SHORT COMMUNICATION

BJCP BRITISH PHARMACOLOGICAL SOCIETY

Effects of dalteparin on anti-Xa activities cannot be predicted in critically ill COVID-19 patients

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Critically ill COVID-19 patients are at high risk of thromboembolic events despite routine-dosed low-molecular-weight heparin thromboprophylaxis. However, in recent randomized trials increased-intensity thromboprophylaxis seemed futile and possibly even harmful. In this explorative pharmacokinetic (PK) study we measured anti-Xa activities on frequent timepoints in 15 critically ill COVID-19 patients receiving dalteparin and performed PK analysis by nonlinear mixed-effect modelling. A linear one-compartment model with first-order kinetics provided a good fit. However, wide interindividual variation in dalteparin absorption (variance 78%) and clearance (variance 34%) was observed, unexplained by routine clinical covariates. Using the final PK model for Monte Carlo simulations, we predicted increased-intensity dalteparin to result in anti-Xa activities well over prophylactic targets (0.2-0.4 IU/mL) in the majority of patients. Therapeutic-intensity dalteparin results in supratherapeutic anti-Xa levels (target 0.6-1.0 IU/mL) in 19% of patients and subtherapeutic levels in 22%. Therefore, anti-Xa measurements should guide high-intensity dalteparin in critically ill COVID-19 patients.

KEYWORDS
anti-Xa, COVID-19, critical care, dalteparin, low-molecular weight heparin, pharmacokinetics, therapeutic drug monitoring

1 | BACKGROUND

Critically ill patients with coronavirus disease 2019 (COVID-19) are at high risk of venothromboembolism (VTE) despite regular thromboprophylaxis with low-molecular weight heparins (LMWHs), with cumulative incidences reported up to 50%.[1–4] These observations have resulted in recommendations to consider increased-intensity thromboprophylaxis in critically ill COVID-19 patients and in

randomized clinical trials investigating the potential benefit of therapeutic-intensity LMWH as primary thromboprophylaxis.[5,6] However, therapeutic-intensity thromboprophylaxis may be associated with a significant number of bleeding complications.[7] Recently, the combined results of three large international clinical trials investigating standard versus therapeutic-dosed anticoagulation for primary prevention of thrombosis in critically ill COVID-19 patients confirmed futility and increased bleeding complications with therapeutic dosing.[8]

LMWHs follow first-order absorption kinetics when applied to the subcutaneous compartment, with a bioavailability of approximately 90%. LMWHs are partially metabolized by desulphation and

The authors confirm that the Principal Investigator for this paper is J. Leentjens and that she had direct clinical responsibility for patients.

depolymerization, and preferentially cleared via the kidneys following first-order elimination.[9] Although it is difficult to directly quantify circulating LMWH concentrations, monitoring of the effect of LMWHs is possible by measuring the anti-Xa activity. The anti-Xa test quantifies the ability of plasma to inhibit coagulation factor Xa, which reflects the concentration of LMWH present.[10] Therefore, although in essence a pharmacodynamic (PD) parameter, anti-Xa is generally used as a surrogate PK parameter.[11,12] Since the PK properties of LMWHs are generally considered predictable in most patients, international guidelines suggest measuring anti-Xa levels only in selected patient groups, such as patients with morbid obesity or severe kidney failure, to individualize therapeutic dosing.[5,13] Therefore, most ICU patients with COVID-19 receive LMWHs without anti-Xa measurements, with dose adjustments based on weight and kidney function per local protocol. However, only a single study to date has investigated the PK properties of a LMWH, enoxaparin, in critically ill COVID-19 patients,[14] while the clinical data above as well as recent reports on anti-Xa target attainment suggest that the pharmacokinetics of LMWHs in these patients might be difficult to predict.[15] This study aimed to describe the pharmacokinetics of dalteparin in critically ill COVID-19 patients and to determine the probability that standard dosing regimens result in attainment of anti-Xa targets as advised in current best practices.

2 | METHODS

Additional information is found in the online Supplement.

