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Original article

Posaconazole bioavailability of the solid oral tablet is reduced during severe intestinal mucositis

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ABSTRACT

Objectives: This study aimed to describe the absolute oral bioavailability of the solid oral formulation of posaconazole and the impact of severe intestinal mucositis in haematology patients. This study also aimed to describe posaconazole protein binding in haematology patients.
Methods: A pharmacokinetic study was performed of patients receiving induction chemotherapy or a haematopoietic cell transplantation who were randomized to receive 7 days of intravenous posaconazole therapy followed by 9 days of oral therapy, or vice versa. Patients received a posaconazole licensed dose until day 12, after which a reduced once-daily dose of 200 mg was given. At days 7, 12, and 16, blood samples were obtained for pharmacokinetic curves, and trough samples were collected on all other days. Total and unbound posaconazole pharmacokinetics were analyzed by population pharmacokinetic modelling. The presence of severe intestinal mucositis was assessed by plasma citrulline levels and analyzed as a binary covariate using 10 μmol/L as the cut-off. Monte Carlo simulations were performed to simulate posaconazole exposure at a steady state.
Results: Twenty-three patients were included for analysis, with 581 total posaconazole concentrations and 91 paired unbound concentrations. Absolute bioavailability in the final model was estimated at 51.4% (percentage relative standard error (%RSE): 56.5) and 67.6% (%RSE: 75.0) in patients with and without severe intestinal mucositis, respectively. Posaconazole unbound fraction was estimated at 2.7% (%RSE: 3.9).
Discussion: Posaconazole bioavailability is reduced in haematological patients with severe intestinal mucositis, requiring an increase in oral posaconazole dose to 400 mg twice daily on day 1, followed by 400 mg once daily or a switch to intravenous therapy. **Anouk M.E. Jansen, Clin Microbiol Infect 2022;28:1003**

Introduction

Posaconazole is the first-line agent for mould prophylaxis in patients with prolonged neutropenia after chemotherapy or conditioning therapy prior to an allogeneic haematopoietic cell transplantation (HCT) and graft-versus-host disease [1,2]. Mucosal barrier injury of the gut or intestinal mucositis has an incidence of 40% to 100% in patients receiving intensive chemotherapy, which may predispose these patients to malabsorption of drugs [3,4]. As a consequence of subtherapeutic exposure,

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breakthrough infections may occur during oral posaconazole prophylaxis [5,6].

The initially marketed posaconazole oral solution demonstrated erratic oral bioavailability affected by food, diarrhoea, and intestinal mucositis, resulting in suboptimal exposure [4,7]. In 2014, the solid oral and intravenous formulations of posaconazole were licensed, offering new treatment possibilities.

The target for posaconazole efficacy is determined as a ratio of the area under the concentration-time curve (AUC) to the minimal inhibitory concentration >200 [8]. Posaconazole trough concentrations (C_{trough}) correlate well with AUC [9]. Currently, a posaconazole target C_{trough} >0.7 mg/L is recommended for prophylaxis [8,10,11].

Absolute bioavailability of the solid oral posaconazole formulation in patients is unknown, and the impact of intestinal mucositis on absorption remains unclear. Two previous studies did not find an impact of mucositis on posaconazole plasma concentrations in patients using the solid oral formulation [12,13], but the inability to find this effect was likely caused by the small sample sizes and insufficient data.

A second factor that requires attention when investigating posaconazole pharmacokinetics is the level of protein binding. In healthy volunteers, posaconazole is approximately >98% bound to plasma proteins, predominantly to albumin [14], but limited information is available on posaconazole protein binding in (haematology) patients.

We investigated posaconazole pharmacokinetics with an in-depth analysis on the bioavailability, impact of severe intestinal mucositis, and protein binding in patients with haematological disorders.

Methods

Study participants

A prospective, multicentre, multiple-dose, multiple-dose-level, open-label, randomized study was conducted in patients at risk for developing invasive fungal disease (IFD). This study was approved by the ethics committees of Radboudumc in Nijmegen, The Netherlands and the University Hospital Leuven in Leuven, Belgium (EudraCT: 2016-001182-87, ClinicalTrials.gov: NCT02805946). Written informed consent was provided by all participants or their representatives.

