CLINICAL PRACTICE

Delayed hypersensitivity to low-molecular-weight heparin (LMWH) in pregnancy

E Schapkaitz, B F Jacobson

Heparin is currently the anticoagulant of choice for the prevention and treatment of thrombo-embolic disease in pregnancy because it does not cross the placenta.[1] The use of low-molecular-weight heparin (LMWH) is preferred to unfractionated heparin (UFH) as it is associated with a lower risk of bleeding, osteoporosis, heparin-induced thrombocytopenia (HIT) and hypersensitivity reactions.[2-5] Fondaparinux is a valuable alternative to LMWH during pregnancy in patients with heparin-induced skin reactions and/or HIT.

Heparin-induced skin reactions are well documented with subcutaneously administered UFH; however they occur rarely (at reported rates between 0.3% and 0.6%) in association with LMWH.[6,7] Reports indicate that heparin-associated skin reactions are more common in pregnancy.[8] HIT can present as isolated skin manifestations and therefore must be excluded when skin lesions develop.[1] The skin reaction may resolve when LMWH preparations are interchanged.[9,10] However, when broad cross-reactivity between heparins develops, the choice of alternative anticoagulants is limited. In the majority of patients with skin necrosis, HIT and thrombosis may occur if heparin is not discontinued. Fondaparinux and other new direct thrombin inhibitors are alternative therapies in patients known to be hypersensitive to LMWH preparations. However, these agents have not been formally evaluated during pregnancy primarily because they cross the placenta.

Fondaparinux was used successfully in a young pregnant woman who presented with severe pulmonary thrombo-embolic disease at 16 weeks' gestation with a twin pregnancy. She developed a hypersensitivity reaction to two LMWH preparations, viz. enoxaparin and nadroparin.

Dr Elise Schapkaitz is a Senior Registrar in the Department of Haematology and Molecular Medicine, National Health Laboratory Service and University of the Witwatersrand, Johannesburg, and has an interest in clinical haematology. She has played an integral part in establishing an anticoagulation clinic at Chris Hani Baragwanath Hospital, Johannesburg.

Professor Barry Jacobson is Head of Clinical Haematology at the NHLS. He has a special interest in thrombosis and haemostasis and is the founding President of the Southern African Society of Thrombosis and Haemostasis. He has numerous publications in the field of thrombosis and is a member of international forums involved in thrombosis research.

Corresponding author: *E Schapkaitz (bradgelbart@icon.co.za)*

Case study

A 30-year-old woman presented with severe pulmonary thrombo-embolic disease at 16 weeks' gestation with a twin pregnancy. Her previous two pregnancies had been uneventful. She had been treated with an ovulation stimulant, clomifene (Clomid) 50 mg. She gave a history of urticaria pigmentosa in infancy, which is associated with an increased risk of hypersensitivity reactions.

She had no family history of thrombophilia and no history of allergy to UFH or LMWH, and was started on therapeutic enoxaparin (Clexane) 60 mg twice a day subcutaneously. Symptoms improved, her platelet count remained normal, and anti-Xa activity was monitored and maintained in the therapeutic range.

About 6 weeks later she developed erythematous, indurated lesions at injection sites on her thigh and abdomen (Fig. 1), accompanied by intense pruritus. There was no decrease in the platelet count. She was changed to nadroparin (Fraxiparine) 0.3 ml daily subcutaneously with a local cortisone cream. The skin reaction improved with no new rashes at the injection sites (Fig. 2), but 3 weeks later she developed a severe skin reaction. At this time (28 weeks' gestation), intramuscular betamethasone (Celestone) 4 mg/ml was given for fetal lung maturity, which resulted in partial resolution and relief from the pruritus. The skin reaction however recurred. Nadroparin was stopped and fondaparinux 2.5 mg was started daily. Anti-Xa activity was not monitored (dose adaptation is not required for patients receiving a fixed dose of 2.5 mg once daily).[11]

Treatment was continued uneventfully until healthy twin girls (birth weights 2 200 g and 2 400 g) were delivered by caesarean section. Cord blood fondaparinux concentration and anti-Xa activity were not measured in the newborn twins because fondaparinux was not given to the mother during the

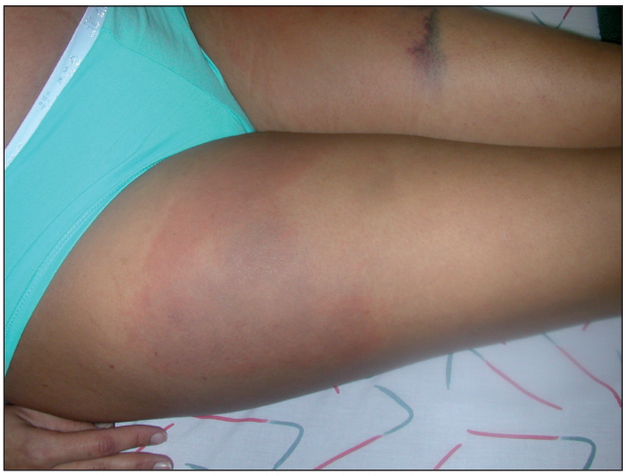

Fig. 1. Erythematous, indurated lesions developed at injection sites on the thigh after 6 weeks on enoxaparin (Clexane) 60 mg twice a day subcutaneously.

