Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Pharmacokinetics of enoxaparin in COVID-19 critically ill patients

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ABSTRACT

Background: In intensive-care unit (ICU) patients, pathophysiological changes may affect the pharmacokinetics of enoxaparin and result in underdosing.
Objectives: To develop a pharmacokinetic model of enoxaparin to predict the time-exposure profiles of various thromboprophylactic regimens in COVID-19 ICU-patients.
Methods: This was a retrospective study in ICUs of two French hospitals. Anti-Xa activities from consecutive patients with laboratory-confirmed SARS-CoV-2 infection treated with 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 (typical value 1.1 L.h-1) was related to renal function estimated by the CKD-EPI formula and volume of distribution (typical value 17.9 L) to actual body weight.
Simulation of anti-Xa activities with enoxaparin 40 mg qd indicated that 64% of the patients had peak levels within the range 0.2 to 0.5 IU.mL-1 and 75% had 12-hour levels above 0.1 IU.mL-1. Administration of a total daily dose of at least 60 mg per day improved the probability of target attainment.
Conclusion: In ICU COVID-19 patients, exposure to enoxaparin is reduced due to an increase in the volume of distribution and clearance. Consequently, enoxaparin 40 mg qd is suboptimal to attain thromboprophylactic anti-Xa levels.

1. 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) [5–8]. On the contrary, the American College of Chest Physicians and the American

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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 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.

2. Patients and methods

2.1. Study overview

This research study was conducted retrospectively from data obtained for clinical purposes. It involved human participants and was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University of Saint-Etienne, France [IRBN502020/CHUSTE] and University of Lille, France [ID-CRB-2020-A00763-36] approved this study. This multicenter cohort study was conducted from February to April 2020 in all consecutive patients with laboratory-confirmed SARS-CoV-2 infection receiving enoxaparin for the treatment or the prevention of venous thrombosis and hospitalized in the ICUs of Lille and Saint-Etienne University Hospitals. As the study took place at the beginning of the COVID-19 pandemic in France, local guidelines for the administration of enoxaparin and for anti-Xa activity measurement were not implemented. Enoxaparin dose regimens and dosing adjustments were at the discretion of the intensive care physicians in charge of the patients. 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. All the available enoxaparin anti-Xa activities were used for this pharmacokinetic study. These activities could be trough or random levels obtained from morning laboratory testing. Anti-Xa activity measured 4 h after at least three injections and then regularly in case of renal insufficiency were used for dose adjustment. Doses were adjusted to maintain anti-Xa levels below 1.2 IU.mL^{-1} in all the patients and above 0.5 IU.mL-1 only in the case of therapeutic-intensity anticoagulation. 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.

2.2. 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) that measures the extent of a person's respiratory illness [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-citrated tubes (0.109 M). After centrifugation (15 min, 2500*g*), plasma anti-Xa levels were measured in fresh plasma samples using a chromogenic anti-Xa activity assay (STA-Liquid Anti-Xa, Diagnostica Stago, Biophen Heparin LRT, HYPHEN BioMed) and a coagulation analyzer (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 0.05–1.75 IU.mL^{-1}. Fibrinogen and D-dimers were measured on a STA-R Max analyzer (Diagnostica Stago) using LiquidFib (Diagnostica Stago) and Liatest DDI-Plus (Diagnostica Stago). 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, as defined by the International Society on Thrombosis and Haemostasis [20], occurring during low-molecular-weight thromboprophylaxis through 72 h after the last dose was administered.

2.3. Population pharmacokinetic analysis

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

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

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 (see [23] for an introduction to the process). The covariates tested were total body weight, lean body weight [24], 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:

$$log(V_i,) = log\left(V_{pop}\right) + \beta_{BW}^{V} \times log\left(\frac{\mathrm{BW}_i}{70}\right) + \eta_i^V$$

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 body size descriptors was fixed at 0.75 and 1 for clearance (Cl) and V parameters, respectively [25].

