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ORIGINAL ARTICLE

Optimal dosing of enoxaparin in overweight and obese children

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Aim: Current enoxaparin dosing guidelines in children are based on total body weight. This is potentially inappropriate in obese children as it may overestimate the drug clearance. Current evidence suggests that obese children may require lower initial doses of enoxaparin, therefore the aim of this work was to characterise the pharmacokinetics of enoxaparin in obese children and to propose a more appropriate dosing regimen.

Methods: Data from 196 unique encounters of 160 children who received enoxaparin treatment doses were analysed. Enoxaparin concentration was quantified using the chromogenic anti factor Xa (anti-Xa) assay. Patients provided a total of 552 anti-Xa samples. Existing published pharmacokinetic (PK) models were fitted and evaluated against our dataset using prediction-corrected visual predictive check plots (pcVPCs). A PK model was fitted using a nonlinear mixed-effects modelling approach. The fitted model was used to evaluate the current standard dosing and identify an optimal dosing regimen for obese children.

Results: Published models of enoxaparin pharmacokinetics in children did not capture the pharmacokinetics of enoxaparin in obese children as shown by pcVPCs. A one-compartment model with linear elimination best described the pharmacokinetics of enoxaparin. Allometrically scaled fat-free mass with an estimated exponent of 0.712 (CI 0.66-0.76) was the most influential covariate on clearance while linear fat-free mass was selected as the covariate on volume. Simulations from the model showed that fat-free mass-based dosing could achieve the target anti-Xa activity at steady state in 77.5% and 78.2% of obese and normal-weight children, respectively, compared to 65.2% and 75.5% for standard total body weight-based dosing.

Conclusions: A population PK model that describes the time course of anti-Xa activity of enoxaparin was developed in a paediatric population. Based on this model, a unified dosing regimen was proposed that will potentially improve the success rate of target attainment in overweight/obese patients without the need for patient body size categorisation. Therefore, prospective validation of the proposed approach is warranted.

KEYWORDS
children, enoxaparin, NONMEM, obesity, population pharmacokinetics

1 | INTRODUCTION

Enoxaparin is a commonly used anticoagulant for treating and preventing thromboembolic disorders in children. Common indications for enoxaparin include deep venous thrombosis/pulmonary embolism, coronary heart disease and prophylaxis in cases of increased thrombotic risk such as surgery and infections. Enoxaparin has largely replaced unfractionated heparin as the parenteral anticoagulant of choice for the management of thrombosis due to favourable pharmacokinetic properties such as a longer half-life and higher subcutaneous bioavailability. It has been shown to achieve similar effectiveness without an increase in the incidence of major bleeding events.[1] This has been purported to be due to a more predictable dose-response relationship.[2]

Dosing guidelines of enoxaparin for paediatric patients typically suggest an initial treatment dose of 1 mg/kg (of total body weight) twice daily, targeting a peak (4 hours post-dose) anti-Xa (aXa) activity of 0.5-1 IU/mL.[3,4] A recent population analysis showed that this dose has a 72.3% probability of achieving the aXa concentration target in hospitalised paediatric patients.[5] Maintenance dosing based on total body weight (Wt) implies that enoxaparin clearance is linearly proportional to Wt. However, this has often been found to be inaccurate in overweight/obese individuals.[6,7] As the body's metabolic processes occur primarily in lean tissues, overweight/obese individuals tend to have lower drug clearance per kilogram of Wt. Therefore, dosing based on Wt will potentially result in overdosing in this population. It has been reported that overweight/obese children achieve a significantly higher aXa activity compared to nonobese children when dosed on a Wt basis.[8] A recent review has shown that overweight/obese paediatric patients required a 12.9% to 37.3% average dose reduction, suggesting they may require lower initial enoxaparin Wt-based doses.[9] Data on the clinical outcomes of enoxaparin treatment in overweight/obese children versus normal-weight children are lacking. However, elevated aXa levels are associated with a higher risk of adverse effects such as bleeding.

The issue of dosing obese patients is becoming more critical as the prevalence of obesity is increasing worldwide.[10] Obesity in adults is usually defined based on the absolute value of body mass index (BMI).[10] However, children are classified as overweight if their BMI is greater than the 85th but less than the 95th percentile respective to age and sex, whereas obesity is defined as a BMI exceeding the 95th percentile for age and sex.[11] In adults, the risk of overdosing obese patients is minimised through alternative practices. A popular alternative to dosing in the obese is to reduce the dose to 0.75 mg/kg twice daily.[12] However, this approach has only been assessed in morbidly obese patients. An alternative dosing strategy is based on fat-free mass (FFM), which has been shown to result in fewer bleeding/bruising events without a decrease in drug effectiveness.[13,14] Some practices also implement dose capping at 100 mg per dose.[15] No alternative dosing strategies have been used or explored in the paediatric population.

What is already known about this subject

- Enoxaparin is typically dosed in children on a milligrams per kilogram basis, which may be suboptimal when used in obese children.
- With standard dosing, obese children achieve higher anti-Xa activity and require more frequent dose reduction compared to normal-weight children.
- No alternative dosing regimens for enoxaparin have been proposed/explored in obese children.

