A review of population pharmacokinetic models of posaconazole

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Abstract

Aims: 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. Methods: 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. Results: 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. In addition, age, sex, total protein, rifampin, phenytoin, intake of nutritional supplements, levels of bilirubin and gamma-glutamyl transferase, and administration of chemotherapy also appeared as covariates in several PopPK models. Conclusion: Posaconazole exposure was found to be influenced by various factors such as the type of formulation, the incidence of diarrhea, body weight, and use of concomitant medications. It was concluded that routine therapeutic drug monitoring was required for dose adjustment and in promoting individualized dosing.

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Conclusion: Posaconazole exposure was found to be influenced by various factors such as the type of formulation, the incidence of diarrhea, body weight, and use of concomitant medications. It was concluded that routine therapeutic drug monitoring was required for dose adjustment and in promoting individualized dosing.

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

1. 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 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[18,23-34] 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[35]. A review published in 2020[22] has summarized the PK parameters of eight of these models. This review aims to comprehensively compare the PK characteristics of these models and examine the effects of covariates and dosing regimens on the PK of posaconazole.

2. Methods

2.1 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'.

2.2 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.

2.3 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.

2.4 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.

3 Results

3.1 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[18,23,25-28,30,31,34] studies included adults, three[29,32,33] included children, and one included[24] both. Of the 11 studies with oral formulations of posaconazole, three[18,23-26,33] were with oral suspensions, four[27,28,31,32] with delayed-release tablets, and one[29] was on both oral suspension and delayed-release tablets. The two[30,34]remaining studies were conducted on intravenous formulations in the obese population and in critically ill patients treated with extracorporeal membrane oxygenation.

3.2 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.

3.3 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[30,34] were better suited to the two-compartment model. With reference to absorption, six[18,23,25,27,29,33] models were described in terms of first-order absorption and two[18,33] with a lag time characterizing the absorption delay[18,33]. Out of the five[27-29,31,32] studies using

delayed-release tablets, two[28,31] studies were described with sequential zero first-order absorption. The mode of absorption for the remaining five[24,26,30,32,34] studies was not mentioned. 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[23,25,27,29,31] fixed it to a certain value according to the published literature. With the exception of four[24,26,29,32] studies not mentioned the elimination of posaconazole, 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[30,34] studies adopting the two-compartment model, 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[18,26-28] 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%).

3.4 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[18,24,25,29,33] studies, 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.

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[32] and M13[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[25] on the exposure of posaconazole seemed to be inconspicuous.

3.5 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[18] could achieve the target concentration of 0.7 mg/L for prophylaxis at a dose of 200 mg thrice daily. 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[26] failed to meet the target exposure at three simulated doses. 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.

4. Discussion

A review published 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). Our review incorporated five new published models into the scope of examination. We focused only on the PopPK of posaconazole for the first time, providing a simulation of posaconazole exposure at different covariates levels and dosing regimens of 13 published models.

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[30,34] involving intravenous administration used two-compartment models, while the studies of oral administration used one-compartment models. Since most studies used sparse sampling lacking absorption phase data 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[18,33] may have obscured the initial distribution pattern[30].

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[23] and M5[18], respectively. In pediatric study models, M8[29] and M12[33], it was reduced by 33% for both. Additionally, the presence of diarrhea in M2[24] and M3[25] increased V and CL by a factor of 1.5. M7[28] examined but did not retain diarrhea in the final model. Unlike the six studies mentioned above, the formulation of posaconazole used in M7[28] was a delayed-release tablet rather than an oral suspension. 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[50,51] by

inhibiting the secretion of gastric acid and increasing the pH of gastric juice. However, for posaconazole, a weakly alkaline drug, its solubility and F may be altered by the concomitant use of PPI[13]. M8[29] found that PPI limited posaconazole absorption to a greater extent than H_2 receptor antagonists. This may be due to the stronger and longer-lasting acid inhibitory effect of PPI than H_2receptor 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[31] and M1[23], respectively. M10[31] showed lower CL in women than in men, 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.[54]speculated that differences in sex hormones and fat content between men and women contributed to the varied PK of posaconazole. 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[59,60] and C-reactive protein (CRP)[54]. M2[24] found that posaconazole exposure decreased with the baseline bilirubin [?] 2 × the upper limit of normal (ULN) or GGT [?] 2 x 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[61] and GGT[62-65]levels. 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[29] and M11[32] but were not retained, 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[18]reported that nutritional supplements increased the F of posaconazole by 129%, 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[25]revealed a 0.6-fold decrease in V as a result of the co-administration of chemotherapy. 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. 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].

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.

5. Conclusions

In this review, we comprehensively summarize the published PopPK models of posaconazole. At regular doses, tablets and intravenous formulations have higher exposure than oral suspensions. Nevertheless, the PK of posaconazole were influenced by various factors such as the incidence of diarrhea, body weight, and concomitant medications. Routine TDM of posaconazole is necessary to ensure drug efficacy and reduce bacterial resistance. 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.

Declarations

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

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Author contributions

Qi Pei and Xin Li provided the concept and design of this study. Shuqi Huang and Qin Ding conducted the data collection and original draft preparation. Zexu Sun and Kaifeng Chen performed the editing and review of the manuscript. All authors have revised, reviewed and approved the manuscript.

