Population pharmacodynamic model for low-molecular-weight heparin nadroparin in morbidly obese and non-obese patients using anti-Xa levels as endpoint

11

Jeroen Diepstraten, Esther J.H. Janssen, Christian M. Hackeng,
Eric P.A. van Dongen, René J. Wiezer, Bert van Ramshorst, Catherijne A.J. Knibbe

Submitted for publication

Abstract

Background
In absence of specific dosing guidelines, the optimal dose of low-molecular-weight heparins for thrombosis prophylaxis in morbidly obese patients (BMI > 40 kg/m^2) remains unknown. In order to guide dosing in this patient group, a pharmacodynamics model is developed for nadroparin in morbidly obese and non-obese patients using anti-Xa levels as an endpoint, thereby characterizing the influence of excessive body weight on different pharmacodynamic model parameters.
Methods
Twenty-eight morbidly obese and seven non-obese patients receiving 5,700 IU and 2,850 IU s.c. nadroparin for surgery, respectively, were included with a mean total body weight (TBW) of 135 kg (range 72–252 kg). Up to 11 anti-Xa levels were collected from start until 24 hours after nadroparin administration. Population pharmacodynamic modelling with covariate analysis was performed using NONMEM.
Results
In a two-compartment pharmacodynamic model with baseline endogenous anti-Xa levels, the effect of nadroparin was found to be delayed and could be best described using a transit compartment. TBW was the most predictive covariate for clearance (CL = 23.0 mL/min * (TBW/70)), while lean body weight (LBW) proved the most predictive covariate for central volume of distribution (V1 = 7.0 L * (LBW/60)).
Conclusion
A pharmacodynamic model was developed characterizing anti-Xa levels after s.c. administration of nadroparin in patients weighing between 72 to 252 kg with TBW and LBW as the major determinant for clearance and volume of distribution, respectively. Based on simulations using the final covariate pharmacodynamic model it appeared that a dose of 5,700 IU nadroparin will lead to target anti-Xa levels in morbidly obese patients with a LBW below 90 kg.

Introduction

Western countries, the incidence of obesity (body mass index (BMI) > 30 kg/m^2) is increasing resulting in a percentage of 30% of the population of the United States (1). In addition, the incidence of morbidly obese patients (BMI > 40 kg/m^2) is on the rise as well (2, 3). Obesity is associated with a two times increased relative risk of venous thromboembolism (VTE) compared to non-obese patients (4). More specifically, the prevalence of pulmonary embolism in hospitalized patients is higher in obese patients than in non-obese patients (5).

Low-molecular-weight heparins (LMWHs) are widely used for the prevention of VTE both in non-obese patients and (morbidly) obese patients, even though for the latter population dosing advices largely vary (6). In addition, different weight scales have been proposed to adjust the dose of LMWH in obese patients, such as total body weight (TBW) (7) and BMI (8, 9). In clinical practice, the prophylactic dose of LMWH for morbidly obese patients is often capped at a certain dose, resulting for instance for nadroparin in a fixed dose of 5,700 IU (= 0.6 mL) for the heterogeneous group of morbidly obese patients in which body weights are still increasing (10).

Population modelling is a well-established approach for the characterization of the pharmacokinetics and pharmacodynamics of a drug and can serve as the scientific basis for the development of rational and individualized dosing schemes (11). Population pharmacodynamic studies of LMWHs describing the influence of body weight are scarce and do often not include morbidly obese patients. For enoxaparin in non-obese patients, both lean body weight (LBW) and TBW have been identified as the best size descriptor for clearance and volume of distribution (12-16). In a population pharmacodynamic analysis of enoxaparin in non-obese and obese patients (TBW range 66 - 160 kg), LBW proved to be the best size descriptor for clearance, while for central volume of distribution TBW was identified (17). As body weights of patients are still increasing, data should be gathered across a wide body weight range including morbidly obese patients to properly study the influence of different weight-based covariates on the pharmacodynamics of LMWHs.

Therefore, in this study a population pharmacodynamic model of nadroparin used for thrombotic prophylaxis is developed in morbidly obese and non-obese patients, using anti Xa-levels as a pharmacodynamic endpoint, in order to characterize the influence of excessive body weight on different pharmacodynamic model parameters. In a systematic covariate analysis, potential factors (TBW, BMI, ideal body weight (IBW) and LBW (18)) influencing the pharmacodynamic parameters of nadroparin are tested for their influence, ultimately to provide a guide for dosing nadroparin in morbidly obese patients.

Methods

Patients

A total of thirty-five patients were included in two prospective clinical studies: twenty-eight morbidly obese patients (BMI > 40 kg/m^2) which were scheduled to undergo laparoscopic gastric banding or gastric bypass surgery and seven non-obese patients which underwent laparoscopic Toupet fundoplication surgery (Study 1: 20 morbidly obese patients, ClinicalTrials.gov/ NCT01097148 (19) and Study 2: 8 morbidly obese patients and 7 non-obese patients, ClinicalTrials/gov/ NCT01309152). Clinical data of 27 of the 28 morbidly obese patients have been published before in a descriptive paper (19). Patients were included if they were between 18 and 60 years old, had an American Society of Anesthesiologists (ASA) physical status classification of II or III in case of morbidly obese patients and I or II for non-obese patients and had a normal renal and liver function as assessed by routine laboratory testing. Exclusion criteria included LMWH administration within 48 hours preceding surgery, pregnancy, breast feeding, epilepsy and known allergy for propofol, soybean oil or egg lecithin. Both study protocols were approved by the hospitals Ethics Committee and written informed consent was signed by each participating patient.

