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A Population Pharmacokinetic Modeling and Simulation Study of Posaconazole Oral Suspension in Immunocompromised Pediatric Patients: A Short Communication

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Abstract:	<p>Background: Posaconazole oral suspension emerged as a promising candidate for prophylaxis of invasive fungal infections in immunocompromised children. Its pharmacodynamic advantages include a broad spectrum of activity and a favorable safety profile. However, these are overshadowed by a large pharmacokinetic (PK) variability, potentially leading to subtherapeutic exposure.</p> <p>Methods: Data were obtained from a prospective interventional study, including hospitalized pediatric patients with a hematologic malignancy treated prophylactically with posaconazole oral suspension. A population PK model was built (NONMEM 7.4). The probability of target attainment (PTA; 100% T ≥ 0.7 mg/L) for prophylaxis under fixed, body weight-based, and body surface area-based dosing was evaluated using Monte Carlo simulation.</p> <p>Results: Fourteen patients contributed 112 posaconazole plasma concentrations. The PK of posaconazole was adequately described by a one-compartment model with lag time of 2.71 h [13%] (typical value [relative standard error]), nonlinear bioavailability ED50 99.1 mg/m² (prior knowledge), first-order absorption rate constant k_a 0.325 h⁻¹ [27%], apparent volume of distribution 1,150 L [34%], and apparent clearance 15.4 L/h [24%] (standardized to a 70-kg individual). The apparent bioavailability</p>

	<p>decreased in the presence of diarrhea and co-administration of a proton pump inhibitor (PPI). The unexplained interindividual variability in posaconazole PK remained large (86.4% coefficient of variation). The PTA was below 85%, irrespective of the simulated dosing strategy. Patients without diarrhea and not receiving a PPI had the highest PTA, approaching 85% under fixed 300 mg dosing four times a day.</p> <p>Conclusion: Therapeutic drug monitoring is recommended during prophylactic posaconazole therapy in immunocompromised pediatric patients. Large scale comparative studies are urged to characterize the PK variability between the different posaconazole formulations in this patient population.</p>
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Opposed Reviewers:

To Editor of *Therapeutic Drug Monitoring*

Leuven, 4/11/2020

Subject: Submission of a Short Communication

Dear Editor of *Therapeutic Drug Monitoring*

We hereby submit our manuscript entitled “A Population Pharmacokinetic Modeling and Simulation Study of Posaconazole Oral Suspension in Immunocompromised Pediatric Patients: A Short Communication” by Elkayal *et al.*

In our manuscript, we report the development of a population pharmacokinetic model of posaconazole oral suspension therapy in immunocompromised children based on data from a rich sampling study (112 posaconazole plasma concentrations contributed by 14 patients). Our analyses provided a more detailed insight into posaconazole pharmacokinetics, more specifically the absorption phase. We performed a simulation study to evaluate prophylaxis target attainment (100% $T \geq 0.7$ mg/L) under fixed, body weight-based, and body surface area-based dosing. The simulated probability of target attainment was below 85%, irrespective of the dosing strategy. Patients without diarrhea not receiving a PPI had the highest probability of target attainment, approaching 85% under fixed 300 mg dosing four times a day. Dose adjustments based on body weight or body surface area did not improve target attainment compared to fixed dosing. Low target attainment, wide interpatient pharmacokinetic variability, and a maximum desired exposure target of 3.75 mg/L (based on the 90th percentile of exposure in Cornely *et al.*) demand the implementation of therapeutic drug monitoring in clinical practice. In case of underexposure on 300 mg four times a day, the tablet or intravenous formulations may be considered. However, we believe that it is essential to further invest in dose optimization of the oral suspension in this specific off-label (and thus non-reimbursed) setting as both the delayed-release tablet and the intravenous formulation are very expensive.

As *Therapeutic Drug Monitoring* is known to be a leading journal for publishing clinical pharmacology research, including population pharmacokinetic modeling and simulation work, we believe our findings would appeal to the readers of *Therapeutic Drug Monitoring*.

