

The risk for cross-reactions after a cutaneous delayed-type hypersensitivity reaction to heparin preparations is independent of their molecular weight: a systematic review

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Summary

Background. Heparins are a widely used class of drugs known to cause delayed-type hypersensitivity (DTH) reactions. Recent publications indicate that the incidence of these may be higher than previously thought. To date, patient-related but no drug-related risk factors for the development of DTH reactions to heparins have been identified, although molecular weight is discussed as a potentially relevant parameter.

Objectives. To address this, a systematic review was conducted on the frequency of cross-reactions after DTH reactions to heparin preparations.

Methods. We electronically searched MEDLINE and EMBASE, hand-searched selected journals and references, and contacted experts for unpublished data.

Results. Sixty-six publications and unpublished data of 14 patients resulted in 198 patients with 1084 tests for cross-reactivity. The primary causative agents were mostly unfractionated heparin (50%) and low molecular weight heparins (49.5%). Cross-reactions were more likely after an initial DTH reaction to unfractionated heparin than after an initial DTH reaction to low molecular weight heparin. Our findings also indicate that molecular weight does not correlate with the risk for cross-reactivity, which is in line with recent observations, indicating that different heparins have to be individually considered.

Conclusions. The available data demonstrated the lowest overall risk for cross-reactions for pentosan polysulfate (36.4%) and fondaparinux (10.4%). In the clinical context, fondaparinux is recommended as the current best alternative when a DTH reaction occurs.

Key words: delayed-type hypersensitivity; fondaparinux; heparin; systematic review.

Heparin has been used as an anticoagulant for over seven decades (1). Since the initial introduction of unfractionated heparin (UFH), several modified preparations, for example low molecular weight heparins (LMWHs),

heparinoids (danaparoid and pentosan polysulphate), and the synthetic pentasaccharide fondaparinux, have been developed (2). Nowadays, heparin preparations (if not otherwise specified, the term 'heparin preparations' refers to UFH, LMWHs, heparinoids, and the pentasaccharide fondaparinux) are in worldwide clinical use. Well-characterized side-effects of heparin therapy are bleeding, osteoporosis, hair loss, immune-mediated heparin-induced thrombocytopenia (HIT) type 2, and HIT type 1. Recently, heparin-induced skin lesions have been increasingly reported, and the evidence suggests that they occur with a far higher incidence than previously

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assumed (3, 4). The most frequently described lesions appear as erythematous plaques followed by eczematous lesions (5–7). More specifically, 7.5% of all medical inpatients receiving therapy with heparins developed skin lesions, all of which could be diagnosed as delayed-type hypersensitivity (DTH) reactions. Although not included as primary endpoints, a higher body mass index, long duration of heparin therapy and female sex have been identified as risk factors for heparin-induced skin lesions; these have also previously been assumed to be associated with a higher risk of developing this adverse drug reaction (3, 8).

In addition to the clinical challenge of identifying the cause of the diagnosed heparin-induced skin lesion, cross-reactions among heparin preparations further complicate the treatment of patients with DTH reactions to heparin preparations (3). There are several reports of DTH patients who have multiple sensitizations to heparin preparations. Hence, substitution with a different heparin preparation may not only lead to similar symptoms, but also lead to further sensitization and cross-reactivity, and even generalized DTH, leading to a generalized maculopapular skin rash (9). The latter may best be described as a systemic reactivation of allergic dermatitis (10).

Both cross-reactivity and initial sensitization to heparin have been suggested to correlate with the molecular weight of heparin preparations; that is, an increasing risk of sensitization with increasing molecular weight (11). In contrast, Grims et al. found no such correlation (12). However, both trials were too underpowered to allow firm conclusions to be drawn.

To clarify the contribution of molecular weight to the risk for cross-reactivity among heparin preparations a systematic review was conducted. On the basis of these data, we aimed to investigate the frequency of cross-reactions for the heparin preparations in clinical use by substance group (UFH, LMWHs, heparinoids, and fondaparinux).

