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Letter to the Editors-in-Chief

Treatment of a woman with lupus and thromboembolism and cutaneous intolerance to heparins using fondaparinux during pregnancy

Sir,

We report on the first case of use of fondaparinux in early pregnancy. Treatment of venous thromboembolism during pregnancy is performed with aPTT-adjusted subcutaneous unfractionated heparin UFH). During the second and third trimester of pregnancy, anticoagulation may be switched to vitamin K antagonists [1]. The limitations of treatment with UFH and vitamin K antagonists have prompted the use of low-molecular-weight (LMWH) heparins, especially of dalteparin, throughout pregnancy [2]. Local intolerance to UFH, LMW-heparins and danaparoid has been reported and may complicate treatment during pregnancy [3,4].

Cutaneous lesions usually develop 2–4 days after injection and are erythematous, infiltrated and sometime eczematous in nature. Lesions become generalised if treatment is continued. The structural similarities of UFH and LMW-heparins entail a likelihood of cross-reactions between different kinds of heparin preparations. Cross-reactivity between heparins and heparinoids has been described using scratch test and intracutaneous testing [4].

Fondaparinux is a synthetic pentasaccharide binding to antithrombin and inhibiting factor Xa without inhibiting thrombin. The pentasaccharide domain is too small to be recognised by platelet factor 4 and the majority of heparin reactive antibodies [5]. Fondaparinux did not increase lipopolysaccharide induced cytokine production in isolated human monocytes and in whole blood in contrast to heparin, suggesting that it may not be an immunomodulator like heparin [6]. Fondaparinux reduced interleukin 6 and macrophage inflammatory proteins-2 expression and decreased neutrophil accumulation in the injured kidneys. Inflammation and neutrophil accumulation were mainly inhibited by recruitment of neutrophils through fondaparinux [7]. Thus, fondaparinux should not induce local immunological reactions leading to erythema and skin lesions. Accordingly, it was safely and effectively given to patients with delayed type allergy to LMW-heparin and semisynthetic heparinoids [8,9]. An in vitro human cotyledon model has shown that fondaparinux does not cross the placental barrier [10]. Since only minor if any placental passage of very low-molecular-weight pentasaccharide [11] and no teratogenic effects were reported [12], we decided to use fondaparinux for prophylaxis of thromboembolism in a patient with a history of lupus, thrombosis and cutaneous intolerance to heparin, LMW-heparins and danaparoid.

Fondaparinux has been shown to prevent effectively postoperative venous thromboembolism at a dose of 2.5 mg/day [13]. Treatment of acute deep venous thrombosis and pulmonary embolism was demonstrated using once daily 7.5 mg fondaparinux [14,15].

A 31-year-old woman, weight 76 kg, height 160 cm, suffered from systemic lupus with nephropathy, pleuritis and thrombocytopenia in 1991 and 1997. During pregnancy in 2001, she developed shill-blain lupus with purples red nodules at hands and feet. She suffered from two spontaneous episodes of venous thromboembolism 12 and 3 years and abortion at month 3 of pregnancy 2 years ago. She also had local intolerance to heparin, LMW-heparins and danaparoid, objectively documented by intracutaneous tests. Systemic antinuclear antibodies supported the suspicion of systemic lupus. Laboratory examinations revealed positive antinuclear antibodies (ANA) of 1:160 to 1:320 (normal $<$1:40) and elevated DNA of 40 IU/ml (normal $<$10 IU/ml), anticardiolipin IgG antibodies ranging from 22 to 48 IU/ml, IgM antibodies ranging from 12 to 31 IU/ml and negative SS-A and SS-B antibodies. Lupus anticoagulant was positive. Factor V-Leiden-, prothrombin mutation- and methyltetrahydrofolate-reductase mutation, antithrombin, protein C and protein S deficiencies were excluded. Before the current pregnancy, she was on stable vitamin K antagonist therapy with phenpro-

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coumon at an international normalised ratio (INR) of 2—3. Before initiation of pregnancy, the patient gave written informed consent to switch to oral anticoagulation to 1×2.5 mg fondaparinux combined with 100 mg acetylsalicylic acid/day.

During pregnancy, fondaparinux was well tolerated. The patient did not develop any signs or symptoms or laboratory indications for a recurrent episode of systemic lupus disease. The sonographic examinations of the foetus were regular until month 24. Thereafter, the diameter of the head was below the lower 95 percentile of normal range. Then, foetal growth retardation developed due to placental insufficiency. At week 34, the heard rate of the infant decreased to values between 100 and 120 per minute and delivery of the child was performed by caesarean operation. The newborn child (weight 1240 g, height 38 cm, cranial circumference 28 cm, APGAR of 08/08/10) was transferred to the neonatal intensive care unit due to respiratory distress syndrome grade 1 for 22 days. The neonate was transferred to a regular ward for another 24 days before discharged at home (bodyweight 2060 g, height 42 cm, cranial circumference 30 cm).

