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Meta-pharmacokinetic analysis of posaconazole following dosing of oral suspension, delayed-release tablet, and intravenous infusion in patients vs. healthy volunteers: Impact of clinical characteristics and race

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ABSTRACT

Objectives: To investigate the potential impact of clinical characteristics and the Chinese race on posaconazole pharmacokinetics in patients using an integrated population pharmacokinetic model for posaconazole oral suspension (SUS), delayed-release tablet (DR-tablet), and intravenous (IV) infusion that was developed in healthy volunteers (HV).

Methods: 1046 concentrations from 105 prospectively studied Caucasian patients receiving either of the three posaconazole formulations were pooled with 3898 concentrations from 182 HV. Clinical characteristics were tested for significance. The impact of Chinese race was assessed using 292 opportunistic samples from 80 Chinese patients receiving SUS.

Results: Bioavailability of SUS (F_{sus}) in patients decreased from 38.2% to 24.6% when the dose was increased from 100 mg to 600 mg. Bioavailability of DR-tablet (F_{tab}) was 59% regardless of dose. Mucositis, diarrhoea, administration through a nasogastric tube, and concomitant use of proton pump inhibitors or metoclopramide reduced F_{sus} by 61%, 36%, 44%, 48%, and 29%, respectively, putting patients with these characteristics at increased risk of inadequate exposure. Clearance decreased from 7.0 to 5.1 L/h once albumin levels were <30 g/L. Patients showed an 84.4% larger peripheral volume of distribution (V_p) and 67.5% lower intercompartmental clearance (Q) compared with HV. No racial difference could be identified.

Conclusions: Pharmacokinetics of posaconazole in patients differ considerably to those in HV, with altered F_{sus} that is also impacted by clinical covariates, an F_{tab} similar to fasted conditions in HV, and altered parameters for clearance, V_p, and Q. There was no evidence to indicate that Chinese patients require a different dose to Caucasian patients.

1. Introduction

Posaconazole is widely used for preventing or treating invasive fungal diseases (IFDs). It is available as an oral suspension (SUS), delayed-release tablet (DR-tablet), and intravenous (IV) infusion [1,2]. An integrated analysis was conducted to characterise the pharmacokinetics of all three formulations in healthy volunteers (HV), but the findings from this analysis cannot be directly extrapolated to patients as their physiology may be altered or impacted by concomitant treatment. Pathologies and concomitant treatments are anticipated to decrease posaconazole exposure, particularly in haematology patients, thereby putting patients at risk for breakthrough infections or therapeutic failure [3–5]. Moreover, the Chinese population has been reported to have reduced clear-

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ance (CL) compared with the global population [6], but this has not been confirmed in clinical practice. Although exact targets are debated, higher treatment success rates were achieved in patients with higher posaconazole exposure in both prophylactic and therapeutic settings [7,8].

In this study, the integrated population pharmacokinetic model for the three posaconazole formulations in HV was expanded to patients, with the aim to quantify the pharmacokinetics and investigate the influence of clinical characteristics and Chinese race.

2. Methods

2.1. Data included in the analysis

Pharmacokinetic data were pooled from two studies in patients, hereafter referred to as patient study 1 (SUS) [7] and patient study 2 (DR-tablet and IV) [9], and eight studies in HV [10], which included mainly Caucasian individuals (see Table 1). The data comprise 1046 concentrations from 105 patients (92% were diagnosed with haematological malignancy) receiving either of the three posaconazole formulations under various dosage regimens [7,9] and 3898 concentrations from 182 HV that were analysed previously [10].

In addition, a total of 292 opportunistic blood measurements (>90% trough level) from 80 Chinese patients receiving posaconazole SUS were collected from the First Affiliated Hospital of Xi'an Jiaotong University between January 2016 and June 2018 (Table 1). For these samples, a validated liquid chromatography-tandem mass spectrometry assay was used to measure posaconazole plasma concentrations within a quantification range from 0.005 to 5.0 mg/L [18]. Information on drug prescriptions, sampling times, and covariates was retrieved from the electronic health record using a standardised template. The actual dosing time of SUS for these Chinese patients was not reported and was thus assumed to be each mealtime at 8:00, 12:00, and 19:00, starting at the first meal after the prescription.

All study protocols were approved by the local ethics committees. A summary of study design, subject characteristics and pharmacokinetic data for all studies included in the current analysis is presented in Table 1.

2.2. Population pharmacokinetic model

The population pharmacokinetic model was developed using the non-linear mixed-effects modelling software NONMEM 7.5.0 supported by Pirana 3.0.0, PsN 5.2.6, and Xpose 4.7.2 [19]. For patients, 3.44% of the concentrations were below the quantification limit and were excluded.

The model structure was adapted from the HV model [10], which included a two-compartment model with four and eight absorption transit compartments for SUS and DR-tablet, respectively. In patients, adjustments to the number of absorption transit compartments were tested for the DR-tablet (study 2) [9], but not for SUS because the data were sparse (study 1) [7]. Inter-individual variability (IIV) was included on bioavailability (F), the first-order rate constant between absorption transit compartments

Table 1
Summary of pharmacokinetic data from healthy volunteers and patients[a] included in the analysis.