2.1 | Patients

In this explorative, observational study, we prospectively included all adult patients in the ICU of the Radboudumc, the Netherlands, between 19 and 30 November 2020 with PCR-proven COVID-19 who received dalteparin in standard-intensity (5000 IU once daily [OD]), intermediate-intensity (5000 IU bidaily [BD]) or therapeutic-intensity dosage for primary or secondary thromboprophylaxis by discretion of the treating physician. Patients who did not have an arterial line for blood sampling or received additional systemic treatment with heparin (eg, on continuous renal replacement therapy) or direct oral anticoagulants were excluded. The study was carried out in the Netherlands in accordance with the applicable rules concerning clinical research. The Institutional Review Board waived the need for informed consent due to the observational nature of and negligible burden associated with this study.

2.2 | Study design

Anti-Xa levels were sampled on one to three separate days for all patients, at least four times daily (in the hour before subcutaneous dalteparin administration [$t = 0$] and at the time to maximum

> **What is already known about this subject**
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> - Critically ill patients with COVID-19 are at high risk of venous thromboembolism, despite thromboprophylaxis with low-molecular weight heparins.
> - Recent randomized trials investigating standard versus therapeutic-dosed anticoagulation were prematurely stopped because of futility and possible increased bleeding complications.
>
> **What this study adds**
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> - This study describes the pharmacokinetic properties of dalteparin in COVID-19 patients for the first time.
> - This study shows that dalteparin pharmacokinetics in COVID-19 patients are described by a one-compartment model with first-order absorption and elimination, as has previously been described for other patient populations.
> - Moreover, this study shows that absorption and elimination of dalteparin in critically ill COVID-19 patients show a wide interindividual variation, which is unexplained by routine clinical covariates and therefore unpredictable for the individual patient.
> - Monte Carlo simulation showed that anti-Xa activities are often off-target, both with current prophylactic and therapeutic dosing regimens. Levels over intended ranges are frequently observed.

concentration [T_{max}] $t = 3$ or 4 hours, $t = 5$ or 6 hours and $t = 7$ or 8 hours after dalteparin administration) to capture a rich dataset throughout the dosing interval. Patient characteristics and clinical parameters were collected from the medical charts of patients and included dalteparin dosing, age, sex, body weight, indication for dalteparin treatment and dalteparin dose history. At the moment of sampling, vasopressor use, capillary refill time (seconds) and oedema score[16] were collected. In all patients, serum creatinine and an 8-hour urine sample collection (for volume and creatinine concentration) was used to calculate the endogenous creatinine clearance on each sampling day.

2.3 | Laboratory measurements

Anti-Xa (STA liquid ANTI-Xa, Stago, France) was measured on a STA-EVO (Stago, Asnières sur Seine, France) hemostasis analyser. The anti-Xa activity was determined using specific calibration lines for LMWH

(aXa-LMWH) (STA Multihep Calibrator). The validated calibration range of the anti-Xa assay used, was 0.0-2.0 IU/mL. Data below the limit of quantitation (0.1 IU/mL), but above the limit of detection were included in the population PK analysis according to the "all data method" as proposed previously.[17] The manufacturer's reported coefficient of variation is 2-5% for repeatability and within-laboratory precision (STA liquid ANTI-Xa[18]). Creatinine in both plasma and urine was performed on the Cobas8000 (Roche Diagnostics, Basel, Switzerland).

2.4 | PK modelling

Population PK analysis of dalteparin was performed by nonlinear mixed-effect modelling using NONMEM version 7.4 (Icon plc, Dublin, Ireland). A linear one-compartment PK model was fitted to the data, based on earlier findings with dalteparin[19] and other LMWHs. In line with best practice,[20] multicompartment distribution was evaluated based on goodness-of-fit plots and improvement of model fit. The first-order conditional estimation method with interaction was used throughout model building. Interindividual variability was assumed to be log-normally distributed and a proportional residual error model was implemented. Parameter uncertainty was obtained from the covariance step in NONMEM. Rate constants, volume and clearance parameters were allometrically scaled to a total body weight of 70 kg, in line with common practice.[21] Potential covariates were tested based on physiological plausibility and they were retained in the model if they significantly improved model fit (P < .05). We tested vasopressor use (yes/no), oedema scores[16] and capillary refill time as covariates for absorption and relative bioavailability. As covariates for clearance of dalteparin both the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[22] based on serum creatinine and endogenous creatinine clearance (= (1000 × creatinin$_{urine}$ [mmol/l]/ creatinin$_{serum}$ [μmol/l]) × ([3 × 8 h urine volume (ml)]/1440) were tested as a covariate for dalteparin clearance. Since PK steady state may not be present in critically ill patients, we implemented the missing dose method by estimating the residual anti-Xa activity in the observation compartment just before the administration of the first dose.[23] Model diagnostics were performed in line with best practice[20] using goodness-of-fit plots and predictive visual predictive checks.

