observed to be as high as 16.7% and 45.9%, respectively (5, 7).

Elective patients

As a once- or twice-daily s.c. application is far more practical than continuous i.v. infusion (especially in an outpatient setting), the above mentioned alternatives are less applicable for elective patients. Patients with a known CHS response to heparin who will have to undergo elective therapy should be tested for alter-

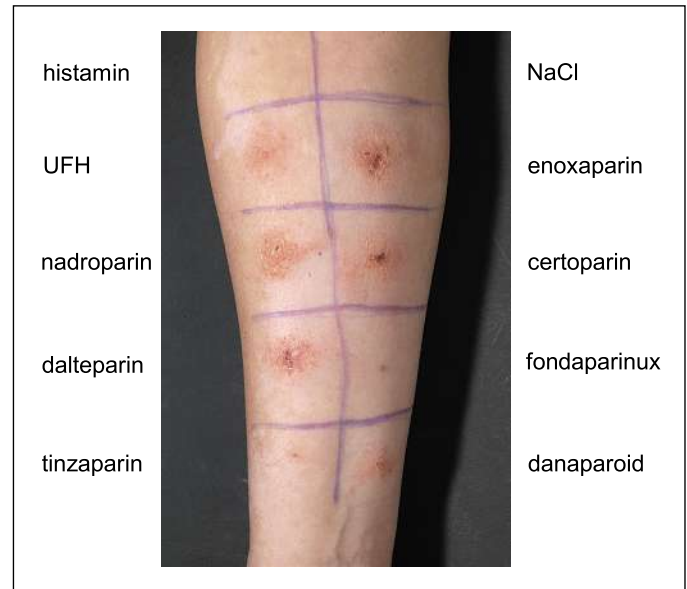


Figure 4: Example of test results from intracutaneous testing of heparin preparations. Forearm of a patient four days after intracutaneous application of indicated substances. Severe, blistering responses can be observed in sites exposed with nadroparin and enoxaparin. Only histamine, NaCl, fondaparinux and tinzaparin yielded negative results. However, after subcutaneous challenge with therapeutic doses of either tinzaparin or fondaparinux, an eczematous lesion developed within four days.

natives before the treatment – or ideally 6–8 weeks after clearance of eczematous lesions at heparin injection sites. Without prior allergy test, no anticoagulant should be given to these patients, as a high cross-reactivity with other heparin preparations (6, 12, 46, 47), as well as heparinoids (5–7, 22, 48), has been observed. For validation of CHS response towards a certain heparin preparation, as well as testing for alternative anticoagulants, intracutaneous application of undiluted anticoagulants, followed by subcutaneous challenge of negatively tested substances at a single therapeutic dose, is the most sensitive method (5, 7, 9, 30). Development of eczematous lesions at test sites (Fig. 4) should be monitored 24, 48, 96 and 120 hours after application. To increase specificity, negatively tested anticoagulants should then be injected s.c., and injection sites monitored for occurrence of eczematous lesions (10). Relatively often, immediate type reactions are observed; as these also develop frequently in healthy controls (49, 50), they should be regarded as an unspecific reaction – unless the patient has a history of type I reactions after s.c. heparin application. Prick- or epicutaneous tests with heparin preparations only seldomly show a positive reaction, and hence are of low specificity (5, 7, 24).

Recent attention has focused on the pentasaccharide fondaparinux (Table 2), which mimics the heparin antithrombin binding site, as the drug has repeatedly been reported to be well tolerated by patients with cutaneous heparin-hypersensitivity reactions (21, 27, 51, 52). However, evidence is now accumulating that some patients can mount CHS responses towards fondaparinux as well (5, 7, 10, 11, 53). Nonetheless, compared to heparins, these are only rarely observed for the pentasaccharide (5, 7, 21, 54).

