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Population pharmacokinetics of dexamethasone in critically ill COVID-19 patients: Does inflammation play a role?

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ABSTRACT

Purpose: The aim of this study is to design a population pharmacokinetic study to gain a deeper understanding of the pharmacokinetics of dexamethasone in critically ill COVID-19 patients in order to identify relevant covariates that can be used to personalize dosing regimens.
Methods: Blood samples from critically ill patients receiving fixed-dose intravenous dexamethasone (6 mg/day) for the treatment of COVID-19 were sampled in a retrospective pilot study. The data were analyzed using Nonlinear Mixed Effects Modeling (NONMEM) software for population pharmacokinetic analysis and clinically relevant covariates were selected and evaluated.
Results: A total of 51 dexamethasone samples from 18 patients were analyzed and a two-compartment model fit the data best. The mean population estimates were 2.85 L/h (inter-individual-variability 62.9%) for clearance, 15.4 L for the central volume of distribution, 12.3 L for the peripheral volume of distribution and 2.1 L/h for the inter-compartmental distribution clearance. The covariate analysis showed a significant negative correlation between dexamethasone clearance and CRP.
Conclusions: Dexamethasone PK parameters in ICU COVID patients were substantially different from those from non-ICU non-COVID patients, and inflammation may play an important role in dexamethasone exposure. This finding suggests that fixed-dose dexamethasone over several days may not be appropriate for ICU COVID patients.

1. Introduction

COVID-19 is a widespread infectious disease and global COVID death toll has crossed six million with a cumulative infection–fatality ratio of 0.4% [1,2]. The mortality rate of patients admitted to the ICU is nearly 30% [3,4]. Death in ICU patients is often caused by severe acute respiratory distress syndrome (ARDS), sepsis, and multi-organ failure, which are often in turn caused by hyperinflammatory states triggered by cytokine storms [5,6]. Thus, for the later stage of infection, anti-inflammatory therapy is more important than antiviral therapy.

Dexamethasone is a corticosteroid drug that has gained attention from clinicians as a potential treatment for COVID-19 because of its strong anti-inflammatory effects. Dexamethasone suppresses the hyperinflammatory phase of COVID and has been shown to improve clinical outcomes and reduce mortality [7-9].

Dose and duration of dexamethasone in COVID-19 differs from community-acquired pneumonia (CAP), which uses 5 mg IV infusion over 4 days in hospitalized patients [10].The current dexamethasone dose strategy for COVID is 6 mg per day for 10 days from RECOVERY trial [8]. Another study showed that higher dose (12 mg per day) did not increase overall survival/survival days [11]. However, both studies use a fixed dose regimen, while it is still unclear whether a “one dose fits all” strategy for COVID ICU patients is appropriate, and the optimal dose and therapeutic target of dexamethasone remains uncertain.

Dexamethasone is primarily metabolized by the cytochrome P450 (CYP) system, particularly by CYP3A4 [12]. On the other hand, dexamethasone has a relatively low hepatic extraction rate [13], suggesting that clearance of dexamethasone is primarily driven by the content and

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Table 1
The basic characteristic of the patients.

Characteristics	N = 18
Age, years (median, range)	63.5 (27–74)
Male, n(%)	12 (67%)
Female, n(%)	6 (33%)
Weight, kg (median,range)	87.5 (55–120)
BMI (median, range) kg/m^2	29.45 (21.22–43.34)
BSA (median, range) m^2	2 (1.56–2.43)
Blood chemistry, serum levels (median, range)	
Albumin, g/L	22.5 (18–32)
Creatinine, μmol/L	92.5 (33–272)
Urea, mmol/L	7.1 (4.2–22.6)
ASAT, U/L	59 (13–1826)
ALAT, U/L	74.5 (8–1787)
Bilirubin, μmol/L	8 (3−21)
Gamma-glutamyl transferase, U/L	170 (14–1210)
CRP, mg/L	20 (0.6–449)
PCT, ng/mL	0.27 (0.05–100)
IL-6, pg/mL	160 (2–9730)
WBC, 10^9	10.8 (2.7–22)
Ferritin, ng/mL	1284 (247–75,148)
D-dimer	1.23 (0.23–35.2)
Lactate dehydrogenase, IU/L	443 (166–2573)
Medication	
Tocilizumab	12 (66%)
Voriconazole	1 (5.6%)
Blood samples collected, median (range)	3 (1–5)

ASAT: Aspartate-aminotransferase test, ALAT: alanine aminotransferase TEST, BMI: Body mass index, BSA: Body Surface Area, CRP: C-reactive protein, PCT: Procalcitonin, WBC: white blood cell.

activity of CYP3A4. However, the CYP3A4 activity is influenced by many factors including liver failure, acute kidney injury and inflammation [14,15], which all are common in the ICU patients.

