

CASE REPORT

Fondaparinux in an Obese Child with Heparin-Induced Thrombocytopenia and a History of Renal Failure

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A 9-year-old obese child with a history of ulcerative colitis was admitted to the intensive care unit for significant blood loss, hemorrhagic shock, and acute renal failure. Following complications from total colectomy secondary to multiple perforations, the patient developed heparin-induced thrombocytopenia (HIT) and subsequent portal vein thrombosis. Subcutaneous (SQ) fondaparinux therapy was initiated because the patient was unable to transition to oral anticoagulation. An anti-factor Xa assay was developed and used to adjust his fondaparinux therapy. Based on hemorrhagic complications and fondaparinux-based anti-factor Xa assay results, the fondaparinux was adjusted to a final dosage of 4.5 mg (0.066 mg/kg) SQ daily. In children unable to transition to oral anticoagulation, fondaparinux may be an alternative for the treatment of thrombosis associated with HIT. We noted that our patient required a lower dose per kilogram of fondaparinux than described in previous published reports. Despite this lower dosage per kilogram, our patient developed bleeding despite dosage reductions; subsequently, a few doses were held. It is unclear if this was related to his obesity, history of renal failure, or a combination of factors. Future studies should determine the optimal dose for special populations of children (e.g., those with obesity and renal failure). Until then, clinicians should routinely monitor and titrate fondaparinux therapy, ideally using a fondaparinux-specific anti-factor Xa assay.

INDEX TERMS children, fondaparinux, heparin-induced thrombocytopenia, obesity

J Pediatr Pharmacol Ther 2013;18(4):303–310

INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is an immune-mediated response following exposure to unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), resulting in platelet activation and thrombocytopenia.^{1,2} Platelet counts decline to $<100,000/\text{mm}^3$ or by $>50\%$ of baseline within 5 to 14 days of first exposure to heparin. HIT is caused by formation of antibodies against heparin-platelet factor 4 (PF4) complexes, which are involved in activation of platelets.^{1,2} Diagnostic tests include immunological testing (e.g., enzyme-linked immunosorbent assay [ELISA]) to detect antibodies to heparin-PF4 complexes and functional assays (e.g., serotonin release assay and heparin-induced platelet

aggregation tests).^{2,3} The functional assay tests remain the gold standard for diagnosing HIT but are cumbersome and available only at a few reference centers. In addition, validated clinical scoring tools such as the 4Ts pretest probability score have been developed to help clinicians assess the probability of HIT.^{4,5} A recent study by Ruf et al⁵ found a high level of sensitivity and specificity for an algorithm incorporating the 4Ts pretest probability score, the ELISA assay, and optical density.

Approved HIT treatment options for adults include direct thrombin inhibitors (e.g., argatroban). Several factors limit the use of direct thrombin inhibitors, including the requirement for a continuous intravenous infusion. Fondaparinux is a synthetic derivative of UFH that may have a

place in therapy for HIT. It is a pentasaccharide anticoagulant that binds to antithrombin, leading to enhanced inhibition of factor Xa. Fondaparinux has a US Food and Drug Administration (FDA)-labeled indication in adults for the treatment and prophylaxis of pulmonary emboli and deep venous thrombi (DVT).⁶ Currently, fondaparinux does not have an FDA-labeled indication for HIT; however, the American College of Chest Physicians (ACCP) recognizes the theoretical value of fondaparinux in this setting.¹ To date, there are limited data available on the safety and efficacy of fondaparinux in children.⁷⁻¹⁵

Fondaparinux, like LMWH agents, usually does not need to be monitored except in special populations (e.g., patients with obesity or renal failure and children). The ACCP provides limited recommendations for monitoring in adults, as the therapeutic anti-factor Xa range for fondaparinux has not been determined.¹⁶ We report our experience with an obese child with HIT and a history of renal failure who received fondaparinux.