What this study adds

- The first population model was developed for enoxaparin pharmacokinetics in obese children.
- The model was used to identify a dosing regimen of enoxaparin that consistently achieves the target anti-Xa activity in both obese and normal-weight children.
- The proposed regimen potentially eliminates the need for categorising children based on their body weight and simplifies dose calculation in clinical practice.

1.1 | Objectives

The objectives of this study were (1) to evaluate the performance of published models of enoxaparin pharmacokinetics against our dataset in both normal-weight and overweight/obese children, (2) to develop and evaluate a population pharmacokinetic (PK) model to predict the optimal dosing regimen of enoxaparin in overweight/obese paediatric patients and (3) to evaluate the current dosing guidelines in overweight/obese children and identify optimal dosing strategies for those patients.

2 | METHODS

2.1 | Data

The data used in this analysis consisted of retrospectively collected aXa measurements from 160 paediatric patients who received a

treatment dose of enoxaparin between 1 January 1996 and 31 December 2016 in the Primary Children's Hospital, Salt Lake City, Utah, USA, and had at least one recorded aXa measurement. The study received approval from the University of Utah institutional review board (IRB# 01101489). All patients who concomitantly received other anticoagulants were excluded from the study. As per institutional protocol, infants younger than 2 months received 1.5 mg/kg every 12 hours while older infants and children received 1 mg/kg every 12 hours. aXa activity was determined using the chromogenic one-stage assay (Heparin anti-Xa LMWH 0030144 kit; Diagnotsica Stago, Milan, Italy) with a lower limit of quantification of 0.1 IU/mL. The intra-assay coefficient of variation was 3%. Patients were categorised as overweight or obese if their BMIs were higher than the 85th or 95th percentile, respectively, for their age and sex as per the Centres for Disease Control and Prevention (CDC) growth charts.[16]

One hundred and sixty patients who provided 552 aXa samples during 196 unique encounters met the inclusion criteria and were available for this analysis. Patients received a median enoxaparin dose of 1.16 mg/kg (interquartile range [IQR] 0.93-1.39 mg/kg) twice daily. Dose adjustment based on measured aXa occurred in 7.29% of dosing records, of which 35.12% were dose reductions and 13.17% were in overweight/obese patients. The median number of doses per encounter was 10 (IQR 7-14 dose/encounter) and the median aXa activity in the included data was 0.58 U/mL (IQR 0.42-0.81 IU/mL). The demographics of the population of this study are summarised in Table 1. Figure 1 shows the distribution of age versus weight in the study sample broken down by sex and body size category.

TABLE 1 Demographic characteristics of the study population

Characteristic	Median or *n*	Range or %
Sex (male/female)	92/68	57.5/42.5
Weight (kg)	19.2	1.51-151
Age (years)	5.85	0.0004-18
Number of observations per encounter	3	1-13
Body mass index (kg/m^2)	16.58	8.44-52.35
Number of overweight/obese	34	21.3

2.2 | Evaluation of published models

Two population PK models of enoxaparin in children were identified. The first described the pharmacokinetics of enoxaparin in children younger than 1 year of age,[17] while the other examined children between 1 and 18 years of age.[5] Both models, described in detail in **Appendix S1**, were fitted to the data of this study and then evaluated using prediction-corrected visual predictive check (pcVPC) plots to determine model fit to the whole dataset and fit to specific patient subpopulation based on size categories.

2.3 | Model building

Data from all 160 patients who met the inclusion criteria were included in the model-building process. Two patients had no recorded value of height or weight. These were imputed with a single imputation from a multivariate distribution of age, sex, weight and height. The root mean squared errors for the imputation of weight and height were 0.854 kg and 11.9 cm, respectively. The final model was re-estimated with the data from patients with missing weight/height excluded and estimates were compared to the full dataset.

One- and two-compartment models with linear and nonlinear elimination and zero- and first-order absorption were tested to describe the kinetics of aXa activity. Covariates considered on model parameters were postnatal age (Age), postmenstrual age (PMA) (calculated as age + 40 weeks), sex, Wt, BMI,[18] FFM,[19] body surface area (BSA),[20] normal fat mass (NFM),[21] and allometrically scaled Wt and FFM with fixed (0.75 or 0.67) or estimated exponents (see Equations 1-5).

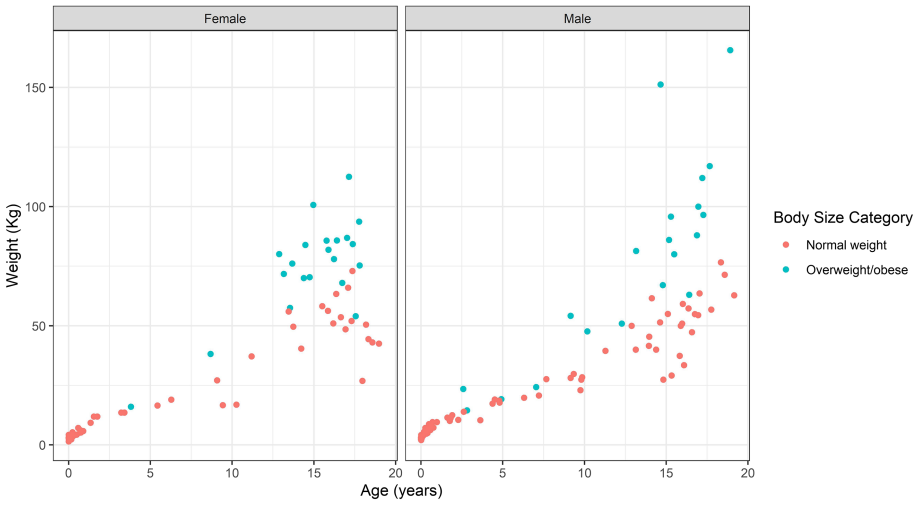

FIGURE 1 The distribution of age versus weight in the study sample broken down by sex and body size category

