Development of a population pharmacokinetic-pharmacodynamic model of a single bolus dose of unfractionated heparin in paediatric patients

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Current dosing and monitoring guidelines of heparin in children are largely extrapolated from adult studies
- There is evidence to suggest that the dose-response of heparin in children is different to adults even when PK and PD parameters are scaled to size, this can potentially result in over- or under-dosing
- There are currently no PKPD models of heparin in children, such models can potentially improve dose selection in this patient group

WHAT THIS STUDY ADDS

- A heparin PKPD model for children was developed and evaluated and can potentially be used to improve dosing guidelines
- Fat-free mass as a covariate on the clearance parameter was shown to improve model fit
- The model is derived on data that was based on a single high dose of heparin thus could not be extrapolated to the smaller infusion doses more commonly used in clinical practice; data in that region of the dose-response curve is needed in order to for the model to be used clinically

Abstract:

Background: Unfractionated heparin (UFH) is the anticoagulant of choice in paediatric patients undergoing a variety of cardiac procedures. There are currently no population pharmacokinetic-pharmacodynamic (PKPD) models for UFH in paediatrics.

Objective: To develop and evaluate a PKPD model of UFH in paediatrics.

Methods: Data from 64 children who received 75-100 IU/kg of UFH during cardiac angiography were analysed. Five blood samples were collected at baseline and at 15, 30, 45, and 120 minutes post-dose. UFH concentration was quantified using a protamine titration assay. UFH effect was quantified using activated partial thromboplastin time (aPTT). A PKPD model was fitted using the non-linear mixed effects modelling. Patient covariates such as sex, weight (WT), and fat-free mass (FFM) were tested. The final model was evaluated using the likelihood ratio test and visual predictive checks (VPCs).

Results: A one compartment model with linear elimination provided the best fit for the dose-concentration data. FFM was a significant covariate on clearance. A linear model provided the best fit for the concentration-effect data using aPTT as a biomarker for effect. The models performed well using VPCs. However, when used to simulate UFH infusion (at a much lower dose), the model overpredicted target aPTT responses.

Conclusions: A PKPD model to describe the time-course of UFH effect was developed in a paediatric population. FFM was shown to describe drug disposition well. However, when applied to smaller UFH infusion doses, the model overpredicts target aPTT responses. This unsuccessful extrapolation may be attributed to a possible non-linear relationship of heparin PKPD.

Background

Unfractionated heparin (UFH) is an anticoagulant used for the treatment and prevention of thromboembolism (TE). UFH comprises a heterogeneous mixture of glycosaminoglycans of various chain lengths (average molecular weight of 15 kDa) normally derived from porcine or bovine intestines.[1] UFH binds to antithrombin (AT) via a pentasaccharide sequence and induces a conformational change which enhances AT binding to activated clotting factors such as Xa. Additionally, long UFH molecules (≥ 18 saccharide units, MW > 5 kDa) serve as a catalytic template to which both AT and factor IIa bind, effectively inhibiting IIa.[2]

UFH is widely used in paediatric patients, principally due to its long history of clinical use and ease of reversibility.[3, 4] Its relatively short half-life makes it an ideal anticoagulant for use in critically ill children, who may be at a greater risk of bleeding. Current guidelines on the use of antithrombotic agents in children recommend that UFH be used as a first-line intervention to treat arterial and venous TE.[5] UFH is also recommended for primary thromboprophylaxis (e.g. cardiac angiography, cardiopulmonary bypass, and haemodialysis).

Compared to the prevalence of TE in adult populations, TE in infancy and childhood is a relatively infrequent occurrence. This fact has hindered the conduct of robust clinical trials of anticoagulant therapies within this age group. As a result, the majority of anticoagulant therapy recommendations are based on cohort studies and extrapolation from adult data.[5] However, there is evidence that extrapolation of adult-derived data may be inappropriate due to significant pharmacokinetic and pharmacodynamic differences between neonates, infants, children, and adults. [6-11]

There are standard dosing nomograms for UFH in children.[12] The current recommendation is for a UFH bolus to be no greater than 100 units/kg with bolus doses to be withheld or reduced in the presence of significant bleeding risks.[5] Given the between- and within-subject variability of dose requirements for UFH, blood monitoring is advocated. However, applying the activated partial thromboplastin time (aPTT) target range from adults to paediatric patients is not appropriate.[13-16]

