ELSEVIER

European Journal of Pharmaceutical Sciences, 8 (1999) 119–125

EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES

Population pharmacokinetic of nadroparin calcium (Fraxiparine®) in children hospitalised for open heart surgery

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Received 11 September 1998; received in revised form 30 November 1998; accepted 2 December 1998

Abstract

Administration of low molecular weight heparin following heart surgery in paediatric patients in order to prevent thromboembolic events results in a large variation in anti-Xa activities. A population study was undertaken to determine pharmacokinetic parameters after nadroparin calcium (Fraxiparine®) administration and the effects of potential covariates; this study included 154 children divided into two groups: a model group (124 patients) and a validation group (30 patients). The 432 anti-Xa activities were analysed using NONMEM on the basis of a one-compartment model with three parameters: apparent clearance, apparent volume of distribution and absorption rate. The influence of body weight, age, sex and dose regimen (once or twice daily) were investigated. The best fit corresponds to the formula: apparent clearance (l/min)=$0.541 \cdot \text{weight}^{1.51}/(6.15^{1.51}+\text{weight}^{1.51})$ and apparent volume (l)=$0.355 \cdot$weight. The inter-individual variability (expressed in coefficient of variation) of these parameters are high, especially with regard to the apparent volume (92%), but no other available covariate was found to explain this variability.

Keywords: Heparin; Paediatrics; Heart surgery; Population pharmacokinetic; NONMEM

1. Introduction

The incidence of pulmonary embolism in hospitalised neonates and children is globally evaluated at about 4%, which is probably an under-estimation (Evans and Wilmott, 1994). A variety of characteristics are indeed likely to predispose paediatric patients to thromboembolic events. Buck et al. (1981) have described the risk factors for pulmonary embolism in paediatric patients; immobility and heart disease are the most important clinical risk factors in children after catheterisation and both are found in children hospitalised for an open heart surgery. This is why the 1995 Fourth ACCP Consensus Conference on Antithrombotic Therapy recommended the administration of a prophylactic antithrombotic treatment to children after heart surgical operations such as Blalock–Taussig shunts or Fontans operation (Michelson et al., 1995). Standard heparin is the reference antithrombotic drug in this indication; however, low molecular weight heparins (LMWH) are now available which have a prominent anti-factor Xa activity but do not influence coagulation tests such as APTT or PT.

The use of LMWH has moreover many obvious advantages as compared to the use of unfractionated heparin. Indeed, even if both unfractionated heparin and LMWH can be administered subcutaneously, the bioavailability of LMWH is greater than that of unfractionated heparin and the volume of LMWH injected per injection is smaller, which is particularly convenient when administered to very young children. All these advantages have led us to administer LMWH to children as a prevention against thromboembolism after open heart surgery (either systemico-pulmonary shunts or Fontan-type operations).

Even if the prophylactic efficacy of LMWH in the adult population for the prevention of venous thromboembolic disease is no more to be demonstrated (Nurmohamed et al., 1992; Leizorovicz et al., 1992), the prescription of LMWH to children, when based only on results obtained in adults, remains debatable. Indeed, optimal prevention of thromboembolic complications is probably different in children and in adults because of the important ontogenic

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0928-0987/99/$ – see front matter
PII: S0928-0987(98)00064-5

features in the process of haemostasis that affect both the physiopathology of the thrombotic process and the response to antithrombotic agents in children (Schmidt and Andrew, 1988).

Additionally, no preliminary pharmacokinetic (PK) studies concerning the administration of LMWH to children have been performed. The only prospective study which has been carried out concerning this subject seemed to show that the PK characteristics of children differ from that of adults, with a potential link between doses and age (Massicotte et al., 1996). PK characteristics are related to the anti-Xa activity, a pharmacodynamic parameter used in the evaluation of the PK of heparins since the plasma concentrations of these products cannot be assessed. Further information is thus needed concerning the administration of LMWH in children. PK studies are however considerably limited because the amount of blood that can be reasonably drawn from these patients is small. The number of samples needed for each subject can be reduced by the use of such PK analytical approaches as the nonlinear mixed effect model (NONMEM) (Beal, 1984) which makes it possible to study the PK characteristics of a population using only limited data for each subject (Sheiner and Ludden, 1992).

