Population Pharmacokinetic Analysis of Dalteparin in Pediatric Patients With Venous Thromboembolism

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Abstract

This article describes the population pharmacokinetics (PK) of dalteparin in pediatric patients with venous thromboembolism (VTE). A prospective multicenter open-label study was conducted in children who required anticoagulation for the treatment of VTE. The study population included children with and without cancer. The goal was to describe the pharmacokinetics of dalteparin using anti-Xa as a surrogate marker and to determine the dose required to achieve therapeutic anti-Xa levels (0.5-1.0 IU/mL). The anti-Xa data were supplemented with 2 published studies and analyzed using population pharmacokinetic approaches. The pharmacokinetics of dalteparin following subcutaneous injection in pediatric patients was described by a 1-compartment model with linear absorption and elimination. Body weight was added as a covariate on both CL/F and Vd/F as a power function with fixed exponents of 0.75 and 1.0, respectively. The estimates of CL/F and Vd/F in the full model were 929 mL/h and 7180 mL, respectively, for a reference female patient aged 12 years with body weight of 43 kg. Body weight-normalized CL/F decreased with age. Cancer status and sex did not have significant effects on CL/F and Vd/F. Simulations were conducted to select starting doses of dalteparin that would rapidly achieve therapeutic anti-Xa levels. These simulations suggested that the recommended starting doses of dalteparin administered subcutaneously in pediatric patients of different age cohort groups for treatment of VTE were 150 IU/kg every 12 hours (1 month to <2 years), 125 IU/kg every 12 hours (≥2 to <8 years), and 100 IU/kg every 12 hours (≥8 to <19 years).

Dalteparin sodium (Fragmin) is a low-molecular-weight heparin (LMWH). The antithrombotic effect of dalteparin is a result of its ability to increase the inhibition of factor Xa and thrombin. Dalteparin has greater ability to increase the inhibition of factor Xa than to prolong the time for clot formation in plasma. Dalteparin has a relatively small effect on platelet function and platelet adhesiveness compared with heparin, thereby a small effect on primary hemostasis.[1] Dalteparin is approved for the primary prophylaxis of proximal deep vein thrombosis in subjects undergoing abdominal surgery and hip surgery, in subjects with severely restricted mobility during acute illness, and for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin therapy.[2] Dalteparin is also approved for the extended treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence of VTE in adult patients (aged ≥ 18 years) with cancer.[2] This is based on the results of a phase 3 clinical trial of dalteparin versus oral anticoagulant therapy for long-term anticoagulation in cancer subjects with VTE (CLOT study).[3] The CLOT study was a multinational, prospective, randomized clinical trial in subjects with cancer to show superiority of dalteparin over standard-of-care therapy using vitamin K antagonists for the secondary prophylaxis

of recurrent VTE. However, the CLOT study did not include pediatric subjects.

VTE in children is often associated with serious underlying illness such as cancer or congenital heart disease.[4,5] In addition to the underlying serious illness, VTE can lead to significant complications and even death. Although the steps involved in the coagulation/anticoagulation cascade are similar in adult and pediatric subjects, there are notable differences in the hemostatic system and the

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pharmacokinetics/pharmacodynamics of anticoagulants in pediatric subjects compared with adults.[6] The hemostatic system is dynamic and evolving in children, which may affect not only the frequency and natural history of VTE in children but also the response to therapeutic agents.[7] The distribution, binding, and clearance of antithrombotic drugs also appear to be age dependent. The frequency and type of underlying illnesses that cause VTE also differs with age. Nonetheless, published data indicate that the course of VTE and the effects of dalteparin appear to be sufficiently similar in the pediatric population to permit extrapolation of starting doses.[8] In addition, the course of VTE appears to be sufficiently similar in pediatric cancer and noncancer populations.[9]

LMWHs have been used in pediatric patients, mainly off-label, because of their favorable safety profile, absence of interference with other drugs or diet, and minimal monitoring requirements.[6,10] Consequently, various investigators have published their experience with use of dalteparin in pediatric patients.[11-13] However, there has been no systematic evaluation of the pharmacokinetic of dalteparin across the entire pediatric age range. The pharmacokinetics of dalteparin are measured using anti-factor Xa (anti-Xa) activity as a surrogate pharmacodynamic marker because of the analytical difficulty in measuring dalteparin in plasma and the instantaneous pharmacologic effect on anti-Xa level.[14-16]

This clinical trial was undertaken to investigate the safety, efficacy, and pharmacokinetics of dalteparin in pediatric patients with and without cancer requiring anticoagulation for the treatment of acute VTE. The results of this study contributed to the US Food and Drug Administration approval of dalteparin in the United States for treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients 1 month of age and older. It is currently the first and only anticoagulation therapy approved for the treatment of VTE in pediatric patients. This article describes the population pharmacokinetics of dalteparin for the treatment of VTE in pediatric patients and provides evidence of recommended starting doses for the different pediatric age groups.