To complicate matters further, ICU patients are highly heterogeneous due to hemodynamic instability and various medical interventions such as fluid therapy, renal replacement therapy, and mechanical ventilation. Their pharmacokinetic parameters will be quite different from the non-ICU patients. Thus, the administered drug will have different drug exposure and half-life. Available pharmacokinetic parameters related to dexamethasone are mainly from studies in healthy people, cancer patients or other non-critically ill patients [16-20].

Dexamethasone treatment is a double-edged sword which could influence the normal function of multiple organs. Some hormones, like growth hormone (GH) and insulin-like growth factor (IGF), were influenced by dexamethasone in a dose dependent manner [21]. In addition, dexamethasone could also increase the risk of ventilator-associated pneumonia (VAP) in mechanically ventilated COVID-19 patients [22,23] and some adverse reaction (leukocytosis, hyperglycemia) also showed increase trend in higher dose dexamethasone group [24].

Hence, the current dexamethasone fix dosing strategies over several days may not suitable for ICU patients and might result in overdose leading to toxicity or underdose leading to treatment failure [25]. Thus, a more personalized dosing strategy are needed for the ICU COVID-19 patients.

The aim of this study is to explore the pharmacokinetics of dexamethasone in critically ill patients with moderate to severe COVID-19 pneumonia. And then try to identify potential covariates that might explain individual variability in PK parameters. The result will be of great significance for the rational clinical use of dexamethasone and represent the first step towards precision medicine, ultimately improving the survival rate of severely ill COVID-19 patients.

2. Method

2.1. Study population

2.1.1. Study design

A retrospective, single center study was performed in critically ill patients admitted at the department of intensive care at the Erasmus University Medical Center (EMC). This study was conducted in accordance with the principles of the Declaration of Helsinki (version: October 2008 and approved by the Institutional Review Board). Informed consent was obtained from each patient's legally authorized representative given all patients who are on supplemental oxygen or ventilatory support. The inclusion criteria were patient with moderate/severe COVID-ARDS, on invasive mechanical ventilation and treated with dexamethasone. Patients received 6 mg dexamethasone IV bolus once for maximum of 10 days, which according to national protocol in the EMC for the treatment of ICU COVID at that time.

2.1.2. Data collection

The blood concentrations were collected prior or after the administration of each morning dose. Serum samples (1 mL, purple tube with EDTA) were drawn from an arterial line and were immediately sent to the laboratory of the endocrinology laboratory and stored at −80 °C until analysis. Serum levels of albumin, creatinine, urea, bilirubin and C-reactive protein (CRP), PCT, Ferritin, WBC, ASAT, ALAT, Gamma-glutamyl Transferase (GGT), lactate dehydrogenase (LDH), NT-pro BNP, estimated renal function (Cockcroft-Gault Equation and CKD-EPI), IL-6, d-dimers and platelet count were determined according to standard clinical care on the ICU. Other parameters that were collected were age, gender, BMI, body surface area (BSA) and co-medication like tocilizumab, voriconazole, fluconazole and erythromycin. Serum dexamethasone concentrations were analyzed via validated Liquid Chromatography tandem Mass Spectrometry (UPLC-MS/MS), linearity, lower limit of quantification (LLOQ), validated according to FDA/EMA.

2.2. Data analysis

2.2.1. Model building

The pharmacokinetic analysis of dexamethasone was performed using the nonlinear effects modeling approach in NONMEM® first-order conditional estimates (FOCE) with interaction [version 7.4, ICON, Development Solutions, MD, USA], Pirana version 2.9.9 [Certara, NJ, USA], and data were further analyzed in R version 4.2.2 [R Foundation

Table 2
The PK parameters for base model and final model.

Parameter	Base model	RSE%	Shrinkage%	final model	RSE%	Shrinkage%	Bootstrap of the final model		
							Median	90% percentile (lower)	90% percentile (upper)
CL (L/h)	2.77	18		2.85	18		2.94	2.22	4.06
V1 (L)	14.2	29		15.4	48		15.24	4.75	32.15
V2 (L)	12.8	28		12.3	18		13.02	9.25	29.09
Q (L/h)	3.66	56		2.11	45		2.08	0.8	15.23
CRP-coefficient				−0.169	17		−0.18	−0.27	−0.12
IIV-CL (%)	70.3%	14	11	62.90%	21	11			
Residual variability	0.54	16	14	0.498	20	14	0.46	0.31	0.64

CRP: C-reactive protein, CL: clearance, IIV-CL: inter-variability on clearance, V1: central volume of distribution, V2: peripheral volume of distribution, Q: inter-compartmental clearance, IIV-CL: inter-individual variability on clearance.