Methods

A systematic review of the literature was conducted. All articles describing patients with DTH to a heparin preparation, who underwent further allergy testing, were included. A skin reaction was considered to be delayed

when it appeared at least 24 hr after initial heparin application. Patients who showed skin lesions during this time according to Table 1 were defined as DTH patients. The causative drug was defined in line with the decisions made within the individual reports, as this judgement is dependent on both the clinical context and the individual test results. A reaction to a heparin preparation different from the causative one during consecutive testing was defined as a cross-reaction. This had to be investigated by patch and/or intracutaneous testing and/or subcutaneous provocation, and data had to be reported on the individual patient level. Articles where the causative heparin preparation was unclear or not named were excluded.

The databases MEDLINE and EMBASE (Ovid) were searched electronically from inception until 30 April 2010 for the heparin preparations (Table 2) combined with terms for DTH, using a sensitive stepwise search term including brand and substance names of the heparin preparations and synonyms of DTH. Hand search was performed in six journals, including the supplements (*Allergy*, *Archives of Dermatology*, *British Journal of Dermatology*, *Clinical and Experimental Dermatology*, *Contact Dermatitis*, and the *Journal of the American Academy of Dermatology*), from 1988 until the end of 2009. Experts in this field – meaning scientists who published two or more articles included in this systematic review – were asked to provide further data on patients and publications. We searched the references of included articles, and made no language restrictions throughout the studies.

The initial screening of titles and abstracts for inclusion was performed independently and by two reviewers. Inclusion or disagreement resulted in the full articles being obtained. Final inclusion of articles was also performed through independent assessments by two investigators, with any disagreements being resolved through discussions until consensus was reached. The evaluation of the electronic search strategy was performed by direct comparison with the hand search results in the six journals.

Data abstraction was performed in the same way, with the use of a predefined abstraction sheet. All publications were abstracted concerning the number of patients reported, age, gender sex, reason for antithrombotic treatment, causative heparin preparation, and results of

Table 1. Clinical pattern

Pattern	Plaques	Eczema	Erythema	Exanthema	Other ^a	Unknown ^b
Number of patients	82	16	24	3	59	14
% of all patients	41.41	8.08	12.12	1.52	29.80	7.07

^aFor example, itching, maculopapular rash, and infiltrate.

^bNo information on the pattern was given in the study.

Table 2. Frequency of cross-reactivity in delayed type hypersensitivity to heparin preparations

Heparin preparation (no. of patients tested)	Molecular weight (10 ⁻²⁴ kg)	Overall cross-reactivity (%) (SD)	Cross-reactivity after sensitization to heparin (%) (SD)	Cross-reactivity after sensitization to LMWH (%) (SD)
Heparin				
UFH (176)	24.91	67.5 (5.3)	NA	67.1 (5.4)
LMWHs				
Tinzaparin (58)	10.79	56.9 (6.5)	60.6 (8.5)	52.0 (10.0)
Certoparin (91)	10.79	65 (5.3)	82.9 (5.9)	44.7 (8.1)
Dalteparin (157)	9.96	69.9 (3.8)	78.0 (4.6)	59.0 (6.3)
Enoxaparin (148)	7.47	80.6 (3.8)	86.6 (4.2)	70.7 (7.1)
Reviparin (47)	7.31	80.9 (5.7)	93.1 (4.7)	61.1 (11.5)
Nadroparin (151)	7.14	80 (3.5)	89.7 (3.4)	64.7 (6.7)
Bemiparin (20)	5.98	75 (9.7)	62.5 (17.1)	83.3 (10.8)
Heparinoids				
Danaparoid (106)	9.96	65.7 (4.6)	66.7 (6.8)	64.9 (6.3)
Pentosan polysulfate (55)	7.80	36.4 (6.5)	28.1 (7.9)	45.5 (10.6)
Pentasaccharide				
Fondaparinux (77)	2.87	10.4 (3.5)	16.1 (6.6)	6.7 (3.7)

LMWH, low-molecular-weight heparin; NA, not applicable; SD, standard deviation; UFH, unfractionated heparin.

cross-reactivity tests for each substance used. As outcome findings of interest have been reported on an individual patient level in the articles, data analysis was performed directly for all heparin preparations with more than one test result.

