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REVIEW

A Review of Population Pharmacokinetic Models of Posaconazole

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Abstract: Posaconazole is often used for the prophylaxis and treatment of invasive fungal infections (IFI). However, intra- and inter-individual differences and drug interactions affect the efficacy and safety of posaconazole. Precision dosing of posaconazole based on the population pharmacokinetic (PopPK) model may assist in making significant clinical decisions. This review aimed to comprehensively summarize the published PopPK models of posaconazole and analyze covariates that significantly influence posaconazole exposure. Articles published until May 2022 for PopPK analysis of posaconazole were searched in PubMed and EMBASE databases. Demographic characteristics, model characteristics, and results of PopPK analysis were extracted from the selected articles. In addition, the steady-state pharmacokinetic profiles of posaconazole were simulated at different covariate levels and dosing regimens. Out of the 13 studies included in our review, nine studies included adults, three included children, and one included both adults and children. All oral administration models were one-compartment models, and all intravenous administration models were two-compartment models. Body weight, proton pump inhibitors, and incidence of diarrhea were found to be important covariates. Clinically, the potential impact of factors such as patient physiopathologic characteristics and comorbid medications on posaconazole pharmacokinetics should be considered. Dose adjustment in combination with TDM or replacement with a tablet or intravenous formulation with higher exposure may be an effective way to ensure drug efficacy as well as to reduce fungal resistance. Meanwhile, published models require further external evaluation to examine extrapolation.

Keywords: posaconazole, population pharmacokinetics, nonlinear mixed effects modeling, therapeutic drug monitoring

Introduction

Posaconazole is a second-generation triazole antifungal agent derived from the structure of itraconazole.[1] Similar in action to itraconazole, posaconazole blocks the synthesis of ergosterol, a major sterol found on the membrane of fungal pathogens, by inhibiting the activity of the enzyme, lanosterol 14α-demethylase. The properties and function of fungal cell membranes get altered due to the accumulation of 14α-methyl sterol precursors, obstructing cell growth and division and resulting in an antifungal effect.[2,3] Posaconazole is a broad-spectrum antifungal agent active against various fungi, including common pathogens such as *Candida* species and *Aspergillus* species, as well as novel pathogens such as *Cryptococcus neoformans, Fusarium* species, and *Zygomycetes* species.[4]

Posaconazole is available in three types of formulations: oral suspension, delayed-release tablet, and intravenous injection.[5] In 2006, posaconazole suspension was approved by the United States (US) Food and Drug Administration (FDA) for the prevention of invasive *Candida* and *Aspergillus* infections in patients ≥ 13 years of age with severe immunodeficiency conditions, such as acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). It was also approved by the US FDA for treating patients with other neutropenic hematological malignancies and those who had

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undergone hematopoietic stem cell transplantation.[6,7] Posaconazole delayed-release tablet and intravenous injection were approved by the FDA in 2013 and 2014, respectively.[8]

Up to now, a large number of literature have studied the pharmacokinetic characteristics and influencing factors of posaconazole. The pharmacokinetics (PK) of posaconazole vary significantly among individuals.[9–12] The absorption of posaconazole oral suspension is saturable, resulting in high variability in bioavailability (F) and serum exposure levels.[8] In addition, gastric acid, the presence of food, and gastrointestinal movement also affect bioavailability.[13–15] The absorption of posaconazole is reduced, thus decreasing its F on administration with drugs that inhibit gastric acid secretion such as proton pump inhibitors (PPI) and histamine (H_2) receptor antagonists and drugs that alter gastrointestinal motility such as metoclopramide.[16–18] The development of delayed-release tablets and intravenous injections has effectively improved the PK of posaconazole and increased drug exposure.[19] However, regardless of the formulation, the therapeutic effect of posaconazole on invasive aspergillosis was closely related to its serum concentration level.[16,20] In addition, the metabolism of posaconazole almost does not depend on the cytochrome P450 (CYP450) enzyme system but achieves limited metabolism under the action of uridine diphosphate glucuronic acid transferase (UDP-glucuronosyltransferases, UGTs). Drugs that can interact with the UGT enzyme, such as phenytoin, rifampicin, and fosamprenavir may affect the plasma concentration of posaconazole.[21,22] Therefore, considering the inter- and intra-individual differences of posaconazole, the interactions between drugs, and the effect of serum drug concentration on efficacy, routine therapeutic drug monitoring (TDM) of posaconazole is recommended to ensure the adequate exposure required to achieve maximum efficacy for prophylaxis or treatment.[19]

Some population pharmacokinetics (PopPK) models of posaconazole have been developed to better describe the PK characteristics of posaconazole in different target populations and to assist in adjusting the dosing regimen.[18,23–35] A review published in 2020 has summarized the PK parameters of eight of these models.[22] However, to our knowledge, there are no studies that have performed simulation analysis on the developed posaconazole PopPK models. The aim of this review is to comprehensively compare the PK characteristics of these models and to examine the effects of covariates and dosing regimens on posaconazole PK by Monte Carlo simulation.

Methods

Search Strategy

PopPK studies of posaconazole from inception to May 2022 were searched from PubMed and EMBASE databases using the following keywords: "posaconazole" in title or abstract, "population pharmacokinetic", "popPK", "pop PK", "PPK", "population pk model", "compartmental pharmacokinetic", "pharmacokinetic model", "population model", "NONMEM", "nonlinear mixed effects modeling", "NLME", "mixed effect", "WinNonmix", and "Monolix".

Inclusion/Exclusion Criteria

All literature articles describing the PopPK models of posaconazole were included according to the retrieval results. Studies that met the following criteria were included in this review: (1) the study population was human, whether adult or pediatric patients or healthy volunteers; (2) posaconazole was used as the research drug, with no limitation on the type of formulation; and (3) the PK analysis was carried out and a PopPK model was established. The following studies were excluded: (1) reviews, case reports, methodological articles, and in vitro studies; (2) non-English language publications; (3) papers that lack a source for details of methods or results; (4) studies using non-compartmental or non-parametric methods.

Data Extraction

The following information was extracted from the PopPK models that met inclusion and exclusion criteria: (1) population characteristics, such as country, sex, weight, age, disease, administration route, dose and posaconazole concentration; (2) model characteristics, such as the number of samples collected, the method of modeling, evaluation, and dose simulation; (3) results of PopPK analysis, such as structural models, statistical models (inter-individual and residual variation), parameter estimates, and covariates examined and retained.

Comparison of Studies

The population characteristics, modeling strategies, and model information for each study have been summarized in tabular form. The steady-state concentration-time profiles of posaconazole at different covariate levels were simulated. The daily dose of 300–600 mg was set as the instructions. For categorical covariates, 0 and 1 represented the absence or presence, respectively. Continuous covariates were simulated with three levels: adult weight (60, 120, and 180 kg), child weight (10, 20, and 30 kg); age (20, 40, and 60 years); and total protein (4.8, 6.5, and 7.8 g/dL).