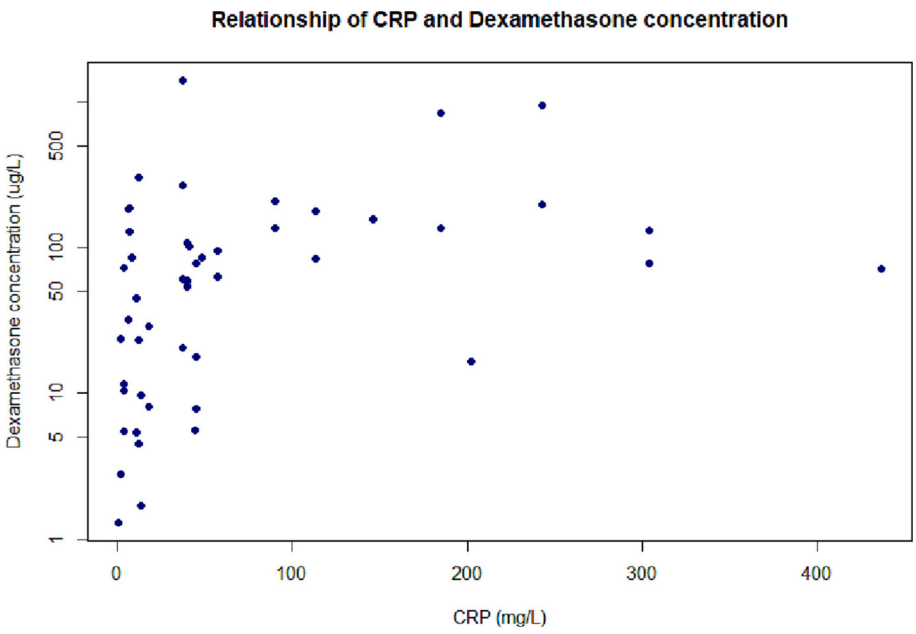

Fig. 1. Relationship of CRP and dexamethasone concentration. y axis: Patient dexamethasone concentration (μg/L), x axis: CRP (mg/L). CRP: C − reactive protein.

for Statistical Computing, Vienna, Austria]. All the concentration data were log transformed. The data were first fitted to a one-compartment model and tested sequentially for inter-individual variability (IIV) on CL, V. More complex models were tested and evaluated by the change in the objective function values (dOFV) and precision of the estimated PK parameters. A constant error model was used on the log transformed data to describe the residual error in the model predicted plasma concentrations.

2.2.2. Covariate analysis

Physiological and biochemical indicators, and age, gender, length, weight, BMI, BSA, albumin, ASAT, ALAT, GGT, LDH, eGFR, IL-6, CRP, PCT, WBC and potential interaction drugs including tocilizumab, potential CYP3A4 related drug interaction medication like erythromycin, voriconazole and fluconazole were tested as covariates.

For the covariate analysis the stepwise covariate modeling with forward inclusion-backward elimination method was applied. In the forward process a 3.84-point decrease in OFV for one degree of freedom was considered a significant improvement of the model with a p-value of <0.05. For the backward elimination process, the statistical criterion was set to an increase of OFV to 6.64 (p value 0.01) for one degree of freedom in the covariate selection.

2.3. Model evaluation

The diagnostic goodness of fit (GOF) plots were implemented for model comparison using R (4.2.2, 2022-10-31) and Xpose4 (4.7.2, 2022-06-09). The population/individual predicted concentration versus observed concentration and the individual/conditional weighted residual versus time after dose were plotted. The model was further validated using visual predictive checks (VPCs) by simulating 1000 datasets and was analyzed by the Xpose4 R package (version 4.7.2).The parameter shrinkage threshold was set to below 30% [26]. The condition number was used to estimate the collinearity of the parameters by a threshold of 1000 [27,28].

The bootstrap method was applied to test the robustness of the parameter estimations in Pirana/PsN. 1000 bootstrap dataset were generated by random repeated sampling from the original dataset with replacement and each model parameters were calculated. The parameters of the original dataset were compared with the median and the corresponding 95% confidence intervals of bootstrap replicates.

2.4. Model simulation

To show an illustration of the covariate effect in the final model on the plasma concentrations of dexamethasone, Monte Carlo simulations were performed by using NONMEM. The dexamethasone plasma concentrations under different covariates were simulated over a time course of 98 h and 6 mg intravenous doses were administered every 24 h for a total of ten doses. The median concentrations under different covariates were shown graphically.

