Short communication

Association of heparin-induced skin lesions, intracutaneous tests, and heparin-induced IgG

J. Harenberg
G. Huhle
L. Wang
U. Hoffmann
Ch. Bayerl
M. Kerowgan

Authors' affiliations:
J. Harenberg, G. Huhle, L. Wang, U. Hoffmann, Department of Medicine, Faculty of Clinical Medicine, University of Heidelberg, Heidelberg, Germany
Ch. Bayerl, Department of Dermatology and Venereology, Faculty of Clinical Medicine, University of Heidelberg, Heidelberg, Germany
M. Kerowgan, Institute of Blood Transfusion, Faculty of Clinical Medicine, University of Heidelberg, Heidelberg, Germany

Correspondence to:
J. Harenberg, MD
Professor of Medicine
University Hospital Mannheim
I. Department of Medicine
Faculty of Clinical Medicine
Ruprecht-Karls-University Heidelberg
University of Heidelberg
Theodor-Kutzer-Ufer
68167 Mannheim
Germany

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Key words: danaparoid; heparin allergy; intracutaneous test; low-molecular-weight heparin; r-hirudin.

Background: Cutaneous heparin-induced allergic reactions to subcutaneous heparin may begin 2–5 days after administration. The relation of the delayed-type hypersensitivity and a systemic immunologic response is controversial. The present investigation aimed to analyze the occurrence of thromboembolic complication, pathologic heparin-induced platelet activation (HIPA), and the presence of circulating heparin-induced IgG in patients with heparin-induced skin reactions.

Methods: Intracutaneous tests, HIPA assay, and heparin-heparin IgG antibodies were performed in nine patients with heparin-induced skin lesions.

Results: Six of eight patients showed positive intracutaneous tests to heparin and to four low-molecular-weight heparins. Three of six heparin-positive patients presented hypersensitivity to a heparinoid, too. Two of three patients had a positive HIPA test and elevated heparin-induced IgG antibodies. Both patients developed complications presenting as heparin-induced skin necrosis or arterial thrombosis. Two of nine patients were treated with danaparoid, 4/9 patients received r-hirudin, and 1/9 received oral coumarin. In 2/9 patients, anticoagulant therapy was stopped, but these patients will receive r-hirudin if indicated.

Conclusions: On the basis of the coincidence of local and systemic hyperreactivity to heparin and danaparoid, patients with heparin-induced skin lesions should receive r-hirudin, a nonheparin compound, for anticoagulant treatment.

For more than 50 years, heparin has been used in the prophylaxis and treatment of thromboembolism; more recently, low-molecular-weight (LMW) heparins have been used. One of the rare but clinically relevant side-effects is

Table 1. Initials of patients, consecutive number (*n*), sex, age (years), skin lesions and compound inducing skin lesions of patients, and results of HIPA-test and heparin-induced IgG assay are given

Initials	*n*/sex/ age (years)	skin lesion	Compound	HIPA	HI-IgG
EA	1/F/70	Red plaques	UFH, LMWH	–	–
YF	2/F/62	Red plaques	UFH, LMWH, danaparoid	–	–
EM	3/F/67	Red plaques	UFH, LMWH, danaparoid	+	–
SJ	4/F/70	Red plaques	UFH, LMWH	+	+
StH	5/F/59	Red plaques	Heparinoid	–	–
WM	6/F/66	Red plaques	UFH, LMWH	–	–
WU	7/F/43	Skin necrosis	UFH, LMWH	+	+
MF	8/F/78	Red plaques	UFH, LMWH	–	–
MG	9/F/72	Red plaques	UFH, LMWH, danaparoid	–	–

UFH: unfractionated heparin; LMWH: low-molecular-weight heparin.

the heparin-induced skin lesions which follow subcutaneous injection. About 100 cases of heparin-induced skin lesions have been reported in the literature so far (1, 2). Local allergy has been reported also to LMW heparin (3) and heparinoid (4).

Some patients developed thrombocytopenia without or with thromboembolic complication; i.e., heparin-induced thrombocytopenia (HIT) type II. In other reports, cutaneous necrosis following subcutaneous heparin has also been observed, whereas necrosis to subcutaneous LMW heparin occurred only in a few patients. Cutaneous necrosis was observed once, distant from the injection site of unfractionated subcutaneous heparin. Surprisingly, subcutaneous LMW heparin was successfully used without side-effects in patients with heparin-induced skin necrosis (5).