$$\text{FFM (males)} = \left[0.88 + \left(\frac{(1-0.88)}{\left[1+\left(\frac{\text{Age}}{13.4}\right)^{-12.7}\right]}\right)\right] \times \left[\frac{9270 \times \text{Wt}}{6680 + (216 \times \text{BMI})}\right] \quad (1)$$

$$\text{FFM (females)} = \left[1.11 + \left(\frac{(1-1.11)}{\left[1+\left(\frac{\text{Age}}{7.1}\right)^{-1.1}\right]}\right)\right] \times \left[\frac{9270 \times \text{Wt}}{8780 + (244 \times \text{BMI})}\right] \quad (2)$$

$$\text{BMI} = \frac{\text{Wt}}{(\text{Ht}/100)^2} \quad (3)$$

$$\text{BSA} = \sqrt{\frac{\text{Wt} \times \text{Ht}}{3600}} \quad (4)$$

$$\text{NFM} = \text{FFM} + \text{Ffat} \times (\text{Wt} - \text{FFM}) \quad (5)$$

where Ht is the height and Ffat is a model parameter that estimates the fractional contribution of fat mass to the NFM.

Continuous covariates were normalised to the population median. The influence of PMA on the maturation of clearance (CL) was evaluated using the sigmoid hyperbolic maturation function described for maturation of glomerular filtration rate (Equation 6).[22] The covariates were added to the model using forward inclusion backward elimination:

$$F_{age} = \frac{PMA_i^{\gamma}}{PMA50^{\gamma} + PMA_i^{\gamma}} \quad (6)$$

Here F_{age} is the fractional clearance adjustment for maturation for a child of a given post-menstrual age (PMA_i), γ is the sigmoidicity coefficient that controls the steepness of the maturation curve (fixed at 3.4 as per Anderson and Holford[22]) and PMA50 is the age at which clearance is 50% mature (fixed at 47.7 weeks as per Anderson and Holford[22]).

2.4 | Model selection

This analysis was performed in NONMEM v7.4[23] with PsN v5.0.0[24] and the first-order conditional estimation method with interaction was used. Residual unexplained variability (RUV) was modelled using combined proportional and additive error models. The criteria for model selection were (1) a reduction in the objective function value (OFV), (2) visual goodness-of-fit evaluation, (3) biological plausibility of parameter estimates and (4) precision of parameter estimates as determined by the nonparametric bootstrapping-based confidence intervals.

Comparison of the OFV for model selection was based on the likelihood ratio test at the $\alpha = 0.05$ significance level. Since the difference in the OFV between two nested models is χ^2-distributed, a difference of 3.84 units was considered equivalent to $P = .05$ for one degree of freedom.

2.5 | Model evaluation

The final model was evaluated using pcVPCs,[25] which were constructed by plotting the 10th, 50th and 90th percentiles (and their corresponding 95% confidence intervals) of the predicted concentrations from 1000 simulated datasets against time overlaid by the same percentiles of the observed data. The precision of parameter estimates was evaluated from the confidence intervals calculated from nonparametric bootstrapping. To that end, 1000 bootstrap samples were simulated and used for the estimation of model parameters. Runs with unsuccessful minimisation were excluded and substituted with additional successful ones.

2.6 | Simulation of dosing regimens

The final PK model was used to simulate the current guidelines of enoxaparin dosing in children, which is 1 mg/kg of Wt twice daily for children older than 2 months. The success rate of attaining the target, which is 4-hour post-dose aXa activity between 0.5 and 1 IU/mL after the first-dose and at steady-state dose, was calculated assuming no dose adjustment. The target activity was selected as per the CHEST guidelines for antithrombotic therapy in neonates and children.[4] All simulations assumed infinite dose banding (doses were administered with infinite accuracy). Ten thousand virtual patients were randomly sampled from the Third National Health and Nutrition Examination Survey (NHANES III) database published by the CDC.[26] The sampled covariates were then used as a part of the covariate model to generate group parameters. The fixed and random effects of the final model, excluding RUV, were used to simulate the aXa time profiles in R v4.0.2[27] and deSolve package v1.28.[28] We note that RUV and parameter uncertainty (RSE) were not included in the simulations since the aim of the simulations was to compare the outcomes of different dosing regimens, which was done using the same model. Therefore, inclusion of RUV and RSE in the simulations was not expected to change the conclusion as to which regimen was optimal.

Dosing regimens based on age, FFM, BSA and a combination of these were explored. The dose amount that had the highest rate of target achievement for each of these dose regimen types was estimated through iterative dose adjustments and success rate calculation. The highest target attainment rate for alternative dosing strategies was compared to current dosing guidelines for both obese/overweight patients and normal-weight patients. The R code used in the simulation is provided in **Supplement 1**.