Characteristics		SUS			DR-tablet		IV	
Population [reference]		HV [11–13]	Patients [7]		HV [12,14]	Patients [9]	HV [12,15–17]	Patients [9]
No. of studies		3	1 (study 1)	1	3	1 (study 2)	4	1 (study 2)
No. of subjects		75	82	80	67	19	74	21
Race		Caucasian	Caucasian [7]	Chinese	Caucasian	Caucasian	Caucasian	Caucasian
Dosage (mg)	Single dose	100	NA	NA	100, 300, 400	NA	50, 100, 200, 250, 300	NA
	Multiple dose	Day 1: 200 qd; Day 2: 200 bid; Day 3-10: 400 bid	median dose (range): prophylaxis: 200 tid (40 bid - 300 tid); treatment: 400 bid (200 tid - 400 tid)	median dose: 400 mg bid (range 100 mg bid to 300 mg tid)	300 mg bid on day 1 followed by 300 qd	Day 1: 300 bid; Day 2-12: 300 qd; Day 13: 200 qd	NA	Day 1: 300 bid; Day 2-12: 300 qd; Day 13: 200 qd
Duration of sampling after the last dose (h)	Single dose	168	NA	NA	168	NA	48 - 168	NA
	Multiple dose	12	21	94	48	26	NA	28
No. of concentrations		1028	465	292	1924	263	946	318
No. of BQL concentrations		141 (13.7%)	35 (7.5%)	0 (0%)	110 (5.7%)	1 (0.38)	48 (5.1%)	0 (0%)
No. of concentrations per subject, median (range)		13 (11-16)	3 (1-42)	2.5 (1-18)	13 (2-65)	17 (1-28)	12 (10-20)	16 (1-26)
Available covariates		Food status	Mucositis, administration through a nasogastric tube, diarrhoea, PPIs, metoclopramide, ranitidine, sex, age, weight, BMI	Diarrhoea, PPIs, sex, age, weight	Food status, comedications (antacid, ranitidine, esomeprazole, metoclopramide)	Mucositis, plasma citrulline, albumin, haematocrit, sex, age, weight, BMI	NA	Sex, age, weight, BMI

SUS oral suspension, *DR-tablet* delayed-release tablet, *IV* intravenous infusion, *HV* healthy volunteer, *NA* not applicable, *BQL* below the quantification limit, *bid* twice daily, *tid* three times daily, *qd* once daily, *PPIs* proton pump inhibitors, *BMI* body mass index.

[a] 89% of all patients were haematology patients. The proportion of haematology patients in Caucasian patients who received posaconazole SUS [7], in Chinese patients who received posaconazole SUS, and in Caucasian patients who received crossover DR-tablet and IV [9] was 91%, 85%, and 100%, respectively.

(k_{tr}), CL, and volume of distribution of the central compartment (V_c). Different error models were assessed for each patient study to describe residual unexplained variability. Structural and stochastic model selection was based on the reduction objective function value (OFV) of >3.84 (P<0.05) for nested models being considered statistically significant, on the physiological plausibility of the parameter estimates, on the relative standard error of parameter estimates being <50%, and on the goodness-of-fit (GOF) plots stratified by formulation and population.

Concentration non-linearity was tested on CL using the Michaelis-Menten equation. As for HV [10], dose non-linearity on F was incorporated a priori for SUS in patients using a sigmoidal function, but with parameters re-estimated to values independent of food-status, as data on this were missing. Tested covariates and their distribution are summarised in Table S1 and Table S2, respectively. Correlation among the continuous covariates is summarised in Figure S1. Binary covariates, including concurrent diarrhoea, mucositis, administration through nasogastric tubes, and comedication of proton pump inhibitors (PPIs), metoclopramide, or ranitidine, were investigated on both k_{tr} and F of SUS (F_{sus}). Mucositis as binary covariate and continuous citrulline levels were tested as covariates on both k_{tr} and F of the DR-tablet (F_{tab}). Albumin and haematocrit levels were available from patient study 2 [9] and were investigated as continuous covariates on CL, V_c, the peripheral volume of distribution (V_p), and intercompartmental clearance (Q). Hypoalbuminaemia was also tested as a binary covariate, with three different cut-offs at <35, <30, and <25 g/L. Demographic covariates, including sex, age, and weight, were tested on the disposition parameters. Being a patient was tested as a binary covariate on each pharmacokinetic parameter, as well as an additional IIV at the end of the covariate analysis, to prevent early identification of this covariate as a surrogate for a more mechanistic covariate. If a covariate was unique to a specific study, it was exclusively evaluated within that study. The covariate analysis followed a forward inclusion and backward deletion step, using an OFV decrease of >3.84 (P<0.05) and >10.83 (P<0.001) for statistical significance, respectively. Shark plots in Xpose 4 were used to ascertain that the statistical significance of covariate effects was driven by a sufficient number of individuals [20].

Potential pharmacokinetic differences in Chinese patients were assessed. First, the final model developed for Caucasian patients was directly extrapolated to Chinese patients to inspect the fit from (stratified) GOF-plots and normalised prediction distribution error (NPDE). Second, the distribution of individual parameter values between the Chinese patients and Caucasian patients was visually inspected for potential bias. Subsequently, the Chinese race was tested as binary covariate on all parameters. Finally, the model fit was assessed upon inclusion of a 25% CL reduction in Chinese patients, according to a previous finding in Chinese subjects [6].