All authors have read and approved the manuscript and agree with its submission to *Therapeutic Drug Monitoring*. The author contributions, the sources of funding, and the conflicts of interest of all authors are explicitly mentioned in the manuscript. We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal.

We hope that our paper will be considered for publication in *Therapeutic Drug Monitoring*.

Yours sincerely, on behalf of all authors

Erwin Dreesen

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A Population Pharmacokinetic Modeling and Simulation

Study of Posaconazole Oral Suspension in

Immunocompromised Pediatric Patients

A Short Communication

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Abstract

Background: Posaconazole oral suspension emerged as a promising candidate for prophylaxis of invasive fungal infections in immunocompromised children. Its pharmacodynamic advantages include a broad spectrum of activity and a favorable safety profile. However, these are overshadowed by a large pharmacokinetic (PK) variability, potentially leading to subtherapeutic exposure.

Methods: Data were obtained from a prospective interventional study, including hospitalized pediatric patients with a hematologic malignancy treated prophylactically with posaconazole oral suspension. A population PK model was built (NONMEM 7.4). The probability of target attainment (PTA; 100% $T \geq 0.7$ mg/L) for prophylaxis under fixed, body weight-based, and body surface area-based dosing was evaluated using Monte Carlo simulation.

Results: Fourteen patients contributed 112 posaconazole plasma concentrations. The PK of posaconazole was adequately described by a one-compartment model with lag time of 2.71 h [13%] (typical value [relative standard error]), nonlinear bioavailability ED_{50} 99.1 mg/m² (prior knowledge), first-order absorption rate constant k_a 0.325 h⁻¹ [27%], apparent volume of distribution 1,150 L [34%], and apparent clearance 15.4 L/h [24%] (standardized to a 70-kg individual). The apparent bioavailability decreased in the presence of diarrhea and co-administration of a proton pump inhibitor (PPI). The unexplained interindividual variability in posaconazole PK remained large (86.4% coefficient of variation). The PTA was below 85%, irrespective of the simulated dosing strategy. Patients without diarrhea and not receiving a PPI had the highest PTA, approaching 85% under fixed 300 mg dosing four times a day.

Conclusion: Therapeutic drug monitoring is recommended during prophylactic posaconazole therapy in immunocompromised pediatric patients. Large scale comparative studies are urged to characterize the PK variability between the different posaconazole formulations in this patient population.

Key Words: Posaconazole; Pediatrics; Therapeutic drug monitoring; Population pharmacokinetics; Oral suspension

Introduction

Posaconazole is often used in the prevention and treatment of invasive fungal infections (IFIs) in pediatric patients with graft-versus-host disease after stem cell transplantation and febrile neutropenia due to its broad antifungal activity, its favorable safety profile, and the lack of more appropriate alternatives.¹⁻⁴ Since posaconazole is prescribed off-label in this setting, the oral suspension is most commonly used given its lower cost and ease of administration as compared to the delayed-release tablet and intravenous formulation. The challenge facing posaconazole suspension is the large pharmacokinetic (PK) variability between patients, particularly in terms of absorption, often leading to suboptimal exposure.^{1,5} It has been shown that in children, the standard (adult) dosing fails to assure the therapeutic posaconazole trough concentrations at steady-state of 0.7 mg/L and 1.0 mg/L for prophylaxis and treatment of IFIs, respectively.⁴ Therefore, therapeutic drug monitoring (TDM) has been used as a tool to quantify posaconazole exposure and to adapt dosing accordingly.⁶

To date, no pediatric posaconazole dosing regimen has been agreed upon for none of the different posaconazole formulations. Some clinical centers have published their experience with TDM of posaconazole in pediatric patients.⁷⁻¹¹ The large variability in exposure and the negative impact of diarrhea and concomitant proton-pump inhibition (PPI) was established in these studies. Vanstraelen *et al.* proposed dosing in pediatric patients based on the body surface area (BSA) using a dosage regimen of 120 mg/m² three times a day.¹²