Methods

Study Design
This was a prospective multicenter open-label study in children with and without cancer who required anticoagulation for the treatment and secondary prophylaxis of VTE.[17] The study was approved by the institutional review board of each participating center, parents/guardians of the subjects gave their informed consent prior to enrollment, and children were asked to provide assent dependent on child's age, mental status, and local laws. The goal of the study was to describe the pharmacokinetics of dalteparin and to determine the median dose (IU/kg) required to achieve therapeutic anti-Xa levels (0.5 to 1.0 IU/mL) based on subject age and weight. The study was conducted at 15 study sites across North America and Europe. The study was divided into 3 phases, namely, dose adjustment phase (up to 7 days), pharmacodynamic phase (up to 7 days), and follow-up phase (up to 90 days of dalteparin treatment). Dalteparin was given subcutaneously twice a day to the groups at the beginning of the dose adjustment phase at the following doses: 0 to <8 weeks, 125 IU/kg; 8 weeks to <2 years, 150 IU/kg; 2 to <8 years, 125 IU/kg; 8 to <12 years, 125 IU/kg; and 12 to <19 years, 100 IU/kg. During this phase, the first anti-Xa level was collected 4 ± 1 hour after the first, second, or third dose per institutional standard, and plasma samples were analyzed for anti-Xa levels at both the local and central laboratories. Dalteparin doses were adjusted in increments or decrements of 25 IU/kg to achieve the target anti-Xa level of 0.5 to 1.0 IU/mL. On achieving the target anti-Xa level, patients entered the pharmacodynamic phase, during which dalteparin dosing was continued using the maintenance therapeutic dose achieved during the dose adjustment phase. The pharmacodynamic phase lasted up to 7 days, and anti-Xa samples were collected after any dose during this phase. During the pharmacodynamic PD phase, 2 blood samples for anti-Xa measurement were collected from each subject. Subjects from each age group were randomized to 2 different pharmacodynamic sampling windows (1 to 3, 5 to 8, 3 to 5, or 8 to 12 hours). Plasma samples collected during the pharmacodynamic phase of the study were shipped to the central laboratory for analyses of anti-Xa levels. During the follow-up phase, dalteparin dosing was continued with the same maintenance therapeutic dose, unless routine anti-Xa and safety monitoring indicated that titration was required. The end of study was day 90 ± 14 days after study baseline.

The anti-Xa data from the study were supplemented with data from 2 published studies. The Kids-DOTT study was a multicenter prospective, randomized, controlled clinical trial.[11] This study was approved by the institutional review board of each participating center, and parents/guardians of the subjects gave their informed consent prior to enrollment. The design included 2 phases, with the first phase a pilot study with an interim analysis and the second phase the definitively powered trial. The primary objective was to compare the efficacy of short-duration (6 weeks) and conventional-duration (3 months) anticoagulation therapy in VTE patients. The pharmacokinetic substudy was an open-label dose-finding pilot study of

dalteparin as primary treatment for VTE in children aged 0 to 21 years, the objective of which was to determine the dalteparin dose required to achieve an anti-Xa level of 0.5-1.0 U/mL 4 to 6 hours post-dose. Per-protocol, starting doses given twice daily by subcutaneous injection were: birth to <12 months, (150 IU/kg; 1 to <13 years, 125 IU/kg; and 13 to <21 years, 100 IU/kg. Anti-Xa activity was measured 4 to 6 hours after the first, second, or third dose, and starting doses were adjusted by 10%-20%, if needed, to achieve anti-Xa activity between 0.5 and 1.0 IU/ mL. A total of 18 subjects received therapeutic doses of dalteparin and provided anti-Xa data for the population pharmacokinetic analyses.

The second published study was conducted by investigators at the Mayo Clinic.[12] This study was a retrospective chart analysis, which analyzed the clinical and laboratory outcomes of prophylactic and therapeutic treatment of dalteparin in children (0 to 18 years old). The study was approved by the Mayo Clinic Institutional Review Board. For therapeutic use, patients received dalteparin 100 IU/kg twice a day or 200 IU/kg once a day. Plasma anti-Xa activity was measured 4-6 hours after at least 3 doses, and the doses were adjusted to a target range of 0.5 to 1.0 IU/mL for therapeutic indications. Anti-Xa data from this study included in the population pharmacokinetic analyses were obtained from 34 pediatric subjects who received therapeutic doses of dalteparin and had documented sampling date/time, time postdose, and dose.

