THE JOURNAL OF
Obstetrics and Gynaecology Research
The official Journal of Asia and Oceania Federation of Obstetrics and Gynaecology
Japan Society of Obstetrics and Gynecology
doi:10.1111/jog.13302 J. Obstet. Gynaecol. Res. Vol. 43, No. 5: 943–945, May 2017

Use of fondaparinux for thromboprophylaxis in an unfractionated heparin-intolerant pregnant woman with thrombotic predisposition

Shoji Haruta[1], Kana Maruta[2], Yoshiyuki Nakajima[2] and Naoki Masaoka[2]

Departments of [1]Cardiology and [2]Maternal and Fetal Medicine, Tokyo Women's Medical University, Yachiyo Medical Center, Yachiyo, Japan

Abstract

A 34-year-old primigravida who had undergone thrombectomy for deep venous thrombosis (DVT) in her leg and exhibited low protein S activity, indicating predisposition to thrombosis, developed DVT of the leg. No pulmonary embolism was detected. After anticoagulant therapy with unfractionated heparin was discontinued because of liver dysfunction, danaparoid treatment was administered in hospital. The patient had a normal delivery after 39 weeks' gestation with no recurrence of thrombosis. During her second pregnancy four years later, she gave herself fondaparinux injections. She delivered normally after 38 weeks' gestation without experiencing DVT. Fondaparinux may be a useful anticoagulant for heparin-intolerant pregnant women.

Key words: fondaparinux, heparin intolerance, pregnancy.

Introduction

Individuals with congenital thrombotic predisposition have a high risk of thrombosis during pregnancy, delivery and the post-partum period.[1] Protein S deficiency is the most common cause of congenital predisposition to thrombosis in Japan. The prevalence of this condition is 0.03–0.13% among Europeans and North Americans, and approximately 1.12% among Japanese patients.[2] In Europe and North America, low-molecular-weight heparin (LMWH) is used as an anticoagulant to prevent venous thrombosis during pregnancy in high-risk individuals.[3] However, the 2011 Guidelines for Obstetrical Practice in Japan recommend the use of unfractionated heparin in such cases, and the use of LMWH is not covered by Japanese health insurance.[4] LMWH may be used in patients who experience side effects after receiving unfractionated heparin, although crossover with unfractionated heparin has been reported and similar side effects may still occur.[5]

New anticoagulants, such as fondaparinux, have emerged as replacements for heparin, but these products are rarely used in Japan and their safety has not been established. Hence, these drugs are restricted to cases where the benefits outweigh the potential risks or where other treatments cannot be used because of side effects. In this report, we describe the case of a pregnant woman with a thrombotic predisposition who was successfully treated as an outpatient through self-administered injections of fondaparinux. The patient ultimately delivered her child safely with no recurrence of venous thrombosis.

Case Report

The patient had no family history of thrombosis, although she had undergone a thrombectomy for deep venous thrombosis (DVT) in her left leg at the age of 16. She had subsequently been receiving oral warfarin (4.0–4.5 mg/day), which she discontinued at the age of 34 because she wanted to have children. She became pregnant with her first child five months later. At six weeks of gestation, she presented at our

Received: July 7 2016.
Accepted: December 26 2016.
Correspondence: Dr Shoji Haruta, Department of Cardiology, Tokyo Women's Medical University, Yachiyo Medical Center, 477-96, Oowada-shinden, Yachiyo, Chiba, 276-8524, Japan. Email: sharuta@tymc.twmu.ac.jp

hospital with pain in her left leg. Physical findings at the initial examination revealed height 154 cm, weight 49.9 kg, body mass index 21.0 kg/m^2, blood pressure 120/70 mmHg, pulse 63 beats per minute (regular), clear respiratory sounds and no audible cardiac murmur. An examination of the lower left leg revealed pigment deposition, tenderness and induration along the course of a surface vein. Ultrasonography revealed a deep venous clot, and the patient was admitted to hospital.

Laboratory testing revealed a prothrombin time > 100%, activated partial thromboplastin time (aPTT) 30.8 s, aPTT correctable with plasma (aPTT-c) 29.0 s, aPTT ratio (aPTT/aPTT-c) 1.06, fibrinogen levels 345 mg/dL, antithrombin III levels 30.8 mg/dL (15–31 mg/dL), D-dimer levels 10.71 μg/mL, lupus anticoagulant 0.9, protein C activity 101%, protein S activity 11%, antinuclear antibody titer < 1:40, anticardiolipin antibody titer 8.0 U/mL and anti-beta 2 glycoprotein 1 antibody titer < 0.7 U/mL. According to electrocardiography and echocardiography findings, the right ventricle was not enlarged and there were no signs of pulmonary hypertension. Based on the patient's thrombotic predisposition (low protein S activity and a history of thrombosis), we diagnosed the patient with DVT induced by the discontinuation of anticoagulant therapy and pregnancy. As the patient wanted to bear the child, we commenced anticoagulant therapy using unfractionated heparin and her D-dimer levels gradually declined. However, her liver enzyme levels also began to increase (aspartate aminotransferase levels up to 453 U/L, alanine aminotransferase levels up to 521 U/L), although testing did not reveal any other abnormal findings. Therefore, we diagnosed the patient with heparin-induced hepatotoxicity and discontinued heparin treatment on day 9. Her liver function subsequently returned to normal and we obtained the patient's informed consent to administer intravenous danaparoid (2500 U/day). At that time, tests for heparin-induced thrombocytopenia (HIT) were negative. The patient developed a subchorionic hematoma on day 26, which led us to reduce the dose of danaparoid (1875 U/day subcutaneously). She subsequently experienced a normal spontaneous vaginal delivery at week 39 of gestation, and we recommenced oral warfarin therapy to continue the anticoagulant therapy.

