

Nadroparin carries a potentially high risk of inducing cutaneous delayed-type hypersensitivity responses

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Summary

Background. Heparins are widely used for the prophylaxis/treatment of thromboembolic events. As adverse effects, heparin-induced skin lesions occur frequently (in 7.5–39% of patients). Skin lesions may be the only clinical manifestation of life-threatening immune-mediated heparin-induced thrombocytopenia, but are commonly caused by a delayed-type hypersensitivity response [heparin-induced delayed-type hypersensitivity (HIHS)]. Risk factors have not been prospectively identified.

Objectives. To identify possible risk factors for heparin-induced skin lesions from three independent clinical trials in a combined analysis.

Methods. A pooled analysis from prospective studies was performed, and possible risk factors were included in a multiple logistic regression analysis.

Results. Obesity (body mass index of > 25), prolonged anticoagulant therapy, prior heparin exposure and younger age (< 55 years) were confirmed as independent risk factors for HIHS. The choice of anticoagulant preparation had the greatest influence. On comparison of dalteparin, enoxaparin, fondaparinux, unfractionated heparin, and nadroparin, the latter was associated with the highest risk of eliciting HIHS (odds ratio of 30.2, 95%CI: 11.7–77.9).

Conclusions. The high risk associated with nadroparin has been validated in controlled trials, and this emphasizes the singularity of each heparin preparation in terms of allergenicity and that individualized anticoagulation is required.

Key words: allergy; heparin; heparin-induced delayed-type hypersensitivity response; heparin-induced thrombocytopenia; HIHS; HIT; low molecular weight heparin; skin.

Heparins comprise a heterogeneous mixture of polysaccharide chains of different lengths and molecular weights (MWs) [unfractionated heparin (UFH) 3000–30 000, low molecular weight heparin (LMWH)

2000–9000]. The synthetic, ultra-low MW pentasaccharide fondaparinux (MW 1728) carries an active antithrombin-binding pentasaccharide sequence that is derived from the natural pentasaccharide sequence of

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Table 1. Summary of suspected and known risk factors for heparin-induced delayed-type hypersensitivity (HIHS) development

Study	Risk factor	Details	Type of study
Ludwig et al. (19)	Molecular weight of heparin	Correlation of heparin's molecular weight with the degree of sensitization in allergy testing	Case series (n = 12)
Ludwig et al. (7)	Female sex	92.5% of reported patients are female	Review of case reports/case report series
	Older age	Average age at diagnosis: 56 + 15 years	
	Pregnancy	47.8% of patients aged ≤ 40 years were reported to be pregnant	
	Obesity	Several patients have been reported to be overweight	
Schindewolf et al. (9)	BMI > 25	OR 4.6 (95%CI: 1.7–15.3)	Prospective epidemiological investigation
	Duration of therapy	Anticoagulant therapy for > 9 days (median duration): OR 5.9 (95%CI: 1.9–26.3)	
	Female sex	OR 3.0 (95%CI: 1.1–8.8)	
	LMWH preparation	HIHS incidence of 3.9% or 17.1% for enoxaparin or nadroparin, respectively ($p < 0.001$, χ^2 -test)*	
Schindewolf et al. (10)	Duration of therapy	Anticoagulant therapy for > 33 days (median duration): OR 7.9 (95%CI: 1.3–48.4)	Prospective epidemiological investigation
	Previous heparin exposure	OR 6.9 (95%CI: 1.2–39.5)	
	LMWH preparation	HIHS incidence of 4.1% or 54.8% for dalteparin or nadroparin, respectively (OR 0.1 (95%CI: 0.02–0.7 for dalteparin)	
Kaandorp et al. (8)	Nadroparin [†]	39.8% swelling or itching at injection site	Prospective epidemiological investigation

BMI, body mass index; LMWH, low molecular weight heparin; OR, odds ratio.

*Not considered as an endpoint of the study; hence, not considered for power calculation, and bias towards prescription cannot be excluded.

