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FondaKIDS: A Prospective Pharmacokinetic and Safety Study of Fondaparinux in Children Between 1 and 18 Years of Age

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Background. The incidence of thromboembolic disease is increasing in children. New anticoagulants have been licensed in adults and need to be studied in children. This report describes the first prospective study of fondaparinux in children. ***Procedure.*** The purpose of the study was to determine the dosing, pharmacokinetics, and safety of fondaparinux in children with deep vein thrombosis (DVT) or heparin-induced thrombocytopenia (HIT). Hospitalized children between 1 and 18 years of age with DVT or HIT received fondaparinux 0.1 mg/kg once daily. Fondaparinux-based anti-factor Xa levels were assessed at 2, 4, 12, and 24 hr following the first dose, and peak levels were measured twice weekly thereafter. Detailed pharmacokinetic analyses were performed. ***Results.*** Twenty four subjects in 3 age cohorts were enrolled and completed the study. Pharmacokinetic modeling demonstrated that a once-daily dose of fondaparinux at 0.1 mg/kg resulted in similar concentrations known to be efficacious in adults. Safety was demonstrated with only two bleeding events: one which may have pre-dated study drug administration and one which led only to temporary discontinuation of study drug. ***Conclusion.*** Dosing of fondaparinux at 0.1 mg/kg once daily in children resulted in PK profiles comparable to those in adults receiving standard dosing. Fondaparinux can be considered an attractive alternative to LMWH given its once-daily dosing, acceptable safety data, and other favorable properties. Pediatr Blood Cancer 2011;57:1049–1054.

Key words: anticoagulation; children; fondaparinux; thrombosis

INTRODUCTION

The incidence of thromboembolic disease in children has increased significantly in recent years [1]. Treatment with anticoagulant medications is often required in order to prevent thrombus extension and embolization, which could result in significant short- and long-term complications. Over the past 15 years, low molecular weight heparins (LMWH) have become the most commonly prescribed anticoagulants in children [1]. While LMWH are generally considered efficacious and safe, with published guidelines [2] recommending their use for a variety of situations, they have several limitations which highlight a need to study newer alternative anticoagulants in the pediatric population.

Concerns with use of LMWH in the pediatric population include their subcutaneous administration and relatively short half-life, necessitating twice a day injections [3–5]. In addition, LMWH are animal-derived, leading to possible contamination as occurred in 2008 with unfractionated heparin [6]. LMWH can also affect bone metabolism [7] potentially leading to ostepenia [8], and can, on rare occasion, cause HIT in children. A potential alternative to use of LMWH in children is fondaparinux (Arixtra, GlaxoSmithKline, Philadelphia, PA). While fondaparinux must also be administered subcutaneously, its longer half-life [9] allows for once-daily injections in adults. In addition, fondaparinux has no effect on bone metabolism [10] and has been used to treat HIT in both adults and children [11–13]. Finally, fondaparinux is a synthesized compound and is thus almost free of risk of contamination by animal proteins.

Previous reports on the use of fondaparinux in children are limited to case reports [14–18]. As such, we performed a pilot, dose-finding and pharmacokinetic study of fondaparinux in children with DVT or HIT. The aims of this study were to determine in children: (1) the appropriate dose and dosing interval for fondaparinux, (2) its pharmacokinetic profile, and (3) its safety profile with respect to bleeding symptoms and other adverse events.

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METHODS

Study Design

This was an open label, single arm, dose-finding, pharmacokinetic, and safety study of fondaparinux as primary treatment for DVT or HIT in children between 1 and 18 years of age. The study was conducted under an investigator-initiated IND 71,946 and was funded by the Food and Drug Administration Office of Orphan Product Drugs (Grant number 1FD003091). Of note, the FDA did not grant an IND to study children less than one year of age for this initial study. The study was approved by the institutional review boards of the participating centers (Children's Hospital Los Angeles, Texas Children's Hospital, Nationwide

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Conflict of interest: This study was funded entirely by the Food and Drug Administration Office of Orphan Product Drugs (Grant No. 1FD003091). Following accrual of all subjects, GlaxoSmithKline (the manufacturer of fondaparinux) requested and was granted access to the data for the payment of a licensing fee to Children's Hospital Los Angeles, the grant recipient and primary study site. Guy Young and Rachna Khanna received a distribution from this licensing fee. April Barbour, the clinical pharmacologist involved in the data analysis is an employee of GlaxoSmithKline. The other authors have no conflicts.

