

- 31 McGrath NM, Parker GN, Dawson P. Early presentation of type 2 diabetes mellitus in young New Zealand Maori. *Diabetes Res Clin Pract* 1999; **43**: 205–9.
- 32 *Health and Pacific peoples in New Zealand*. Wellington: Statistics New Zealand and Ministry of Pacific Island Affairs; 2011.
- 33 Grey C, Wells S, Riddell T, Kerr A, Gentles D, Pylypchuk R *et al*. A comparative analysis of the cardiovascular disease risk factor profiles of Pacific peoples and Europeans living in New Zealand assessed in routine primary care: PREDICT CVD-11. *N Z Med J* 2010; **123**: 62–75.
- 34 Scott A, Toomath R, Bouchier D, Bruce R, Crook N, Carroll D *et al*. First national audit of the outcomes of care in young people with diabetes in New Zealand: high prevalence of nephropathy in Maori and Pacific islanders. *N Z Med J* 2006; **119**: U2015.
- 35 Stedman KV, Leland LS. Obesity and intellectual disability in New Zealand. *J Intellect Dev Disabil* 2010; **35**: 112–5.
- 36 Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB *et al*. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry* 2015; **14**: 339–47.
- 37 Melkersson K, Jansson E. Effects of the atypical antipsychotic clozapine on insulin release *in vitro*. *Neuro Endocrinol Lett* 2007; **28**: 854–60.
- 38 Newcomer JW, Hennekens CH. Severe mental illness and risk of cardiovascular disease. *JAMA* 2007; **298**: 1794–6.
- 39 Narasimhan S, Weinstock RS. Youth-onset type 2 diabetes mellitus: lessons learned from the TODAY study. *Mayo Clin Proc* 2014; **89**: 806–16.
- 40 Carrero JJ, Grams ME, Sang Y, Ärnlöv J, Gasparini A, Matsushita K *et al*. Albuminuria changes are associated with subsequent risk of end-stage renal disease and mortality. *Kidney Int* 2017; **91**: 244–51.
- 41 Tan J, Zwi J, Collins J, Marshall MR, Cundy T. Presentation, pathology and prognosis of renal disease in type 2 diabetes. *BMJ Open Diabetes Res Care* 2017; **5**: e000412.
- 42 Witt N, Wong TY, Hughes AD, Chaturvedi N, Klein BE, Evans R *et al*. Abnormalities of retinal microvascular structure and risk of mortality from ischemic heart disease and stroke. *Hypertension* 2006; **47**: 975–81.
- 43 Liew G, Mitchell P, Wong TY, Wang JJ. Retinal microvascular signs are associated with chronic kidney disease in persons with and without diabetes. *Kidney Blood Press Res* 2012; **35**: 589–94.

doi:10.1111/imj.13659

BRIEF COMMUNICATIONS

Non-immediate heparin and heparinoid cutaneous allergic reactions: a role for fondaparinux

Elina Tan ¹, Grace Thompson ^{1,2}, Charlotta Ekstrom¹ and Michaela Lucas^{1,3,4,5}

¹Department of Clinical Immunology, and ³PathWest Laboratory Medicine, Sir Charles Gairdner Hospital, QEII Medical Centre, ²Department of Clinical Immunology, Fiona Stanley Hospital, ⁴School of Medicine and Pharmacology, University of Western Australia, and ⁵Institute for Immunology and Infectious Diseases, Murdoch University, Perth, Western Australia, Australia

Key words

hypersensitivity, unfractionated heparin, low molecular weight heparin, anticoagulation, venous thromboembolism, immunology.

Correspondence

Elina Tan, Department of Clinical Immunology, Sir Charles Gairdner Hospital, QEII Medical Centre, Hospital Avenue, Nedlands, WA 6009, Australia
 Email: elina.tan@health.wa.gov.au

Received 30 January 2017; accepted 12 June 2017.

Abstract

Non-immediate allergic cutaneous reactions to heparins have been increasingly reported, typically manifesting as large, eczematous plaques at sites of subcutaneous injection. Patients may demonstrate cross-reactivity between unfractionated heparin, low molecular weight heparin and semi-synthetic heparinoids, making finding an alternative difficult. Fondaparinux has been identified as a useful alternative in such patients; here we present the first two documented cases in Australia and a literature review.

Funding: None.

Conflict of interest: None.