3. Result

3.1. Study population

Data of 51 blood concentrations from 18 COVID-19 critically ill patients in Erasmus Medical Center were included in the analysis. An overview of the patient characteristics are summarized/presented in Table 1. One to six blood samples were collected for each patient and the sampling day after dosing range from day 1 to day 8. The sampling times ranged from peak (0–4 h after dose, $n = 8$), median (4–12 h after dose, $n = 18$) and the trough ($\geq$12 h after dose, $n = 25$). (see supplement file table). The patients had a median age of 63.5 years, and the majority were male (67%). Most of these patients were overweight or obese with high BMI or BSA. Tocilizumab was used in 12 of the 18 patients (the other 6 patients were sampled in the early phase of the pandemic when tocilizumab was not yet introduced). The potential drug interaction candidate, voriconazole, a CYP3A4 inhibitor, was identified in only one patient. Other laboratory tests, such as CRP, PCT and D-dimer, also showed wide variations from normal to extremely high values.

3.2. Data analysis

3.2.1. Model building

The logarithmic transformed concentration data were best described by a two-compartment model with an additive error used for the residual error. Due to sparse sampling and collinearity issues between the IIV estimates of CL and V1, only the inter-individual variability (IIV) on the clearance (CL) parameter was included using an exponential form.

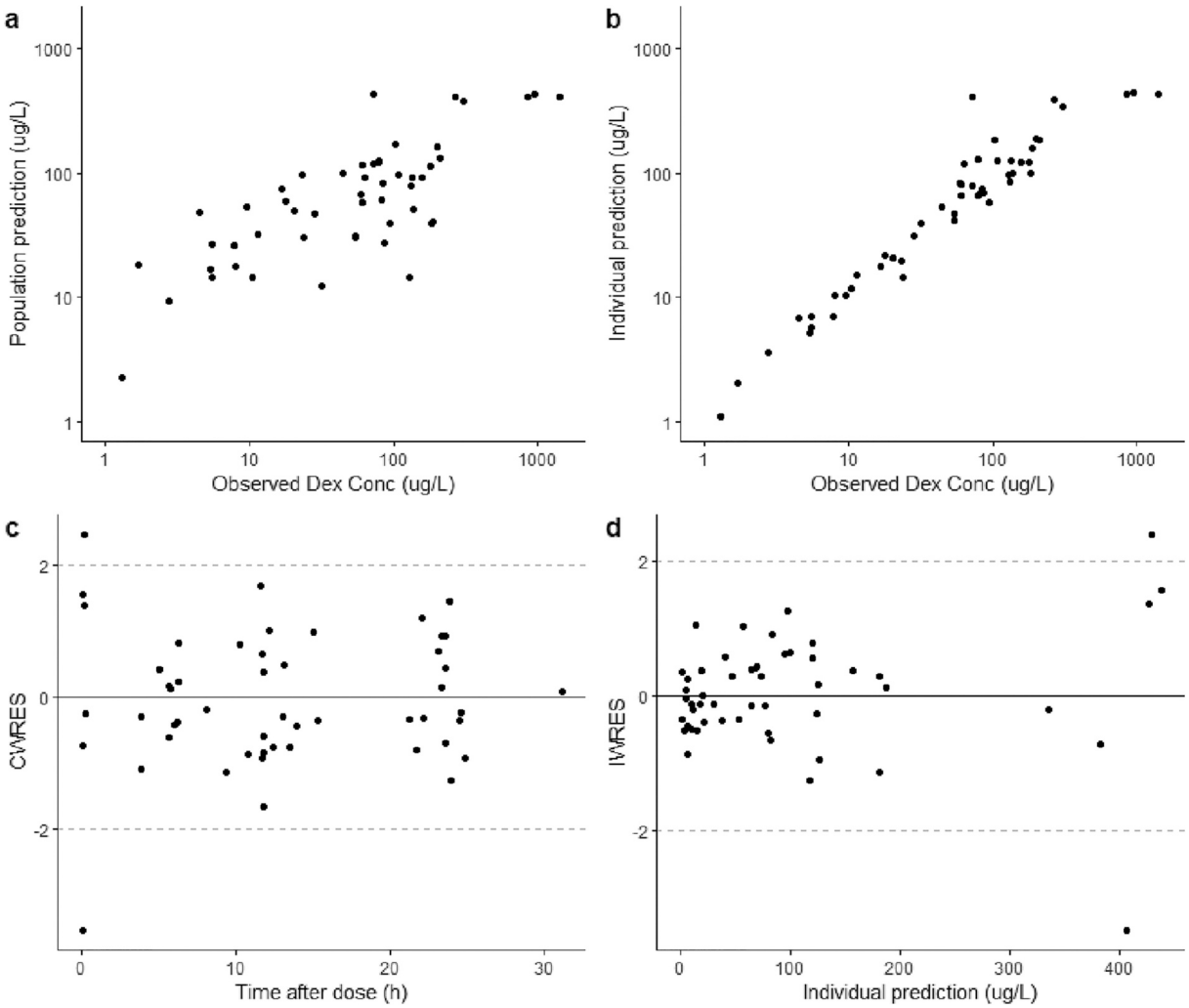

Fig. 2. Basic goodness of fit plots for the final model: population predictive concentration versus observed concentration (DV) (**upper left**); individual predictive concentration versus observed concentration (DV) (**upper right**); time after dose versus individual weighted residuals (IWRES) (**lower left**); time after dose versus conditional weighted residuals (CWRES) (**lower right**). CWRES: conditional weighted residuals, DV: dependent variable, IWRES: individual weighted residuals.

Estimated pharmacokinetic parameters included clearance (CL), inter-compartimental clearance (Q), volume of distribution in the central compartment (V1), volume of distribution in the peripheral (V2). We also tried to normalize the CL on bodyweight, but this did not improve the model and did not change the PK parameters. Table 2 listed the pharmacokinetic parameters, covariate coefficients, inter-individual