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Children's Hospital, Children's Hospital of Orange County) and parents/guardians of the subjects gave their informed consent prior to enrollment. The study was registered on the clinicaltrials.gov website (NCT 00412464).

Patients

Inclusion criteria were: children between 1 and 18 years of age with an objectively confirmed DVT or clinically diagnosed HIT. Exclusion criteria were: serum creatinine $>1.2 \times$ normal, an unexplained prothrombin time (PT) >3 sec or activated partial thromboplastin time (PTT) >5 sec above normal range, active bleeding, a contraindication to anticoagulation, or planned surgery/invasive procedures within 2 days of study drug initiation. For safety reasons, this study was restricted to the inpatient setting (children with DVT are in general admitted to the hospital). Once patients were discharged, study drug administration was discontinued and ongoing anticoagulation was at the discretion of the treating physician.

Medication, Imaging, and Laboratory Analyses

Fondaparinux was purchased from the manufacturer (GlaxoSmithKline). Patients were diagnosed with a DVT based on the results of an objective diagnostic imaging modality which included Doppler ultrasonography, computed tomography, magnetic resonance imaging, echocardiography, or venography. Prestudy laboratory analysis included a PTT, PT, fibrinogen levels, D-dimer, complete blood count (CBC), and blood chemistry analysis all of which were performed at the respective study sites utilizing standard methods. All fondaparinux levels were performed at the Hemostasis Reference Laboratory of the Blood Center of Wisconsin utilizing a fondaparinux-based chromogenic anti-factor Xa assay with results expressed in mg/L of the commercial formulation (fondparinux sodium). For safety considerations, the target peak fondaparinux sodium level (4 hr) was set at 0.5–1 mg/L, which is lower than the achieved peak level of 1.2–1.26 mg/L in adults. In addition, if the 12 hr level was below 0.2 mg/L (minimal to no drug activity), a second daily dose was to be administered at 12 hr leading to twice-daily dosing.

Study Medication Administration and Monitoring

Initial dosing was based on the first report of the use of fondaparinux in a child (the only published report at the time this study was designed and initiated) [12]. A fondaparinux level was drawn prior to the initial dose and at 2, 4, 12, and 24 hr after the initial dose. Subsequently, levels were drawn 4 hr after the dose (presumed peak) twice weekly until study drug discontinuation. Dose adjustments were made based on a predetermined algorithm and a repeat fondaparinux level was drawn after each dose adjustment (Table I). Patients could remain on study drug until hospital discharge or for up to 21 days, whichever came first.

TABLE I. Dose Adjustment of Fondaparinux

Level (mg/L)	Dose adjustment
<0.3	Increase dose by 0.03 mg/kg
0.3–0.5	Increase dose by 0.01 mg/kg
0.5–1	No change
1–1.2	Decrease dose by 0.01 mg/kg
>1.2	Decrease dose by 0.03 mg/kg

Safety

All study subjects were inpatients which allowed for close observation for bleeding symptoms and other adverse events. Major bleeding was defined by the occurrence of bleeding into a critical space (intracranial, retroperitoneal, or visceral) or overt bleeding necessitating a blood transfusion. Minor bleeding was defined as all other bleeding and classified as clinically significant if medical interventions were utilized to manage the bleeding. Other adverse events (including severe adverse events) were defined per usual criteria for clinical trials [19]. As this study was not designed to assess efficacy, follow-up imaging was performed at the discretion of the treating physician.

Statistical Analysis

All data were analyzed by age group (1–5, 6–12, and 13–18 years). Missing data were considered as such and no imputation was used. For continuous data, the following summary statistics were calculated: n, mean, standard deviation (SD), median, minimum, and maximum.

Pharmacokinetic Analysis

To develop the pediatric population PK model, the data from this pediatric study was combined with data from adults due to the sparse nature of the sampling scheme in this pediatric study and the small number of patients enrolled. The adult data was obtained from a randomized, two-period crossover bioequivalence study of 16 healthy male adult volunteers that each received a single 2.5 mg dose per period [20].

