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Voriconazole exposure is influenced by inflammation: A population pharmacokinetic model

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ABSTRACT

Background: Voriconazole is an antifungal drug used for the treatment of invasive fungal infections. Due to highly variable drug exposure, therapeutic drug monitoring (TDM) has been recommended. TDM may be helpful to predict exposure accurately, but covariates, such as severe inflammation, that influence the metabolism of voriconazole have not been included in the population pharmacokinetic (popPK) models suitable for routine TDM.

Objectives: To investigate whether the effect of inflammation, reflected by C-reactive protein (CRP), could improve a popPK model that can be applied in clinical care.

Patients and methods: Data from two previous studies were included in the popPK modelling. PopPK modelling was performed using Edsim++. Different popPK models were compared using Akaike Information Criterion and goodness-of-fit plots.

Results: In total, 1060 voriconazole serum concentrations from 54 patients were included in this study. The final model was a one-compartment model with non-linear elimination. Only CRP was a significant covariate, and was included in the final model and found to affect the maximum rate of enzyme activity (V_{max}). For the final popPK model, the mean volume of distribution was 145 L [coefficient of variation percentage (CV%)=61%], mean Michaelis–Menten constant was 5.7 mg/L (CV%=119%), mean V_{max} was 86.4 mg/h (CV%=99%) and mean bioavailability was 0.83 (CV%=143%). Internal validation using bootstrapping resulted in median values close to the population parameter estimates.

Conclusions: This one-compartment model with non-linear elimination and CRP as a covariate described the pharmacokinetics of voriconazole adequately.

1. Introduction

1.1. Background

Voriconazole is one of the preferred antifungal drugs for treatment and prophylaxis of invasive aspergillosis. It is metabolized by the cytochrome P450 (CYP) isoenzymes CYP2C9, CYP2C19 and CYP3A4, partly explaining its highly variable serum concentrations [1,2]. The targeted trough concentration (C_{min}) is based on the area under the curve/minimum inhibitory concentration

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(AUC/MIC) ratio [3,4]. To maximize therapeutic success, the targeted AUC_{0-24}/MIC ratio is 18–22, corresponding with a C_{min} ranging from 1 to 6 mg/L [3,5].

In observational studies, higher voriconazole concentrations have been observed during severe inflammation, reflected by higher C-reactive protein (CRP) concentrations [6–8]. Many studies have reported an association between CRP and voriconazole metabolism in adults [7–16], but four studies in children have reported conflicting results. Two studies described this association in paediatric patients [17,18], while one study described no significant association in paediatric patients [19], and another study described a significant association in children aged 11–18 years but no association in children aged 2–10 years [20]. The popPK model of Gastine et al. [21] of voriconazole investigated the effect of CRP on voriconazole clearance, but the data did not support the inclusion of CRP. There is no additional information why they did not include CRP; however, this was a model developed for children, and the CRP levels were low in this study (median 0.6–1.4 mg/dL). Jiang et al. [22] included CRP in a popPK model, but did not have many blood samples. In addition, in a retrospective analysis, a strong correlation was observed between children aged ≥12 years and CRP [23]. As voriconazole is predominantly metabolized by CYP2C19, the link between the high voriconazole concentration and CRP was nicely demonstrated by an in-vitro study showing an interleukin-6 (IL-6)-driven decrease in CYP2C19 mRNA of 30–50% in human hepatocytes [24]. Another study used omeprazole, a typical CYP2C19 substrate, to validate the finding of inflammation influencing the CYP2C19 activity [25].

Target-concentration-driven drug dosing of voriconazole has been a challenge in clinical practice when severity of inflammation, reflected by CRP levels, is variable, as the available popPK models do not predict exposure accurately. The aim of this study was to investigate whether the effect of inflammation, reflected by CRP, could improve a popPK model that can be applied in clinical care [10].

