Fondaparinux (arixtra®), as an alternative antithrombotic prophylaxis when there is hypersensitivity to low molecular weight and unfractionated heparins

During the last decade, new anticoagulant drugs with anti-factor-Xa properties have been described.[1,2] These include fondaparinux, which has been licensed recently. This is a pentasaccharide mimicking the site where heparin binds to antithrombin III.[1] This new drug has produced very promising clinical results in the prophylaxis of venous thrombosis after orthopedic surgery.[3] Here we report two different clinical situations in which fondaparinux has yielded a successful outcome: first, a patient with repeated cutaneous reaction to several different low molecular weight heparins (LMWH), and second, a patient with severe heparin-induced thrombocytopenia (HIT). We decided to use fondaparinux in both cases since it is commercially available in Spain and mostly because the absence of *in vitro* cross-reaction with heparins, as discussed later.

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Case 1. In November 2002, a sixty-eight year-old female, with no pathologic antecedents of interest, suffered an episode of saphenous vein thrombosis on the left leg. The LMWH, bemiparin (Hibor®, Laboratorios Rovi, Madrid), was administered at therapeutic doses (7500 aXa IU/d sc). After the fifth day of heparin therapy, she developed a local urticariform reaction around the point of administration. So, her treatment was changed to another LMWH, tinzaparin (Innohep®, Farmacusi, Barcelona) 10000 aXa IU/d. The same skin reaction was observed immediately. Also, enoxaparin (Clexane®, Aventis Pharma, Madrid) at a dose of 6000 aXa IU/12h produced identical side effects. Due to this allergy to these LMWH, oral warfarin (Aldocumar®, Laboratorios Aldounion, Barcelona) was administered and was clinically well tolerated. Her platelet count was within the normal range (>190x10^9/L) in successive analyses on days 6, 15 and 20 after the start of LMWH. Because the patient had a spontaneous venous thrombosis, screening for occult cancer was done and an endometrial adenocarcinoma was detected. Radical surgery was programmed. Three days before surgery, warfarin was discontinued and preoperative prophylaxis was initiated with fondaparinux (Arixtra®, Sanofi Synthelabo, Barcelona), at 2.5 mg/d sc (accepted standard dose). The time between the first administration of LMWH and the start of fondaparinux was 24 days. The standard dose of fondaparinux was maintained for a week after surgery, until an adequate INR range was obtained with warfarin. Blood levels of platelets, before and after the operation, were up 200x10^9/L. The patient did not suffer any thrombotic and/or hemorrhagic complications. In addition, no local skin reactions following fondaparinux administration were observed.

Case 2. In December 2002, a thirty-two year-old female with systemic lupus erythematosus underwent a voluntary abortion. A few days later, she developed fever, diffuse abdominal pain, vomiting and diarrhea; neither neurological deficiencies nor other symptoms were present. Her blood analysis showed moderate normocytic anemia and moderate thrombocytopenia (80x10^9/L). She also presented with acute renal failure and a high count of peripheral schistocytes. Progressively, she showed hyperconsumption and intravascular hemolysis: a D dimer concentration of 10550 ng/L (Liatest D-Dimer, Roche Diagnostics, Mannheim), high dehydrogenase lactate plasma levels and absence of haptoglobin. Signs of ileitis were visible by abdominal ultrasound. A laparoscopy demonstrated intraperitoneal liquid and disseminated purpura along the intestinal mucosa. Renal biopsy showed type IV glomerulonephritis and kidney thrombotic microangiopathy. Plasmapheresis (a total of six sessions) and immunosuppressive treatment with cyclophosphamide and steroids were started. In addition, unfractionated heparin (UFH) was administered at prophylactic doses. Her platelet count increased to 150x109 /L. Eleven days after heparin initiation, the platelet count decreased progressively until it reached 50x10^9/L (Figure 1). HIT was confirmed by the presence of antibodies against the PF4-heparin complexes (Diamed®, DiaMed Iberica, Barcelona). Heparin therapy was replaced by fondaparinux (Arixtra®) therapy at adjusted doses of 0.5 mg/day because of renal insufficiency. In successive analysis after heparin suppression, no increase of fondaparinux dose was needed based on the anti factor-Xa activity measured in the STA Coagulation Analyzer (Roche) using the reactive Rotachrom anti-Xa® from Roche Diagnostics, Mannheim (Figure 2). Two days after initiating fondaparinux the thrombocytopenia returned to normal (Figure 1). Renal function improved progressively after the starting of oral anticoagulation and became normal by day 34. No other relevant complications were observed.

Discussion. Patients who undergo heparin therapy (with UFH and, more rarely, with LMWH) may develop clinical complications such as allergic reactions in the

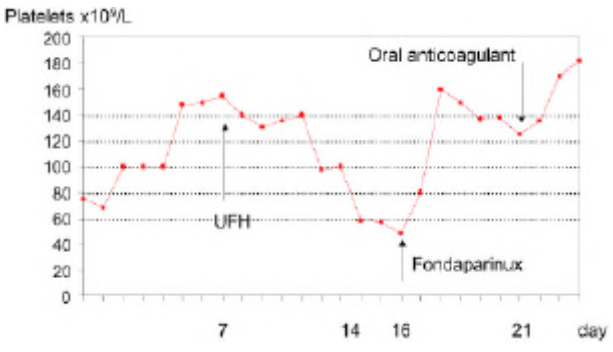

Figure 1. Case 2. Platelet count during the clinical course.

