Treatment of Thrombosis With Fondaparinux (Arixtra) in a Patient With End-stage Renal Disease Receiving Hemodialysis Therapy

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Summary: Treatment of thrombosis in children with end-stage renal disease (ESRD) is extremely challenging owing to the underlying risk of bleeding. Fondaparinux (Arixtra, Sanofi-Synthélabo), a synthetic pentasaccharide, is contraindicated in patients with compromised renal function as it is excreted via kidneys. We describe a unique case with ESRD and pulmonary embolism who was treated with fondaparinux owing to the toxicity and poor compliance with low-molecular-weight heparin. Despite regular hemodialysis, a gradual rise in drug levels was observed without significant bleeding complications. This report implies that although low dose fondaparinux can be an option in patients with ESRD under special circumstances, guidelines for laboratory monitoring and appropriate dose adjustments are urgently required to ensure the safety of the patient.

Key Words: fondaparinux, hemodialysis, end-stage renal disease

(*J Pediatr Hematol Oncol* 2007;29:581–584)

BACKGROUND

Thromboembolic complications are increasingly being recognized in patients with end-stage renal disease (ESRD).[1] No treatment guidelines are available for managing patients with ESRD and thrombosis as patients with ESRD are often excluded from clinical trials due to risk of bleeding. Pharmacologic options for the treatment of venous thromboembolism (VTE) include vitamin K antagonists (warfarin derivatives), heparin derivatives [unfractionated heparin (UFH), low-molecular-weight heparins (LMWH)], synthetic pentasaccharides (fondaparinux), and direct thrombin inhibitors (hirudin, lepirudin, and argatroban).[2,3] A variety of factors like physician preference, formulary recommendations, extent of thrombosis, potential complications associated with thrombosis, risk factors for thrombosis, impending risk of bleeding, history of heparin-induced thrombocytopenia (HIT), patient compliance, interaction with other medications, presence of other comorbid conditions affect the safety, efficacy, and selection of appropriate VTE therapy in this patient population.[4] LMWH and fondaparinux are contraindicated in patients with ESRD, as they are primarily excreted via kidneys. UFH is inconvenient as a maintenance therapy owing to its mode of administration (continuous intravenous infusion) and requirement of frequent monitoring of activated partial thromboplastin time (APTT) to maintain therapeutic efficacy. Warfarin derivatives compete with various medications frequently encountered in ESRD such as multivitamins, antibiotics, proton-pump inhibitors etc, hence maintaining therapeutic International Normalized Ratio is extremely challenging. Direct thrombin inhibitors are not used as a first line of therapy for the treatment of VTE in children. Their use in children is limited to HIT. Therefore, every child with ESRD and VTE poses a new therapeutic challenge for the treating physician. In this article, we share our experience of treating a VTE in a renal failure patient with fondaparinux sodium (Arixtra, Sanofi-Synthélabo).

Fondaparinux sodium is a synthetic pentasaccharide, which has been recently approved by FDA for the treatment and prevention of thrombosis in adults. The antithrombotic activity of fondaparinux sodium is mediated through the antithrombin (AT)-mediated selective inhibition of factor Xa.[5,6] Its advantages over other anticoagulants are its predictable linear pharmacokinetics requiring no therapeutic monitoring,[7,8] a half-life of 12 to 17 hours requiring once daily dosing,[8,9] and the lack of cross-reactivity with heparin-induced antibodies.[10] Renal excretion accounts for 55% to 85% of its clearance; therefore, a dose reduction is required for patients with renal failure.[8] The treatment dose of fondaparinux is based on the weight of the patient (50 to 75 kg, 5 mg; 75 to 100 kg, 7.5 mg; and 100 kg and above, 10 mg) (Arixtra package insert, 2006). A major limitation for fondaparinux use is the absence of published peak and trough levels that correlate with clinical outcome. In addition, there is a lack of guidelines for dose modifications in