2. Patients and methods

2.1. Study population and sampling

Data from two previous prospective studies were used: one study is unpublished (CCMO No. P06.0360L, METC No. 2005-184) and the other study is by Veringa et al. [6]. These two studies included adult patients treated with voriconazole. They received voriconazole for prophylaxis and treatment of invasive fungal infection. Patients received two voriconazole loading doses of 6 mg/kg on day 1 followed by a maintenance dose of 4 mg/kg twice daily intravenously, or a loading dose of 400 mg twice daily followed by a maintenance dose of 200 mg twice daily orally. The dose of voriconazole was adjusted if the trough concentration was <1.5 mg/L or >5.5 mg/L. In brief, the quantity by which the dose was adjusted depended on the deviation of the trough concentration from the target concentration, and ranged from an increase or decrease of 50–200 mg per dose for oral administration or 0.5–3 mg/kg for intravenous administration. If the trough concentration was >5.5 mg/L, a dose could be skipped depending on the presence of adverse events and subsequent administration of a lower maintenance dose. The first prospective study included 18 patients, and total voriconazole concentrations were measured pre-dose at the first administration and 1, 2, 4, 8 and 12 h after this administration. On days 3, 5 and 8 of treatment, blood samples were collected directly before, and 1 and 3 h after the morning dose. For the other study, total voriconazole concentrations were measured in leftover blood samples collected longitudinally during treatment for 36 patients [6]. For eight of these patients, at least one additional random (non-trough) voriconazole concentration was measured [6]. All 54 patients were included for development of the popPK model. Data and patient characteristics were obtained from the original study [6] and the electronic medical records.

2.2. Population pharmacokinetic model

As a starting point for the popPK model, the literature was searched to obtain an overview of all published voriconazole popPK models (Table S1, see online Supplementary material). The selection criteria for this table were: (1) popPK models for voriconazole; (2) the study population were humans; (3) the study population were adults; and (4) the full text was available in English. Based on a review of popPK [26], the parameters were initially set to: bioavailability (F)=0.84 for oral administration and 1.00 for intravenous administration, absorption rate constant (Ka)=1/h, volume of distribution (V_d)=150 L (for one-compartment models) or 90 L [compartment 1 ($V_{d,1}$) of two-compartment models] and 120 L [compartment 2 ($V_{d,2}$) of two-compartment models), and intercompartmental clearance was initially set to 25 L/h for a two-compartment model. For models with Michaelis–Menten elimination, the Michaelis constant (K_m) was initially set to 2 mg/L and the maximum rate of enzyme activity (V_{max}) was set to 30 mg/h. For linear elimination models, clearance was initially set to 10 L/h for a one-compartment model and 5 L/h for a two-compartment model [26].

The modelling software used for this study was Edsim++ Version 1.9.1.30 (Mediware, Prague, Czech Republic). Edsim++ is an object-oriented visual PK/PD modelling application that generates a set of ordinary differential equations (ODEs) from a visual representation of the model. ODEs are solved using the fourth-order Runge–Kutta method using adaptive step error control. Model parameters can be estimated based on one or more observations of one or more variables. The KinPop++ plugin of Edsim++ is used for population modelling purposes in which multiple patients are analysed simultaneously using an iterative two-stage Bayesian method yielding a set of common population parameters, and for each patient, a set of individual parameters. Covariates can considered by so-called 'parameter modulation'.

One- and two-compartment models with linear and/or Michaelis–Menten elimination were tested. All models were compared using the Akaike Information Criterion (AIC), where AIC is defined as (-2)log-(maximum likelihood) + 2 (number of independently adjusted parameters within the model) [27]. When comparing the models, AIC corrects for added parameters in contrast to the objective function value, which is defined as: (-2)log-(maximum likelihood). The model with the lowest AIC value was considered as the best model to describe the data. In addition, goodness-of-fit plots were used to compare models.

After the best base model was selected, based on AIC and goodness-of-fit plots, covariates were tested in terms of V_d and V_{max} to develop the final model. The following covariates were tested: body weight (BW), CRP, alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT). CRP was tested with an exponential correlation, according to the findings of Veringa et al. [6]; all other covariates were tested with a linear correlation. BW was tested on both V_d and V_{max}, and all other covariates were tested on V_{max} alone. Using an exponential relationship for CRP avoids negative covariate effect values at high CRP levels which would occur in a linear relationship.