The final model was used to perform Monte Carlo simulations (n = 1000 virtual patients for each scenario) to predict anti-Xa target attainment at T_{max} = 4 hours for a population with average weight 90 kg (±20%) (based on the weight distribution of Dutch COVID-19 patients[1,24]). The targets are 0.2-0.4 IU/mL in the standard prophylactic setting,[25] 0.3-0.7 IU/mL in an intensified prophylactic setting[6] and 0.6-1.0 IU/mL in a therapeutic setting.[26]

3 | RESULTS

Demographic characteristics are listed in Table 1. We included 15 patients with a total of 102 samples of anti-Xa during dalteparin

TABLE 1 Patient characteristics

Number of patients	15
Age, years (median [range])	61 (32-76)
Sex (% male)	73
Weight, kg (median [range])	83 (70-110)
APACHE II (median [range])	13 (17-24)
SOFA score on first day of sampling (median [range])	7 (5-7)
CKD-EPI ml/min/1.73m^2 (median [range])	106 (31-158)
Endogenous creatinine clearance, calculated, ml/min (median [range])	102 (16-214)
Vasopressor use (% yes)	39
Oedema scores (median [range])	0 (0-2)
Capillary refill, s (median, range)	1.5 (1-5)
Bilirubin on first day of sampling, μmol/L (median [range])	5 (4-7)
Alanine transaminase on first day of sampling, U/L (median [range])	65 (56-83)
Gamma-glutamyltransferase on first day of sampling, U/L (median [range])	182 (94-260)
Alkaline phosphatase on first day of sampling, U/L (median [range])	100 (61-171)

TABLE 2 Estimated PK parameters

Vd	14 600 mL (RSE 14%)
Ka	0.813/h (RSE 32%)
Interindividual variablility, *Ka*	78.0% (RSE 56%)
Cl	918 mL/h (RSE 19%)
Interindividual variablility, *Cl*	34.2% (RSE 87%)

Abbreviations: *Cl*, clearance; *Ka*, absorption rate constant; *Vd*, volume of distribution.

dosing. Before the first sampling, all patients had received dalteparin for at least 60 hours. A total of six patients received a prophylactic dose of dalteparin (5000 IU OD for those <100 kg, 5000 IU BD for those >100 kg) and nine were administered a therapeutic dose (7500 IU BD or 10 000 IU BD, depending on weight and kidney function).

3.1 | Population PK modelling

A one-compartment linear disposition model with first-order absorption and elimination provided a good fit. The calculated shrinkage on all random effect parameters ranged from 13.5% to 30.8%. The estimated PK parameters of the model are shown in Table 2. A wide interindividual variation in the absorption rate constant *Ka* and the clearance *Cl* was observed, unexplained by any of the previously described covariates (P > .05). In particular, creatinine clearance calculated by the CKD-EPI of endogenous creatinine clearance showed no correlation with dalteparin clearance (ρ − 0,18, P = .35 and ρ − 0,20,

$P = .29$, respectively). The residual proportional error of the model was 25% (RSE 27%).

Supporting Information Figure S1 shows the prediction-corrected visual predictive check of our model on our data,[27] showing its good internal validity. Supporting Information Figure S2 shows additional goodness-of=fit plots.