Instead, a heparin concentration (determined by protamine titration) of 0.2 to 0.4 units/mL or an anti-Xa concentration of 0.35 to 0.7 units/mL is advocated.[17]

Variability in the dose-response of UFH necessitates consideration of the individual risk factors for bleeding and the perceived risk of thrombosis.[5] Accounting for the sources of this variability could potentially optimise treatment. One possible source is variability in body size and composition. Literature evidence in adult patients gives credence to the use of fat-free mass (FFM) as a suitable body size descriptor of drug clearance hence potentially optimal for drug dosing. FFM, when compared to total body weight (WT), correlates well with metabolism and drug clearance.[18]

Objectives

To develop and evaluate a PKPD model to predict the dose-response relationship of UFH in paediatric patients. Also, to explore the use of FFM to guide dose-individualisation of UFH in this population.

Methods

Data

The data used in this analysis has been described previously by Newall et al.[10] Briefly, sixty-four children requiring cardiac angiography who received a single intravenous bolus dose of unfractionated heparin (UFH) participated in this study (Table 1). Patients received no antiplatelet or anticoagulant therapy in the 10 days preceding the scheduled procedure. Blood samples were collected at baseline and at 15, 30, 45 and 120 minutes post-UFH administration. UFH concentration (231 measurements) was determined using a modified protamine titration method.[19] The aPTT was measured (290 measurements with 43% above the upper limit of quantification) using the PTT-A® kit (Diagnostica Stago) with the upper limit of clot detection modified to measure up to 999 seconds on the STA-R analyser (Diagnostica Stago). This is to accommodate the high single dose used in this study.

Table 1 Demographic characteristics of study population. Values are expressed as mean (range). N is number of subjects.

N	**64**
Sex (M:F)	30:34
Age (y) **- age < 2 years (n)**	6.7 (0.5 to 15.5) 8
Weight (kg)	23.6 (6.7 to 68.6)
Height (cm)	115.7 (65 to 176)
BMI (kg/m^2)	16.1 (11.5 to 24.7)
UFH Dose (IU)	2020 (600-5000)

UFH dose per weight (IU/kg)	91 (47.9 to 105.4)

Model building

Data from all 64 patients were included in the model-building process. Two patients had no recorded value of height and their height was imputed using multivariate linear regression using the distribution of age, sex, and weight in the dataset.

Linear and non-linear elimination one- and two-compartment disposition models were considered to describe the concentrations of UFH. Emax, sigmoid Emax, linear, and log linear models were considered to describe the concentration-effect relationship. PD parameters were estimated sequentially using the population pharmacokinetic parameters and data (PPP & D) estimation method.[20] A sequential estimation method was chosen in order to avoid introducing bias to the PK model estimation.[21]

Censored PD data (above the upper limit of quantification) were accounted for using Beal's M3 likelihood estimation (modified to account for right-censoring of data).[22] This was implemented in NONMEM using the F-Flag variable where the likelihood of an observation being above the upper limit of quantification is calculated and maximised with respect to model parameters

Covariate selection

Age, sex, total body weight (WT), allometric weight with a fixed exponent[23], allometric weight with the exponent estimated, body surface area[24], and fat-free mass (FFM)[25] were considered as

covariates on model parameters. The covariates were added to the model using forward inclusion backward elimination.

FFM and WT were standardised to their median values in the population (15 kg for FFM and 20 kg for WT).

Model selection

The analysis was performed in NONMEM v7.2 [26] (with Wings for NONMEM v720 [27]) using the first-order conditional estimation method with interaction and combined residual error (RUV) model. Between-subject variability (BSV) was implemented using exponential models. Model selection was guided by (1) the decrease in the objective function value (OFV, the minimisation criterion in NONMEM); (2) visual goodness-of-fit analysis; and (3) the estimated uncertainty in parameter estimates as reported by the 95% confidence interval of parameter estimates based on nonparametric bootstrapping.

Model selection was based on the likelihood ratio test. The OFV of NONMEM is proportional to minus twice the log-likelihood (-2LL). The difference in the OFV between two nested models is χ^2-distributed, meaning that a difference of 3.84 corresponds to P = 0.05 for one degree of freedom.