Received for publication January 19, 2007; accepted May 18, 2007.
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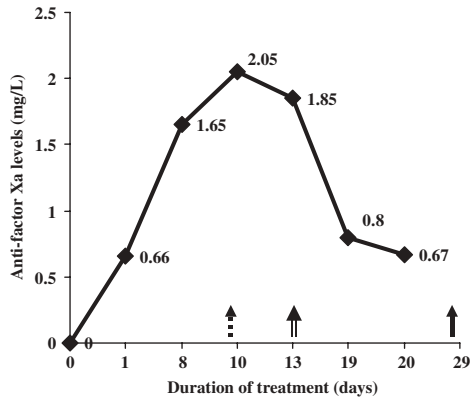
select patient populations including children, renal failure, pregnant women, and unavailability of definitive antidote to reverse its action. In patients with renal failure, the incidence of major bleeding correlates with the degree of renal failure, ranging from 0.4% to 1.6% in patients with a mild renal dysfunction to 4.8% to 7.3% in those with severe renal dysfunction (Arixtra package insert, 2006).[11] Hence, it is rarely preferred for treating VTE in this population. So far, there are only 2 case reports on adult patients receiving hemodialysis (HD) therapy; 1 patient had HIT and another one had an allergic reaction to LMWH.[12,13] Pharmacokinetics of fondaparinux in patients with ESRD who are on regular dialysis is not known. Here, we report our experience with the use of fondaparinux sodium in a 15-year-old girl receiving chronic HD. Fondaparinux was chosen owing to local side effects associated with LMWH administration and noncompliance to a LMWH regimen.

CASE REPORT

This 108-kg adolescent became HD-dependent after the development of acute pancreatitis and acute cortical necrosis. She was dialyzed through a double-cuff hemocatheter, 3 times per week of 4-hour sessions using Polyflux dialyzer (Gambro, Renal Product, Lakewood, CO). Owing to obesity and immobilization, she was appropriately maintained on prophylaxis with a 5000 IU subcutaneous (SC) twice daily regimen of UFH. As she required a pancreatic pseudocyst surgery, her UFH prophylaxis was temporarily withheld. Postoperatively, she developed pulmonary embolism for which she was started on LMWH (Enoxaparin, Aventis Sanofi, USA) 60 mg SC twice daily. Her anticoagulation was optimized to maintain peak anti-factor Xa level measured 4 hours after administration between 0.6 and 1.0 IU/mL. During that time period, she also had frequent clotting of her HD circuit and blood loss requiring packed cell transfusions. Her thrombophilia work up revealed persistent elevation of factor VIII and high von Willebrand's factor (> 200%; reference 50% to 150%), contributing to shortening of her APTT and activated protein C resistance at 21.3 seconds (reference: 23.3 to 30.2 s) and 1.0 (reference: > 1.7), respectively. Her fibrinogen levels were elevated above 1000 mg/dL (reference: 150 to 450 mg/dL) with high D-dimers at 10.1 mg/dL (reference: 0.4 to 2.5 mg/dL). These laboratory values were reflective of her underlying inflammatory process contributing to endothelial activation. Antiphospholipid antibody studies were negative, including anticardiolipin antibodies, β_2-microglobulin-1 antibodies, antineutrophil antibodies, dilute Russel viper venom time, and tissue thromboplastin inhibition assays. Mixing studies were not performed, as the patient did not have prolongation of the APTT. Levels of protein C activity and antigen, free protein S antigen, AT activity and antigen, homocysteine, and lipoprotein (a) were within normal limits. Molecular studies were negative for factor V Leiden and Prothrombin 20210 mutations. She was heterozygous for C677T mutation of methylenetetrahydrofolate reductase. Four months after her illness, she was adamant not to continue LMWH because of the twice daily SC injections and local reaction related to LMWH administration. A trial of once daily (100 mg SC) administration of LMWH also failed because of excessive bruising and hematoma formations at the site of LMWH injection. Oral warfarin sodium was not considered an option as she was on multiple medications (antibiotics, proton-pump inhibitors, and multivitamins). In addition, her clinical condition was not stable requiring multiple hospitalizations which could potentially compromise warfarin therapy. To improve her compliance, we decided to stop LMWH and start 5 mg of fondaparinux (0.05 mg/kg/d). This dose was 50% of the required dose based on her weight (required dose for weight > 100 kg is 10 mg/d) (Arixtra package insert, 2006). It was chosen because of the consideration that fondaparinux was likely dialyzable during HD with its small molecular weight (1.7 kd) and lack of binding to plasma proteins, except AT, and other drugs.[14] Blood samples were collected immediately before HD (~16-h level) and were sent to The Blood Center of Southeastern Wisconsin, Milwaukee, WI, where fondaparinux levels were measured using an automated chromogenic anti-factor Xa assay calibrated with fondaparinux standards. Fondaparinux levels were obtained on days 1, 4, 8, 10, 13, and 21 after the start of therapy (Fig. 1). Due an error related to transport of plasma samples to the appropriate laboratory, a fondaparinux level on day 4 was not available. As the patient received UFH intravenous bolus at the beginning of each HD therapy, attempts to examine the dialysis clearance of fondaparinux were not successful owing to the interference with the fondaparinux assay from UFH in the ultrafiltrate. Despite continued HD, she showed gradual accumulation of fondaparinux requiring drug dose adjustments. As shown in Figure 1, fondaparinux levels clustered between 1.65 and 2.05 mg/L between days 8 and 14, indicating the reach of a steady state. During this period, she developed epistaxis and bruising at the injection site. Therefore, the dose was decreased to 2.5 mg once daily. On day 13, the dose was further reduced to 2.5 mg every other day, which subsequently led to fondaparinux levels of 0.8 (day 19) and 0.65 mg/L (day 21), approximately half of the levels between days 8 to 14. Because of the concern for her intermittent nausea and vomiting, fondaparinux was discontinued on day 29 of the treatment and LMWH was resumed. Her gastrointestinal symptoms, however, persisted for months, making fondaparinux unlikely to be the cause. During the entire fondaparinux treatment, her dialyzers were free of clotting. She later underwent a successful renal transplant.