During pregnancy, the anticoagulant effect of 2.5 mg fondaparinux/day subcutaneously was determined by factor Xa inhibition assays. Factor Xa inhibition was measured using the chromogenic S2222 assay (normal range <0.01 μg fondaparinux/ml, Chromogenix, Essen, Germany). Heptest coagulation assay, which determines the biological activity of mainly anti-factor Xa activity of heparins and of fondaparinux, was done from all samples (normal values <21 s or <0.01 μg fondaparinux/ml, Haemachem Inc., St. Louis/Missouri, USA). Normal values in the umbilical cord were also <21 s [16]. Using a dilution curve of fondaparinux, the coagulation times in sec were converted to μg/ml. The lower limit of detection was 0.01 μg/ml fondaparinux in both assays. During pregnancy, blood samples were taken before and 2 h after the morning injection of fondaparinux into plastic tubes containing 3.8% sodium citrate (v/v: 9/1, blood/sodium citrate) by clean puncture of a vein of the forearm. The results of concentration and the biological activity 2 h after the subcutaneous injection of fondaparinux using the chromogenic S2222 assay and the heptest coagulation assay before, during and after pregnancy are given in Fig. 1. The concentration of fondaparinux in the S2222 assay ranged from 0.34 to 0.57 μg/ml. The values before pregnancy and after delivery were slightly higher than during pregnancy. The coagulation values of heptest ranged from 75 to 106 s (data not shown). The calculated concentration of fondaparinux using heptest ranged from 0.28 to 0.60 μg/ml. The values during pregnancy were also lower with this method compared to the values before and after pregnancy. At the day of delivery, the morning injection of fondaparinux was omitted. Fondaparinux was restarted at the same dose the day after delivery. Aspirin was given continuously without stopping before delivery. Three days after delivery, fondaparinux was switched to vitamin K antagonist therapy with phenprocoumon in combination with 100 mg aspirin daily.

The coagulation values in the plasma of the neonatal were 19.8 s (heptest) and the concentration in the S2222 assay <0.01 μg/ml fondaparinux at the day of delivery. In the umbilical cord, heptest was 30.7 s and the concentration of fondaparinux in the S2222 assay <0.01 μg/ml. The coagulation time of the Heptest assay would correspond to 0.028 μg/ml using a dilution curve of fondaparinux in pool plasma. The concentration of fondaparinux in the mothers plasma was 0.4 μg/ml during delivery. Accordingly, about 7% of fondapar-

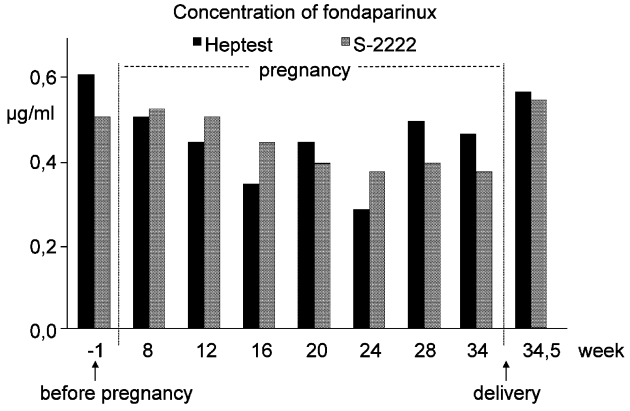

Figure 1 Concentration and biological activity of fondaparinux determined by S2222 chromogenic assays and heptest assay (μg/ml), respectively, before, during and after pregnancy in maternal plasma.

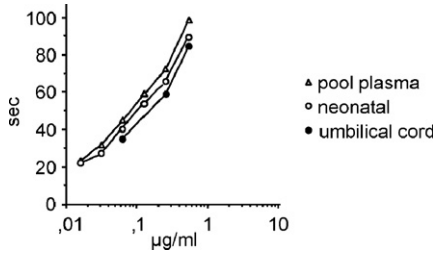

Figure 2 Spiking of pool plasma, plasma of the neonatal and the umbilical cord with fondaparinux (µg/ml) and coagulation times of the heptest assay (s).

inux was detected in the umbilical cord plasma using heptest and no fondaparinux using the chromogenic S2222 assay, which was present in the plasma of the mother, and of the umbilical cord of the neonatal. This difference is likely to be caused by the different methods, since the chromogenic assay uses supplementation with human pool plasma and heptest determines also non-antifactor Xa activities of and endogenous anticoagulants.