[†]Heparin-induced skin lesions included as the secondary endpoint, and no further information on the cause of skin lesions available. Nadroparin was the only LMWH preparation administered.

heparins. Binding to antithrombin accelerates the inactivation of several coagulation factors (IIa, Xa, IXa, XIa, and XIIa) (1). For decades, heparins have been commonly used for the prophylaxis and treatment of thromboembolic diseases (1, 2). Skin lesions constitute one possible adverse effect of heparin treatment (3), which was first noted in 1953 (4). Heparin-induced skin lesions were assumed to be underreported (5–7). Recent prospective epidemiological investigations have confirmed this notion, reporting an incidence of heparin-induced skin lesions ranging from 7.5% to 39.5% in medical and obstetric patients, respectively (8–10). Heparin-induced skin lesions can manifest as several diseases, such as pustulosis (11), immediate-type hypersensitivity responses (12), recall urticarial reactions (13), bullous eruptions (14), necrosis of unknown pathogenesis (15), or immune-mediated heparin-induced thrombocytopenia (HIT) (16). Most commonly, heparin-induced skin lesions are caused by a delayed-type hypersensitivity response [heparin-induced delayed-type hypersensitivity (HIHS)] (3, 9, 17, 18).

Case reports and case series have indicated several risk factors for HIHS (Table 1). Initially, the MW of the

individual heparin preparation or the synthetic pentasaccharide fondaparinux was shown to correlate with the degree of sensitization as determined by allergological testing (19). This concept was first challenged by the observation of high cross-reactivity to bemiparin, an LMWH with a MW of 3600, in patients with HIHS (20). However, these studies included only 12 and 8 patients, respectively, so firm conclusions cannot be drawn from them. However, we recently observed a varying frequency of HIHS in medical patients treated with either nadroparin (MW 4300; 17.1% HIHS) or enoxaparin (MW 4500; 3.9% HIHS) (9). Furthermore, in a cohort of pregnant women requiring anticoagulant therapy, HIHS was less frequently observed after dalteparin treatment (MW 6000; 4.1% HIHS) than after nadroparin treatment (MW 4300; 54.8% HIHS), although the difference did not reach statistical significance (10). This frequent occurrence of HIHS in pregnant women receiving nadroparin was confirmed in independent studies (8, 21). Therefore, different heparin preparations and fondaparinux, respectively, seem to carry distinct risks for eliciting HIHS. A meta-analysis of 198 HIHS patients with > 1000 tests for cross-reactivity among heparins supports this

Table 2. Characteristics of patients treated with different low molecular weight heparins (LMWHs) and fondaparinux

Treatment with	n	HIHS occurrence (%)	Female sex (%)	BMI*	Duration of therapy (days)	Age (years)	Pregnant (%)	Cohort (medical/obstetric)
Dalteparin	82	4.9	100.0	24 ± 6	29 (7–310)	32 ± 5	98.8	9/91
Enoxaparin	207	2.9	45.4	25 ± 6	9 (7–570)	59 ± 18	7.7	94/6
Fondaparinux	231	0.4	35.5	26 ± 6	11 (7–274)	59 ± 19	0.0	100/0
Nadroparin	139	25.9	62.6	27 ± 7	14 (7–1.095)	54 ± 19	22.3	71/19

BMI, body mass index; HIHS, heparin-induced delayed-type hypersensitivity response.

BMI, mean ± standard deviation (SD); Duration of therapy, median and range; Age, mean ± SD; Pregnant, calculated for all patients; Cohort, indicates how many patients (%) were from one of the two medical patient cohorts or from the obstetric cohort.

*The pregestational BMI was used in cases of pregnancy.

notion: although the risk of cross-reactivity was higher when the initial HIHS developed in response to UFH than when it developed in response to LMWH, no correlations with MW and the risk of cross-reactivity were observed (22). Regarding patient-related risk factors (Table 1), female sex, obesity, pregnancy and older age seemed to be associated with an increased risk of developing HIHS (7, 23). In detail, > 90% of reported HIHS patients were female, the average age at diagnosis was 56 years, almost 50% of the younger female patients were pregnant, and, in most case reports, patients were described as obese (24, 25).

