

Fondaparinux as anticoagulant in a pregnant woman with heparin allergy

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We report a patient who had a history of deep vein thrombosis in a previous pregnancy. She was treated with heparins without any reactions in the index pregnancy. Subsequently, when the patient became pregnant again, she developed an acute cutaneous reaction to the low molecular heparin enoxaparin 3 weeks after initiation of therapy. She developed a similar reaction to dalteparin as well. She was therefore treated with warfarin until 36 weeks of gestation. Then she was treated with fondaparinux (Arixtra, Sanofi-Synthelabo, Paris, France) 2.5 mg daily for the remainder of the pregnancy. Delivery was at term by induction of labour. Fondaparinux was stopped on the day of the induction of labour. It was re-started 6 h post-delivery and the patient was anticoagulated with warfarin in the post-partum period. There were no bleeding tendencies or

recurrences of thrombosis during fondaparinux therapy. Both mother and baby were well after delivery. *Blood Coagulation and Fibrinolysis* 17:147–149 © 2006 Lippincott Williams & Wilkins.

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Introduction

Fondaparinux sodium is a synthetic pentasaccharide. It has been used in prevention and treatment of venous thrombo-embolism (VTE), especially in orthopaedic practice. Heparin allergy has become more common in pregnancy since its use became widespread for thromboprophylaxis. VTE remains one of the leading causes of maternal deaths in the United Kingdom. We describe a case of a woman who was on thromboprophylaxis due to the past history of proven deep vein thrombosis in a previous pregnancy. The patient was managed on alternative therapies as she developed acute severe skin reaction to low molecular weight heparins. Fondaparinux was used successfully from 36 weeks of gestation until the early post-partum period.

Case report

We report the case of a pregnant woman who was treated with fondaparinux due to heparin allergy.

The patient, a 20-year-old female, underwent splenectomy for warm-type autoimmune haemolytic anaemia in 1998.

In 2001 she became pregnant for the first time at the age of 17 years. During her pregnancy, there was evidence of increasing haemolysis with falling haemoglobin and a reticulocytosis. Her platelet count remained persistently elevated post splenectomy. Around 26 weeks she developed a large left ileo-femoral deep vein thrombosis, which was confirmed by Doppler ultrasound. She was treated with therapeutic levels of low molecular weight

heparin (dalteparin) and aspirin 75 mg due to the high platelet count. She continued on heparin until delivery without reaction.

In 2004 she became pregnant again. Given her past history, evidence of on-going haemolysis and thrombocytosis, she was started on a prophylactic dose of low molecular weight heparin at around 11 weeks of gestation after the viability of the pregnancy was confirmed.

Two weeks later she presented with a delayed-type acute skin reaction (localized pruritic eczematous plaques) around the injection site following heparin injections. Dalteparin was stopped immediately. She was admitted to the hospital with a view of starting enoxaparin, a different variety of low molecular heparin, while under observation. However, the patient developed a reaction to enoxaparin with eczematous plaques initially at the site of administration but rapidly becoming disseminated. Enoxaparin was therefore discontinued. She has been on prophylactic penicillin ever since her splenectomy but has never had any allergic reaction to this.

At 13 weeks gestation the patient was started on warfarin and her International Normalized Ratio was maintained between 2 and 3. Aspirin was discontinued once the therapeutic range was achieved.

At 36 weeks of gestation warfarin was discontinued to avoid haemorrhagic complications for both mother and baby. Fondaparinux sodium was started at a dose of 2.5 mg subcutaneous once daily. No allergic reactions

were noted and the pregnancy progressed without complications. Foetal well-being was checked routinely and was satisfactory.

The patient was induced at 39 weeks and 5 days gestation for social and childcare reasons. Fondaparinux was stopped on the day of the induction of labour. Her labour was uncomplicated and she had only 300 ml blood loss at the delivery. She delivered a baby boy weighing 3.57 kg. She did not require an episiotomy. The baby was admitted to the special care baby unit but required only minimal input from the paediatricians.

Fondaparinux was restarted at the same dose 6 h after the delivery. Warfarin was restarted on the second day postpartum and the fondaparinux was discontinued when the patient's International Normalized Ratio was between 2 and 3 for 48 h. Warfarin was continued for 6 weeks postpartum.

Discussion

The use of heparins in pregnancy has increased recently to prevent complications such as foetal loss, intra-uterine growth restriction, early-onset pre-eclampsia and to prevent VTE in patients at high thrombotic risk (including haemolysis). The number of patients presenting with heparin-associated complications is therefore rising. Despite the recent availability of new anticoagulants, data relating to their use during pregnancy are lacking.