and residual variability, and their relative standard errors (RSE) for the base and final population pharmacokinetic models. Compared with the base model, the parameters did not change much in the final model, however, the variability of residual error and inter-individual improved in the final model. The parameters in the final model were within the 5%–95% bootstrap results as shown in the 90% lower and upper percentile column in Table 2.

3.2.2. *Covariate analysis*

Covariates including patient basic characteristics (age, sex, weight, BMI, BSA), lab test (creatinine, albumin, bilirubin, ASAT, ALAT, CRP, PCT, IL-6, WBC, D-dimer) and comedication (voriconazole, tocilizumab) were screened on the inter variability on clearance. For continuous variables such as WBC, CRP, and PCT, we used the value divided by the median as covariate on the clearance. For categorical variables like gender and comedication, we gave different variables a value and multiplied it with typical clearance value. Only CRP, PCT and creatinine showed significant improvement on the model in a univariate analysis with a dOFV of 9.2, 9.7 and 10.3. Of these covariates the CRP showed a large improvement on the residual error (shown in Table 2) and PCT showed a large improvement on the IIV. On the other hand, the creatinine clearance related covariates (CRCL,CKD-EPI, MDRD) did not show any significant improvement on the model. Since adding both CRP and PCT to the model did not result in any improvement over including either covariate alone, after comprehensive consideration, we chose the CRP in the final model. Adding CRP into the equation decreased the objective function value (dOFV) about 9.7, which explained 10% of the IIV on CL. The relationship of CRP and dexamethasone was shown in Fig. 1.

3.3. *Model evaluation*

Fig. 2 showed that, except for three unusually high peak concentration values, when plotted against observed concentrations (DV), both population predictions (PRED) and individual predictions (IPRED) were evenly distributed around the mean line.

A visual predictive check (VPC) was executed (Fig. 3) to validate the model by simulating 1000 data sets, comparing the observed concentration with the distribution of simulated concentrations [29]. Fig. 3 showed the 95% confidence intervals derived from the VPC simulation contained the majority of the observed median and percentile values.