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

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

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 $\beta 1^{cl}{}_{SOFA=1}$ corresponds to the regression coefficient for SOFA score equal to 1. The parameter $\beta 1^{cl}{}_{SOFA=1}$ corresponds to the regression coefficient for SOFA score equal to 2. The parameter $\beta 1^{cl}{}_{SOFA=1}$ 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 [26]. 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.

2.4. 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 1000 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 60 mg 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. [27] 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}), the maximum plasma concentration ($Cmax_{d3}$) and the minimum plasma concentration ($Ctrough_{d3}$). The probability of target attainment for each regimen was calculated. For prophylactic and intermediate regimen, two targets were chosen: a $Cmax_{d3}$ value in the range 0.2 to 0.5 IU.mL-1 [28] and a 12-hour anti-Xa level above 0.1 IU.mL-1 [29]. For therapeutic dose administration, the target range for $Cmax_{d3}$ was 0.5 to 1.2 IU.mL-1 [30].

3. Results

3.1. 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 (± SD) weight of 88 ± 17 kg, 40% had a body mass index above 30 $kg.m^{-2}$. The mean (± SD) estimated glomerular filtration rate (CKD-EPI formula) was 87 ± 22 mL.min-1, 14% of the subjects had moderate or severe renal failure (CKD-EPI <60 mL.min-1). The mean (± 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% 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%).

Table 1
Characteristics of the patients at admission to the intensive care unit.

Number of patients		95
Sex-no. (%)	Female	22 (23%)
Age-yr	Mean ± SD	63 ± 11
	Min - Max	29 - 82
Weight-kg	Mean ± SD	88 ± 17
	Min - Max	55 - 150
Body Mass Index-$kg.m^{-2}$#	Mean ± SD	29 ± 6
Body Mass Index-$kg.m^{-2}$#	≥ 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 ± SD	4.6 ± 2.7
	Min - Max	1 - 12
Cockroft & Gault equation-$mL.min^{-1}$	Mean ± SD	115 ± 54
Chronic kidney disease-epidemiology collaboration equation-$mL.min^{-1}$	Mean ± SD	87 ± 22
	Min - Max	14 - 138
D-Dimer-$ng.ml^{-1}$	Mean ± SD	3047 ± 3651
	Min - Max	0 - 20,000
Fibrinogen-$g.l^{-1}$	Mean ± SD	6.9 ± 1.6
	Min - Max	2.8 - 11
Enoxaparin regimen	Prophylactic ≤60 mg qd	34 (36%)
	Intermediate 40 or 60 mg bid	36 (38%)
	Full dose 1 $mg.kg^{-1}$ bid	25 (26%)

Data was unavailable for 5 (#) and 1 (@) patients.

3.2. Data sampled

A total of 391 anti-Xa samples were measured for the 95 patients analysed. The mean number of measurements per patient was 3.9 (range1 to 13). A total of 24 anti-Xa (6.1%) were below the limit of quantification. The mean number of doses of enoxaparin administered per patient was 19.5.

3.3. 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). Inter-subject 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

Table 2
Pharmacokinetic parameters.

Parameters	Value (r.s.e)	IIV (r.s.e)
Ka (h^{-1})	0.48 (20.9)	
Cl ($L.h^{-1}$) = θ1 × $(eGFR/87)^{\theta 2}$		0.40 (20.3)
θ1	1.1 (5.3)	
θ2	0.18 (8.3)	
V (L) = θ3 × (Wt/85)		0.44 (9.8)
θ3	17.9 (9.2)	
σ^2 proportional (CV%)	0.28 (4.9)	

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; r.s.e relative standard error (%).