Patients aged >18 years with a haematological malignancy undergoing myeloablative or reduced-intensity conditioning for an allogeneic HCT or receiving remission-induction chemotherapy for acute myeloid leukaemia/myelodysplastic syndrome were eligible for inclusion. The exclusion criteria were documented history of sensitivity to (any excipient of the formulation of) posaconazole, history or presence of cardiovascular disorders, signs or symptoms of IFD (according to local diagnostic protocols using two weekly assessment of serum galactomannan <0.5, bronchoalveolar lavage galactomannan <1.0, and no signs on high-resolution computed tomography [11]) or use of antifungal drugs for IFD within the previous month, and concomitant use of drugs potentially causing clinically relevant pharmacokinetic interactions [15].

Treatment protocol and supportive care

Myeloablative conditioning chemotherapy consisted of high-dose cyclophosphamide and total body irradiation. Reduced-intensity conditioning chemotherapy consisted of fludarabine, busulfan, and antithymocyte globulin [16]. Patients who underwent an HCT initated cyclosporine A on the day of HCT as graft-versus-host disease prophylaxis. Remission-induction chemotherapy consisted of idarubicin or daunorubicin in combination with cytarabine (200 mg/m^2 continuous infusion for 7 days) or high-dose cytarabine (3000 mg/m^2 twice daily for 4 days). Patients received antibacterial prophylaxis, central venous catheter management, and a diagnostic-driven approach for managing IFD [17].

Study design

Patients were randomized to receive either 7 days of intravenous posaconazole therapy followed by 9 days of oral therapy or 7 days of oral therapy followed by 9 days of intravenous therapy, starting within 7 days after HCT or the last administration of the remission-induction chemotherapy course. Posaconazole was dosed 300 mg twice daily on the first day, followed by 300 mg once daily. From day 13 onward, a step down to 200 mg was performed. Blood samples were collected on days 7, 12, and 16 immediately before dosing and 0.5, 1 (after oral dose), 1.5 (end of infusion), 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours after intravenous or oral administration. Additional trough samples were collected daily on all other study days.

The presence or absence of severe intestinal mucositis was assessed daily with plasma citrulline levels, because these reflect the small intestinal enterocyte mass decreasing during mucositis [18,19]. Plasma citrulline levels were quantitated with a validated assay [20]. Additionally, intestinal mucositis was evaluated by means of a daily gut score.

Sample size and study design justification

We performed a sample size calculation to reach at least 90% power based on the stochastic simulation and estimation of 500 virtual studies using the proposed design and pharmacokinetic model by Dolton et al. [4], assuming mucositis in 40% of patients. The number of patients to provide a 96.2% power to detect a clinically relevant change (20%) in posaconazole exposure (AUC) due to mucositis with an α of 0.05 was 20.

Bioanalytical assay

Total and unbound posaconazole concentrations in plasma were quantified using a fully validated liquid chromatography-tandem mass spectrometry assay. The unbound posaconazole fraction was obtained with ultrafiltration (1650 g for 20 minutes at 37°C during centrifugation) using an Amicon® 30K Ultra Centrifugal filter. The dynamic ranges for total and unbound posaconazole concentrations were 0.05 to 10.0 mg/L and 0.001 to 0.5 mg/L, respectively.

Pharmacokinetic model

Total and unbound posaconazole pharmacokinetics were integrally analyzed by means of nonlinear mixed effects modelling with the software program NONMEM, version 7.4.1. The first-order conditional estimation method was used, with the interaction option in case of a proportional residual error model.

Parameters were allometrically scaled to a total body weight of 70 kg with an exponent of 0.75 for flow parameters (e.g. clearance (CL)), 1 for volume parameters, and −0.25 for rate parameters. Inter- and intraindividual variability were assumed to be log-normally distributed. Residual variability was evaluated using additive, proportional, and combined additive and proportional models.