Non-immediate allergic reactions to unfractionated heparin (UFH) and low molecular weight heparin (LMWH) have been increasingly reported, with more than 75 cases documented in the literature. Typical presentations include painful, erythematous plaques at injection sites, generalised rashes and heparin-induced thrombocytopenia Type II, with incidence likely under-reported. Finding alternatives can be challenging due to anticoagulant cross-reactivity. More recently, the anticoagulant fondaparinux has been identified as an alternative. Here we describe two cases which are, to the authors' knowledge, the first documented Australian cases of non-immediate, severe allergic cutaneous reactions to heparins and heparinoids, where fondaparinux was successfully used as an alternative anticoagulant. Additionally, a review of the literature regarding fondaparinux as an alternative anticoagulant in the setting of non-immediate hypersensitivity to heparins and heparinoids has been performed, to provide clinicians with an overview of the field.

Two patients were referred to clinical immunology outpatient clinics with a history of pruritic, erythematous plaques at abdominal injection sites, 12–48 h after administration of heparins. Patient 1, a 64-year-old woman (height, 1.63 m; weight, 120 kg; body mass index (BMI), 45.2) on warfarin for recurrent deep vein thrombosis (DVT) and pulmonary embolism, presented with previous reactions to subcutaneous LMWHs enoxaparin and dalteparin during periods of subtherapeutic international normalised ratio levels. Subsequent subcutaneous challenge to heparin (5000 units) and graded subcutaneous challenge to semi-synthetic heparin danaparoid at 1:10 and full doses (150 and 1500 units) resulted in severe local eczematous reactions within 24 h. Patient 2, a 41-year-old woman (height, 1.69 m; weight, 160 kg; BMI, 56.0), also developed non-immediate severe local eczematous allergic reactions to UFH given for DVT prophylaxis and later against enoxaparin, given for DVT treatment. Intracutaneous delayed readings (7 days; 1:100; 1:10) to heparin (50 and 500 units), enoxaparin (0.2 and 2 mg), dalteparin (50 and 500 units), danaparoid (7.5 and 75 units) and fondaparinux (0.025 and 0.25 mg) revealed positive reactions 6 days post-challenge to all except danaparoid and fondaparinux. Subsequent subcutaneous danaparoid challenge was unsuccessful. Subcutaneous challenge performed with both patients against fondaparinux at 1:10 and full doses (0.25 and 2.5 mg) resulted in no evidence of non-immediate cutaneous reactions. Rechallenge with fondaparinux in Patient 1 was successful (2.5 mg) (Fig. 1).



Figure 1 (Patient 1) Results of subcutaneous unfractionated heparin testing, 72 h post-injection into the abdomen.

Discussion

Heparins are mucopolysaccharides derived from bovine or porcine tissues, commonly used for prophylaxis and treatment of thromboembolism. Non-immediate hypersensitivity cutaneous reactions to heparins usually present as erythematous and tender lesions at the site of injection. These reactions are not infrequent and are likely an underreported phenomenon. Highlighting this, in a prospective study in Germany which investigated non-immediate reactions to subcutaneous heparins in patients under care of internal medicine, 24 of 320 patients showed signs of non-immediate reactions to heparins (incidence 7.5%).¹ Significant risk factors identified for such reactions include treatment duration >9 days (odds ratio (OR) 5.9), obesity (BMI > 25; OR 4.6) and female sex (OR 3.0).¹ For diagnosis, subcutaneous testing is considered the gold standard as false negative results are seen with intracutaneous testing and patch testing.^{2,3} Typical histological findings from biopsies of cutaneous reaction sites exhibit dermal oedema and mixed perivascular infiltrate with increased eosinophils.³

Identification of an alternative anticoagulant in cases of non-immediate cutaneous hypersensitivity can be challenging (Box 1). Substitution of one LMWH with another without testing is not recommended due to high rates of cross-reactivity.³ Alternatives to LMWH include heparinoids, hirudins and fondaparinux. Heparinoids (e.g. danaparoid) are semi-synthetic mixtures of porcine-derived glycosaminoglycans. Cross-reactivity between heparinoids and heparins is less common, therefore testing

is reasonable. Hirudins (e.g. desirudin) are peptides that are usually produced in the salivary glands of leeches; their mode of action is through thrombin inhibition.⁴ For medical use, recombinant hirudins are produced from yeasts.⁴ Cross-reactivity between hirudins and UFH and LMWH is observed less frequently, however significant allergic reactions, including severe eczematous reactions, fatal anaphylaxis and bleeding have been described,⁵ making this class a less appealing option.