Evaluation of model performance

The final PK and PKPD models were evaluated using visual predictive checks (VPCs). [28] One thousand datasets were simulated and the 5^{th}, 50^{th}, and 95^{th} percentiles from the simulated response data were plotted against time with the same percentiles of the observed data (and the 95% confidence intervals around the percentiles) superimposed. Additionally, the 95% confidence intervals of parameter estimates in the final model were calculated using nonparametric bootstraps. One thousand bootstrap samples were simulated and used to estimate model parameters. Runs with terminated minimisation were excluded and replaced with additional successful runs.

Simulation of current dosing guidelines

Current dosing guidelines for UFH infusion for the treatment of thromboses were used to simulate the dose-response and success rate in attaining the therapeutic target (defined as aPTT between 50-90 seconds) was calculated using FFM-based, WT-based, and age-and-WT-based dosing. Ten thousand virtual patients were simulated in MATLAB (version 2013b, MathWorks, Natick, MA) using parametric resampling based on a large children dataset.[29] A joint multivariate normal distribution [30, 31] of sex, age, weight, and height was constructed and randomly sampled. The covariates were then used as a part of the covariate model to generate the population parameters. The fixed and random parameters of the final heparin PKPD model were used for the simulation.

The current guidelines for UFH infusion in children recommend a bolus dose based on a patient's weight followed by a continuous infusion of 20 IU/kg for children between 1-12 years and 18 IU/kg for children between 12-18 years.[5] As the model was developed using a single high (mean = 91 IU/kg) interventional prophylactic dose of UFH, the dosing guidelines were simulated at steady state where the influence of a bolus dose is negligible.

The success rates for achieving a target aPTT of 50-80 seconds at steady state were calculated with the assumption that no subsequent dose-adjustments occurred. Additionally, the dose-rate based on the PKPD model was explored further by calculating a FFM-based dose through a regression of the target biomarker vs dose curve.

Results

Sixty-four paediatric patients provided PK and PD data following a single high dose of UFH during a cardiac catheterisation procedure. None of the patients were being treated for thromboses at the time of the study.

Population pharmacokinetics

A one compartment model with linear elimination with a combined (additive and exponential) residual error model provided the best fit for the dose-concentration data (Table 2). Size (WT and FFM) on both CL and V had significant influence on model performance and resulted in a 90 point reduction in the OFV. FFM as a covariate on CL and WT as a covariate on V as well as allowing the CL and V to covary using a block covariance matrix resulted in the lowest variance of CL and V, lowest additive error (without increasing the proportional error), and lowest OFV. See table A1 in the Appendix for covariate model building steps. Bootstrap estimates of final model parameters were similar to model estimates and the precision (95% CI) was reasonable except for the additive error bootstrap estimate which had a wide 95% CI (Table 2). Diagnostic plots in the form of VPC show the model has performed well when 1000 datasets were parametrically bootstrapped (Figure 1).

Table 1 Final PK model parameter estimates. Bootstrap results are presented as mean and 95% confidence interval.

Parameter	Covariate model	Parameter estimate	Bootstrap (95% CI)
θ_{CL} (L/h/15 kg)	$CL = \theta_{CL} \times FFM/15$	0.603	0.601 (0.528 to 0.684)
ω_{CL} (%)		50	50 (40 to 61)
θ_V (L/20 kg)	$V = \theta_V \times WT/20$	0.751	0.745 (0.656 to 0.840)
ω_V(%)		40	39 (29 to 48)
$Corr_{(\mathrm{CL,V})}$		0.75	0.74 (0.40 to 0.99)
θ_{D1} (h)		0.1*	
σ_{prop}(%)		17	16 (11 to 22)
σ_{add} (U/L)		90	93 (1 to 204)

* The infusion rate parameter D1 was fixed

θ is the mean value of the fixed effect parameter; ω represents the between subject variability (presented as coefficient of variation percentage, CV%); $Corr_{(\mathrm{CL,V})}$ is the correlation between heparin CL and V; σ_{prop} is the proportional component of the residual variability (presented as CV%); and σ_{add} is the additive component of the residual variability (presented as standard deviation).

Figure 1 VPC plot for the final PK model. Median of observed (line, closed circles) and predicted (line) data are depicted. Also, 5th and 95th percentiles of observed (dashed line, closed circles) and predicted (dashed line) data are shown. Grey bands are the 95% CIs.

