

Brief report

Fondaparinux is a safe alternative in case of heparin intolerance during pregnancy

Lucia Mazzolai, Patrick Hohlfeld, Francois Spertini, Daniel Hayoz, Marc Schapira, and Michel A. Duchosal

Heparin is the drug of choice for the treatment or the prevention of thromboembolic disease during pregnancy. However, treatment options are limited when heparin cannot be used because of hypersensitivity skin reactions. Despite the re-

cent availability of new anticoagulant agents, data relating to their use during pregnancy are lacking. This report describes the successful management with fondaparinux, during 150 days, of a pregnant patient with protein S deficiency and

prior deep vein thrombosis (DVT) who developed heparin and danaparoid hypersensitivity. (Blood. 2006;108:1569-1570)

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Introduction

Adverse reactions to low-molecular-weight heparins (LMWHs) are rare events. They may present with urticarial rash, a type I immediate hypersensitivity reaction, with skin necrosis due to vasculitis (type III Arthus reaction), or with heparin-induced thrombocytopenia (HIT). In absence of severe cutaneous manifestations and HIT, a particular LMWH may be replaced with another one with success. If the skin symptoms do not improve following LMWH change, cutaneous tests may help detect the presence of a cross-reactivity between the available preparations of LMWHs and danaparoid sodium, and guide the choice for a suitable anticoagulant. Indeed, in the presence of a negative subcutaneous provocation test, the compound can be used with low risk. If all LMWHs and danaparoid sodium yield a positive skin test, oral anticoagulants or hirudin can be used.

Fondaparinux is a synthetic pentasaccharide that has been extensively studied for use in surgery prophylaxis and the treatment of thromboembolic diseases.¹ It has been recently reported that anti-PF4/heparin antibodies are generated in a few patients during treatment with fondaparinux, however none developed thrombocytopenia.² Indeed, these antibodies do not bind well to PF4/fondaparinux complexes, thus are not able to activate platelets in the presence of fondaparinux. Along the same line, a recent case report described successful treatment of HIT with fondaparinux.³ However, it is still not clear whether cross-reactivity exists with fondaparinux in patients known to have hypersensitivity to several LMWH preparations. A few case reports described either formation of eczematous lesions at the injection site of a single dose of fondaparinux or tolerance.⁴⁻⁹

When heparin intolerance occurs in pregnant patients with a high risk of thrombosis, choices of alternative anticoagulation are limited. Danaparoid has been used to treat pregnant women with heparin intolerance or a history of HIT.¹⁰ The successful use of subcutaneous lepirudin¹¹ has also been reported in women with pregnancies complicated by HIT.^{12,13} Hirudin derivatives have been accompanied by fetal toxicities, and their use in this setting is contraindicated in Switzerland. Vitamin K antagonists cross the placenta and are associated with a risk of embryopathy between the

sixth and twelfth week of pregnancy. We report here successful treatment of a young pregnant woman, with broad cross-reactivity between several heparins and heparinoids, using fondaparinux.

Results and discussion

A 39-year-old pregnant patient with known protein S deficiency, with previous deep vein thrombosis (DVT) and family history of thromboembolic disease (TED) requires anticoagulant prophylactic therapy during pregnancy. Because of severe cutaneous allergic reactions to LMWH and unfractionated heparin (UFH) in the past (Table 1), she was initially treated with danaparoid sodium (subcutaneous injections twice daily). However, she soon developed severe skin reactions at the site of injections. Danaparoid treatment was stopped and subcutaneous injections of fondaparinux 2.5 mg daily were started. Treatment was continued uneventfully for 150 days until delivery. The patient did not develop any allergic reactions at the injection site, and no thromboembolic event or abnormal bleeding was observed. Platelet count remained within normal range, and no anti-fondaparinux-PF4 antibodies were detected. Anti-Xa activity was monitored during pregnancy. For this purpose, we adapted our standard laboratory method for determination of the anti-factor Xa activity of heparin based on inhibition of a constant amount of FXa, whose activity is determined by a specific chromogenic substrate (Sxa-11; Hyphen BioMed, Neuville-sur-Oise, France). However, in this setting fondaparinux was used instead of heparin for calibration, and measured fondaparinux levels were expressed in milligram per liter of the fondaparinux calibrator. Peak plasma levels of fondaparinux (about 3 hours after the dose) were the following: 0.35 mg/L, 0.43 mg/L, and 0.43 mg/L during the first, second, and third trimester, respectively. These concentrations are within the expected range of 0.3 to 0.5 mg/L for patients receiving 2.5 mg once daily, suggesting that during pregnancy no dose adaptation may be necessary.¹⁴ Cord blood fondaparinux concentration and anti-Xa activity were not measured in the newborn since fondaparinux was not administered

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Table 1. Results of allergologic investigations

Anticoagulants tested (tested doses)	Prick test	Intradermal test		Subcutaneous test
		20 min	7 d	
Enoxaparin (20 mg)	–	–	+*	–
Dalteparin (2500 UI)	–	–	+*	–
Nadroparin (2850 UI)	–	Positive	+*	–
Certoparin (3000 UI)	–	–	+*	–
Unfractionated heparin (5000 UI)	–	–	–	+
Desirudin (60 mg)	–	–	–	–

+ indicates papule larger than 8 mm with erythema.

*With eczema.

to the mother during the 24 hours preceding cesarean section. No adverse effects were observed in the newborn.

New direct thrombin inhibitors have not yet been formally evaluated during pregnancy. LMWH and UFH are the anticoagulants of choice, however their use may be complicated by occurrence of immunologic adverse reactions. Therefore, based on its efficacy and tolerability and on the basis of the present report,

fondaparinux may be a valuable alternative during pregnancy. To our knowledge, this is the sixth case reported in the literature, the longest in terms of treatment duration, of a pregnant patient with heparin and danaparoid hypersensitivity successfully treated with fondaparinux. Fetal safety is always an issue when considering maternal pharmacologic treatment. In a recently published report, a minor transplacental passage of fondaparinux was found in vivo. Five pregnant patients were treated with fondaparinux for 1 to 101 days, and anti-factor Xa activity in umbilical cord plasma of newborns was found to be one tenth the concentration of maternal plasma. This concentration was well below that required for effective anticoagulation.¹⁵ However, based on available data, one cannot exclude a potential deleterious effect of fondaparinux on the fetus even at very low doses. From animal studies, it seems that fondaparinux has no effect in the prevention of fetal death within the context of antiphospholipid antibodies.¹⁶ Therefore, the use of fondaparinux in pregnant women, until larger scale studies are available, should be limited to those patients with either severe allergic reactions to heparin, as was the case of our patient, or eventually to those with HIT.

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