All parameters were Bayesian fitted, except for additive error and proportional error. The errors were common population fitted. Common population is a setting in Edsim++ where the parameter is estimated but is the same for every patient. It was possible to estimate the absolute F of voriconazole because patients received both intravenous and oral doses. In some cases, F was estimated to

Table 1
Baseline patient demographics of the patients that were used for the population pharmacokinetics analysis.

Characteristics	*n*
Patients, *n* (%)	54
Male/female	38/16 (70/30)
Admitted to intensive care unit	15 (28)
Solid organ transplantation	8 (15)
Haematological malignancy	33 (61)
Observation time (days)	11 (0.5–114)
Age (years)	52 (19–73)
Body weight (kg)	77 (49–118)
Body height (cm)	174 (116–198)
Body mass index (kg/m^2)	25.7 (15.7–50.5)
CRP (mg/L)	91 (0.3–434)
ALP (U/L)	149 (11–527)
AST (U/L)	44 (10–511)
ALT (U/L)	54 (8–743)
GGT (U/L)	190 (7–1367)
Bilirubin (μmol/L)	20 (2–155)

CRP, C-reactive protein; ALP, alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyltransferase.
Data are presented as median (range), unless otherwise specified.

be >1, which is impossible. Therefore, in this model, F was parameterized as 1-F ('bio-unavailability') in order to maximize its value to 1.0.

For internal model validation, 1000 bootstrap replicates were used. The 95% confidence interval and median values were compared with the final model. No inter-occasion variability was evaluated in this model because that would conflict with the hypothesis that CRP reflects voriconazole in a highly time-dependent manner. Dividing the treatment period into occasion slots would potentially mask this effect.

3. Results

Twenty-two popPK models were retrieved from the literature (Table S1, see online Supplementary material). The most common model structure in the literature was a one-compartment model with first-order absorption and elimination, and was found in both rich datasets and datasets consisting of C_{min} measurements alone. Therefore, this model was chosen as the initial model to test if other models could fit the data better. In total, 1060 voriconazole concentrations were included, obtained from 54 patients. Sixty-one percent of these patients had haematological malignancy, and 15% had a solid organ transplantation. Of these 54 patients, 28% were admitted to the intensive care unit (ICU). The median number of samples per patient was 15, and the median and mean days of observation were 11 and 16 days, respectively. Baseline patient characteristics are shown in Table 1, and Fig. S1 (see online Supplementary material) shows the relationship between cumulative AUC and cumulative dose given.

For development of the base model, different models were used to test if these models fit the data better than the one-compartment model with first-order absorption and elimination. One- and two-compartment popPK models were tested. Subsequently, models with linear elimination and/or Michaelis–Menten elimination were tested. Finally, k_a, lag time (t_{lag}) and F were tested. All tested models are described in Table 2. All models without F or t_{lag} in this table had a fixed F of 1 and a fixed t_{lag} of 0 h. Models 1–9 in Table 2 had a fixed additive error of 0 mg/L and a fixed proportional error of 15%. These errors were fitted in Models 10–23.

A one-compartment model with Michaelis–Menten elimination was found to be the best base model due to the lowest AIC (4635) and the best goodness-of-fits plots. In this model, there was no t_{lag}, and F was estimated but maximized to 1. Finally, the proportional and additive errors were fitted.

Table 2
All tested models to find the best base model and final model for voriconazole. Values in bold are the models that had the lowest AIC value and were used to test more parameters. An empty row means a parameter is added.

Model tested	AIC value
Base model	
C1_ME	10769
C1_NL	**9023**
C1_ME_NL	9249
C2_ME	10845
C2_NL	9024
C2_ME_NL	9267
C1_NL_F	**8558**
C1_NL_t_{lag}	9193
C1_NL_F_t_{lag}	8678
C1_NL_F_t_{lag} with fitted errors	4934
C1_NL_F with fitted errors	**4635**
Covariates for Final model	
LnCRP-NL	**4094**
LnCRP-NL + BW-NL	5085
LnCRP-NL + BW-V	5067
LnCRP-NL + BW-NL + BW-V	5073
BW-NL	4664
BW-V	4637
BW-V + BW-NL	4655
ALT-NL	5457
BIL-NL	5480
AST-NL	5365
ALP-NL	5749
GGT-NL	5742

ALP = alkaline phosphatase, ALT = alanine transaminase, AST = aspartate transaminase, BIL = bilirubin, BW = bodyweight, C1 = one-compartment model, C2 = two-compartment model, LnCRP = C-reactive protein exponentially estimated, F = bioavailability, GGT = gamma-glutamyltransferase, ME = linear metabolic elimination, NL = non-linear elimination, t_{lag} = lag time, V = volume of distribution.