The predictive performance of the final model in Caucasian patients was assessed by an NPDE analysis based on 1000 simulations and stratified by formulation. Validation results for HV were presented previously [10].

2.3. Illustration of model findings

To illustrate differences between the posaconazole formulations and the obtained covariate effects, typical concentration-time profiles of recommended dosage regimens were simulated for each formulation in hypothetical patients with different covariates. For SUS this included 200 mg three times daily (tid) for prophylaxis of IFDs, and 400 mg two times daily (bid), and 200 mg four times daily (qid) for treatment purposes. For the DR-tablet and IV, a loading dose of 300 mg bid on the first day followed by a maintenance dose of 300 mg once daily (qd) was simulated [1,2]. Stochastic simulations incorporating the IIV were performed in 1000 virtual patients to illustrate the distribution of trough concentrations (C_{trough}) and 24-h area under the curve (AUC_{24h}) on days 1, 5, and 14.

3. Results

3.1. Population pharmacokinetic model

The number of transit compartments for the HV remained the best option for describing the absorption of the DR-tablet in patients (patient study 2) [9]. Figure S2 shows the model structure [10] that was used to describe the pharmacokinetic data in patients and HV. A proportional and a combined residual error model were applied for patient study 1 [7] and patient study 2 [9], respectively. Parameter estimates of the final model are presented in Table 2 and the corresponding NONMEM code is provided in the supplementary information.

Patients showed an 84.4% larger V_p and 67.5% lower Q than HV. However, there was no significant difference in V_c and CL between patients and HV. A different non-linear F_{sus}, with a lower maximum F_{sus}, was identified in patients vs. HV. Using a non-linear equation (see Table 2), F_{sus} in patients was shown to decrease from 38.2% to 24.6% with a dose increase from 100 mg to 600 mg, regardless of food-status. Additionally, mucositis, diarrhoea, administration through a nasogastric tube, and concomitant use of PPIs or metoclopramide reduced the F_{sus} proportionally by 60.8%, 36.2%, 44.0%, 48.4%, and 29.2%, respectively. PPIs were also found to reduce the k_{tr} of SUS by 85.7%, causing a delay in peak concentrations. For the DR-tablet, F in patients was 58.8%, which is comparable to the value for HV. The typical F of the two posaconazole oral formulations under various scenarios is illustrated in Fig. 1. Incorporating non-linear CL in patients did not significantly improve the model (P>0.05). In contrast to incorporating albumin as a continuous covariate on CL, having hypoalbuminaemia as a binary covariate with an optimised cut-off at 30 g/L statistically significantly improved the fit. The estimates indicated that patients presenting with hypoalbuminaemia have an altered CL of 5.1 L/h compared with 7.0 L/h in those who do not have this condition. There were no significant differences in IIV between HV and patients.

Stratified GOF-plots of the final model in supplementary Figures S3 and S4 indicate that the model describes the data well for each formulation for both HV and Caucasian patients. The stratified NPDE results in supplementary Figures S5 and S6 indicate an accurate predictive performance of the final model regarding the structural and stochastic model for both populations under each formulation. The GOF-plots in Fig. 2 and the NPDE results in Figure S7 demonstrate that the pharmacokinetics in Chinese patients are not distinct from those in Caucasian patients after employing a direct extrapolation from the final model. The increased variability in Chinese patients observed in the NPDE likely results from assumptions for dose time. Moreover, the distribution of individual parameter deviations of Chinese patients vs. Caucasian patients (Figure S8), approximates a normal distribution with a mean of 0, as expected for a population that does not deviate from the population used to develop a model. Estimated deviations in parameter values for Chinese patients compared to Caucasian patients were negligible and lacked statistical significance. Incorporating 25% lower CL for the Chinese patients did not improve the model fit coupled with an increased OFV (P<0.001). All these results combined indicate that the pharmacokinetics of posaconazole in Chinese patients does not differ from those in Caucasian patients.

3.2. Illustration of model findings

As all clinical covariates retained in the final model are binary, the exposure for each clinical scenario was independently simu-

Table 2
Posaconazole pharmacokinetic parameter estimates in the final model.