The heparin-induced skin lesions present as painful red plaques or as skin necrosis around the injection sites. The reactions may begin 2–5 days after the onset of therapy. Only some of these patients developed thrombocytopenia and thrombosis together with heparin-dependent, platelet-activating IgG (1). In the group of patients with cutaneous allergic reactions to intracutaneous heparin, tests were positive to heparin and LMW heparin, but not to danaparoid (1).

Hirudin is a protein containing 65–66 amino acids with a molecular mass of about 7 kDa. It is secreted by the salivary glands of the leech *Hirudo medicinalis* and is characterized as a specific, tight-binding thrombin inhibitor. Today, hirudin is produced by recombinant DNA technology in sufficient amounts and is used for anticoagulant and antithrombotic therapy. Successful anticoagulation and treatment of patients with heparin-induced thrombocytopenia and thrombosis (HIT type II) was reported with intravenous r-hirudin (6). This therapy may offer effective and safe anticoagulation also in patients with heparin-induced allergic skin reactions. In the present paper, we describe an association of heparin-induced skin lesions with delayed-type hyperreactivity in intracutaneous tests to heparin, LMW heparins, and danaparoid, and circulating antibodies to heparin-platelet factor 4 and HIT type II.

Material and methods

Nine patients with heparin-induced skin lesions were studied between 1994 and 1997. Heparin-induced skin lesions had to meet the following criteria (1):

1) occurrence within 5 days of subcutaneous heparin injection
2) localization of lesions at the sites of heparin injection
3) appearance either of erythematous plaques or necrosis.

These appearances were regarded as typical of the diagnosis of heparin-induced skin reaction as described previously, without requiring histopathologic examination (1). Skin biopsies for immunologic research were not accepted by the ethics committee. At 3–9 days after onset of the clinical symptoms, intracutaneous tests were performed with unfractionated heparin (Hofmann La Roche, Basel, Switzerland), LMW heparins Dalteparin (Pharmacia & Upjohn, Erlangen, Germany), Nadroparin (Sanofi Winthrop, Munich, Germany), Reviparin (Knoll BASF, Ludwigshafen, Germany), Certoparin (Novartis Pharma, Nuremberg, Germany), and the heparinoid Danaparoid (Organon BV, Oss, The Netherlands), except in the patient with skin necrosis. The skin prick test was performed in the patients using anticoagulants. If the test was negative, the intracutaneous testing used undiluted anticoagulants. Positive and negative testing was done in every patient with histamine diluted 1:1000 and 1:10 000 and physiologic saline (Allergopharma, Hamburg, Germany), respectively. The cutaneous reactions to the allergens were observed at 15 min and after 1–5 days at daily intervals and were documented photographically. After having given informed consent, three healthy persons without history of allergic reactions were subjected to intracutaneous tests using the same protocol as for the patients. r-Hirudin was not included among the test reagents, because skin sensitization has not

Table 2. Results of intracutaneous tests after 5 days. Results were divided into positive and negative reactions to allergen

Patient no.	Heparin	LMWH1	LMWH2	LMWH3	LMWH4	Danaparoid	Therapy
1	+	+	+	+	+	–	Danaparoid
2	+	+	+	+	+	–	r-Hirudin
3	–	–	–	–	–	–	r-Hirudin
4	+	+	+	+	+	+	r-Hirudin
5	+	+	+	+	+	+	No anticoagulation
6	–	–	–	–	–	–	Phenprocoumon
7	nd	nd	nd	nd	nd	nd	No anticoagulation
8	+	+	+	+	+	–	Danaparoid
9	+	+	+	+	+	+	r-Hirudin

LMWH1: Certoparin; LMWH2: Dalteparin; LMWH3: Nadroparin; LMWH4: Reviparin; nd: not done, due to heparin-induced skin necrosis.

been reported in the Buehler guinea pig model (4) or in the large clinical trials in myocardial infarction or unstable angina.

Heparin-induced platelet activation assay (HIPA) was performed as described previously (7). Heparin-induced IgG was purified from serum of patients and quantified as reported recently (8).

Results

The biographic data and the kinds of heparin which induced the skin lesion are given in Table 1. Seven patients developed red plaques and one patient skin necrosis within 3 days of subcutaneous heparin and LMW heparin. One patient presented local hypersensitivity to a heparinoid-containing ointment (Bayer AG, Leverkusen, Germany).



Figure 1. Positive intracutaneous tests to unfractionated heparin (calciparin), low-molecular-weight heparins, and danaparoid (orgaran) of patient no. 5.