Bioanalyses

In the Pfizer-sponsored trial, anti-Xa samples were analyzed by both local and central laboratories. The local anti-Xa data were used to for dose adjustment, whereas the central laboratory anti-Xa data collected during all phases were used in the population PK analysis. At the central laboratory (Esoterix/Labcorp Inc., Englewood, Colorado), a specific and sensitive chromogenic assay for the quantitative determination of anti-Xa activity in citrated human plasma was validated using commercially available Biophen Anti-Xa kit reagents (Hyphen Biomed, Paris, France) and an STA Compact (Diagnostica Stago Inc., Parsippany, New Jersey) instrument.

In the Kidd-DOTT substudy, plasma anti-Xa levels were monitored locally at each clinical site in accordance with the standard of care at each institution. All the clinical sites used a chromogenic assay method (STA Liquid Anti-Xa assay) to measure anti-Xa activity (Diagnostica Stago Inc., Parsippany, New Jersey).

In the Mayo Clinic retrospective analysis, plasma anti-Xa levels were assessed using the amidolytic method with a chromogenic substrate (Starchrom Heparin; Diagnostica Stago Inc., Parsippany, New

Jersey) on a STA-R Evolution platform (Diagnostica Stago Inc., Parsippany, New Jersey), and the assay was performed according to the manufacturer's instructions for the study period. The test principle was based on the in vitro inhibition of factor Xa by ATIII heparin (unfractionated heparin [UFH] or LMWH) complexes. An excess of purified ATIII was added to ensure that any existing deficiency of this protein was compensated. The quantity of para-nitroaniline released at 405 nm was inversely proportional to the amount of heparin (UFH or LMWH) present in the plasma.

Population Pharmacokinetic Analysis

The objectives of this analysis were to describe the pharmacokinetics of anti-Xa levels following dalteparin administration in pediatric patients, to identify patient covariates that explain between-subject variability, to identify the residual variability in anti-Xa level, and to perform simulations to determine the starting dose of dalteparin to achieve target therapeutic anti-Xa levels of 0.5-1.0 IU/mL. Based on protocol-defined age groups, patients were stratified into 5 groups: newborn, 0 to <8 weeks; infant, ≥8 weeks to <2 years; preschool, ≥2 to <8 years; school, ; and teen, ≥12 to <19 years.

Model-based evaluation was conducted using the nonlinear mixed-effects modeling software package NONMEM (version 7.2 or above; ICON Development Solutions, Dublin, Ireland). Visual predictive checks (VPCs) and bootstraps were conducted using Perl-speaks-NONMEM (PsN-4.2.0 or higher). The software R (version 2.12.2 or above) was used for data manipulation, exploratory analysis, postmodeling assessment, and dose simulations.

Model development was based on prior knowledge of dalteparin pharmacokinetics.[18] Both CL/F and V/F increased with weight as a power function, with exponents fixed to allometric scaling values of 0.75 and 1.0, respectively. The full model estimation method was used in the inclusion of covariates in the final population pharmacokinetic model. The relevant covariates based on physiology and/or pharmacology as well as prior knowledge and data availability were added to the pharmacokinetic parameters of interest in the model. The model was fitted to the data and bootstrapped (1000 runs) to generate 95%CIs for the pharmacokinetic parameters, from which the impact of covariates on pharmacokinetic parameters was evaluated. The diagnostic plots of the full covariate model were used to evaluate the goodness of fit of the model to the data. The stability of the model was examined via the condition number of the covariance matrix of the estimates. The shrinkage on the empirical Bayes prediction of interindividual random effects was assessed. A VPC was used to evaluate the predictive performance of the model. Five hundred replicates were simulated

Table 1. Demographic and Baseline Characteristics of Pediatric Patients Included in the Population Pharmacokinetic Analyses

Parameter	Overall	0 to <8 Weeks	≥8 Weeks to <2 Years	≥2 to <8 Years	≥8 to <12 Years	≥12 to <19 Years
Sample size, n	89	6	13	14	11	45
Males, n (%)	59 (66.3)	5 (83.3)	9 (69.2)	11 (78.6)	6 (54.5)	28 (62.2)
Age (years), median (range)	12.0 (0.04-19.5)	0.06 (0.04-0.14)	0.5 (0.2-1.9)	4.5 (2.0-7.6)	9.6 (8.0-10.5)	15.9 (12-19.5)
Weight (kg), median (range)	43.4 (2.3-161)	3.5 (2.3-4.0)	6.8 (3-13.7)	14.6 (11.5-161)	36.1 (25.4-66)	61.8 (19.2-106)
With Cancer, n (%)	43 (48.3)	0 (0)	3 (23.1)	8 (57.1)	8 (72.7)	24 (53.3)
Pfizer sponsored, n (%)	37 (41.6)	1 (16.7)	2 (15.4)	8 (57.1)	6 (54.5)	20 (44.5)
External, n (%)	52 (58.4)	5 (83.3)	11 (84.6)	6 (42.9)	5 (45.5)	25 (55.5)

to visually compare simulated and observed anti-Xa concentrations versus time after the dose.