Procedure

In both studies, before induction of anesthesia an antecubital infusion line, an indwelling arterial blood pressure line and a three-lead ECG were installed. No pre-anesthetic medication was given and all patients were fasting for 6 hours before surgery to minimize the risk of aspiration during induction. Following a propofol bolus injection, intravenous fentanyl and cefazolin were given in fixed doses of 250 µg and 2 g, respectively. Then 5,700 IU (0.6 ml) nadroparin for morbidly obese patients and 2,850 IU (0.3 ml) nadroparin for non-obese patients was administered subcutaneously in the thigh, the exact time being recorded. Anesthesia was maintained with continuous infusions of propofol and remifentanil according to routine clinical practice.

Blood sampling and analysis

Blood samples for determination of anti-Xa levels were collected before induction of anesthesia (t=0), at 10, 30, 60, 90, 120, 180, 240, 300 and 420 minutes after nadroparin dosing and the next morning within 24 hours

after administration in the 20 morbidly obese patients of Study 1 and 7 non-obese patients of Study 2, and before induction of anesthesia, 120 and 240 minutes after nadroparin dosing and the next morning within 24 hours after administration in 8 morbidly obese patients of Study 2. Blood samples were collected in 3.2% buffered sodium citrate containing tubes and were immediately stored on ice until centrifugation. All samples were centrifuged at 4 °C within one hour after collection to obtain plasma samples, and stored at –80 °C until analysis within one month after collection. Plasma levels of anti-Xa activity were measured with a STA-Rack Evolution (Diagnostica Stago, Asnières, France) using an anti-Xa clotting assay (STA Rotachrom®Heparin 4, Diagnostica Stago, Asnières, France). The rate of chromophobe appearance at 405 nm was measured. Calibration occurred with eight concentrations of nadroparin (Lot number used for patients) in normal pooled plasma. The calibration curve was found to be linear between 0.00-1.60 IU/ml. The within assay and among assay precision (coefficient of variation) were 4.2% and 4.7%, respectively. Regression analysis was used to determine the calibration curve values from which the experimental values were obtained.

Data analysis and internal validation

The analysis was performed by means of non-linear mixed effects modelling using NONMEM (version VI, release 1.1; GloboMax LLC, Hanover, MD, USA) (20) with S-plus (version 6.2; Insightful software, Seattle, WA, USA) for data visualization. Discrimination between different models was made by comparison of the objective function value (OFV, i.e.–2 log likelihood). A significance level of $p<0.05$, corresponding to a decrease of 3.8 in OFV, was considered statistically significant. In addition, goodness-of-fit plots (observed versus individually-predicted anti-Xa level-time, observed versus population-predicted anti-Xa level-time, conditional weighted residuals versus time and conditional weighted residuals versus population-predicted anti-Xa level-time plots) were used for diagnostic purposes. Furthermore, the confidence interval of the parameter estimates, the correlation matrix and visual improvement of the individual plots were used to evaluate the models.

The internal validity of the models was assessed by the bootstrap re-sampling method using 250 replicates (20). Parameters obtained with the bootstrap replicates were compared with the estimates obtained from the original data set. Besides, normalized prediction distribution errors (NPDE) method was used to validate the model (21). This method was implemented using the NPDE add-on software package that was run in R. In this study, each observation was simulated 1000 times. The results of NPDE method are visualized in different graphs: (i) a histogram showing the distribution of the NPDEs, which are expected to follow normal distribution; (ii) a scatterplot NPDE vs. time; and (iii) a scatterplot NPDE vs. predicted anti-Xa levels.

Pharmacodynamic model of nadroparin

A one-compartment and a two-compartment model were tested to fit observed anti-Xa levels. To describe the observed delay in effect of subcutaneously administrated nadroparin, different absorption models were evaluated including a lag time model (20) and a model with one or more additional transit compartments (22). Transit compartments were described using a first-order rate constant describing the transfer from the dose compartment into the transit compartment and subsequently into the central compartment (22).

The individual value (empirical Bayes estimate) of the parameters of the i^{th} individual was modeled by (equation 1):

$$\Theta_i = \Theta_{mean} * e^{\eta_i} \qquad \text{(Eq. 1)}$$

where θ_{mean} is the population mean, and η_i is a random variable with a mean of zero and variance of ω^2, assuming log-normal distribution in the population.

The intraindividual variability, resulting from assay errors, model misspecifications and other unexplained sources, was best described with an additive error model while a proportional error model and a combination of an additive and a proportional error model were tested as well. This means for the j^{th} observed anti-Xa level of the i^{th} individual, the relation (Y_{ij}) is described by equation 2.

$$Y_{ij} = C_{pred,ij} + \varepsilon_{ij} + BLS \qquad \text{(Eq. 2)}$$

where c_{pred} is the predicted anti-Xa level, and ε_{ij} is a random variable with a mean of zero and variance of σ^2. Incorporation of baseline endogenous anti-Xa levels (BLS) into the model was explored as reported before (23, 24). This means for the j^{th} observed anti-Xa level of the i^{th} individual, the relation (Y_{ij}) is described by equation 2, where BLS represents the baseline endogenous anti-Xa level.