At the age of 38, the patient discovered that she was pregnant (week 5 of gestation), and discontinued warfarin treatment. Protein S activity was < 11% at the time. After obtaining approval from our hospital ethics committee and informed consent from the patient, therapy was altered to self-administered subcutaneous injections of fondaparinux (Arixtra; 2.5 mg/day). Venous thrombosis did not occur during the outpatient treatment. The patient experienced a normal delivery at 38 weeks of gestation. Fondaparinux injections recommenced the day after the delivery, and were ultimately replaced by warfarin therapy on an outpatient basis.

Discussion

Thrombosis prevention in pregnant women with a congenital thrombotic predisposition, such as protein S deficiency, is a significant challenge. The 2011 Guidelines for Obstetrical Practice in Japan divides the risk factors for venous thrombosis into three categories: (i) use of anticoagulant therapy before pregnancy, more than two past occurrences of DVT, one occurrence accompanied by thrombotic predisposition or one occurrence not associated with rest, dehydration or surgery; (ii) one occurrence of DVT related to temporary risk factors, such as dehydration or rest, thrombotic predisposition without a history of DVT or diseases including heart disease, lung disease and systemic lupus erythematosus; and (iii) more than three risk factors, such as age ≥ 35 years, body mass index > 30 kg/m^2, smoking and systemic infectious disease. Appropriate thromboprophylaxis options are recommended for each category.[4] Unfractionated heparin is recommended during pregnancy for the first category, and during pregnancy or temporarily for the second and third categories. Our patient fell into the first category, as she had developed DVT during her first pregnancy after discontinuing anticoagulant therapy. Hepatotoxicity after unfractionated heparin administration resulted in a switch to danaparoid. Warfarin treatment, which was replaced with fondaparinux injections during the second pregnancy, was reinstated after the second delivery.

In Japan, unfractionated heparin or LMWH may be used as an anticoagulant to prevent venous thrombosis during pregnancy in high-risk individuals. However, crossover reactions with heparin and side effects, including HIT, liver dysfunction and skin complications, have been reported.[5] The reported incidence of hypersensitivity reactions to LMWH in pregnant women is about 20%.[6] Apart from unfractionated heparin or LMWH, danaparoid and fondaparinux are used as anticoagulants in pregnant women.

Danaparoid is a low-molecular-weight heparinoid composed primarily of heparin sulfate, which selectively blocks factor Xa. In a study of heparin intolerance, of 91

pregnancies in which danaparoid was used for thrombosis prevention, 90% were unproblematic.[7] The rates of live births were superior, while those of spontaneous miscarriages and pre-eclampsia were inferior to those of other antithrombotic drugs. However, the premature birth rate was high, and the safety of danaparoid was unidentified.

Fondaparinux is a pentasaccharide that is the smallest effective unit of heparin. It is the first synthetic antithrombogenic drug, and acts by selectively blocking factor Xa through its high affinity for antithrombin. The completely synthetic nature of fondaparinux means that there is no risk of animal-derived contaminants (unlike unfractionated heparin or LMWH), and it binds almost completely to antithrombin with no affinity for other proteins or cells. For example, fondaparinux does not interact with platelet factor 4 to affect platelet aggregation. Hence, it cannot generate new epitopes that can cause type II HIT as *in vitro* studies have revealed that fondaparinux does not cross-react with type II HIT-related antibodies. A study including 15 pregnant women with heparin intolerance suggested that fondaparinux might be a safe and efficacious alternative anticoagulant; however, the number of cases in this study was small.[8] A review of fondaparinux use in pregnant women with a high risk of thrombosis showed that in 65 pregnancies, fondaparinux was well tolerated and the rate of pregnancy complications was similar to that observed in general populations. Pregnancy was interrupted because of fetal abnormalities in one case.[9] Reportedly, fondaparinux does not pass through human placenta *in vitro*, but a few placental transfers and a shift to a fetus can be seen in rats *in vivo*.[10] Hence, the safety of fondaparinux for a human fetus needs to be established.

Fondaparinux is dispensed in prefilled syringes, which makes self-injection simple, and this ease of management increases its potential for preventing venous thrombosis in pregnant women. The use of fondaparinux in heparin-intolerant pregnant women may be necessary, and we anticipate that its effectiveness and safety will soon be established.

Disclosure

The authors have no potential conflicts of interest.

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