The effect of different dosing regimens on posaconazole steady-state concentration profile was also simulated. The dosage for oral suspensions was set at 200, 300, and 400 mg thrice daily. A loading dose of 200, 300, and 400 mg twice on the first day and a maintenance dose of 200, 300, and 400 mg once daily was set for tablets and intravenous formulations. The infusion time of the intravenous formulations was set at 90 min.

Results

Overview of Studies

A total of 204 papers were initially retrieved from the databases. After screening according to the predetermined inclusion and exclusion criteria, 13 PopPK models (M1-M13) published between 2010 and 2022 were retained in this review.[18,23–34] The screening process of the study is shown in Figure 1. Table 1 summarizes the demographic information of patients in the studies. The median number of subjects in each study was 37 (range, 6 to 335) with 38.46% of the studies having numbers more than 50. With the exception of three studies that also included healthy volunteers,[18,28,30] the other studies included only patients with different pathological states such as obesity, immune deficiency, hematological malignancies, and pulmonary fibrosis. Nine studies included adults,[18,23,25–28,30,31,34] three included children,[29,32,33] and one included both.[24] Of the 11 studies with oral formulations of posaconazole, three were with oral suspensions,[18,23–26,33] four with delayed-release tablets,[27,28,31,32] and one was on both oral suspension and delayed-release tablets.[29] The two

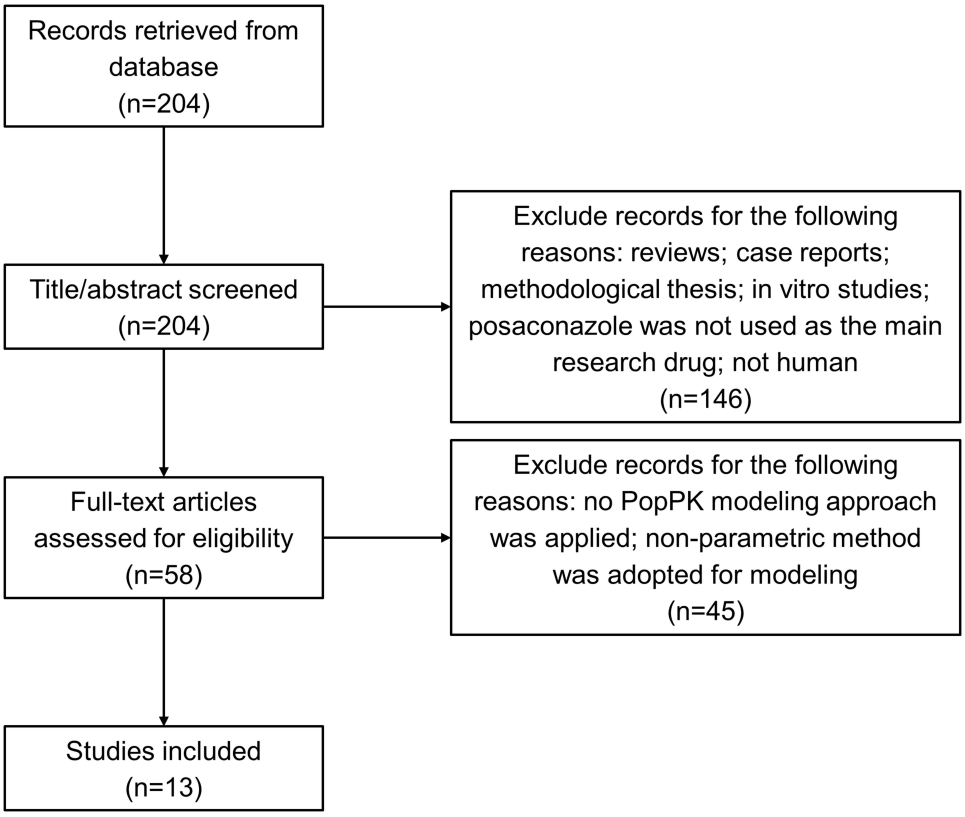

Figure 1 Flow chart of the article selection process.

Table 1 Population Characteristics of the Studies Included in the Review

Study	Year	Country	Study Design	N(Male/ Female)	Age(Year)[a]	Body Weight(kg)[a]	Subject Characteristic	Routes	Dose(mg)	Assay
M1[23]	2010	Germany	Single, P	32 (16/16)	49.5 (17–66)	68.5 (49–115)	Adults, SCT recipients with hematological malignancies	PO	NA	HPLC
M2[24]	2010	USA	Multi, P	215 (117/98)	52	70	Adults & pediatrics, neutropenic patients receiving chemotherapy for AML/MDS	PO	200 tid	LC-MS/MS
M3[25]	2012	Germany	Single, P	84 (42/42)	55 (19–73)	77.7 (48.0–119.2)	Adults, patients with AML/MDS	PO	200 tid	HPLC
M4[26]	2012	Germany	Single, P	15 (6/9)	58 (41–79)	NA	Adults, patients in a SICU	Nasogastric Tube	200 q6h	HPLC
M5[18]	2014	Australia, Netherlands	Multi, R	102 (58/44)	Study1: 38 (18–54) Study2: 50 (18–79)	Study1: 74 (44–104) Study2: 71(38–122)	Adults, healthy volunteers(study1) and patients(study2)[b]	PO	Study1: 200–800 Study2: 160–1200[c]	HPLC
M6[27]	2017	France	Single, P	49 (29/20)	53 (19–73)	72 (50–125)	Adults, hematological malignancies	PO	Day1: 300 bid, Maintenance: 300 qd	LC-MS/MS
M7[28]	2018	USA	Multi, P	335 (205/130)	Study1:31.4±7.1 Study2:36.0±11.9 Study3:38.2±7.3 Study4:37.7±9.8 Study5:45.8±9.0 Study6:51.0±14.0	Study1:74.3±10.0 Study2:76.1±14.7 Study3:79.6±13.9 Study4:76.8±12.0 Study5:73.9±11.3 Study6:77.1±17.7	Adults, healthy volunteers(study1, study2, study3, study4, study5) and patients(study6)[d]	PO	Study1:100[e] Study2:300[f] Study3:400[e] Study4:100[e] Study5:200, 400[f] Study6:200, 300[g]	NA
M8[29]	2019	UK	Single, R	117 (43/74)	5.7 (0.5–18.5)	17.8 (6.05–74.8)	Infants & Children, immunocompromised	PO	200 (32–630)[a]	NA
M9[30]	2020	Netherlands	Multi, P	24 (12/12)	Normal(300mg IV): 22(20–37); Obese(300mg IV): 51 (31–63); Obese (400mg IV): 37.5 (25–50)	Normal(300mg IV):72.3 (61.4–85.4) Obese(300mg IV): 129 (109–190) Obese(400mg IV): 144 (107–175)	Adults, obese and non-obese healthy volunteers	IV	Obese:300/400 Normal:300	UPLC
M10[31]	2021	Spain	Single, P	36 (17/19)	53 (27–73)	68.3 (40.0–103.5)	Adults, SCT recipients	PO	Day1: 300 bid, Maintenance: 300 qd	UPLC