Covariate analysis

Covariates were plotted independently against the individual empirical Bayes estimates of the pharmacodynamic parameters to visualize potential relations. The following continuous covariates were tested: total body weight (TBW), body mass index (BMI), ideal body weight (IBW) (25), lean

body weight (LBW) (18) and age. For calculating LBW, equations 3 and 4 were used (18):

$$LBW_{male}(kg) = \frac{9270 * TBW}{6680 + 216 * BMI} \quad \text{(Eq. 3)}$$

$$LBW_{female}(kg) = \frac{9270 * TBW}{8780 + 244 * BMI} \quad \text{(Eq. 4)}$$

Continuous covariates were tested using linear and power equations:

$$P_i = P_p \cdot (\frac{Cov}{Cov_{standard}})^z \quad \text{(Eq. 5)}$$

in which P_i and P_p represent individual and population parameter estimates, respectively, Cov represents the covariate and $Cov_{standard}$ represents a standardized (i.e. 70 kg for TBW) or median value of the covariate for the population. The exponent z represents the exponential scaling factor, which was fixed at 1 for a linear function or an estimated value for a power equation, while also a 0.75 fixed value of the exponent was tested when TBW was the covariate (26). Categorical covariates (e.g. the subgroups morbidly obese patients and non-obese patients, and sex) were tested by estimation of an additional parameter on a structural parameter for one of the categories. Potential covariates were separately entered into the model and statistically tested using the objective function and if applicable the 95% confidence interval values of the additional parameter. A $p<0.005$ was applied to evaluate the covariates in the forward inclusion (OFV decrease >7.9), while the backward deletion procedure used a stricter criterion (OFV decrease >10.8, $p<0.001$). When two or more covariates were found to significantly improve the model, the covariate causing the largest reduction in objective function was left in the model. Additional covariates had to reduce this OFV further to be retained in the model. The choice of the covariate model was further evaluated as under the section Data analysis and internal validation.

Simulations

Based on the final pharmacodynamic model, simulations in morbidly obese patients were performed to aim for a target anti-Xa level of 0.2 IU/ml 4 hours after administration (27).

Results

Patients and data

A total of 35 patients were enrolled in two studies resulting in a total of 28 morbidly obese patients and 7 non-obese patients, from which 319 anti-Xa levels were available. Clinical data of 27 of the 28 morbidly obese patients were published before in a descriptive manner (19). Morbidly obese patients had a mean total body weight (TBW) of 148 kg (range 107 – 252 kg) and a mean BMI of 49 kg /m² (38 – 79 kg/m²) while non-obese patients had a TBW of 86 kg (72 – 105 kg) and a mean BMI of 28 kg/m² (24 – 31 kg/m²). Demographic characteristics are summarized in Table I.

Table I *Patient characteristics of the total study population of thirty-five patients consisting of twenty-eight morbidly obese patients and seven non-obese patients from two studies.*

	Total study population Mean (Range)	Morbidly obese (Study 1) Mean (SD)	Morbidly obese (Study 2) Mean (SD)	Non-obese (Study 2) Mean (SD)
Number (n)	35	20	8	7
Gender (M / F)	14/21	9/11	1/7	4/3
Age (years)	45 (22 – 59)	44 (11)	40 (6)	53 (6)
Total body weight (kg)	135 (72 – 252)	151 (33)	140 (23)	86 (12)
Ideal body weight (kg)	66 (50 – 86)	67 (11)	64 (7)	68 (9)
Lean body weight (kg) (18)	68 (44 – 100)	73 (15)	66 (9)	58 (11)
Body mass index (kg/m²)	45 (24 – 79)	50 (10)	47 (6)	28 (3)

SD = standard deviation

Pharmacodynamic analysis

A two-compartment pharmacodynamic model (NONMEM VI) parameterized in ADVAN5 adequately described the time course of the anti-Xa levels after subcutaneous dosing of nadroparin, parameterized in terms of the volume of distribution of the central compartment (V1), volume of distribution of the peripheral compartment (V2), inter-compartmental clearance from the central compartment to the peripheral compartment (Q) and clearance from the central compartment (CL) (Figure 1). A two-compartment model was superior over a one-compartment model, showing a reduction in objective function value (OFV) of 28 points and significantly improved diagnostic plots. In the two-compartment model, the peripheral compartment was set equal to the volume of the central compartment for statistical reasons (i.e.

convergence), which resulted in adequate diagnostic plots and improvement of the fit of the data compared with a one-compartment model.

The observed delay in appearance of anti-Xa levels after subcutaneous administration of nadroparin was described with a single transit compartment (see Figure 1), which proved superior over a lag time model (20) or a model with a first order rate absorption. Incorporation of additional transit compartments did not improve the fit of the data any further. It appeared that the model improved significantly (OFV reduction = 15 points , $p<0.05$) when k_a and k_{tr} were estimated separately. Implementation of a basal anti-Xa level (BLS) into the model was found to largely improve the diagnostic plots.

The results of the systematic covariate analysis are shown in Table II and

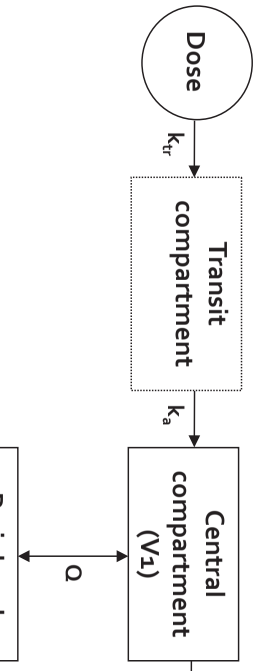


Figure 1 *Schematic representation of the pharmacodynamic model for nadroparin based on a two-compartment pharmacodynamic model with a single transit compartment with parameters k_{tr} and k_a.*