The base model was a standard two compartment model parameterized in terms of clearance (CL), central volume of distribution (V2), peripheral volume of distribution (V3), intercompartmental Clearance (Q), and absorption rate (KA), using the ADVAN4 TRANS4 model in NONMEM VI (ICON Development Solutions, Ellicott City, MD). The absorption of fondaparinux is rapid and complete and, therefore, the apparent pharmacokinetic parameters equal the absolute pharmacokinetic parameters, i.e., apparent clearance is equal to clearance. Inter-individual variability (IIV) terms were added to the model and estimated using an exponential model as appropriate. The data were natural log-transformed prior to analysis. The residual error model was a log-additive model. The first order conditional estimation method (with interaction) was used for all runs. Inter-individual variability parameters were added to the model one at a time, and the model re-fit. The additional parameters were accepted into the model based on an objective function drop of at least 11 points (X^2, $P < 0.001$, 1 d.f.), as well as improvement in goodness of fit plots and acceptable standard errors. Once a final base model was selected, patient covariates (creatinine clearance, weight, gender) were examined for their impact on CL, V2, and V3. A drop in the objective function of at least 11 points (X^2, $P < 0.001$, 1 d.f.), lack of pattern in partial residual plots and overall improvement in fit based on standard goodness of fit plots was required to add a covariate to the model. Continuous covariates were entered into the model as exponential terms centered at 70 kg for weight and 120 ml/min for creatinine clearance. The model building process showed the exponential terms for the effect of weight on clearance and central volume of distribution to be close to the known exponential values, $\sim$0.75 and $\sim$1,

respectively, and therefore these terms were fixed in the final model. Additionally, fixing these terms rather than estimating them did not cause a significant increase in the objective function. The categorical covariate, i.e., gender, was added to the model as typical value parameter + Theta × (1 − SEX), where SEX = 0 for males and 1 for females. A two-compartment body model with first-order absorption and elimination adequately described the data. The model was used to support simulations in a virtual population in order to evaluate the 0.1 mg/kg/day dose by comparing expected steady state peak (C_{maxss}) and trough (C_{minss}) achieved in pediatric patients to the known peak and trough levels achieved in adults which are described in the prescribing information [21].

RESULTS

Patients

A total of 24 pediatric patients were enrolled: the demographics of the study population are summarized in Table II. The indication for anticoagulation included DVT in 23 patients (one of which was in a reconstructed venous segment of a Fontan repair) and HIT in one patient. Catheter-related thrombosis was the primary cause of the thrombosis in 12 patients with DVT while for the other 11, the primary causes were infection in 4 all leading to regional DVT (3 with head and neck infections and one with a infection of hardware in the leg), congenital heart disease in 3, malignancy in 2 (non-catheter related) and idiopathic in 1 although this child was found to be heterozygous for factor V Leiden. Patients were recruited between September, 2006 and June, 2009.

Dosing

The main goal of the study was to determine if once-daily dosing with 0.1 mg/kg/day would achieve appropriate plasma therapeutic levels. Results of pharmacokinetic modeling (see below) support the use of a 0.1 mg/kg/day dose for pediatric patients 1–18 years of age with DVT since the therapeutic targets achieved in this study were in the same range of those expected in adults receiving treatment for VTE. The observed data from the study fell within the 95% prediction interval of the simulated adult data. Thus, the fondaparinux exposure achieved in this pediatric population was similar to that observed in adults given recommended doses of fondaparinux to treat DVT. Furthermore, 21 of the 24 subjects achieved target peak fondaparinux concentrations following the first 0.1 mg/kg dose (all 24 after no more than 2 dose adjustments) and only 2 of the 24 patients had 12 hr levels below the target minimum lending more support to the notion that the dose of 0.1 mg/kg once daily is the appropriate initial dose (Table III). The mean peak fondaparinux sodium levels (in mg/L measured at 4 hr after the dose) were 0.68 ± 0.21 (n = 24), 0.72 ± 0.33 (n = 9), 0.67 ± 0.04 (n = 4), 0.62 ± 0.11 (n = 5), and 0.6 ± 0.16 (n = 2) on days 1, 3, 7, 10, and 14, respectively. The decreasing sample size is due to patients being discharged thus going off study.

