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Adverse Skin Reactions to Low Molecular Weight Heparins

Frequency, Management and Prevention

Robert Wütschert, Pierre Piletta and *Henri Bounameaux*

University Hospital of Geneva, Geneva, Switzerland

Contents

Abstract

Adverse skin reactions to low molecular weight heparins (LMWH) are rare even though their true incidence is probably underestimated because of underreporting. These reactions may occur as an urticarial rash, presumably due to local histamine release or have the features of a classic type I immediate hypersensitivity reaction. They can also present as skin necrosis often due to vasculitis (type III Arthus reaction) or heparin-induced thrombocytopenia. Erythematous, well circumscribed lesions without necrosis are usually secondary to a delayed type IV hypersensitivity reaction.

Although most LMWH-induced skin lesions are benign, treatment should be discontinued. In type I reactions or in the presence of skin necrosis with or without heparin-induced thrombocytopenia, the LMWH should be replaced by an alternative medication such as danaparoid sodium or hirudin. Platelet counts should be monitored to diagnose heparin-induced thrombocytopenia. In a type IV delayed hypersensitivity reaction, in the absence of severe, extensive, life-threatening mucocutaneous manifestations, a first-line pragmatic approach consists, in our view, of replacing the particular LMWH with another one. If the skin symptoms do not improve, cutaneous tests may help detect the presence of a cross-

reactivity between the available preparations of LMWHs and danaparoid sodium. In the presence of a negative subcutaneous provocation test, the compound can be used with little risk. If all types of LMWH and danaparoid sodium are positive in skin testing, mechanical prevention or oral anticoagulants should be used, and intravenous injections of any kind of heparin should be avoided because of the potential risk of anaphylactic shock. Alternatively, hirudin might be administered but experience with this compound is still very limited.

Prevention is only possible in type IV hypersensitivity skin reactions, by avoiding long term LMWH therapy, particularly in middle-aged, obese women and during pregnancy. In these patients, oral anticoagulation should be preferred, whenever possible.

In conclusion, though rare, skin reactions to LMWH may have important consequences which can be reduced by rapid diagnosis and appropriate management.

Low molecular weight heparin (LMWH) fractions were developed in the late 1970s after the elucidation of heparin's structure and the identification of the pentasaccharide as being its minimal active fragment. In fact, LMWHs are prepared from unfractionated heparin (UFH) which is a heterogenous mixture of linear polysaccharide chains with variable molecular weight and biological activity.[1] The advantages of LMWHs include a more predictable anticoagulant response, an improved bioavailability, and a longer half-life.[2]

The first large scale trial on the thromboprophylactic effects of LMWHs was published by Kakkar and Murray in 1985.[3] More recently, they have proven to be well tolerated and effective in the treatment of venous thromboembolism. Since the last decade, their use has become widespread in most European countries, but they have only recently begun to be used in the US.[2]

The major adverse effect of UFH is bleeding, with a rate of major bleeding of 2 to 4% for a 5- to 10-day treatment course in thromboembolic disease.[4] This rate seems to be lower with LMWHs.[5] Other adverse effects include heparin-induced thrombocytopenia, osteoporosis, hypoaldosteronism, alopecia and skin reactions. Generally speaking, adverse effects are less frequent with LMWHs than with UFH, probably because of the smaller size of the molecules, the greater homogeneity of the substance, and the exclusive porcine origin of the new compounds.