M11[32]	2021	UK	Single, R	37 (13/24)	14 (7–17)	45.55 (25–82.8) Age 6–11 years: 31.5(25–58) Age 12–17 years: 50(34.7–82.8)	Pediatrics, cystic fibrosis	PO	300(100–600) Age 6–11 years: 300(100–300)[a] Age 12–17 years: 300(200–600)[a]	2D HPLC-MS/MS
M12[33]	2021	Romania	Multi, P	14 (5/9)	6.7 ± 2.8	19.9 ± 6.1	Pediatrics, hematologic malignancies	PO	100 (77.3–100)[a], tid	HPLC
M13[34]	2021	Belgium, Netherlands, France	Multi, P	6 (3/3)	44 (40–57)	76 (67–97)	Adults, critically ill patients during ECMO	IV	Day1: 300 q12h, Day2: 300 q24h, with an infusion duration of 90min	HPLC

Notes: [a]Values are expressed as median (range), mean (range) or mean ± standard deviation. [b]Patients with underlying condition: AML; Acute lymphoblastic leukemia; Non-Hodgkin's lymphoma; MDS; Multiple myeloma; Diabetes mellitus type 2; Chronic lymphocytic leukemia; Myelofibrosis; Hodgkin's lymphoma; acute biphenotypic leukemia; gray-zone lymphoma; T-polylymphocytic leukemia; chronic myeloid leukemia; aplastic anemia; HIV positivity; rheumatoid arthritis; Crohn's disease; and none (Histoplasma). [c]Healthy volunteers: day 1, 200 mg; day 2, 200 mg twice daily; days 3–10, 400 mg twice daily; Patients: multiple dosing:160–1200 mg total daily dose. [d]Patients with the following primary diagnosis at study entry: AML; GVHD, graft-versus-host disease (the subjects underwent allogeneic hematopoietic stem cell transplantation); MDS. [e]Single dose. [f]Single or multiple doses. [g]Multiple doses.

Abbreviations: Multi, Multicenter; P, prospective; R, retrospective; NA, not available; SCT, allogeneic stem cell transplant; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; ECMO, extracorporeal membrane oxygenation; SICU, Surgical Intensive Care Unit; PO, oral administration; IV, intravenous administration; HPLC, high-performance liquid chromatography; LC-MS/MS, liquid chromatography–tandem mass spectrometry; UPLC, ultra-high-performance liquid chromatography; 2D HPLC-MS/MS, 2D TurboFlow high-performance liquid chromatography-tandem mass spectrometry.

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remaining studies were conducted on intravenous formulations in the obese population and in critically ill patients treated with extracorporeal membrane oxygenation.[30,34]

Model Building and Evaluation

Table 2 summarizes the information about model building and evaluation. The median number of the plasma samples used for modeling was 226 (55 to 5756). About half of the studies used sparsely sampled data from clinical TDM, with the rest of the rich data obtained mostly from PK studies. NONMEM software was used in all studies for modeling except in one study that used Monolix.[27] The deviation, reliability, and accuracy of the models were internally evaluated by goodness-of-fit (GOF), Jackknife technique, visual predictive check (VPC), and normalized prediction distribution errors (NPDE) or bootstrap. Almost all models exhibited satisfactory predictive performance and robustness in internal validation. Few studies had simulated dosing regimens based on the model and had proposed recommended doses for different conditions. Detailed recommended programs and target definitions are shown in Table 2.

Structural Model

Table 3 summarizes the characteristics of the final model, such as the type of structural model used, estimated pharmacokinetic parameters, model variability, and excluded and retained covariates. The PK characteristics of studies comprising oral suspensions and tablets were well described by the one-compartment model, while the two studies involving intravenous administration were better suited to the two-compartment model.[30,34] With reference to absorption, six[18,23,25,27,29,33] models were described in terms of first-order absorption and two with a lag time characterizing the absorption delay.[18,33] Out of the five studies using delayed-release tablets,[27–29,31,32] two studies were described with sequential zero first-order absorption.[28,31] The mode of absorption for the remaining five studies was not mentioned.[24,26,30,32,34] The absorption rate constant (k_a) was estimated from 11 oral administration studies with a median-(range) of 0.494 h^{-1} (0.0396–1.26 h^{-1}), five of which fixed it to a certain value according to the published literature.[23,25,27,29,31] With the exception of four studies not mentioned the elimination of posaconazole,[24,26,29,32] the remaining studies was best described by first-order elimination kinetics. Clearance (CL) and volume of distribution (V) varied considerably in the different models, with a median (range) for clearance of 14.95 L/h (7.3–195 L/h). The median (range) of V in the one-compartment model was found to be 1100 L (186–5280 L). In the two studies adopting the two-compartment model,[30,34] V for the central compartment (V_1) and peripheral compartment (V_2) were estimated to be in the range of 26.2–150 L and 96.2–396 L, respectively.

The median (range) of inter-individual variability (IIV) of CL and V (or V_1) was found to be 37.9% (21.8–87.8%) and 29.9% (15.6–52.4%) respectively. Only four studies reported the inter-occasion variability (IOV) of related PK parameters.[18,26–28] The proportional, additive, or combined residual error was applied to the final models. The median (range) of the most widely used proportional residual error (coefficient of variation, % CV) was found to be 14.8% (1.79–53.8%).

Covariates

The stepwise covariate model (SCM) building exercise with forward inclusion, and backward elimination was the most commonly used method for building covariate models. The statistical criteria used in each study were slightly different. Multiple factors that potentially influenced the exposure of posaconazole were tested during modeling, and covariates such as weight, sex, age, total protein, incidence of diarrhea, use of drugs such as PPI, phenytoin, rifampin, fosamprenavir, nutritional supplements, and chemotherapeutic agents were retained in the final model of different studies to account for changes in PK parameters such as CL, V, and F.

In our review, the incidence of diarrhea and the use of PPI were the most common covariates included in the final model of six[18,23–25,29,33] and five studies,[18,24,25,29,33] respectively, with a negative effect on the bioavailability of posaconazole. Body weight appeared as a final covariate in 31% of the studies and also negatively correlated with posaconazole exposure. In addition, each of the other covariates such as the sex, age, total protein, and use of phenytoin were found in only one study.