TABLE III. Percent of Patients Reaching Target Therapeutic Ranges in the First 24 hr After Administration of Fondaparinux

	Peak (4 hr) (n = 24)	12 hr (n = 24)
Sub-therapeutic	2 (8%)	2 (8%)
Therapeutic	21 (88%)	22 (92%)
Supra-therapeutic	1 (4%)	0

For peak levels, sub-therapeutic, therapeutic, and supra-therapeutic levels are <0.5, 0.5–1, and >1 mg/L. For the 12 hr levels, sub-therapeutic is ≤0.2 mg/L and therapeutic is >0.2 mg/L.

Pharmacokinetic Analysis

The final data set contained 621 samples, 484 samples from healthy adult volunteers and 137 samples from the pediatric patients. A two-compartment body model with first-order absorption and elimination adequately fit the data. Visual predicted checks for the data from healthy adult volunteers and pediatric patients are provided in Figures 1 and 2, respectively. The pharmacokinetic parameters are provided in Table IV. The volume of distribution determined from the modeling agrees with previous reports and suggests that fondaparinux primarily distributes to blood volume as fondaparinux is completely absorbed [20]. Additionally, body weight was a significant covariate on both clearance (objective function drop of 59) and central volume of distribution (objective function drop of 86) justifying weight based dosing of fondaparinux in pediatric patients. It was not surprising that during the model building process, creatinine clearance did not present as a significant covariate since this study excluded patients with renal dysfunction and healthy volunteers were selected for bioequivalence study. To determine whether a 0.1 mg/kg/day dosing regimen is acceptable for all pediatric patients or if there is any potential bias in younger or older patients, the simulated and observed data were separated into the 3 cohorts based on body weight (approximate ages 1–5, 6–12, and 13–18 years). The data did not demonstrate any significant bias across the groups confirming that the 0.1 mg/kg/day dose is appropriate children between 1 and 18 years of age (Fig. 3).

Simulations were performed to evaluate the 0.1 mg/kg/day dose by comparing expected steady state peak (C_{maxss}) and trough (C_{minss}) achieved in pediatric patients to the peak and trough achieved in adults. The concentrations achieved in adults after

TABLE II. Summary of Demographic and Baseline Characteristics

Age group (years) (n)	1–5 (10)	6–12 (7)	13–18 (7)	Total (24)
Sex (M/F)	6/4	2/5	2/5	10/14
Weight in kg [mean (range)]	11.7 (8–20)	34.3 (17–47)	66.1 (47–130)	34.2 (8–130)
Number of days on study drug [mean/median (range)]	6.8/4.5 (2–19)	5.7/4 (2–14)	4.4/3 (2–12)	5.8/3.5 (2–19)

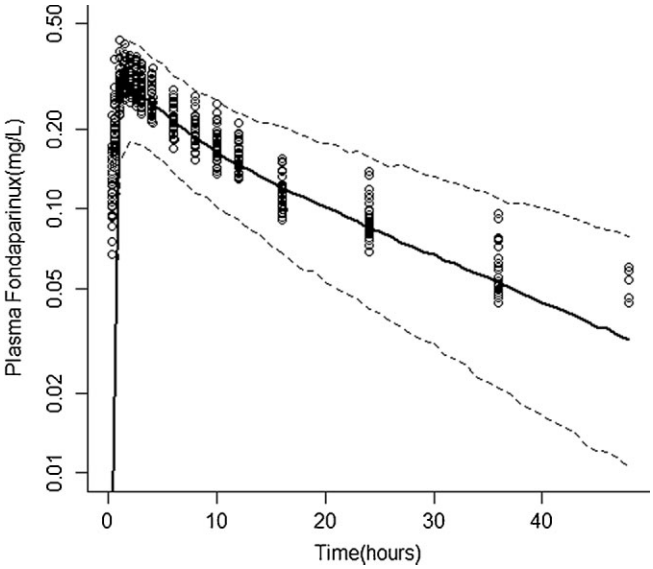

Fig. 1. Model validation using visual predictive check for the adult data. Simulations are represented by lines (median-solid line, 95% prediction interval-dashed lines) with the observed data (open circles) overlaid.

treatment for DVT or pulmonary embolism with fondaparinux are C_{maxss} = 1.2–1.26 mg/L and C_{minss} = 0.46–0.62 mg/L free acid [22]. The population PK model predicted a C_{maxss} and C_{minss} achieved in pediatric patients were approximately equal to the C_{maxss} and C_{minss} achieved in adults suggesting that this dosing regimen is appropriate (Table V). Additionally, the observed pediatric data fall within the 95% prediction interval of the adult data lending further evidence that 0.1 mg/kg/day is an appropriate dose in pediatric patients (Fig. 4).