The covariates that were tested to develop the final model were: BW, CRP, ALT, AST, bilirubin, ALP and GGT. None of the covariates tested on V_d improved the model. CRP was the only covariate that improved the model, with an impact on V_{max}. The fitted exponential factor of CRP (mg/L) was 0.0046, and $V_{max,pop}$ is the population value of V_{max} (= 86.4 mg/h), so the formula to determine V_{max} is:

$$V_{max} = V_{max,\ pop} \cdot e^{-0.0046\ \cdot\ CRP}$$

From this equation, it can be calculated that with every 150 mg/L increase in CRP, V_{max} is halved. This exponential influence of CRP on V_{max} means that the influence of the same increase of CRP concentration is greater at lower CRP concentrations than higher CRP concentrations.

Based on the results in Table 2, the final model was a one-compartment model with Michaelis–Menten elimination including CRP as a covariate on V_{max} (Table 3). Next to that, the results of bootstrapping are shown. The median bootstrap values were close to the population estimates. Finally, the goodness-of-fit plots of the final model are shown in Figs 1 and 2.

4. Discussion

This popPK model incorporated CRP as a covariate for the clearance of voriconazole. This model, with the incorporation of CRP as a covariate for V_{max} of voriconazole, confirms the findings of previous research investigating the relationship between CRP and voriconazole concentrations [6] (Fig. S2, see online Supplementary material). Due to the saturation pharmacokinetics of the model, there will be a CRP concentration where steady state will not be achieved. Therefore, the figure is limited to a certain CRP concentration, depending on the dose. The popPK were best described

Table 3
Pharmacokinetic parameters of the final model of voriconazole and the bootstrap validation.

Base model								
	F	k_a (1/h)	V_d (L)	K_m (mg/L)	V_{max} (mg/h)	CRPE.k	Additive error (mg/L)	Proportional error (%)
Mean	0.86	0.62	179	2.6	31	-	0.04	-
CV% (%)	156	127	65	173	52	-	-	-
Final model								
Mean	0.83	0.62	145	5.7	86	0.0046	0.31	12
CV% (%)	143	135	61	119	99	120	-	-
Shrinkage (%)	44.2	45.2	14.0	29.9	25.3	24.4		
RSE (%)	19	19	8	16	13	16	6	5
Median	0.83	0.62	145	5.7	80	0.0048	-	-
Bootstrap								
Median	0.86	0.62	147	5.8	79	0.0041	0.39	14
95% CI	0.73–0.95	0.22–1.38	120–182	2.61–49.7	47–595	0.0025–0.0070	0.17–0.58	0.087–0.23

CV%, coefficient of variation percentage; RSE, relative standard error; CI, confidence interval; V_d, volume of distribution; K_m, Michaelis constant; V_{max}, maximum velocity of the reaction; F, bioavailability; k_a, absorption rate constant; CRPE.k, exponential factor of CRP on V_{max}.

