

### Clinical Patterns of Heparin Allergy: Cross-reactivity Between Low-Molecular-Weight Heparins and Unfractionated Heparins

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**Palabras clave:** Heparinas no fraccionadas. Heparinas de bajo peso molecular. Test intradérmicos. Prueba de provocación simple ciego. Valor predictivo negativo.

Heparins are important anticoagulants used in the prophylaxis and treatment of thromboembolic disorders [1]. They include unfractionated heparins (UFHs) and low-molecular-weight heparins (LMWHs).

Hypersensitivity reactions to LMWHs are not uncommon. Delayed-type hypersensitivity reactions are the most frequently reported [2]. Immediate reactions to UFH and LMWHs have also been reported [3]. Furthermore, these agents can trigger type 2 hypersensitivity reactions (thrombocytopenia) and type 3 reactions (Arthus reaction) [4].

Little is known about cross-reactivity between heparins; therefore, tolerance must always be demonstrated. Tolerance does not seem to depend on molecular weight [5].

Twenty-five patients with a history of hypersensitivity reactions to LMWHs were diagnosed with heparin hypersensitivity in our Allergy Department between 2013 and 2017.

We recorded age, sex, clinical patterns, culprit drug, skin test results, and single-blind challenge tests (SBCTs) performed.

We performed intradermal testing (IDT) with the culprit LMWH (Table), UFH, and a battery of LMWHs, using the same concentrations as that of the original undiluted drug. Readings were taken after 20 minutes and at 48 and 96 hours in the case of delayed reactions and after 20 minutes in immediate reactions.

In delayed reactions, the SBCT was performed with LMWH (subcutaneous administration), and the therapeutic dose was reached in several days.

In order to prove tolerance to UFHs, the drug was administered at increasing doses at intervals of 48 hours. On

the first day, we administered 25% of the therapeutic dose, followed 60 minutes later by another 25% of the total dose. Fifty percent of the total dose was administered 48 hours later. The other 50% of the total dose was given 1 hour later (maximum 70 IU/kg, 5000 IU).

Female sex, older age, and longer exposure to heparins seem to be risk factors for heparin allergy [6].

We found enoxaparin to be the most frequent heparin involved in delayed reactions (80.76%). Bemiparin was

Table. Single-Blind Challenge Test Results

No.	Heparin Involved	Diagnosis	IDT with UFH	SBCT with UFH
1	Enoxaparin	IDT	+	NP
2	Enoxaparin	SBCT	-	+
3	Enoxaparin and bemiparin	IDT	+	NP
4	Enoxaparin	Clinical history	-	-
5	Enoxaparin	IDT	+	-
6	Enoxaparin	IDT	-	+
7	Enoxaparin	IDT	+	-
8	Enoxaparin	Clinical history	-	+
9	Bemiparin	SBCT	-	-
10	Enoxaparin	IDT	-	-
11	Enoxaparin	IDT	-	-
12	Bemiparin	IDT	-	-
13	Enoxaparin	IDT	-	-
14	Unknown	IDT	-	+
15	bemiparin	IDT	-	NP
16	Enoxaparin	IDT	-	-
17	bemiparin	IDT	-	-
18	Enoxaparin	IDT	-	NP
19	Enoxaparin and bemiparin	IDT	-	-
20	Enoxaparin	IDT	+	NP
21	Bemiparin	IDT	+	NP
22	Enoxaparin	Clinical history	-	-
23	Enoxaparin	Clinical history	-	-
24	Enoxaparin	SBCT	-	-
25	Enoxaparin	IDT	-	-

Abbreviations: IDT, intradermal test; NP, not performed; SBCT, single-blind challenge test; UFH, unfractionated heparin; +, positive; -, negative.

the culprit in 19.23% of delayed reactions and in 100% of immediate reactions.

A total of 25 patients were diagnosed with heparin allergy (19 females [76%], 6 males [24%]). The mean (SD) age was 68.8 (14.45) years (median, 72.5). Only 26.92% had a personal history of atopy. The most common clinical pattern in the 25 patients diagnosed with LMWH allergy from the total number of delayed reactions (92%) was local erythematous plaques (73.91%). The other 26.08% of reactions mostly involved maculopapular exanthema. We registered only 2 cases (8%) of type 1 immediate reactions, both consisting of urticaria.

All patients underwent IDT with the culprit agent and a battery of LMWHs including enoxaparin, bempaparin, nadroparin, dalteparin, tinzaparin, fondaparinux, and heparin sodium. The result was positive with enoxaparin in 16 cases (64%), with bempaparin in 13 (52%), with nadroparin in 18 (78.26%), with dalteparin in 15 (65.21%), and with tinzaparin in 18 (78.26%). All IDT results with fondaparinux were negative, although IDT results with heparin sodium were positive in 6 patients (24%).

SBCT was performed with several drugs according to the clinical history of the individual patient (Table). Delayed reactions to heparins were diagnosed based on IDT in 16 patients (69.56%), a suggestive clinical history in 4 patients (17.39%), and a positive SBCT result in 3 (13.04%).

Of the 23 patients diagnosed with delayed LMWH allergy, SBCT with UFHs performed in 15 patients yielded negative skin test results. The SBCT was positive in 3 of 15 patients (20%). All 3 patients presented maculopapular exanthema. The negative predictive value for IDT was 80%.

Two cases of immediate reaction were diagnosed based on a positive IDT result. SBCT with UFHs was negative in both. The negative predictive value for IDT was 100%, although the number of cases was too small to confirm this finding.

Hypersensitivity reactions to heparins are not uncommon, with delayed reactions being more frequent than immediate reactions.

Tolerance to fondaparinux is well known in patients who react to LMWHs [7].

Intravenous SBCT with UFHs was well tolerated in most cases, as reported elsewhere [8].

Pföhler et al [9] performed an intravenous challenge test with UFHs in 10 patients with a history of delayed reactions due to LMWH allergy. The drug was well tolerated in all cases. Gaigl et al [10] performed an intravenous challenge test with UFHs in 28 patients with a history of heparin sodium allergy after subcutaneous injection; all 28 patients tolerated the drug, possibly as a result of the difference in antigen processing and presentation and preferential homing of selectively sensitized lymphocytes in the dermis, but not in other locations. Pföhler et al reported data on 15 patients diagnosed with delayed reactions to LMWHs of whom SBCT with UFHs was performed in 10, all of whom tolerated the drug. Gaigl et al carried out an SBCT with intravenous UFHs in 28 patients with subcutaneous UFH allergy, and all patients tolerated the drug well. Not performing SBCT with UFHs is a viable option, since this is a complicated challenge test requiring intravenous administration.

Nevertheless, it is noteworthy that of the total number of delayed reactions in our study, 6 patients had a positive IDT result with UFHs, and 3 had positive results with SBCT, with total cross-reactivity between LMWHs and UFHs of 36% and 26% respectively. Therefore, cross-reactivity between LMWHs and UFHs is not uncommon.

IDT results are very useful for diagnosis, but they are not diagnostic in 100% of cases, with SBCT remaining the gold standard test in drug allergy.

Since UFH continues to be the heparin with the shortest half-life and the easiest to monitor during interventions, skin tests and SBCTs with UFHs should be performed in all patients with confirmed allergy to LMWHs.

The cross-reactivity we observed indicates the need to confirm tolerance to UFHs in patients diagnosed with heparin allergy.

In patients with allergic reactions to LMWHs, a full allergy work-up should be performed with skin tests and SBCT based on UFHs and all available LMWHs.

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#### *Conflicts of Interest*

The authors declare that they have no conflicts of interest.

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