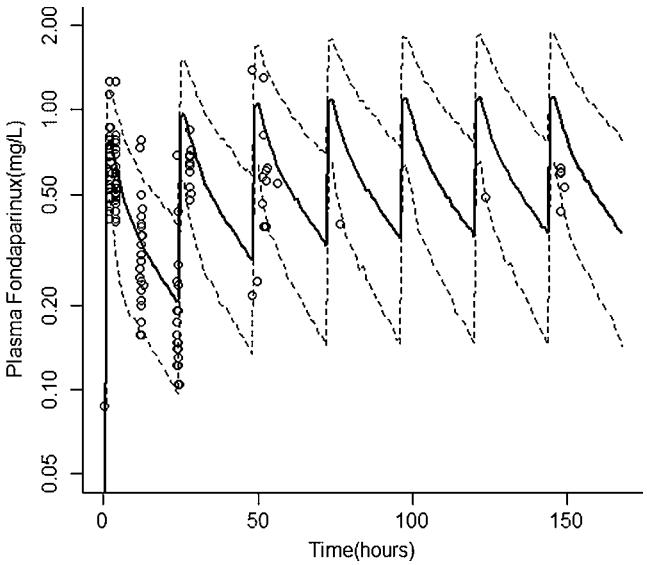

Fig. 2. Model validation using visual predictive check for the pediatric patients. Simulations are represented by lines (median-solid line, 95% prediction interval-dashed lines) with the observed data (open circles) overlaid.

TABLE IV. Summary of Parameters of the Final Population Pharmacokinetic Model for Fondaparinux

PK parameters	Point estimate (% standard error)	Inter-individual variability (% CV)
CL[a]	0.337 (5.52%)	30.1%
V2[b]	5.49 (3.79%)	18.2%
V3	2.21 (5.52%)	NE[c]
Q	0.371 (11.8%)	NE
KA	1.45 (7.93%)	30.1%
$Covariance_{CL,V2}$		21.7%
$Residual\ error_{Adult\ BE}$		8.8%
$Residual\ error_{Pediatric}$		31.3%

[a]Individual CL = TVCL × $(WGT/70)^{0.75\ (fixed)}$. TVCL, typical value of clearance; [b]Individual V2 = TVV2 × $(WGT/70)^{1\ (fixed)}$. TVV2, typical value of central volume of distribution; [c]NE, not evaluated.

Safety

In general fondaparinux was well tolerated in this pediatric study population. Two hemorrhagic AEs occurred. One patient was a 12-year-old female with drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome who presented a week prior to study drug initiation with severe hypertensive encephalopathy. She had significant neurologic impairment at that time and at study drug initiation. She was noted to have an intracranial bleeding event on day 5 of treatment on a magnetic resonance imaging study which was performed due to persistent headache. Her fondaparinux level was therapeutic. The radiologist reported the hemorrhage as subacute and consistent with hypertensive encephalopathy. It is possible this bleed preceded study drug

