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PHARMACOKINETICS OF ENOXAPARIN IN COVID-19 CRITICALLY ILL PATIENTS

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Authors' contributions:

- Contributed substantially to the conception and design of the study (PJZ, XD) the acquisition of data (AD, JL, AB, LJ, LL) or the analysis (XD, SS) and interpretation (XD, PZ) of the data
- Drafted (PZ, XD) or provided critical revision of the article (all other authors)
- Provided final approval of the version submitted for publication (all authors)

Take-home message: Despite low-molecular weight thromboprophylaxis, ICU COVID-19 patients are at high risk of venous thrombosis. This pharmacokinetic study indicates that exposure to enoxaparin in this special population is decreased. Randomized trials are required to evaluate the benefit of an increase dosage of enoxaparin.

Tweet: a pharmacokinetic study indicates that exposure to enoxaparin is decreased in ICU COVID-19 patients.

ABSTRACT

Purpose

In intensive-care unit (ICU) patients, pathophysiological changes may affect the pharmacokinetics of enoxaparin and result in underdosing. The aim of this study was to develop a pharmacokinetic model of enoxaparin to predict the time-exposure profiles of various thromboprophylactic regimens in COVID-19 ICU-patients.

Methods

Anti-Xa activities from consecutive ICU-patients with laboratory-confirmed SARS-CoV-2 infection treated by enoxaparin for the prevention or the treatment of venous thrombosis were used to develop a population pharmacokinetic model using non-linear mixed effects techniques. Monte Carlo simulations were then performed to predict enoxaparin exposure at steady-state after three days of administration.

Results

A total of 391 anti-Xa samples were measured in 95 patients. A one-compartment model with first-order kinetics best fitted the data. The covariate analysis showed that enoxaparin clearance was related to renal function estimated by the CKD-EPI formula and volume of distribution to actual body weight. Simulations indicated that compared to enoxaparin 40 mg qd in medical patients, enoxaparin 30 mg bid in ICU COVID-19 patients achieved similar 24-hour area under the plasma concentration–time curve values while therapeutic dose anticoagulation increased median exposure by 2.8 fold.

Conclusion

To achieve exposures similar as those expected in non-ICU non-COVID-19 patients a 50 percent increase in dose administration is required.

INTRODUCTION

Patients with COVID-19 are at a high risk of venous thromboembolism despite the use of thromboprophylaxis. [1] The rates of thrombotic complications have been found to be higher in COVID-19 patients admitted to intensive care units (ICU) compared to ICU non-COVID-19 patients and to non-ICU hospitalized COVID-19 patients. [2] Only few data are available supporting thromboprophylaxis regimen in ICU and guidelines highlight the need for future studies. [3] Furthermore in overweight and obese patients weight-adapted guidelines are also lacking. In this context, a number of European guidelines have suggested for COVID-19 ICU-patients to increase the usual recommended dose for thromboprophylaxis in ICU (e.g. enoxaparin 40 mg once-daily) [4] with intermediate-dose low-molecular-weight heparin (e.g. enoxaparin 0.5 mg/kg twice-daily or enoxaparin 40 mg twice-daily). [5] [6] [7] [8] On the contrary, the American College of Chest Physicians and the American Society of Hematology Guidelines Panel have recommended to maintain their prophylactic dose anticoagulation recommendation for ICU patients (e.g. enoxaparin 30 mg twice-daily) because of the potential concern of a higher odds of major bleeding with intermediate or therapeutic dose anticoagulation. [9] [10]

In ICU-patients, pathophysiological changes impact on pharmacokinetics of mainly hydrophilic drugs such as low-molecular-weight heparins and often lead to underdosing. [11] After low-molecular-weight heparin administration, ICU-patients show lower anti-Xa activities compared with medical ward patients. [12] [13] Similar findings have recently been found in COVID-19 patients. [14]. These data suggest that previous population pharmacokinetic analysis of enoxaparin in non-ICU patients would predict inaccurate anti-Xa activities in COVID-19 ICU-patients. [15]

The aim of this study was to develop a population pharmacokinetic model of enoxaparin in COVID-19 ICU-patients to predict the time-exposure profiles of various thromboprophylactic regimens in COVID-19 ICU-patients.