Pharmacokinetic parameters were parameterized on total posaconazole concentrations. One- and two-compartment models were considered for the description of posaconazole plasma

concentrations. Different absorption models were evaluated: first-order absorption, zero-order absorption, sequential zero- and first-order absorption, and multicompartment absorption models with various numbers of transit compartments. Both empirical models and semiphysiological models, such as the well-stirred liver model, were evaluated [21,22]. In this model, the intrinsic hepatic CL (CL_{int}) for posaconazole was estimated, assuming a liver blood flow (Q_H) of 90 L/hour. Liver plasma flow (Q_{HP}) was calculated according to Equation 1:

$$Q_{HP} = Q_H \cdot (1 - Ht) \quad (1)$$

where Ht is haematocrit. Hepatic extraction (E_H) was defined per Equation 2:

$$E_H = \frac{CL_{int} \cdot f_u}{Q_{HP} + (CL_{int} \cdot f_u)} \quad (2)$$

where f_u is the unbound fraction of posaconazole. Hepatic CL (CL_H) was calculated using Equation 3:

$$CL_H = E_H \cdot Q_{HP} \quad (3)$$

Hepatic volume (V_L) was calculated with the formula proposed by Small et al. [23] for non-Japanese patients:

$$V_L = 0.822 \cdot BSA^{1.108 \cdot age^{-0.022}} \quad (4)$$

where BSA is the body surface area. Flow from the liver compartment to the central compartment is described by $\frac{Q_{HP} \cdot (1-E_H)}{V_L}$, and vice versa by $\frac{Q_{HP}}{V_1}$. Flow from the liver compartment out of the system is described by $\frac{CL_H}{V_L}$.

Protein binding

Posaconazole protein binding was analyzed with different approaches based on visual inspection of the observed data. Linear and capacity-limited protein binding models were fitted to the data. For the linear-binding model, unbound posaconazole concentrations were related to total concentrations with Equation 5:

$$C_u = f_u \cdot C_{tot} \quad (5)$$

where C_u and C_{tot} are the unbound and total concentration, respectively, and f_u is the unbound fraction.

For the capacity-limited binding model, unbound posaconazole concentrations were related to total concentrations using Equations 6 and 7:

$$C_b = \frac{B_{max} \cdot C_u}{K_D + C_u} \quad (6)$$

$$C_{tot} = C_b + C_u \quad (7)$$

where C_b is the bound concentration, B_{max} is the maximum binding concentration of posaconazole, and K_D is the equilibrium dissociation constant.

Covariate analysis

In the covariate analysis, the effect of severe intestinal mucositis on oral posaconazole bioavailability was evaluated with the base model as a binary covariate, with citrulline levels of 10 μmol/L as the cut-off [19]. Measured concentrations were converted from continuous to dichotomous variables, dividing patients in those with severe mucositis and those with moderate, mild, or no mucositis.

Simulations

The final population pharmacokinetic model for total and unbound posaconazole concentrations was used to simulate posaconazole exposure at steady state in patients receiving posaconazole, based on a real-life database from our haematology department with demographic data of 1576 haematology patients. Monte Carlo simulations were performed for patients with and without severe mucositis receiving posaconazole intravenously and orally.

Results

Patient characteristics

In total, 23 patients were included for analysis with 581 total and 91 paired unbound posaconazole concentrations. Patient characteristics are summarized in Table 1. There were no breakthrough IFDs in the studied population. Sixteen patients had episodes with and without severe mucositis, six patients had severe mucositis during the entire study, and one patient did not experience severe mucositis. During episodes of severe mucositis, reflected by citrulline levels of <10 μmol/L, the median mucositis score was 1 (interquartile range, 0–3). The median treatment duration was 12.2 days (range, 4.1–17.0 days).

Of all total concentrations included, 246 (42.3%) were trough concentrations. The median observed posaconazole trough level was 1.07 mg/L (range, 0.09–3.39 mg/L). Fifty-two trough concentrations were below target for antifungal prophylaxis (>0.7 mg/L) on or after day 2 of posaconazole treatment, of which almost all (90.4%) were obtained during severe mucositis. Because of carry-over effects, no discrimination in route of administration was made.