3.2 | Monte Carlo simulations

Monte Carlo simulations were performed to investigate anti-Xa target attainment. Prophylactic dosing of dalteparin was simulated to result in target attainment (anti-Xa at T_{max} 0.2-0.4 IU/mL) in almost 80% of patients <100 kg (anti-Xa at T_{max} > 0.4 IU/mL in 15%), compared to 55% in patients ≥100 kg (anti-Xa at T_{max} > 0.4 IU/mL in 40%) (Supporting Information Figure S3).

Figure 1 shows the simulated anti-Xa levels expected after prophylactic or therapeutic dosing of dalteparin. Prophylactic dalteparin dosing per protocol (to aim for a conventional prophylactic range of anti-Xa at T_{max} 0.2-0.4 IU/mL) would result in suboptimal dosing in 6% of patients and supra-optimal dosing in 22% of patients (individuals <100 kg and ≥100 kg combined). With this prophylactic dosing, 56% of patients would even reach a high-prophylactic anti-Xa target at T_{max} 0.3-0.7 IU/mL. With therapeutic-intensity dosing, around 60% of patients are in the therapeutic anti-Xa range at T_{max} 0.6-1.0 IU/mL, with 22% of patients being suboptimally dosed, while 19% would still reach anti-Xa levels over the intended range.

Total body weight showed a significant but weak correlation with simulated anti-Xa at T_{max} after therapeutic dosing (Supporting Information Figure S4).

4 | DISCUSSION

We report that anti-Xa levels show a wide interindividual variation in critically ill COVID-19 patients on dalteparin thromboprophylaxis, caused by large variations in both absorption and elimination of this LMWH. Consequently, anti-Xa levels in the individual patient cannot reliably be predicted, nor can a dosing algorithm be designed based on readily available clinical parameters. In particular, creatinine clearance was not identified as a relevant covariate for dalteparin clearance.

To our knowledge, we are the first to investigate the PK properties of dalteparin in critically ill COVID-19 patients. We found dalteparin pharmacokinetics to be best described by a one-compartment linear PK model with first-order kinetics, as previously reported[28,29] and estimated parameters to be largely in line with previous reports, except for a slightly higher Vd, which is commonly seen for hydrophilic drugs in ICU patients due to oedema.[11,14,28,29] However, the large interindividual variation in PK parameters could well explain why anti-Xa levels are off-target in many critically ill COVID-19 patients.[15]

Our simulations show that only a small number of patients is expected to be below the conventional prophylactic anti-Xa range at T_{max} with our prophylactic dosing regimen, but a significant one out of five patients reaches levels above this range, a number that is even higher in those ≥100 kg in whom dalteparin prophylaxis is doubled. Moreover, over 40% of patients are expected to be out of the internationally advised therapeutic anti-Xa range at T_{max} when dalteparin is dosed according to current guidelines on therapeutic thromboprophylaxis. This may explain the doubling of the incidence of bleeding observed in the recently terminated trials on therapeutic anticoagulation for primary prophylaxis in critically ill COVID-19 patients.[8] Of note, the incidence of bleeding under therapeutic anticoagulation in these trials was still relatively limited (3,8%).

The variation in the absorption of dalteparin did not correlate with oedema scores, capillary refill or vasopressor use, while previous small studies report conflicting data,[30,31] Possibly, these parameters do not accurately reflect peripheral circulation. Alternatively, our study may have been underpowered to sense a relevant effect.

It seems surprising that dalteparin elimination did not correlate to renal clearance in our study. This finding contrasts with a recent study that investigated population PK of enoxaparin in COVID-19 ICU patients,[14] although here a wide interindividual variation in LMWH
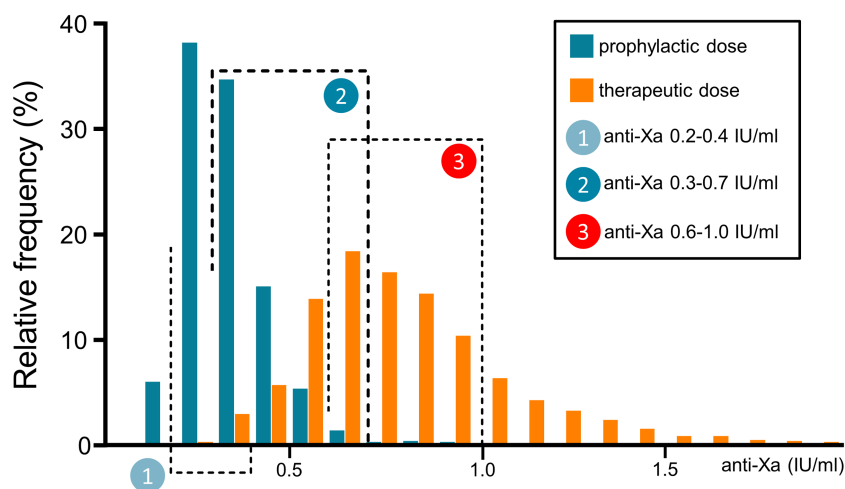
FIGURE 1 Monte Carlo simulations of expected anti-Xa levels at T_{max} with prophylactic and therapeutic dalteparin dosed per protocol. Simulated for an average weight of 90 kg (±20%)