PATIENTS AND METHODS

Study overview

This retrospective multicenter cohort study was conducted from 03/13/2020 to 03/31/2020 in all consecutive patients with laboratory-confirmed SARS-CoV-2 infection treated by enoxaparin for the treatment or the prevention of venous thrombosis and hospitalized in the ICUs of Lille and Saint-Etienne University Hospitals. The study was approved by the institutional review board [IRBN502020/CHUSTE for Saint-Etienne, France and ID-CRB-2020-A00763-36 for Lille, France]. Enoxaparin dose regimens and dosing adjustments were at the discretion of the intensive care physicians in charge of the patients. As the study took place at the beginning of the COVID-19 pandemic in France, local guidelines for the administration of enoxaparin were not implemented. Schematically, doses for thromboprophylaxis were 40 mg once daily at the beginning of the study and were increased throughout the study to intermediate dose (40 or 60 mg twice daily) after French proposals for preventing venous thrombosis in hospitalized patients with COVID-19.[5] Patients with asymptomatic deep venous thrombosis or asymptomatic pulmonary embolism were fully anticoagulated. Subjects were not eligible for inclusion in the study if they were treated with a non-vitamin K oral anticoagulant or unfractionated heparin prior to the administration of enoxaparin as these anticoagulants could have interfered with the dosing of the enoxaparin anti-Xa activity.

Data collection

Data were extracted from electronic medical records trial with respect to the characteristics of the trial participants at ICU admission (age, weight, height, gender, Sequential Organ Failure Assessment (SOFA) score, [16] World Health Organization Ordinal Scale for Clinical Improvement (OSCI), [17] renal function estimated by the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation [18] and the Cockcroft and Gault formula [19], D-Dimer and fibrinogen) and to enoxaparin anti-Xa activities. As low molecular weight heparin plasma concentration cannot easily be measured, anti-Xa activity was considered as a surrogate for enoxaparin concentration. Blood samples were collected routinely throughout treatment. Venous blood was collected in sodium-citrate tubes (0.109 M). After centrifugation (15 min, 2500 g), plasma was stored at -80°C . Anti-Xa levels were measured in

plasma using a chromogenic anti-Xa activity (STA-Liquid Anti-Xa, Diagnostica Stago, Biophen Heparin LRT, HYPHEN BioMed) on STA-R system (Diagnostica Stago). Intra and inter assay coefficient of variation was 3.1% and 6%, respectively. The lower limit of quantification of the assay was 0.05 IU.mL^{-1} , and linearity was demonstrated over the range of $0.05\text{--}1.75 \text{ IU.mL}^{-1}$. We also extracted outcomes related to enoxaparin administration: Venous thromboembolic events occurring during hospitalisation (pulmonary embolism, deep venous thrombosis or catheter related thrombosis) which had to be objectively confirmed and major bleedings occurring during low-molecular-weight thromboprophylaxis through 72 hours after the last dose was administered. [20]

Population Pharmacokinetic analysis

Enoxaparin anti-Xa activities values were analysed using the following nonlinear mixed-effect model framework:

$$aXa_{i,j} = f(t_{i,j}, \varphi_i) + \left(a_{PK} + b_{PK} \times f(t_{i,j}, \varphi_i) \right) \times \varepsilon_j$$

Where $aXa_{i,j}$ is the observed anti-Xa activity for patient i , at time j . The functions $f(t_{i,j}, \varphi_i)$ correspond to the anti-Xa activity returned by the models for patient i , at time j with the individual parameters φ_i . Parameters a_{PK} and b_{PK} are the constant and proportional parts of the error model with $\varepsilon_j \sim N(0,1)$.

Data were analysed using MONOLIX, a non-linear mixed effects modelling software (MonolixSuite 2020) using the SAEM algorithm. [21] The parameters of the model were assumed to be log-normally distributed. Data below the lower limit of quantification were simulated in a right-truncated Gaussian distribution using the SAEM algorithm. [22] The model was built using a stepwise procedure, initially identifying the best structural model and then the effect of covariates on enoxaparin exposure were evaluated. The covariates tested were total body weight, lean body weight, [23] age, height, sex, renal function (estimated by the Cockcroft & Gault and CKD-EPI formula) and disease severity scores (SOFA and OSCI score). Continuous covariates were tested with allometric scaling according to the following equation, using volume of distribution (V) as an example:

$$\log(V_{i,\cdot}) = \log(V_{pop}) + \beta_{BW}^V \times \log\left(\frac{BW_i}{70}\right) + \eta_i^V$$

where V_i denote the volume of distribution of compartment of patient i ; V_{pop} the typical volume of distribution; BW_i the bodyweight of patient i . Parameters η_i^V represent the between subject variability of parameter V of patient i . The parameter β_{BW}^V corresponds to the regression coefficient. The regression coefficient of size descriptor was fixed at 0.75 and 1 for clearance (Cl) and V parameters, respectively.[24]