3 | RESULTS

3.1 | Evaluation of published models

The re-estimated published models were able to capture the overall data reasonably well, as shown by the pcVPC (Figure 2). However,

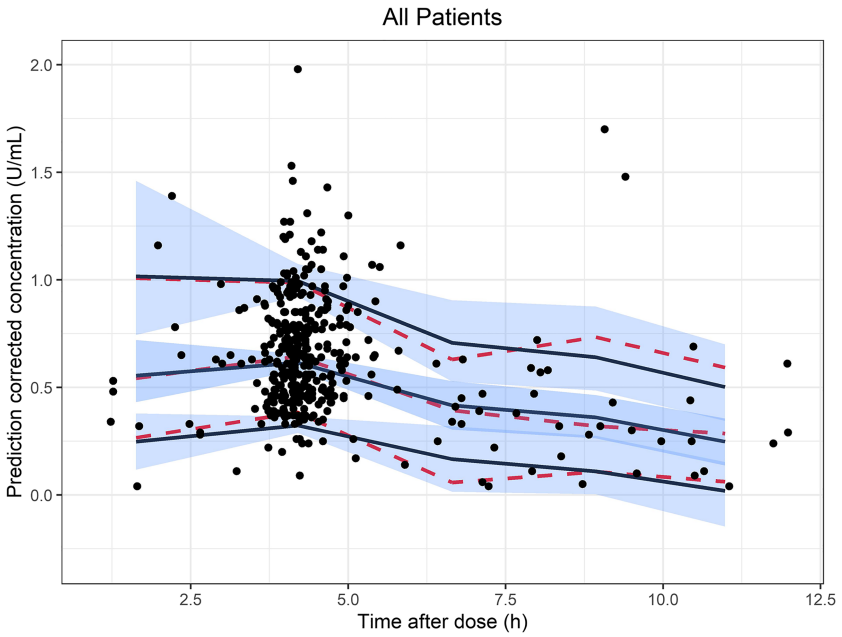

FIGURE 2 Prediction-corrected visual predictive checks for the published models against the whole study dataset. Dashed red lines represent the 10th, 50th and 90th percentiles of observed data. Solid black lines represent the same percentiles of simulated data. Shaded areas represent the 95% CI around the simulated percentiles. Solid black dots represent the observations

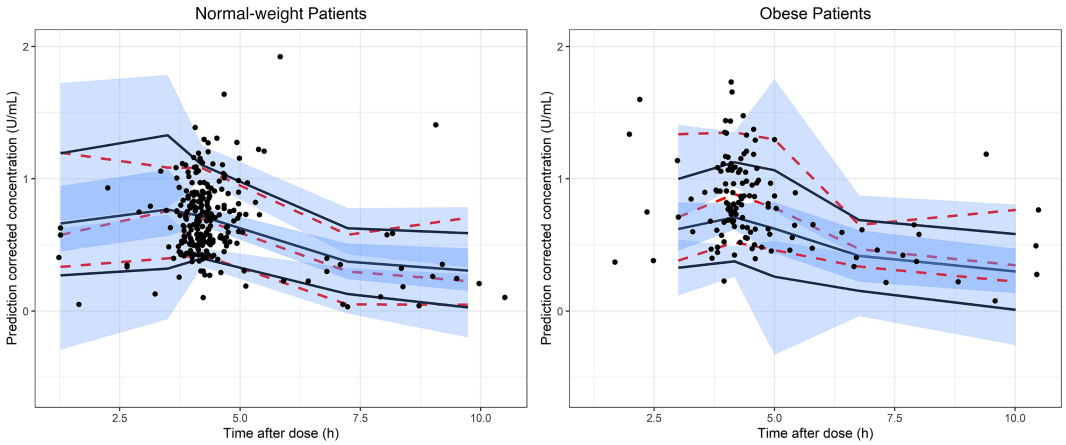

FIGURE 3 Prediction-corrected visual predictive checks for the published models stratified by body size category (left, normal-weight patients; right, overweight/obese patients). Dashed red lines represent the 10th, 50th and 90th percentiles of observed data. Solid black lines represent the same percentiles of simulated data. Shaded areas represent the 95% CI around the simulated percentiles. Solid black dots represent the observations

when pcVPCs were stratified by body size category, the models showed systematic underprediction of concentrations in overweight/obese patients which was not evident in the normal-weight group (Figure 3).

3.2 | Population pharmacokinetic model

The data were best described by a one-compartment model with linear elimination and a combined additive and proportional error model. Estimates of fixed and random effects parameters of the model are illustrated in Table 2. Allometric scaling of FFM on CL and linear scaling of FFM on volume of distribution (V) yielded the most significant improvement on model performance and resulted in reduction in OFV of 522 and 366 points, respectively, compared to the base model (see **Appendix S2** for further details). Allowing CL and V to co-vary by estimating a block covariance matrix reduced the variance of both CL and V, lowered the additive residual error and significantly reduced the OFV (P value = 0.0021). Bootstrap analysis of the final model showed similar median values of the population parameters to those estimated in the final model. All parameters were estimated with reasonable precision, as shown by the 95% CI, except for ω_{ka}, where the CI was relatively wide due to the limited amount of data available in the absorption phase (Table 2). Additionally, excluding data from patients with imputed height/weight did not significantly change the parameter estimates (**Appendix S3**). pcVPC

plots for all patients (Figure 4) when stratified by patient size category (Figure 5) showed robust model performance. The NONMEM code file for the final model is included in **Supplement 2**.