In this review, we will focus on skin reactions of LMWHs. To achieve this goal, we performed a computerised literature search (up to December 1997) followed by a manual search in order to include all case reports describing a LMWH-induced skin lesion. Different types of reactions have been documented. They may occur: (i) as an urticarial rash, presumably due to local histamine release; (ii) as a classic type I immediate hypersensitivity reaction; (iii) as skin necrosis, often caused by vasculitis (type III Arthus reaction) or heparin-induced thrombocytopenia; or, (iv) as a type IV delayed hypersensitivity reaction.[6]

Skin reactions to heparin were first described by Plancherel in 1952[7] and were repeatedly reported over the past 40 years. Their frequency is estimated to be 0.2%.[8] In 1987, Cordoliani et al.[9] were the first group to report a patient with a skin reaction due to a LMWH,[9] and we found only 32 further case reports which mentioned this rare skin reaction. Severe complications such as skin necrosis are certainly very rare: Fried et al.[10] surveyed approximately 8000 subcutaneous injections of enoxaparin sodium, one of the first marketed LMWHs, at a dosage of 40 mg/day, administered in their institution over a 2-year period, and they observed only 2 cases of skin necrosis.[10] However, the incidence of mild LMWH-skin reactions

is probably underestimated because of underreporting.

1. Type I Immediate Hypersensitivity Reactions

Reactions suggestive of immunoglobulin (Ig) E-mediated hypersensitivity (e.g. rhinitis, conjunctivitis, asthma, urticaria, angioedema and anaphylaxis) were reported shortly after the introduction of heparin in clinical medicine[11] and have been reviewed by Bernstein in 1956[12] and Rajka and Skog in 1962.[13] At those times, patients also experienced fever with chills suggestive of a immune complex hypersensitivity reaction (type III). These reactions may have resulted from sensitivity to contaminant proteins in the commercial heparins of that era. In the last 2 decades, reports of immediate-type hypersensitivity reactions to heparin have become exceedingly rare, probably in part because of improved purification procedures and a trend towards shorter treatment courses. Some reports have attributed the reactions of UFH to preservatives (chlorocresol, chlorbutol, mercuriothiolate, benzyl alcohol and parabens).[14-16]

Commercial LMWHs do not contain any preservatives, however, and are well purified. Thus, we could only find one case report describing an immediate type hypersensitivity reaction in a 67-year-old woman, without history of allergy, who was given enoxaparin sodium 20 mg/day for thrombosis prophylaxis and developed widespread urticaria and angioedema 3 days later. Symptoms resolved after stopping enoxaparin sodium. No rechallenge with a LMWH was performed.[17]

2. Skin Necrosis

O'Toole in 1973,[18] was the first to describe skin necrosis at subcutaneous UFH injections sites,

Table I. Description of patients with skin necrosis caused by low molecular weight heparins (LMWH)

Author	Localisation	LMWH preparation	Daily doses (IU)	Delay (days)	Gender	Age	Previous heparin exposure
Cordoliani et al.[9]	*In situ* + distant	Nadroparin calcium	3075	10	F	54	No
Monserrat et al.[27]	*In situ*	Dalteparin sodium	5000	10	M	61	No
Ojeda et al.[28]	*In situ*	Nadroparin calcium	3075	5	F	68	No
Balestra et al.[29]	Distant	Dalteparin sodium	2500	7	F	87	No
Koch et al.[30]	*In situ*	Enoxaparin sodium	4000	10	F	48	Yes (UFH)
Real et al.,[31] Grau et al.[32]	*In situ*	Dalteparin sodium	150/kg	8	M	68	Yes (UFH)
Fried & Kahanovich[10]	*In situ*	Enoxaparin sodium	4000	6	F	59	No
	In situ	Enoxaparin sodium	4000	10	F	34	No
Vonderweidt[22]	*In situ*	Enoxaparin sodium	2000	5	M	66	Yes (UFH & LMWH)
	In situ	Enoxaparin sodium	4000	6	M	77	Yes (UFH)
Lefebvre[33]	Distant	Enoxaparin sodium	2000	7	F	87	No
Plath et al.[34]	*In situ*	Certoparin sodium	5000	8	F	71	Yes (UFH)
Tonn et al.[35]	*In situ*	Enoxaparin sodium	NA	<15	F	43	Yes (UFH)

F = female; **M** = male; **NA** = not available; **UFH** = unfractionated heparin.