Categorical covariates (disease severity scores, sex) were tested using the following equation, using clearance (Cl) as an example:

$$\log(Cl_i) = \log(Cl_{pop}) + \begin{cases} \beta 1_{SOFA=1}^{cl} \\ \beta 2_{SOFA=2}^{cl} + \eta_i^{cl} \\ \beta n_{SOFA=n}^{cl} \end{cases}$$

where Cl_i denote the clearance of patient i ; Cl_{pop} the typical Clearance; Parameters η_i^{cl} represent the between-subject variability of parameter Cl of patient i . The parameter $\beta 1_{SOFA=1}^{cl}$ corresponds to the regression coefficient for SOFA score equal to 1. The parameter $\beta 2_{SOFA=2}^{cl}$ corresponds to the regression coefficient for SOFA score equal to 2. The parameter $\beta n_{SOFA=n}^{cl}$ corresponds to the regression coefficient for SOFA score equal to n .

The statistical significance of covariate was individually assessed during the stepwise procedure at the $p < 0.001$ level. Model evaluation and selection were based on visual inspection of the goodness-of-fit plots, the precision of parameter estimates, and the decrease in objective function (calculated by importance sampling). The prediction-corrected visual predictive check (pcVPC) was generated by simulating 1000 times datasets using the model of interest and the design of the observed data. [25] The ability of the model to describe the observations was evaluated by visual inspection of the distribution of the simulated concentrations. The median parameter values and the 90% prediction interval of the pcVPC replicates were compared with the observations comprising the original dataset.

Simulations

From the variance-covariance matrix of the estimated pharmacokinetic parameters of the final pharmacokinetic model, Monte Carlo simulations were performed using Simulx software (MonolixSuite 2020). A total of 200 individuals were generated using the patient's characteristics of the study.

The time-exposure profiles for the following enoxaparin regimen were simulated for 3 days:

enoxaparin 40 mg once-daily (qd), enoxaparin 30 mg twice-daily (bid), enoxaparin 40 mg bid, enoxaparin 0.5 mg.kg⁻¹ bid and enoxaparin 1 mg.kg⁻¹ bid.

To compare enoxaparin exposure in COVID-19 ICU patients with non COVID-19 non-ICU patients, the pharmacokinetic model developed by Berges et al. [26] was used to simulate anti-Xa activities in medical patients receiving enoxaparin 40 mg qd for 3 days.

Individual predicted enoxaparin exposure markers at steady state, after three days of administration, were calculated for each dosage regimen. These markers comprised the 24-hour area under the plasma concentration–time curve (AUC_{d3}) and the maximum plasma concentration ($C_{max_{d3}}$).

RESULTS

Patients

From February to April 2020, 95 confirmed COVID-19 ICU patients had at least one dose of enoxaparin and one anti-Xa measurement. The characteristics of these patients are presented in Table 1. On admission in ICU, patients had a mean (\pm SD) weight of 88 ± 17 kg, 40% had a body mass index above 30 kg.m^{-2} . The mean (\pm SD) estimated glomerular filtration rate (CKD-EPI formula) was $87 \pm 22 \text{ mL.min}^{-1}$, 14% of the subjects had moderate or severe renal failure (CKD-EPI $<60 \text{ mL.min}^{-1}$). The mean (\pm SD) SOFA score was 4.6 ± 2.7 , 47% of the patients required invasive mechanical ventilation. Intermediate-intensity or therapeutic-intensity anticoagulation (enoxaparin > 60 mg per day) was administered to 64 percent of the patients on admission in ICU. During hospitalisation venous thromboembolic events occurred in 25 patients (26%), twenty patients were diagnosed with pulmonary embolism. Major bleeding during low-molecular-weight thromboprophylaxis occurred in three patients (3.2%)

Data sampled

A total of 391 anti-Xa samples were measured for the 95 patients analysed. The number of measurements per patient ranged from 1 to 13. A total of 24 anti-Xa (6.1%) were below the limit of quantification.