A reduced final model with all insignificant covariates removed was used in the dose simulations. One thousand subjects were simulated together with their anti-Xa profiles at steady state for a given dose. Simulations were performed on each of the 5 age groups (n = 1000), with doses ranging from 75 to 300 IU/kg in increments of 25 IU/kg twice a day (every 12 hours). A total of 1000 subjects per age group with their ages and body weights were generated based on the age-weight relationship in the current population pharmacokinetic data set. Anti-Xa plasma concentration-time profiles at steady state were simulated for 1000 subjects per age group for a given dose. For each dose and age group, the probability of target attainment (PTA) was calculated as the proportions of 1000 simulated subjects who had their anti-Xa steady-state concentration 4 hours postdose (C4hss) within the therapeutic target range of 0.5-1.0 IU/mL. Similarly, for each dose and age group, the probability of underattainment (C4hss < 0.5 IU/mL) and probability of overattainment (C4hss > 1.0 IU/mL) were also calculated.

Results

Observed Data

The final analysis data set combined from the 3 studies included 266 observations from 89 subjects. Concentrations below the analytical assay quantitation limit were excluded from this data analysis. Demographics and baseline data are summarized in Table 1. There were 59 males (66%) and 40 white patients (45%). Age ranged from 15 days to 19.5 years (median, 12 years), with >50% 12 years or older and 21% (19 of 89) younger than 2 years. The majority of the patients (63%) in the neonate and infant groups (age < 2 years) were from the Mayo Clinic study. Body weight ranged from 2.3 to 161 kg (median, 43 kg). Forty-eight percent of the patients had cancer. Anti-Xa concentrations (log scale) versus time after dose are presented in Figure 1. Most anti-Xa concentrations were collected between 3 and 6 hours postdose. They appeared to decline afterward in a monoexponential manner, suggesting that a 1-compartment model might be used to describe the concentration-time profiles.

Population Pharmacokinetic Analysis

Initial model development was started with the prior published dalteparin pharmacokinetic model.[18] The initial base model was refined by replacing the endogenous anti-Xa level term with an additive term in the error model because there were only a few predose samples to obtain a reasonable estimate and removal of interindividual variability (IIV) for k_a because of sparse data collected in the absorption phase. Age, sex, and cancer status on CL/F were then added to the model to obtain the full covariate model. The model equations for CL/F and V/F are presented below:

$$TVCL = \theta_1 \cdot (WT/43)^{\theta_6} \cdot (AGE/12)^{\theta_8} \cdot \theta_{14}^{I(SEX=male)}$$
$$\cdot \theta_{15}^{I(CANCERST=without\ cancer)}$$