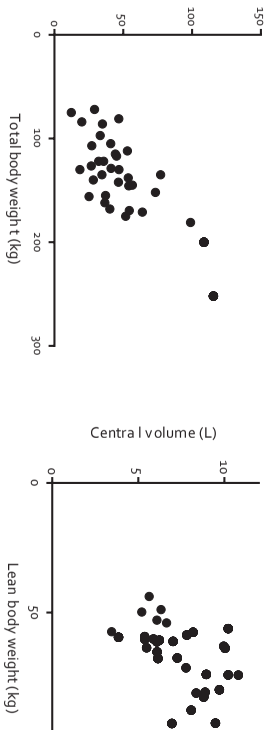


Figure 2 *Empirical Bayes estimates for clearance versus total body weight and central volume versus lean body weight for the base two-compartment pharmacodynamic model for nadroparin in twenty-eight morbidly obese patients and seven non-obese patients using anti-Xa levels as an endpoint.*

Table II *Stepwise covariate analysis for the pharmacodynamic model of nadroparin in thirty-five morbidly obese and non-obese patientst*

Parameter	Model	Relationship of covariate	No. of structural parameters	ΔOFV
-	Base model	-	10	
CL	Age	$CL_i = CL_{pop} / (1+(Age_i/40)*x)$	11	- 5.1
CL	BMI linear	$CL_i = CL_{pop} \bullet (BMI_i/25)$	10	- 10.7
CL	LBW (18) linear	$CL_i = CL_{pop} \bullet (LBW_i/60)\ (LBW_i/60)$	10	- 12.8
CL	TBW allometric	$CL_i = CL_{pop} \bullet (TBW_i/70)^{0.75}$	10	- 14.2
CL	TBW linear	$CL_i = CL_{pop} \bullet (TBW_i/70)$	10	- 17.2
CL	TBW power	$CL_i = CL_{pop} \bullet (TBW_i/70)^z$	11	- 19.1
V1	TBW linear	$V1_i = V1_{pop} \bullet (TBW_i/70)$	10	- 7.7
V1	LBW (18) linear	$V1_i = V1_{pop} \bullet (LBW_i/60)$	10	- 13.6
Final model CL and V1	TBW and LBW linear	$CL_i = CL_{pop} \bullet (TBW_i/70)$ $V1_i = V1_{pop} \bullet (LBW_i/60)$	10	- 29.1

BMI = body mass index; CL = clearance; CL_i = clearance in i^{th} individual; CL_{pop} = population mean value for clearance; CV = coefficient of variation of the parameter values; LBW = lean body weight; ΔOFV = delta objective function value compared to base model; TBW = total body weight; V1 = central volume of distribution; $V1_i$ = central volume of distribution in i^{th} individual; $V1_{pop}$ = population mean value for central volume of distribution; x = exponent for age = 4.6 (CV = 11%); z = scaling factor for clearance = 1.4 (CV = 13 %).

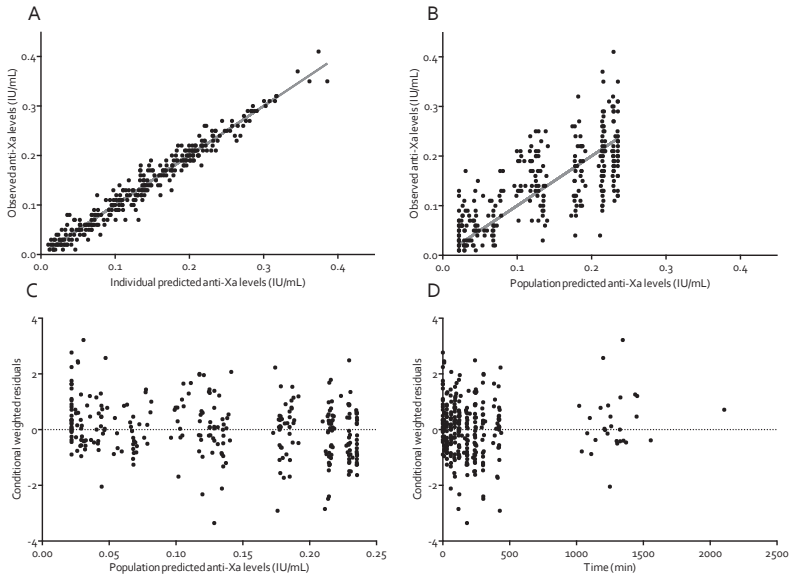
Figure 2. TBW proved the most significant covariate on the basis of a linear function (-17.2 points, 10 degrees of freedom, p<0.005) compared a power function (- 19.1 points, 11 degrees of freedom, p<0.005) given the objective function in relation to the number of structural parameters (Table II). Adding lean body weight (LBW) as a linear covariate on V1 further improved the model in a significant manner (-11.9 points, p<0.005). No covariates were identified for the other pharmacodynamic parameters. After incorporation of these two covariates, interindividual variability on clearance and volume of distribution substantially decreased (Table III), and both individual plots and goodness-of-fit plots improved (Figure 3). The pharmacodynamic parameter estimates of the base model without covariates and the final covariate model along with the results of the bootstrap analysis are shown in Table 3. Figure 4 shows the results of the NPDE validation in all patients. The histogram follows a normal distribution expected by the solid line with very limited bias over time and predicted anti-Xa levels.