occurring after 5 to 9 days of treatment.[18] Since then, more than 30 other cases have been reported in the English literature.[19] Skin necrosis was also observed at locations distant from the site of subcutaneous heparin injection,[20] or after intravenous heparin therapy.[21]

Several pathophysiological mechanisms have been proposed:[22] (i) heparin-induced thrombocytopenia, which is triggered by the binding of antibodies to a platelet-heparin complex, leading to platelet activation and aggregation;[23] (ii) vasculitis induced by type III hypersensitivity reaction (Arthus phenomenon with deposit of immune complexes on endothelial structures); (iii) local trauma at injection sites; (iv) poor vascularisation of adipose tissue inducing a diminished absorption of heparin, as seen in diabetic lipodystrophy. Clinically, the lesions are usually located at injection sites, with well circumscribed, erythematous infiltrated plaques, often accompanied by pruritus. The lesions may rapidly become haemorrhagic and necrotic which can result in deep skin necrosis. These cutaneous lesions are clinically very similar to warfarin-induced skin necrosis, although these lesions differ from each other from a pathological point of view.[19]

The major systemic complications related to skin necrosis are similar to those found in heparin-induced thrombocytopenia, with multiple venous and arterial thromboses which can lead to a fatal outcome.[24] In the absence of thrombocytopenia, only few distant organ complications such as glomerulonephritis[25] have been described.

The incidence of heparin-induced skin necrosis should theoretically have decreased with the use of LMWH as did the incidence of heparin-induced thrombocytopenia.[26] Nevertheless, in the literature we identified 13 patients who presented with this severe adverse effect (table I). All commonly used preparations of LMWH were involved in skin necrosis. As with UFH, skin necrosis is usually located at subcutaneous injections sites, but in 3 cases, distant trophic lesions were also observed. Skin necrosis develops after the same delay with LMWH and UFH and this delay does not seem to be shortened by a previous administration of UFH. Middle-aged women appear to be more prone to this rare but feared complication.

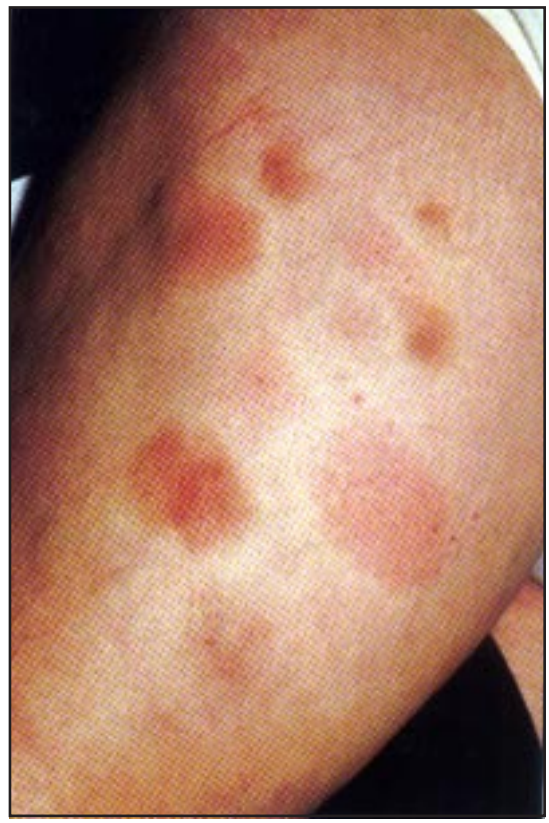

Fig. 1. Typical, well circumscribed erythematous skin lesions at the site of a subcutaneous low molecular weight heparin injection caused by a delayed hypersensitivity reaction.