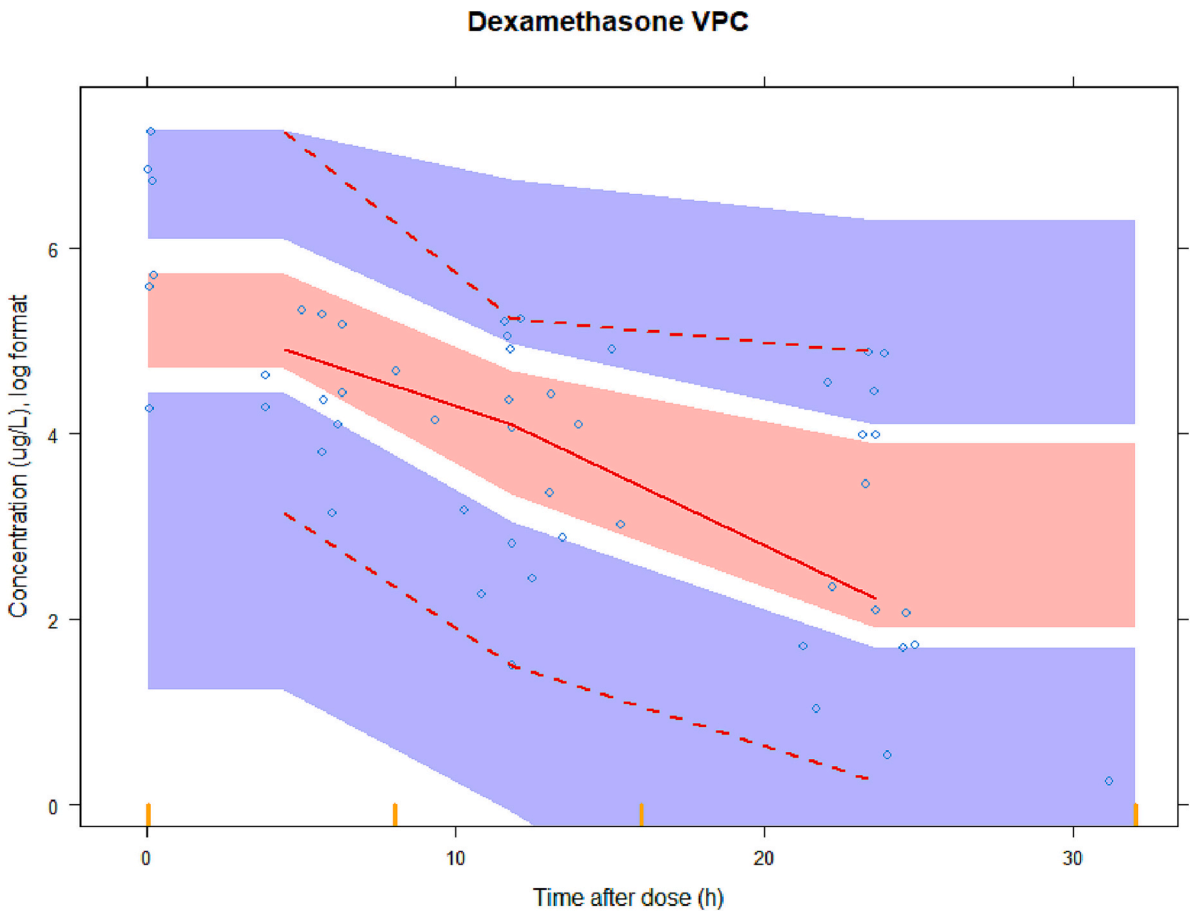

Fig. 3. The visual predictive check (VPC) of dexamethasone in the final. The x − axis is time after dose (h) and y − axis is concentration of dexamethasone in log transformed format. VPC: visual predictive check.

3.4. Model simulation

The simulation (n = 1000) results of the concentration with fixed dose dexamethasone (6 mg) under different CRP levels (5, 20, 50,100, 200 mg/L) on day 10 were shown in Fig. 4. The trough concentration (Time = 215.99 h) of the dexamethasone increased from 12 μg/L to 47 μg/L when the CRP increased from 5 mg/L to 200 mg/L in one dosing interval. Table 3 showed the 24-h AUC (AUC_{24hrs}) and the accumulated AUC over 0–256 h ($AUC_{0\text{-}256h}$) at different levels of CRP. We could see the median of AUC_{24hrs} and $AUC_{0\text{-}256h}$ increased from 1658 to 3094 μg*h/L and 16,550 to 30,602 μg*h/L respectively with the CRP increase from 5 to 200 mg/L.

4. Discussion

This is the first population pharmacokinetic study of dexamethasone in critically ill COVID patients. In our study, a two-compartment model with first-order kinetics best fitted the data. Our study found high heterogeneity in dexamethasone concentrations in ICU patients with COVID-ARDS.CRP level was an important covariate which explained between-subject variability of the dexamethasone clearance. The relation between inflammation (CRP) and pharmacokinetics of a corticosteroid have not been reported before and might have clinical relevance.

The clearance of dexamethasone in the ICU patients was 2.8 L/h, which was lower than previously published non-ICU dexamethasone pharmacokinetic studies (median range from 9 to 40 L/h) [20,30-32]. Consequently, ICU patients exhibited a longer half-life of dexamethasone, approximately 9 h, compared to the previous published studies in the non-ICU population (with a range of 1 to 5 h) [30,33,34]. In our study the half-life of dexamethasone in ICU patients could range from 5 to 19 h, hence after 24 h the dexamethasone might have already disappeared in some patients but remained relatively high in other patients. So individualize the dosing interval might prove to be beneficial. A longer half-life indicates higher drug exposure in COVID ICU patients compared to outpatients or healthy individuals. As higher dexamethasone AUC may indicate stronger anti-inflammatory effect [17,35] the same dose of dexamethasone in ICU patients may excerpt higher anti-inflammatory effect than in the non-ICU patient. This might partly explain why a higher dose (12 mg) did not improve efficacy and patient outcomes compared with conventionally administered doses (6 mg) [11], which may indicate the corticosteroids levels for the COVID critically ill patients were already higher than expected.