The aim of the present population study was thus to pinpoint the patterns of variability in the disposition of a LMWH (nadroparin calcium, Fraxiparine®) in children after open heart surgery and to identify patient characteristics associated with inter-individual variability. Such information could be useful since the adaptation of LMWH dosing to patients characteristic (i.e. age, etc.) (Massicotte et al., 1996) and according to anti-factor Xa levels seems to be even more necessary in a children population than in an adult population.

2. Materials and methods

2.1. Patients

The 154 paediatric patients included into the study were hospitalised for open heart surgery at the Centre Chirurgical Marie-Lannelongue, Le Plessis-Robinson, France. The operations performed were either palliative operations (arterial banding, Rashkind's balloon septostomy, Blalock-type operations) or repairing operations (cure of Fallot, Fontan's procedure, systemico-pulmonary shunts, etc.).

2.2. Nadroparin calcium (Fraxiparine®) administration

Nadroparin calcium was rapidly introduced in the intensive care unit, i.e. 24 to 48 hours after surgery, and was administrated during a mean period of about 7 days. Since no data concerning the use of LMWH in children were available, no specific rule was established for the determination of initial dose, dosage regimen, sampling time and dosage adaptation. Each of these parameters was thus arbitrarily determined by the clinician and the haematologist based on the experience they had acquired since 1989. The initial dose of LMWH varied from 330 IU aXa to 3300 IU aXa and the expected biological effect was arbitrary fixed around 0.2–0.4 IU aXa/ml. The doses could thus be modified by the haematologist whenever he considered that they had to be increased or decreased depending on the measured anti-Xa values. Anti-Xa activity was prospectively determined during routine therapeutic care. Drug treatment and blood sampling were not affected by the study protocol but were based on clinical considerations.

2.3. Data collection and assay methods

Venous blood was collected in tubes containing sodium citrate. Plasma was obtained by centrifugation for 20 min at $+4$°C ($3000\times g$). The quantitative determination of the plasma levels of Fraxiparine® was assessed by the measurement of its anti-Xa activity (analysed on fresh plasma) in a competitive system, using a synthetic chromogenic substrate (STA®-Rotachrom® HBPM/LMWH-4, Diagnostica Stago, Asnières, France). All samples were assayed in the same laboratory. The assay was carried out automatically by the Behring coagulation timer BCT® (Dade-Behring, Paris, France) at 405 nm, with a CV less than 5% for the intra- and inter-assay reproducibility values. A platelet count was also performed about three times a week.

The dosing history at time of sampling as recorded on the data collection form was used to create a NONMEM input file (Beal et al., 1993).

2.4. Data analysis

The population analysis was performed using the NONMEM® software version IV (Beal et al., 1993). Descriptive statistics were performed with the SAS® system version 6.11 (SAS Institute Inc., 1990) and graphic analysis was performed with SPLUS® software version 4.5.

2.5. Model building

We divided the whole data set into two groups before beginning the analysis: a model group comprising 124 individuals for model building and a test group comprising the remaining 30 individuals for validation. The latter subjects were randomly selected.

Model building was performed according to the general procedure described by Mandema et al. (1992). We first developed a simple one-compartment model without any covariate using the NONMEM subroutines ADVAN2 TRANS2 and assuming an additive error model. Empirical Bayes estimates of the individual parameters were computed (POSTHOC).

The potential influence of covariates was then evaluated thanks to the visual considerations of smooth functions and tree models between the time-independent variables and the individual parameters (apparent clearance [$CL=cl/f$], apparent volume of distribution [$V=v/f$] and absorption rate [K_a]) on the one hand and between the time-dependant variables (dose) and the weight residuals errors on the other hand. The apparent influence of patient and dosage regimen covariates was assessed by incorporating into the model the relationships between the PK parameters and these covariates. The potential influence was evaluated with the minimum objective function value (log-likelihood difference). Regression relations were refined by repeating exploratory analysis by use of inter-individual variability of individual parameter estimates and weight residual errors. A full model was determined when no additional improvement seemed possible. Additive, proportional and additive plus proportional error models were compared. A covariance between *CL* and *V* was also evaluated. Only covariates showing a significant contribution were conserved in the full model: comparisons between models were based on comparison of the minimum objective function values (the difference between the full and the reduced model has an asymptotic χ^2 distribution with the degree of freedom equal to the number of additional parameters in the full model). The predictive performance of the model was assessed by measuring the median bias and precision of the prediction (Sheiner and Beal, 1981). This bias was expressed as a percentage of the difference between individual predicted and observed values relative to observed values.