CASE REPORT

A 9-year-old (68-kg, 147-cm) obese African-American male with a history of ulcerative colitis was hospitalized for fever, emesis, and bloody diarrhea. On hospital day 6, he was noted to have significant blood loss, respiratory distress, and hemorrhagic shock. At that time, he was noted to have multiple bowel perforations and underwent an emergency total colectomy. Following surgery, he was transferred to the pediatric intensive care unit. He remained mechanically ventilated and empirical therapy with meropenem and vancomycin was initiated. On hospital day 7, he was noted to have a blood culture positive for *Rhodococcus equi* and abdominal fluid culture positive for *Escherichia coli* and *Bacteroides fragilis*. His hospital course was further complicated by the need for multiple abdominal surgeries.

On hospital day 6, the patient received heparin (2 units/mL) at 3 mL/hr to maintain patency of his arterial line. His platelet count dropped to a nadir of 46,000/mm³ from a baseline of 118,000/mm³ on hospital day 12. This raised concerns for development of HIT, and a workup was initiated. The PF4-heparin antibody ELISA result was found to be probable for HIT, with an optical density of 1.287 (negative range is <0.4 and gray area = 0.4-1.0). His 4Ts pretest probability score

was 6, also suggesting a high probability for HIT (Table 1). At this time, all heparin products were discontinued. Abdominal ultrasonography revealed a portal vein thrombus that occluded blood flow. Three doses of alteplase were given from hospital days 15 to 17 to achieve thrombus dissolution, which was unsuccessful. On hospital day 15, the patient was began continuous renal replacement therapy (CRRT) secondary to renal failure with fluid overload. A continuous infusion of argatroban was used as the systemic anticoagulant for CRRT from hospital days 17 to 27. Argatroban was titrated to an activated partial thromboplastin time of 60 to 70 seconds. On hospital day 27, the patient had improved urine output and a glomerular filtration rate (GFR) of 100 mL/min/1.73 m². CRRT was discontinued, and he was given scheduled intermittent intravenous furosemide.

The patient had an extensive coagulation workup due to the development of thrombosis. Diagnostic testing confirmed the presence of lupus anticoagulant antiphospholipid syndrome. A computed tomography scan of the chest, abdomen, and pelvis revealed improved blood flow through the portal vein but confirmed the presence of a clot. Anticoagulation therapy was indicated at this time. Due to his intestinal injury, administration of oral anticoagulation was not an option. The hematology/oncology service was consulted, and the decision was made to initiate fondaparinux therapy (Arixtra; GlaxoSmithKline; Research Triangle Park, NC) on hospital day 31.

Little published evidence exists for fondaparinux dosage in children. He was initially started on 7.5 mg subcutaneously (SQ) daily (0.11 mg/kg/day) (Table 2). At this time, his GFR was 63.7 mL/min/1.73 m² (Table 2). The goal at this time was to achieve an anti-factor Xa peak concentration based on the fondaparinux curve of 1.2 to 1.26 mg/L, based on published data for adults.^{16,17} Our laboratory did not have the ability to assess anti-factor Xa concentrations based on the fondaparinux curve, so the samples had to be sent to a reference laboratory. The significant lag time required to obtain the anti-factor Xa concentrations based on the fondaparinux curve limited the clinical applicability of these results. Therefore, a decision was made to assess anti-factor Xa concentrations based on the LMWH curves to adjust his dosages until a fondaparinux

Table 1. Estimation of the Patient's 4Ts Score for Probability of Heparin-Induced Thrombocytopenia

Criteria	Points			Present Patient's Score
	2	1	0	
Thrombocytopenia	>50% platelet fall to nadir of ≥ 20 AND no surgery within preceding 3 days	>50% platelet fall but surgery within preceding 3 days OR 30%-50% platelet fall or nadir 10-19	<30% platelet fall OR nadir < 10	2
Timing of onset of platelet fall	Days 5-10 after start of heparin OR platelet within 1 day of heparin AND exposure within past 5-30 days	Platelet fall days 5-10 but timing unclear OR platelet fall within 1 day of heparin AND exposure within 31-100 days OR platelet fall after day 10	Platelet fall \leq day 4 without exposure in last 100 days	2
Thrombosis	Confirmed new thrombosis (venous or arterial) OR skin necrosis at injection site OR anaphylactic reaction to heparin bolus OR adrenal hemorrhage	Recurrent venous thrombosis in patient with therapeutic anticoagulants OR suspected thrombosis (awaiting imaging) OR erythematous skin lesions at injection site	Thrombosis suspected	2
Other causes of platelet fall	None evident	Possible other causes are evident (e.g., sepsis without proven microbial source)	Probable other causes are evident (e.g., confirmed bacteremia/fungemia, 72 hours following surgery, chemotherapy)	0*
Total Score				6[†]