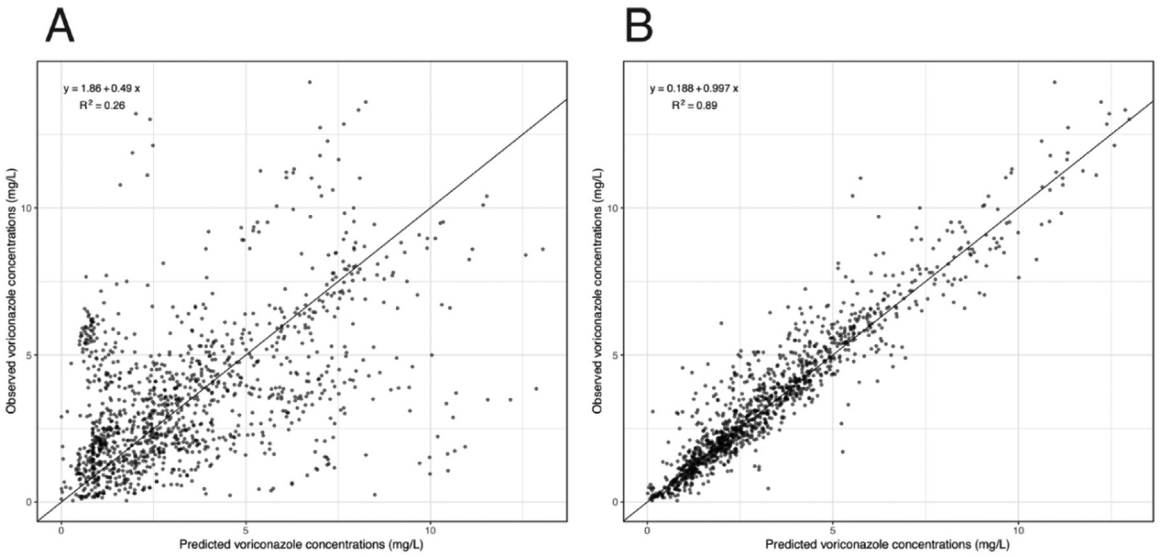

Fig. 1. Goodness-of-fit plots for voriconazole for the final model including C-reactive protein as covariate. (A) Observed vs predicted population concentrations. (B) Observed vs predicted individual concentrations.

with a one-compartment model with Michaelis–Menten elimination. The only covariate that showed significant correlation with the concentration of voriconazole was CRP on V_{max}.

A one-compartment voriconazole popPK model has been described previously [28–33]. However, only one of the published one-compartment models used Michaelis–Menten elimination [34]. This is remarkable because the pharmacokinetics of voriconazole are non-linear due to capacity-limited elimination (i.e. CYP2C19) [35,36]. However, to estimate the degree of non-linearity in a model in individuals or populations, multiple dosing regimens are required [37]. In the study population, dosing regimens changed over time within a patient if therapeutic concentrations were not achieved earlier. This could explain why it was possible to determine non-linear elimination for voriconazole.

V_{max} for voriconazole in the model was 86.4 mg/h [coefficient of variation percentage (CV%)=99%]. The high CV% could be explained by an insufficient number of samples within the dosing interval, and the large inter- and intrapatient variability in voriconazole exposure. Compared with the only one-compartment model with both non-linear elimination and linear elimination, the estimated V_{max} is higher. Mangal et al. [34] reported V_{max} of 48.4 mg/h for normal and intermediate CYP2C19 metabolizers, and V_{max} of 62.4 mg/h for rapid and ultrarapid CYP2C19 metabolizers; however, no information on the CYP2C19 genotype for each patient was available to investigate this difference in phenotype. In addition, the CV% for V_{max} increased when CRP was included (from 52% in the base model to 99% in the final model). The overall model fit and parameters improved because the individual estimations were better; as such, CRP was included in the final population model.

K_m in this popPK model was 5.7 mg/L (CV%=119%). This is higher than the values found in the literature, which range from 1.15 mg/L [38] to 3.33 mg/L [39]. In addition, the fitted CV% was >100% with a value of 6.8 mg/L, and therefore there is large variation in the population. The large CV% could be a result of model misspecification. Model misspecification means that the popPK model is too simplistic, and the model does not account for all regressions. This results in larger errors and CV% to compensate for these regressions [40], such as for the CYP2C19 phenotype. As the CYP2C19 genotype was unknown for 33/54 (61%) patients, no analysis could be performed for this covariate, but other published models that included CYP2C19 phenotype as a covariate [29,30,34,39,41,42] still reported large CV% or standard deviation values (Table S1, see online Supplementary material). In addition, the large CV% could also be a result of retrospective patient data. Compared with systematic measurements and dosing, retrospective patient data lead to more heterogeneous data with inherent variability. In addition, one patient had more than 100 voriconazole samples, and this could also have influenced the results. Further research with more than one concentration measurement during