$$TVV = \theta_2 \cdot (WT/43)^{\theta_7}$$

$$\eta_i^V = \theta_5 \cdot \eta_i^{CL}$$

where TVCL and TVV are the population mean values for CL/F and V/F, respectively, θ terms are the parameters to be estimated by the data, and I(.) is an indicator function, that is, I(statement) = 1 if the statement in the parentheses is true and = 0 if false. θ_6 and θ_7 are the allometric scaling factors for CL/F and V/F, and they were fixed at 0.75 and 1.0, respectively. The IIV for V/F (η_i^V) was estimated relative to that of CL/F, where θ_5 is a scaling factor. A 1-compartment model with first-order absorption and elimination, parameterized in terms of CL/F, V/F, and k_a fit the anti-Xa concentration-time data well. The population-PK model was converged successfully. The objective function value was −547.675, and the condition number was 10.3 (the square root of the ratio of the largest eigenvalue to the smallest eigenvalue of the correlation matrix), indicating a stable model. The shrinkage for CL/F and residual error was 31.6% and 7.8%, respectively. The parameter estimates of the full
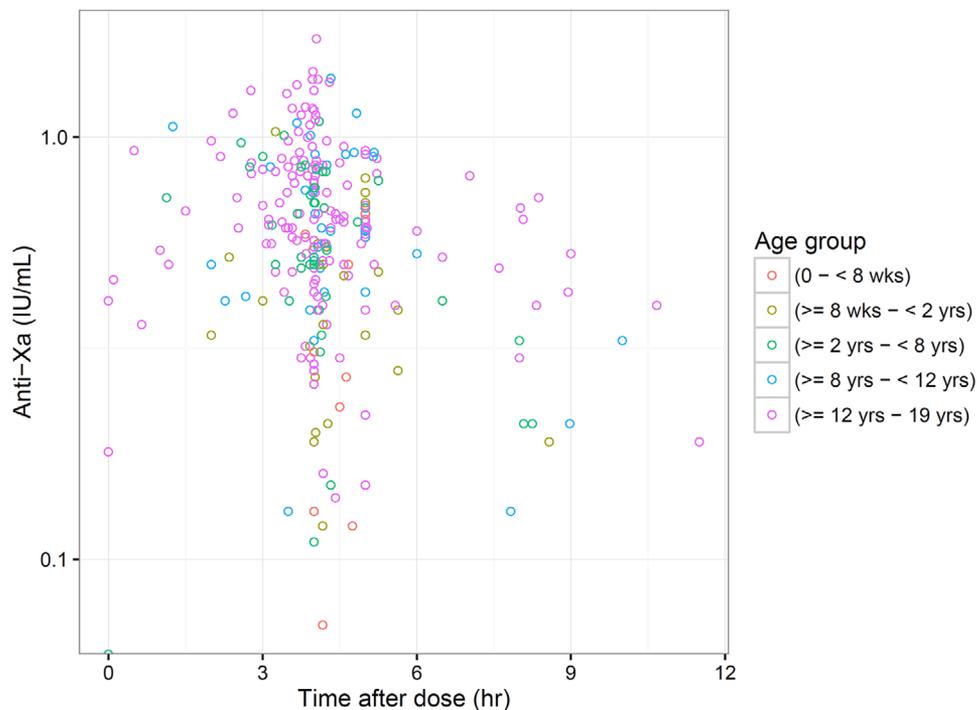
Figure 1. Observed plasma anti-Xa concentration versus time following administration of dalteparin.

Table 2. Parameter Estimates of the Full Model

| Parameter	Estimate	SE	%RSE	Bootstrapped Median (95%CI)
CL/F θ_1, mL/h	929	87.4	9.41	913 (770-1080)
V/F θ_2, mL	7180	1080	15	6870 (2460-8800)
K_a θ_3, l/h	1.04	0.747	71.8	0.961 (0.24-14.50)[a]
Scaling of IIV for V/F θ_5	1.73	1.2	69.4	1.84 (0.481-5.94)
WT in CL/F θ_6	0.75	-	-	—
WT in V/F θ_7	1	-	-	—
AGE in CL/F θ_8	-0.0687	0.0263	-38.3	-0.0672 (−0.122 to −0.0158)
SEX = 1 in CL/F θ_{14}	1.03	0.0796	7.73	1.04 (0.908-1.2)
CANCERST = 1 in CL/F θ_{15}	0.885	0.0777	8.78	0.878 (0.744-1.02)
$\omega^2_{CL/F}$	0.0369	0.0249	67.5	0.0318 (0.00571-0.0728)
σ^2_P	0.0519	0.0219	42.2	0.0545 (0.021-0.0959)
σ^2_A	0.016	0.0074	46.2	0.0141 (0.0026-0.0273)

CI, confidence interval; IIV, interindividual variability; SE, standard error; σ, residual variability; ω, interindividual variability.

Note that %RSE = (SE/Estimate) × 100%.

[a] Median and confidence intervals were based on 950 bootstrap runs with minimization successful and k_a estimate ≤ 100.

model are presented in Table 2. The estimate of typical CL/F and V/F from the full model was 929 mL/h and 7180 mL, respectively, for a 12-year-old female patient with cancer who had a body weight of 43 kg. Both CL/F and V/F increased with weight. The estimate of k_a was 1.04/h. CL/F decreased slightly with age. male subjects (SEX = 1) tended to have slightly larger clearance with the adjustment of other covariates in the model. Similarly, the patients without cancer (CANCERST = 1) had a slightly lower population mean clearance. The IIV for CL/F was estimated at 19% CV. The IIV for V/F was 33% CV but could not be directly estimated and