Perspective

The advent of more specific inhibitors of the coagulation cascade, e.g. direct thrombin- or factor Xa inhibitors (55) may provide additional alternatives for patients with cutaneous type IV allergic reactions to heparin for several reasons: First, they are chemically different from heparin. Hence, crossreactivity is very unlikely to occur. Second, several of these substances which currently are under development / evaluated in clinical trials are orally active (55), avoiding the s.c. application route.

One should keep in mind, however, that heparins possess many properties beyond anticoagulation, e.g. inhibition of inflammation (56, 57) and metastatic spread (58–61) mediated by

numerous activities (62). Similar to the differences observed regarding the sensitization potential of individual heparin preparations (5), these activities are independent of the anticoagulant properties (63, 64). We therefore propose that different heparins should be regarded as individual drugs and that anticoagulant therapy should be based on the individual activity profile of the anticoagulant preparation. In case of patients with CHS responses to heparin, i.v. UFH or s.c. fondaparinux are currently the most appropriate therapeutic alternatives.

References

- Alban S. From heparins to factor Xa inhibitors and beyond. *Eur J Clin Invest* 2005; 35 (Suppl 1): 12–20.
- Lane DA. Heparin binding and neutralizing proteins. In: Heparin. London: Edward Arnold, 1989: 363–91.
- Alban S, Greinacher A. Role of sulfated polysaccharides in the pathogenesis of heparin-induced thrombocytopenia. In: Heparin-induced thrombocytopenia. New York: Marcel Dekker, 2004: 197–221.
- Plancherel P. Klinische und gerinnungsphysiologische Untersuchungen mit einem neuem Heparindepotpräparat. *Z Klin Med* 1952; 150: 213–59.
- 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.
- 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.
- Utkal J, Peitsch WK, Bookin D, et al. Hypersensitivity to the pentasaccharide fondaparinux in patients with delayed-type heparin allergy. *Thromb Haemost* 2005; 94: 895–6.
- 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.
- Bircher AJ. Allergische Reaktionen vom Spättyp auf Heparine. *Allergologie* 1993; 16: 268–74.
- Hirsch K, Ludwig RJ, Lindhoff-Last E, et al. Intolerance of fondaparinux in a patient allergic to heparins. *Contact Dermatitis* 2004; 6: 383–4.
- Jappe U, Juschka U, Kuner N, et al. Fondaparinux: a suitable alternative in cases of delayed-type allergy to heparins and semisynthetic heparinoids? A study of 7 cases. *Contact Dermatitis* 2004; 51: 67–72.
- Koch P, Munssinger T, Rupp-John C, et al. Delayed-type hypersensitivity skin reactions caused by subcutaneous unfractionated and low-molecular-weight heparins: tolerance of a new recombinant hirudin. *J Am Acad Dermatol* 2000; 42: 612–9.
- Greiner D, Schöfer H. Allergic drug exanthema to heparin. Cutaneous reactions to high molecular and fractionated heparin. *Hautarzt* 1994; 45: 569–72.
- Figarella I, Barbaud A, Lecompte T, et al. Cutaneous delayed hypersensitivity reactions to heparins and heparinoids. *Ann Dermatol Venereol* 2001; 128: 25–30.
- Patrizi A, Di L, V, Patrone P. Generalized reaction to subcutaneous heparin. *Contact Dermatitis* 1989; 20: 309–10.
- Harenberg J, Hoffmann U, Huhle G, et al. Cutaneous reactions to anticoagulants. Recognition and management. *Am J Clin Dermatol* 2001; 2: 69–75.
- Mora A, Belchi J, Contreras L, Rubio G. Delayed-type hypersensitivity skin reactions to low molecular weight heparins in a pregnant woman. *Contact Dermatitis* 2002; 47: 177–8.