In order to obtain a more detailed understanding of patient-related and drug-related risk factors for the development of HIHS, we analysed all available data from three large prospective investigations on the incidence of HIHS in LMWH-treated or fondaparinux-treated patients (9, 10, 26). In all patients, skin lesions were attributable to HIHS; none was caused by HIT or other conditions. As we noted a marked difference in incidence among different heparin preparations/fondaparinux during the studies, we hypothesized that individual heparins and fondaparinux, respectively, are associated with varying risks of inducing HIHS.

Patients and Methods

Study cohorts

For this analysis, data from three independently performed prospective clinical investigations to determine the incidence and causes of heparin-induced skin lesions were pooled (9, 10, 26). In contrast to the previously reported studies, we now only included data on the initially prescribed anticoagulant or the drug that induced heparin-induced skin lesions. Cross-reactivities among different heparin preparations and fondaparinux, respectively, were thus not included in this analysis. All studies aimed to determine the incidence and the causes of heparin-induced skin lesions. As identification of risk

factors was initially not considered as a study endpoint, the initial power calculation for the individual studies did not take this into account.

Statistics

For multiple logistic regression analysis, the open-source software R (www.r-project.org) was used. For covariate selection, several approaches were applied: (i) logistic regression on single covariates (including R package 'car' with function 'Anova'), and (ii) stepwise minimization of Akaike's Information Criterion (AIC) of a logistic regression on combined covariates (starting from a model containing all covariates). Possible interactions between covariates were disregarded in the logistic regression models. The influence of covariates was assessed with a likelihood-ratio test.

Results

Study cohort and statistical model

We first determined the characteristics of the combined study cohort. In total, 661 patients were included in the combined study cohort. The mean (± standard deviation) age was 55 ± 19 years, body mass index (BMI) was 26 ± 6 kg/m², and 56.9% of the patients were females, of whom 33.5% were pregnant. Forty-seven of 661 patients showed skin reactions; 46 of these showed erythematous cutaneous lesions localized at the heparin injection sites, ranging from mild erythema to moderately or severely infiltrated plaques. In several cases, these lesions were accompanied by slight scaling or surrounding papulovesicles. A secondary generalized eczematous reaction was observed in 4 of 47 patients. One patient did not show any erythematous skin reactions, but reported recurrent local itching at heparin injection sites. Necrotic, pustular, bullous or urticarial reactions were not observed in any of the patients. In all patients, skin lesions were attributable to HIHS.

Table 3. Risk factors for heparin-induced delayed-type hypersensitivity response (HIHS) identified by analysis of three prospective epidemiological investigations

Risk factor	Unadjusted			Adjusted		
	OR	95%CI	<i>p</i> -value	OR ²	95%CI ²	<i>p</i> -value ²
Age > 55 years*	0.17	0.08–0.36	< 0.0001	0.26	0.10–0.67	0.003
Obesity (BMI > 25) [†]	1.32	0.72–2.4	0.37	2.88	1.26–6.62	0.010
Therapy duration > 11 days	7.79	3.26–18.6	< 0.0001	4.62	1.66–12.9	0.001
Sex hormone intake	1.26	0.29–5.52	0.77	ND	ND	ND
Pregnancy	5.77	3.13–10.6	< 0.0001	ND	ND	ND
Prior heparin exposure	1.56	0.78–3.12	0.20	2.9	1.07–7.86	0.026
Male sex*	0.21	0.09–0.48	< 0.0001	0.35	0.13–0.94	0.029
Nadroparin treatment	18.5	8.71–39.4	< 0.0001	30.2	11.7–77.9	< 0.0001
Enoxaparin treatment	2.05	1.13–3.72	0.020	5.88	2.38–14.5	< 0.0001
Dalteparin treatment [‡]	1.63	0.76–3.5	0.23	ND	ND	ND
Fondaparinux treatment [‡]	0.08	0.02–0.31	< 0.0001	ND	ND	ND
UFH treatment	18.2	6.96–47.4	< 0.0001	8.65	1.8–41.5	0.007

Unadjusted analysis of single covariates (left) and logistic regression on combined covariates (right).

BMI, body mass index; CI, confidence interval; ND, not determined; OR, odds ratio; UFH, unfractionated heparin.