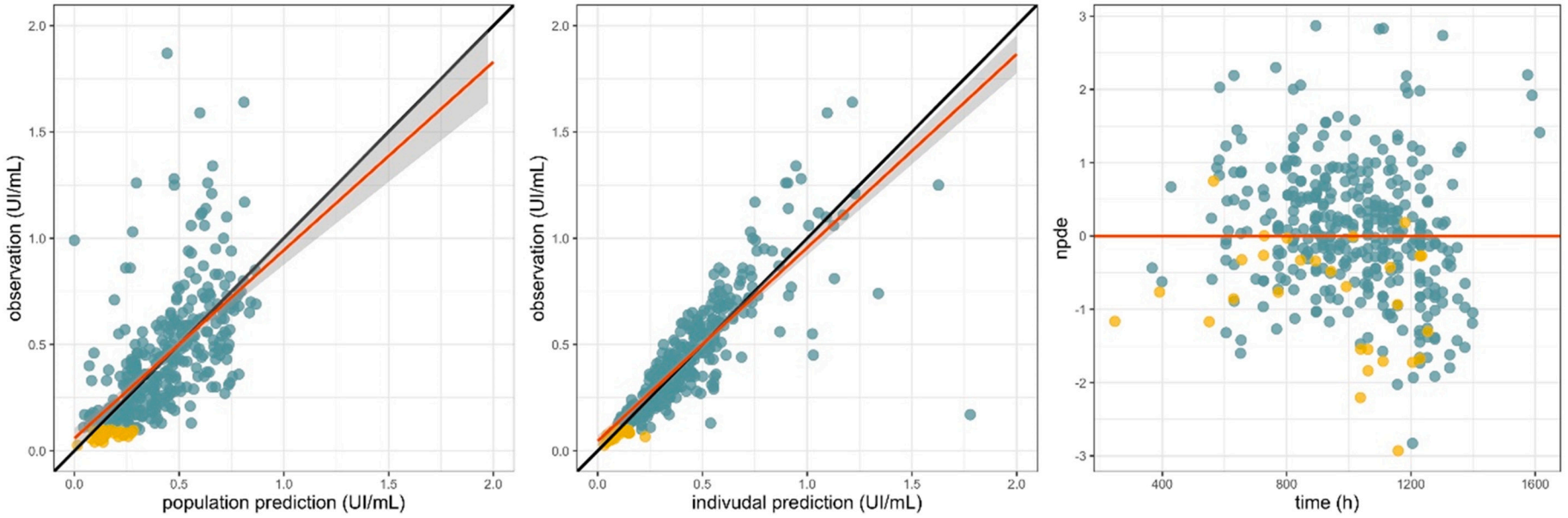

Fig. 1. Goodness-of-fit plots of the final pharmacokinetic model for enoxaparin
Left panel, observed anti-Xa activities versus population predictions; middle panel, observed anti-Xa activities versus individual predictions; right panel, normalized prediction distribution error (NPDE) versus time. Yellow points represent data below the limit of quantification. Left and middle panel: the black line corresponds to the identity line, the red line, with its shaded 95 percent confidence interval, is a linear regression of the data. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