- Erdmann S, Hertl M, Merk HF. Spättypreaktionen auf Heparine und Heparinoide – Hirudin als therapeutische Alternative. *Z Hautkrank* 1998; 7/8: 505–10.
- Tosti A, De Padova MP, Patrizi A, et al. Unusual reaction to subcutaneous heparin. *Contact Dermatitis* 1985; 13: 190.
- Koch P, Bahmer FA, Schafer H. Tolerance of intravenous low-molecular-weight heparin after eczematous reaction to subcutaneous heparin. *Contact Dermatitis* 1991; 25: 205–6.
- Koch P, Hindi S, Landwehr D. Delayed allergic skin reactions due to subcutaneous heparin-calcium, enoxaparin-sodium, pentosan polysulfate and acute skin lesions from systemic sodium-heparin. *Contact Dermatitis* 1996; 34: 156–8.
- 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.
- Mendez J, Sanchis ME, de la FR, et al. Delayed-type hypersensitivity to subcutaneous enoxaparin. *Allergy* 1998; 53: 999–1003.
- Bircher AJ, Itin PH, Tsakiris DA, et al. Delayed hypersensitivity to one low-molecular-weight heparin with tolerance of other low-molecular-weight heparins. *Br J Dermatol* 1995; 132: 461–3.
- Warkentin TE, Sheppard JA, Sigouin CS, et al. Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. *Blood* 2006; Epub ahead of print (PMID: 16857993).
- Bircher AJ, Fluckiger R, Buchner SA. Eczematous infiltrated plaques to subcutaneous heparin: a type IV allergic reaction. *Br J Dermatol* 1990; 123: 507–14.
- 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.
- Moreau A, Domp Martin A, Esnault P, et al. Delayed hypersensitivity at the injection sites of a low-molecular-weight heparin. *Contact Dermatitis* 1996; 34: 31–4.
- Szolar-Platzter C, Aberer W, Kranke B. Delayed-type skin reaction to the heparin-alternative danaparoid. *J Am Acad Dermatol* 2000; 43: 920–2.
- Trautmann A, Hamm K, Bröcker EB, et al. Spättyp-Allergie gegen Heparin. *Z Hautkrank* 1997; 6: 447–50.
- Greinacher A, Warkentin TE. Recognition, treatment, and prevention of heparin-induced thrombocytopenia: Review and update. *Thromb Res* 2006; 118: 165–76.
- Warkentin TE. New approaches to the diagnosis of heparin-induced thrombocytopenia. *Chest* 2005; 127 (2 Suppl): 35S–45S.
- Trautmann A, Brocker 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.
- 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.
- 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.
- Greinacher A, Lubenow N. Recombinant hirudin in clinical practice: Focus on lepirudin. *Circulation* 2001; 103: 1479–84.
- Song X, Huhle G, Wang L, et al. Generation of anti-hirudin antibodies in heparin-induced thrombocytopenic patients treated with r-hirudin. *Circulation* 1999; 100: 1528–32.
- Huhle G, Hoffmann U, Song X, et al. Immunologic response to recombinant hirudin in HIT type II patients during long-term treatment. *Br J Haematol* 1999; 106: 195–201.
- Eichler P, Friesen HJ, Lubenow N, et al. Antihirudin antibodies in patients with heparin-induced thrombocytopenia treated with lepirudin: incidence, effects on aPTT, and clinical relevance. *Blood* 2000; 96: 2373–8.
- Badger NO, Butler K, Hallman LC. Excessive anticoagulation and anaphylactic reaction after rechallenge with lepirudin in a patient with heparin-induced thrombocytopenia. *Pharmacotherapy* 2004; 24: 1800–3.
- Greinacher A, Lubenow N, Eichler P. Anaphylactic and anaphylactoid reactions associated with lepirudin in patients with heparin-induced thrombocytopenia. *Circulation* 2003; 108: 2062–5.
- Bircher AJ, Czendlik CH, Messmer SL, et al. Acute urticaria caused by subcutaneous recombinant hirudin: evidence for an IgG-mediated hypersensitivity reaction. *J Allergy Clin Immunol* 1996; 98: 994–6.
- Harenberg J, Huhle G, Wang L, et al. Association of heparin-induced skin lesions, intracutaneous tests, and heparin-induced IgG. *Allergy* 1999; 54: 473–7.