Box 1 Non-immediate cutaneous hypersensitivity to heparins

- Non-immediate hypersensitivity reactions to heparins include localised skin reactions, generalised rashes and heparin-induced thrombocytopenia.
- Non-immediate cutaneous hypersensitivity reactions to heparins typically present as large erythematous, eczematous, painful and pruritic lesions at the site of subcutaneous injection.
- Subcutaneous challenge is the gold standard for diagnosis
- Significant risk factors identified include treatment duration >9 days, obesity and female sex.
- Fondaparinux, a subcutaneous anticoagulant that potentiates the activity of anti-thrombin, is a useful alternative.
- Non-immediate cutaneous allergic reactions to fondaparinux are rare, with an incidence of 0.4%.

Fondaparinux is the first in a new class of anticoagulants, comprising of a fully synthetic pentasaccharide sequence which binds to anti-thrombin and enhances its ability to inactivate factor Xa by 300-fold. Fondaparinux can be given for thromboembolism treatment and prophylaxis and is administered once daily subcutaneously with dose based on weight.

Based on the current literature, fondaparinux has been a useful alternative in at least 40 cases of non-immediate cutaneous reactions from heparins and heparinoids.^{3,5-11} Various studies and case reports from centres in Germany, Austria and Spain demonstrated that cross-reactivity is not uncommon between various types of UFH and LMWH and between heparins and heparinoids. In a total of 48 cases where patients with confirmed non-immediate reactions to heparins or heparinoids were challenged with fondaparinux, 43 did not demonstrate any non-immediate cutaneous reaction to fondaparinux.^{3,6-13} There are only five cases of cross-reactivity to fondaparinux reported, with three of these reactions occurring only after rechallenge.^{7,11-13} All five reactions were localised cutaneous reactions with no reports of anaphylaxis. Findings based on the current literature are presented in Table 1.

In a prospective study by Schindewolf (2010), of 231 patients administered fondaparinux and observed for subsequent cutaneous reactions, the incidence of cutaneous reaction was 0.4%. The primary aim of this

study was to assess the incidence and types of skin reactions to fondaparinux. The one patient who reacted to fondaparinux was a 44-year-old female with BMI of 35 who had not previously been exposed to heparins. Of the 231 patients administered fondaparinux, five had a history of previous non-immediate cutaneous reactions to heparins or heparinoids; however none of these patients demonstrated cross-reactivity to fondaparinux. Phan *et al.* (2014) identified patients with positive skin test(s) to at least one heparin, then tested for reactivity to heparins, hirudins and fondaparinux by intracutaneous challenge. All 11 patients tested against fondaparinux had negative readings. However on subsequent subcutaneous administration, two of seven patients followed up developed localised reactions, highlighting importance of re-challenge. Another three case reports from Germany also document reactions to fondaparinux. The first describes a 64-year-old female who reacted to UFH, LMWH and danaparoid also reacted to fondaparinux.⁷ The second case involves a 39-year-old female who had a documented history of non-immediate cutaneous hypersensitivity to several LMWHs. On initial subcutaneous exposure to fondaparinux, there was no documented reaction. However on subsequent exposure a localised eczematous reaction developed, again highlighting importance of re-challenge to confirm.¹² Finally, the third case describes a 59-year-old female who developed non-immediate cutaneous reactions to nadroparin. On testing with various LMWH, hirudins and fondaparinux, initially no reaction was demonstrated on intracutaneous testing. However following subcutaneous administration of fondaparinux, a non-immediate hypersensitivity cutaneous reaction developed. BMI was not documented for these latter three case reports.

The basis for cross-reactivity between heparins, heparinoids and factor Xa inhibitors (such as fondaparinux) is likely attributable to shared epitopes between these classes. Fondaparinux has potential to cross-react, because it represents the shortest sequence within the heparin molecule that is required to interact with factor Xa. The difference between these classes of anticoagulants in regards to their antigenicity and ability to induce non-immediate cutaneous reactions has been postulated to be related to their molecular heterogeneity, with heparins comprising large molecular weight structures (Mr 3000–58 000 Da) of high heterogeneity.^{6,11} This heterogeneity is not surprising given they are naturally occurring molecules sourced from various tissues of different species (porcine and bovine). In contrast, fondaparinux is a fully synthetic pentasaccharide structure (Mr 1700 Da), which is therefore homogenous in terms of its molecular structure and thus has fewer potential epitopes.