Table III *Population pharmacodynamic parameters for the base model and final model for nadroparin in thirty-five morbidly patients and non-obese patients*

Parameter	Base model (CV%)	Final model (CV%)	Bootstrap final model (%)
CL/F (ml/min)	41.1 (7)		
$CL_{70\,kg}$/F (ml/min)#		23.0 (7)	99
V1/F (ml)	7380 (12)		
$V1_{60\,kg\,LBW}$/F (ml/min)*		7020 (4)	100
V2/F (ml) = V1/F			
Q/F (ml/min)	81.2 (11)	85.5 (2)	100
k_{tr} (min^{-1})	0.031 (18)	0.032 (17)	99
k_a (min^{-1})	0.0073 (7)	0.0076 (7)	103
BLS (anti-Xa IU)	0.022 (37)	0.021 (20)	100
OFV	- 1909	- 1938	101
Interindividual variability (%)			
CL	56.4 % (40)	38.9 % (29)	100
V1	35.4 % (33)	27.7 % (33)	98
k_{tr}	87.9 % (39)	82.0 % (41)	96
BLS	111.6 % (47)	109.6 % (33)	105
Additive intraindividual error	0.00041 (17)	0.00041 (13)	99

#: $CL_i = CL_{70kg} * (TBW/70)$
**: $V1_i = V1_{60kg} * (LBW/60)$*
BLS = Baseline; CL = clearance; CL_{70kg} = clearance in an individual of 70 kg; CL_i = clearance in the i^{th} individual; CV = coefficient of variation of the parameter values; k_a = absorption rate constant; k_{tr} = transit rate constant; OFV = objective function value; Q = compartmental clearance between V1 and V2; TBW = total body weight; V1 = central volume of distribution; V2 = peripheral volume of distribution.

Base model



Final model

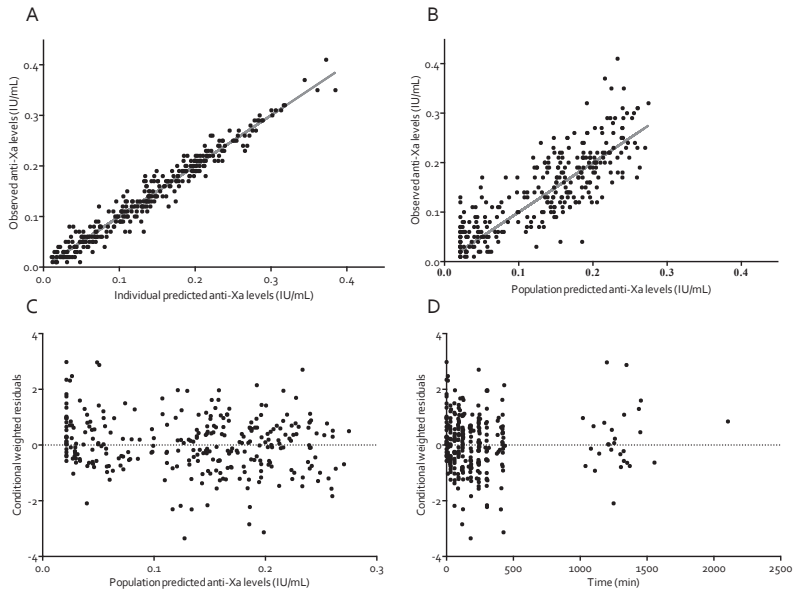


Figure 3 *Diagnostic plots for nadroparin pharmacodynamics in morbidly obese and non-obese patients showing individual anti-Xa level predictions versus observed anti-Xa levels, (A) population model anti-Xa level predictions versus anti-Xa levels (B), conditional weighted residuals versus population predicted anti-Xa levels (C) and time (D) for both the base model and final covariate model. The solid grey line represents the line of identity, x=y.*

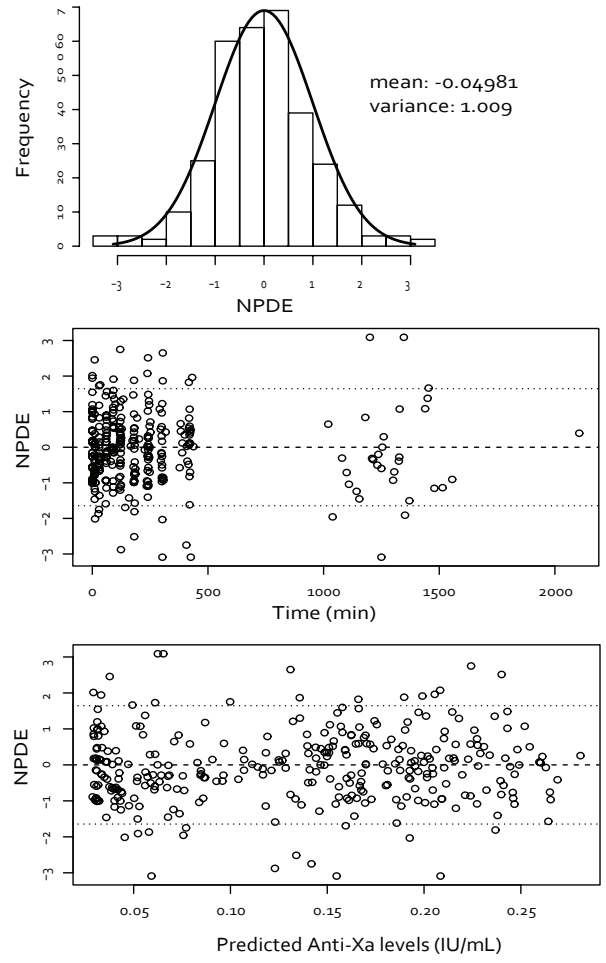


Figure 4 *Results of the internal validation with the NPDE method. The histograms show the NPDE frequency distribution for anti-Xa levels, the solid line indicates a normal distribution. The distribution of NPDE versus time and NPDE versus anti-Xa levels are also shown. The dotted lines represent the 90% distribution of the NPDE.*

Simulations

Based on the final pharmacodynamic model, simulations were performed aiming for anti-Xa levels of 0.2 IU/mL 4 hours after administration for morbidly obese patients. For these simulations, typical values without interindividual variability for all parameters were used to illustrate the influence of the covariates that were identified in this study. Supported by the results of the final covariate model, it seemed that morbidly obese patients with a lean body weight higher than 90 kg should receive 7,600 IU (0.8 ml) nadroparin and morbidly obese patients with a lean body weight lower or equal to 90 kg 5,700 IU (0.6 ml) nadroparin. Results of the simulation of the traditional dose of 5,700 IU (0.6 mL) nadroparin and the model based dose of nadroparin in three representative morbidly obese patients are depicted in Figure 5.