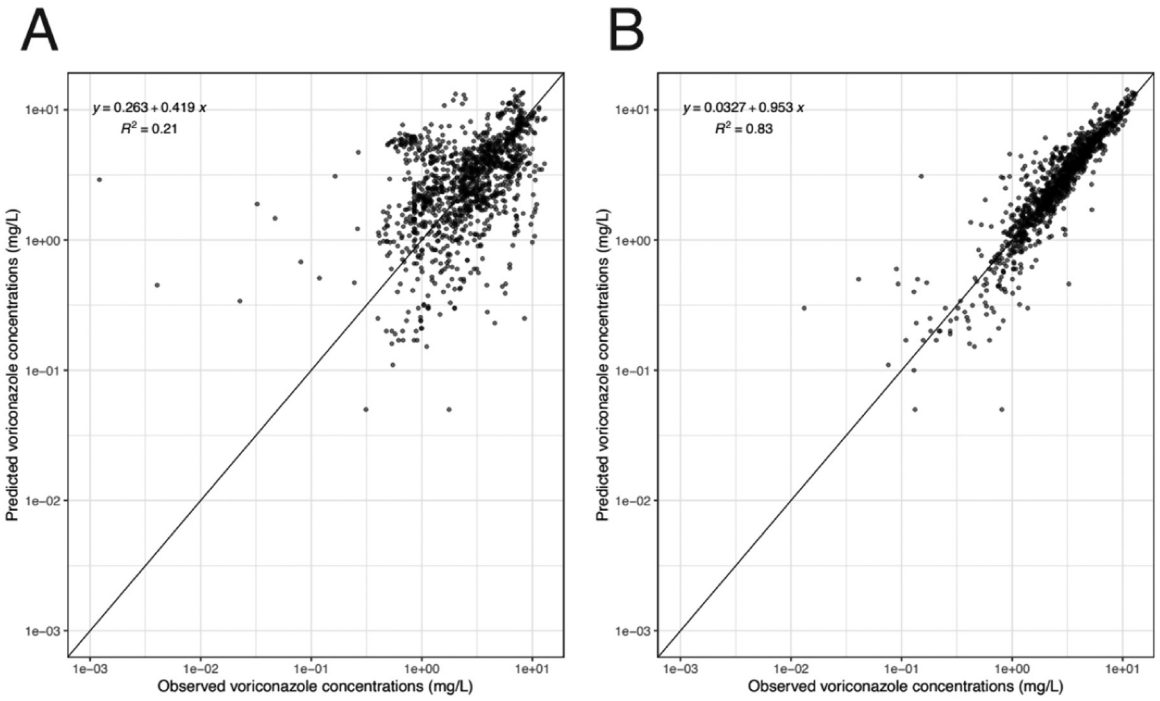

Fig. 2. Goodness-of-fit plots with log-transformed concentrations for voriconazole for the final model including C-reactive protein as covariate. (A) Observed vs predicted population concentrations. (B) Observed vs predicted individual concentrations.

the dose interval is needed to lower CV% and make a better estimate of the non-linear parameters.

V_d of this model was 145 L, which is in line with the range of 68.7–200 L reported in other studies [43,44]. The estimated F of 0.83 and the estimated k_a of 0.62/h were in the range of other studies (0.459–0.942 [39,45] and 0.163–316/h [44,46], respectively).

This popPK model incorporated CRP as a confounder for the non-linear clearance of voriconazole with an exponential factor of 0.0048. This means the metabolic rate of voriconazole decreases by 50% for every 150 mg/L increase in CRP. Interestingly, Chantharit et al. found serum albumin to be a novel marker for voriconazole clearance [28]. Inflammation may cause hypoalbuminaemia, expressed by IL-6 and tumour necrosis factor-α [47,48]. IL-6 may inhibit albumin synthesis but also stimulate CRP synthesis [49,50]. This indicates that both CRP and serum albumin levels are influenced by inflammation, and may therefore act as covariate on voriconazole clearance. The popPK model of Gastine et al. [21] of voriconazole investigated the effect of CRP on voriconazole clearance, but the data did not support the inclusion of CRP. There is no additional information why they did not include CRP; however, this was a model developed for children, and the CRP levels were low in this study (median 0.6–1.4 mg/dL). Jiang et al. [22] included CRP in a popPK model, but did not have many blood samples. In addition, in a retrospective analysis, strong correlation was observed between children aged ≥12 years and CRP [23].