Table 2 Model Characteristics of the Studies Included in the Review

Study	Samples		Modelling				Simulation	
	Total	Per Subject	Data	Software, Algorithm	P value (Forward / Backward)	Validation	Optimal Dosing Regimen	Target (mg/L)
M1[23]	149	5(1–12)	Sparse data from a TDM study	NONMEM, FOCE-I	0.05/NA	GOF, modified jackknife evaluation	NA	NA
M2[24]	702	3–5	Sparse data from a multicenter PK study	NONMEM, FOCE	NA/NA	Bootstrap	NA	NA
M3[25]	643	5 (1–22)	Sparse data from a TDM study	NONMEM, NA	0.05/0.05	VPC, GOF, modified jackknife evaluation	NA	NA
M4[26]	270	18	Rich data from a study	NONMEM, FOCE-I	NA/NA	GOF	NA	NA
M5[18]	905	Healthy volunteers:11 Patients:1	Rich data from a PK study; sparse data from an observational study of TDM	NONMEM, FOCE-I	0.005/0.001	pvcVPCs, bootstrap	NA	Prophylaxis: C_{min} >0.7
M6[27]	205	4.2	Sparse data from a study	Monolix, NA	NA/NA	GOF, NPDE, VPC	Prophylaxis C_{min}≥1.5mg/L at 48h or day 7 or 8, reduction of the dose from 300 mg to 200mg	Prophylaxis: C_{min}≥0.7, Treatment: C_{min}≥1.0 at 48h and at day 10
M7[28]	5756	17.6	Rich data from five Phase I study; Sparse data from a Phase III study	NONMEM, FOCE	0.01/0.001	Diagnostic plot, VPC, bootstrap	Day1 300mg twice daily, followed by 300mg/d for maximum of 27 days	C_{min} and C_{avg} >0.5
M8[29]	338	3(1–11)	Sparse data from a TDM study	NONMEM, FOCE-I	0.05/0.01	Diagnostic plot, VPC, bootstrap	NA	Prophylaxis: $C_{min,\ ss}$≥0.7 Treatment: $C_{min,\ ss}$ ≥1.0
M9[30]	226	10	Rich data from a multicenter PK study	NONMEM, FOCE-I	0.05/0.01	pcVPC	Treatment WT < 140 kg:300mg/d; WT 140–190 kg: 400mg/d; WT > 190 kg: 500mg/d Prophylaxis WT <190 kg: 300mg/d	Prophylaxis: C_{min}≥0.7; C_{avg}≥0.5 Treatment: C_{min}≥1.0; C_{avg}≥3.75
M10[31]	55	1.5	Sparse data from a TDM study	NONMEM, FOCE-I	0.05/0.01	VPC, bootstrap	NA	AUC/MIC[a]≥200

(*Continued*)

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Table 2 (Continued).

Study	Samples		Modelling				Simulation	
	Total	Per Subject	Data	Software, Algorithm	P value (Forward / Backward)	Validation	Optimal Dosing Regimen	Target (mg/L)
M11[32]	100	2(1/9)	Sparse data from a TDM study	NONMEM, FOCE-I	0.05/0.01	GOF, VPC, bootstrap	Aged 6–11 years: 300mg q12h for two doses (loading), then 300mg qd; Aged 12–17 years: 400mg q12h for two doses then 400mg qd	C_{min}≥1.0 AUC≥30 mg·h/L
M12[33]	112	8	Rich data from a multicenter PK study	NONMEM, FOCE-I	0.01/0.001	pcVPC, bootstrap	NA	$C_{trough,ss}$ ≥0.7, $C_{avg,ss}$:0.5–2.5; population geometric mean $C_{trough,ss}$≥1.0, $C_{avg,ss}$≥1.2
M13[34]	83	13	Rich data from a multicenter study	NONMEM, NA	NA/NA	GOF, VPC	NA	Prophylaxis: C_{min}≥0.7 Treatment: C_{min}≥1.0

Notes: [a]MIC=0.06 mg/L for Candida albicans, Candida dubliniensis, Candida parapsilosis and Candida tropicalis; MIC=0.25 mg/L for Aspergillus fumigatus and Aspergillus terreus; MIC=0.5 mg/L for Aspergillus flavus, Aspergillus nidulans and Aspergillus niger.

Abbreviations: TDM, therapeutic drug monitoring; PK, pharmacokinetic; FOCE, first-order conditional estimation; FOCE-I, first-order conditional estimation method with interaction; NA, not available; GOF, Goodness-of-fit plots; VPC, visual predictive check; pcVPC, prediction-corrected visual predictive check; pvcVPCs, prediction-and variability-corrected visual predictive checks; NPDE, normalized prediction distribution errors; WT, body weight; C_{min}, trough concentration; C_{avg}, average blood concentration; $C_{trough,ss}$, total posaconazole trough concentration at steady-state; $C_{avg,ss}$, average concentrations at the steady-state; AUC, area under the concentration–time curve; MIC, minimum inhibitory concentration.