For more detailed analysis, serial dilutions of fondaparinux (0.018 to 0.56µg/ml) were added to pool plasma from 12 healthy subjects, to plasma of the neonatal and 0.07 to 0.56µg/ml to plasma of its umbilical cord vein. The differences between the coagulation time versus concentration curves should detect the amount of fondaparinux transferred by placental passage from the mother to the neonatal during pregnancy. The heptest coagulation times increased in a parallel manner after spiking the plasmas of the adult healthy pool, of the neonatal plasma and the plasma from the umbilical cord with serial dilutions of fondaparinux (Fig. 2). There were no difference between pool and neonatal plasma. The calculated amount of fondaparinux in plasma of the neonate and of the umbilical cord showed a 0.02µg/ml fondaparinux in umbilical cord plasma after the addition of all concentrations of fondaparinux in vitro. The S2222 assay did not show any difference between the three dilution curves (data not shown). This indicates first that both assays determine the activity and the concentration of fondaparinux in plasma from neonatal and umbilical cord. Secondly, the differences in the heptest assay may be caused by the lower plasma levels of coagulation factors in the umbilical cord and in the neonatal plasma compared to adult human pool plasma and not by fondaparinux. This is supported by a lower sensitivity of the chromogenic assay towards reduced levels of coagulation factors.

So far, fondaparinux was given for 1 to 101 days before delivery in five regnant women [11]. This is the first report on the safe and effective use of 2.5mg fondaparinux/day subcutaneously during the whole pregnancy for prophylaxis of venous thromboembolism. The woman suffered from a history of thromboembolism, cardiolipin antibodies and intolerance to heparins and danaparoid. Our data suggest that fondaparinux does cross the placenta into the foetal circulation to a very small amount if at all. A minimal amount of less than 0.02µg fondaparinux in foetal and neonate plasma is highly unlikely to be of any clinical significance.

References

[1] Büller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;**126:**401–28 [Suppl].

[2] Sanson BJ, Lensing AW, Prins MH, Ginsberg JS, Barkagan ZS, Lavenne-Pardonge E, et al. Safety of low-molecular-weight heparin in pregnancy: a systemic review. *Thromb Haemost* 1999;**81:**668–72.

[3] Warkentin TE. Heparin-induced skin lesions. *Br J Haematol* 1996;**92:**494–7.

[4] Harenberg J, Huhle G, Wang LC, Hoffmann U, Bayerl Ch, Kerowgan M. Association of heparin-induced skin lesions, intracutaneous tests, and heparin-induced IgG. *Allergy* 1999;**54:**473–7.

[5] Amiral J, Lormeau JC, Marfaing-Koka A, Vissac AM, Wolf C, Boyer-Neumann C, et al. Absence of cross-reactivity of SR90107A/ORG31540 pentasaccharide with antibodies to heparin-PF4 complexes developed in heparin-induced thrombocytopenia. *Blood Coagul Fibrinolysis* 1997;**8:**114–7.

[6] Hinzelmann M, Bosshart H. Fondaparinux sodium lacks immunomodulatory effects of heparin. *Am J Surg* 2004;**187:**111–3.

[7] Frank RD, Schabbauer G, Holscher T, Sato Y, Tencati M, Pawlinski R, et al. The synthetic pentasaccharide fondaparinux reduces coagulation, inflammation and neutrophil accumulation in kidney ischemia-reperfusion injury. *J Thromb Haemost* 2005;**3:**531–40.

[8] Jappe U, Juschka U, Kuner N, Hausen BM, Krohn K. Fondaparinux: a suitable alternative in cases of delayed-type allergy to and semisynthetic heparinoids? A study of 7 cases. *Contact Dermatitis* 2004;**51**:67—72.

[9] 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.

[10] Lagrange F, Vergnes C, Brun JL, Paolucci F, Nadal T, Leng JJ, et al. Absence of placental transfer of pentasaccharide (Fondaparinux, Arixtra) in the dually perfused human cotyledon in vitro. *Thromb Haemost* 2002;**87:**831–5.

[11] Dempfle CE. Minor transplacental passage of fondaparinux in vivo. *N Engl J Med* 2004;**350:**1914–5.

[12] Sanofi-Synthelabo Recherche and Organon NV. Clinical Investigator's Brochure Org31540/SR90107A; 2001, April 9, Edition E10.

[13] Turpie AG, Bauer KA, Eriksson BI, Lassen MR, for PENTATHALON 2000 Study Steering Committee. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replace-

ment surgery: a randomised double-blind trial. *Lancet* 2002;**359:**1721–6.
[14] Büller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al., for Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003;**349:**1692–702.
[15] Büller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al., for the Matisse Investigators. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med* 2004;**140:**867–73.
[16] Harenberg J, Schneider D, Heilmann L, Wolf H. Lack of anti-factor Xa activity in umbilical cord vein samples after subcutaneous administration of heparin or low molecular mass heparin in pregnant women. *Haemostasis* 1993; **23:**314–20.

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