2.6. Model validation and final model

To verify the predictive value of the population model for new individuals, we compared the true anti-Xa activities measured in the validation group with the corresponding predicted values by the population model adjusted on the model group data by computing the bias and precision. Finally, data from the model and validation groups were pooled and the full model was adjusted to the whole data set to obtain the most accurate parameter estimates.

3. Results

3.1. Description of the study population

The data obtained for 154 young patients (67 boys and 57 girls) receiving a twice or once daily dose of nadroparin calcium, i.e. a total of 432 anti-Xa activity measurements, were included in the analysis. Among those patients, 10% were younger than 1.5 months (no premature infants were included), 25% were younger than 5 months, and 25% were older than 4 years; the age ranged from 15 days to 8 years (mean±S.D.: 30±27 months; median: 25 months) and the body weight between 2.7 and 25.5 kg (10.1±5.5 kg).

The children included were suffering from a congenital heart disease (147 patients) or from a coronary disease (seven patients); 131 patients were operated on according to a cardiopulmonary bypass procedure; 23 patients were not.

LMWH were administered subcutaneously twice daily in 148 patients and once daily in six patients. The initial dose of LMWH varied from 330 to 3300 IU aXa (1120±510 IU aXa). The follow-up lasted from 2 h to 30 days (4.3±4.4 days), which does not always correspond to the duration of an heparin treatment; for ethical reasons, samples for anti-Xa activities measurement were indeed not drawn when the clinician considered that the anticoagulation level reached by each subject was correct, i.e. approximately between 0.3 and 0.5, and stable, i.e. quite similar to the previous level. The number of evaluations of the anti-Xa activity performed for each patient ranged from one to 18 with an average of 3.2 evaluations per patient.

The population was divided into two groups, the model group and the validation group. The description of the two patient groups is summarised in Table 1. The comparability of the two groups was verified.

3.2. Model building

According to a one-compartment PK model, the estimates of the population means and inter-individual variability (expressed as coefficient of variation) without

Table 1
Description of the model group and validation group populations

	% or mean±S.D.[a] [range]	
	Model group ($n=124$)	Validation group ($n=30$)
Sex (boys)	54%	63%
Age (years)	2.5±2.3 [15 days–8 years]	2.7±2.2 [30 days–7 years]
Body weight (kg)	10.1±5.5 [2.7–25.5]	10.3±5.2 [3.2–21.0]
Dose (IU aXa)	1117±518 [330–3300]	1165±470 [330–2200]
Dose (IU aXa/kg)	146±68 [33–447]	124±44 [50–232]
Follow-up (days)	4.4±4.7 [2 h–30 days]	4.0±2.9 [11 h–10 days]
Sampling per patient	3.1±2.5 [1–18]	3.5±2.6 [1–11]

[a] S.D. denotes standard deviation.

covariates were CL=0.330 l/h (CV=37%), V=0.331 l (CV=84%) and K_a=0.137 h^{-1} (CV=62%).

The graphic explanatory analysis showed that individual estimates of CL were correlated to age and body weight according to a hyperbolic relationship (Fig. 1). The tree models applied to CL, V and K_a detected a cut-off value of age at about 2 months for CL and V. The population model building steps are summarised in Table 2. The combination of weight and age was tested (model 5 and model 6, Table 2), but the two covariates are highly correlated. Thus the integration of one of these two variables results in the absence of influence of the second one (full model, Table 2). No other covariate was found to significantly improve the NONMEM fit. An error model combining an additive and a proportional term seems to be better than a simple additive error model (Table 2). Trying to integrate a covariance between CL and V seems to improve the fit (Table 2). When the deletion of the covariates of age and weight in CL and V did not significantly decrease the efficacy of the fit, the covariates were excluded from the model. The formulas adopted on the basis of the model group were as follows:

$$CL\ (\mathrm{l/h}) = 0.465 \cdot \mathrm{WGT}^{2.57}/(4.10^{2.57} + \mathrm{WGT}^{2.57})$$

$$V(\mathrm{l}) = 0.306 \cdot \mathrm{WGT}$$

$$K_a(\mathrm{h}^{-1}) = 0.801$$

The estimates of the inter-individual variability of CL and V were, respectively, 30 and 79% (expressed as coefficient of variation). Since the majority of samples were collected in the post-absorptive phase, the estimated inter-individual variability in K_a was near 0; K_a was thus considered to be constant for all patients. The coefficient of variation of residual variability was estimated at about 40%, and the additive term was estimated at 0.002 UI aXa/ml.

The median bias was 0%; the first and third quartiles as a measure of precision were, respectively, −16 and 32%.

3.3. Model validation

The anti-Xa activities predicted thanks to the last model for patients of the validation group versus the corresponding observed values yielded a median bias of

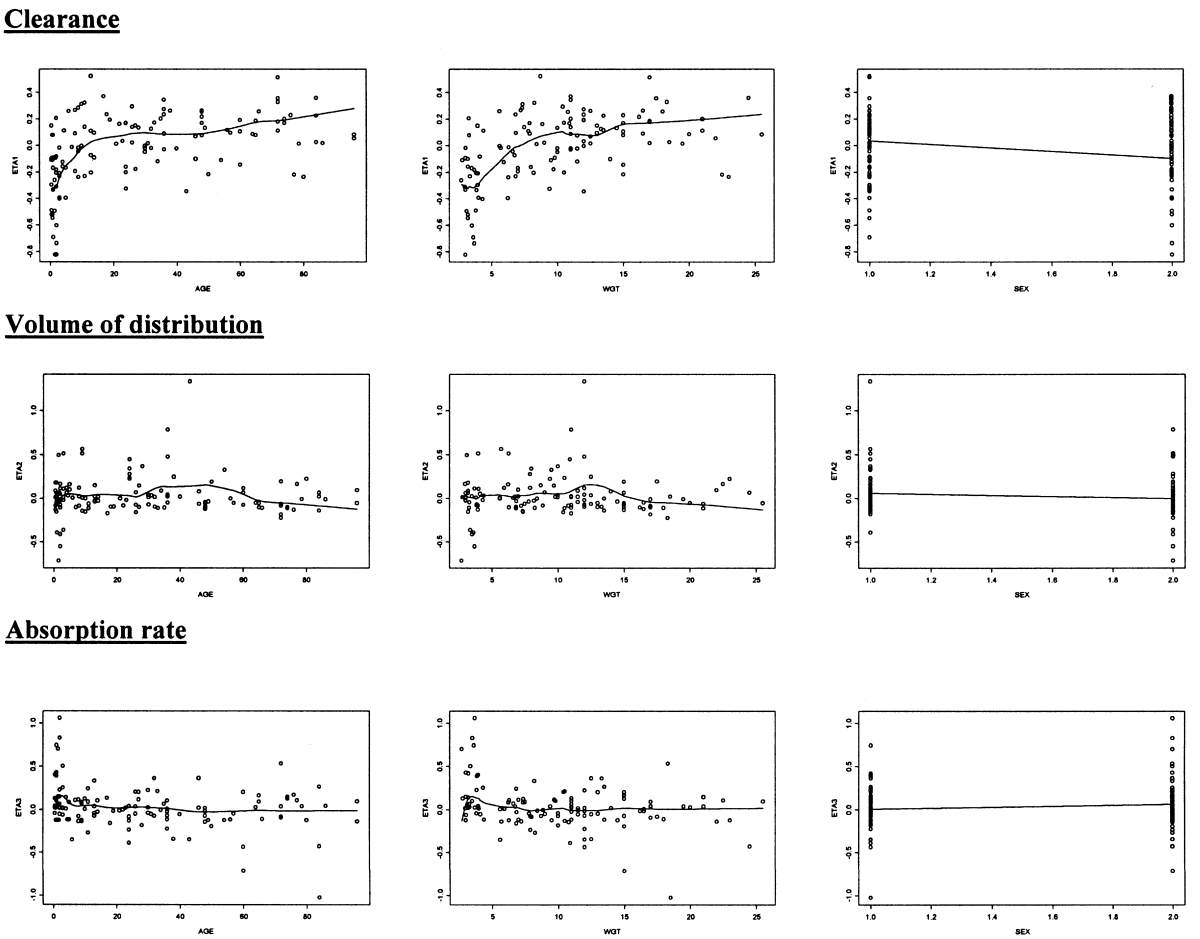

Fig. 1. Inter-individual variability of individual clearance, volume of distribution and absorption rate (assessed in the model group without covariates) against age (left), body weight (middle) and sex (right). Individual points are superimposed on a smooth with use of a spline function.