Population parameter value [unit]	Parameter estimate (RSE%) [%shrinkage]
$F_{sus} = F_{sus,max} \times (1 - \frac{Dose}{Dose+D_{50}}) \times (1 + \theta_{F_{sus},MUC}) \times (1 + \theta_{F_{sus},PPIs}) \times (1 + \theta_{F_{sus},NG}) \times (1 + \theta_{F_{sus},DIAR}) \times (1 + \theta_{F_{sus},METO})$	
$F_{sus,max}$ [%]	0.429 (10.5)
D_{50} [mg]	806 (fixed)
$\theta_{F_{sus},MUC}$ [-]	-0.608 (6.80)
$\theta_{F_{sus},PPIs}$ [-]	-0.484 (9.0)
$\theta_{F_{sus},NG}$ [-]	-0.440 (13.0)
$\theta_{F_{sus},DIAR}$ [-]	-0.362 (19.2)
$\theta_{F_{sus},METO}$ [-]	-0.292 (32.4)
F_{tab} [%]	0.588 (fixed)
$k_{tr,sus} = k_{tr,sus,noCOV} \times (1 + \theta_{k_{tr},\ sus,PPIs})$	
$k_{tr,sus,\ noCOV}$ [h^{-1}]	2.21 (3.30)
$\theta_{k_{tr},\ sus,PPIs}$ [-]	-0.857 (2.70)
$k_{tr,tab}$ [h^{-1}]	2.52 (2.40)
$CL = CL_{noCOV} \times (1 + \theta_{CL,hypoalbuminaemia})$	
CL_{noCOV} [L/h]	7.03 (3.30)
$\theta_{CL,hypoalbuminaemia}$ [-]	-0.276 (20.3)
V_c [L]	144 (4.70)
$V_{p,PAT} = V_{p,HV} \times (1 + \theta_{V_p,PAT})$	
$V_{p,HV}$ [L]	119 (3.10)
$\theta_{V_p,PAT}$ [-]	0.844 (29.7)
$Q_{PAT} = Q_{HV} \times (1 + \theta_{Q,PAT})$	
Q_{HV} [L/h]	50.6 (4.90)
$\theta_{Q,PAT}$ [-]	-0.675 (10.3)
Inter-individual variability in %CV	
F_{sus} [a,b]	0.285 (22.7) [43.4]
F_{tab} [a,b]	0.553 (58.4) [55.7]
$k_{tr,sus}$	20.5 (10.1) [58.3]
$k_{tr,tab}$	27.3 (11.2) [53.0]
CL	32.1 (6.10) [14.5]
V_c	38.3 (11.5) [29.6]
Residual error in %CV	
$\sigma_{prop,study1}$	47.6 (5.50) [6.90]
$\sigma_{prop,study2}$	16.2 (10.8) [4.80]
$\sigma_{addi,study2}$ (mg/L)	0.0712 (31.6) [4.80]

RSE relative standard error of the estimate, *F* absolute oral bioavailability, F_{sus} population value of F for the oral suspension $F_{sus,max}$ the maximum F_{sus}, D_{50} oral suspension dose that could achieve half the $F_{sus,max}$, $\theta_{F_{sus},MUC}$ proportional influence of mucositis on F_{sus}, $\theta_{F_{sus},NG}$ proportional influence of using a nasogastric tube on F_{sus}, $\theta_{F_{sus},PPIs}$ proportional influence of concomitant use of proton pump inhibitors on F_{sus}, $\theta_{F_{sus},DIAR}$ proportional influence of diarrhoea on F_{sus}, $\theta_{F_{sus},METO}$ proportional influence of concomitant use of metoclopramide on F_{sus}, *DR-tablet* delayed-release tablet, F_{tab} population value of F for DR-tablet, k_{tr} first-order absorption rate constant, and the rate constant between absorption transit compartments, $k_{tr,sus}$ k_{tr} of the oral suspension, $k_{tr,sus,noCOV}$ $k_{tr,sus}$ without covariate impact, $\theta_{k_{tr},\ sus,PPIs}$ proportional influence of concomitant use of proton pump inhibitors on $k_{tr,sus}$, $k_{tr,tab}$ k_{tr} of the DR-tablet regardless of food intake, *CL* clearance, $CL_{noCOV,}$ CL without covariate impact, $\theta_{CL,\ hypoalbuminemia}$ proportional influence of hypoalbuminaemia on CL, V_c volume of distribution of the central compartment, V_p volume of distribution of the peripheral compartment, $V_{p,PAT}$ V_p in patients, $V_{p,HV}$ V_p in healthy volunteers, $\theta_{V_p,PAT}$ proportional influence of being a patient on V_p, Q intercompartment clearance between central and peripheral compartments, Q_{PAT} Q in patients, Q_{HV} Q in healthy volunteers, $\theta_{Q,PAT}$ proportional influence of being a patient on Q, *CV* coefficient of variation, $\sigma_{prop,study1}$ proportional residual error in study 1 [7], $\sigma_{prop,study2}$ proportional residual error in study 2 [9], σ_{addi} additive residual error in study 2 [9].

[a] The variability of F was added within the logit domain and is presented as the variance.

[b] A 95% distribution interval with the 2.5th and 97.5th percentiles calculated by $(\frac{e^{ln(\frac{F}{1-F} - 1.96 \times \sqrt{\omega_F^2})}}{1+e^{ln(\frac{F}{1-F} - 1.96 \times \sqrt{\omega_F^2})}}, \frac{e^{ln(\frac{F}{1-F} + 1.96 \times \sqrt{\omega_F^2})}}{1+e^{ln(\frac{F}{1-F} + 1.96 \times \sqrt{\omega_F^2})}})$ was used to describe the inter-individual variability of F. The 95% distribution interval for 200 mg and 400 mg of oral suspension were 15.5-59.9% and 12.4-53.4%, respectively. The 95% distribution interval for the DR-tablet was 24.9-86.0% regardless of dose.

lated and compared with the scenario where the covariate was absent. Figure 3 presents the simulated typical concentration-time profiles in patients receiving recommended dosages of the three posaconazole formulations. All covariate effects, except for hypoalbuminaemia, lead to a decreased exposure of SUS, because of a decreased F_{sus}. The standard DR-tablet regimen does not have an equivalent exposure to the IV formulation. Despite a lower daily dose compared with SUS regimens, the DR-tablet attains a similar or higher exposure in the presence of a single covariate. Among the three SUS regimens, 200 mg qid was associated with the highest exposure.