3.3 | Simulation of dosing regimens

Simulations from the final PK model showed that the current standard of care (SoC) dosing of 1 mg/kg twice daily achieved an overall (in both body size groups) success rate of target attainment of 46.9% after the first dose and 72.6% at steady state. After the first dose, most out-of-range patients (93.8%) had subtherapeutic aXa activities.

Although obese patients had a higher success rate after the first dose under SoC dosing than normal-weight patients (55.7% *vs* 43.4%), a larger proportion had supratherapeutic aXa activities at steady state (29.5% for overweight/obese *vs* 9% for normal-weight patients), as illustrated in Table 3 and Figure 6.

These results suggest that the success rate could be optimised by including a loading dose in the regimen to address subtherapeutic aXa activities after the first dose and decreasing the total dose administered to obese/overweight patients. Among the different dosing alternatives tested (see **Appendix S4** for more details), the regimen that achieved the highest success rate was 1.8 mg/kg of FFM as the loading dose followed by 1.2 mg/kg of FFM twice daily for maintenance (Figure 7). This regimen achieves similar aXa activities to the SoC regimen for normal-weight patients at steady state. However, the proposed regimen performs better after the first dose for both normal-weight and overweight/obese patients as well as at steady state for overweight/obese patients (see Figure 8). The success rates for FFM-based dosing with the loading dose approach for both normal weight and overweight/obese patients are summarised in Table 3.

TABLE 2 Final population pharmacokinetic model parameter estimates

Parameter	Estimate (RSE)	Bootstrap mean (95% CI)
Fixed effects parameters		
θ_{CL} (mL/h/20 kg FFM)	4.09 (4%)	4.09 (3.81-4.39)
θ_{V} (mL/20 kg FFM)	34.3 (7%)	34.19 (29-39.6)
θ_{ka} (/h)	0.659 FIX	0.659 FIX
Allometric exponent ($\theta_{CL,FFM}$)	0.712 (4%)	0.71 (0.66-0.76)
Random effects parameters		
ω_{CL} (%)/shrinkage (%)	22.9/15	22.64 (17.5-26.9)
ω_{V} (%)/shrinkage	33.4/15	33.4 (22.9-42.5)
ω_{ka} (%)/shrinkage	58.2/75	58.0 (26.9-92.6)
Corr (CL,V) (%)	100	100 (100-100)
σ_{prop} (%)/shrinkage	4.69/11	4.5 (1.5-7.5)
σ_{add} (U/mL)/shrinkage	0.0059/11	0.0061 (0.0003-0.0124)

Abbreviations: CI, confidence interval; FFM, fat-free mass; RSE, relative standard error.

4 | DISCUSSION

This study developed a model to describe the pharmacokinetics of enoxaparin in overweight/obese children. The model described data well in both overweight/obese patients and normal-weight patients, and had precisely estimated parameters. For the model, FFM was a better descriptor than Wt for the effect of body size on the CL and V of enoxaparin in children.

Wt is often used to describe the influence of body size on clearance and as a scalar for drug doses. This practice requires the

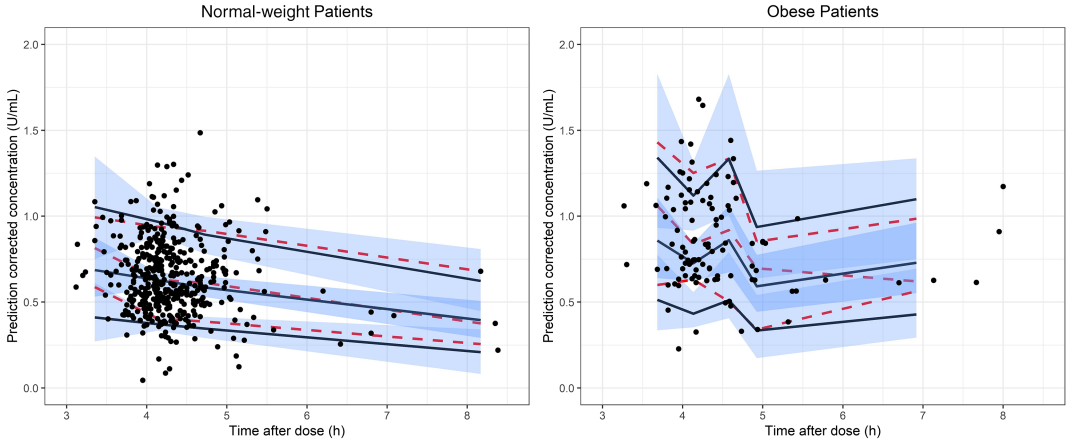

FIGURE 4 Prediction-corrected visual predictive checks for the final model against the whole dataset. Dashed red lines represent the 10th, 50th and 90th percentiles of observed data. Solid black lines represent the same percentiles of simulated data. Shaded areas represent the 95% CI around the simulated percentiles. Solid black dots represent the observations. Note that observations outside the limits of the time axis are omitted from the plot to enhance the visual interpretability. The limits of the time axis are determined based on the mid-points of the first and last bin