Table 3 Results from Published Population Pharmacokinetic Models of Posaconazole

Study	Structural Model	Pharmacokinetic Parameters	Model Variability			Covariates Excluded	Covariates Retained
			IIV	IOV	Residual Variability		
M1[23]	1-Compartment model with first-order absorption and first-order elimination	CL/F=67×$\theta_{Di}^{diarrhea*}$ L/h V/F=[2250-(AGE-49)×θ_{AGE}]×$\theta_{Di}^{diarrhea*}$ L K_a=0.4 h^{-1}(fixed)	CL/F: 26.9%	NA	42%	WT, HT, SEX, fever, daily dose of posaconazole, ethnicity (Caucasian/ other), stem cell transplantation, coadministration of chemotherapy, ranitidine, pantoprazole, cyclosporine, or tacrolimus, fever, GGT levels	CL/F: diarrhea V/F: diarrhea, AGE
M2[24]	1-Compartment model	CL/F =65.1 L/h V/F = 3290×$1.5^{diarrhea*}$ ×1.43^{PPI*}× $1.84^{bilirbin*}$ ×1.17^{GGT*} ×0.79^{race*} L K_a=0.0396 h^{-1} K_e=0.0198 h^{-1}	V/F: 15.6% K_e: 2.21%	NA	1.03%	IFIPP/IFIPPP, SEX, AGE, WT, BSA, mucositis, neutropenia, vomiting, H_2-receptor antagonist, AST, ALT	V/F: Race (non-white vs white), diarrhea, PPI, bilirubin levels ≥2× ULN, GGT levels ≥2×ULN
M3[25]	1-Compartment model with first-order absorption and first-order elimination	CL/F=42.5×θ_{PPI}^{PPI*}×$\theta_{Di}^{diarrhea*}$ L/h V/F=[2770+(WT-78)×θ_{WT}]×θ_{CHEM}^{CHEM*} L K_a=0.4 h^{-1}(fixed)	CL/F: 25.3%	NA	23.2%	AGE, HT, SEX, fever, daily dose of posaconazole, ethnicity (Caucasian/other), ranitidine, fever, GGT levels, number of leucocytes in blood	CL/F: diarrhea, PPI V/F: chemotherapy, WT
M4[26]	1-Compartment model	CL/F=195 L/h V/F=5280 L K_a=0.77 h^{-1}	CL/F: 51.8% V/F: 52.0%	CL/F: 48.4% V/F: 21.1%	11.6% 2.8%	WT, HT, BMI, SEX, AGE, albumin, GGT, glutamine-oxalacetic transaminase, glutamatepyruvate transaminase, bilirubin	NA
M5[18]	1-Compartment model with first-order absorption with a lag time, and first-order elimination	CL/F=30.2×7.21^{PHE*}×7.21^{RIF*}×1.342^{FOS*}L/h V/F=1100 L K_a=1.26 h^{-1} T_{lag}=1.79 h F=0.549^{PPI*}×0.655^{MET*}×2.29^{NUT*}×0.423^{MUC*}×$0.549^{diarrhea*}$	CL/F: 46.4% V/F: 30.2% K_a: 53.4%	F: 23.6%	6.76% (study1) 53.8% (study2)	WT, AGE, SEX, ranitidine	CL/F:phenytoin, rifampin, fosamprenavir F:PPI, metoclopramide, nutritional supplement, mucositis, diarrhea

(*Continued*)

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Table 3 (Continued).

Study	Structural Model	Pharmacokinetic Parameters	Model Variability			Covariates Excluded	Covariates Retained
			IIV	IOV	Residual Variability		
M6[27]	1-Compartment model with first-order absorption and first-order elimination	CL/F=7.3 L/h V/F=420 L K_a=0.588h^{-1}(fixed)	CL/F: 24.2% V/F: 28.2%	CL/F: 31.9%	14.8%	AGE, WT, BMI, ALT, AST, ALK, GGT, SEX, bilirubin, disease	NA
M7[28]	1-Compartment model with Sequential zero first-order absorption and first-order elimination	CL/F=9.70 L/h V/F=393 L K_a=0.853 h^{-1} D1=2.54 h WT on F1: −1.03 Tablet A/B on F1: 0.247 AML/MDS on F1: −0.165 Dosing regimen on CL: 0.750 Food on k_a: 0.530	CL/F: 37.9% K_a: 57.5% F1: 24.2%	K_a: 71.1% D1: 48.6% F1: 21.4%	0.42 (phase1 study) 0.322 (phase3 study)	AGE, SEX, BMI, CLcr, race, diarrhea	CL/F: dosing regimen (single dose, multiple dose) K_a: food status relative F(F1): WT, disease state (AML/MDS), tablet formulation (A/B vs C/D)
M8[29]	1-Compartment model with first-order absorption	CL/F = 14.95×$(WT/70)^{0.75}$ L/h V/F=201.7×(WT/70) L β_{dose} = 99 mg/m^2(fixed) If FORM=1(suspension) K_a =0.588× $(WT/70)^{-0.25}$ h^{-1}(fixed) F=1 If FORM=2(tablet) K_a =0.197× $(WT/70)^{-0.25}$ h^{-1}(fixed) F= [1 - D/(D + β_{dose})] × $0.67^{diarrhea*}$×0.58^{PPI*}	CL/F: 63%	NA	47.29% 0.02mg/L	treatment/prophylaxis, macrolides, echinocandins, terbinafine, ciclosporin, tacrolimus, mycophenolate, rifamycin, carbamazepine, phenytoin, histamine H_2-receptor antagonists, valaciclovir	CL/F: WT V/F: WT F: diarrhea, PPI
M9[30]	2-Compartment model with first-order elimination	CL = 5.83×$(TBW/70)^{0.54}$ L/h Q=60.3 L/h V_1= 150×$(TBW/70)^{0.77}$ L V_2 = 96.2×$(TBW/70)^{1.16}$ L	V_1: 29.5%	NA	16.4%	LBW, BMI, BSA, IBW, AGE, SEX	CL: TBW V_1: TBW V_2: TBW

M10[31]	1-Compartment model with Sequential zero first-order absorption and first-order elimination	CL/F=8.02×0.613^{SEX*}×(PROT/6.4)$^{-1.48}$ L/h V/F=548 L K_a=0.795 h^{-1}(fixed) D1=2.62 h (fixed)	CL: 28.9% V: 52.4%	NA	21.6%	TBW, BMI, BSA, bilirubin, ALK, AST, ALT, GGT, AGE, eGFR, albumin, ANC, hemoglobin, diagnosis, time since allogeneic transplant, hepatic, digestive GVHD status	CL/F: SEX, PROT
M11[32]	1-Compartment model	CL/F=8.43 L/h V/F=186 L K_a=0.16 h^{-1}	CL/F: 38%	NA	36% 0.15 mg/L	Liver function: ALT, ALK, AST, GGT, bilirubin. potential interacting medicines that were identified in patients included in the dataset: Orkambi(lumacaftor/ivacaftor), rifampicin, rifabutin, clarithromycin, histamine H_2-receptor antagonists, PPI	NA
M12[33]	1-Compartment model with first-order absorption with a lag time, and linear elimination	CL/F = 15.4×(WT/70)$^{0.75}$ L/h V/F = 1150×(WT/70) L K_a = 0.325× (WT/70)$^{0.25}$ h^{-1} T_{lag} = 2.71h β_{dose} = 99.1mg/m^2(fixed) F= [1 - D/(D + β_{dose})] × 0.67^{diarrhea*}×0.58^{PPI*}	CL/F: 87.8%	NA	11%	NA	CL/F: WT V/F: WT K_a: WT F: PPI, diarrhea
M13[34]	2-Compartment model with first-order elimination	CL=7.7 L/h Q=128 L/h V_1=26.2 L V_2=396 L	CL: 21.8% V_2: 23.4%	NA	1.79%	NA	NA

Notes: *Diarrhea/ PPI/CHEM/PHE/RIF/FOS/MET/NUT/MUC =0 in the absence of this covariate, diarrhea/ PPI =1 in the presence of this covariate; bilirubin=0 if the bilirubin levels<2×ULN, bilirubin=1 if the bilirubin levels≥2×ULN; GGT=0 if the GGT levels<2×ULN, GGT=1 if the GGT levels≥2× ULN; race=0 if the patient is nonwhite, race=1 if the patient is white; SEX=0 for men and SEX=1 for women.