arrow indicates fondaparinux dose was changed to 2.5 mg on once day;
arrow: fondaparinux was changed to 2.5 mg alternate day;
arrow indicates fondaparinux was discontinued

FIGURE 1. Graphical representation of anti-factor Xa levels (mg/L) at various time-points during fondaparinux therapy.

DISCUSSION

Pediatric literature using fondaparinux is limited to only 7 children with the indication of HIT.[15–17] All those children had normal renal function. Boshkov et al[15] used a 0.15 mg/kg SC daily dose in a 3-month-old (weight, 3 kg) infant with HIT and central venous line related thrombosis. In this study, Boshkov et al[15] performed a pharmacokinetic study by serial blood levels of fondaparinux which showed that the peak plasma fondaparinux level was 0.71 to 0.77 mg/L (drawn at 2 h after administration) after her fourth and fifth doses, with a trough concentration of 0.18 mg/L. This patient received an outpatient treatment with fondaparinux without any bleeding manifestations. In this report, the authors also attempted to correlate fondaparinux activity using both fondaparinux and LMWH reference curves. The results of these assays demonstrated a close correlation ($r = 0.939$) between fondaparinux levels and anti-factor Xa activity using a LMWH curve. This information is clinically significant as the close correlation between these 2 assays implies that the anti-factor Xa assay standardized for LMWH could be potentially used to monitor the anticoagulant effect of fondaparinux. The clinical information on whether this child was monitored using a fondaparinux curve or LMWH curve and what therapeutic range was targeted for the treatment of VTE is not explicit in this report. Young and Nutescu[16] treated a 6-month-old infant with fondaparinux who was diagnosed with HIT. The authors initiated therapy with a 0.25 mg/kg dose and monitored anticoagulation with anti-factor Xa levels referenced against a fondaparinux curve and thromboelastography at 2, 4, and 23 hours after a dose on 2 occasions. Similar to pharmacokinetic data from adult studies, the peak and trough anti-factor Xa levels were comparable with adult values: 0.89 (mg/L) after 2 hours (peak level) and 0.20 mg/L (trough level) after 23 hours. Interestingly, simultaneous thromboelastography studies showed that clot formation was absent at hour 2, significantly reduced at hour 4 and normal at hour 23 correlating with anti-factor Xa levels. Three days later, repeat pharmacokinetic studies demonstrated rising levels at 1.79, 1.04, and 0.67 mg/L indicating accumulation. On the basis of these values, the authors reduced the dose to 0.15 mg/kg/d and achieved therapeutic levels. Both of these abstracts lacked information on how the therapeutic target for fondaparinux treatment was determined.[15,16] Grabowski and Bussel[17] used daily SC fondaparinux for long-term anticoagulation in 5 pediatric patients who presented with VTE (3 cases) or VTE with HIT (2 cases). Using a similar assay as in our patient, anti-factor Xa levels in their patients were maintained in the range of 0.5 to 1.2 mg/mL at 3 to 4 hours after the third dose.[17]

There are only 2 reports regarding the use of fondaparinux in patients on HD who had a history of HIT.[12,13] Haase et al[12] administered 2.5 mg fondaparinux pre-HD on a 52-year-old patient and used anti-factor Xa time (RECALMIX, Amax-Accuclott Heptest, Trinity Biotech, USA) to monitor anticoagulation and maintained the patient within a therapeutic range of 70 to 110 seconds. This patient was free of clotting or bleeding during the 7-week treatment. The timing of anti-factor Xa time monitoring, details on anti-factor Xa time, and its correlation with fondaparinux levels however has not been described (M. Haase, personal communication). Parody et al[13] described a 32-year-old, 80-kg woman with renal failure whose anti-factor Xa levels were maintained in a prophylactic range with a daily fondaparinux dose of 0.5 mg.

