

Development of a population PKPD model of single dose unfractionated heparin in paediatric patients



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Background

- Unfractionated heparin (UFH) is the anticoagulant of choice in paediatric patients undergoing a cardiac procedure
- UFH is administered as a bolus intravenous (IV) injection followed by a continuous IV infusion. The bolus dose is based on the patient's total body weight (WT) and the continuous infusion rate is adjusted based on patient's response (aPTT)
- WT is often used to scale drug doses but it may not correlate well with drug clearance (CL) and can potentially result in over- or under-dosing
- Recently a fat-free mass (FFM) model was developed for children and may be a suitable descriptor of size in relation to drug disposition [1]

$$FFM_{females} = \left(1.11 + \left(\frac{1 - 1.11}{1 + \left(\frac{Age}{7.1} \right)^{-1.1}} \right) \right) \times \frac{9270 \times WT}{8780 + 244 \times BMI}$$

$$FFM_{males} = \left(0.88 + \left(\frac{1 - 0.88}{1 + \left(\frac{Age}{13.4} \right)^{-12.7}} \right) \right) \times \frac{9270 \times WT}{6680 + 216 \times BMI}$$

Aims

- To develop and evaluate a model to predict the dose-response of UFH in paediatrics using various size descriptors as covariates

Methods

- Data from 64 infants and children that received a bolus dose of UFH during cardiac angiography were analysed (Table 1)
- Blood samples were collected at baseline and at 15, 30, 45, and 120 minutes post-dose. UFH concentrations (231 measurements) were determined using protamine titration
- aPTT (290 measurements) was determined using the PTT-A® kit (Diagnostica Stago). 43% of aPTT data were above the upper limit of quantification and were accounted for using the M3 method [2]
- Modelling was performed using NONMEM v7.2
- PD parameters were estimated sequentially using the PPP & D method
- Covariates tested include WT, allometric weight, body surface area, and FFM
- The final model was evaluated using the likelihood ratio test and visual predictive check (VPC) plots

Table 1: Patient characteristics of study population [3]. Values are expressed as mean (range)

N	64
Sex (M:F)	30:34
Age (y)	6.7 (0.5 to 15.5)
Weight (kg)	23.6 (6.7 to 68.6)
Height (cm)	115.7 (65 to 176)
Dose (IU)	2020 (600 to 5000)
BMI (kg/m ²)	16.1 (11.5 to 24.7)
UFH dose per weight (IU/kg)	90.9 (47.9 to 105.4)

Results

- A one compartment PK model with linear elimination provided the best fit for the dose-concentration data (Table 2)
- Size (WT & FFM) had significant influence on model performance; FFM on CL was preferred statistically
- The model performed well as shown on the VPC plot (Figure 1)

Table 2: Final PK model parameter estimates. Bootstrap results are presented as mean and 95% confidence interval

Parameter	Covariate	Estimate	Bootstrap (95% CI)
θ_{CL} (L/h/15 kg)	$TVCL = \theta_{CL} \times FFM/15$	0.60	0.60 (0.53 to 0.68)
ω_{CL} (CV%)		50	50 (40 to 61)
θ_V (L/20 kg)	$TVV = \theta_V \times WT/20$	0.75	0.75 (0.66 to 0.84)
ω_V (CV%)		40	39 (29 to 48)
Corr (CL, V)		0.75	0.74 (0.40 to 0.99)
D1 (h)		0.1*	FIXED
σ_{prop} (CV%)		17	16 (11 to 22)
σ_{add} (U/L)		90	93 (1 to 204)

- A linear model provided the best fit for the PD data (Table 3).
- The model performed well as shown on the VPC plot (Figure 1)

Table 3: Final PD model parameter estimates. Bootstrap results are presented as mean and 95% confidence interval

Parameter	Covariate	Estimate	Bootstrap (95% CI)
θ_{E0} (s)		35.6	35.6 (34.6 to 36.7)
ω_{E0} (CV%)		0.4	0.44 (0.38 to 0.51)
θ_{SLP}		0.67	0.67 (0.58 to 0.78)
ω_{SLP} (CV%)		64	63 (50 to 76)
σ_{prop} (CV%)		30	30 (26 to 33)
σ_{add} (s)		0.005	0.005 (0.001 to 0.010)

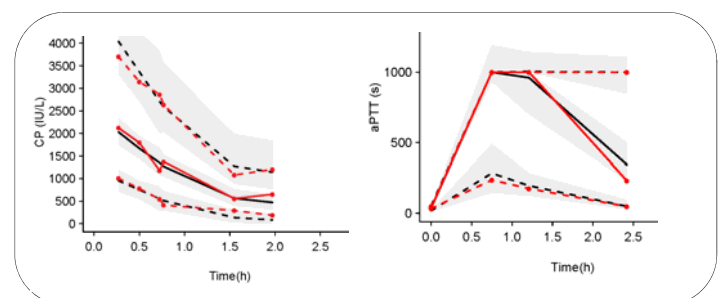


Figure 1: VPC plots for the final PK (left) & PKPD (right) models. 10th, 50th, & 90th percentiles of observed (red) and predicted (black) data depicted. Grey bands are the 95% CIs.

Conclusions

- A PKPD model to describe the time-course of UFH effect was developed in a paediatric population that received a high IV bolus dose
- FFM described drug disposition well and can potentially be used in dose calculation after appropriate evaluation

References

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- Beal. *J Pharmacokinet Pharmacodyn* 2001; 28(5):481-504
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