Table 1 Overview of studies testing cross-reactivity to fondaparinux

Authors	Study features	Anticoagulant confirmed to cause non-immediate cutaneous reactions (route)	Time frame until positive reaction	Patients tested with fondaparinux (successful/unsuccessful)
Phan <i>et al.</i> , 2014 ⁹ (<i>n</i> = 19)	Retrospective study. Patients with history of reaction to heparins	UFH (IC) LMWH (IC) Heparinoid (IC) Hirudin (IC) Fondaparinux (IC)	(ND)	9/2†
Schindewolf <i>et al.</i> , 2010 ¹¹ (<i>n</i> = 231)	Prospective study. Primary outcome was to determine incidence and causes of skin reactions after administration of fondaparinux. Five patients had history of non-immediate reactions to LMWH or heparinoid, but did not cross-react with fondaparinux.	LMWH (ND) Heparinoid (ND)	(ND)	5/0
Pföhler <i>et al.</i> , 2008 ³ (<i>n</i> = 15)	Single centre case series. Patients with history of reaction to LMWH.	UFH (IC, SC, patch, IV) LMWH (IC, SC, patch) Danaparoid (IC, SC)	20 min to more than 120 h (time frames for individual agents not specified)	14/0
Grims <i>et al.</i> , 2007 ⁶ (<i>n</i> = 8)	Single centre case series. Patients with history of reaction to LMWH	LMWH (SC) Danaparoid (SC)	24–72 h (ND)	8/0
Jappe <i>et al.</i> , 2004 ⁷ (<i>n</i> = 7)	Single centre case series. Patients with history of reaction to heparins and heparinoids	UFH (IC) LMWH (IC) Heparinoids (IC) Fondaparinux (IC, SC)	9 days to 3 weeks 2 days to 4 weeks 48 h 48 h	5/1
Parody <i>et al.</i> , 2003 ⁸ (<i>n</i> = 1)	Case report. Patient with history of reaction to LMWH	LMWH (SC)	5 days	1/0
Santiago Sánchez-Mateos <i>et al.</i> , 2010 ¹⁰ (<i>n</i> = 1)	Case report. Patient with history of reaction to heparins	UFH (IC, SC, patch) LMWH (IC, SC, patch)	7 days 4–7 days	1/0
Hirsch <i>et al.</i> , 2004 ¹² (<i>n</i> = 1)	Case report. Patient with history of reactions to heparins	UFH (IC) LMWH (IC, SC) Fondaparinux (IC, SC)	4 days 4 days 4 days	0/1†
Maetzke <i>et al.</i> , 2005 ¹³ (<i>n</i> = 1)	Case report. Patient with history of reactions to heparins	UFH (IC, patch) LMWH (IC, patch) Heparinoid (patch) Fondaparinux (IC, SC)	48 h 3 days 3 days 24 h	0/1

†Reaction only on rechallenge.

IC, intracutaneous; IV, intravenous; LMWH, low molecular weight heparin; ND, not documented. SC, subcutaneous; UFH, unfractionated heparin.

To the authors' knowledge, the two female patients described in our clinical record represent the first two reported cases of non-immediate cutaneous hypersensitivity reaction due to heparins from Australia, in whom fondaparinux has been identified as an alternative. The two patients both share the risk factors for non-immediate cutaneous hypersensitivity reactions to heparins; namely female sex, BMI > 35 and prolonged therapy. In summary, considering these two Australian cases and following a review of the international literature, cross-reactivity between UFH, LMWH and heparinoids is common and likely underreported, and fondaparinux is a useful alternative. We

recommend that in patients who demonstrate non-immediate cutaneous allergic reactions to heparin or LMWH, subcutaneous testing with heparinoids and fondaparinux should be performed if the patient has access to an allergy clinic with ability to perform such testing. Importantly, a negative result should be confirmed with a subsequent subcutaneous rechallenge. In the absence of availability of subcutaneous testing, and if an alternative to heparin or heparinoids is required imminently, fondaparinux can be substituted as it has a very low potential to cross-react. Closer monitoring for cutaneous reactions after subcutaneous administration of heparins should be

Table 2 Overview of test doses of anticoagulants used in our cases and in the literature

