Successful desensitization with un-fractionated heparin in a patient with heparin allergy and tolerance to fondaparinux

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Summary

Immediate hypersensitivity to low molecular weight heparin (LMWH) is rare, and we present here a case with an anaphylaxis-like symptoms to enoxaparin. The diagnosis of hypersensitivity to enoxaparin was confirmed by the clinical picture and positive skin tests. In this case, palmo-plantal itching after application of heparin was an early sign of immediate type hypersensitivity. His skin and provocation tests showed cross-reactivity with other types of LMWHs and un-fractionated heparin (UFH). Fondaparinux and desensitization with UFH were found to be safe alternative treatment options in this patient with heparin allergy. ***(Asian Pac J Allergy Immunol 2012;30:162-6)***

Key words: *Allergy, desensitization, fondaparinux, heparin, urticaria*

Introduction

Anticoagulants which are administered to prevent thrombosis may provoke allergic reactions besides adverse events including haemorrhage, osteoporosis or thrombocytopenia.[1] Local skin reaction and delayed-type hypersensitivity are the most frequently reported reactions in the literature,[2] whereas immediate-type hypersensitivity to heparins is extremely rare despite their frequent administration.[3] Un-fractionated heparin (UFH) derived from natural sources is thought to be more likely to cause allergic reactions, whereas the frequency of heparin allergic reactions began to decline after the production of low-molecular-weight heparins (LMWH)s obtained by fractionation of heparin.[1] On account of rarity of allergic reactions to heparins, both the diagnosis and the treatment is a problem due to lack of sensitive skin testing reagents. Here we report a diagnostic and therapeutic approach in a patient sensitive to multiple heparins.

Case report

A 26-year-old-male patient with acute deep venous thrombosis (DVT) experienced palmo-plantal pruritus followed by generalised urticaria, angioedema on his lips, and dyspnea 30 minutes after the first dose of enoxaparin administered subcutaneously (8000IU anti-XA/0.8mL). In the emergency department, heparin treatment was discontinued and pheniramine 91mg and methylprednisolone 40mg were administered. He was immediately referred to Allergy Department for alternative anticoagulants. During admission, a few urticarial plaques on his hands and rhonchi were detected on examination. He had a history of intermittent dyspnea for one year and a 2 pack-year smoking history. No history of allergy to drugs, foods, or insects was noted. The blood eosinophil count was 300/mm^3, total serum IgE was 294kU/l, and serum specific IgE for aeroallergens was negative. His pulmonary function tests revealed a forced expiratory volume in 1st second (FEV_1) of 2.23L (70% of predicted value), FEV_1/Forced vital capacity (FVC) ratio of 65%, and FEV_1 reversibility of 0.3L (19%). A diagnosis of asthma and enoxaparin allergy was made and treatment with salbutamol, pheniramine 45.5mg/2mL, methylprednisolone 40mg was prescribed for 2 days with complete improvement of his symptoms. He underwent diagnostic tests, beginning with UFH in order to avoid possible cross-reaction with other LMWHs. Although his medication might have had

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Table 1. Skin and challenge test results with unfractionated heparin (UFH), low molecular weight heparins (LMWH), and fondaparinux

Drug	Equivalent of 1:1*	Prick Test 1:1	Intradermal Test 1:100	Intradermal Test 1:10	Provocation Test 1:1
UFH;					iv, 0.1 mL
Heparin-sodium	5000 IU/mL	(-)	(-)	(-)	(+)
LMWHs;					sc, 0.05 mL
Enoxaparin	100 IU/mL	(-)	(-)	(+)	nd
Nadroparin	95 IU/mL	(-)	(-)	(-)	(+)
Dalteparin	100 IU/mL	(-)	(-)	(-)	(+)
Tinzaparin	100 IU/mL	(-)	(-)	(-)	(+)
Fondaparinux	0.5 mg/mL	(-)	(-)	(-)	(-)

iv: intraveneous, nd: not done, sc: subcutaneous
*: the amount in 1mL available in commercial preparation