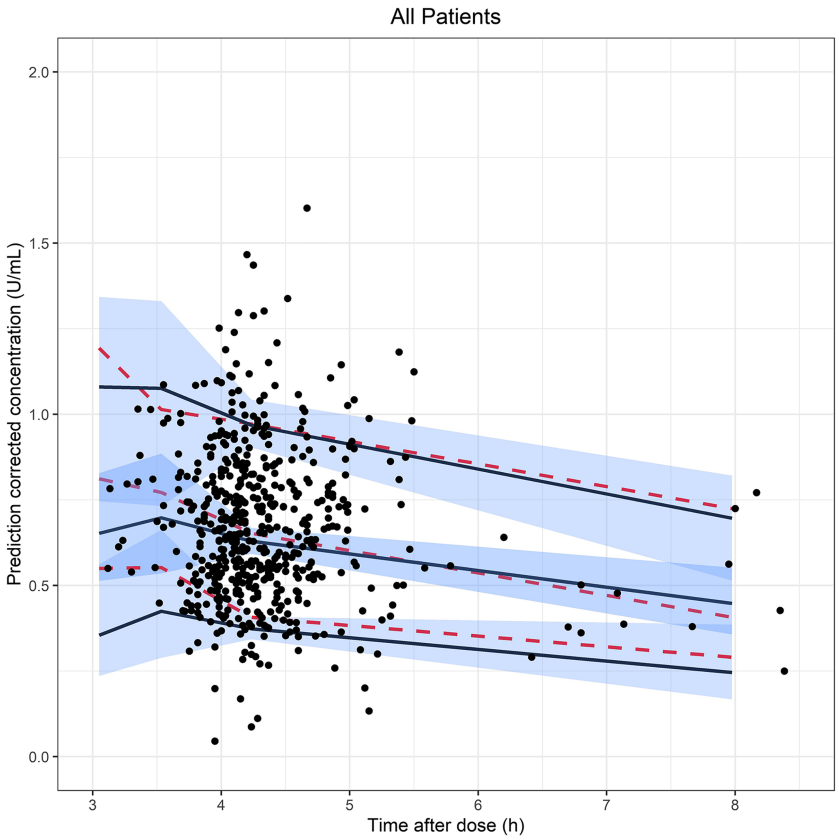

FIGURE 5 Prediction-corrected visual predictive checks for the final model stratified by body size category (left, normal-weight patients; right, overweight/obese patients). Dashed red lines represent the 10th, 50th and 90th percentiles of observed data. Solid black lines represent the same percentiles of simulated data. Shaded areas represent the 95% CI around the simulated percentiles. Solid black dots represent the observations

TABLE 3 The success rate of attaining 4-hour post-dose aXa activity within target under FFM dosing with a loading dose (FFM-based) and SoC dosing

	First dose		Steady state	
Body size category	FFM-based	SoC	FFM-based	SoC
Normal body weight	71.5	43.4	77.5	75.5
Overweight/obese	72.5	55.7	76.7	65.2

Abbreviations: FFM, fat-free mass; SoC, standard of care.
Numbers are presented as percentages.

assumption that body composition is consistent across weight ranges and therefore clearance would vary proportionally with Wt. However, overweight/obese individuals have less metabolically active lean mass per kilogram of Wt compared to normal-weight individuals and therefore are likely to have less than proportional change in CL with respect to Wt.[6,7] Two population PK models of enoxaparin in children have been published which use allometrically scaled Wt as a covariate on clearance.[5,17] However, when both models were fitted to our dataset and evaluated using pcVPCs overlaid with the data, they performed well overall but significantly underpredicted concentration in the overweight/obese group (see Figure 3). This is probably due to CL being overestimated as a result of the assumption of proportionality to Wt. Finding a more suitable body size descriptor in overweight/obese children is particularly important given the increasing prevalence of obesity worldwide. In this study, CL was found to be proportional to allometrically scaled FFM with an estimated exponent of 0.71 (CI 0.66-0.76). It is reasonable to expect CL to scale linearly with FFM as the elimination occurs primarily in the fat-free portion of the body. However, our analysis has shown that CL scales less than proportionally with FFM with an estimated exponent of 0.71 (CI 0.66-0.76), which is not significantly different from the standard value of 0.75.

Due to the limited observations that were available in the absorption phase, it was not possible to precisely estimate the absorption rate constant (ka), which was therefore fixed to 0.659/h.[5] This has probably contributed to the higher prediction percentiles compared with observations in the first bin in overall (Figure 4) and stratified pcVPCs (Figure 5). Nonetheless, observed percentiles still lie within the confidence intervals of the simulated percentiles. Additionally, a high degree of correlation between CL and V (100%) was observed. This is likely due to the high correlation of patient covariates (eg, age, weight, height and FFM) in this population.