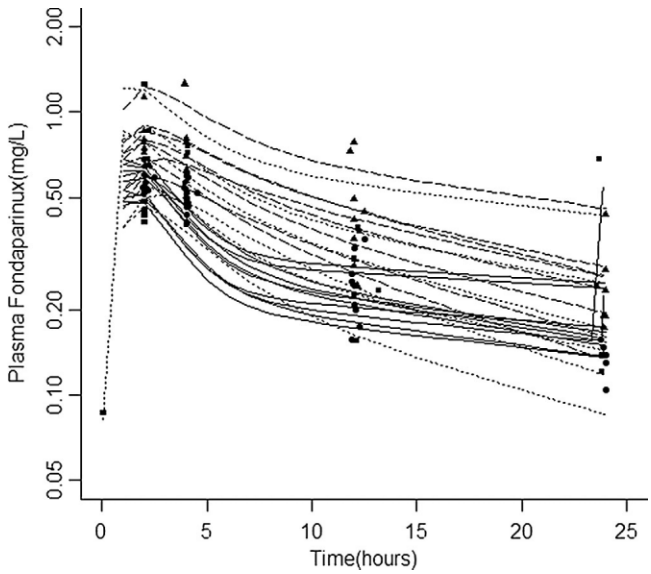

Fig. 3. Predicted (lines) and observed (symbols) fondaparinux concentration-time profiles for each subject in the first 24 hr grouped by body weight. Body weight ≤20 kg (approximate ages ≤5 years) represented by solid lines and closed circles, body weight 20–46 kg (approximate age 6–12 years, inclusive) represented by dotted lines and closed squares, and body weight ≥ 46 kg, (approximate ages ≥13) represented by dashed lines and closed triangles.

TABLE V. Median and 95% Prediction Interval for C_{max} and C_{min} at Steady State for Adults (n = 1,000) and Pediatric Patients (n = 1,000)

Population	Median C_{max}(95% PI)	Median C_{min} (95% PI)
Adult	1.23 (0.691, 2.15)	0.420 (0.170, 0.888)
Pediatric	1.12 (0.650, 1.89)	0.364 (0.144, 0.772)

administration. Nevertheless, the study drug was discontinued upon discovery of the intracranial hemorrhage. Her peak fondaparinux level at this time was 0.73. Although the hemorrhage resolved, she remained with neurologic sequelae though this was in all likelihood secondary to the DRESS and hypertensive encephalopathy. The second hemorrhagic event occurred in a 1-year-old male on study day 5 and was classified as a minor, clinically significant gastrointestinal bleeding event. He was noted to have occult blood in the stool which resulted in withholding of study medication on study days 6–8. His peak fondaparinux level on day 3 was 0.53. Study drug was resumed from study day 9 through day 18, the final day of study for this patient with no further bleeding. In addition to the 2 hemorrhagic events, 9 adverse events were reported involving 6 subjects. Of these, one (rash) resulted in discontinuation of study drug and one (prolongation of hospitalization due to sepsis that was considered unrelated to study drug) was classified a serious adverse event. In summary, the adverse events reported in this small study in pediatric patients were consistent with the current known safety profile of fondaparinux in adults [20].

DISCUSSION

This is the first prospective study of fondaparinux in children and demonstrates that a dose of 0.1 mg/kg administered once-daily is safe and effectively achieves concentrations approximately equal to those achieved in adults known to provide anticoagulation. Nearly all patients (21 of 24) achieved the targeted therapeutic range after the first dose and all 24 achieved the therapeutic range after no more than two dose adjustments. Two patients whose 12 hr level would have mandated a second dose came off study prior to the availability of these results such that no data are available for twice daily dosing. Importantly, detailed pharmacokinetic analysis demonstrated that at the starting dose utilized in this study (0.1 mg/kg), both the simulated and observed pediatric data are nearly equivalent to the data available in adults for measured peak and trough levels. There was no significant difference across the 3 age cohorts, suggesting that this dose is appropriate for children between 1 and 18 years of age. Of note, PK analysis demonstrated that time to C_{max} occurred at approximately 2 hr, however, levels at 4 hr were nearly identical to the 2 hr levels (Fig. 3) such that assessing C_{max} can be done anytime between 2 and 4 hr though in adults it is recommended to measure the C_{max} at 3 hr.

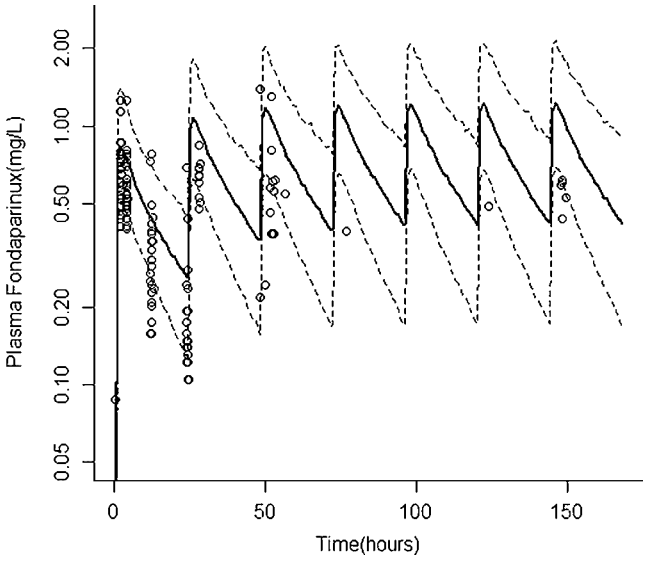

Fig. 4. The observed fondaparinux concentration data from the pediatric study (open circles) were overlaid on a plot of a simulation of 1,000 adult subjects receiving the recommended dosing regimen for treatment (median-solid line, 95% prediction interval-dashed lines).