3. Delayed Type IV Skin Reactions

Delayed hypersensitivity reactions at the injection site of heparin was first reported by Plancherel in 1952.[7] Up to May 1995, almost 60 cases had been published, mainly in women who were obese (female to male ratio: 10 : 1).[36,37] Erythematous, well circumscribed skin lesions develop at the site of subcutaneous injection, approximately 10 days after initiation of treatment (fig. 1). However, clinicians must be aware that the timing of skin necrosis and delayed type IV reactions are very similar. Rarely, the lesions appear as late as several

months after the beginning of heparin administration.[38]

The surface reaction depends on the anatomical level of injections, with deep injections resulting in erythematous swelling, and more superficial injections causing a dermoepidermal response with vesicles and occasionally bullaes.[39] General reactions, such as fever, generalised exanthema and 'baboon syndrome' have been reported when treatment was pursued with subcutaneous injections of UFH.[40] To our knowledge, no life-threatening mucocutaneous reactions, such as erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis (Lyell's syndrome) have ever been ascribed to any kind of heparin. Differential diagnosis includes haematoma, infection, contact allergy to antiseptics or preservatives,[41] and cutaneous signs of thrombosis associated with heparin-induced thrombocytopenia, which may begin as erythematous plaques before progressing to skin necrosis.[38] As described in sections 4.1 to 4.3, histology, immunochemistry and cutaneous tests support the hypothesis of a delayed hypersensitivity type IV reaction. Whereas glycosaminoglycans have been shown to induce humeral immune responses, this kind of delayed hypersensitivity reaction occurs only after attachment to peptides or proteins, because of the carbohydrate nature of heparin. Therefore, Klein et al.[42] consider binding of heparin molecules to unknown dermal or subcutaneous structures as a prerequisite for the formation of erythematous, infiltrated plaques. Because of the striking predominance of women among affected people, it has been suggested that the hormonal status may trigger this binding, or be involved in the pathogenesis of erythematous plaques.

18 cases of delayed hypersensitivity skin lesions due to LMWH have been reported so far (table II). We excluded cases in patients who had a known allergy to UFH along with a positive response to subcutaneous provocation tests with LMWH from this series. All cases, but one, were in women, generally in the postmenopausal period. Those who were less than 40 years old were either pregnant or in the postpartum period, except one.[44] These findings further support the hypothesis of an hormonal influence on the pathogenesis of the delayed hypersensitivity skin reaction to LMWH. About half of the patients had a previous history of allergy to UFH, which should be investigated before starting a treatment with LMWH, especially in women who are pregnant. All types of LMWH can induce a delayed type IV skin reaction, even at prophylactic dosages. In the vast majority of patients, the reactions are limited to the injections sites. However, in 3 cases, they were accompanied by a maculopapular rash.

4. Diagnosis

4.1 Histology

In heparin-induced skin necrosis, biopsy usually reveals epidermal and dermal necrosis with numerous intravascular thrombi in the superficial dermis, accompanied sometimes by signs of leucocytoclastic vasculitis. Histology was done in 7 of the 13 patients described in table I: intravascular thrombi, hyalinised vessels or vasculitis were found in all cases. Immunohistochemistry was performed in only 1 patient[9] and showed intravascular deposits of IgM and C3 on parietal cells.

In the delayed hypersensitivity skin reaction, biopsy shows eczema with spongiosis and exocytosis, without microthrombi or signs of vasculitis. Sometimes, a mild superficial dermal perivascular infiltrate may be observed. Immunochemistry reveals an increased number of HLA-DR-bearing keratinocytes and a predominance of helper/inducer T cells in the perivascular infiltrate, which is in favour of a type IV allergic reaction.[36,42] In practice, the histopathological examination of the skin is rarely useful and is not routinely recommended.