In our patient, we chose to start with 50% of the required dose of fondaparinux. Owing to the molecular weight of fondaparinux, it was anticipated that a significant amount of plasma fondaparinux would be dialyzed off during HD as the high flux dialysis membrane can clear molecules up to 3.8 kd. The continued rise of anti-factor Xa levels with treatment suggested its accumulation despite continued HD (Fig. 1). We speculated that this accumulation was likely related to its high affinity binding with AT.[14] As the molecular weight of AT is 5.8 kd, the binding of fondaparinux to AT would greatly reduce its clearance through the dialysis membrane. This was indirectly supported by our finding that plasma AT levels were 94% before HD, 92% at 2 hours into HD, and 93% at the end of HD.

Overall, the reported experience of using fondaparinux in children and patients with renal failure implies that the issue about monitoring of fondaparinux in this high-risk population has not been addressed so far. Apart from a handful of case reports, the precise information on fondaparinux pharmacokinetics is not available in children. Young et al[16] have initiated a pilot study evaluating the pharmacokinetics of fondaparinux in children with HIT (www.clinicaltrials.gov). However, this study excludes children with renal insufficiency (creatinine level above 1.2 times the upper limit of normal expected for age). Hence, availability of a uniform assay measuring fondaparinux levels and establishment of uniform fondaparinux dosing guidelines are urgently required for the treatment of thrombosis in patients with ESRD. In pharmacokinetic studies, fondaparinux levels were measured in gravimetric units expressed as mg/dL[8], whereas conventional anti-factor Xa levels (IU/mL) are commonly used for titrating the anticoagulation of heparin derivatives. Anti-factor Xa levels reflect the coagulant activity of a drug, which has clinical significance in the treatment of thrombosis. Although the report by Boshkov et al[15] has suggested the potential utility of using LMWH curves for clinical monitoring of fondaparinux, Dapasse et al[18] have cautioned that expression of the fondaparinux levels as LMWH anti-factor Xa IU/mL will not be accurate because of: (1) fundamental differences in the chemical structure of fondaparinux and LMWH and (2) risk of variation in fondaparinux levels according to assays used for LMWH anti-factor Xa levels. This group has also attempted to correlate fondaparinux drug levels with fondaparinux activity using chromogenic assays and clot-based assays referenced for both fondaparinux and LMWH. The results of this study showed that a linear relationship was obtained for fondaparinux

concentrations ranging from 0 to 2 μg/mL for the 1-step chromogenic assays and up to 1.5 μg/mL for the 2-step chromogenic assay, provided log-linear coordinates were used. Although this study throws more light on the relationship between fondaparinux drug levels and its activity, the clinical correlate of fondaparinux levels/anti-factor Xa activity is still unknown as fondaparinux level monitoring was not performed in any of the published clinical trials.[19] Thus the correlation between fondaparinux levels and its therapeutic efficacy needs further clarification in clinical studies before establishing any clinical guidelines.

In summary, our experience in this patient suggests that fondaparinux is likely poorly dialyzable and accumulates in patients on chronic HD due to its affinity to AT. A reduced dose of fondaparinux should be used in children with ESRD who are on dialysis therapy and further studies are needed to examine its safety and efficacy in these patients. A correlation between fondaparinux levels/anti-factor Xa activity and its therapeutic efficacy needs further clarification.

ACKNOWLEDGMENTS

The authors thank Kenneth D. Friedman (Associate Professor, Director, Hemostasis Reference Lab, Blood Center of Wisconsin), Kenneth A. Bauer (Associate Professor of Medicine, Harvard Medical School) for providing more insight on fondaparinux assays and issues related to its monitoring in clinical practice. They also thank Guy Young (Assistant Professor, UCLA Health Sciences) for providing an update on fondaparinux use in children.

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