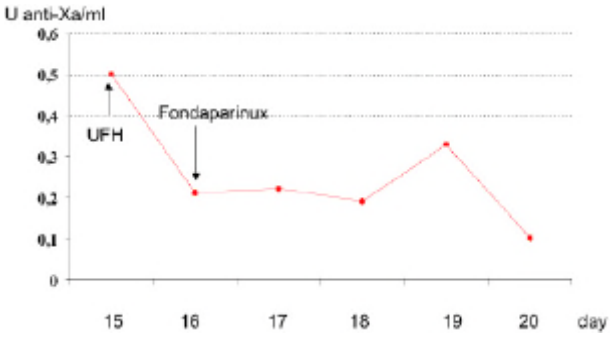

Figure 2. Case 2. Anti-Xa activity during fondaparinux treatment.

skin. This secondary effect may begin 2-5 days after subcutaneous administration of heparin.[4] In a patient not previously exposed to heparin, type II HIT characteristically occurs five to ten days after heparin initiation. Because it is associated with a significant morbidity and mortality, new and safe alternatives to heparin therapy are needed. Several alternative drugs are available such as thrombin-specific inhibitors, e.g., lepirudin and argatroban, and danaparoid sodium, an heparinoid agent. Unfortunately, there is no consensus on the use of these drugs because each one has its limitations. Hirudin and its recombinant form, lepirudin, must be adjusted in cases of renal insufficiency and patients can develop anti-hirudin antibodies which diminish its anticoagulant activity. Recently, severe anaphylactic reactions have been reported following hirudin therapy.[5] The dose of argatrobán needs to be adjusted in cases of hepatic disease, but immune responses are not common. Danaparoid sodium occasionally produces anti-PF4 antibodies.[2] A good alternative and likely the drug of choice appears to be fondaparinux, whose biological action is based on the selective inhibition of activated Factor X, with no effect on aPTT and PT, and no binding to PF4.[6] Its bioavailability after subcutaneous administration is almost 100%, and a singledose of 2,5 mg/day is a standardized prophylactic dose, because of the drug's long half-life of 17 hours. The dose must be adjusted when there is renal insufficiency.[7,8] According to phase III assays, fondaparinux is at least as useful as LMWH in the prophylaxis of thromboembolic disease.[3] Neither a significant increase of severe bleeding nor secondary induced thrombocytopenia has been described following fondaparinux use. There are no *in vitro* cross-reactions between heparins and fondaparinux,[9,10] and presumably the same would apply *in vivo*. To our knowledge, the two clinical cases reported here are the first description of the use of fondaparinux in the presence of hypersensitivity to UFH or LMWH. We have demonstrated that this new anticoagulant drug is a safe alternative to others in these circumstances. Further studies are necessary to definitely establish the beneficial use of fondaparinux in other similar cases.

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References

1. Walenga JM, Jeske WP, Bara L, Samama MM, Fareed J. Biochemical and pharmacologic rationale for the development of a synthetic heparin pentasaccharide. Thromb Res 1997;86:1-36.
2. Alving BM. How I treat heparin-induced thrombocytopenia and thrombosis. Blood 2003;101:31-7.
3. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery. A meta-analysis of 4 randomized double-blind studies. Arch Intern Med 2002;162:1833-40.
4. Harenberg J, Huhle G, Wang L, Hoffmann U, Bayerl C, Kerowgan M. Association of heparin-induced skin lesions, intracutaneous tests, and heparin-induced IgG. Allergy 1999 May;54:473-7.
5. Anonymous. Fatal anaphylactic shock caused by lepirudin. Prescrire Int 2003; 64:64.
6. Walenga JM, Jeske WP, Samama MM, Frapaise FX, Bick RL, Fareed J. Fondaparinux: a synthetic heparin pentasaccharide as a new antithrombotic agent. Expert Opin Investig Drugs 2002;11:397-407.
7. Samama MM, Gerotziafas GT. Evaluation of the pharmacological properties and clinical results of the synthetic pentasaccharide (fondaparinux). Thromb Res 2003;109:1-11.
8. Reverter JC. Fondaparinux. Drugs Today 2002;38:185-94.
9. Elalamy I, Lecrubier C, Potevin F, Abdelouahed M, Bara L, Marie JP, et al. Absence of in vitro cross-reaction of pentasaccharide with the plasma heparin-dependent factor of twenty-five patients with heparin-associated thrombocytopenia. Thromb Haemost 1995 ;74:1384-5.
10. Amiral J, Lormeau JC, Marfaing-Koka A, Vissac AM, Wolf M, 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.