Adapted from Pouplard et al. *J Thromb Haemost.* 2007;5(7):1373-1379.

*The patient had abdominal sepsis and was noted to have blood culture positive for *R equi* and abdominal fluid culture positive for *E coli* and *B fragilis*.

†Pretest probability scores: 6-8 indicates high probability; 4-5 indicates intermediate probability; and 0-3 indicates low probability.

curve could be established at our institution. In order to develop the fondaparinux curve, samples were sent to the inhouse laboratory for an anti-factor Xa concentration based on the LMWH curve. Separate samples were sent to a reference laboratory to assess the anti-factor Xa concentration based on an established fondaparinux curve (Table 2).

An elevated anti-factor Xa concentration, based on the LMWH curve, occurred on hospital day 40; his dose was held for the day and restarted at 5 mg on the following day. On hospital day 42, an anti-factor Xa concentration based on the LMWH curve was obtained and found to be below the therapeutic range based on the LMWH curve. His dose was subsequently increased to 6 mg. On hospital day 54, his dose was held due to bleeding from wound sites and was resumed

the following day without incident. At this time his GFR declined to a nadir of 31.8 mL/min/1.73 m² (Table 2). The following day, his fondaparinux therapy was reinitiated at 6 mg. Due to the bleeding that he experienced, the decision was made to target the lower end of the anti-factor Xa peak concentration based on the LMWH curve of 0.5 to 1 IU/mL, until the actual value for the fondaparinux curve could be determined. On hospital day 68, his dose was again held as he was noted to have blood loss associated with decreased hemoglobin and platelet counts. He required several blood products and was returned to the operating room for evacuation of a hematoma. The fondaparinux was restarted the following day at a decreased dose of 5.5 mg. A fondaparinux-specific assay was established and validated at our institution on hospital day 69; his

Table 2. Fondaparinux Doses, Renal Function Data, and Anti-Factor Xa Assay Concentrations

Hospital Day	Fondaparinux Dose: mg (mg/kg/dose)	Glomerular Filtration Rate (mL/min/1.73 m ²)	Anti-Xa Concentrations for Fondaparinux (mg/L)	Anti-Factor Xa Concentrations for LMWHs (units/mL)
31	7.5 (0.11)	63.7	0.23	0.46
32	7.5 (0.11)	53.1	ND	ND
33	7.5 (0.11)	53.1	ND	ND
34	7.5 (0.11)	53.1	ND	0.9
35	7.5 (0.11)	53.1	ND	1.06
36	7.5 (0.11)	53.1	ND	ND
37	7.5 (0.11)	63.7	ND	ND
38	7.5 (0.11)	79.6	ND	0.88
39	7.5 (0.11)	106.2	ND	ND
40	NA	79.6	ND	1.74
41	5 (0.074)	79.6	ND	0.39
42	6 (0.088)	63.7	ND	0.25
43	6 (0.088)	79.6	ND	ND
44	6 (0.088)	79.6	ND	ND
45	6 (0.088)	45.5	0.75	ND
46	6 (0.088)	53.1	0.76	ND
47	6 (0.088)	45.5	0.67	ND
48	6 (0.088)	53.1	ND	ND
49	6 (0.088)	39.8	0.66	ND
50	6 (0.088)	39.8	ND	ND
51	6 (0.088)	45.5	ND	ND
52	6 (0.088)	45.5	ND	ND
53	6 (0.088)	45.5	ND	ND
54	NA	31.8	ND	ND
55	6 (0.088)	35.4	ND	ND
56	6 (0.088)	39.8	0.51	ND
57	6 (0.088)	45.5	ND	ND
58	6 (0.088)	53.1	ND	ND
59	6 (0.088)	63.7	ND	ND
60	6 (0.088)	79.6	ND	ND
61	6 (0.088)	79.6	ND	ND
62	6 (0.088)	79.6	ND	ND
63	6 (0.088)	79.6	ND	ND
64	6 (0.088)	63.7	0.82	ND
65	6 (0.088)	ND	ND	ND
66	6 (0.088)	ND	ND	ND
67	6 (0.088)	ND	ND	ND
68	NA	79.6	ND	ND
69	5.5 (0.081)	63.7	0.62	ND
70	5.5 (0.081)	ND	0.71	ND
71	5.5 (0.081)	53.1	0.86	1.02
72	5.5 (0.081)	ND	0.77	0.91
73	5.5 (0.081)	ND	ND	ND
74	4.5 (0.066)	79.6	ND	ND
75	4.5 (0.066)	106.2	ND	ND
76	4.5 (0.066)	ND	ND	ND