4.2 Laboratory

Platelet count may be decreased in patients with heparin-induced skin lesions. Thrombocytopenia is classically associated with heparin-induced thrombocytopenia in skin necrosis. This clinico-

pathological syndrome should be diagnosed on the basis of 2 criteria: (i) one or more clinical events associated with this syndrome, such as thrombocytopenia ($<150 \times 10^9$/L), a greater than 50% decrease in the platelet count even if it does not reach thrombocytopenic levels, venous or arterial thromboembolic complications or necrotic skin reactions usually at injections sites; (ii) laboratory evidence for the presence of a heparin-dependent Ig (usually IgG).[23] Typically, the platelet count nadir is between 40 to 60×10^9/L, lower platelet counts being rare. In patients with skin necrosis related to subcutaneous heparin, the decrease in platelet count is usually milder, and the diagnosis of heparin-induced thrombocytopenia often necessitates serological tests.[55]

Two types of assays are available: functional and antigen assays, but none is completely reliable. The 'gold standard' is the ^{14}C-serotonin-release assay with washed platelets, but this test requires extensive quality controls and can only be done in very few, specialised, laboratories. The most commonly used test is an enzyme-linked immunosorbent assay (ELISA) for heparin-induced thrombocytopenia-Ig using the heparin-platelet factor 4 target antigen. This method is easier to perform, but still quite expensive. Although the agreement between this antigen assay with functional assays is high, approximately 10 to 20% of patient samples yield discordant results.[23]

Platelet-activating IgG seem to be often detectable in the presence of heparin-induced skin lesions. However, they seem to predict thrombotic complications of heparin-induced thrombocytopenia only in patients with skin necrosis or an associated decrease in platelets.[56] The presence of these platelet-activating IgGs in patients with erythematous skin lesions without necrosis or a significant decrease in platelet count is still unclear. Therefore, we do not recommend to perform these

Table II. Description of patients with delayed (type IV) skin reaction caused by low molecular weight heparins (LMWH)

Author	Localisation	LMWH preparation	Daily doses (IU)	Delay (days)	Gender	Age	Previous allergy
Bircher et al.[43]	Localised	Dalteparin sodium	2500	3	M	49	No
Koch et al.[44]	Localised	Nadroparin calcium	8000	NA	F	37	No
Manoharan[45]	Localised	Dalteparin sodium	2500	3	F	24	No
Phillips et al.[46]	Localised	Dalteparin sodium	NA	7	F	25	Yes (UFH)
Rasmussen et al.[47]	Localised	Dalteparin sodium	5000	8	F	26	No
Dacosta et al.[48]	Localised	Nadroparin calcium	6150	10	F	40	Yes (UFH)
Greiner & Schöfer[49]	Localised + generalised	Nadroparin calcium	3075	1	F	75	Yes (UFH)
Krasovec et al.[50]	Localised	Nadroparin calcium	NA	2	F	NA	No
	Localised	Dalteparin sodium	NA	NA	F	NA	NA
	Localised	Dalteparin sodium	NA	NA	F	NA	NA
Sivakumaran et al.[6]	Localised	Dalteparin sodium	NA	2	F	33	Yes (UFH and LMWH)
Bircher et al.[38]	Localised	Certoparin sodium	3000	150	F	59	No
Krasovec et al.[51]	Localised	Dalteparin sodium	2500	8	F	66	Yes (topical UFH and polysulfuric mucopolysaccharide)
Garijo & Arranz[39]	Localised	Nadroparin calcium	4100	15	F	71	No
Koch et al.[52]	Localised + generalised	Enoxaparin sodium	4000	14	F	45	Yes (UFH)
Méndez et al.[53]	Localised	Enoxaparin sodium	4000	13	F	73	No
Moreau et al.[36]	Localised	Enoxaparin sodium	NA	4	F	47	Yes (UFH)
Ojukwu et al.[54]	Localised + generalised	NA	NA	12	F	20	Yes (UFH)

F = female; **M** = male; **NA** = not available; **UFH** = unfractionated heparin.

tests routinely. In our literature review of LMWH-induced skin lesions, 4 patients with skin necrosis had a significant fall in platelet count.[22,29,34,35] Of those patients, 3 were tested with serological tests for heparin-induced thrombocytopenia, and all of them were positive. Bircher et al.[43] described a patient with erythematous skin lesions at injection sites, associated with a maculopapular rash, a normal platelet count and a positive functional test for heparin-induced thrombocytopenia without any clinical complications.