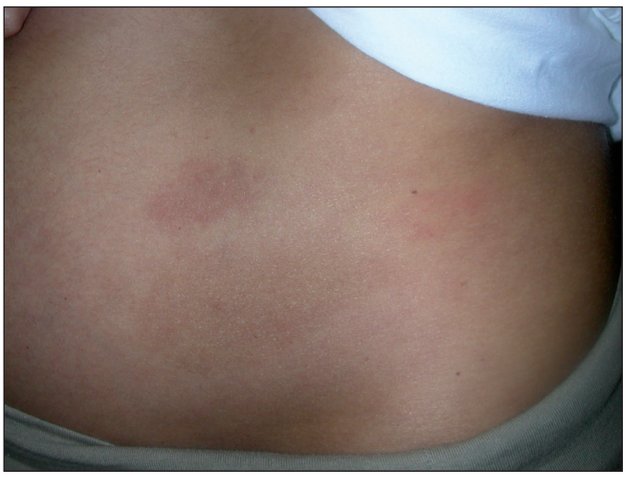

Fig. 2. Evidence of an initial improvement in the skin reaction with no new rashes at the injection sites after enoxaparin (Clexane) was stopped and nadroparin (Fraxiparine) with a local cortisone cream was commenced.

24 hours preceding caesarean section and cord blood was sent for stem cell harvesting.

Post partum she is fully warfarinised and is well.

Discussion

Skin complications occur more frequently with long-term use of LMWH.[12] This reaction, which in this case presented as tender erythematous lesions at the injection sites, probably represents a moderate delayed type IV skin reaction. These lesions may progress to necrotic patches. In some cases, histological examination of the skin lesions has shown thrombosis of the cutaneous vessels associated with HIT.[13]

In most patients with skin necrosis, heparin-induced thrombocytopenia and thrombosis (HIT type II) may occur if heparin is not discontinued.[14] However, in pregnancy choices of alternative anticoagulants are limited.

In South Africa only enoxaparin and nadroparin are recommended in pregnancy because anti-Xa levels can be monitored. Dalteparin is currently not recommended, as accurate anti-Xa monitoring is not available locally.

Vitamin K antagonists are generally contraindicated because they cross the placenta and are associated with a significant risk of brain damage in the fetus secondary to intracerebral haemorrhage, as well as teratogenesis in the first trimester.[15]

The successful use of hirudin derivatives has been reported in one case of pregnancy with heparin allergy. No adverse fetal outcome was demonstrated in animal models.[16]

Danaparoid, a low-molecular-weight heparinoid with low placental permeability, is considered by some to be the drug of choice for heparin allergy in pregnancy,[12,17-19] but is currently not available in South Africa and was therefore not an option in this patient.

Fondaparinux and other new direct thrombin inhibitors have not been formally evaluated during pregnancy, but large orthopaedic clinical trials have shown it to be as safe and effective as LMWH.[20,21] Fondaparinux is a synthetic pentasaccharide that inhibits factor Xa, and therefore could be used in patients known to be hypersensitive to LMWH preparations.[11] *In vitro* studies have failed to demonstrate cross-reactivity with fondaparinux in LMWH-intolerant patients. Reports of successful use of fondaparinux in patients who experienced hypersensitivity reactions to LMWH also suggest that cross-reactivity does not occur *in vivo*.[22, 23] Similarly, other studies indicate that fondaparinux is associated with a low risk of HIT.[24]

An advantage of fondaparinux is that it produces a predictable anticoagulant response and can be administered without anticoagulation monitoring. Alternatively, anti-Xa levels can be measured using assays similar to those used to monitor LMWH.[25] A recently published report indicated that fondaparinux does cross the placental barrier.[26] The anti-Xa activity detected in the umbilical cord blood was below the level required to have a therapeutic anticoagulant effect. It is not known whether fondaparinux potentially has a harmful effect on the fetus, and its use should be restricted to patients with either severe allergic reaction to heparin, as in our case, or HIT.

We wish to thank Hilda Jacobson for editing the manuscript.

1. Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(3): Suppl, 627S-644S.
2. Ginsberg JS, Chan WS, Bates SM, Katz S. Anticoagulation of pregnant women with mechanical heart valves. *Arch Intern Med* 2003; 163(6): 694-698.
3. Monreal M, Lafoz E, Olive A, del Rio L, Vedia C. Comparison of subcutaneous unfractionated heparin with a low molecular weight heparin (Fragmin) in patients with venous thromboembolism and contraindications to coumarin. *Thromb Haemost* 1994; 71(1): 7-11.
4. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126(3): Suppl, 311S-337S.

5. Warkentin TE, Roberts RS, Hirsh J, Kelton JG. Heparin-induced skin lesions and other unusual sequelae of the heparin-induced thrombocytopenia syndrome: a nested cohort study. *Chest* 2005; 127(5): 1857-1861.
6. Phillips JK, Majumdar G, Hunt BJ, Savidge GF. Heparin-induced skin reaction due to two different preparations of low molecular weight heparin (LMWH). *Br J Haematol* 1993; 84(2): 349-350.
7. Sanson BJ, Lensing AW, Prins MH, *et al*. Safety of low-molecular-weight heparin in pregnancy: a systematic review. *Thromb Haemost* 1999;81:668-672.
8. Baglin TP. Low-molecular-weight heparins and new strategies for the treatment of patients with established venous thrombosis. *Haemostasis* 1996; 26: Suppl 2, 10-15.
9. Bircher AJ, Itin PH, Tsakiris DA, Surber C. Delayed hypersensitivity to one low-molecular-weight heparin with tolerance of other low-molecular-weight heparins. *Br J Dermatol* 1995; 132(3): 461-463.
10. Mora A, Belchi J, Contreras L, Rubio G. Delayed-type hypersensitivity skin reactions to low molecular weight heparins in a pregnant woman. *Contact Dermatitis* 2002; 47(3): 177-178.
11. Samama MM, Gerotziafas GT. Evaluation of the pharmacological properties and clinical results of the synthetic pentasaccharide (fondaparinux). *Thromb Res* 2003; 109(1): 1-11.
12. Bank I, Libourel EJ, Middeldorp S, Van Der Meer J, Buller HR. High rate of skin complications due to low-molecular-weight heparins in pregnant women. *J Thromb Haemost* 2003; 1(4): 859-861.
13. Tonn ME, Schaiff RA, Kollef MH. Enoxaparin-associated dermal necrosis: a consequence of cross-reactivity with heparin-mediated antibodies. *Ann Pharmacother* 1997; 31(3): 323-326.
14. Warkentin TE. Heparin-induced skin lesions. *Br J Haematol* 1996; 92(2): 494-497.
15. Iturbe-Alessio I, Fonseca MC, Mutchinik O, Santos MA, Zajarias A, Salazar E. Risks of anticoagulant therapy in pregnant women with artificial heart valves. *N Engl J Med* 1986; 315: 1390-1393.
16. Aijaz A, Nelson J, Naseer N. Management of heparin allergy in pregnancy. *Am J Hematol* 2001; 67(4): 268-269.
17. Harrison SJ, Rafferty I, McColl MD. Management of heparin allergy during pregnancy with danaparoid. *Blood Coagul Fibrinolysis* 2001; 12(2): 157-159.
18. Lindhoff-Last E, Kreutzenbeck HJ, Magnani HN. Treatment of 51 pregnancies with danaparoid because of heparin intolerance. *Thromb Haemost* 2005; 93(1): 63-69.
19. Myers B, Westby J, Strong J. Prophylactic use of danaparoid in high-risk pregnancy with heparin-induced thrombocytopaenia-positive skin reaction. *Blood Coagul Fibrinolysis* 2003; 14(5): 485-487.
20. Bauer KA, Hawkins DW, Peters PC, *et al*. Fondaparinux, a synthetic pentasaccharide: the first in a new class of antithrombotic agents - the selective factor Xa inhibitors. *Cardiovasc Drug Rev* 2002; 20: 37-52.
21. Eriksson BI, Bauer KA, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *N Engl J Med* 2001; 345(18): 1298-304.
22. Sacher C, Hunzelmann N. Tolerance to the synthetic pentasaccharide fondaparinux in heparin sensitization. *Allergy* 2003; 58(12): 1318-1319.
23. 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(6): 276-280.
24. Warkentin TE, Levine MN, Hirsh J, *et al*. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995; 332(20): 1330-1335.
25. Weitz JI. Emerging anticoagulants for the treatment of venous thromboembolism. *Thromb Haemost* 2006; 96(3): 274-284.
26. Dempfle CE. Minor transplacental passage of fondaparinux *in vivo*. *N Engl J Med* 2004; 350(18): 1914-1915.