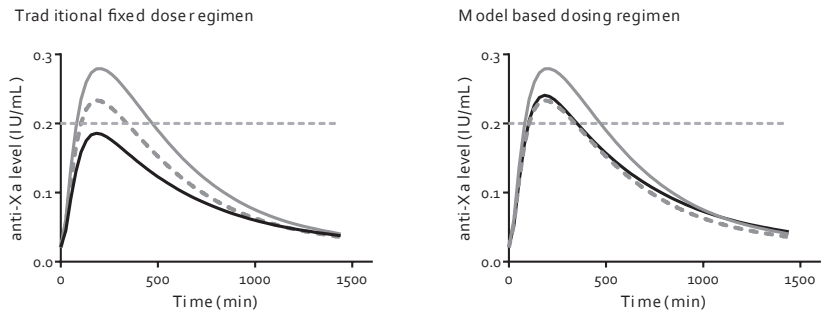


Figure 5 *Model based predictions of anti-Xa levels upon a traditional fixed dose dosing regimen of 5,700 IU =0.6 mL nadroparin for all morbidly obese patients (left panel) and upon a model based dosing regimen of 5,700 IU =0.6 mL nadroparin for patients with a lean body weight (LBW) lower than 90 kg and 7,600 IU (=0.8 mL) nadroparin for patients with a LBW higher than 90 kg (right panel). Profiles are simulated in three representative morbidly obese patients of the current study (grey solid line = total body weight (TBW) 107 kg and LBW of 53 kg, grey dotted line = TBW 135 kg and LBW = 65 kg and black solid line = TBW 162 kg and LBW = 94 kg.) . The horizontal dotted line represents the lower limit of prophylactic range (0.2 IU/mL).*

Discussion

In order to study the influence of body weight on the pharmacodynamics of low-molecular weight heparin (LMWH) nadroparin in morbidly obese and non-obese patients, a population pharmacodynamic model was developed using anti-Xa levels as endpoint. In this model, clearance proved to scale best with total body weight (TBW) and central volume of distribution with lean body weight (LBW).

As body weights are still increasing, there is high interest in the characterization of the influence of excessive body weight on pharmacokinetic and pharmacodynamics parameters of drugs in order to guide dosing in this special group of patient. For LMWHs such as nadroparin, central volume of distribution is the parameter of interest as this parameter mainly determines the maximum anti-Xa level, which is attained around 4 hours after administration, and for which a prophylactic range has been defined (27). As LMWH are assumed to mainly distribute over vascular tissue and blood, and plasma volume is known to increase in a non-linear manner with TBW (28) and most probably with LBW, it has been suggested before to guide safe and effective dosing of a LMWH on the basis of LBW (29). However, in patients up to 160 kg, TBW proved the best size descriptor for central volume of enoxaparin, which is another LMWH (15-17, 30). The current study is the first study describing the pharmacodynamics of nadroparin for patients up to 252 kg. For this wide body wide range, LBW proved the best body size descriptor for central volume in this analysis of both non-obese and morbidly obese patients.

While there are no other reports on the pharmacodynamics of nadroparin in morbidly obese patients, previous reports on enoxaparin concerning the best body size descriptor for clearance of anti-Xa in non-obese adults suggest a non-linear function for TBW (16). However, for patients up to 160 kg, the increase in clearance was described with a linear function using LBW as body size descriptor (17). However, this study used an outdated formula to calculate LBW that was found to be inconsistent at extremes of size (31). A recently reported formula for LBW that we used in our analysis, proved to be more reliable to estimate the fat free mass in both non-obese and obese patients (18) and was found to provide good predictive performance of the measured fat free mass in another study (1). Another way to describe the non-linear increase of clearance with TBW is allometric scaling (26), which has gained popularity most recently. The a priori use of allometry in obese patients is however considered to imply that obese individuals can be viewed as 'large individuals' (a different body size) instead of individuals 'having excess body fat' (a different body composition) (32). In the present study in morbidly obese and non-obese patients, we estimated an allometric scaling factor of 1.4, which was not significantly different from a linear function requiring a smaller number of structural parameters. As such, while testing all available body size descriptors, in this analysis in which a very large range in TBW (72 – 252 kg) could be evaluated, TBW was the best descriptor for clearance of anti-Xa in both morbidly obese and non-obese patients using a linear function.

In this study we found a delay in anti-Xa appearance in plasma. Different ways to describe the observed delay in effect were investigated. Using a lag

time model (20), the time of dosing shifts as if the drug was administered at a delayed time point. In a transit model, the absorption delay is described as a drug transition through one or a chain of compartments that are linked to the central compartment (22). The latter approach in which the absorption rate gradually increases was found to adequately describe the observed profile of nadroparin in blood over time and proved superior over a lag time model.