Population PK analysis

A one-compartment model with first-order absorption best described the pharmacokinetics of enoxaparin in ICU COVID-19 patients. The model was parameterized in terms of apparent clearance (Cl), apparent volume of distribution (V) and absorption rate constant (Ka).

Intersubject variabilities were estimated for Cl and V. A proportional error model provided the best results for residual variability. Among the covariates, actual body weight was found to have a statistically significant effect on V. It also appeared that enoxaparin clearance was significantly related to renal function estimated by the CKD-EPI formula. The regression coefficient of body weight was fixed to 1 for V. Estimates of the population pharmacokinetic parameters are presented in Table 2. The typical clearance and volume of distribution for a patient with a glomerular filtration rate of 87 mL.min^{-1} and an actual body weight of 88 kg were 1.1 L.h^{-1} and 17.9 L respectively.

Model validation

The goodness-of-fit plots of the final models are presented in Figure 1. The data exhibited no apparent bias in model predictions. According to the pcVPC (supplementary data), the average observed values were well predicted. Only extreme profiles were not within 90% of the simulated values, demonstrating good predictive capacity of the models.

Simulations

Derived from the equations of the pharmacokinetic model and covariates distribution, simulations were performed to estimate the time-exposure profiles of enoxaparin for different dosing regimens. These simulations are presented in Figure 2 and indicate for a standard dose a lower exposure profile for ICU COVID-19 patients compared to medical non-COVID-19 patients.

For enoxaparin 40 mg qd, the median (90 percent predicted interval) AUC_{d3} was 3.35 (1.76 to 6.16) $IU.h.mL^{-1}$ and 5.15 (3.29 to 8.54) $IU.h.mL^{-1}$ in ICU COVID-19 patients and medical non-COVID-19 patients respectively (table 3). Compared to enoxaparin 40 mg qd in medical patients, enoxaparin 30 mg bid in ICU COVID-19 patients achieved similar AUC_{d3} values while therapeutic dose anticoagulation increased median exposure by 2.8 fold (table 3). At steady state, $C_{max_{d3}}$ values with intermediate dose anticoagulation in ICU COVID-19 patients did not exceed the range of predicted $C_{max_{d3}}$ values in medical patients with a prophylactic dose.

DISCUSSION

To our knowledge, this is the first study to evaluate the pharmacokinetic of enoxaparin in ICU COVID-19 patients using a population approach model. The analysis showed that the pharmacokinetic for subcutaneous enoxaparin was adequately described by a one-compartment model with first-order elimination. The mean volume of distribution and clearance were estimated to be 17.9 L and 1.1 L.h⁻¹, respectively. These values contrast with those described previously in non-ICU patients.[15] The clearance value was in the higher range but the volume of distribution value was outside of the normal range and increased by approximately 1.5 to 2 fold. Thus for a normalized dose of enoxaparin, exposition in ICU COVID-19 patients will be reduced compared to non-ICU non-COVID-19 patients. This discrepancy between ICU and non-ICU patients has previously been observed in non-COVID patients [12] [13] and recently in COVID-19 patients, [14] suggesting that the high values of CL and V in our study are more related to the severity of the illness rather than the illness itself. The pathophysiological changes in critically ill patients (third spacing from increase vascular permeability and reduce oncotic pressure) and the administration of fluid resuscitation to maintain blood perfusion all contribute to an increase in the volume of distribution of hydrophilic drugs such as low-molecular-weight heparins. [11] In ICU patients, the use of vasopressors and the presence of oedema have both been associated with lower enoxaparin anti-Xa activities. [12] [27] These findings could be due to an increase in the volume of distribution but also to a decrease of subcutaneous absorption of enoxaparin due to cutaneous vasoconstriction or edema. Enoxaparin is partially eliminated by the kidney and requires dose adjustment in case of renal impairment. [28] [29] Acute kidney injury occurs in 10 percent of all hospitalized COVID-19 patients and 4 percent will require renal replacement therapy. [30] However one study has reported that 38 percent of their ICU COVID-19 patients had augmented renal clearance. [31] Augmented renal clearance is related to an increased cardiac output and lower systemic vascular resistance which has been observed in mechanically-ventilated COVID-19 patients [32] and may have contributed to the high values of enoxaparin clearance observed in our pharmacokinetic model.