Pharmacokinetic model

Posaconazole pharmacokinetics were best described by a two-compartment disposition model with sequential zero- and first-order absorption and first-order elimination using a well-stirred liver model. A schematic depiction of the structural model with rate constants describing the flow is presented in Figure S1. Inter-individual variability in CL_{int}, V_1, k_a, and F were estimated at 50.7%, 65.9%, 62.3%, and 53.9%, respectively. No intraindividual variability could be estimated. Data obtained during therapy with a reduced posaconazole dose of 200 mg once daily were insufficient to study the potential nonlinearity in absorption and clearance. The model significantly improved after adding the correlation between the residual error for total and unbound concentrations.

Table 2 summarizes the parameter estimates of the base model. Absolute bioavailability in this model was estimated at 56.5% (percentage relative standard error (%RSE): 28.1). Standard goodness-of-fit scatter plots are presented in Figure S2. For unbound posaconazole concentrations, the goodness-of-fit plots showed a little more deviation from the lines of unity, but fits were considered acceptable given the scarceness of the data. The prediction-corrected visual predictive checks in Figures S3 and S4 show the internal validity of the model. Figure S3 suggests a slight overprediction of our model for patients receiving posaconazole orally.

Protein binding

Posaconazole protein binding could not be described with a capacity-limited binding model. Unbound posaconazole concentration-time data were therefore fitted to a linear binding

Table 1
Patient characteristics

Characteristics	IV–PO ($n = 12$)	PO–IV ($n = 11$)	Total ($N = 23$)
Age (y), median (range)	56 (18–70)	58 (27–71)	57 (18–71)
Female sex, *n* (%)	6 (50.0)	7 (63.6)	13 (56.5)
Weight (kg), median (range)	76.1 (49.1–97.2)	77.3 (54.3–103.7)	77.3 (49.1–103.7)
Height (cm), median (range)	170 (154–193)	172 (167–185)	172 (154–193)
Body mass index (kg/m^2), median (range)	25.1 (20.7–32.1)	26.3 (19.2–31.7)	25.5 (19.2–32.1)
Albumin (g/L), median (range)	31.0 (21.0–43.5)	31.0 (23.0–37.9)	31.0 (21.0–43.5)
Citrulline (μmol/L), median (range)	8.6 (4.5–20.2)	9.0 (2.6–26.4)	8.7 (2.6–26.4)
Haematocrit (fraction), median (range)	0.30 (0.24–0.32)	0.26 (0.17–0.31)	0.27 (0.17–0.32)
Haematological disease, *n* (%)			
Acute myeloid lymphoma	5 (41.7)	5 (45.5)	10 (43.5)
Myelodysplastic syndrome	3 (25.0)	3 (27.3)	6 (26.1)
B-acute lymphatic leukaemia	1 (8.3)	1 (9.1)	2 (8.7)
chronic myelomonocytic leukaemia	1 (8.3)	0 (0.0)	1 (4.3)
Lymphoma	2 (16.7)	0 (0.0)	2 (8.7)
T-prolymphocytic leukaemia	0 (0.0)	1 (9.1)	1 (4.3)
Mixed phenotype acute leukaemia	0 (0.0)	1 (9.1)	1 (4.3)
Treatment, *n* (%)			
Allogeneic haematopoietic cell transplantation (myeloablative or reduced intensity conditioning)	6 (50.0)	9 (81.8)	15 (65.2)
Remission-induction chemotherapy	6 (50.0)	2 (18.2)	8 (34.8)
Pharmacokinetic assessment, *n* (%)			
Day 7	10 (83.3)	10 (90.9)	20 (87.0)
Day 12	7 (58.3)	4 (36.4)	11 (47.8)
Day 16	2 (16.7)	4 (36.4)	6 (26.1)

IV–PO, intravenous followed by oral therapy; PO–IV, oral followed by intravenous therapy.

model, which corresponds with the observed unbound fractions versus unbound concentrations shown in Fig. 1. In the final model, the estimate for posaconazole f_u was 0.027 (%RSE: 3.9).

Covariate analysis

In the covariate analysis, severe intestinal mucositis was identified as a significant covariate on bioavailability. Parameter estimates of the final model are depicted in Table 2, and the model control stream is available in the Supplementary Materials. Absolute bioavailability in the final model was estimated at 67.6% (% RSE: 75.0) and 51.4% (%RSE: 56.5) for patients without and with severe intestinal mucositis, respectively.