We found that the CRP and PCT were important covariates which can explain the inter-individual variability (IIV), but based on covariate screening, only CRP was left in the final model. This is an interesting finding because in the past, we only studied the effect of the corticosteroids on inflammation, not the other way around. Although dexamethasone induces its own metabolism through induction of CYP3A, hence accelerating drug clearance, this may take several days or weeks to achieve and might be dose dependent [36]. Our finding showed that the inflammation itself might affect dexamethasone drug clearance and that CRP levels could be a good indicator to describe this effect. With high CRP level, the clearance will be lower thus the drug exposure will be relatively higher. This is an interesting finding, which suggested that the current fixed-dose strategy of dexamethasone for several days in ICU COVID patients may not be appropriate. The drug exposure might be too high for some patients during the hyperinflammatory state which might be beneficial for rapid anti-inflammatory effect, but might also increase

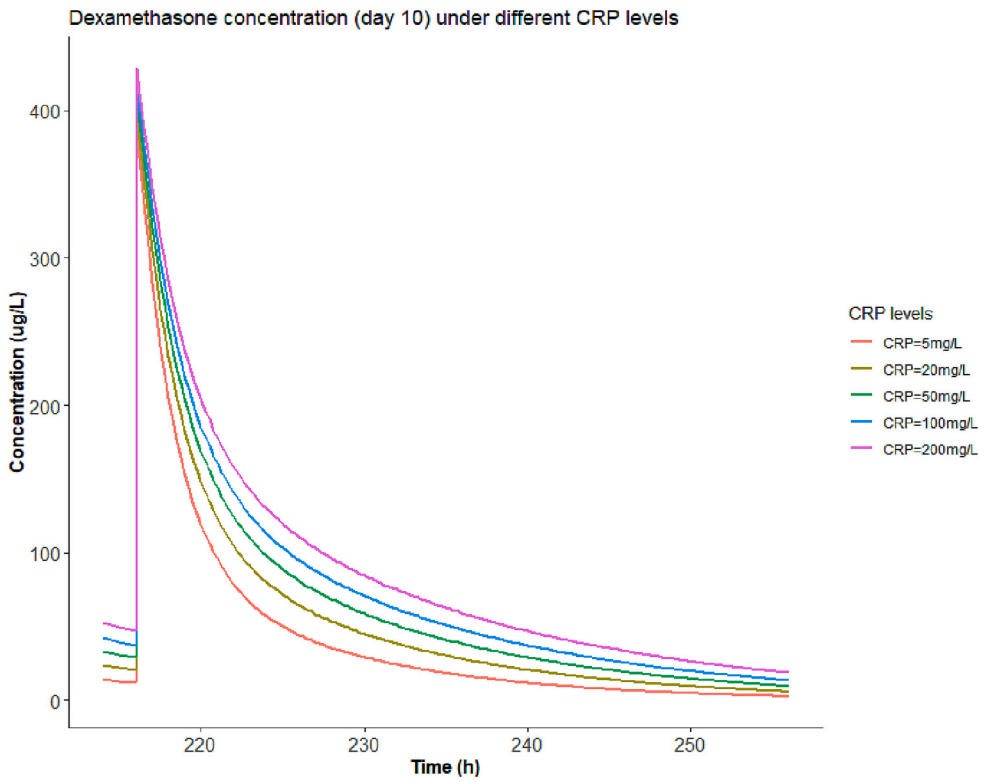

Fig. 4. Simulation results of different CRP levels on the concentration of dexamethasone in standard ICU patient on day 10. effect of different CRP levels (5, 20, 50, 100 mg/L) on the dexamethasone concentration, All dexamethasone simulations were performed at a dose of 6 mg q24h for 10 days, the last dose was on time = 216 h, the median concentrations are used to plot the simulation. CRP: C-reactive protein.

Table 3
The AUC results for dexamethasone concentration simulation under different CRP levels.