LMWH, low-molecular-weight heparin; NA, not administered; ND, no data available.

actual concentration was found to be 0.62 mg/L. The decision was made to continue the current dose despite the fact that the concentration was lower than the published therapeutic range of 1.2 to 1.26 mg/L based on adult data, due to his history of bleeding episodes.

As his clinical status improved and he was able to tolerate enteral feeds, warfarin therapy was initiated on hospital day 73. His fondaparinux dose was further decreased to 4.5 mg on hospital day 74. Because of his history of hemorrhagic complications and hematoma formation, his international normalized ratio (INR) goal range was 1.5 to 2.0. Fondaparinux was discontinued on hospital day 76, once his INR with warfarin was within this goal range. He was transferred to the general inpatient service on hospital day 81. Warfarin was continued upon discharge to a long-term rehabilitation facility on hospital day 105.

DISCUSSION

This is one of the few reports of fondaparinux therapy in a child with HIT. There is a paucity of dosing recommendations for children receiving fondaparinux, with even less evidence for special populations (e.g., obese patients, pregnant patients, or patients with renal failure). Therefore monitoring is essential. The ACCP provides recommendations for monitoring based on data in adults.¹⁶ The expected peak anti-factor Xa concentration (based on a fondaparinux assay) is 0.30 to 0.50 mg/mL 3 hours after a 2.5-mg SQ prophylactic dose; whereas, the peak concentration is 1.20 to 1.26 mg/L, 3 hours following a 7.5-mg SQ treatment dose.^{16,17} Our patient was a 9-year-old obese child with a history of renal failure. He had a body mass index (BMI) of 31.5 kg/m² and was classified as obese according to the CDC definition, with a BMI percentile above the 99th percentile for age and sex.¹⁸ Initial dosing adjustments were made based on the LMWH anti-factor Xa curve and adverse effects. The ACCP cautions that this practice is “problematic” because these agents are different chemical entities. However, it was deemed necessary to use the LMWH curves due to the delay in the receipt of the fondaparinux anti-factor Xa assay values from the reference laboratory. On hospital day 69, we established a local fondaparinux-specific curve for further monitoring and dosing modifications.

Once this assay was developed, the patient's dose was not increased due to bleeding. At the time of this case study, fondaparinux dosing adjustments were planned based on the published anti-factor Xa assay reference range for adults. Young et al¹² recently conducted an open-label study using a different anti-factor Xa assay to assess the pharmacokinetics and safety of fondaparinux in 24 children with a history of DVT or HIT. The investigators set the peak anti-factor Xa concentration based on a fondaparinux assay at 0.5 to 1 mg/L, 4 hours after fondaparinux administration due to concerns for safety. Based on these results, our patient would have achieved therapeutic anti-factor Xa concentration on hospital days 69 to 76. However, it is difficult to truly determine the clinical application of their findings for our patient as that study was an open-label, dose-finding trial. Further research should be conducted to determine the target therapeutic range of fondaparinux in children.