Simulations

The results of the simulated AUC and C_{trough} at steady state are shown in Fig. 2. In patients receiving posaconazole orally, the group with severe mucositis showed lower AUC and C_{trough} compared with the other group. In 48% of patients with severe

Table 2
Population pharmacokinetic parameters of the final model

	Base model		**Final model**	
Parameter	**Estimate (%RSE)**	**Shrinkage (%)**	**Estimate (%RSE)**	**Shrinkage (%)**
Structural model				
CL_{int} ($L \cdot h^{-1}$)	235 (22.8)		235 (25.4)	
Q ($L \cdot h^{-1}$)	23.4 (6.2)		23.8 (6.7)	
V_1 (L)	68.7 (24.0)		68.1 (32.3)	
V_2 (L)	239 (9.5)		238 (9.7)	
k_a (h^{-1})	0.250 (66.0)		0.285 (114.4)	
D (h)	4.17 (27.8)		4.50 (44.9)	
F (%)	56.5 (28.1)		67.6 (75.0)	
Mucositis impact on F	—		0.761 (56.5)	
f_u	0.0271 (2.6)		0.027 (3.9)	
Interindividual variability				
IIV CL_{int} (%)[a]	54.1 (28.4)	2.3	54.1 (31.1)	2.2
IIV V_1 (%)[a]	73.7 (47.4)	17.4	77.9 (88.6)	17.0
IIV k_a (%)[a]	68.8 (111.0)	41.8	77.1 (163.8)	40.1
IIV F (%)[a]	58.0 (48.1)	12.8	53.3 (63.8)	13.4
Residual error				
Proportional $error_{total}$ (%)[a]	19.6 (7.4)	4.2	19.3 (9.1)	4.2
Proportional $error_{unbound}$ (%)[a]	25.8 (44.4)	4.7	24.9 (48.7)	3.2
Correlation	0.414 (140.2)	—	0.378 (164.0)	—

Correlation means correlation factor taking into account the high degree of correlation between the residual error on total and unbound concentrations. CL_{int}, intrinsic clearance; D, duration of zero-order absorption into the oral depot compartment; F, absolute bioavailability; f_u, fraction unbound; k_a, first-order absorption rate constant; RSE, relative standard error; Q, intercompartmental clearance; V_1, central volume of distribution; V_2, peripheral volume of distribution.

[a] Transformed from log normal variance to %CV with $\sqrt{(e^{\omega^2} - 1)}$.

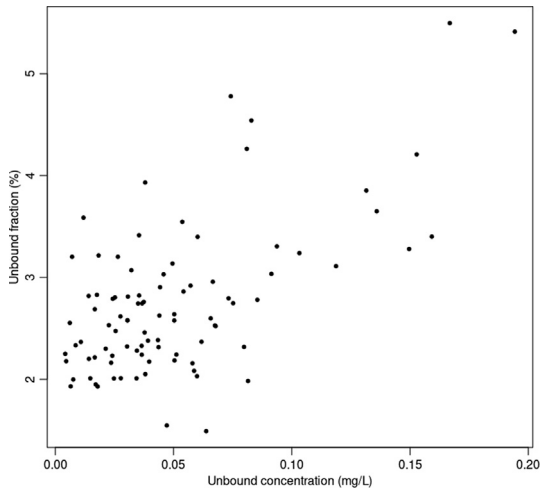

Fig. 1. Posaconazole unbound fraction (%) versus unbound concentration (mg/L).

intestinal mucositis receiving the standard dose of the solid oral posaconazole formulation, simulated C_{trough} at steady state was below the predefined target C_{trough} of >0.7 mg/L. In these patients, an increase in dose to 400 mg twice daily on day 1, followed by 400 mg once daily, resulted in better posaconazole exposure.