A population PK (popPK) model may provide insight into sources of variability in exposure, can be used to support dose-finding simulations, and may be used to facilitate model-based TDM if warranted. One posaconazole popPK model has previously been published by Boonsathorn *et al.*, in which concomitant PPI and diarrhea explained variability in the bioavailability of the posaconazole oral suspension.¹³ Based on their model, the authors suggested several dosing strategies for posaconazole in children. However, since their model was based on sparse TDM sampling, the absorption parameters could not be estimated. Also, an external evaluation of their model and dosing suggestions is awaited. Our aim was to develop a popPK model based on rich sampling, leading to a more detailed insight into the PK of the posaconazole oral suspension. We performed Monte Carlo simulations to evaluate target attainment under fixed, body weight-based, and BSA-based dosing. Finally, the predictive performance of both our newly developed model and the previously published was compared.

Materials and Methods

Patients and Data Collection

Data were obtained from a prospective study by Vanstraelen et al.¹² In this study, 14 immunocompromised children aged 13 years or younger with a hematological malignancy were treated prophylactically with the posaconazole oral suspension (Noxafil, Merck, Brussels, Belgium) at a dose of 120 mg/m² three times daily, taken with a meal.¹² Eight blood samples were collected from each patient during one dosing interval at steady-state (after at least eight days of treatment). The study protocol was approved by the local Ethics Committee (NCT02372357). Written informed consent was obtained from each child's relative. The study was conducted in accordance with the Declaration of Helsinki.

Analytical Procedures

All heparinized blood samples were centrifuged immediately after sampling (10 minutes, 1,500g, 20°C), plasma was stored at -20°C until further analysis.¹² Total posaconazole plasma concentrations were measured using high-performance liquid chromatography followed by fluorescence detection.^{12,14}

Population Pharmacokinetic Modeling

Software

Dataset formatting and exploration were performed using R (version 3.5.1, R Core Team, Vienna, Austria) using custom scripts based on packages including *dplyr* and *ggplot2*.^{15,16} PopPK analysis was performed using NONMEM (version 7.4; ICON Development Solutions, Gaithersburg, Maryland, USA).¹⁷

Model Development

Parameter estimation was performed using first-order conditional estimation with interaction (FOCE-I) and differential equation solver ADVAN 6. A structural base popPK model was developed. Different structural models with varying numbers of compartments, and linear and nonlinear absorption and elimination processes were explored. Allometric scaling was tested with exponents of 0.75, 1, and 0.25 on clearance (CL/F), volume of distribution (V_d/F), and absorption rate constant (k_a/F), respectively.¹⁸ Since the posaconazole suspension has been shown to demonstrate nonlinear absorption¹⁹, the bioavailability F of the oral suspension was described as

$$F=1-\frac{D}{D+ED_{50}} \quad (\text{Eq. 1})$$

where D is the dose in mg/m² BSA and ED₅₀ is the estimated dose in mg/m² that yields a 50% decrease in relative bioavailability of the suspension. ED₅₀ was fixed to 99 mg/m² based on previous literature.¹³

Individual PK parameters were assumed to be log-normally distributed, which was achieved using an exponential formula, *e.g.*, the clearance (CL) parametrization followed this equation:

$$CL_i = TVCL \times \exp(\eta_i) \text{ with } \eta_i \propto N(0, \omega^2) \quad (\text{Eq. 2})$$

with CL_i the clearance of subject *i*, TVCL the typical population value of the clearance, and η_i the individual patient's deviation from the typical value.

The base model was selected based on objective function value (OFV) comparisons (difference ≥ 3.84 points; $P \leq 0.050$), plausibility and precision of parameter estimates, and goodness-of-fit plots. A final model, including covariate effects, was built through a two-way stepwise covariate modeling (SCM) procedure (forward inclusion $\alpha=0.010$; backward elimination $\alpha=0.001$). The tested covariates were weight, co-treatment with a PPI, and presence of diarrhea.