The safety profile of fondaparinux is acceptable and consistent with the safety of fondaparinux reported in adults and at least as good if not better than with the use of low molecular weight heparins in pediatric patients treated for DVT. The bleeding rate for major and minor bleeding in adults treated for DVT is 4.3% [19]. In a review of pediatric studies of LMWHs, the overall bleeding rate was 26% (3% major bleeding and 23% minor bleeding) [22]. The one serious hemorrhagic event may have occurred prior to study drug initiation, however, illustrates the need to be vigilant for bleeding in all patients on anticoagulants. The other bleeding event resulted in temporary study drug discontinuation, however, was not deemed to be serious enough to lead to permanent discontinuation. The only other event felt to be possibly related to fondaparinux was a generalized rash which occurred in a child who was on multiple antibiotics, including vancomycin. Of note, it should be pointed out that while protamine is effective at reversing unfractionated heparin and partially effective at reversing the effect of LMWH, it has no effect on fondaparinux. Thus, there is no antidote for fondaparinux.

In addition to these data, one can consider fondaparinux an attractive alternative to LMWH for management of DVT and HIT in children for the following reasons. First, the once-daily dosing is an important enhancement given the difficulties with subcutaneous administration of medication in children. Although Trame et al. [23] recently published a population PK study suggesting once-daily enoxaparin is feasible, this study only incorporated such dosing after the acute period which was stated as 10–14 days and among the patients in the once-daily cohort, 47% had sub-therapeutic levels at 24 hr. In contrast, in this study, fondaparinux was used during the acute period and concentrations throughout the treatment cycle remained in the therapeutic range (Fig. 4). Other similar pharmacologic studies in children of enoxaparin [3], dalteparin [4], and tinzaparin [5] demonstrated sub-therapeutic levels when once-daily dosing was used. Second, fondaparinux does not appear to lead to HIT despite a few reports [24] and in fact is considered a treatment option for adults with HIT [11] and has been used in a few cases in children [12–16]. Although the risk for HIT in children is very low with LMWH, it does occur and can have devastating consequences. Third, available data suggest that LWMH adversely affects bone metabolism in children [25], whereas experimental evidence suggests that

fondaparinux will not lead to osteopenia [10]. Fourth, fondaparinux is a synthesized drug whereas LMWH are derived from animal tissue (porcine intestine). As was recently demonstrated with unfractionated heparin [26], contamination of such drugs by animal proteins is possible and will remain a risk. Lastly, while this study did not examine the efficacy of fondaparinux with respect to clot resolution, available data suggest that fondaparinux may be superior to LMWH in adults in terms of clinical outcomes [27].

There are a number of limitations of the present study. First, this pilot study was not designed to assess the efficacy of fondaparinux with respect to clot resolution. Follow-up imaging was not required. However, upon exiting the study, no subject had evidence of worsening thrombosis or pulmonary embolism. As all the subjects were followed by the investigators after the study period ended, a post-hoc analysis is planned which will address this issue. Second, the sample size was small, but comparable to that of previous, similarly designed studies of LMWH in children [28,29]. Third, subjects less than 1 year were not recruited as a result of the restriction on the IND imposed by the FDA. Thus the current data are relevant only to children older than 1 year. As neonates and infants have physiologically different coagulation systems and different drug metabolism capabilities, a separate study addressing dosing in those under a year old will need to be performed before fondaparinux can be utilized safely in that age group.

In conclusion, this first prospective pediatric study of fondaparinux has defined the dosing of this agent in children as well as demonstrated an acceptable safety profile. Fondaparinux can be considered an alternative to LMWH given its once-daily dosing and favorable properties although further studies are required to provide evidence for efficacy and to study the pharmacology and safety in children less than 1 year of age.

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