Data were obtained from three independently performed prospective epidemiological studies. As identification of risk factors was initially not considered as a study endpoint, the data have to be interpreted with care, owing to a possible selection bias. (a) OR including 95%CI and likelihood-ratio test *p*-value (unadjusted for multiple testing); logistic regression on single covariates. (b) OR including 95%CI and likelihood-ratio test *p*-value; logistic regression on combined covariates after optimization of Akaike's Information Criterion (AIC) by stepwise dropping of single covariates.

*Protective risk factors. The *p*-value indicates a significant increase or decrease in HIHS risk.

[†]The pregestational BMI was used in cases of pregnancy.

[‡]Dropped from the final model.

The following variables were included in the regression model: age > 55 years (mean age), sex, BMI > 25 (as definition of obesity; in case of pregnancy, the pregestational BMI was used), anticoagulant preparation, duration of heparin therapy of > 11 days (mean duration), prior exposure to heparin, and pregnancy. The characteristics of patients treated with different LMWHs and fondaparinux are summarized in Table 2. Diagnostic procedures of the three studies are summarized in Table S1.

HIHS risk factors

In a logistic regression model, the following variables had an independent and significant (according to the likelihood-ratio test) influence on elicitation of HIHS (Table 3): age (*p* = 0.003), sex (*p* = 0.03), BMI (*p* = 0.01), nadroparin (*p* ≤ 0.0001), enoxaparin (*p* < 0.0001), UFH (*p* = 0.007), duration of heparin therapy (*p* = 0.001), and prior exposure to heparin (*p* = 0.03). Pregnancy had no influence on the elicitation of HIHS. The predictive quality of this model was optimal in terms of an AIC of 200; omitting sex, BMI, duration of therapy, prior exposure to heparin or pregnancy as model covariates slightly worsened the AIC to 202–229. In contrast, elimination of the heparin preparation as a covariate strongly worsened the AIC to 273, indicating a predominant contribution of the

individual heparin preparations to the risk of developing HIHS. Interestingly, the risk factor 'prior exposure to heparin' was not visible in a single risk factor analysis, but only after all risk factors had been combined in one model. According to the corresponding odds ratios of the optimal logistic regression model (female sex, age < 55 years, duration of therapy of < 11 days, no prior exposure to heparin, not pregnant and use of enoxaparin), treatment with nadroparin, enoxaparin, or UFH, obesity, prolonged anticoagulant treatment, prior exposure to heparin and younger age could be confirmed as independent risk factors for the elicitation of HIHS (Table 3). Male sex seemed to offer protection from HIHS. In contrast, our data did not reveal any relevant influence of fondaparinux and pregnancy on HIHS development.

Discussion

We recently concluded three independent clinical investigations to determine the incidence and cause of heparin-induced skin lesions in medical and obstetric patients (9, 10, 26). In all patients, skin lesions were attributable to HIHS. During these studies, we noted marked differences in the frequency of HIHS, which seemed to depend on the cohort studied, sex, BMI, duration of heparin therapy, pregnancy, and the heparin

preparation. We therefore hypothesized that elicitation of HIHS depends on several patient-related and heparin-related risk factors. The combined analysis of all three studies presented here has clearly identified younger age (< 55 years), female sex, obesity (BMI > 25), prior heparin exposure and a long duration of heparin therapy (> 11 days) as patient-related risk factors for HIHS (Table 3).

Regarding heparin-related risk factors, nadroparin had a greater influence than enoxaparin and UFH in our regression analysis model on the risk of developing HIHS (Table 3). Therefore, the choice of anticoagulant treatment seems to have more impact on the elicitation of HIHS than any other identified risk factor. As the selection of anticoagulant therapy was independent from the study, the high incidence of HIHS in patients treated with nadroparin may have been caused by a selection bias. As a BMI of > 25, female sex and a long duration of heparin therapy also determine the risk of developing HIHS, we investigated whether nadroparin-treated patients had a selection bias for these risk factors. Patients receiving nadroparin treatment had a higher BMI than dalteparin-treated, enoxaparin-treated or fondaparinux-treated patients, which may explain the higher HIHS incidence. However, a greater potential selection bias towards higher HIHS incidence was observed in dalteparin-treated patients, as all patients treated with dalteparin were female (as compared with 62.6% for nadroparin) and the median duration of therapy with dalteparin was longer than that with any other anticoagulant preparation evaluated in this study (Table 2). Therefore, the high incidence of HIHS in nadroparin-treated patients is indeed most likely attributable to the anticoagulant itself.