The covariate analysis showed that enoxaparin volume of distribution was related to total body weight and clearance to CKD-EPI. The identification of these two covariates as sources of variability is in accordance with population pharmacokinetic studies of enoxaparin in non-

ICU patients. [15] A previous study recommended in obese patients to adjust therapeutic dose of enoxaparin to lean body weight. [33] We did not find that the use of this body size descriptor improved model fitting compared to total body weight probably because our study did not include patients with a range of body weights that was large enough, although a high proportion of obese patients were included. It has also been proposed to adjust enoxaparin administration to renal function using the Cockcroft and Gault equation, with ideal body weight used as the size descriptor. [29] Yet, in ICU patients, estimated glomerular filtration rate formulas are imprecise in assessing creatinine clearance with CKD-EPI being the less inaccurate formula. [34] The inter-individual variability of the final model for V and CL was high. This suggests that in the population in which the model was developed, adjusting dose to total body weight or to CKD-EPI values would have very little impact. This is illustrated by the similar time-exposure profiles of enoxaparin 40 mg bid with enoxaparin 0.5 mg.kg⁻¹ bid (figure 2).

To explore the time-exposure profile of enoxaparin in ICU COVID-19 patients, we simulated various regimens encompassing regimens recommended in non COVID-19 ICU patients (40 mg qd and 30 mg bid), suggested intermediate regimens for COVID-19 ICU patients (40 mg bid, 0.5 mg.kg⁻¹ bid) and a therapeutic dose anticoagulation currently investigated in COVID-19 ICU patients (1 mg.kg.m⁻¹ bid). We also simulated, the thromboprophylactic regimen recommended for prophylaxis in medical patients (40 mg qd) using a pharmacokinetic model that was developed in non-COVID ward patients. [26] The results indicated that to achieve enoxaparin exposure profiles in ICU COVID-19 patients similar to those in medical non-COVID-19 patients, a 50 percent increase in dose administration was required. There is however no clear relationship between anti-Xa activities and the efficacy or safety of low-molecular-weight heparin thromboprophylaxis. [35] At present no target or range of anti-Xa activities can be recommended in particular in COVID-19 patients. The simulation in medical patients was for illustrative purposes only.

In non-COVID-19 critically ill patients, low-molecular-weight heparins reduce the risk of deep venous thrombosis without significantly increasing the risk of major bleeding.[36] The dose of enoxaparin studied in these patients was 40 mg qd or 30 mg bid. As the rates of thrombotic complications have been found to be higher in COVID-19 patients admitted to intensive care units (ICU) compared to ICU non-COVID-19 patients, [2] an increase in the dosage of enoxaparin has been proposed [5] [6] [7] [8] but this could expose patients to an

increase of bleeding events. The ongoing randomized clinical trials in COVID-19 patients will provide valuable information on the optimal dose for thromboprophylaxis.

This study has several limitations. The capacity of the model to predict exposures in patients that differ from our study is unknown. In particular, great care should be taken in patients above 120 kg and in those that develop acute kidney injury. The covariates tested in our model were those observed at ICU admission. We did not consider time-varying covariates. In ICU, patient's condition may change quickly.[37] This could explain the relative high unexplained inter-individual variability of the final covariate model and that the disease severity scores (SOFA and OSCI score) did not improve model predictions. Finally, thromboprophylaxis was not standardized (thromboprophylaxis regimen could vary for an individual and vary between individuals) and screening for venous thromboembolic events was not protocolized (chest CT-scan at admission and doppler venous ultrasound during ICU stay were not mandatory). This precluded any PK/PD analysis.

Conclusion

Exposure to enoxaparin in ICU COVID-19 patients is reduced due to an increase in the volume of distribution and clearance. To achieve exposures similar as those expected in non-ICU non-COVID-19 patients a 50 percent increase in dose administration is required.