Figure 4 presents the distribution of simulated posaconazole C_{trough} and AUC_{24h} in patients on day 1, 5, and 14 in 1000 simulated patients. Without a covariate effect, the probability of target attainment (PTA) of a C_{trough} of ≥0.7 mg/L on day 14 was 66%, 55%, and 90% using the recommended prophylactic regimens of SUS 200 mg tid, and DR-tablet and IV 300 mg qd, respectively. Patients who had mucositis, diarrhoea, administration through a nasogastric tube, or concomitant use of PPIs or metoclopramide receiving the prophylactic SUS regimen, achieved a PTA of C_{trough} ≥0.7 mg/L on day 14 ranging from 10 to 44%. Without covariate effect, the PTA of C_{trough} ≥1.0 mg/L was 65%, 31%, 28%, and 71% using the recommended therapeutic regimen of SUS 200 mg qid and 400 mg bid, and DR-tablet and IV 300 mg qd, respectively. This decreased to 48%, 18%, 15%, and 51% for the target of C_{trough} ≥1.25 mg/L.

4. Discussion

This study is the first to characterise the pharmacokinetics of all available formulations of posaconazole in predominantly Caucasian haematology patients and compare these with the pharmacokinetics in HV. Posaconazole pharmacokinetics in patients is considerably different to that in HV, with altered F_{sus} that is also impacted by clinical covariates, an F_{tab} similar to fasted conditions in HV, and altered parameters for CL, V_p, and Q. F_{tab} is higher overall than the dose-dependent, non-linear F_{sus} and is unaffected by the tested

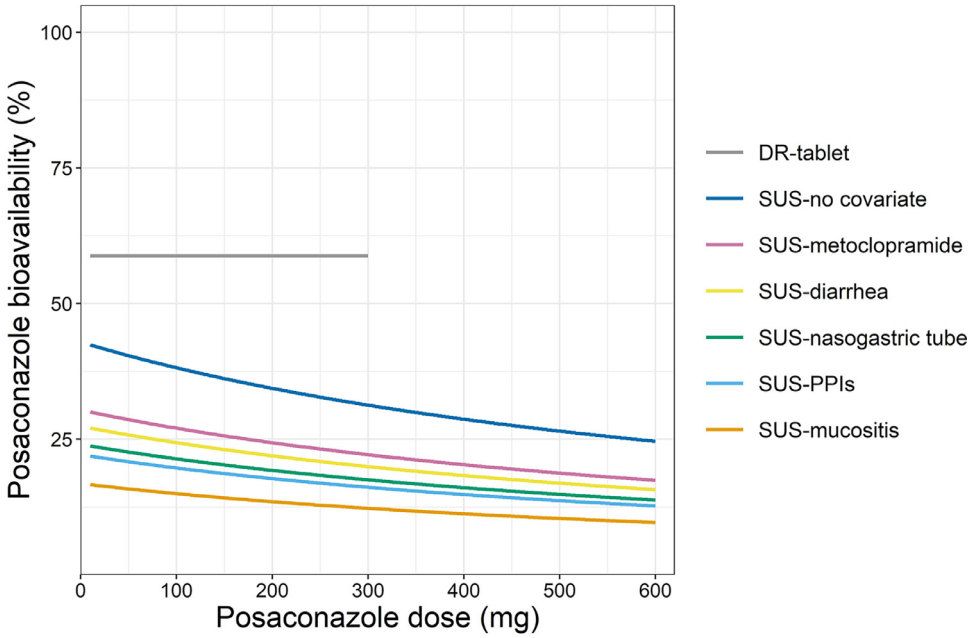

Fig. 1. Posaconazole bioavailability vs. dose in the studied dose ranges for the delayed-released tablet (DR-tablet, no covariates were identified) and the oral suspension (SUS) in patients with and without the presence of a single covariate effect.
PPIs proton pump inhibitors.

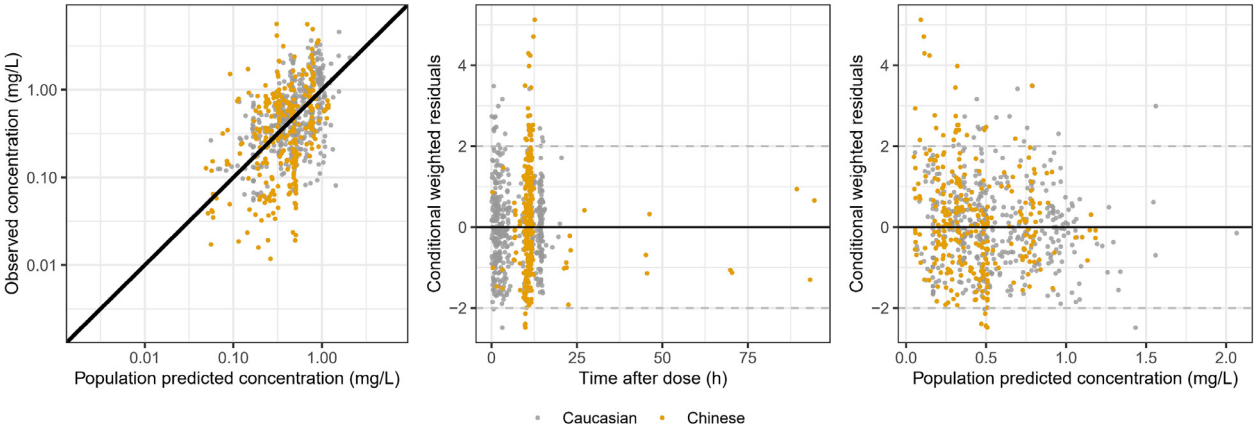

Fig. 2. Goodness-of-fit plots of the final model in the Caucasian (grey) and Chinese (orange) patients receiving the oral suspension.