Population pharmacokinetics-pharmacodynamics

aPTT

A linear model provided the best fit for the concentration-effect data using the PPP & D sequential estimation method [20] (Table 3). When asymptotic models (such as Emax and sigmoid Emax) were attempted the estimates for Emax and C50 become very large and implausible and the correlation between these two parameters was high. Between-subject and residual variability were also estimated. The PKPD model performed well using visual predictive checks (Figure 2) especially once censored data were accounted for.

Table 2 Final PKPD model parameter estimates. Bootstrap results are presented as mean and 95% confidence interval. $E0$ is baseline aPTT in seconds. SLP is the slope of the linear model.

Parameter	Covariate model	Parameter estimate	Bootstrap (95% CI)
θ_{CL} (L/h/15 kg)	$CL = \theta_{CL} \times FFM/15$	0.603*	
ω_{CL} (%)		50*	

θ_V (L/20 kg)	$V = \theta_V \times WT/20$	0.751*	
ω_V(%)		40*	
$Corr_{(CL,V)}$		0.745*	
θ_{D1} (h)		0.1*	
θ_{E0} (s)		35.6	35.6 (34.6 to 36.7)
ω_{E0} (%)		0.43	0.44 (0.38 to 0.51)
θ_{SLP}		0.67	0.67 (0.58 to 0.78)
ω_{SLP} (%)		64	63 (50 to 76)
σ_{prop}(%)		30	30 (26 to 33)
σ_{add} (IU/L)		0.005	0.005 (0.001 to 0.012)

* Fixed

θ is the mean value of the fixed effect parameter; ω represents the between subject variability (presented as coefficient of variation percentage, CV%); $Corr_{(CL,V)}$ is the correlation between heparin CL and V; σ_{prop} is the proportional component of the residual variability (presented as CV%); and σ_{add} is the additive component of the residual variability (presented as standard deviation).

Figure 2 VPC plot for the final PKPD model using aPTT response. Median of observed (line, closed circles) and predicted (line) data are depicted. Also, 5th and 95th percentiles of observed (dashed line, closed circles) and predicted (dashed line) data are shown. Grey bands are the 95% CIs.

Simulation of heparin infusion

The simulation showed that the majority of patients had aPTT above 80 seconds with a mean aPTT of 380 seconds. An optimal dose that would result in approximately 57% success in attaining a target aPTT of 65 seconds at steady state was found to be 2.4 IU/kg. This dose, however, is much smaller than what is observed in clinical practice which suggests the model cannot be extrapolated to the smaller infusion doses.

Discussion

This is the first study to describe a PKPD model of unfractionated heparin in children. The model described the data well despite having a third of the aPTT data above the upper limit of quantification (> 999 s). To account for these censored values, a modified version of Stuart Beal's M3 method was used.[22] The method improves the model fit by calculating the likelihood that a datum falls outside the limit of quantification.[32] This is in line with good population modelling practice as censoring data has been known and shown to cause bias in model parameter estimation.[33, 34]

The covariate model which provided the best fit to the data included WT on the V parameter and FFM on the CL parameter. No measures of hepatic or renal function were included in the covariate model because none of the patients suffered from hepatic or renal impairment. The model showed FFM to be a better measure of the influence of size on drug clearance. WT has often been used to scale drug doses but this has been found to over predict drug clearance in obese adults.[18] Finding a more suitable size descriptor is particularly important given the rise of obesity in both developed and developing countries, including in children.

The PKPD model was based on data collected from 64 children who received a large (~ 92 IU/kg) single bolus dose during cardiac catheterisation. The model was found to be linear which is inconsistent with literature evidence of UFH pharmacology. Evidence from the literature suggests that UFH is cleared through a mixture of saturable mechanism, through binding to endothelia cells and macrophages, and first-order mechanism through the kidneys.[35] As a result, the dose-response of UFH is considered non-linear with the half-life increasing from ~ 30 minutes after a single dose of 25 IU/kg to ~ 60 minutes after a dose of 100 U/kg. [36-38]

In the PKPD model, the average CL was found to be 0.6 L/h (per 15 kg FFM) and the average V was 0.75 L (per 20 kg WT). This results in a half-life of approximately 52 minutes. It is likely that the model describes an incomplete segment of heparin dose-response and would overpredict aPTT when

a small dose is given. This became evident when the model was applied to the infusion dosing guidelines which utilise doses of 18-28 IU/kg. In clinical practice, aPTT is measured frequently during heparin infusion and the infusion rate is adjusted accordingly in order to reach target aPTT. The average aPTT predicted by the model was 380 seconds instead of the 50-80 seconds observed in clinical practice. Data covering a larger range of dose and concentration would have made this model more clinically applicable.