This study had some limitations. Albumin as a covariate could not be evaluated, as neither study reported serum albumin data. Therefore, it was not possible to confirm the relationship as proposed by Chantharit et al. [28]. Secondly, for 28 patients, C_{min} alone was measured, resulting in large variability of V_{max} and K_m. Thirdly, one patient had 162 voriconazole samples, which is a substantial contribution to the total of 1060 voriconazole samples; this could have influenced the results. In addition, genotype and ethnicity were not included in the model development process. This could be considered as a limitation; however, in practice, genotyping lasts for several weeks and when someone is admitted with a serious infection, genotype is not usually available at the start of therapy. CRP, however, is available immediately. In addition, ethnicity does not predict genotype accurately. Furthermore, the data set included a diverse patient cohort, including 61% patients with haematological malignancy, and 28% ICU patients and patients who had undergone organ transplantation. Recently, it has been shown that ICU patients with liver failure have a higher half-life of voriconazole [51]. In addition, patients admitted to the ICU [52,53] generally have fluid balance changes due to fluid therapy and/or oedema, altered renal and hepatic function, and can have increased cardiac output. This can lead to altered clearance and V_d, with a prolonged half-life leading to changes in plasma concentrations.

The study population was variable, which means that there was inherent interpatient variability in the data set. As the study was not powered for subgroup analysis, separate analyses were not performed for different patient groups. Finally, Edsim++ does not currently support visual predictive checks, so these were not created for this model. In addition, a sensitivity analysis was not performed for influential individuals because this is covered by the bootstrap analysis, as patients may be completely absent or over-represented in individual bootstrap runs. This also addresses outlier patients.

PopPK models are not often developed for use in model-informed precision dosing [54]. The use of this popPK model can serve as a suitable approach for TDM of voriconazole. It is likely that the clearance of more drug-metabolizing enzymes is affected by the inflammatory state [55], and more research is required to investigate this influence. In addition, dose adjustments are not only based on patient characteristics, but also on the state of illness. Other biomarkers, such as IL-10, procalcitonin and galactomannan, can be used to guide anti-infective therapy and should be incorporated in popPK models [54,56]. In these studies, the degree of inflammation was expressed by CRP concentrations. These values, however, are dependent on the pro-inflammatory cytokine response and the subsequent down-regulation of CYP-isoenzymes [6]. CRP itself is a non-specific marker, and is therefore dependent on which pro-inflammatory cytokines play a role in specific underlying diseases resulting in CRP changes. Furthermore, before this

popPK model can be implemented fully in clinical care, assessment of predictive performance and validation with a separate external dataset should be performed.

To conclude, a popPK model was developed for TDM of voriconazole incorporating CRP as a measure of inflammation suitable for routine TDM. The metabolic rate of voriconazole decreased by 50% for every 150 mg/L increase in CRP.

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Competing interests

None declared.

Ethical approval

This study was a post-hoc analysis of previously published data [6]. The original study was evaluated and approved by the local ethics committee of University Hospital Medical Centre Groningen (IRB 2013-511), and registered at ClinicalTrials.gov under registration number NCT02074462. For this post-hoc analysis, ethical approval was waived by the same local ethics committee.

Author contributions

Conception and design of the study: DJT.
Acquisition of the data: AV, TvdW, JWCA.
Analysis and interpretation of the data: AvdB, AGM, NCP, MGGS.
Drafting the manuscript: AvdB, AGM.
Revising the manuscript: AV, NCP, TvdW, JWCA, MGGS, DJT.
Approval for submission: DJT.
All authors approvedthe final version for submission.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.106750.

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