Discussion

To the best of our knowledge, this is the first prospective, randomized, crossover study describing posaconazole pharmacokinetics after administration of both the solid oral and intravenous formulations in haematology patients, thereby establishing the absolute oral bioavailability. The impact of severe intestinal mucositis on posaconazole exposure was confirmed by severe mucositis as a covariate for posaconazole bioavailability, reflected by a reduced absolute bioavailability of 51.4% in patients with severe mucositis compared with 67.6% in patients without. We predicted that almost half of patients with severe mucositis would not

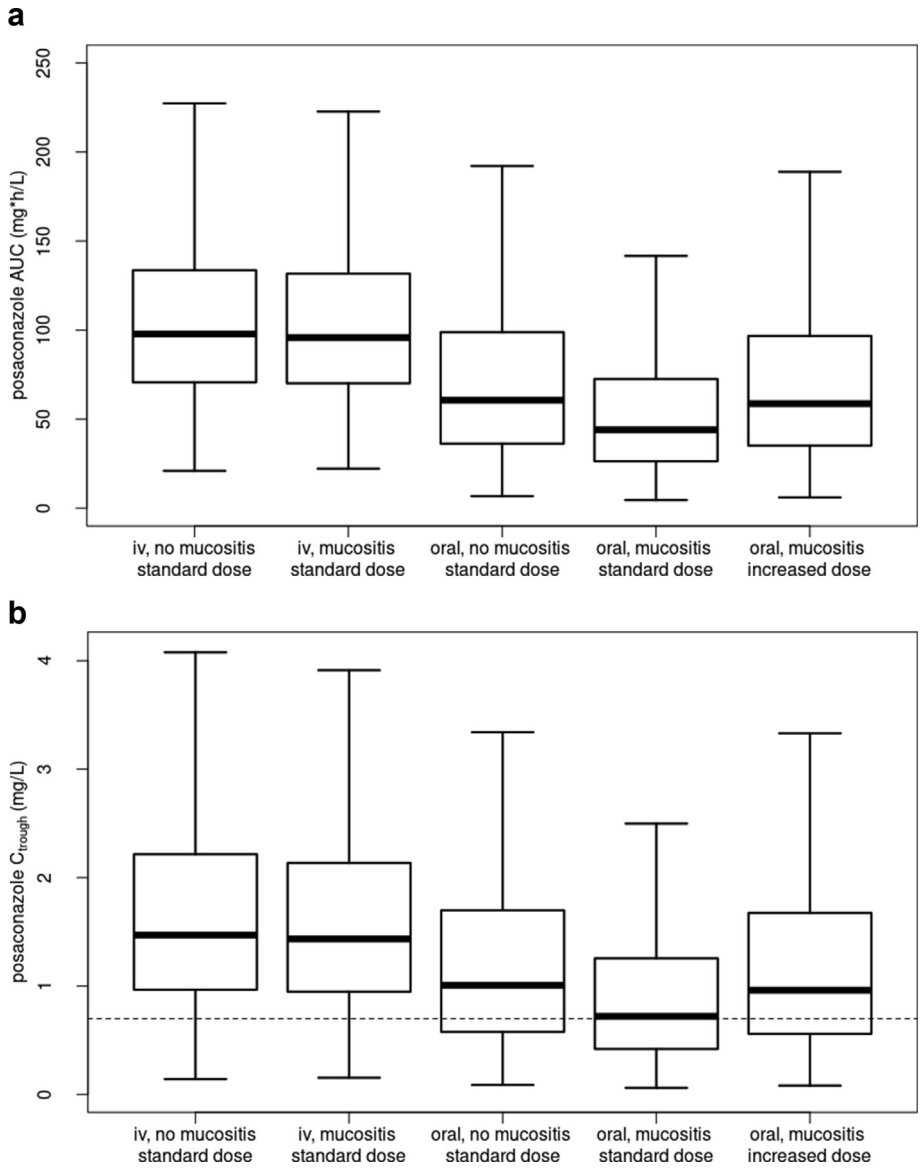

Fig. 2. (a) Boxplots of simulated posaconazole exposure at steady state. (b) Boxplots of simulated posaconazole trough concentrations at steady state. Dotted line: threshold of 0.7 mg/L for prophylaxis. Whiskers are minimal and maximal values. AUC, area under the concentration time curve; C_{trough}, trough concentration; iv, intravenous.

achieve the C_{trough} target of >0.7 mg/L at steady state at the standard oral dose.