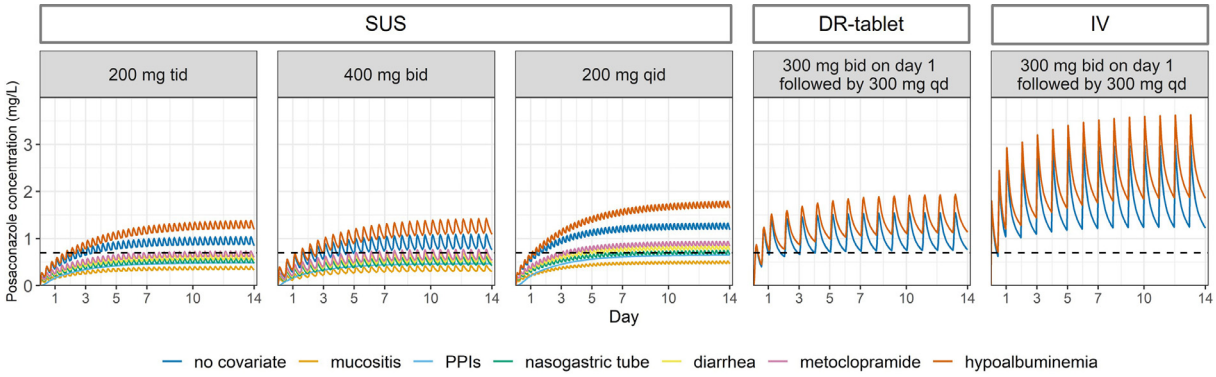

Fig. 3. Typical concentration-time profiles in patients receiving recommended posaconazole doses for oral suspension (SUS), delayed-release tablet (DR-tablet), and intravenous infusion (IV) for two weeks. Profiles were simulated under scenarios with or without single covariates, with only relevant covariates included for each formulation. The horizontal dashed line (0.7 mg/L) represents the trough concentration target for prophylaxis in patients.
PPIs proton pump inhibitors, *tid* three times daily, *bid* two times daily, *qd* once daily.

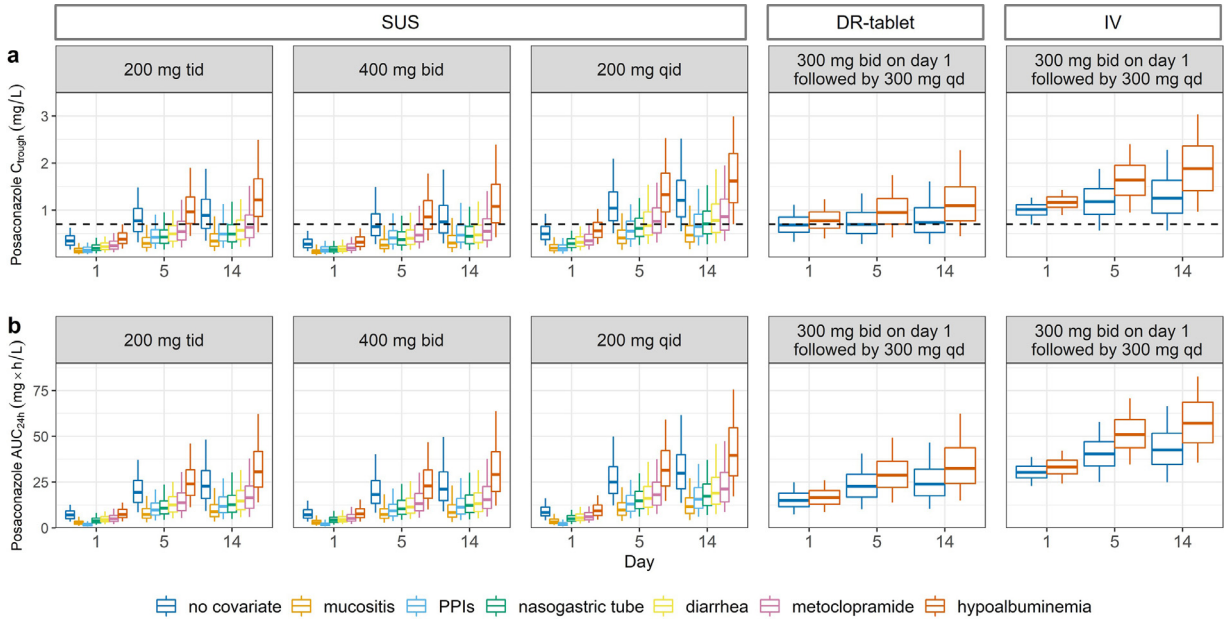

Fig. 4. Distribution of trough concentrations (**a**) and area under the curve per day (AUC_{24h}) (**b**) in 1000 simulated patients receiving recommended posaconazole regimens for oral suspension (SUS), delayed-release tablet (DR-tablet) and intravenous infusion (IV). Profiles were simulated under scenarios with or without single covariates, with only relevant covariates included for each formulation. The boxes represent the 25th, 50th (median), and 75th percentiles, and whiskers represent the 5th and 95th percentiles (i.e., 90% distribution interval). In **a**, the horizontal dashed line represents the concentration target for prophylaxis (0.7 mg/L).
tid three times daily, *bid* two times daily, *qid* four times daily dosing, *qd* once daily.

covariates, reasserting the pharmacokinetic superiority of the DR-tablet in patients. There was no evidence of a racial difference for Chinese patients.