was determined as a multiple of the variance on CL/F. The proportional and additive terms of the residual variability were estimated at 23% CV and 0.016 IU/mL, respectively. The pharmacokinetic parameters in the full model were estimated with good precision, with %RSE of 9.4% for CL/F and %RSE of 15% for V/F, where k_a was estimated with less precision at an %RSE of 71.9%. Figure 2 presents the diagnostics for the full model. Points were distributed around the line of identity or the horizontal line at 0 without showing any peculiar trends, indicating a reasonable fit to the data.
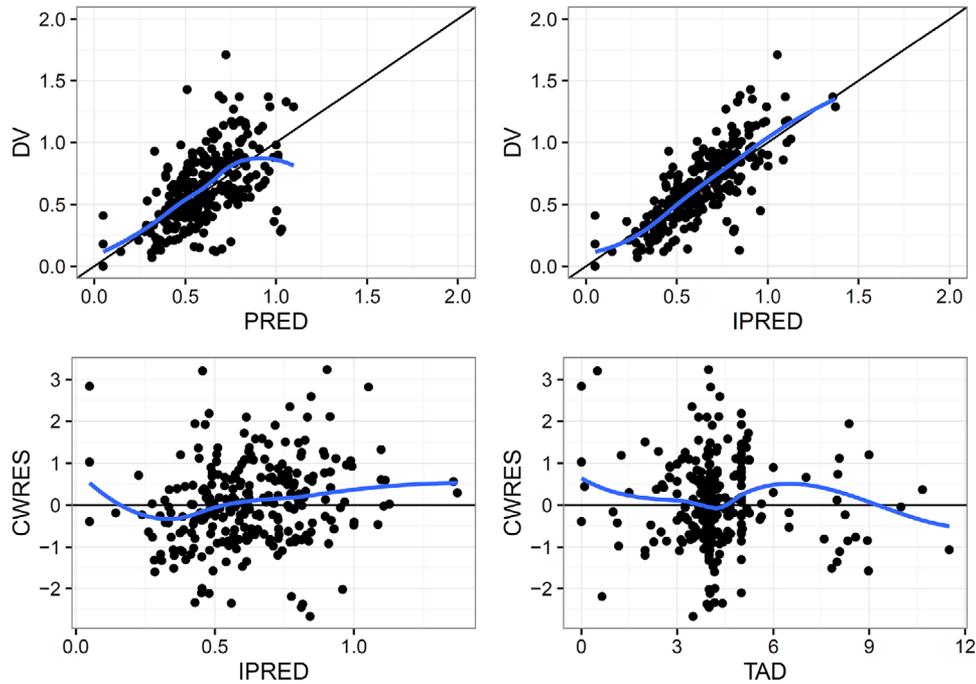
Figure 2. Diagnostic plots for the full model. CWRES, conditional weighted residuals; DV, dependent variable, observed anti-Xa concentrations; IPRED, individual predicted concentrations; PRED, population-predicted concentration; TAD, time after dose in hours.
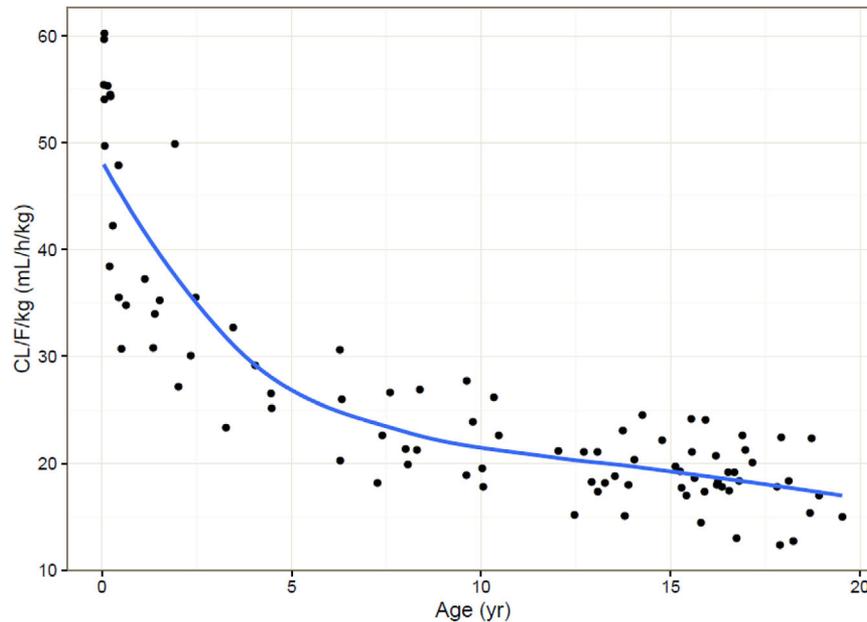

Figure 3. Relationship between body-weight-normalized clearance and age.

The pharmacokinetic parameters CL/F (929 mL/h) and V/F (7180 mL) in the current analysis were slight higher than those estimated in the prior published dalteparin pharmacokinetic model (CL/F, 809 mL/h; V/F, 5818 mL).[18] This could be because of differences in the age distribution of the study population. In the current data set, we have more younger subjects in the neonate to 8-year-old groups; thus, age was a significant covariate on CL/F, which was not the case with the prior published model.