Table 2
Summary of the exploratory analysis and elimination procedure

Model number	Characteristics	Objective function value	Compared to model number	*P* value	Model conserved
Exploratory analysis					
1	Basic (no covariate), additive error model $CL=\theta1$, $K_{el}=\theta2$, $K_a=\theta3$	−997			
2	$CL=\theta6+\ \theta1\cdot WGT^{\theta5}/(\theta4^{\theta5}+WGT^{\theta5})$	−1086	1	<0.001	2
3	$CL=\theta6+\theta1\cdot AGE^{\theta5}/(\theta4^{\theta5}+AGE^{\theta5})$	−1084	2	/	2
4	$V=\theta7+\theta2\cdot WGT$	−1109	2	<0.001	4
5	$CL=\theta6+\theta1\cdot WGT^{\theta5}/(\theta4^{\theta5}+WGT^{\theta5})$ if age >2 months, $\theta8$ otherwise	−1109	4	NS	4
6	$V=\ \theta7+\theta2\cdot WGT$ if age >2 months, $\theta8$ otherwise	−1116	4	<0.01	6
7	$V=\theta7+\theta2\cdot WGT$ if age >2 months, $\theta8$ otherwise, if sex=2 $\theta9\cdot[\theta7+\theta2\cdot WGT$ if age >2 months, $\theta8$ otherwise] if sex=1	−1117	6	NS	6
8	Additive and proportional error model $CL=\theta6+\theta1\cdot WGT^{\theta5}/(\theta4^{\theta5}+WGT^{\theta5})$ $V=\theta7+\theta2\cdot WGT$ if age >2 months, $\theta8$ otherwise $K_a=\theta3$	−1142	6	<0.001	8
9	Covariance between *CL* and *V*	−1161	8	<0.001	9
Elimination procedure					
10	$V=\theta2\cdot WGT$ if age >2 months, $\theta8$ otherwise (i.e. $\theta7=0$)	−1161	9	NS	10
11	$V=\theta2\cdot WGT$ whatever the age is	−1155	10	NS	11
12	$CL=\theta1\cdot WGT^{\theta5}/(\theta4^{\theta5}+WGT^{\theta5})$ (i.e. $\theta6=0$)	−1155	11	NS	12
13	$CL=\theta1$ whatever the weight is	−1049	12	<0.001	12
Final	$CL=\theta1\cdot WGT^{\theta5}/(\theta4^{\theta5}+WGT^{\theta5})$ $V=\theta2\cdot WGT$ $K_a=\theta3$				

NS indicates that the change in objective function was not significant.

−4.5%. The precision computed with the first and third quartiles were, respectively, −25 and 46%. In adults, when an adaptive control of LMWH is recommended, it is performed on the observed C_{max} values (i.e. 3–6 h after administration). In our paediatric population, the median bias and precision were not increased when calculated only with anti-Xa activities around C_{max} (the median bias was estimated at −0.6% and the quartiles at −27 and 46%, respectively.

3.4. Final model

Final parameter estimates of the final model adjusted on both the model group and the validation group (154 patients) are presented in Table 3. There were minor differences in the parameter estimates between the model group and the total population. For a 10 kg body weight child, the *CL* of nadroparin calcium was estimated at 0.37 l/h, with a half-life of about 6.5 h. The median bias was 4.7%; the first and third quartiles as a measure of precision were, respectively, −17 and 34%.