Hypereosinophilia associated or not with skin lesions, has only rarely been reported. In 1993, Giustolisi et al.[57] published 5 case reports of patients with hypereosinophilia and erythematous skin lesions at injection sites. They did not find any correlation between the type of skin lesion, the degree of hypereosinophilia, the duration of treatment or the total amount of heparin administered. The mechanism by which subcutaneous heparin could cause hypereosinophilia remains unclear. Bircher et al.[58] suggest that hypereosinophilia is more frequent in patients undergoing long term subcutaneous heparin therapy, which provides long-lasting antigen presentation that may stimulate CD4+ cells. Activated CD4+ lymphocytes are a source of several cytokines, including granulocyte-macrophage colony-stimulating factor and interleukins 3 and 5, which induce and stimulate growth and activation of eosinophils.[58] Hypereosinophilia has been reported in 2 patients with type IV hypersensitivity LMWH-induced skin lesion.[48,49] There is, so far, no clinical evidence that these patients need to be treated in a different way, so that screening for hypereosinophilia does not seem to be useful in the diagnostic strategy.

Protein C and S deficiencies have sometimes been associated with heparin skin necrosis. The decrease of these proteins at the beginning of oral anticoagulant therapy is responsible for the so-called warfarin skin necrosis, which is clinically and histologically similar to heparin skin necrosis. However, typical features of warfarin skin necrosis include the absence of thrombocytopenia, the absence of progression of areas of skin necrosis even if drug administration is continued, and the pre-existence of (i.e. in the absence of warfarin) deficiencies in protein C and S.[19] Low protein C levels have only been described in 2 patients[30,59] who had no evidence of a congenital defect. This measurement is not useful in the presence of a pure heparin-induced skin lesion.

In vitro tests such as determination of total IgE antibodies, or specific IgE antibodies [radio-allergo sorbent test (RAST) method] or lymphocyte-stimulating tests are disappointing[60] for documentation of heparin allergy and were only exceptionally performed in patients given LMWH.

4.3 Skin tests

4.3.1 Prick Tests

Prick tests are generally used if a type I hypersensitivity reaction is suspected. Different dilutions can be tested varying from 1 : 100 to 1 : 1 heparin concentration. Test reading is usually done after 20 minutes. These tests are negative in type IV reactions and should not be done for this condition. Unfortunately, the test was not performed in the only reported case of type I hypersensitivity reaction to LMWH.[17] On the other hand, it was performed in 3 cases of type IV reactions, and as expected, all were negative.

4.3.2 Patch Tests

Patch tests are generally used with various available nondiluted LMWHs in Leucotest chambers, test readings being performed after 2 and 4 days. In type IV hypersensitivity reactions due to UFH, epicutaneous tests are not sensitive: Klein[42] described positive reactions in only 3 out of 14 patients with typical erythematous delayed heparin skin reactions, so a negative patch test should not rule out allergy.

4.3.3 Intradermal Tests

Intradermal tests can be done with 0.05ml of various dilutions of LMWH (classically 1 : 100, 1 : 10 and 1 : 1). Reading is generally performed at 20 minutes, and after 1, 2 and 4 days. Intradermal tests with heparin are usually positive in such cases at 48 hours, and the response looks very similar to

that of a tuberculin-type IV delayed hypersensitivity reaction. These tests are more sensitive than epicutaneous tests, but their sensitivity is still insufficient to exclude the diagnosis. Indeed, Klein[42] described 5 out of 16 false negative results in the presence of delayed hypersensitivity to UFH.