Table 1 Characteristics of the patients at admission to the Intensive Care Unit

Data was unavailable for 5 (#) and 1 (&) patients

Number of patients		95
Sex-no. (%)	Female	22 (23%)
Age-yr	Mean \pm SD	63 \pm 11
	Min - Max	29 - 82
Weight-kg	Mean \pm SD	88 \pm 17
	Min - Max	55 - 150
Body Mass Index-kg.m ⁻² #	\geq 30	36 (40%)
Ordinal Scale for Clinical Improvement &	4	33 (35%)
	5	17 (18%)
	6	27 (29%)
	7	17 (18%)
Sequential Organ Failure Assessment score	Mean \pm SD	4.6 \pm 2.7
	Min - Max	1 - 12
Chronic Kidney Disease-Epidemiology Collaboration equation-mL.min ⁻¹	Mean \pm SD	87 \pm 22
	Min - Max	14 - 138
D-Dimer-ng.ml ⁻¹	Mean \pm SD	3047 \pm 3651
	Min - Max	0 - 20,000
Fibrinogen-g.l ⁻¹	Mean \pm SD	6.9 \pm 1.6
	Min - Max	2.8 - 11
Enoxaparin regimen	Prophylactic \leq 60 mg qd	34 (36%)
	Intermediate 40 or 60 mg bid	36 (38%)
	Full dose 1 mg.kg ⁻¹ bid	25 (26%)

Table 2. Pharmacokinetic parameters

Parameters	Value	IIV
Ka (h ⁻¹)	0.48	
Cl (L.h ⁻¹) = $\theta_1 \times (\text{eGFR}/87)^{\theta_2}$		0.40
θ_1	1.1	
θ_2	0.18	
V (L) = $\theta_3 \times (\text{Wt}/85)$		0.44
θ_3	17.9	
σ^2 proportional (CV%)	0.28	

Ka, absorption rate constant; CL, clearance; V, volume of distribution; eGFR, estimated glomerular function rate (mL.min⁻¹) according to the CKD-EPI formula; Wt, actual body weight (kg); σ^2 , residual variance; IIV, inter-individual variability.

Table 3 Enoxaparin exposure markers at steady state

The predicted enoxaparin exposure markers at steady state, after three days of administration were simulated using the model presented in this study for COVID-19 ICU patients and using the model developed by Berges *et al.* [26] for non-COVID-19 medical patients. AUC_{d3}, area under the plasma concentration–time curve at day 3; Cmax_{d3}, maximum plasma concentration on day 3.

enoxaparin regimen	AUC _{d3} IU.h.mL-1 median [90% prediction interval]	Cmax _{d3} IU.mL-1 median [90% prediction interval]
COVID-19 ICU patients		
enoxaparin 40 mg qd	3.35 [1.76 – 6.16]	0.22 [0.13 – 0.37]
enoxaparin 30 mg bid	4.93 [2.69 – 8.80]	0.25 [0.14 – 0.42]
enoxaparin 40 mg bid	6.54 [3.59 – 11.90]	0.33 [0.19 – 0.57]
enoxaparin 0.5 mg/kg bid	7.17 [3.54 – 13.18]	0.36 [0.20 – 0.63]
enoxaparin 1 mg/kg bid	14.60 [7.41 – 26.76]	0.72 [0.41 – 1.27]
Non COVID-19 medical patients		
enoxaparin 40 mg qd	5.15 [3.29 – 8.54]	0.45 [0.31 – 0.68]