	Drug tested	Range of doses used (concentration)	Usual prophylactic dose
Intradermal testing	UFH	50 units (1:100), 500 units (1:10)	5000 units twice daily
	Enoxaparin	0.2 mg (1:100), 2 mg (1:10)	20–40 mg once daily
	Dalteparin	50 units (1:100), 500 units (1:10)	2500–5000 units once daily
	Danaparoid	7.5 units (1:100), 75 units (1:10)	750–1500 units twice daily
	Fondaparinux	0.025 mg (1:100), 0.25 mg (1:10)	2.5 mg once daily
Subcutaneous challenge	UFH	500 units (1:10), 5000 units (neat)	5000 units twice daily
	Dalteparin	1250 units (neat)	2500–5000 units once daily
	Danaparoid	7.5 units, (1:100) 75 units (1:10)	750–1500 units twice daily
	Fondaparinux	150 units (1:10), 375 units (neat); 1500 units (neat) 0.25 mg (1:10), 1.5 mg (neat), 2.5 mg (neat), 5 mg (neat), 7.5 mg (neat), 10 mg (neat)	2.5 mg once daily

Doses used in our cases are in bold. UFH, unfractionated heparin.

performed in those with risk factors of obesity, female sex and prolonged therapy. Fondaparinux is an anticoagulant with low allergic potential, likely owing to its fully synthetic pentasaccharide structure which has fewer potential epitopes¹¹ compared to the heterogeneous mix of

glycosaminoglycans that constitute heparins and heparinoids. It has emerged as a useful alternative for subjects with non-immediate cutaneous reactions to heparins, which can be used for both prevention and treatment of venous thromboembolism.

References

- 1 Schindewolf M, Schwaner S, Wolter M, Kroll H, Recke A, Kaufmann R *et al*. Incidence and causes of heparin-induced skin lesions. *CMAJ* 2009; **181**: 477–81.
- 2 Grassegger A, Fritsch P, Reider N. Delayed-type hypersensitivity and cross-reactivity to heparins and danaparoid: a prospective study. *Dermatol Surg* 2001; **27**: 47–52.
- 3 Pföhler C, Müller C, Pindur G, Eichler H, Schäfers H, Grundmann U *et al*. Delayed-type heparin allergy: diagnostic procedures and treatment alternatives – a case series including 15 patients. *World Allergy Organ J* 2008; **1**: 194–9.
- 4 Markwardt F. Hirudin as alternative anticoagulant – a historical review. *Semin Thromb Hemost* 2002; **28**: 405–14.
- 5 Koch P. Delayed-type hypersensitivity skin reactions due to heparins and heparinoids. Tolerance of recombinant hirudins and of the new synthetic anticoagulant fondaparinux. *Contact Dermatitis* 2003; **49**: 276–80.
- 6 Grims R, Weger H, Arbab E, Kränke B, Aberer W. Delayed-type hypersensitivity to low molecular weight heparins and heparinoids: cross-reactivity does not depend on molecular weight. *Br J Dermatol* 2007; **157**: 514–17.
- 7 Jappe U, Juschka U, Kuner N, Hausen BM, Krohn K. Fondaparinux: a suitable alternative in cases of delayed-type allergy to heparins and semisynthetic heparinoids? A study of 7 cases. *Contact Dermatitis* 2004; **51**: 67–72.
- 8 Parody R, Oliver A, Souto JC, Fontcuberta J. Fondaparinux (Arixtra®), as an alternative anti-thrombotic prophylaxis when there is hypersensitivity to low molecular weight and unfractionated heparins. *Haematologia* 2003; **88**: 147–8.
- 9 Phan C, Vial-Dupuy A, Autegarden J, Amsler E, Gaouar H, Abuaf N *et al*. A study of 19 cases of allergy to heparins with positive skin testing. *Ann Dermatol Venereol* 2014; **141**: 23–9.
- 10 Santiago Sanchez-Mateos DI, Eguren C, de Argila D, Sanchez-Perez J. Fondaparinux and lepirudin as therapeutic alternatives in a disseminated eczematous skin reaction to low-molecular-weight heparin. *Actas Dermosifiliogr* 2010; **101**: 556–8.
- 11 Schindewolf M, Scheuermann J, Kroll H, Garbaraviciene J, Hecking C, Marzi I *et al*. Low allergenic potential with Fondaparinux: results of a prospective investigation. *Mayo Clin Proc* 2010; **85**: 913–19.
- 12 Hirsch K, Ludwig RJ, Lindhoff-Last E, Kaufman KR, Boehncke W-H. Intolerance of fondaparinux in a patient allergic to heparins. *Contact Dermatitis* 2004; **50**: 383–4.
- 13 Maetzke J, Hinrichs R, Schneider L-A, Scharffetter-Kochanek K. Unexpected delayed-type hypersensitivity skin reactions to the ultra-low-molecular-weight heparin fondaparinux. *Allergy* 2005; **60**: 413–15.