Our patient was started on 7.5 mg of fondaparinux SQ daily. A total of 3 published abstracts, one letter to the editor, 5 case reports, and 1 study, representing a total of 36 children ranging from 2 months to 18 years of age, provide a description of fondaparinux for treatment of thrombosis and/or HIT.⁷⁻¹⁵ The initial dosing in the case reports ranged from 0.05 to 0.25 mg/kg/dose SQ daily. In these reports, pharmacokinetic monitoring with anti-factor Xa assay was conducted, although there was significant variability in the goal therapeutic range. The final dosing from these reports ranged from 0.01 to 0.15 mg/kg/dose SQ daily.⁵⁻⁹ Data from the open-label study by Young et al determined that a dose of 0.1 mg/kg/dose SQ daily would achieve an anti-factor Xa concentration of 0.5-1 mg/L.¹² Initially, our patient was started on 0.11 mg/kg/dose SQ daily. The dose of fondaparinux was decreased over the next several weeks based on anti-factor-Xa assay results and bleeding complications to a final dose of 4.5 mg SQ daily (0.066 mg/kg/dose). Two factors that could have been integral in the decreased dose requirements for our patient are his history of renal dysfunction and obesity.

There is a paucity of data for fondaparinux in obese patients. Our patient had a BMI greater than the 99th percentile based on his age, sex, and height. In adults, fondaparinux doses are typically given according to weight. Patients

with pulmonary emboli or DVT who weigh <50 kg receive 5 mg daily; those between 50 and 100 kg receive 7.5 mg; and those >100 kg receive 10 mg daily.⁶ Various pharmacokinetic alterations have been noted in obese patients, including increased renal blood flow and glomerular filtration rate and a higher volume of distribution for lipophilic medications.¹⁹⁻²⁰ In a subanalysis of the Matisse trials, Davidson et al²¹ compared the safety and efficacy of fondaparinux with control heparin derivatives (i.e., enoxaparin and UFH) for treatment of DVT in obese adult patients. In the original studies, fondaparinux doses were followed according to the standard FDA-labeled dosing. The authors found no differences in bleeding or thrombotic complications between the obese and nonobese groups, using standard fondaparinux dosing. A recent report by Martinez et al²² evaluated the effect of anti-factor Xa concentrations in obese adults with a BMI >40 kg/m² receiving fondaparinux 2.5 mg SQ daily. The investigators found that prophylactic concentrations were achieved only in 53% of adult patients, suggesting that this population requires a higher dose because of increased plasma clearance of fondaparinux. Although our patient was obese, these results are difficult to extrapolate to obese children due to potential differences in age-related pharmacokinetics.²² For example, Bartelink et al²³ noted that body weight-normalized clearance in children exceeds that of adults, requiring potentially more frequent dosing and/or a higher “mg/kg” doses than adults.²³

Our patient’s history of renal failure may have also contributed to the lower final dose. Fondaparinux is eliminated primarily unchanged in the urine; therefore, there are concerns for accumulation in patients with renal insufficiency.⁶ The fondaparinux prescribing information states that it is contraindicated in a patient with a creatinine clearance less than 30 mL/min/1.73 m².⁶ In addition, the ACCP recommends that the dose of fondaparinux should be decreased by 50% in individuals with a creatinine clearance between 30 and 50 mL/min.¹⁶ Sharathkumar et al¹¹ described the use of fondaparinux in an adolescent with end-stage renal disease requiring intermittent outpatient hemodialysis and history of a pulmonary embolism. This patient’s fondaparinux therapy was begun at 0.05 mg/kg/dose SQ daily. Pharmacokinetic monitoring with anti-factor Xa concentrations was used, and the

final dose was 0.02 mg/kg/dose SQ every other day. Our patient suffered from acute renal impairment on hospital day 15 and received CRRT for approximately 12 days. On hospital day 27, CRRT was discontinued as his renal function and urine output improved. The patient’s GFR on the day of fondaparinux initiation was 63.7 mL/min/1.73 m², and while dialysis was not reinitiated, his GFR did fluctuate throughout his fondaparinux therapy. It is difficult to draw significant conclusions about whether our patient’s dose was affected by his obesity, his history of renal failure, or a combination of these or other factors.