LEGEND to FIGURES

Figure 1: goodness-of-fit plots of the final model

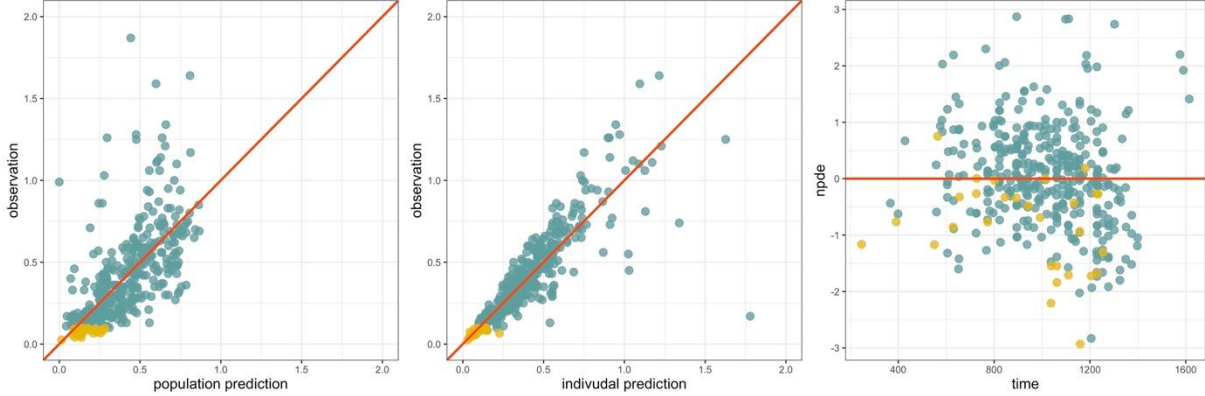
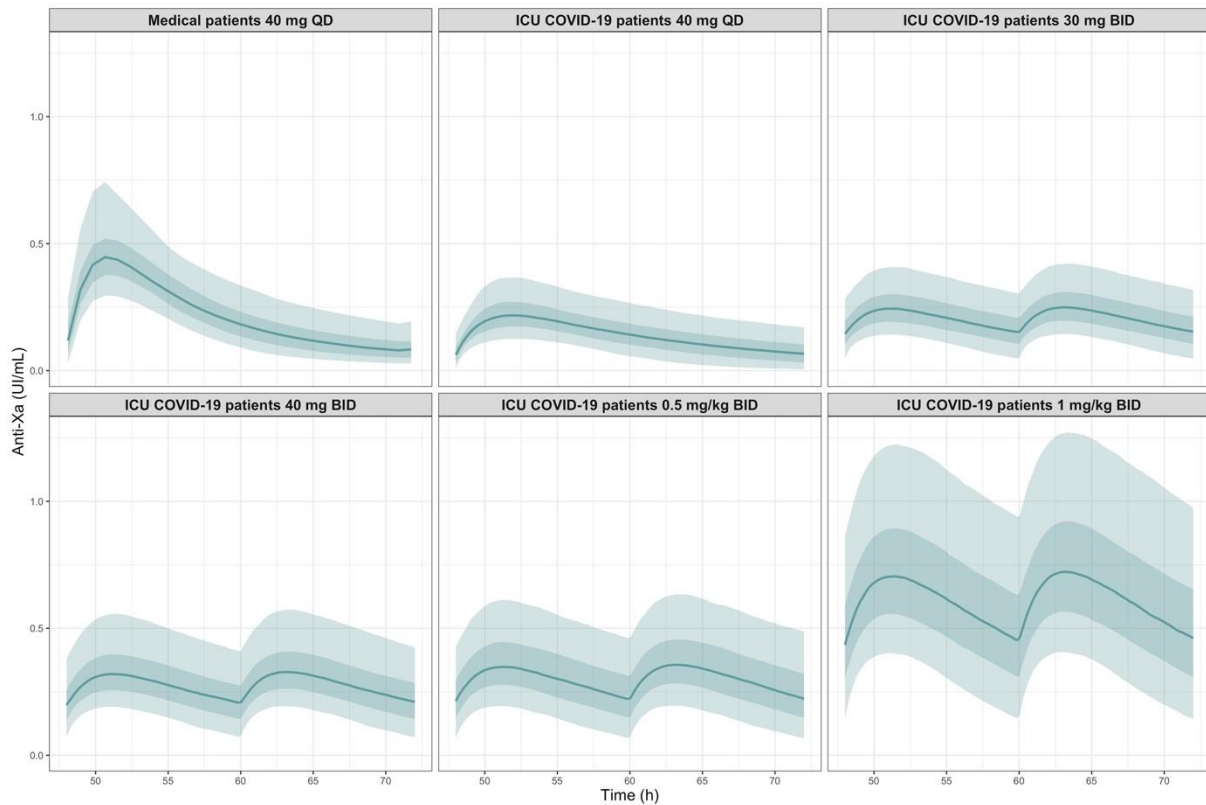