The primary mode of enoxaparin elimination is through glomerular filtration.[29] This suggests that maturation of glomerular filtration rate (GFR) would significantly impact enoxaparin clearance, especially in infants. However, in this analysis, serum creatinine data were not available and therefore an empirical GFR maturation function[22] was used as a covariate on CL but did not achieve any significant improvement in model fitness. This is probably because the FFM calculation includes age therefore summarises the effects

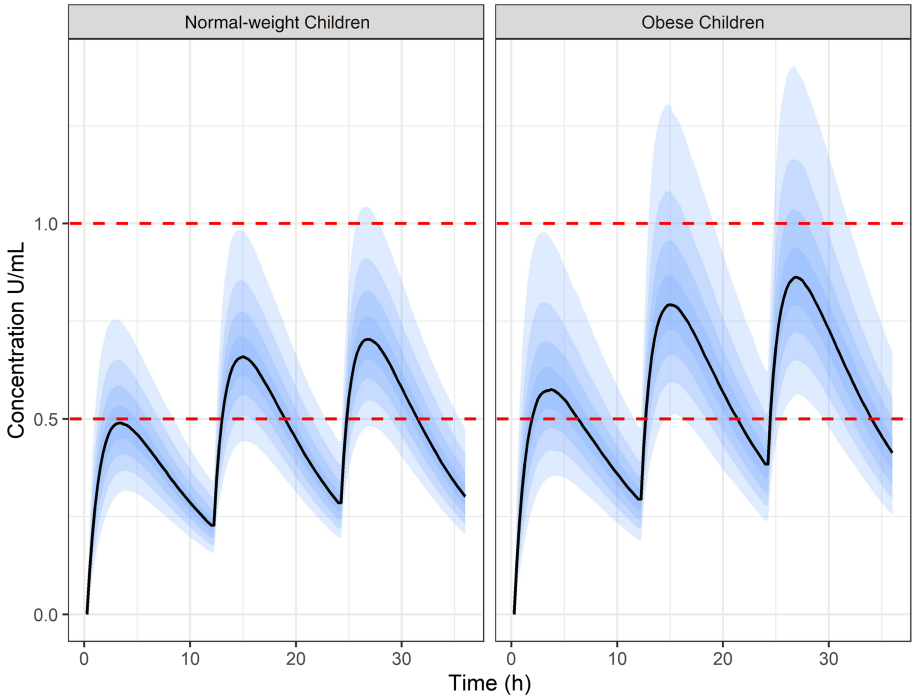

FIGURE 6 Simulations of aXa activities from the final population PK model for Wt-based dosing. The black line represents the median predicted aXa activity. Shaded areas represent the 80%, 60%, 40% and 20% prediction intervals. Dashed red lines represent the boundaries of the therapeutic target

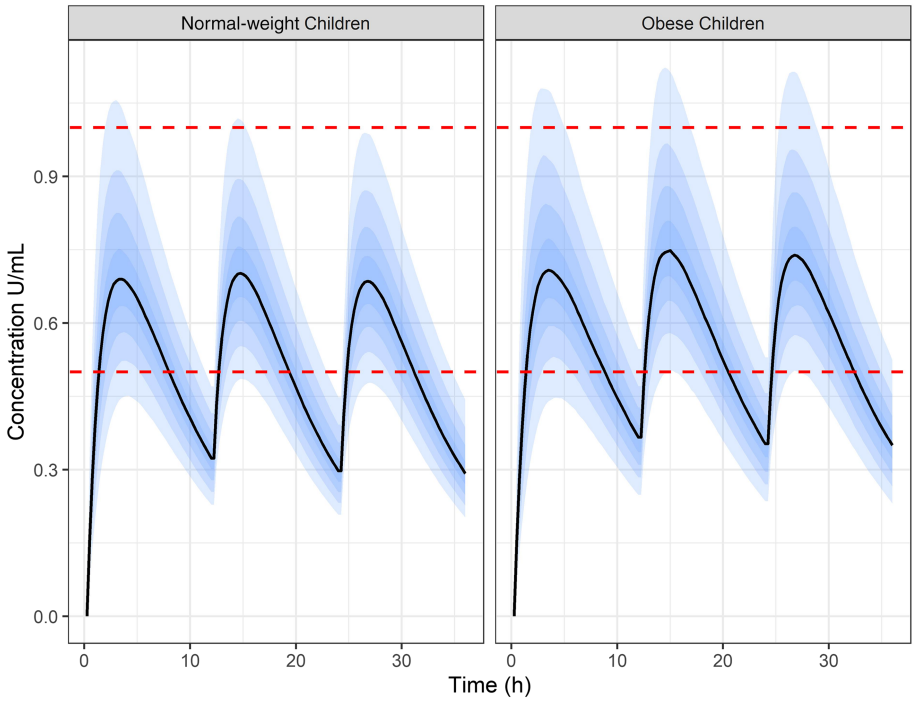

FIGURE 7 Simulations of aXa activities from the final population PK model for FFM-based dosing with loading dose. The black line represents the median predicted aXa activity. Shaded areas represent the 80%, 60%, 40% and 20% prediction intervals. Dashed red lines represent the boundaries of the therapeutic target

of both size and maturation (Equations 1 and 2). In paediatric patients with normal renal function (for size) further adjustment based on impaired renal function was not required.