clearance was described. Although it is generally assumed that LMWHs are primarily cleared via a nonsaturable renal route,[9,12] nonrenal routes are of additional importance. Preclinical and PK studies of LMWHs suggest that large LMWHs, such as dalteparin, show more dependency on nonrenal clearance[9] than small LMWHs such as enoxaparin. This is also the most likely explanation for the higher incidence of the subprophylactic anti-Xa range with prophylactic LMWH dosing in ICU patients: these studies generally report on small LMWHs[14,32,33] and enhanced renal clearance is a well-known phenomenon in ICU patients.

The DIRECT study detected no dalteparin accumulation (and a good prophylactic target attainment) in over 120 critically ill patients with a creatinine clearance <30 mL/min who received thromboprohylaxis[34] and other smaller studies report similar findings.[35,36] Based on these observations, the unexplained variation in clearance of dalteparin might relate to variation in nonrenal elimination. Moreover, the mechanism of renal clearance of dalteparin is suggested to be at least in part dependent on active renal tubular processes,[37] rather than glomerular filtration rate. Interindividual variation in tubular uptake might therefore alternatively explain our findings.

Our study has several limitations. First, the sample size of our study is small. However, this sample size is accepted as adequate for this kind of explorative PK studies.[11,30,36] Second, our study was not designed to correlate anti-Xa levels to clinical events that may determine patient outcome, such as VTE and bleeding. Considering these two limitations, this study should be seen as a learning study aimed to direct future confirmatory research that in addition investigates whether standardized anti-Xa measurements improve target attainment and outcomes. Third, in our Monte Carlo simulation we accounted for interindividual variability, but not parameter uncertainty. However, as carrying forward would have introduced more variability in the predicted anti-Xa activity, we consider our findings a best-case scenario. Last, our data cannot automatically be extrapolated to other LMWHs because of different PK/PD properties and dosing.[29]

In conclusion, our study demonstrates that dalteparin (primary and secondary) thromboprophylaxis per protocol results in a wide interindividual variation in anti-Xa activities in critically ill COVID-19 patients, which cannot reliably be predicted with readily available clinical parameters. The clinician should be aware that intermediate-intensity or therapeutic-intensity dalteparine will likely result in anti-Xa activities well over generally used prophylactic and even therapeutic targets. Anti-Xa measurements should therefore be considered to guide increased- and therapeutic-intensity dosing in the critically ill COVID-19 patient, especially with a high risk of bleeding.

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CONTRIBUTORS

J.L., P.P., T.F., R.H., R.B. and C.D.C.C.H. conceived and designed the experiments. E.J.K., J.W.J.W.S., R.H. and E.P.L.M.G. performed the experiments. C.D.C.C.H. and R.H. analysed the results. C.D.C.C.H., E.J.K., R.H. and J.L. wrote the manuscript. All other authors critically read and adjusted the manuscript.

COMPETING INTERESTS

Nothing to declare.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was carried out in the Netherlands in accordance with the applicable rules concerning clinical research. The Institutional Review Board (Commissie Mensgebonden Onderzoek, Arnhem-Nijmegen) waived the need for informed consent due to the observational nature of and negligible burden associated with this study.

DATA AVAILABILITY STATEMENTS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.