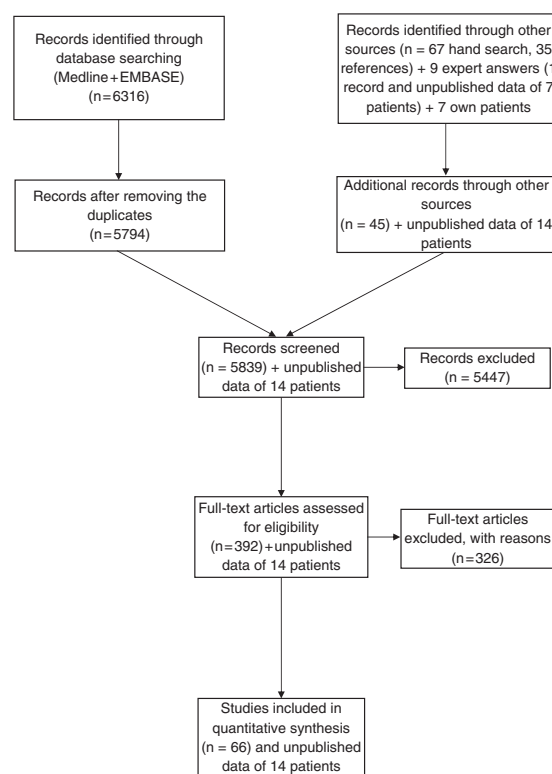
Pearson product–moment correlation was used to determine the relationship between the molecular weights of the heparin preparations and their risk for cross-reactivity. Binomial data were analysed with the Fisher exact test or the R/C contingency test, and $p < 0.05$ was considered to be significant. Sensitivity analyses to test for the robustness of data on the risk for cross-reactivity were performed. Therefore, articles with lower numbers of included patients were eliminated in a stepwise approach, with investigation of a possible publication bias in smaller case series, which might tend to over-report patients with higher frequencies of cross-reactions.

Results

The search described in Fig. 1 resulted in 66 included articles (3, 5–7, 11–72). Nine of 15 experts answered the query described in Methods, which yielded one additional publication (60) and unpublished data from 7 additional patients (73). Overall, including unpublished data of our 7 own patients, 198 patients with a total of 1084 tests of heparin preparations were identified.

Search strategy evaluation

The electronic searches revealed all publications found by hand search in the six journals (100%). Altogether, half of all included articles (50%, 33/66) were retrieved within

**Fig. 1.** Flow diagram for the conduct of the systematic review.

the journals picked for hand search, thus confirming it as a representative sample for the evaluation of the electronic search strategy. *Contact Dermatitis* contributed most articles (18), followed by *Allergy* (8), the *British*

Journal of Dermatology (5), and the *Journal of the American Academy of Dermatology* (2).

Patient characteristics

The mean age of patients was 56.0 ± 15.0 years; 92.3% were female. The reason for anticoagulant prescription, when indicated, was prophylactic in 66.7% and therapeutic in 22.7%. Pregnancy was the reported indication in 13.6% of females. Intradermal testing was performed most (161 patients), followed by subcutaneous provocation (136 patients), patch testing (117 patients), and prick testing (59 patients). The primary causative substances for DTH reactions were UFH and LMWHs, in 50% and in 49.5%, respectively. The heparinoid danaparoid was reported once as the primary causative anticoagulant for a DTH reaction. Among the LMWHs, enoxaparin was the most common trigger, being reported in 24.2% of all patients, followed by nadroparin (11.1%), which might, at least partly, be attributed to prescription habits. Interestingly, no patient with initial DTH reaction to fondaparinux could be included in the study, because of lack of further allergy testing for cross-reactions. Skin lesions varied, but were predominantly plaques, eczema, or erythema (Table 1).