Final Model Evaluation

The final model was evaluated using a prediction-corrected visual predictive check (pcVPC; $n=1,000$ simulated replicates of the original dataset). Furthermore, bootstrapping was performed to obtain nonparametric estimates of uncertainty in parameter estimates ($n=2,000$ bootstraps).

Dosing Simulations

Monte Carlo simulations were performed using the final popPK model to evaluate different posaconazole dosing strategies that have recently been suggested in literature.^{5,6,12,13} In each dosing scenario, PK profiles of 1,000 patients were simulated at steady-state, and the probability of target attainment (PTA) for prophylaxis (total posaconazole concentration 100% $T \geq 0.7$ mg/L) was calculated. Continuous covariates were randomly sampled from a uniform distribution within the range of the original data set. Combinations of binary covariates were assigned in equal proportions.

Predictive Performance Assessment

External (Boonsathorn *et al.*¹³) and internal predictive performance were assessed.²⁰ Model-predicted and observed individual concentrations were compared by calculating the relative bias (rBias) and relative root mean squared error (rRMSE).²⁰

$$rBias = \frac{1}{N} \sum_1^j \frac{\text{individual predicted}_j - \text{observed}_j}{(\text{individual predicted}_j + \text{observed}_j)/2} \times 100\% \quad (\text{Eq. 3})$$

$$162 \quad \text{rRMSE} = \sqrt{\frac{1}{N} \sum_1^j \frac{(\text{individual predicted}_j - \text{observed}_j)^2}{((\text{individual predicted}_j + \text{observed}_j)/2)^2}} \times 100\% \quad (\text{Eq. 4})$$

163 with N the total number of observed posaconazole concentrations.

Results

Patient Characteristics

A total of 14 patients (median [IQR] age 7 [5-8] years, body weight 20.5 [16.9-21.9] kg) contributed 112 plasma samples to the analysis. Eight out of 14 patients (57%) achieved the prophylaxis target. Six patients were suffering from diarrhea and ten patients were concomitantly treated with a PPI.

Population Pharmacokinetic Model

Base Model

A one-compartment model with a lag time, nonlinear relative bioavailability, first-order absorption, and linear elimination best described the data (*Table 1*). Allometric scaling was implemented. The unexplained interindividual variability in the apparent clearance was estimated at 87.9% [25%] (coefficient of variation [relative standard error]). A proportional error model was used to describe the unexplained residual variability.

Final Model

Inclusion of the effects of diarrhea and PPI comedication on the relative bioavailability did not result in a significant drop in OFV ($\Delta\text{OFV} = -1.1$ and -1.2 , respectively). Nevertheless, inclusion of these effects on F using fixed parameter values derived from literature improved the accuracy of the parameter estimates (*Table 1*).¹³

Model Evaluation

Goodness-of-fit plots confirmed that the final model adequately described the observed data (not shown). The pcVPC showed a good agreement between the observed data and model simulations (*Figure 1A*). Median values of the nonparametric bootstrap were in good agreement with the FOCE-I point estimates (*Table 1*).

Dosing Simulations

The predicted PTA under fixed, body weight-based, and BSA-based dosing are given in *Figure 1B-D*. Posaconazole dose adjustments based on body weight or BSA did not improve the PTA as compared to fixed dosing. Posaconazole trough concentrations and thus the PTA were negatively affected by the presence of diarrhea and PPI co-administration. The highest PTA (85%) was attained for the dosage regimens of 300 mg four times a day and 24 mg/kg four times a day in patients not suffering from diarrhea and not receiving PPI co-administration. Due to saturable absorption, the PTA plateaued when increasing the dose above 300 mg and 24 mg/kg.

Predictive Performance Assessment

Predictive performance assessment demonstrated that the previously published model underpredicted posaconazole exposure in our study data (rBias -9.8%, pcVPC not shown). Our model not only predicted the observed posaconazole concentrations with negligible bias (0.4%) but also with higher precision (rRMSE 10.7%) as compared to the literature model (25.6%).