We previously observed a high HIHS incidence of 19.5% in pregnant patients (10), which is in line with previous observations of a high incidence of heparin-induced skin lesions in pregnant women, amounting to 29% or 39.8% (8, 21). As compared with medical patients treated with LMWH (9), the HIHS incidence in pregnant women was increased from twofold to fivefold. However, pregnancy could not be confirmed as an independent risk factor for elicitation of HIHS in our model, which might be explained by the study design. On the basis of the overall elevated HIHS incidence in pregnant patients as compared with medical patients, we still consider pregnancy to be a potential risk factor. However, marked differences exist between patients of the medical cohort (9) and of the pregnant cohort (10). For example, pregnant patients requiring anticoagulant therapy have been exposed to heparin for a prolonged treatment period, which significantly enhances the risk of

developing HIHS. More specifically, the median duration of heparin LMWH therapy was 9 days in medical patients (9), as compared with 42 days in pregnant patients (10). Hence, the cause of the increased incidence of HIHS in pregnancy may be the prolonged exposure to heparin. Furthermore, age, sex, BMI and heparin preparations show marked differences between the populations (Table 2). Overall, controlled clinical trials, taking long treatment intervals into account, are needed to allow further conclusions on pregnancy as an HIHS risk factor to be drawn.

Interestingly, younger patients (< 55 years) were at greater risk of developing HIHS than older patients, defined by being younger or older than the median age of the study population. However, younger patients were predominantly female patients who received prolonged anticoagulant therapy during pregnancy. This may have led to a bias towards more HIHS in younger patients.

As expected, fondaparinux could not be identified as a risk factor for the development of HIHS. Fondaparinux is a chemically synthesized sulfated pentasaccharide, specifically inhibiting factor Xa (2), which has been presumed to be well tolerated in patients with HIHS (27–31). Recently, however, several case reports on intolerance to fondaparinux have been published (32–34). Results from our prospective investigation now clearly show a low allergenic potential of fondaparinux treatment (26). Again, a selection bias may be responsible for this observation. Hence, a controlled trial, comparing fondaparinux with a defined LMWH, is required to determine the allergenic potential of fondaparinux as compared with heparins.

These findings underscore the notion that different heparin preparations have to be considered as individual drugs, each possessing distinct activities and adverse events (35–37). However, the underlying mechanism for the observed differences in sensitization, for example molecular differences among the heparin preparations, but also patient-specific aspects such as hormonal or adrenergic factors, is still unclear at the moment. Therefore, we propose that heparins should be used according to their risk-to-benefit profiles (e.g. anti-inflammatory and anti-metastatic effects, renal clearance, osteoporosis, HIT risk, and antagonizability), as well as to their individual risks of eliciting adverse events such as HIHS (e.g. choosing preparations with possibly lower sensitization potential, i.e. fondaparinux, over highly allergenic preparations, i.e. nadroparin), thus tailoring heparin therapy in a patient-specific way.

For several reasons, the results of this analysis have to be interpreted carefully: In none of the studies (9, 10, 26) did the investigators have an influence on the selection of

anticoagulant therapy. Therefore, potential influences of the respective anticoagulants on HIHS development have not been taken into account, and thus were not considered when the required sample size was calculated; also, the possibility cannot be excluded that 'allergy-prone' patients were selected for/treated with nadroparin. Further limitations result from the fact that the patients from the three studies were heterogeneous, were selected from different departments with different backgrounds, and received different heparin preparations; the diagnostic criteria applied were not stringent in some patients, and the number of patients with HIHS was limited.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Diagnosis of heparin-induced delayed-type hypersensitivity (HIHS) reactions.

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