One factor that must be considered with fondaparinux is fondaparinux-induced thrombocytopenia (FIT). Fondaparinux has a small pentasaccharide structure with fewer negatively charged sulfate groups and does not interact with PF4, theoretically making it less likely to cause HIT.^{2,3,6} Despite this theoretical mechanism, several reports of FIT have been reported in the literature.²⁴⁻²⁶ Three adult female patients receiving prophylactic fondaparinux therapy following orthopedic surgical procedures had drops in platelet counts by >50%.²⁴⁻²⁶ All 3 patients also had a positive heparin-PF4 antibody ELISA result, whereas 2 had positive results for serotonin release assays to fondaparinux, indicating a high likelihood of FIT. It is hypothesized that a clinical syndrome similar to HIT featuring platelet activation may be possible when patients receive highly negatively charged agents such as fondaparinux.²⁶ Despite these reports, Tokgoz et al¹⁴ recently described the use of fondaparinux in a 12-year-old patient with HIT and DVT. This patient was placed on fondaparinux, 7.5 mg SQ daily (0.1 mg/kg/daily), for 3 weeks of therapy before the initiation of warfarin; the authors noted that there were no significant decreases in the patient’s platelet count. In our patient, no thrombocytopenia was noted following initiation of fondaparinux.

CONCLUSIONS

This case report provides a description of the use of a fondaparinux in an obese child with a history of renal failure and HIT and portal vein thrombosis. We noted that the patient’s final adjusted fondaparinux dose was lower than previously published reports in children. Future prospective studies should be conducted to deter-

mine the optimal regimen in special populations (e.g., obesity and renal failure) such as those that include our patient. Until then, it seems prudent that fondaparinux be reserved as an alternative agent. In such cases, clinicians should use pharmacokinetic monitoring with anti-factor Xa concentrations, using specific fondaparinux curves for obese patients, patients with renal failure, and children until further research is performed.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

ABBREVIATIONS ACCP, American College of Chest Physicians; BMI, body mass index; CRRT, continuous renal replacement therapy; DVT, deep venous thrombosis; ELISA, enzyme-linked immunosorbent assay; FIT, fondaparinux-induced thrombocytopenia; GFR, glomerular filtration rate; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; LMWH, low molecular weight heparin; PF, platelet factor; SQ, subcutaneous; UFH, unfractionated heparin