Using the patient's first pre-dose concentration in a Bayesian forecasting scenario, both models predicted the second pre-dose concentration with acceptable bias (1.2% and -4.9% using our study model and the literature model, respectively). However, our model performed better in terms of precision (23.2%) than the literature model (41.8%).

Discussion

We performed a popPK modeling and simulation study of posaconazole oral suspension therapy in immunocompromised children. Our analyses provided a more detailed insight into posaconazole PK and resulted in dosing recommendations in this specific setting. Furthermore, we compared the predictive performance of our model and a previously published model.

The one-compartment model with lag time and inter-individual variability on clearance best described the PK of posaconazole. The inclusion of a lag time is the main structural improvement compared to the previously published posaconazole popPK model.¹³ This additional PK feature is attributed to the insight that the rich sampling scheme provided to our model. The capture of a lag time is in line with the finding from Dolton *et al.* in an adult population.²¹ Rich sampling also enabled us to estimate the first-order absorption rate constant, which needed to be fixed in the previously published model that was built using sparse TDM data. The difference in absorption rate constant in our model (0.325 h^{-1}) and the previously published value (0.197 h^{-1}) is likely to be explained by the lack of a lag time in the latter.²² While the apparent clearance in our model is in line with the previously published value, the volume of distribution in our model (1,150 L; standardized to a 70-kg patient) is closer to the known high volume of distribution of posaconazole.²³

Previously published popPK models of posaconazole in both adults and children included the effects of diarrhea on bioavailability.^{13,21,24,25} Diarrhea is common in patients suffering from graft-versus-host disease, critically ill patients, and post-chemotherapy patients. In our cohort, six out of 14 patients had diarrhea. Since our study was underpowered to identify the effect of diarrhea, it was added to the model based on prior knowledge, resulting in a 33% decrease in the apparent bioavailability of the oral posaconazole suspension. Similarly, the co-administration of a PPI is common practice in this setting and has been shown to affect posaconazole bioavailability negatively (reduced dissolution).^{13,14,26–28} Likewise, the impact of concomitant PPI intake was implemented in our model, making the apparent bioavailability decrease with 42%. Since the Boonsathorn *et al.* model is based on a large patient cohort, we feel confident putting our trust in their parameter estimates. Due to the limited number of patients in our study, we were cautious when testing more covariates like age and concomitant use of an H_2 -receptor antagonist to avoid overfitting the model. Future studies with higher patient numbers may evaluate these and other potential covariate effects like concomitant food intake and vomiting. All patients in our cohort received posaconazole with a high-fat meal/supplement and vomiting was not reported.

Our simulation results showed that dose adjustment based on body weight or BSA did not improve target attainment compared to fixed dosing. Irrespective of the dose and dosing interval, the PTA did not exceed 85%. Due to the saturable nature of posaconazole absorption, the PTA plateaued around 300 mg, making further dose increases futile.¹³ On the other hand, our simulations showed that dose fractionation

effectively increases the PTA, although dosing more than four times a day may be impractical. A fixed 300 mg dose of posaconazole administered four times a day resulted in the highest predicted mean PTA, approaching 85%. Low PTA, wide interpatient variability, and a maximum desired exposure target of 3.75 mg/L (based on the 90th percentile of exposure in Cornely *et al.*²⁹) demand the implementation of TDM in clinical practice. In case of underexposure on 300 mg four times a day, the tablet or intravenous formulations may be considered. Unfortunately, the difficulty of swallowing and high cost may undermine their second-line place.

Considering a role for TDM during posaconazole oral suspension therapy, we evaluated the predictive performance of our model (internal validation) and the literature model (external validation) in a model-informed precision dosing (MIPD) context. Bayesian forecasting of the next posaconazole trough concentration based on the current trough concentration showed acceptable bias (<5%) when using either model. However, the published model had an unacceptably high rRMSE (41.8%), while our model was still within the arbitrarily accepted range (<25%). Future qualification of our model for MIPD using multiple external datasets may be needed to support generalizability of our findings.³⁰