Abbreviations: IIV, inter-individual variability; IOV, inter-occasion variability; CL, clearance; Q, intercompartmental clearance; V_1, central volume of distribution; V_2, peripheral volume of distribution; TBW, total body weight; PROP, proportional; LBW, lean body weight; BMI, body mass index; BSA, body surface area; IBW, ideal body weight; AGE, age; SEX, sex; CL/F, apparent oral clearance from whole blood; V/F, apparent oral volume of distribution in whole blood; β_{dose}, estimated dose in mg/m^2 for suspension bioavailability to drop to half that of the tablet; K_a, absorption rate constant; WT, weight; PPI, proton pump inhibitor; ADD, addictive; FORM, formulation; F, bioavailability; D1, duration of zero-order absorption into depot compartment; F1, relative bioavailability; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; CLcr, creatinine clearance; HSCT, hematopoietic stem cell transplantation; PHE, phenytoin; RIF, rifampin; FOS, fosamprenavir; MET, metoclopramide; NUT, nutritional supplement; MUC, mucositis; Tlag, absorption lag time; ULN, upper limit of normal; GGT, gamma-glutamyl transferase; IFIPP, proven or probable invasive fungal infection; IFIPPP, proven, probable, or possible invasive fungal infection; ALT, alanine aminotransferase; AST, aspartate aminotransferase; K_e, elimination rate constant; ALK, alkaline phosphatase; PROT, total proteins; eGFR, epidermal growth factor receptor; GVHD, disease of graft versus host disease; CHEM, co-administration of chemotherapy; HT, height.

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To characterize the manner and extent of influence of the covariates on the corresponding models, we performed simulations of steady-state 24-hour plasma concentrations at different covariate levels. Since no covariates were included for model M6,[27] M11 and M13,[32,34] and incomplete information was available for M7,[28] no simulation was performed for these models. According to the type of formulation, the models were divided into two groups for simulation: (A) oral suspension, (B) tablet or intravenous infusion. Tablets and intravenous formulations were placed together because they have similar plasma exposure. The simulation results have been shown in Figure 2. For most of the models, the effect of different covariate levels on the steady-state plasma concentration of posaconazole was clearly observable. Nevertheless, the effects of age in M1,[23] gamma-glutamyl transferase (GGT) in M2,[24] and weight and chemotherapy in M3 on the exposure of posaconazole seemed to be inconspicuous.[25]

Dose Simulation

The therapeutic target and model-based dosing regimen adjustments are shown in Table 2. The simulation endpoint concentration of the final model in most studies was set as the minimum concentration of 0.7 mg/L for prophylaxis and 1.0 mg/L for treatment. To intuitively compare the exposure levels and attainment of posaconazole, we simulated the steady-state plasma concentration-time profiles at different dosing regimens for each model except M7,[28] because there was not enough information to reproduce the model, and the results are shown in Figure 3. In the adult population using oral suspensions, only M5 could achieve the target concentration of 0.7 mg/L for prophylaxis at a dose of 200 mg thrice daily.[18] On increasing the dose of posaconazole to 300 mg thrice daily or 400 mg thrice daily, more models were able to achieve posaconazole exposure for the prophylaxis or treatment. Nevertheless, M4 failed to meet the target exposure at three simulated doses.[26] The pediatric population receiving 200 mg of oral suspension thrice daily could already reach the target concentration. At doses of 200, 300, and 400 mg daily, all models using tablet and intravenous formulations achieved the target concentrations.

Discussion

A review published by Chen et al in 2020[22] had reported nine PopPK models of posaconazole (one could not be found online, and the full text was not available even after contacting the author). In addition to the inclusion of the newly published models, our review has some differences from Chen et al. First, Chen et al conducted a multifaceted and comprehensive analysis of the characteristics of posaconazole in terms of pharmacokinetics, pharmacodynamics, toxicity, resistance, and special population dosing, while our review focused mainly on the PopPK of posaconazole for a more in-depth and detailed analysis. Second, the pharmacokinetic section of Chen et al emphasized the absorption, distribution, metabolism and excretion of posaconazole, whereas this review highlights the differences in posaconazole exposure due to different characteristics across models. Third, in addition to summarizing the PK characteristics of the different models, our review performs an exploratory analysis to visualize the differences in posaconazole exposure across models at different covariates and dose levels through simulated steady-state concentration-time profiles.

Without limiting the population, only three of our included studies considered the pediatric population as the primary study population.[29,32,33] During the literature screening, there were few PK or clinical reports of posaconazole in the pediatric population, which may be related to the limited use of posaconazole in pediatrics. Posaconazole has not been approved for use in children under 13 years of age. Nevertheless, there have been some cases of posaconazole being used off-label for the prevention of high-risk IFI in children ≤12 years old.[36] This is not only due to the satisfactory efficacy and safety of posaconazole in adults,[37,38] but also because posaconazole is more effective than other antifungal agents such as fluconazole and itraconazole in pediatric patients with hematologic malignancies.[39–42] Plasma concentrations of posaconazole are highly variable in the younger pediatric population,[43,44] which may lead to large fluctuations in efficacy and safety. In pediatric patients treated with posaconazole, TDM is necessary to ensure that the required drug exposure is achieved and to minimize the occurrence of adverse events.

In this review, the structural model appears to be linked to the route of administration, as demonstrated by the fact that the two studies involving intravenous administration used two-compartment models,[30,34] while the studies of oral administration used one-compartment models. Since most studies used sparse sampling lacking absorption phase data