44. Smith KJ, Rosario-Collazo J, Skelton H. Delayed cutaneous hypersensitivity reactions to hirudin. *Arch Pathol Lab Med* 2001; 125: 1585–7.
45. Zollner TM, Gall H, Volpel H, et al. Type IV allergy to natural hirudin confirmed by in vitro stimulation with recombinant hirudin. *Contact Dermatitis* 1996; 35: 59–60.
46. Bank I, Libourel EJ, Middeldorp S, et al. High rate of skin complications due to low-molecular-weight heparins in pregnant women. *J Thromb Haemost* 2003; 1: 859–61.
47. Borch JE, Bindslev-Jensen C. Delayed-type hypersensitivity to heparins. *Allergy* 2004; 59: 118–9.
48. Bauer KA. Fondaparinux sodium: a selective inhibitor of factor Xa. *Am J Health Syst Pharm* 2001; 58 (Suppl 2): S14–S17.
49. Korstanje MJ, Bessems PJ, Hardy E, et al. Delayed-type hypersensitivity reaction to heparin. *Contact Dermatitis* 1989; 20: 383–4.
50. Koch P, Schäfer H, Bahmer F. Allergische Hautreaktionen gegen Standard- und niedermolekulare Heparine. *Z Hautkrank* 1991; 66: 435.
51. Sacher C, Hunzelmann N. Tolerance to the synthetic pentasaccharide fondaparinux in heparin sensitization. *Allergy* 2003; 58: 1318–9.
52. 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.
53. Hohenstein E, Tsakiris D, Bircher AJ. Delayed-type hypersensitivity to the ultra-low-molecular-weight heparin fondaparinux. *Contact Dermatitis* 2004; 51: 149–51.
54. Poza-Guedes P, Gonzalez-Perez R, Canto G. Different patterns of cross-reactivity in non-immediate hypersensitivity to heparins: from localized to systemic reactions. *Contact Dermatitis* 2002; 47: 244–5.
55. Bauer KA. New anticoagulants: Anti IIa vs anti Xa—Is one better? *J Thromb Thrombolysis* 2006; 21: 67–72.
56. Bowler SD, Smith SM, Lavercombe PS. Heparin inhibits the immediate response to antigen in the skin and lungs of allergic subjects. *Am Rev Respir Dis* 1993; 147: 160–3.
57. Vancheri C, Mastruzzo C, Armato F, et al. Intranasal heparin reduces eosinophil recruitment after nasal allergen challenge in patients with allergic rhinitis. *J Allergy Clin Immunol* 2001; 108: 703–8.
58. Altinbas M, Coskun HS, Er O, et al. A randomized clinical trial of combination chemotherapy with and without low-molecular-weight heparin in small cell lung cancer. *J Thromb Haemost* 2004; 2: 1266–71.
59. Kakkar AK, Levine MN, Kadziola Z, et al. Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS). *J Clin Oncol* 4 A.D.; 10: 1948.
60. Lebeau B, Chastang C, Brechot JM, et al. Subcutaneous heparin treatment increases survival in small cell lung cancer. „Petites Cellules“ Group. *Cancer* 1994; 74: 38–45.
61. Lemoine NR. Antithrombotic therapy in cancer. *J Clin Oncol* 2005; 23: 2119–20.
62. Zacharski LR, Ornstein DL. Heparin and cancer. *Thromb Haemost* 1998; 80: 10–23.
63. Ludwig RJ, Alban S, Bislian R, et al. The ability of different forms of heparins to suppress P-selectin function in vitro correlates to their inhibitory capacity on blood-borne metastasis *in vivo*. *Thromb Haemost* 2006; 95: 535–40.
64. Stevenson JL, Choi SH, Varki A. Differential metastasis inhibition by clinically relevant levels of heparins—correlation with selectin inhibition, not anti-thrombotic activity. *Clin Cancer Res* 2005; 11: 7003–11.