Quantitative results

Overall risk for cross-reactivity. By allergy testing, 92.9% of all included patients revealed at least one cross-reaction. On average, 4.5 (range 1–9) cross-reactivity tests were performed per patient, with a median of 3 (range 0–8) positive results. When they were tested for cross-reactivity, the average risk for a positive test result among all heparin preparations was 64.2%. Among the four distinct pharmacological categories (UFH, LMWHs, heparinoids, and pentasaccharide), the risk for cross-reactivity varied. When UFH was tested for cross-reactivity independently of the causative heparin preparation, the resulting average risk was 67.5%. For the LMWHs, this average risk was similar, at 73.2%, but for heparinoids it seemed to be lower, at 55.6%. Only the pentasaccharide fondaparinux showed cross-reactions notably less often, with only 10.4% of all test results being positive ($p < 0.000001$).

Cross-reactivity risks according to causative agent. Among patients with an initial DTH reaction to UFH, the overall risk for a positive cross-reaction was 72.2%. LMWHs gave positive test results in 82.2% of the patients, heparinoids in 51.3%, and fondaparinux in 16.1%. After sensitization to LMWHs, the specific risk for a cross-reaction to heparin was 67.1%, and that for a different LMWH was 60.6%.

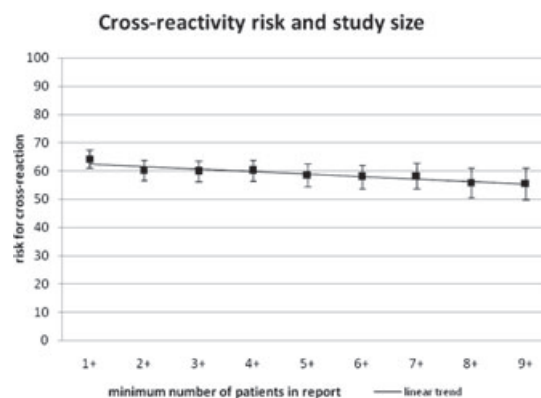


Fig. 2. Risk for cross reaction and size of case series.

Cross-reactivities to heparinoids after sensitization to LMWHs were reported in 59.5% of the patients, and to fondaparinux in only 6.7%. After primary sensitization to LMWH, the overall risk for a positive cross-reactivity test result was 56.1%, which is significantly lower than after initial administration of heparin ($p < 0.000001$).

Substance-related frequencies of cross-reactions. The risk for cross-reactivity of each substance among the LMWHs was constantly higher when UFH was the primary causative drug than when it was LMWH ($p < 0.000001$) (Table 2). Only bemiparin differed in this analysis, with higher reported cross-reactivity after sensitization to LMWH (83.3%), but it also showed the widest standard deviation, owing to the low overall number of tests. For the individual heparin preparations, the risk for cross-reactivity was always $>50\%$ for UFH, LMWHs, and the heparinoid danaparoid. Only the heparinoid pentosan polysulfate and, especially, fondaparinux showed lower frequencies of cross-reactivity, as shown in Table 2.

Cross-reactivity and molecular weight. Despite the different risks for cross-reactivity among the four groups of heparin preparations, no correlation was found between molecular weight and risk for DTH reaction among the heparin preparations ($p = 0.1803$, $r = 0.44$).

Sensitivity analyses. When study reports with lower numbers of included patients were eliminated, the risk for cross-reactivity was only slightly decreased, from 64.2% when all reports were included to 55.6% when they were restricted to case series with at least 9 patients (Fig. 2).

Discussion

In this systematic review, a high risk for cross-reactivity among heparin preparations in patients with a DTH

reaction towards one of these substances was found, and a group-specific risk profile was shown. Overall, a correlation between molecular weight and the risk for cross-reactivity among different heparin preparations could not be shown.