4.3.4 Subcutaneous Tests

Subcutaneous tests are still the gold standard. They are performed with 0.1ml of undiluted LMWH or possibly with a 1 : 10 dilution. Most reactions appear after 3 to 4 days (range 1 to 5 days), but hypersensitivity may persist for a longer period. To avoid false negative reactions, it is important to do a last reading at day 5.[36] Reaction intensity varies considerably, but higher doses of heparin usually induce a stronger reaction. The advantage of this test is its high reliability. However, it can induce severe adverse effects such as anaphylactic shock or heparin-induced thrombocytopenia. These reactions have never been reported with heparins, but some authors suggest that for safety reasons, prick and intradermal tests should be performed first.[38] Subcutaneous provocation tests are then performed only if these first step tests are negative. In our literature survey, 18 patients were shown to have delayed type IV LMWH-induced skin lesions, 6 out of 8 patients had positive patch tests, 6 out of 7 had positive intradermal tests, and 5 out of 5 were positive for subcutaneous testing.

5. Diagnostic Strategy

At the present time, there is no consensus about how to test skin allergy to LMWH. Table III proposes a tentative diagnostic strategy. Baseline platelet counts should be performed in all patients at the beginning of heparin therapy, especially in women who are pregnant, in patients in whom it is foreseen that therapy will last for more than 5 days or in those with previous history of heparin allergy.

If a skin lesion occurs, platelet count should be performed every day. Heparin-dependent Ig testing (functional or serological) should be performed if the platelet count decreases by more than 50%, in the presence of thrombocytopenia and perhaps in patients who present with skin necrosis, in order to diagnose heparin-induced thrombocytopenia. A systematic search for platelet-activation in patients with erythematous skin lesions without a decrease in platelet count is useless because they are not clinically relevant. Histology should be performed if the clinical picture does not allow type III reactions to be distinguished from type IV induced-LMWH skin lesions, but it is invasive and time consuming until results is available.

Skin provocation tests have to be performed particularly if a delayed hypersensitivity type IV skin reaction is suspected, so as to confirm the diagnosis and to search for a potential cross-reactivity with other brands of LMWH and eventually UFH. In such uncomplicated skin lesions, direct subcutaneous tests should be preferred to avoid false negative responses, to accelerate the diagnostic procedure, and also because the potential risk of producing a serious adverse effect is exceedingly low. In type I hypersensitivity, a prick test should be performed to confirm the diagnosis and to look for cross-reactions with other LMWHs. In case of skin necrosis, heparin-induced thrombocytopenia or type I reaction, heparin should be avoided in the future and skin tests should not be performed since they are rarely useful to detect potential cross-

Table III. Tentative diagnostic guidelines in the presence of low molecular weight heparin (LMWH)-induced cutaneous allergy

Hypersensitivity type	Platelet count	Heparin-dependent Ig testing	Prick test	Intradermal test	Subcutaneous test
Type I (angioedema, anaphylactic shock)	X		X		
Type III (skin necrosis)	X	X			
Type IV (erythematous plaques)	X	(X)[a]	(X)[b]	(X)[b]	X

a In cases of thrombocytopenia or decrease of platelet count by >50%.

b Can be performed before subcutaneous testing.

Ig = immunoglobulin; **X** = perform this test; **(X)** = possibly perform this test.

reactivity between LMWH brands and even small amounts of heparin may lead to life-threatening complications.

6. Management

At the slightest suspicion of a LMWH-induced skin reaction, treatment should be discontinued. It is then important to identify the pathogenesis of heparin-induced skin lesions in order to obtain the correct diagnosis, to prevent complications, and to be able to introduce safe treatment alternatives.[61]

In patients with type I or skin necrosis reactions or heparin-induced thrombocytopenia, withdrawal of the LMWH is crucial to avoid potentially fatal complications. Optimal anticoagulant therapy, especially for heparin-induced thrombocytopenia, remains uncertain. Oral anticoagulants are ineffective and may even be deleterious: a syndrome of venous limb gangrene has been reported with the use of warfarin during the first few days of use in heparin-induced thrombocytopenia, due to disturbances in the procoagulant/anticoagulant balance.[23] Oral anticoagulants should not be given for at least 3 to 5 days after discontinuing LMWH and should always be administered together with another anticoagulant drug. The most accepted options include recombinant hirudin and danaparoid sodium.