CRP (mg/L)	AUC_{24hrs} (μg*h/L)			$AUC_{0\text{-}256h}$ (μg*h/L)		
	5%	50%	95%	5%	50%	95%
5	623	1658	4346	6230	16,550	42,445
20	788	2096	5493	7874	20,880	52,863
50	919	2447	6411	9191	24,327	60,897
100	1034	2752	7204	10,332	27,293	67,616
200	1162	3094	8089	11,613	30,602	74,902

the adverse reaction or toxicity related to dexamethasone. On the other hand, in some stable patients with inflammatory markers in the normal range, dexamethasone exposure may be too low, with a risk of insufficient anti-inflammatory effect. ICU patients may frequently experience hyper- and hypo-inflammatory states during treatment and dexamethasone exposure might be quite different in different dosing occasion and time. The within patient variability on clearance is comparable to the interindividual patients variability on the clearance. Dosage adjustment should be considered when the patient's inflammatory state changes to balance adverse drug reactions (immune dysfunction) [37,38] and insufficient anti-inflammatory effects.

The negative correlation between inflammation levels and drug clearance, where higher CRP or IL-6 results in lower clearance, had been observed in previous studies in this population for other drugs (midazolam, voriconazole) as well [39,40]. However, for dexamethasone the situation is even more complex since the dexamethasone itself could reduce the inflammation, so it is more difficult to distinguish the cause/result direction. In our study the CRP relationship with the dexamethasone clearance reached its maximum effect at 100 mg/L, this might be due to several reasons. One explanation might be the inflammation reached its maximum effect on clearance the CRP exceeds 100 ng/mL. It could also be that when CRP was continuously elevated, the patients were more likely severely ill and many other factors might affect the PK of dexamethasone, thereby weakening the effect of CRP on dexamethasone clearance. Another reason might be most patients in our study had CRP under 100 mg/L, thus blurred effects of higher CRP levels on dexamethasone clearance.

Dexamethasone is mainly metabolized by CYP3A4 and many studies have shown the drug interaction with dexamethasone [41-43]. For the ICU COVID-19 patients, many drugs used in the treatment may have drug-drug interactions with dexamethasone, including anti-COVID medication nirmatrelvir-ritonavir and disease specific related medication (azoles, rifampin, clarithromycin etc.). However, in our study, only one patient had a potential drug-drug interaction (voriconazole), thus we failed to detect the covariate effect of co-medication on dexamethasone due to the lack of statistical power for the clearance. Further studies should include more data to explore the impact of drug interactions on the pharmacokinetics of dexamethasone. In addition, in our study IL-6 had no significant improvement on model, this maybe two reasons, one is that 12 of these patients received tocilizumab which will interfere the IL-6 concentration. Another reason might be that one study had shown the therapeutic effect of dexamethasone did not involve the IL-6 pathway [44].

Our results showed that dexamethasone concentrations in patients with severe COVID-19 were highly heterogeneous and need to be monitored and dosed individually. This is also consistent with the clinical situation, as patients with severe COVID-19 are more likely to be elder, obese, and have more underlying diseases and comorbidities (diabetes, hypertension). For those different patient subgroups, they may have different PK parameters and which was reflected in the highly variability and dispersion of PK parameters in our results.

There were some limitations in our study. First, the number of patients were small and samples were limited and therefore the ability to build more complex models with more accurate estimates of parameters,

such as inter-compartmental distribution clearance (Q) and find more covariates effects may be limited. In addition, we only found an association between CRP and dexamethasone clearance, but were unable to make causal inferences to determine whether inflammation was responsible for the increased dexamethasone clearance. Further and larger studies on pharmacokinetics and pharmacodynamics of dexamethasone under different doses in ICU patients are warranted in order to precision treatment and increase the prognosis or COVID ICU patients.

5. Conclusion

Our study showed that the pharmacokinetics of dexamethasone could be best described by a two-compartment model. The dexamethasone PK parameters of ICU COVID patients were different from those from healthy populations. Inflammation, reflected by CRP, might play an important role in dexamethasone clearance. Further studies are needed in larger groups of patients to explore the PK-PD effect and the ideal concentration target of dexamethasone.

Ethical approval

This study was conducted in accordance with the principles of the Declaration of Helsinki (version October 2008) and approved by the Erasmus MC Medical Ethics Committee (ORACLE study, MEC-2020-0381). Informed consent was obtained from all patients or their legal representatives involved in the study.

Availability of data.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

LL, SS, BK and HE contributed to the conceptualization of the study; acquisition of data, TS, TE, SS and LL contributed to the acquisition of patient related data; SB interpreted the lab related results; LL and SS did the main formal analysis; LL conducted the original draft writing; all authors contributed to the review and editing of the draft. All authors have read and agreed to the published version of the manuscript.

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Declaration of Competing Interest

The authors declared no competing interests for this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2023.154395.

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