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REFERENCES

- Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia. American College of Chest Physicians antithrombotic therapy and prevention of thrombosis guidelines, 9th ed. *Chest*. 2012;141(suppl):e495-530s.
- Papadopoulos S, Flynn JD, Lewis DA. Fondaparinux as a treatment option for heparin-induced thrombocytopenia. *Pharmacotherapy*. 2007;27(6):921-926.
- Blackmer AB, Oertel MD, Valgus JM. Fondaparinux and the management of heparin-induced thrombocytopenia: The journey continues. *Ann Pharmacother*. 2009;43(10):1636-1646.
- Pouplard C, Gueret P, Fouassier M, et al. Prospective evaluation of the "4Ts" score and particle gel immunoassay specific to heparin/PF4 for the diagnosis of heparin-induced thrombocytopenia. *J Thromb Haemost*. 2007;5(7):1373-1379.
- Ruff KM, Bensadoun ES, Davis GA, Flynn JD, Lewis DA. A clinical-laboratory algorithm incorporating optical density value to predict heparin-induced thrombocytopenia. *Thromb Haemost*. 2011(3);105:553-559.
- Arixtra [package insert]. Research Triangle Park, NC: GlaxoSmithKline; February 2011.
- Mason AR, McBurney PG, Fuller MP, et al. Successful use of fondaparinux as an alternative anticoagulant in a 2-month-old infant [letter]. *Pediatr Blood Cancer*. 2008;50(5):1084-1085.
- Young G, Nugent DJ. Use of argatroban and fondaparinux in a child with heparin-induced thrombocytopenia [abstract]. *Pediatr Blood Cancer*. 2004;42(suppl):1756.
- Boshkov LK, Kirby A, Heuschkel M. Pharmacokinetics of fondaparinux by anti-Xa levels and clinical response to anticoagulation in a 4-month old congenital cardiac patient with heparin-induced thrombocytopenia and established venous thrombosis transitioned from argatroban to fondaparinux [abstract]. *Blood*. 2004;104(suppl): 4072.
- Grabowski EF, Bussel JB. Pediatric experience with fondaparinux in deep venous thrombosis [abstract]. *Blood*. 2006;108(suppl):916.
- Sharathkumar AA, Crandall C, Lin JJ, Pipe S. Treatment of thrombosis with fondaparinux (Arixtra) in a patient with end-stage renal disease receiving hemodialysis therapy. *J Pediatr Hematol Oncol*. 2007;29(8):581-584.
- Young G, Lee DL, O'Brien SH, Khanna R, Barbour A, Nugent DJ. FondaKIDS: a prospective pharmacokinetic and safety study of fondaparinux in children between 1 and 18 years of age. *Pediatr Blood Cancer*. 2011;57(6):1049-1054.
- Orostegui L, Medejel N, Kone-Paut I, et al. Fondaparinux (Arixtra) hepatotoxicity in a 6 year-old child. *J Hepatol*. 2012;58(1):195-198.
- Tokgoz H, Caliskan U, Demir M. Successful use of fondaparinux in a child with heparin-induced thrombocytopenia. *Blood Coagul Fibrinolysis*. 2012;23(8):769.

15. Maurer SH, Wilimas JA, Wang WC, Reiss UM. Heparin induced thrombocytopenia and re-thrombosis associated with warfarin and fondaparinux in a child. *Pediatr Blood Cancer*. 2009;53(3):468-471.
16. American College of Chest Physicians. Parenteral anticoagulants. American College of Chest Physicians antithrombotic therapy and prevention of thrombosis guidelines, 9th ed. *Chest*. 2012;141(suppl):e24S-43S.
17. Data on file. GlaxoSmithKline, Arixtra NDA submission, human pharmacokinetics and bioequivalence summary, 2001.
18. US Centers for Disease Control and Prevention. Defining childhood overweight and obesity. www.cdc.gov/obesity/childhood/defining.html. Accessed May 3, 2012.
19. Cheymol G. Effects of obesity on pharmacokinetics. *Clin Pharmacokinet*. 2000;39(3):215-231.
20. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. *Pharmacotherapy*. 2007;27(8):1081-1091.
21. Davidson BL, Buller HR, Decousus H, et al. Effect of obesity on outcomes after fondaparinux, enoxaparin or heparin treatment for acute venous thromboembolism in the Matisse trials. *J Thromb Haemost*. 2007;5(6):1191-1194.
22. Martinez L, Burnett A, Borrego M, et al. Effect of fondaparinux prophylaxis on anti-factor concentrations in patients with morbid obesity. *Am J Health Syst Pharm*. 2011;68(18):1716-1722.
23. Bartelink IH, Rademaker CM, Schobben AF, et al. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. *Clin Pharmacokinet*. 2006;45(11):1077-1097.
24. Rota E, Bazzan M, Fantino G. Fondaparinux-related thrombocytopenia in a previous low-molecular-weight heparin-induced thrombocytopenia. *Thromb Haemost*. 2008;99(4):779-781.
25. Warkentin TE, Maurer BT, Aster RH. Heparin-induced thrombocytopenia associated with fondaparinux. *N Engl J Med*. 2007;356(25):2653-2654.
26. Warkentin TE, Lim W. Can heparin-induced thrombocytopenia be associated with fondaparinux use? Reply to a rebuttal. *J Thromb Haemost*. 2008;6(7):1243-1246.