Clinicians should pragmatically consider increasing the posaconazole oral dose to 400 mg twice daily on day 1 and 400 mg daily from day 2 during severe mucositis. Given our simulation results and previous findings on the tolerability of high-dose posaconazole by others [24], this dose increase is considered safe. Notably, food intake in patients with mucositis may be hampered and thus have an expected slight influence on the absorption of the posaconazole oral tablet as well [25]. In patients who are not receptive to oral intake in the presence of mucositis, intravenous therapy is an alternative treatment option. Our findings for the effect of mucositis on posaconazole bioavailability potentially apply to other orally administered drugs.

It may not be routine practice to assess mucositis through measurement of citrulline levels. Here, mucositis may be evaluated using an oral mucositis assessment scale [26,27]. Citrulline concentrations have been demonstrated to correlate significantly with these assessment scales [27]. With a cut-off citrulline level of 10 μmol/L reflecting severe intestinal mucositis, the current study cannot draw conclusions on the effect of mild or moderate mucositis on the bioavailability of posaconazole.

Final parameter estimates from the developed model were difficult to compare with previous population pharmacokinetic studies because these differed in model structure [28,29]. However, parameter estimates reported previously appear to be in the same order of magnitude (e.g. V_1 and V_2 in the current study was a combined 306.1 L compared with an apparent volume not accounting for bioavailability (V/F) of 410 L and 420 L [28,29]). Posaconazole distribution was described by a two-compartment model, which is in disagreement with earlier studies where one-compartment models were identified [28,29]. This may be the consequence of our data set including concentrations over a wide time range, allowing us to describe the concentration-time course of posaconazole more precisely. Absorption of the posaconazole tablet formulation was best described with sequential zero and first-order absorption, as described previously [28]. Our predictions for exposure were comparable to those previously seen with a comparable patient population [30].

Posaconazole protein binding was described by a linear binding model with our data. These findings are not in line with a previous study that described posaconazole protein binding in critically ill patients by means of a capacity limited binding model [31]. Our data set may not have been rich enough because it consisted of unbound concentrations much lower than the previously reported dissociation constant (K_D), the concentration at which half of the protein binding sites are saturated with posaconazole. We report a population estimate for the unbound fraction of 2.7%. This is comparable to the 2% reported for healthy adults [8], but differs distinctly from the 0.65% seen in critically ill patients [31]. This may be explained by the greater difference in albumin levels compared with those in the healthy population [32].

In conclusion, absolute bioavailability of posaconazole is decreased in patients with severe intestinal mucositis. In these patients, use of the intravenous formulation or an increase in oral posaconazole dose to 400 mg twice daily on the first day of dosing, followed by once-daily 400 mg, is recommended. Future research should confirm whether this approach results in reduced breakthrough infections in patients with severe intestinal mucositis. Our results on the impact of mucositis on the absorption of posaconazole should encourage regulatory agencies to advise an assessment of the impact of mucositis on drug absorption during drug development.

Transparency declaration

JM has received consulting fees, personal fees, and support for attending meetings and/or travel from Merck Sharpe and Dohme Corp (MSD), Gilead Sciences, Pfizer Inc., F2G, Mundipharma, Takeda, Shire, Cidara, and Scynexis. RB has received consulting fees and unrestricted and research grants from Astellas Pharma Inc., Gilead Sciences, MSD, and Pfizer Inc. In addition, he has received consulting fees from F2G, Mundipharma, and Cidara and participated on an advisory board for Pfizer Inc., Astellas Pharma Inc., Gilead Sciences, F2G, Mundipharma, and Cidara. AC has received research grants from Gilead Sciences, MSD, and ViiV, as well as consulting fees from MSD. All contracts were through the institution, and payments were invoiced by the institution. All other authors have no conflicts of interest to declare in relation to this study.

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Author contributions

Anouk M. E. Jansen and Eline W. Muilwijk contributed equally and Nicole M. A. Blijlevens and Rob ter Heine contributed equally to this manuscript.

RB and NB designed the study with help from EM, JM, WvdV, and RtH. EM, JM, RA, and WvdV conducted the study. AJ performed the analysis of the data with RtH and RB. AJ, EM, and RB drafted the manuscript. All authors approved the final version.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.01.029.

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