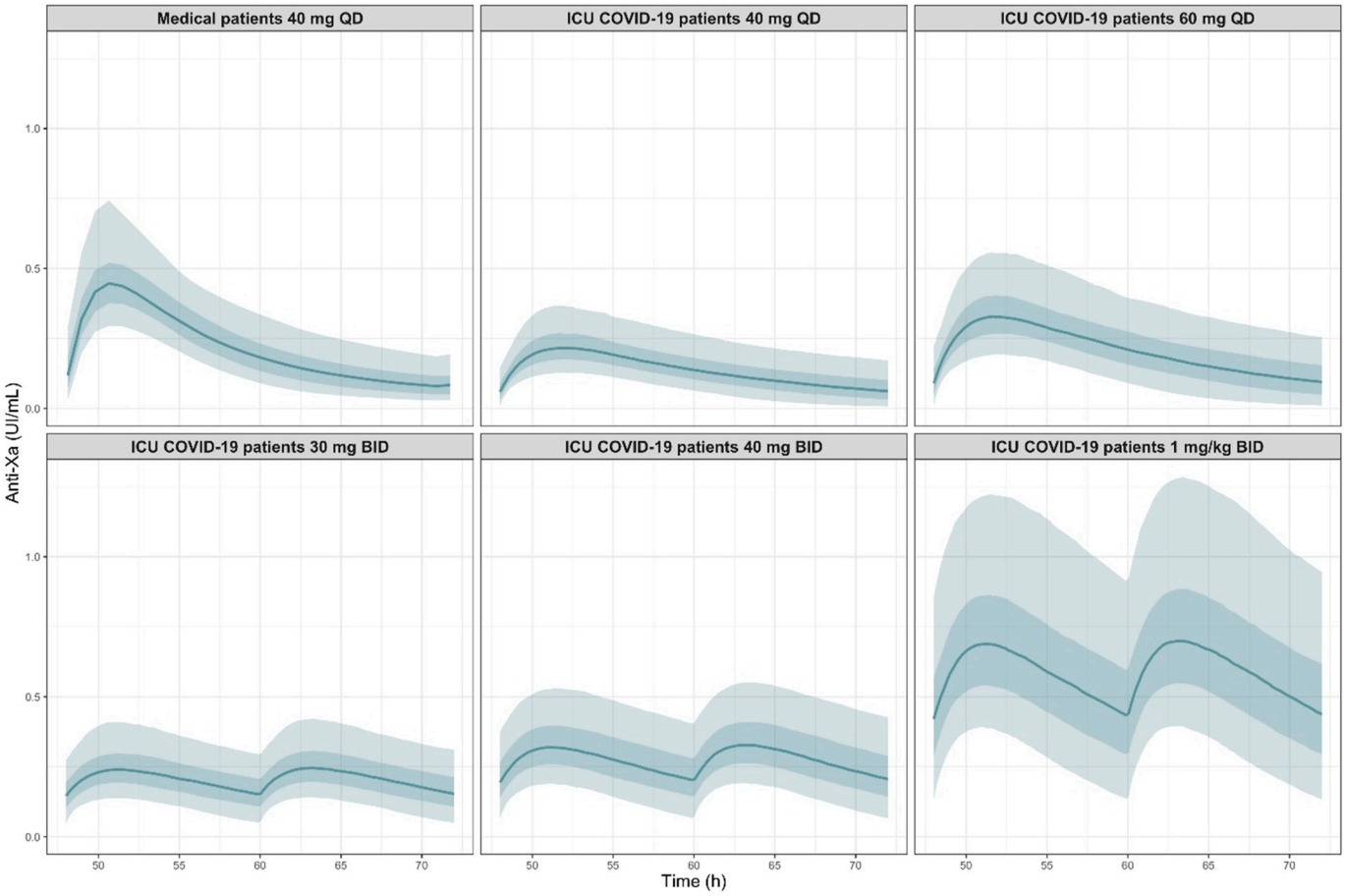

Fig. 2. Pharmacokinetic simulation of enoxaparin exposure on day 3.
The time-exposure profiles of enoxaparin were simulated using (1) the pharmacokinetic model developed by Berges et al. [27] for medical patients and (2) using the pharmacokinetic model presented in this study for COVID-19 ICU patients. 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.

Table 3
Enoxaparin exposure markers at steady state.