Recombinant hirudin has been used successfully to treat heparin-induced thrombocytopenia (level of evidence IV) with the theoretical advantage of lacking immunological cross-reactivity with heparin-induced thrombocytopenia antibodies and of having a direct antithrombin activity.[23] The anticoagulant effect of hirudin is easily monitored by the activated partial thromboplastin time, and this drug is now available in most European countries for this indication.[23] However, type I[62] and IV[63] hypersensitivity skin reactions have also been described with hirudin, but there was no cross-reactivity with LMWH.

Danaparoid sodium is a mixture of anticoagulant glycosaminoglycans representing the alternate anticoagulant with the largest published experience in the presence of heparin-induced thrombocytopenia. Its major handicap is a potential risk of immunological cross-reactivity of the heparin-induced thrombocytopenia-IgG (approximately 10% *in vitro*, but probably less than 5% *in vivo*). Laboratory monitoring of the anticoagulant effect can only be performed, if desired, by measuring the plasma anti-factor Xa level (using a danaparoid sodium calibration curve) and is thus limited to a few specialised laboratories.[23] Cross-reactivity with danaparoid sodium in patients presenting a type IV delayed LMWH-induced skin reaction has been described in only 2 cases.[6,52] For prevention of venous thromboembolism, intermittent pneumatic compression is certainly an attractive alternative, even if its efficacy seems to be less, particularly in high risk orthopaedic surgery.[64]

In type IV hypersensitivity reactions, heparin should also be discontinued. In such cases, in the absence of severe or extensive mucocutaneous manifestations, a first-line pragmatic approach consists in our view in replacing the LMWH used by another one without prior skin tests. Nonetheless, subcutaneous provocation tests should be done if symptoms do not improve with the use of the second LMWH, in order to detect cross-reactivity between the LMWH preparation and danaparoid sodium. If testing is negative, the compound can probably be used safely. If all LMWH preparations and danaparoid sodium are positive in skin testing, intravenous injections of any kind of heparin should be avoided because a generalised exanthem has been described.[65] In these patients, alternative methods consist of using a LMWH in conjunction with antihistamines,[46] mixing corticosteroids with heparin in the same syringe,[54] applying topical corticosteroids to the injection sites,[52] giving hirudin,[23] or conducting a successful desensitisation.[66] However, most, if not all these options have not been tested sufficiently to be recommended.

7. Prevention

Hypersensitivity skin reactions can be prevented by avoiding long term LMWH therapy, particularly in middle-aged women who are obese and

during pregnancy. In these patients, oral anticoagulation should be preferred, whenever possible. In women who are pregnant and need long term anticoagulant therapy, warfarin should be considered as an alternative between the twentieth and the thirty-sixth week, a period which does not carry any risk for embryopathy.[67] Platelet counts should be performed at regular intervals to detect heparin-induced thrombocytopenia early (see section 4.2).

8. Conclusions

LMWH-induced skin reactions are a rare complication although their true incidence is probably underestimated. Different types of heparin-induced skin reactions have been documented and skin lesions can generally be ascribed to one, and rarely to different hypersensitivity types.[68] The clinical diagnosis should, if possible, be confirmed by laboratory analysis or skin provocation tests, to make the correct diagnosis and introduce the right alternative therapy. If the diagnosis is missed, fatal outcomes have been described, especially in patients who have developed a white clot syndrome related to heparin-induced thrombocytopenia in whom heparin was not stopped in time.

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Correspondence and reprints: Dr *Henri Bounameaux,* Division of Angiology and Hemostasis, Hôpital Cantonal Universitaire, 24 rue Micheli-du-Crest, CH-1211 Geneva 14, Switzerland.
E-mail: bounamea@cmu.unige.ch