



Evaluating the Influence of Different Covariates on Enoxaparin Pharmacokinetics in Neonates, Infants and Children

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Background

- Enoxaparin, a low-molecular-weight-heparin, is used off-label in children for prevention of symptomatic thromboembolism when acute anticoagulation or secondary prevention is required due to venous thrombosis or stroke
- Previously we determined the PK of enoxaparin in children and evaluated whether a once or twice daily dosing regimen achieved efficacious plasma levels of enoxaparin [1]
 - a once daily enoxaparin dosing regimen is feasible for at least 50% of children during maintenance therapy if 24h trough levels are within the predicted range of 0.1 – 0.3 IU/mL anti-FXa activity for prophylaxis doses
- Covariates hypothesised to influence the PK of enoxaparin (Serum creatinine (SCr), estimated Glomerular Filtration Rate (eGFR), and Antithrombin (AT)), were not available at the time of our previous analysis [1]

Objectives

Aim of this Analysis

- Test additional covariates of interest, which were not available at the time of our previous analysis [1], to evaluate the PK of enoxaparin in children further, specifically:
 - SCr and eGFR on clearance terms as enoxaparin is cleared renally
 - AT on volume and clearance terms due to enoxaparin-AT binding
- Apply available methodologies for imputation of missing covariates

Methods

Patients

- 126 renally healthy neonates, infants, children, and adolescents received enoxaparin for prevention of symptomatic thromboembolism
- Median body weight (WT) 24 kg (range 2.5 – 97.3 kg)
- Median age 5.9 years (range 0.07 – 25 years)
- Starting dose of enoxaparin**
 - patients < 1 year: 1.5 mg/kg
 - patients > 1 year: 1.0 mg/kg
- Maintenance dose of enoxaparin**
 - patients < 1 year: 1.3 mg/kg
 - patients > 1 year: 1.0 mg/kg
- Dosing regimens were either q12h or q24h
- Blood samples were drawn during steady-state on patient's maintenance dose at baseline prior to next dose, and at 2, 4, 8, and 12 hours after administration

Analytical Method

- All blood samples were analysed on a Dade Siemens BCS XP analyser using Coamatic® Heparin from Chromogenix

Covariate Analysis

- Tested covariates: AGE, WT, HT, BSA, SCr, eGFR, AT
 - baseline covariate values were available for all patients
 - up to 60% of the patients lacked longitudinal covariate values
- Conventional and linearised stepwise covariate model (SCM) building
 - p-value forward inclusion: 0.05
 - p-value backward elimination: 0.01

Imputation of Missing Covariates: Steps 1 – 6

- Postmenstrual age (PMA) was calculated to be the sum out of the patient's age in years + 9 months
- Slope-Intercept model for WT imputation from PMA

$$WT = \text{Slope} * PMA + \text{Intercept} + EPS$$
- Boyd equation, using the imputed WT as independent variable, for BSA imputation [2]

$$BSA = 4.688 * WT^{(0.8168 - 0.0154 * \log(WT))}$$
- Mosteller formula to calculate HT from imputed BSA and WT

$$HT = (3600 * BSA) / WT$$
- Lund-Malmö equation for eGFR imputation if HT was missing [3]

$$eGFR = \exp[4.62 - 0.0112 * SCr * 88.4 - 0.0124 * \text{Age} + 0.339 * \ln(\text{Age})]$$
- Updated Schwartz equation for eGFR imputation using imputed HT if age was missing [4]

$$eGFR = 0.413 * HT / SCr$$

Results

Fixed Effects		
CL/F	(mL h ⁻¹ kg ⁻¹)	15 (8%)
V ₁ /F	(mL kg ⁻¹)	169 (11%)
Q	(mL h ⁻¹)	52 (36%)
V ₂	(L)	12.4 (63%)
k _a	(h ⁻¹)	0.404 (21%)
Random effects		
Interindividual variability		
CL/F	(%)	54 (13%)
V ₁ /F	(%)	24 (41%)
k _a	(%)	68 (26%)
Residual error		
proportional (%)		30 (9.9%)

Table 1. Final Population Parameter Estimates; standard errors in brackets

Covariate Analysis

- ✓ Missing covariates were imputed
- ✓ No parameter-covariate relation was statistically significant for inclusion before and after imputation of all covariates

Pharmacokinetic Analysis

- Two-compartment first order absorption model
- First order conditional estimation method (FOCE) using NONMEM VII
- Exponential model for interindividual variability (IIV) on clearance (CL/F), central volume of distribution (V₁/F), and absorption rate constant (k_a)
- WT as covariate was pre-specified in the base model
 - WT on CL/F and V₁/F
- The high interindividual variability in CL/F and V₁/F in our population highlights the need for monitoring the anti-FXa activity and individualising the dose

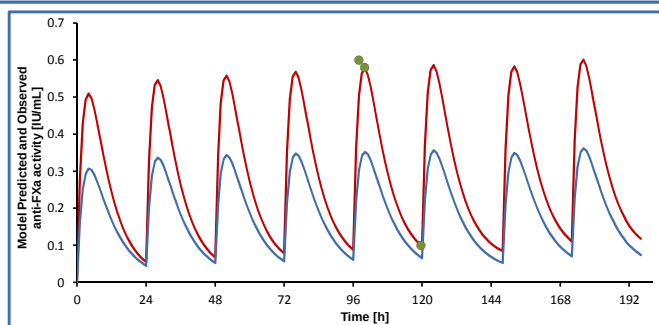


Figure 1. Model predicted and observed anti-FXa activity for one representative patient; red line = individual predicted anti-FXa activity; black line = population model predicted anti-FXa activity; dots = observed anti-FXa activity

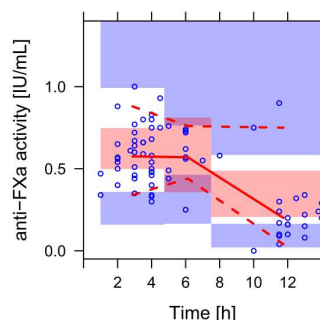


Figure 2. Visual predictive check for the **twice daily enoxaparin dosing regimen**; dashed lines = 5% and 95% CI; solid line = model predicted median; dots = observed anti-FXa activity

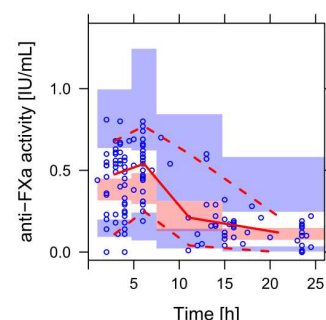


Figure 3. Visual predictive check for the **once daily enoxaparin dosing regimen**; dashed lines = 5% and 95% CI; solid line = model predicted median; dots = observed anti-FXa activity

Conclusions

- This population PK analysis did not find any parameter-covariate relations statistically significant for inclusion in addition to the pre-specified WT in the base model. This supports our previous findings that no other covariate than WT is needed for renally healthy patients to explain the PK of enoxaparin [1].
 - Hypothesised covariates (SCr, eGFR, and AT) were not significant
- The model describes enoxaparin disposition in all age groups in our study population from neonates to adolescents.

References

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