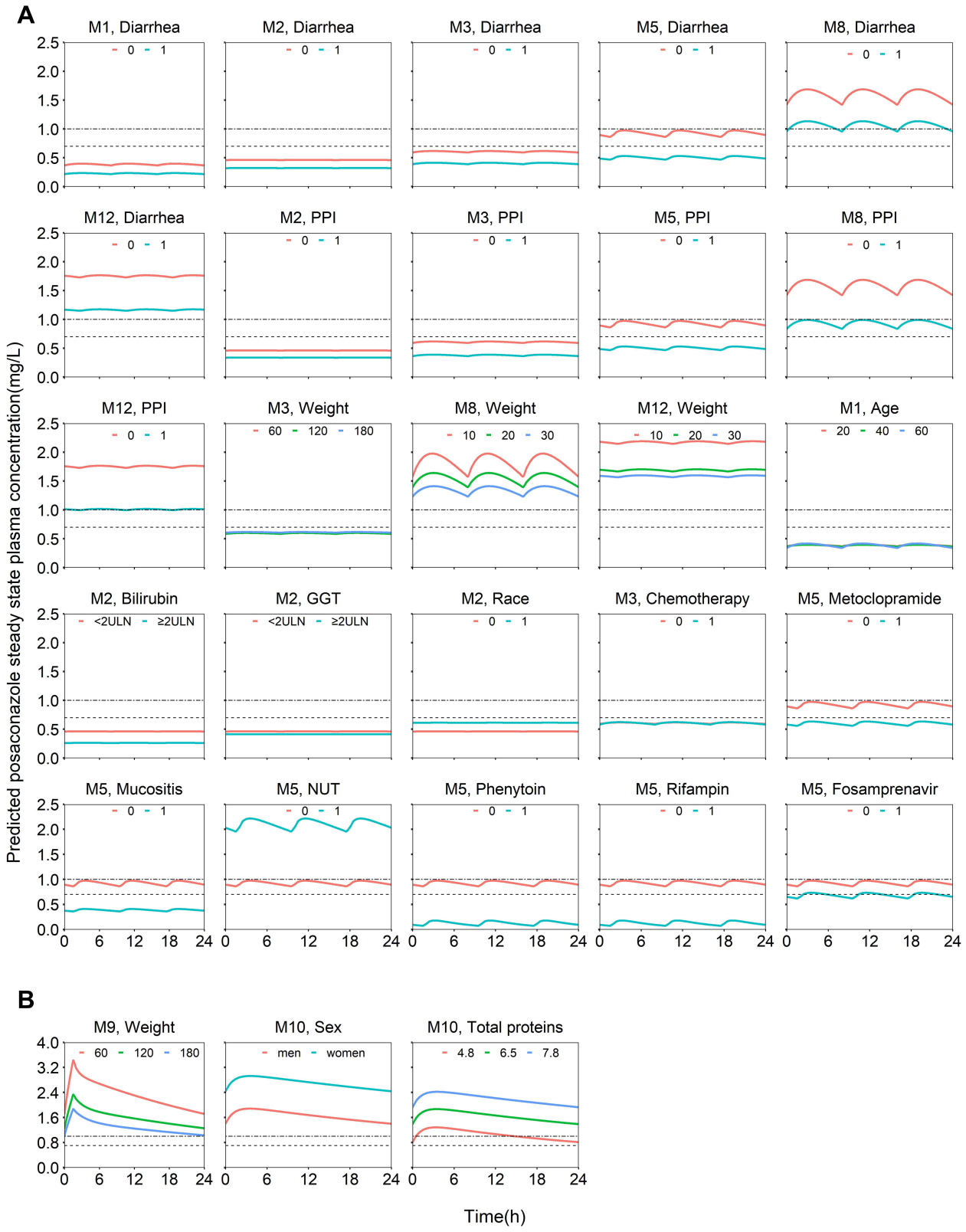

Figure 2 Simulated steady-state concentration-time profiles at different covariate levels for the reported PopPK models. (**A**) oral suspension; (**B**) tablets and intravenous formulations. The dashed line corresponds to a plasma steady state concentration of 0.7 mg/L, and the dash-dotted line corresponds to a plasma steady state concentration of 1.0 mg/L.

Abbreviations: PPI, proton pump inhibitor; GGT, gamma-glutamyl transferase; NUT, nutritional supplements.

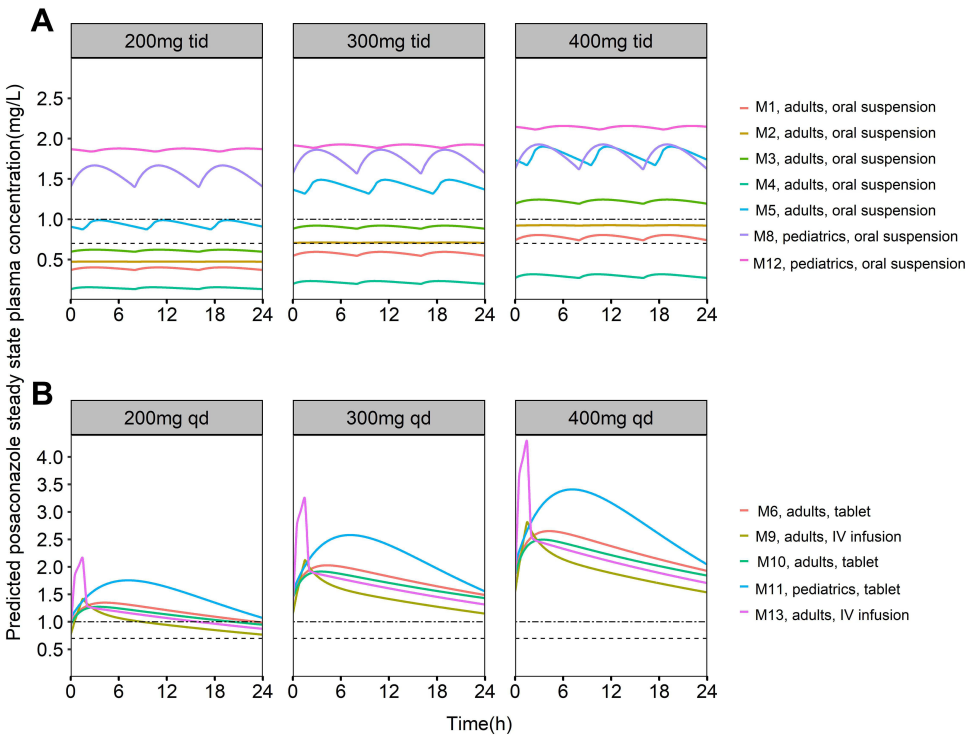

Figure 3 Simulated steady-state concentration-time profiles at different dosing regimens for the reported PopPK models. (**A**) adults or pediatrics receive posaconazole oral suspension 200, 300, and 400 mg thrice daily; (**B**) adults or pediatrics receive tablets or intravenous formulations of 200, 300, and 400 mg twice daily on the first day and once daily for maintenance. The dashed line corresponds to a plasma steady state concentration of 0.7 mg/L, and the dash-dotted line corresponds to a plasma steady state concentration of 1.0 mg/L.

or fixed k_a to a specific value according to the literature, inaccurate estimation of k_a might have affected the judgment of structural models. In addition, two models with absorption delays may have obscured the initial distribution pattern.[18,30,33]

The sample size, evaluation method, inclusion and exclusion criteria of covariates, pathological status, and concomitant medications were different in different studies, which may lead to differences in the influence of covariates in each study.