On the basis of the data presented here and recently published data on the incidence of heparin-induced DTH reactions, we propose that the different heparin preparations have individual risks for inducing sensitization and, ultimately, skin lesions. This concept of a molecular weight-independent, but drug-specific, risk for the development of a DTH reaction to subcutaneous injected heparin preparations is supported by several independent observations:

- (1) A high risk for cross-reactivity to bemiparin, which has a low molecular weight, has been observed (12). However, these findings have to be confirmed in a larger cohort of patients (74).
- (2) Fondaparinux has a low potential to induce cutaneous DTH reactions. In a cohort of over 200 medical patients anticoagulated with fondaparinux, the incidence of skin lesions was as low as 0.4% (75). This study confirmed observations in several case reports on the tolerance to fondaparinux in patients with DTH reactions to heparins (13–17, 76). Nevertheless, fondaparinux should not be used without caution, as it has been reported to induce a cutaneous DTH reaction (17, 18, 77).
- (3) In medical patients anticoagulated with subcutaneous heparin preparations, the incidence of DTH reactions to nadroparin (19%) was significantly higher than that of DTH reactions to enoxaparin (4%) (3). However, this study was not designed to detect differences in incidences among various heparin preparations. Therefore, these data have to be interpreted with some caution. In addition, anticoagulants were selected independently of this study, which may have led to a selection bias.
- (4) A high incidence (almost 40%) of heparin-induced skin lesions (most likely DTH reactions) in nadroparin-treated patients has also been found in pregnant women anticoagulated for recurrent miscarriage (4).

On the basis of these observations and the data presented here, we hypothesize that each different heparin preparation carries a distinct, drug-specific risk for inducing a DTH reaction. However, this assumption needs to be confirmed in a prospective study, comparing the incidence of DTH reactions to different heparin preparations. In the same trial, it is then recommended that all the substances

should be investigated in every patient by epicutaneous, intracutaneous testing as well as by subcutaneous provocation, in order to reliably determine the differences between the various test methods and their predictive values. The available data show that there is a differential degree of cross-reactivity, depending on the anticoagulant primarily inducing the DTH reaction. Currently, LMWHs are most frequently used agents for prophylactic and therapeutic anticoagulant therapy. After elicitation of a DTH reaction by an LMWH, the probability of development of a DTH reaction to UFH is 67.1%. The lowest risk for cross-reactivity among other LMWHs is observed for certoparin (44.7%), and the highest risk for cross-reactivity (83.3%) for bemiparin. The lowest frequency of cross-reactions after an initial DTH reaction to LMWH is observed for fondaparinux (6.6%). These observations may be useful for selection of an alternative anticoagulant in a patient with a DTH reaction to either UFH or LMWHs.

Our systematic review provides the largest available dataset published so far, including not only published patient-level data but also additional unpublished information. Data were systematically retrieved, independently appraised, and controlled via additional hand search and sensitivity analyses. Clearly, the risk for cross-reactivity among different heparin preparations is high, which might be attributable to the selection of patients, who are mostly attending specialized allergy departments. These institutions are more likely to encounter multi-allergic patients. This systematic review cannot provide reliable risk profiles of the heparin preparations before the development of DTH; this needs to be investigated prospectively. In line with this, negative test results from allergy testing do not exclude the development of DTH later, when a given heparin is continuously administered.

Further limitations of this systematic review naturally concern its research design, and are mainly related to the dependence on published data, concerning both quantity and quality. The use of epicutaneous testing, intracutaneous testing and subcutaneous provocation varied among the institutions, which made a direct comparison of the tests impossible, and might have eventually led to an incorrect higher false-negative test rate in this investigation. However, because of the common nature of DTH reactions and the fact that the study data were presented predominantly on a patient level, the combination of data was feasible.

Furthermore, more severe cases or cases with a high frequency of cross-reactions are more commonly published. This latter notion is supported by the observation of a high level of cross-reactivity in case reports and case report series (78), as opposed to a low

level of cross-reactivity in larger cohorts of patients (3, 79).

Conclusions

Our data underscore the notion that each of the currently available heparin preparations shows a distinct risk profile (80). This should be considered when anticoagulant treatment is required; that is, the selection of the anticoagulant should be based on the needs of each individual patient.

The available data showed the lowest overall risk for cross-reactions for pentosan polysulfate (36.4%) and, especially, fondaparinux (10.4%). In a clinical context, we therefore recommend the use of fondaparinux as the current best alternative in cases of DTH reactions.

Pentosan polysulfate may be used if no other alternatives are available.

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