The prick test was negative in all patients and healthy persons. For the intracutaneous tests, histamine showed positive and physiologic saline negative results in all patients and healthy persons. After 15 min, no patient and no healthy person had a positive intracutaneous reaction to heparin, LMW heparin, or danaparoid. Table 2 reports the results of the intracutaneous tests of the patients 5 days after application of the test compounds. The patient with heparin-induced skin necrosis was not subjected to intracutaneous testing. Six of the eight remaining patients developed hyperreactivity to heparin and the four LMW heparins. Three of six patients with positive intracutaneous test to heparins demonstrated hypersensitivity also to danaparoid. Typical positive intracutaneous tests to all heparins and danaparoid are given in Fig. 1.

The results of the HIPA and the heparin-induced IgG assay are given in Table 1. Three of nine patients had positive results in the HIPA assay. Two of three HIPA-positive patients showed elevated heparin-induced IgG titers. Both patients also developed complications upon heparin administration; i.e., skin necrosis (patient no. 7) and heparin-induced arterial thrombosis (no. 4) without decrease of platelet count.

The further anticoagulant therapy of the two patients with systemic complications from heparin was decided as follows. In the patient with skin necrosis (no. 7), the operation was canceled. One patient with hyperreactivity to heparin, LMW heparin, and danaparoid (no. 4) developed arterial thrombosis and was treated with intravenous r-hirudin. Three patients (nos. 2, 3, and 9) developed skin lesions to subcutaneously administered heparin, LMW heparin, and danaparoid and were treated with r-hirudin. One patient (no. 6) received phenprocoumon for further

anticoagulation. Two of nine patients (nos. 1 and 8) had negative intracutaneous tests for danaparoid and were treated with this anticoagulant. Two of nine patients had no further indication for anticoagulant treatment (nos. 5 and 7).

The dosage for the intravenous administration of r-hirudin was 0.1 mg/kg body weight as bolus and as continuous infusion/h (nos. 2, 3, 4, and 9). Thereafter, treatment was switched to 2×25 mg r-hirudin subcutaneously, followed by oral anticoagulation (no. 4). During intravenous administration of r-hirudin, aPTT was prolonged by 1.5–2-fold. Subcutaneous administration of 2×25 mg r-hirudin prolonged aPTT by 1.2–1.5-fold and ecarin clotting time by 1.5–2.5-fold. A dose of 3×750 IU danaparoid (nos. 1 and 8) resulted in an antifactor Xa inhibition of 0.2–0.4 IU/ml 3–4 h after subcutaneous administration. In all patients, r-hirudin and danaparoid were well tolerated.

Discussion

The incidence of heparin-induced thrombocytopenia without thrombosis (HIT type I) was in the range 1–30%, and with thrombotic complications (HIT type II), 0.1–2.0% (1, 6). HIT type II is an immunologic reaction involving binding of heparin to platelet factor 4 (H-PF4). This neoantigen induces the production of IgG, IgM, or IgA antibodies. HIT type I has only minor clinical relevance and is due to direct platelet activation by heparin (9). In patients with heparin-induced skin lesions, Warkentin observed a high frequency of elevated IgG titers, suggesting an immunologic mechanism also in these patients (1). The present results indicate that systemic complications such as thrombosis or skin necrosis occur rather frequently in patients with heparin-induced cutaneous lesions. In postoperative treatment, thrombocytopenia, together with thrombosis and positive heparin-induced antibodies, may occur in about 3% of patients. The data of the present report indicate that the incidence of HIT type II may be as high as 22% (2/9) in patients with heparin-induced skin lesions.

As demonstrated by the intracutaneous tests, allergic reactions are directed to unfractionated heparin as well as to LMW heparins. Delayed hypersensitivity also to danaparoid was observed in more than 50% of patients. Danaparoid contains about 5% heparin, and this content may be responsible for the positive intracutaneous test results.

The present investigations were designed to identify the coincidence of heparin-induced skin lesions; delayed hyperreactivity to LMW heparins and danaparoid in intracutaneous tests; and the occurrence of positive HIPA assays, heparin-induced IgG, and clinical complications such as thrombosis or skin necrosis. We observed that most patients with heparin-induced skin lesions had a positive intracutaneous test to heparin. All patients with a positive intracutaneous test to heparin demonstrated delayed hyperreactivity to various LMW heparins. Of these patients, 50% also had hypersensitivity to danaparoid, a heparinoid containing 5% heparin. Altogether, in about 80% (7/9) of patients with heparin-induced skin lesions, one or more of the dermatologic or laboratory tests were positive. This indicates an involvement of the immunologic system in the development of heparin-induced skin reactions and the usefulness of these tests for the therapeutic management of the patients.