Diarrhea, a common symptom in patients with graft-versus-host disease (GVHD), critically ill patients, and patients after receiving chemotherapy, is associated with a significant decrease in F.[45,46] Nearly half of the studies in our review retained diarrhea in the final model. The F of posaconazole was reduced by 59% and 45% in the adult models M1 and M5,[18,23] respectively. In pediatric study models, M8 and M12,[29,33] it was reduced by 33% for both. Additionally, the presence of diarrhea in M2 and M3 increased V and CL by a factor of 1.5.[24,25] M7 examined but did not retain diarrhea in the final model.[28] Unlike the six studies mentioned above, the formulation of posaconazole used in M7 was a delayed-release tablet rather than an oral suspension.[28] Diarrhea was a risk factor for sub-therapeutic concentration of posaconazole in patients using tablets, but there was a decreasing trend observed in this effect.[47,48] Metoclopramide, which was retained in M5,[18] similar to the diarrhea limited the absorption and altered the exposure of posaconazole by increasing gastrointestinal motility.

The use of PPI was considered an important covariate examined in six models,[18,24,25,27,29,32,33] of which were retained except M11.[32] The ultimate effect of the use PPI in these models was manifested by reduced plasma exposure with the form of raising V or CL, or decreasing F, which was consistent with the results reported in other articles.[15,17,49] PPI can effectively prevent stress mucositis in critically ill patients by inhibiting the secretion of gastric acid and increasing the pH of gastric juice.[50,51] However, for posaconazole, a weakly alkaline drug, its solubility and F may be altered by the concomitant use of PPI.[13] M8 found that PPI limited posaconazole absorption to a greater extent than H_2 receptor antagonists.[29] This may be due to the stronger and longer-lasting acid inhibitory effect of PPI than H_2 receptor antagonists.[52]

Demographic characteristics such as weight, age, and sex were also examined. The influence of body weight on V, CL, and F of posaconazole are described in several models.[25,28–30] The high lipophilicity of posaconazole may be

responsible for extensive lipid tissue distribution,[53] which may account for the greater V in individuals with high body weight. Sex and age were tested in most studies but were retained only in M10 and M1,[23,31] respectively. M10 showed lower CL in women than in men,[31] consistent with the finding that males were associated with reduced posaconazole trough concentrations as mentioned in three reports.[47,54,55] On the contrary, some studies have found that men have higher plasma exposure than women (P = 0.028).[56,57] Jia et al speculated that differences in sex hormones and fat content between men and women contributed to the varied PK of posaconazole.[54] Despite the fact that age was considered to be relevant to the decrease of V in M1,[23] the effect of age on posaconazole concentration was not noticeable in our simulations, which may be explained by the low plasma exposure caused by the large V in M1.

Some studies have also considered the effect of biochemical indicators on the PK of posaconazole. Posaconazole has a plasma protein binding rate of 98% and is primarily bound to albumin.[58] Restricted transmembrane transport caused by protein binding results in a reduction in metabolism and excretion and an elevation of plasma concentrations, which fits with the findings of M10.[31] However, this study did not find a relationship between albumin and PK parameters, indicating that the CL/F of posaconazole may be influenced by other plasma-binding proteins such as lipoprotein and C-reactive protein (CRP).[54,59,60] M2 found that posaconazole exposure decreased with the baseline bilirubin $\geq 2 \times$ the upper limit of normal (ULN) or GGT $\geq 2 \times$ ULN.[24] This may be an indirect effect caused by metabolic disorders due to liver impairment, although liver function is not an absolute condition for changes in bilirubin and GGT levels.[61–65] Other biochemical markers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALK) were also tested in some models but were not retained.

The effect of concomitant medications on posaconazole exposure was mainly reflected in M5.[18] Phenytoin and rifampin presented a remarkable effect on CL/F (621% increase). This effect may arise from enzymatic interactions; phenytoin and rifampin, inducers of the UGT enzyme,[66,67] increase the metabolism of posaconazole, which is metabolized by UGT1A4 by approximately 17%.[22] These two drugs were also tested by M8 and M11 but were not retained,[29,32] possibly because the populations in both studies were pediatric with immature expression of drug-metabolizing enzymes or because of the low proportion of patients with concomitant use of these two drugs. Fosamprenavir also increased CL/F, although this effect was much less than that of phenytoin and rifampin. M5 reported that nutritional supplements increased the F of posaconazole by 129%,[18] in agreement with the findings of published studies.[15,68,69] PK studies have demonstrated that food, especially a high-fat diet, can greatly increase the rate and extent of posaconazole absorption.[70–72] However, for patients with eating disorders due to severe IFI, liquid nutritional supplements are often used as a substitute of food for enteral nutrition.[69] Furthermore, M3 revealed a 0.6-fold decrease in V as a result of the co-administration of chemotherapy.[25] In conclusion, TDM is advisable when used in combination with drugs that may alter the PK of posaconazole.

Regardless of the covariate or dose simulations, there were observable differences in posaconazole steady-state concentrations between models, even at the same dose. Such differences may derive from variation in the race, age, or disease state of the population, the formulation of posaconazole, and the assay conditions of the plasma samples among studies. Nevertheless, the pattern of covariate or dose effects on the exposure of posaconazole was mostly consistent. For example, the three main covariates of diarrhea, PPI, and body weight all reduced posaconazole exposure in ways that decreased bioavailability, or increased volume of distribution or clearance. According to the simulated PK profile, posaconazole tablets and intravenous formulations showed higher concentrations than oral suspensions, which was consistent with the reported finding.[73] This might be because delayed-release tablets with drug-polymer combinations prevent drug recrystallization in the intestinal fluid and therefore exhibit higher F than suspensions.[74] The simulation results showed that M1 to M4 did not achieve the target exposure levels at the conventional dose of 200 mg thrice daily oral suspension, which indicates that appropriate dose adjustment is necessary.

Since only a small number of studies used non-parametric modeling methods,[75,76] we only retained studies using parametric modeling methods, which also ensured the comparability among models. Further discussion is needed if more non-parametric studies are conducted in the future. The other limitation is that the models in this review were evaluated using internal data. Thus, the good predictive performance of the models is only reflected in their own centers and is difficult to apply when extrapolated to other centers. A more rigorous external evaluation of these models is recommended to verify their predictive performance and robustness after extrapolation to other scenarios.

Conclusion

In this review, we comprehensively summarize the published PopPK models of posaconazole. In these models, diarrhea, PPI and body weight were the main factors affecting the pharmacokinetics of posaconazole, resulting in lower plasma exposure. At regular doses, tablets and intravenous formulations have higher exposure than oral suspensions. In clinical practice, the potential impact of the patient's underlying condition (eg, weight, diarrheal status) and combined medications (eg, PPIs, nutritional supplements) on drug exposure deserves to be considered. It is necessary to implement dose adjustments or formulation changes in conjunction with routine TDM to obtain desired concentrations and efficacy as well as to reduce fungal resistance. In addition, more relevant studies are needed to explore the effect of covariates on posaconazole PK and to conduct external validation to examine the extrapolation of the models.

Data Sharing Statement

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

Consent for Publication

All authors listed have approved the submission and publication of the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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