Our study has several strengths. Firstly, our dataset included rich sampling, which enabled us to capture the lag time and absorption rate constant accurately. Secondly, our data had very consistent reporting with no missing samples. Some limitations, however, remain. Firstly, the low number of patients resulted in an artificially inflated interindividual variability, thereby making the covariate search unfruitful. Still, model diagnosis showed an adequate model fit. Secondly, all included patients were treated with posaconazole oral suspension, preventing us from comparing different dosing forms. However, we believe that it is essential to further invest in dose optimization of the oral suspension in this specific off-label (and thus non-reimbursed) setting as both the delayed-release tablet and the intravenous formulation are very expensive. Population modeling of a larger dataset, including rich sampling and including patients treated with the different formulations, is needed to allow well-informed dose-finding for immunocompromised children.

Conclusion

Our modeling and simulation study illustrates the challenges related to the attainment of adequate prophylactic exposure when treating immunocompromised children with the posaconazole oral suspension. Poor target attainment, especially in children with diarrhea and PPI co-treatment, wide interpatient PK variability, and a relatively narrow therapeutic window (0.7-3.75 mg/L), support a role for TDM during treatment with the posaconazole oral suspension.

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Figure legends

Figure 1. (A) Prediction-corrected visual predictive check of the final population pharmacokinetic model. Open circles represent the observed prediction-corrected posaconazole concentrations. The black solid and dash lines represent median and 2.5th and 97.5th percentiles of the prediction-corrected observations, respectively. The shaded areas indicate 90% prediction-intervals of the median and 2.5th and 97.5th percentile of the simulated values. **(B-D)** The simulated probability of target attainment of the 100% $T \geq 0.7$ mg/L prophylaxis target at steady state for fixed dosing, weight-adjusted dosing, and body surface area-adjusted dosing, respectively. b.i.d.: twice daily; PPI: proton pump inhibition; q.i.d: four times daily; t.i.d.: three times daily.

1 Tables

2 **Table 1.** Summary of the population pharmacokinetic model parameter estimates

Parameter	Base model		Final model			Boonsathorn <i>et al.</i> ¹³	
	<i>Estimate</i>	<i>%RSE</i> [%shrinkage]	<i>Estimate</i>	<i>%RSE</i> [%shrinkage]	<i>Bootstrap</i> <i>median</i> <i>(95% CI)</i>	<i>Estimate</i>	<i>%RSE</i>
Typical values							
T_{lag}, h	2.79	15	2.71	13	2.79 (0.8-3.979)	–	–
k_a, h^{-1}	0.258	42	0.325	27	0.315 (0.03-13.99)	0.197 FIX	–
$ED_{50}, mg/m^2$	99.1 FIX	–	99.1 FIX	–	99.1 FIX	99.1	44
$V/F, L$	1,410	43	1,150	34	1,036 (50-3,973)	201.7	38.8
$CL/F, L/h$	21.4	24	15.4	24	15.4 (9.8-25.4)	14.95	34.5
Diarrhea on bioavailability	–	–	-0.33 FIX	–	-0.33 FIX	-0.33	28
PPI on bioavailability	–	–	-0.42 FIX	–	-0.42 FIX	-0.42	14.9
Interindividual variability							
on CL/F, %CV	87.9	15.9 [0]	87.8	20 [0.1]	86.4 (18.7-227.0)	63	23.9
Residual variability							
Proportional error, %CV	16	8 [6]	11	8 [6]	0.01198 (0.008-0.1597)	47.29	0.2
Additive error, mg/L	–	–	–	–	–	0.02	82.7

3 CI: confidence interval; CL/F: apparent clearance; CV: coefficient of variation expressed as $CV(\%) = \sqrt{\exp(\omega^2) - 1} \times 100\%$; ED_{50} : dose in mg/m² for bioavailability to drop to half that of the tablet
4 (Boonsathorn *et al.*); k_a : absorption rate constant; RSE: relative standard error; T_{lag} : lag time; V/F: apparent volume of distribution. 1,791 out 2,000 bootstrap runs (90%) were successful. The
5 condition number was 69.51.

Figure 1

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