The relationship between body weight-normalized clearance (CL/F/kg) and age is displayed in Figure 3. CL/F/kg declined rapidly up to about 5 years of age, and the decrease slowed with further increases in age.
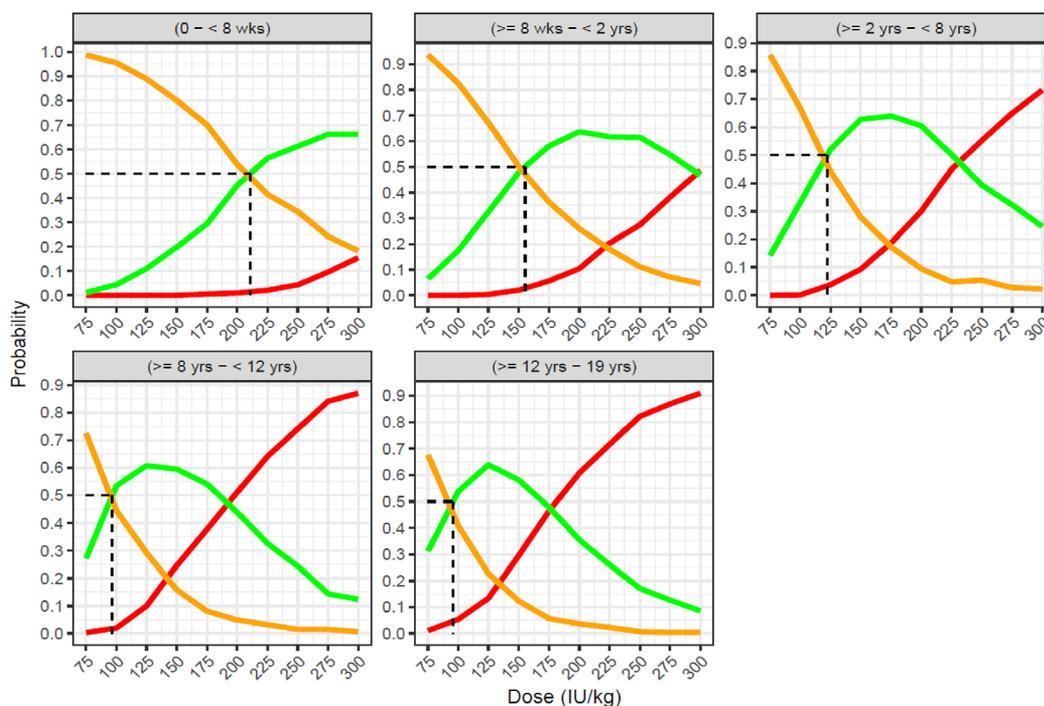
Figure 4. Relationship between dalteparin dose and PTA (green), probability of overattainment (red), and probability of underattainment (yellow) by pediatric age group. Green line represents PTA versus dalteparin dose; red line represents probability of overattainment versus dalteparin dose; yellow line represents probability of underattainment versus dalteparin dose; and black dashed line (—) represents interpolation of dalteparin dose (x axis) for 50% PTA. IU, international units; PTA, probability of target attainment; wks, week; yrs, years.

Simulations

In the full model, age, sex, and cancer status were used as covariates on CL/F. As noted in Table 2, the bootstrapped 95%CI for the categorical covariates sex and cancer status included one indicating that these were insignificant. Hence, a reduced population pharmacokinetic model was used to simulate anti-Xa plasma concentration-time profiles at various doses for dalteparin in pediatric patients. This reduced model was achieved by dropping all insignificant covariates in the full model, sex and cancer status. The resulting reduced model had 2 covariates, with body weight and age on CL/F and body weight on V/F. Simulations were performed on each of the 5 age groups (n = 1000), with doses ranging from 75 to 300 IU/kg in increments of 25 IU/kg twice a day. Figure 4 depicts the relationship between the dalteparin dose versus PTA (green line), probability of underattainment (yellow), and probability of overattainment (red line) by age groups. Note that at each dose level, the sum of the 3 probabilities equals 1.

As demonstrated in Figure 4, dalteparin dose versus PTA (green line) showed a bell-shaped relationship. The PTA increased with increasing doses until it reached a maximum, after which the PTA decreased with further increase in dose. The maximum PTA across age groups ranged between 0.608 and 0.662, meaning approximately one-third of patients would require dose adjust-

ment to establish the target PTA range. Furthermore, it is also evident that at any given dose, there will be some subjects who will be below and some subjects who will be above the target therapeutic range. The dashed black line in Figure 4 intersects the *X* axis to represent the dalteparin dose at which PTA is 0.5; this dose represents a balance between PTA while limiting the probability of overattainment. These simulations provide insights into the starting dose for dalteparin in pediatric patients for the treatment of VTE.