Covariate analysis indicates that patients have an altered typical value of V_p and Q compared with HV, and those with hypoalbuminaemia also have an altered CL. A larger V_p was also reported in patients vs. HV [6], possibly because of capillary leakage, leading to a decreased C_{trough} for all formulations, along with the lower Q found in the current study. Hypoalbuminaemia likely acts as a surrogate for kidney disease and/or severe illness [21], which explains the lower posaconazole CL. In this case, albumin level at 30 g/L, separating normal and mild hypoalbuminaemia from moderate and severe hypoalbuminemia [22], was statistically the best cut-off. Mucositis and citrulline level were not included on the F_{tab} or the k_{tr} of DR-tablet because it did not reach statistical significance ($P<0.05$), or the significance was merely driven by one patient. In the Chinese data, the high proportion of trough concentrations could barely inform the absorption, particularly considering the missing accurate dosing time and food status. An external validation approach was applied to assess the influence of Chinese race. With the limited data, there is no evidence to indicate differences in pharmacokinetics of posaconazole between Chinese and Caucasian patients.

Compared to the data from HV, the patient data are notably sparser during the absorption phase. Despite an average of two to six samples collected within the first six hours after dosing for each patient, this data did not provide sufficient information to support a separate IIV for the two absorption parameters (i.e., F and KTR) in patients as opposed to HV. Consequently, all populations, including HV and patients with varying degrees of illness, shared the same variability, potentially contributing to the significant shrinkage observed in the IIV estimates for F and KTR. However, posaconazole is known to have erratic absorption, and considerable variability has been reported previously and observed in the current data. Despite the high shrinkage values, the inclusion of IIV substantially improved the model fit and was retained in the final model. To achieve the reported, yet not broadly recognised, posaconazole AUC_{24}/MIC target of 167–178 for treating aspergillosis [23–25], a deduced minimum AUC_{24} of 22.3 mg*h/L is required [26]. For this target, the recommended posaconazole SUS therapeutic doses of 400 mg bid or 200 mg qid yield a PTA of >46% or >71%, respectively, at steady state in patients without any of the clinical covariates (Fig. 4) [10]. A lower PTA is achieved when posaconazole SUS is administered to patients with one or more of the identified covariates. The standard IV dose yields an AUC_{24} ≥22.3 mg*h/L in more than 95% of all patients at steady state, whereas the recommended dosage of DR-tablet only yields a PTA of 81% in patients with hypoalbuminaemia and 57% in those without. For this reason, both SUS and DR-tablet should be used with caution for treating aspergillus with MIC ≥ 0.25 mg/L. Starting with a higher dose and applying therapeutic drug monitoring can be helpful, considering the variability in exposure and pathogen susceptibility.

Although lower F for both SUS and DR-tablet was demonstrated in HV under fasted vs. fed conditions, both F in this study represent intermediate values between fasted and fed conditions as details on food status were missing for patients. However, as 91% of the patients receiving posaconazole SUS, and all patients receiving posaconazole DR-tablet, suffered from haematological malignancies and they are commonly not capable of taking food, the estimated F is considered to resemble the F under fasted conditions. The higher dose and dosing frequency of SUS regimens, can to some degree compensate for the low F_{sus}, even resulting in higher C_{trough} compared with the DR-tablet in the absence of covariates (Fig. 3). However, in clinical practice, patients who receive posaconazole SUS but are without any of the clinical covariates are rare, which increases the risk of under-exposure.

In conclusion, patients have altered posaconazole pharmacokinetics compared with HV, and this is also impacted by clinical covariates. Model performance was equal for Caucasian and Chinese patients, indicating that a different dose is not needed. For patients, the DR-tablet is superior to SUS with a higher and more stable F, but is not equivalent to IV, as commonly assumed. A considerable proportion of patients is at risk of inadequate exposure

when receiving oral posaconazole at standard dose, irrespective of prophylaxis or treatment. In patients with insufficient exposure, switching to IV or increasing DR-tablet dose coupled with therapeutic drug monitoring should be considered to ensure adequate drug exposure.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.106995.