Apparently, three constellations occur in different patients. There are patients with positive intracutaneous tests, positive HIPA, and positive HI-IgG antibodies; patients with positive intracutaneous tests, negative HIPA, and negative HI-IgG antibodies; and patients with positive skin reaction but negative tests. These various constellations may be caused by differences in the underlying mechanisms, an explanation which is supported by the courses of the diseases of the patients. The positive HIPA and/or HI-IgG antibodies indicate an activation of the immunologic system with a high probability of developing a HIT type II complication. The positive intracutaneous tests without systemic IgG-antibody production may result from local complement or histamine activation and require therapeutic alternatives, preferentially r-hirudin. The third group of patients may also have developed the local cutaneous reaction to nonheparin compounds, such as the metal of the needle or a contaminant.

In the present study, we determined circulating antibodies against platelets with the HIPA assay and measurement of heparin-induced IgG. Two of three patients with a positive HIPA assay demonstrated also circulating heparin-induced IgG complexes. These two patients developed cutaneous necrosis or arterial thrombosis as systemic complications. According to these observations, in about one-fourth of patients with heparin-induced skin lesions, the immunologic system is activated, produces IgG, and is accompanied by heparin-induced complications such as thromboembolism or skin necrosis. In addition, skin tests for delayed-type hyperreactivity to heparins are necessary in patients with heparin-induced skin reactions to eliminate the allergen from further treatment. Our data do not prove that LMW heparin can be given safely to patients with cutaneous reactions to unfractionated heparins.

In summary, the present paper describes a high association of heparin-induced skin lesions with hyperreactivity to LMW heparins and danaparoid in intracutaneous tests, circulating antiheparin IgG antibodies, and HIT type II. The few patients with heparin-induced skin reaction and negative intracutaneous tests to danaparoid may be treated with this anticoagulant. Most patients with heparin-induced skin lesions also show hyperreactivity to danaparoid, are at high risk of developing thrombotic complications, and need r-hirudin for further anticoagulation.

Note

After submission of this paper, two additional patients with heparin-induced skin lesions; positive intracutaneous test to heparins, LMW heparins, and danaparoid; and negative HIPA and HI-IgG results were treated with r-hirudin.

References

1. Warkentin TE. Heparin-induced skin lesions. *Br J Haematol* 1996;**92**:494–497.
2. Trautmann A, Hamm K, Bröcher EB, Klein CE. Spättyp-Allergie gegen Heparin. *Z Hautkr H & G* 1997;**72**:447–450.
3. Phillips JK, Majumdar G, Hunt BJ, Savidge GF. Heparin-induced skin reaction due to two different preparations of low molecular weight heparin (LMWH). *Br J Haematol* 1993;**84**:349–350.
4. Hunzelmann N, Gold H, Scharfetter-Kochanek K. Concomitant sensitization to high and low-molecular-weight heparins, heparinoid and pentosampolysulfate. *Contact Dermatitis* 1998;**39**:88–89.
5. Drakos P, Uziely B, Nagler A, Gillis S, Eldor A. Successful administration of low-molecular-weight heparin in a patient with heparin-induced thrombocytopenia and coumarin-induced skin necrosis. *Haemostasis* 1993;**23**:259–262.
6. Harenberg J, Huhle G, Piazolo L, Wang LC, Heene DL. Anticoagulation with heparin-induced thrombocytopenia type II. *Semin Thromb Hemost* 1997;**23**:189–195.
7. Amiral J, Bridey F, Dreyfus M, et al. Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocytopenia. *Thromb Haemost* 1992;**68**:95–96.
8. Wang LC, Malsch R, Huhle G, Harenberg J. Quantitative detection of heparin-induced IgG in heparin-induced thrombocytopenia and cross-reactivity with low molecular weight heparin and danaparoid. *J Immunol Methods* 1999;**222**:93–99.
9. Pouplard C, Amiral J, Borg JY, Vissac AM, Delahousse B, Gruel Y. Differences in specificity of heparin-dependent antibodies developed in heparin-induced thrombocytopenia and consequences on cross-reactivity with danaparoid sodium. *Br J Haematol* 1997;**99**:273–280.