a negligible effect on the allergy tests, the histamine control resulted in a positive skin tests confirming that short-term corticosteroid use (less than 1 week) and the prescription of pheniramine, a short-acting antihistamine, didn't affect the immediate skin test response. Skin prick tests (SPTs) and intradermal tests were found to be negative. A provocation test using intravenous injection of 0.1 mL UFH resulted in an immediate reaction including palmar rash, and pruritus followed by urticaria, angioedema, and bronchospasm and was treated with an inhaled β2-agonist, parenteral antihistamine and corticosteroids (Table 1). The next day, we decided to perform a rush desensitization with a heparin-sodium based rapid desensitization protocol.[4] Briefly, premedication, comprising montelukast-10mg, pheniramine-45.5mg, and methylprednisolone-20mg, were administered during the whole procedure at 24 hour intervals. Once the target doses were calculated, we prepared 4 solutions for the drug delivery (Table 2A). On the first day 1/100.000 of the reactive heparin dose was administered in a provocation test and then the heparin dose was doubled in 25 minute intervals until the first day's target dose was reached (Table 2B). The second day's target dose was the individual dose for DVT (18 IU/kg/h) and we followed the first day's procedure. Finally continuous heparin infusion was achieved with an effective activated-coagulation-time and was continued for another 4 days together with premedication. Warfarin was started on the 2nd day of the desensitization. During the desensitization procedure no allergic reaction occurred. A heparin-sodium infusion was discontinued when international normalised ratio (INR) reached a level between 2-3 and he was discharged with warfarin and inhalers for asthma.

The patient was referred to our clinic one month later when he had a recurrent DVT attack, possibly because the INR was lower than the therapeutic. We decided to find an alternative rapid onset anticoagulant for this attack of thrombosis. The patient was verbally informed about the diagnostic tests and gave written consent.

During this admission his coagulation parameters were within normal levels and the SPT, intradermal test and subcutaneous injection with LMWHs (enoxaparin, nadroparin, dalteparin, tinzaparin) and fondaparinux were performed on different days, enoxaparin being tested on the last day (Table 1). Skin tests were found to be negative for all the agents given except enoxaparin, administration of which resulted in an immediate skin rash and pruritus of his hands, followed by cough, dyspnoea with a 1/10 dilution given intradermally. A similar immediate reaction was also observed after subcutaneous injections of nadroparin, dalteparin, tinzaparin. Interestingly, the hypersensitivity response in skin and challenge tests started with palma-plantal pruritus followed by urticaria and angioedemea. The positive responses to skin and provocation tests were treated with inhaled β2-agonist, and parenteral pheniramine (45.5mg/2mL). Finally we tested fondaparinux and no reaction developed during the SPT, using the intradermal or subcutaneous route. Skin tests with heparins were negative in 10 healthy subjects, who were tested to exclude an irritant effect. The patient can safely use fondaparinux besides warfarin if his INR was below 1.5 during his treatment and he didn't have any recurrent emboli attacks.

Table 2. Rush desensitization protocol with UFH-heparin-sodium (Patient weight = 55 kg, starting dose $\leq$ 0.05 IU (1:100.000 of reactive dose [500 IU in 0.1mL]), 1st day's target dose = 500 IU, 2nd day's target dose = 1000 IU/hour [18 IU/kg/hour]).

2A. Prepared solutions

Solution	IU of drug	mL of solvent	Solution concentration (IU/mL)
A	5	250	0.02
B	50	250	0.2
C	500	250	2
D	5000	250	20

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2B. Desensitization protocol (intravenously)

Day	Step	Solution	Solution Concentration (IU/mL)	Time (hour)	Dose (IU)	Volume (mL)	Rate (mL/hr)	Cumulative Volume (mL)	Cumulative Dose (IU)
1	1	A	0.02	0	0.020	1.0	4.0	1.0	0.020
	2	A	0.02	0.25	0.040	2.0	8.0	3.0	0.060
	3	A	0.02	0.50	0.080	4.0	16.0	7.0	0.140
	4	A	0.02	0.75	0.160	8.0	32.0	15.0	0.300
	5	B	0.2	1.00	0.32	1.6	6.4	16.6	0.62
	6	B	0.2	1.25	0.64	3.2	12.8	19.8	1.26
	7	B	0.2	1.50	1.28	6.4	25.6	26.2	2.54
	8	B	0.2	1.75	2.56	12.8	51.2	39.0	5.10
	9	C	2	2.00	5.10	2.6	10.2	41.6	10.2
	10	C	2	2.25	10.20	5.1	20.5	46.7	20.5
	11	C	2	2.50	20.50	10.2	41.0	56.9	40.9
	12	C	2	2.75	41.00	20.5	81.9	77.4	81.9
	13			Run C solution at 75 mL/hour for 2.8 hour					500
2	14	C	2	0	41.00	20.5	81.9	97.4	541
	15	C	2	0.25	81.92	41.0	163.8	118.4	622.9
	16	D	20	0.50	163.84	8.1	32.7	126.1	786.7
	17	D	20	0.75	327.68	16.3	65.5	142.4	1113.7
	18	D	20	1.00	655.36	32.7	131.1	174.4	1778
	19	D	20	1.25	1000	50	50	224.4	2778
	20			Run D solution at 50 mL/hour for 24 hour					24000
3				Run D solution at 50 mL/hour for 24 hour					
4				Run D solution at 50 mL/hour for 24 hour					
5				Run D solution at 50 mL/hour for 24 hour					