Enoxaparin regimen	AUC_{d3} IU.h.mL^{-1} median [90% prediction interval]	$Cmax_{d3}$ IU.mL^{-1} median [90% prediction interval]	$Ctrough_{d3}$ IU.mL^{-1} median [90% prediction interval]	Probability of target attainment (%) at $Cmax_{d3}$	Probability of target attainment (%) at $t = 12$ h
COVID-19 ICU patients					
Enoxaparin 40 mg qd	3.35 [1.76–6.16]	0.22 [0.13–0.37]	0.06 [<0.05–0.17]	64	75
Enoxaparin 30 mg bid	4.93 [2.62–8.59]	0.25 [0.14–0.42]	0.15 [0.05–0.31]	75	76
Enoxaparin 60 mg qd	4.99 [2.69–9.16]	0.33 [0.19–0.56]	0.09 [<0.05–0.26]	85	93
Enoxaparin 40 mg bid	6.54 [3.59–11.90]	0.33 [0.19–0.57]	0.21 [0.07–0.31]	86	86
Enoxaparin 0.5 mg.kg-1 bid	7.17 [3.54–13.18]	0.36 [0.20–0.63]	0.22 [0.06–0.49]	78	88
Enoxaparin 1 mg. kg-1 bid	14.60 [7.41–26.76]	0.72 [0.41–1.27]	0.44 [0.13–0.95]	78	–
Non COVID-19 medical patients					
Enoxaparin 40 mg qd	5.15 [3.29–8.54]	0.45 [0.31–0.68]	0.07 [<0.05–0.17]	68	93

Enoxaparin anti-Xa activities 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. [27] 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; $Ctrough_{d3}$, trough plasma concentration on day 3. The probability of target attainment for each regimen was calculated. For prophylactic and intermediate regimen, the targets were a $Cmax_{d3}$ value in the range 0.2 to 0.5 IU.mL-1 and a 12-hour anti-Xa level above 0.1 IU.mL-1. For enoxaparin 1 mg.kg-1 bid, the target range for $Cmax_{d3}$ was 0.5 to 1.2 IU.mL-1.

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.

3.4. Model validation

The goodness-of-fit plots of the final models are presented in Fig. 1. The data exhibited no apparent bias in model predictions. According to the pcVPC (Supplementary data), the average observed values were well predicted up to time $t = 1200$ h, after which the prediction intervals were wide due to the paucity of data observed. Only extreme profiles were not within 90% of the simulated values, demonstrating good predictive capacity of the models.

3.5. 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 Fig. 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% 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 60 mg qd and 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). In ICU COVID-19 patients receiving enoxaparin 40 mg qd, the probability of target attainment at steady state was 64% for $Cmax_{d3}$ and 75% for 12-hour anti-Xa concentration. Administration of higher daily doses, given either once or twice daily, improved the percentage of patients attaining prophylactic targets. For therapeutic dose administration (enoxaparin 1 mg.kg-1 bid), 78% of the patients were within the 0.5-1.2 IU.mL-1 range.

4. Discussion

To our knowledge, this is the first study to evaluate the pharmacokinetics of enoxaparin in ICU COVID-19 patients using a population approach model. The analysis showed that the pharmacokinetics 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 for enoxaparin in non-ICU non-COVID-19 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, anti-Xa activity levels in ICU COVID-19 patients were reduced compared to non-ICU non-COVID-19 patients. One study previously evaluated the pharmacokinetics of enoxaparin in ICU non-COVID-19 patients [31]. As in other studies with standard prophylactic enoxaparin dosing in critically ill patients [32–34], the anti-Xa activity levels were low in numerous patients which resulted in unreliable estimates of the PK parameters and hinders any comparison with the PK parameters of the present study. The discrepancy between ICU and non-ICU patients for anti-Xa activities has 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 this present study of ICU COVID-19 patients are more related to pathophysiological changes in ICU-patients rather than the SARS-CoV-2 status. 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 [12,31]. 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 [35,36]. Acute kidney injury occurs in 10% of all hospitalized COVID-19 patients and 4% will require renal replacement therapy [37]. However augmented renal clearance defined by a creatinine clearance more than or equal to 130 $mL.min^{-1}.1.73^{-1}$ has been observed in 65% of patients during their first week of admission in ICU [38]. This condition has also been reported in ICU COVID-19 patients [39]. 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 [40] 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 [41]. 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 [36]. Yet, in ICU patients, estimated glomerular filtration rate formulas are imprecise in assessing creatinine clearance with CKD-EPI being the less inaccurate formula [42]. 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 range of the time-exposure profiles of enoxaparin 40 mg bid with enoxaparin 0.5 $mg.kg^{-1}$ bid (Fig. 2 and Table 3).