Heparin-associated skin reactions appear to be more common in pregnant women. This may relate to repeated exposure as a consequence of duration of heparin exposure. Cross-reactivity between heparin preparations, including low molecular weight heparins is common. It has been reported that there are no *in-vitro* cross-reactions between heparin antibodies and fondaparinux [1,2], making this drug a potentially useful alternative to low molecular weight heparins in patients allergic to heparin. Fondaparinux has been used successfully in a patient with repeated cutaneous reaction to several different low molecular weight heparins and also in a patient with severe heparin-induced thrombocytopenia [3].

When a patient presents with heparin allergy in pregnancy the clinician is left with very few choices. Some patients have benefited by changing the formulation of low molecular weight heparin alone (i.e. enoxaparin to dalteparin [4]), but this approach proved unsuccessful in the present case.

Danaparoid (Organon), a heparinoid, has been successfully used in a patient with heparin allergy [5,6], but in one such patient switching to a heparinoid failed as she was allergic to this as well [4]. We therefore decided not to use heparinoids.

Hirudin, a relatively new anti-thrombotic agent, has been shown through animal models to have a very low transplacental transfer and has been successfully used in a pregnant patient who was allergic to heparin, for recurrent deep vein thrombosis [7]. It has been reported, however that patients can develop anti-hirudin antibodies, which diminish its anticoagulant activity. Furthermore, fatal anaphylactic reactions have been reported with hirudin therapy [8]. For this reason we did not use it in our patient, and instead opted for fondaparinux.

Fondaparinux sodium is a synthetic pentasaccharide and a selective activated factor X (FXa) inhibitor. It was developed for the prevention and treatment of VTE. Fondaparinux exhibits complete bio-availability by the subcutaneous route and is rapidly absorbed, reaching its maximum concentration approximately 2 h post-dosing [9]. It has a terminal half-life of 13–21 h, permitting once-daily dosing [9]. Fondaparinux requires minimal dose adjustments due to its linear pharmacokinetic profile and does not require routine homeostatic monitoring [9]. It has been shown to reduce the VTE risk by more than 50% ($P < 0.0001$) without increasing clinically important bleeding compared with low molecular weight heparin [9,10].

Jappe *et al.* investigated seven patients with delayed-type reactions to heparins and semi-synthetic heparinoids for cross-reactivity to fondaparinux. Six of them tolerated fondaparinux, whereas one patient developed delayed-type hypersensitivity reaction [11]. Maetzke *et al.* discussed the alternative treatment for a woman who developed delayed-type hypersensitivity reaction to standard and low molecular heparin, heparinoid and pentosan polysulphate. They recommended use of fondaparinux for thromboprophylaxis [12]. In a different patient, however, Maetzke *et al.* described a delayed-type skin reaction to fondaparinux. They concluded that ultra-low molecular heparins could be used as a therapeutic alternative in some, but not in all, cases of delayed-type hypersensitivity reactions at heparin injection sites [13]. Hohenstein *et al.* described a similar reaction to fondaparinux [14].

Lagrange *et al.* conducted a study *in vitro* to compare the steady-state placental transfer of fondaparinux and enoxaparin at the plasma concentrations reached during acute treatment of venous thromboembolism (1.75 µg/ml and 1 anti-FXa IU/ml, respectively). They reported that no biological activity was detectable in foetal venous effluent during perfusion of enoxaparin, fondaparinux or control media [15].

Dempfle reported that fondaparinux might pass the placental barrier *in vivo*, resulting in measurable anti-FXa activity in umbilical cord blood, but the

concentration of fondaparinux in umbilical cord blood was well below the concentration required for effective anticoagulation and was only approximately one-tenth of the concentration in maternal plasma [16].

Safety data for newer anticoagulants in pregnancy are lacking. This is also true for fondaparinux, but it has been used in five pregnant women without any adverse effects in the mothers or the newborns [16].

The minimal or no placental transfer of fondaparinux makes it a worthy alternative to heparins and heparinoids in patients who develop heparin-induced type 2 thrombocytopenia or severe cutaneous allergic reactions to them.

Our case demonstrates that it is safe at least in the latter part of pregnancy. In the presented case baby and mother were both well at the end of the pregnancy. No allergic reactions at injection sites, thromboembolic events or abnormal bleeding were observed. No adverse effects were detected in the newborn baby. This warrants further research into the use of fondaparinux in pregnancy.

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