4. Discussion

This study shows that children characteristics may influence the PK parameters of nadroparin calcium, since the *CL* and *V* depend on age and weight. For a 10 kg child, nadroparin calcium clearance is estimated at 37 ml/h per kg. Nadroparin calcium PK properties in children are thus likely to be different from those in adults, for whom the *CL* is estimated at about 12.5 ml/h per kg in young healthy volunteers and 11.6 ml/h per kg in patients with deep-vein thrombosis (Mismetti et al., 1998). This means that a higher dosage is needed in children than in adults in order to reach a similar range of anti-factor Xa levels.

Among all tested covariates, weight is the one that produced the largest improvement in the fit. The assessment of several models showed that age was redundant when weight was included in the model.

The results for nadroparin calcium PK obtained in 154 neonates and children showed large inter-patient variability. Indeed, even if the inter-individual variability of *CL* and *V* is partly explained by weight, these parameters remain high, especially with regard to the *V*, with a coefficient of variation of about 90%. Two solutions can be viewed: either the inter-individual variability cannot be explained more precisely than was done, or more relevant covariates (such as body-mass index, apgar score...) are not available in our study to explain another part of the inter-individual variability. The clearance of creatinine was however measured in about 50% of the children included in the study. No relation between the clearance of creatinine and *CL* or *V* was found in this subset.

Table 3
Parameter estimates with the final model adjusted on both the model group and the validation group (154 patients)

	Estimates	Precision of estimates (CV, %)
$CL=\theta1\cdot WGT^{\theta5}/(\theta4^{\theta5}+WGT^{\theta5})$		
$\theta1$	0.541	33.8
$\theta4$	6.15	56.7
$\theta5$	1.51	44.8
CL (l/h)[a]	0.366	/
ω_{CL} (%)[b]	30.0	22.0
$V=\theta2\cdot WGT$		
$\theta2$	0.355	9.0
V (l)[a]	3.55	/
ω_V (%)[b]	92.6	52.7
$K_a=\theta3$		
K_a (h^{-1})	0.723	21.8
ω_{Ka} (%)[b]	0 fixed	/
Residual variances		
$\sigma1$ (%)[c]	29.8	35.4
$\sigma2$ (IU aXa/ml)[c]	0.005	59.7

[a] For a child with a 10 kg body weight.
[b] ω denotes inter-individual variance.
[c] σ denotes residual variance.

In all cases, the influence of variability on prediction is low in terms of biological and clinical relevance compared to the therapeutic index recommended in adults; indeed, the anti-Xa value to be reach 4 h after administration for a curative regimen is about 0.75 UI aXa/ml±0.25, that is to say a 'margin' of 30%. Extrapolating this tolerated margin to paediatric population, most anti-Xa activities (about 75%) were correctly assessed in our PK study. Concerning values outside this tolerated margin, i.e. the 'outliers', they represented single points taken from several patients (not from single patients), in the absence of any specific demographic characteristics or sample times. Several assumptions can be discussed. Firstly, body weight was available for most of the children only on the first day and we know that the body weight changes from one day to another, especially in neonates; we have tried to establish a model for the evolution of the body weight according to the age on the basis of curves established in paediatric services. However, none of these seemed to be adapted to children having undergone open heart surgery. Secondly, we can suppose that the number of samples available for each patient was too small. According to a study carried out in infants, three concentration time points may however be sufficient to make an assessment of PK parameters in neonates accurate enough for practical purposes (Long et al., 1987), even when no non-linear mixed effect model requiring still less concentration time points per patient is used (Sheiner and Ludden, 1992). The most plausible explanation was finally the design of the study itself. The sample times and/or dosing times might have been noted too approximately in clinical practice. Even if the non-experimental design had the advantage of reflecting the real conditions of drug use in the population of interest, this observational design did not make it possible to obtain as precise data as experimental designs do.

Since the use of heparin in paediatric medicine has to be urgently collected, our results have to be confirmed with additional data (more covariates...). This can be done thanks to optimal sample collecting time points, which make it possible to obtain a correct assessment of the PK of nadroparin calcium in children, and maybe by associating this to a comparative study of the efficacy of LMWH and unfractionated heparin in the prevention of thromboembolism. The final aim will be to build a nomogram in order to establish rules for the initiation and maintenance of prophylactic anticoagulation in children.

Acknowledgements

The English text was revised by Claire Rougemont (Lyon). The authors wish to thank Brigitte Tranchand for her helpful comments, and Edith Venet, who helped in the preparation of the data set.

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