In the current study, we incorporated baseline anti-Xa activity into the structural model of nadroparin in both non-obese and morbidly obese patients. The activity of clotting factor Xa is generally used as a surrogate concentration measure as LMWH are mixture of substances (33) and therefore a kinetic assessment is complicated. It is known however that (low) endogenous anti-Xa activity may be present without the use of LMWH. While it is anticipated that this endogenous anti-Xa is due to the heparan sulfates that originate from the endothelial (34), basal activity is not often reported, even though a basal activity is obviously present in some of the reports (35-37). Although interindividual variability of BLS values was large for the entire population of morbidly obese and non-obese patients, the incorporation of a BLS as suggested by Schoemaker et al. (16) and which was also reported for tinzaparin (24), resulted in an improved description of the observations in our study.

Since there are no reports available indicating a reduced biological availability of LMWH in obese patients (38, 39), it may be anticipated that the increased apparent clearance observed in morbidly obese patients compared with non-obese patients is caused by an increased glomerular filtration in morbidly obese patients (40). Creatinine levels and age have been suggested before as covariates for anti-Xa levels after tinzaparin administration (24). In our study, we could not identify any influence of these covariates, possibly due to the small in range of age and creatinine levels.

As stated before, measurement of anti-Xa levels is recommended in morbidly obese patients (41, 42) in absence of established dosing protocols for LMWH for these patients. Reports on these anti-Xa levels show that almost half of the morbidly obese patients exhibit anti-Xa levels below the prophylactic range for non-obese patients 0.2 - 0.5 IU/mL (19), suggesting that increased doses might be necessary. From the current study it seems that 5,700 IU (0.6 ml) nadroparin is appropriate for morbidly obese patients up to a LBW of 90 kg, while for morbidly obese patients with a LBW higher than 90 kg a larger dose of 7,600 IU (0.8 ml) is needed. This dosing regimen based on LBW should be explored as it aims for at least the same anti-Xa levels as non-obese patients (0.2 - 0.5 IU/mL (27)) while it is known that morbidly obese patients are at increased risk for VTE (4). The current pharmacodynamic model can be used even when in the future new target anti-Xa levels are established for thromboprophylaxis for this special group of patients. Therefore, it is advised to carefully monitor morbidly obese patients on bleedings and thrombotic events, as the exact relationship between anti-Xa levels and the occurrence of bleedings or VTE may not be known (43, 44).

Conclusion

In this study, we have developed a pharmacodynamic model for LMWH nadroparin using anti-Xa levels as endpoint in both morbidly obese and non-obese patients for a total body weight range from 72 kg until 252 kg. In the structural model, baseline anti-Xa activity was incorporated and the observed delayed effect of anti-Xa levels was described with a transit compartment. Based on the data available here, it appeared that clearance scaled with total body weight while lean body weight proved the major determinant for volume of distribution. Based on simulations using the final covariate pharmacodynamic model it appeared that a dose of 5,700 IU nadroparin will lead to target anti-Xa levels in morbidly obese patients with a LBW below 90 kg.