Conclusion

A PKPD model to describe the time-course of UFH effect was developed in a paediatric population that received a high single prophylactic bolus dose. FFM was shown to describe drug disposition well and could potentially be used in dose calculation after appropriate evaluation. However, the PKPD model was linear and resulted in overprediction of aPTT when smaller UFH infusion doses were simulated.

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Competing interests:

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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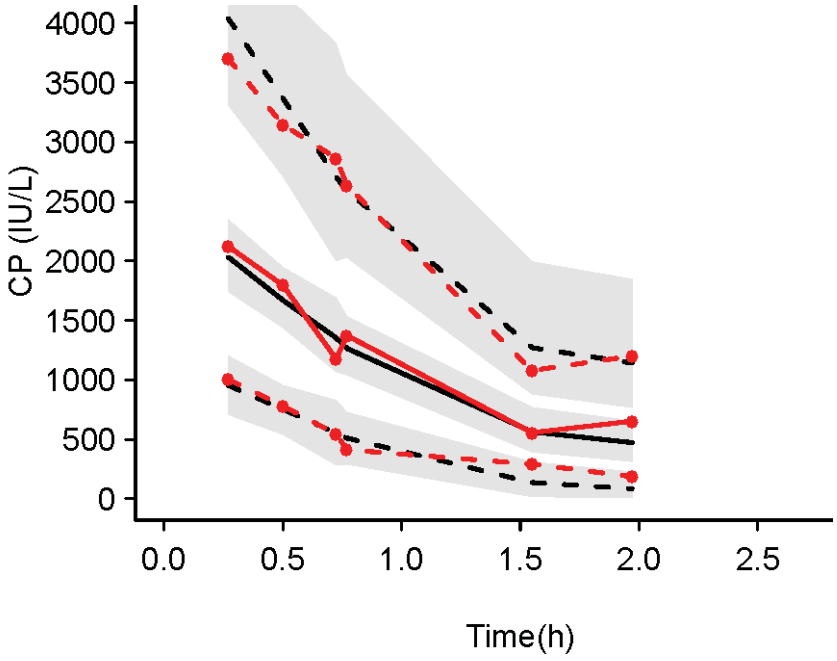

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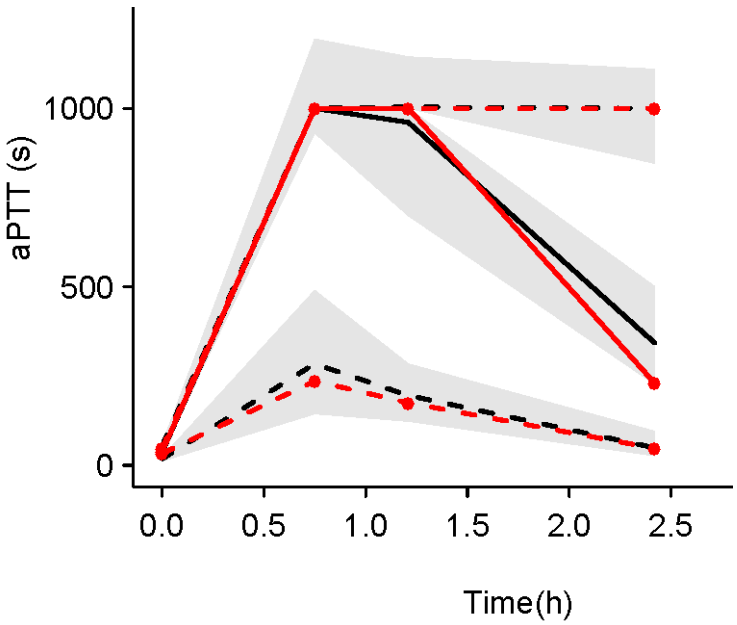

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