FFM was also found to be the only significant covariate on V. This is consistent with its high hydrophilicity, which limits distribution to blood, extracellular fluid and highly perfused tissues,[30] which are well represented by FFM.[31]

Simulations from the final PK model showed two issues with the current SoC dosing regimen. First, the low rate of target achievement after the first dose with a substantial proportion of patients attaining subtherapeutic aXa activities. Although the overall rate of target attainment is similar to that of adults,[32] plots of simulated data (Figure 6) show substantial room for improvement. Second, a significantly higher proportion of overweight/obese individuals achieve

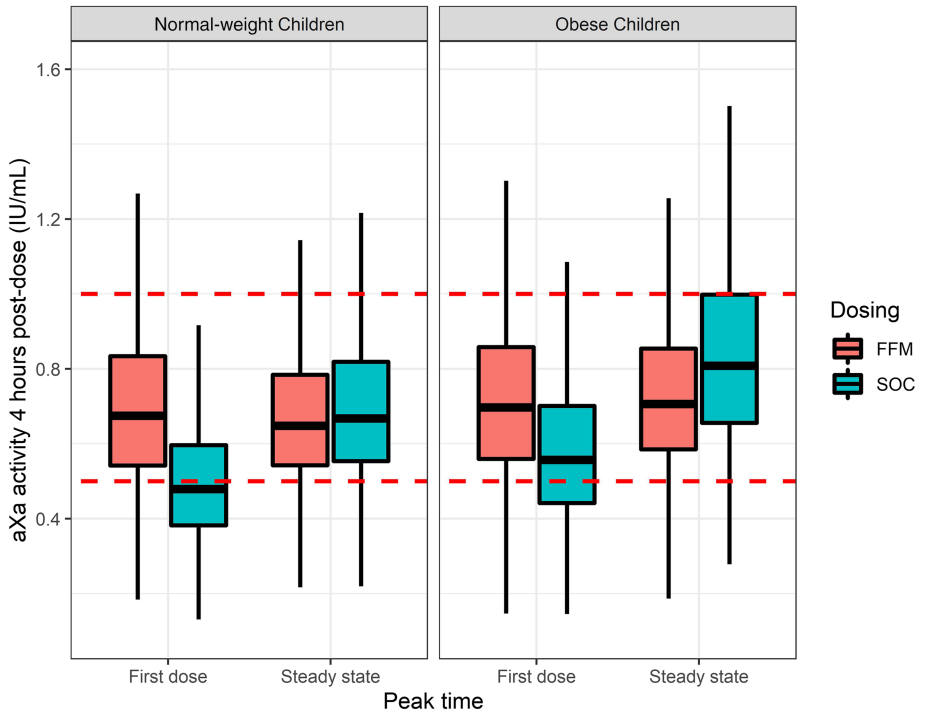

FIGURE 8 The distribution of aXa activity 4 hours post-dose for the first dose and at steady state for SoC dosing and FFM-based dosing with a loading dose. Dashed red lines represent the boundaries of the therapeutic target. Wt, total body weight; FFM, fat-free mass

supratherapeutic aXa activities at steady state compared to the normal-weight group. Therefore, we recommend FFM-based dosing with a loading dose. Simulations showed that this approach had a high target attainment success rate after the first dose and a significant improvement in success rates in overweight/obese patient groups. The success rate under the proposed regimen is similar across body size categories and the success rate in normal-weight patients under the SoC regimen. This suggests that 70-74% is the highest success rate achievable through covariate-based dosing given the variability in enoxaparin pharmacokinetics.

Despite the identification of FFM as a covariate that better accounted for variability in enoxaparin pharmacokinetics, there is still significant unexplained BSV in PK parameters, including 22.9% of variability in CL. Although relatively low compared to many PK analyses,[33] such unexplained variability with a relatively narrow target range resulted in 22.7-28.2% of patients outside the target aXa activity under the proposed dosing regimen. Since no more influential covariates were able to be identified in our analysis, it is only possible to increase the target attainment rates through a more strictly individualised approach such as adaptive feedback control.[34]

Identification of FFM as a covariate on CL allowed the development of dosing recommendations that could achieve the therapeutic target consistently in overweight/obese children, as with normal-weight children. Such a unified dosing approach can be conveniently applied in clinical practice as it eliminates the need for the additional categorisation of patients based on their body size before dose calculation. This is important because the determination of body size category in children is not straightforward as it is based on percentiles of BMI, which differ by age and sex. Additionally, body size and drug dose are continuous variables, therefore discretising doses based on body size is likely to produce less than optimal outcomes.

Based on the proportionality of CL with allometrically scaled FFM, it is expected that patients on the lower end of the FFM range (eg, neonates and infants) require a higher maintenance dose than the recommended regimen. However, this has not been evaluated as it was beyond the scope of this work.

Since enoxaparin is administered subcutaneously, it is expected that obesity and/or maturation may influence on the rate and/or extent of absorption. However, since there were limited observations in the absorption phase, it was not possible to determine such an effect. Although the value of the ka was fixed to the literature value, this value was obtained from studies that were not designed to study the effect of obesity on enoxaparin absorption, and hence misspecification cannot be rolled out. Therefore, an appropriately designed trial can confirm or dispute this and, more importantly, validate the proposed dosing regimen in overweight/obese children.

Of note, the proposed dosing regimen aims to achieve a 4-hour post-dose aXa activity of 0.5-1 U/mL, assuming that this exposure is associated with favourable clinical outcomes. However, such a target has not been validated in children and it is not known if overweight/obese children would have different exposure-effect-outcome relationships to normal-weight children. A further clinical outcome study is warranted.

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COMPETING INTEREST

All authors declare no conflict of interest.

CONTRIBUTORS

H.A., C.S. and K.J. were responsible for the conception and design of this project. C.S. and K.J. were responsible for data collection. A.D., H.A. and S.D. were responsible for the data analysis, interpretation and model evaluations, and the first draft of the manuscript. All authors contributed to the final draft of the manuscript and subsequent revision.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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