References

1.Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. Jama. 2006;295(13):1549-55.
2.Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373(9669):1083-96.
3.WorldHealthOrganisation. Obesity: Preventing and Managing the Global Epidemic. Geneva: World Health Organisation, 1997.
4.Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. Am J Med. 2005;118(9):978-80. Epub 2005/09/17.
5.Stein PD, Matta F, Goldman J. Obesity and pulmonary embolism: The mounting evidence of risk and the mortality paradox. Thromb Res. 2011.
6.Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, et al. Evidence-Based Management of Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e152S-84S.
7.Rondina MT, Wheeler M, Rodgers GM, Draper L, Pendleton RC. Weight-based dosing of enoxaparin for VTE prophylaxis in morbidly obese, medically-Ill patients. Thromb Res. 2010;125(3):220-3.
8.Singh K, Podolsky ER, Um S, Saba S, Saeed I, Aggarwal L, et al. Evaluating the safety and efficacy of BMI-based preoperative administration of low-molecular-weight heparin in morbidly obese patients undergoing Roux-en-Y gastric bypass surgery. Obes Surg. 2012;22(1):47-51.
9.Borkgren-Okonek MJ, Hart RW, Pantano JE, Rantis PC, Jr., Guske PJ, Kane JM, Jr., et al. Enoxaparin thromboprophylaxis in gastric bypass patients: extended duration, dose stratification, and antifactor Xa activity. Surg Obes Relat Dis. 2008;4(5):625-31.
10.Kalfarentzos F, Stavropoulou F, Yarmenitis S, Kehagias I, Karamesini M, Dimitrakopoulos A, et al. Prophylaxis of venous thromboembolism using two different doses of low-molecular-weight heparin (nadroparin) in bariatric surgery: a prospective randomized trial. Obes Surg. 2001;11(6):670-6.
11.Kiang TK, Sherwin CM, Spigarelli MG, Ensom MH. Fundamentals of population pharmacokinetic modelling: modelling and software. Clin Pharmacokinet. 2012;51(8):515-25.
12.Barras MA, Duffull SB, Atherton JJ, Green B. Modelling the occurrence and severity of enoxaparin-induced bleeding and bruising events. Br J Clin Pharmacol. 2009;68(5):700-11.
13.Hulot JS, Vantelon C, Urien S, Bouzamondo A, Mahe I, Ankri A, et al. Effect of renal function on the pharmacokinetics of enoxaparin and consequences on dose adjustment. Ther Drug Monit. 2004;26(3):305-10.
14.Hulot JS, Montalescot G, Lechat P, Collet JP, Ankri A, Urien S. Dosing strategy in patients with renal failure receiving enoxaparin for the treatment of non-ST-segment elevation acute coronary syndrome. Clin Pharmacol Ther. 2005;77(6):542-52.
15.Green B, Greenwood M, Saltissi D, Westhuyzen J, Kluver L, Rowell J, et al. Dosing strategy for enoxaparin in patients with renal impairment presenting with acute coronary syndromes. Br J Clin Pharmacol. 2005;59(3):281-90.
16.Berges A, Laporte S, Epinat M, Zufferey P, Alamartine E, Tranchand B, et al. Anti-factor Xa activity of enoxaparin administered at prophylactic dosage to patients over 75 years old. Br J Clin Pharmacol. 2007;64(4):428-38.
17.Green B, Duffull SB. Development of a dosing strategy for enoxaparin in obese patients. Br J Clin Pharmacol. 2003;56(1):96-103.
18.Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-65.
19.Diepstraten J, Hackeng CM, Van Kralingen S, Zapletal J, Van Dongen EP, Wiezer MJ, et al. Anti-Xa levels 4 hours after subcutaneous administration of 5700 IU nadroparin strongly correlate with lean body weight in morbidly obese patients. Obes Surg. 2012;Epub 1 feb.
20.Beal SL, Sheiner LB, Boeckmann A. NONMEM user's guide. San Francisco: University of California; 1999.
21.Comets E, Brendel K, Mentre F. Computing normalised prediction distribution errors to evaluate nonlinear mixed-effect models: the npde add-on package for R. Comput Methods Programs Biomed. 2008;90(2):154-66.
22.Savic RM, Jonker DM, Kerbusch T, Karlsson MO. Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. J Pharmacokinet Pharmacodyn. 2007;34(5):711-26.
23.Schoemaker RC, Cohen AF. Estimating impossible curves using NONMEM. Br J Clin Pharmacol. 1996;42(3):283-90.
24.Barrett JS, Gibiansky E, Hull RD, Planes A, Pentikis H, Hainer JW, et al. Population pharmacodynamics in patients receiving tinzaparin for the prevention and treatment of deep vein thrombosis. Int J Clin Pharmacol Ther. 2001;39(10):431-46.
25.Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. Ann Pharmacother. 2000;34(9):1066-9. Epub 2000/09/12.
26.Anderson BJ, Holford NH. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet. 2009;24(1):25-36.
27.Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother. 2009;43(6):1064-83.
28.Lemmens HJ, Bernstein DP, Brodsky JB. Estimating blood volume in obese and morbidly obese patients. Obes Surg. 2006;16(6):773-6.
29.Barras MA, Duffull SB, Atherton JJ, Green B. Individualized compared with conventional dosing of enoxaparin. Clin Pharmacol Ther. 2008;83(6):882-8.
30.Feng Y, Green B, Duffull SB, Kane-Gill SL, Bobek MB, Bies RR. Development of a dosage strategy in patients receiving enoxaparin by continuous intravenous infusion using modelling and simulation. Br J Clin Pharmacol. 2006;62(2):165-76.
31.Green B, Duffull S. Caution when lean body weight is used as a size descriptor for obese subjects. Clin Pharmacol Ther. 2002;72(6):743-4.
32.Eleveld DJ, Proost JH, Absalom AR, Struys MM. Obesity and allometric scaling of pharmacokinetics. Clin Pharmacokinet. 2011;50(11):751-3.
33.Samama MM, Gerotziafas GT. Comparative pharmacokinetics of LMWHs. Semin Thromb Hemost. 2000;26 Suppl 1:31-8.
34.Bourin MC, Lindahl U. Glycosaminoglycans and the regulation of blood coagulation. Biochem J. 1993;289 (Pt 2):313-30. Epub 1993/01/15.
35.Hainer JW, Barrett JS, Assaid CA, Fossler MJ, Cox DS, Leathers T, et al. Dosing in heavy-weight/obese patients with the LMWH, tinzaparin: a pharmacodynamic study. Thromb Haemost. 2002;87(5):817-23.
36.Siguret V, Pautas E, Fevrier M, Wipff C, Durand-Gasselin B, Laurent M, et al. Elderly patients treated with tinzaparin (Innohep) administered once daily (175 anti-Xa IU/kg): anti-Xa and anti-IIa activities over 10 days. Thromb Haemost. 2000;84(5):800-4.
37.Harenberg J, Jeschek M, Acker M, Malsch R, Huhle G, Heene DL. Effects of low-molecular-weight dermatan sulfate on coagulation, fibrinolysis and tissue factor pathway inhibitor in healthy volunteers. Blood Coagul Fibrinolysis. 1996;7(1):49-56.
38.Frydman A. Low-molecular-weight heparins: an overview of their pharmacodynamics, pharmacokinetics and metabolism in humans. Haemostasis. 1996;26 Suppl 2:24-38.
39.Sanderink GJ, Le Liboux A, Jariwala N, Harding N, Ozoux ML, Shukla U, et al. The pharmacokinetics and pharmacodynamics of enoxaparin in obese volunteers. Clin Pharmacol Ther. 2002;72(3):308-18.
40.Ribstein J, du Cailar G, Mimran A. Combined renal effects of overweight and hypertension. Hypertension. 1995;26(4):610-5.
41.Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3 Suppl):188S-203S.
42.Harenberg J. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? Yes. J Thromb Haemost. 2004;2(4):547-50.
43.Paige JT, Gouda BP, Gaitor-Stampley V, Scalia PG, Klainer TE, Raum WJ, et al. No correlation between anti-factor Xa levels, low-molecular-weight heparin, and bleeding after gastric bypass. Surg Obes Relat Dis. 2007;3(4):469-75.
44.Bounameaux H, de Moerloose P. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? No. J Thromb Haemost. 2004;2(4):551-4.