Discussion

The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for children receiving LMWH indicate a target range of anti-Xa plasma between 0.5 and 1.0 IU/mL, to be measured 4 to 6 hours postdose.[9] Rapid attainment and maintenance of anti-Xa levels within the target range is critical for the treatment of VTE, but less so for thromboprophylaxis. Low anti-Xa levels (<0.5 IU/mL) are associated with a risk of thromboembolism, whereas higher anti-Xa levels (>1.0 IU/mL) are associated with a significant bleeding risk. Therapeutic drug monitoring (TDM) is commonly used in clinical practice to adjust the dalteparin doses based on anti-Xa levels after a patient has received 3 to 4 doses. Doses can be adjusted upward if anti-Xa levels are subtherapeutic, but the bleeding

events that can arise because of supratherapeutic anti-Xa levels are more difficult to manage clinically. Hence, the key guiding principle for the simulations was to select starting doses of dalteparin that would rapidly achieve the target anti-Xa levels while avoiding, as much as possible, the high levels that could increase the risk of bleeding.

Anti-Xa plasma concentration-time profiles were simulated using various doses of dalteparin (ranging from 75 to 300 IU/kg with increments of 25 IU/kg). The probability that simulated subjects would achieve anti-Xa levels of 0.5 to 1.0 IU/mL was calculated and reported as PTA. Graphical depiction of dalteparin dose versus PTA exhibited a bell-shaped relationship. Initially, an increase in the dalteparin dose resulted in an increase in PTA, but a further increase in dose resulted in a decline in PTA as subjects were pushed into the supratherapeutic range. The maximum PTA across each age group ranged between approximately 61% and 66%. At dalteparin doses associated with the maximum PTA, ≈10% to 20% of pediatric subjects would have an anti-Xa plasma level >1.0 IU/mL, which might be associated with an increased risk of bleeding. There-fore, it was considered clinically necessary to achieve a balance to lower the risk of bleeding and to get subjects in the target therapeutic range. A starting dose based on 50% PTA achieved an acceptable balance in most of the pediatric age cohorts. This dose reduced the PTA across various age groups from 6%1-66% to 50%, but more importantly, it reduced the overattainment of anti-Xa levels across various age groups from a range of 10%-19% to 1%-5%. Dalteparin dose associated with 50% PTA was as follows: 200 IU/kg for neonates aged 0 to <8 weeks, 150 IU/kg for infants aged ≥8 week to <2 years, 125 IU/kg for children aged ≥2 to <8 years, 100 IU/kg for children aged ≥8 to <12 years, and 100 IU/kg for adolescents aged >12 to 18 years. Comparison of these 50% PTA doses showed excellent agreement with starting doses used in clinical studies in all pediatric age groups except for neonates.

In neonates, the starting dose in the study was 125 IU/kg versus the model-predicted 50% PTA dose of 200 IU/kg. A closer examination of the data for neonates suggested that the probability of overattain-ment (red line; Figure 4) was roughly similar between doses of 150 and 200 IU/kg. Considering that neonates are a vulnerable population, it seemed particularly im-portant to exercise caution in proposing a starting dose for this age cohort. Hence, the proposed starting dose for neonates was set conservatively at 150 IU/kg twice a day (every 12 hours), with the understanding that upward dose adjustments may be necessary in this age group based on TDM. Finally, the youngest pediatric patient in this analysis was a 1-month-old baby, and hence, the dosing recommendation was truncated at this age. Additional data are necessary to confirm the doses in neonates from birth to 1 month old.

In summary, after combining age groups with common doses, the recommended starting dose of dalteparin administered subcutaneously in pediatric patients with or without cancer requiring treatment of VTE is as follows: 1 month to <2 years, 150 IU/kg twice a day (every 12 hours); ≥2 to <8 years, 125 IU/kg twice a day (every 12 hours); ≥8 to <19 years, 100 IU/kg twice a day (every 12 hours). The results of this analysis led to the approval of dalteparin in the United States for treatment when symptomatic venous thromboem-bolism (VTE) to reduce the recurrence in pediatric patients 1 month of age and older. It is currently the first and only anticoagulation therapy in approved for the treatment of VTE in pediatric patients.

Conflicts of Interest

Bharat Damle, Nancy Sherman, Darshana Jani, and Kevin Sweeney are employees of Pfizer Inc. Frank Jen was an employee of Pfizer at the time study was conducted.

Data-Sharing Statement

On request and subject to certain criteria, conditions, and exceptions, see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information. Pfizer will pro-vide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies con-ducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or European Union or (2) in programs that have been terminated (ie, development for all indications has been dis-continued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study comple-tion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply via a secure portal. To gain access, data requesters must enter into a data access agreement with Pfizer.

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