The simulation of various dosing regimens of enoxaparin in ICU COVID-19 patients indicated that with enoxaparin 40 mg qd, the probability of target attainment for thromboprophylaxis was suboptimal. The probability of target attainment with enoxaparin 40 mg qd at Cmax on day 3 were similar in Covid-19 ICU patients and in non-ICU patients, 64% and 68% respectively. Yet patients that did not meet the target levels were below target in Covid-19 ICU patients while non-ICU patients were above target. A 50% increase in daily dose administration in Covid-19 ICU patients was required to obtain daily exposures (AUC_{d3}) similar to those in medical non-COVID-19 patients. Although previous studies in surgical and critically ill trauma patients have shown an association of venous thrombotic outcomes with low anti-Xa values (Cmax below 0.2 UI.mL-1 [43], 12 h anti-Xa below 0.1 IU.mL-1 [29,32,44,45]), no randomized controlled trial has demonstrated the efficacy of an anti-Xa level guided regimen for thromboprophylaxis. Thus the proposal to increase the prophylactic 40 mg qd dose of enoxaparin in ICU COVID-19 patients is tentative.

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 [46]. The doses of enoxaparin studied were 40 mg qd and 30 mg bid. As the rates of thrombotic complications have been found to be higher in COVID-19 patients admitted to ICU compared to non-COVID-19 ICU patients [2], an increase in the dosage of enoxaparin has been proposed [5–8]. The results of randomized trials that have evaluated escalated thromboprophylaxis have recently been presented. The INSPIRATION study did not demonstrate a reduction of thromboembolic events with intermediate-dose versus standard-dose enoxaparin prophylactic anticoagulation [47]. Yet diagnostic tests were performed based on clinical judgment of the treating clinicians in this open-label trial; no systematic screening for

thrombotic events was required. This could explain that the rate of venous thromboembolism (3.4%) in the INSPIRATION study was much lower than previously reported [2]. As a result, the study was underpowered to detect a statistically significant difference between groups for this outcome. A multiplatform randomized clinical trial, a collaboration between 3 trial platforms (ATTACC, REMAP-CAP, and ACTIV-4) compared therapeutic-dose vs standard-dose thromboprophylaxis. Preliminary results suggest a reduction of thrombotic events and a non-statistically increase in major bleeding with therapeutic doses [48]. Based on the results of these trials, the optimal regimen for thromboprophylaxis in ICU COVID-19 patients is still unclear.

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 [49]. 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. We chose the model developed by Berges et al. [27] to simulate exposure in non-ICU patients as it is the only available population pharmacokinetic model based on prophylactic enoxaparin dosing (40 mg qd). Patients included in the Berges et al. model were aged over 75 years and had lower body weight and renal clearance values compared to the population of this study. This could have contributed to the differences in enoxaparin exposure between these two populations. 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.

5. Conclusion

In ICU COVID-19 patients, exposure to enoxaparin is reduced due to an increase in the volume of distribution and clearance. As a result, administration of enoxaparin 40 mg qd is suboptimal to attain thromboprophylactic anti-Xa levels. This study suggests to administer a daily dose of at least 60 mg per day for thromboprophylaxis in ICU COVID-19 patients.

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Tweet

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

CRediT authorship contribution statement

Contributed substantially to the conception and design of the study (PJZ, XD) the acquisition of data (AD, JL, AB, JP, JG, LJ, MC, 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).

Summary statement

Despite low-molecular weight heparin thromboprophylaxis, ICU COVID-19 patients are at high risk of venous thromboembolism. This pharmacokinetic study indicates that exposure to enoxaparin in this special population is decreased.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2021.07.010.

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