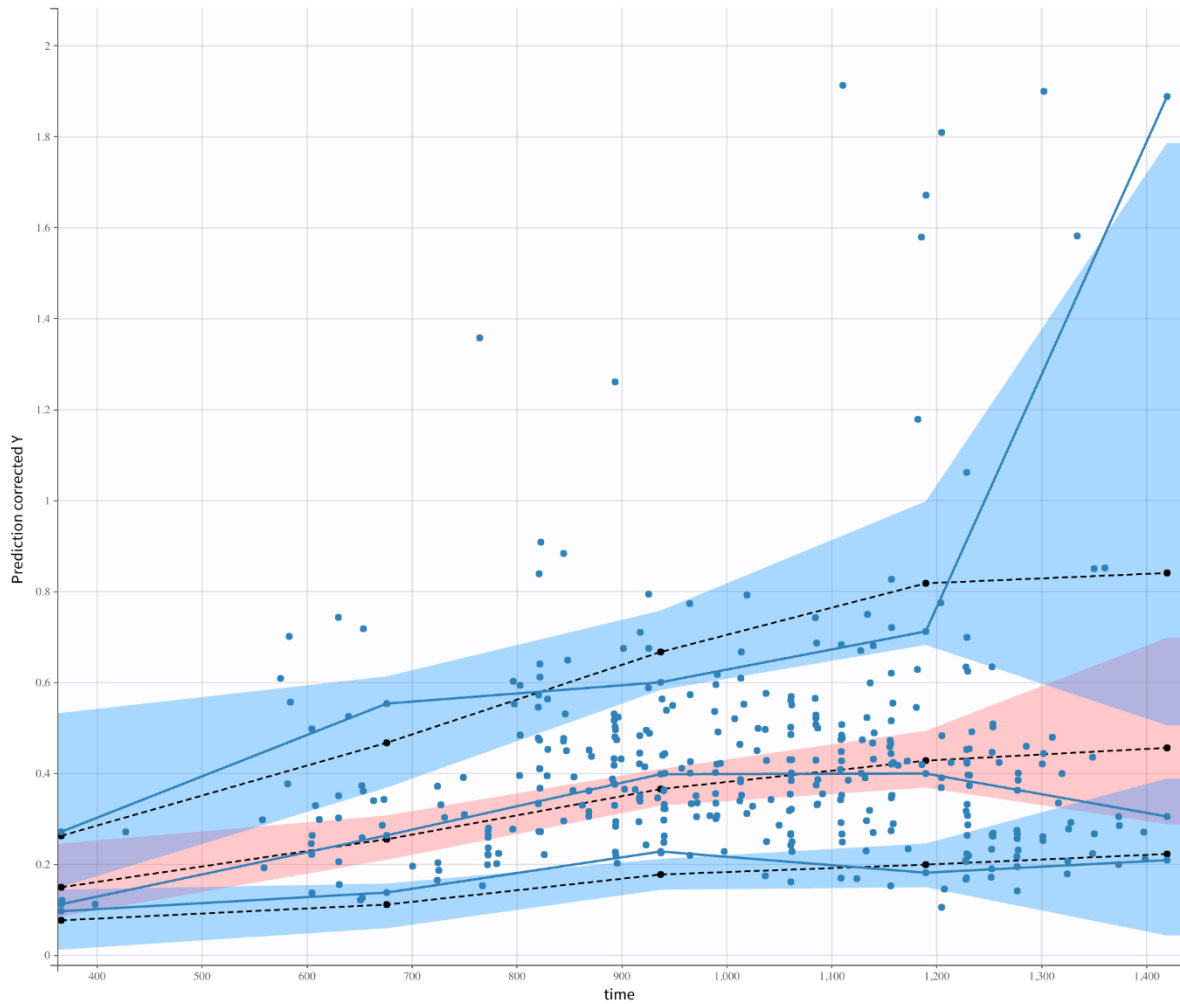
Figure 2: pharmacokinetic simulation of enoxaparin exposure on day 3.

The time-exposure profiles of enoxaparin were simulated using (1) the pharmacokinetic model developed by Berges et al. (16) for medical patients and (2) using the pharmacokinetic model presented in this study for COVID-19 ICU patients. The solid line represents the predicted median exposure, the dark shaded area represents the 50% prediction interval and the light interval the 90% prediction interval



Supplementary data: prediction-corrected visual predictive check.

The black dash curve represents the 5, 50 and 95 empirical observed percentiles. The red and blue shaded envelope represents the prediction interval for the simulations of 5, 50 and 95 percentiles. The blue dots represent the observed enoxaparin activities.



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