References

[1] European Medicines Agency (EMA). Summary of posaconazole characteristics. 2022.
[2] United States Food and Drug Administration (FDA). Noxafil instruction. 2015.
[3] AbuTarif MA, Krishna G, Statkevich P. Population pharmacokinetics of posaconazole in neutropenic patients receiving chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. Curr Med Res Opin 2010;26(2):397–405.
[4] Dolton MJ, Bruggemann RJ, Burger DM, McLachlan AJ. Understanding variability in posaconazole exposure using an integrated population pharmacokinetic analysis. Antimicrob Agents Chemother 2014;58:6879–85.
[5] van Iersel M, Rossenu S, de Greef R, Waskin H. A population pharmacokinetic model for a solid oral tablet formulation of posaconazole. Antimicrob Agents Chemother 2018;62(7):e02465 -17.
[6] European Medicines Agency (EMA). Noxafil EPAR assessment report. 2021.
[7] Dolton MJ, Ray JE, Chen SC, Ng K, Pont L, McLachlan AJ. Multicenter study of posaconazole therapeutic drug monitoring: exposure-response relationship and factors affecting concentration. Antimicrob Agents Chemother 2012;56:5503–10.
[8] Walsh TJ, Raad I, Patterson TF, Chandrasekar P, Donowitz GR, Graybill R, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis 2007;44:2–12.
[9] Jansen AME, Muilwijk EW, Van Der Velden WJFM, Maertens JA, Aerts R, Colbers A, et al. Posaconazole bioavailability of the solid oral tablet is reduced during severe intestinal mucositis. Clin Microbiol Infect 2022;28:1003–9.
[10] Chen L, Krekels EHJ, Heijnen AR, Knibbe CAJ, Bruggemann RJ. An integrated population pharmacokinetic analysis for posaconazole oral suspension, delayed-release tablet, and intravenous infusion in healthy volunteers. Drugs 2023;83:75–86.
[11] Bruggemann RJ, van Luin M, Colbers EP, van den Dungen MW, Pharo C, Schouwenberg BJ, et al. Effect of posaconazole on the pharmacokinetics of fosamprenavir and vice versa in healthy volunteers. J Antimicrob Chemother 2010;65:2188–94.
[12] EMA. Posaconazole tablet assessment report: EPAR-Scientific discussion-Extension. 2014 February 20, 2014 [accessed 2023 November 7]; EMEA/H/C/000610/X/0028]. Available from: https://www.ema.europa.eu/documents/variation-report/noxafil-h-c-610-x-0028-epar-scientific-discussion-extension_en.pdf.
[13] Krishna G, Ma L, Martinho M, O'Mara E. Single-dose phase I study to evaluate the pharmacokinetics of posaconazole in new tablet and capsule formulations relative to oral suspension. Antimicrob Agents Chemother 2012;56:4196–201.
[14] Kraft WK, Chang PS, van Iersel ML, Waskin H, Krishna G, Kersemaekers WM. Posaconazole tablet pharmacokinetics: lack of effect of concomitant medications altering gastric pH and gastric motility in healthy subjects. Antimicrob Agents Chemother 2014;58:4020–5.
[15] EMA. Posaconazole injection assessment report: EPAR-assessment report-Variation. 2014 July 24, 2014 [accessed 2022 November 7]; EMEA/H/C/000610/X/0033]. Available from: https://www.ema.europa.eu/en/documents/variation-report/noxafil-h-c-610-x-0033-epar-assessment-report-variation_en.pdf.
[16] Kersemaekers WM, van Iersel T, Nassander U, O'Mara E, Waskin H, Caceres M, et al. Pharmacokinetics and safety study of posaconazole intravenous solution administered peripherally to healthy subjects. Antimicrob Agents Chemother 2015;59:1246–51.
[17] Wasmann RE, Smit C, van Donselaar MH, van Dongen EPA, Wiezer RMJ, Verweij PE, et al. Implications for IV posaconazole dosing in the era of obesity. The Journal of Antimicrobial Chemotherapy 2020;75(4):1006–13.
[18] Niu Z, Cheng X-l, Wang T-t, Dong Y-l. Liquid chromatography-mass spectrometry method for the quantification of posaconazole in human plasma. Central South Pharmacy 2016:708–11.
[19] Keizer RJ, Karlsson MO, Hooker A. Modeling and simulation workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. CPT Pharmacometrics Syst Pharmacol 2013;2:e50.
[20] Jonsson EN, Hooker A. Xpose 4 Bestiary. version 1.0 ed.
[21] Gatta A, Verardo A, Bolognesi M. Hypoalbuminemia. Intern Emerg Med 2012;7(Suppl 3):S193–9.
[22] Zhang J, Zhang R, Wang Y, Li H, Han Q, Wu Y, et al. The level of serum albumin is associated with renal prognosis in patients with diabetic nephropathy. J Diabetes Res 2019;2019:7825804.
[23] Howard SJ, Lestner JM, Sharp A, Gregson L, Goodwin J, Slater J, et al. Pharmacokinetics and pharmacodynamics of posaconazole for invasive pulmonary aspergillosis: clinical implications for antifungal therapy. J Infect Dis 2011;203:1324–32.
[24] Lepak AJ, Marchillo K, Vanhecker J, Andes DR. Posaconazole pharmacodynamic target determination against wild-type and Cyp51 mutant isolates of *Aspergillus fumigatus* in an in vivo model of invasive pulmonary aspergillosis. Antimicrob Agents Chemother 2013;57:579–85.
[25] Mavridou E, Bruggemann RJ, Melchers WJ, Mouton JW, Verweij PE. Efficacy of posaconazole against three clinical *Aspergillus fumigatus* isolates with mutations in the cyp51A gene. Antimicrob Agents Chemother 2010;54:860–5.
[26] EUCAST. The European Committee on Antimicrobial Susceptibility Testing. Posaconazole: Rationale for the EUCAST clinical breakpoints, version 3.0. 2020.