Discussion

The pathogenesis of heparin reactions includes both a pseudo-allergic mechanism, such as activation of the kinin-kallikrein pathway by contaminants of UFH, or immunologic reactions, particularly of the cytotoxic-type (e.g. heparin-induced thrombocytopenia by IgG antibody against platelet-factor-4), immune complex-type (e.g. vasculitis), and cell mediated-type reactions (e.g. erythematous plaques/dermatitis generally at injection sites).[1] There are very few case reports with immediate-type hypersensitivity including urticaria, angioedemea, bronchospasm, and anaphylactic shock to UFH and LMWH.[3-7] In our case, anaphylaxis like symptoms after enoxaparin administration and skin test positivity suggested an immediate-type hypersensitivity reaction.

Even though allergic reactions to heparins have been known for a long time, immediate hypersensitivity to heparin is rare. In a case of suspected hypersensitivity, the treatment should be stopped.[8] Skin tests should be performed with all anticoagulants and preservatives with normalised coagulation parameters to prevent the development of hematoma.[1] For immediate-type reactions SPTs may be done with undiluted drugs and if these are negative, intradermal test with diluted drugs should be performed, due to the irritant effect of undiluted heparin as a result of its histamine-liberating activity.[1] Patch tests with undiluted doses of heparins may also be done to diagnose delayed-type reactions. Provocation tests with the original drug by parenteral or oral administration is the gold standard for diagnosis, but should be only performed by experienced and trained physicians in an appropriate

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surveillance setting.[9] However; in this case we were able to test some commercially avaible anticoagulants and evaluate the intradermal test after 48-72 hours to rule out late reaction instead of patch tests.

There are also in vitro tests for drug hypersensitivity, including the specific IgE and basophil activation-test.[1] Even though they may avoid the risk of performing a provocation test, their sensitivity and specificity for heparin is not yet reliable. Also tryptase levels may be measured in case of anaphylaxis. Both heparin specific IgE and tryptase were absent in our patient.

The treatment approach to heparin allergic patient depends on drug provocation tests in order to find an alternative anticoagulant to which the patient is nonreactive. Even though warfarin is said to be tolerated in heparin allergic patients, oral anticoagulation may not be appropriate in patients with acute embolism, those undergoing haemodialysis or cardiopulmonary bypass surgery.[3,7]

In some publications, patients with immediate hypersensitivity to UFH tolerated LMWHs, whereas patients with delayed hypersensitivity to LMWHs tolerated UFH.[1] However, in patients with immediate UFH allergy, cross-reaction to LMWHs,[6] and in patients with delayed-type reaction to LMWHs, cross-reaction to subcutaneous heparin or heparinoid have been reported.[9,10] Furthermore, different cross-reactive patterns are also possible, as documented in previously reported cases of anaphylaxis to anticoagulants.[6,3] So, as in our case there might be cross-sensitivity among the heparins due to common polysaccharide composition and as an alternative anticoagulant fondaparinux was found to be safe alternative in such patients.[2,11] Fondaparinux -factor Xa inhibitor- could be offered due to its low allergic potential and lack of cross reactivity with heparins, probably because of its full synthetic structure, ultra-low-molecular weight and different allergenic epitope.[9]

Desensitization is a therapeutic option in immediate-type hypersensitivity to heparin which aims to achieve antigen specific basophiles and mast cell desensitization.[1] It is achieved by administering progressive doses of drug from very small amounts to a full therapeutic dose at every 15-60 minutes intervals.[4,7] The procedure may be associated with acute allergic reactions requiring immediate treatment or the addition of premedication and should be continued up to the previous reactive dose. Thus desensitization is a temporary process that depends on the continuous administration of the drug. However, it is difficult to apply in primary health care centres and fondaparinux could be offered in the patient after negative skin and provocation tests.

Conclusion

In conclusion, we present a case of anaphylaxis-like symptoms due to enoxaparin whose skin/provocation tests showed cross-reactivity to other LMWHs and UFH. Palmo-plantal pruritus after application of heparins was an early sign of the immediate type hypersensitivity reaction. Fondaparinux and desensitization with UFH were found to be safe alternatives for immediate heparin allergy. Because of increasing use of heparin in daily medical practice, physicians should be aware of hypersensitivity symptoms to heparin. As heparins are important emergency drugs, this case provides guidance with regard to the diagnosis and treatment of heparin allergic patients. Assessment of a suspected hypersensitivity reaction to an anticoagulant should be tailored to each patient's needs.

Conflict of interest

None of the authors have any potential conflicts of interest.

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