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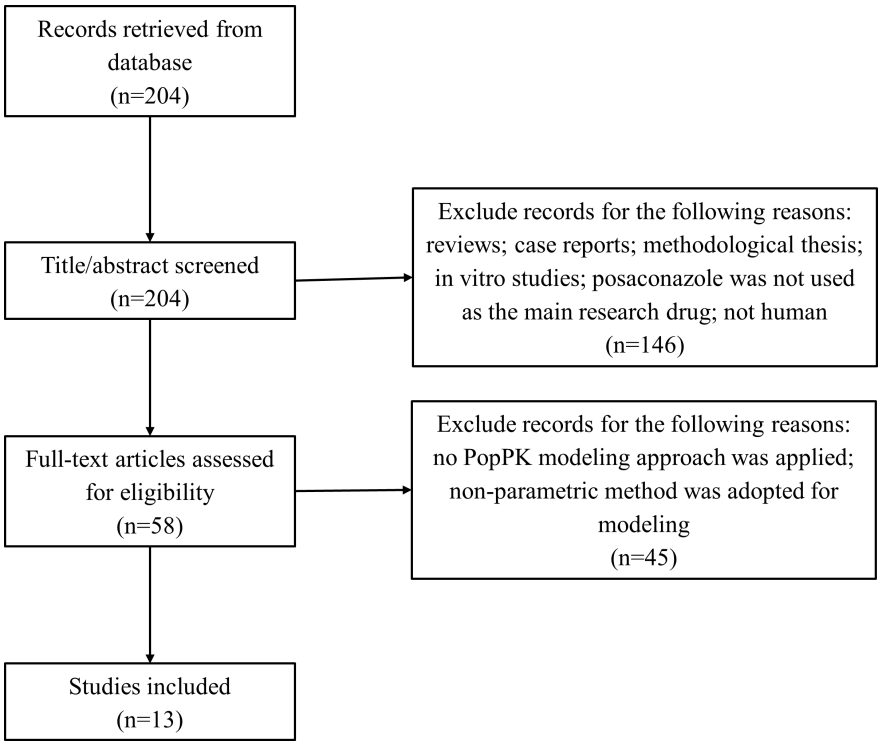

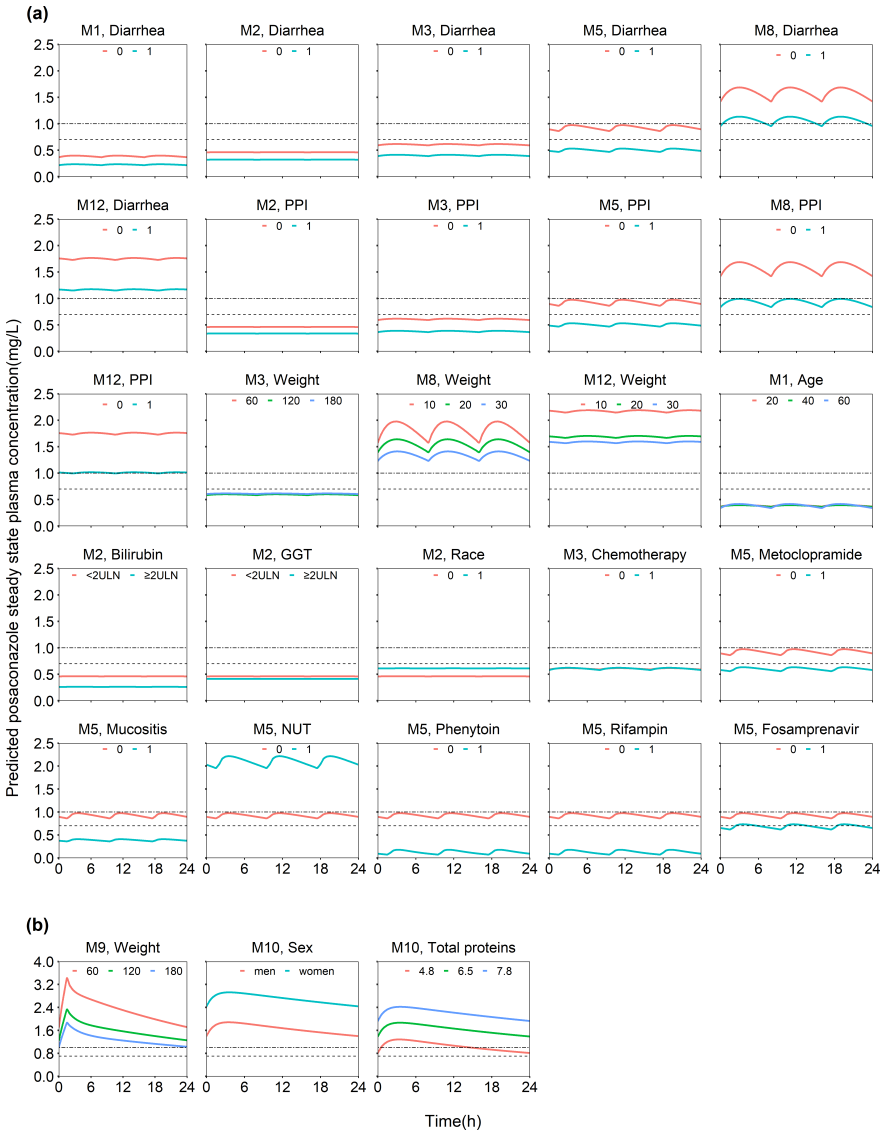

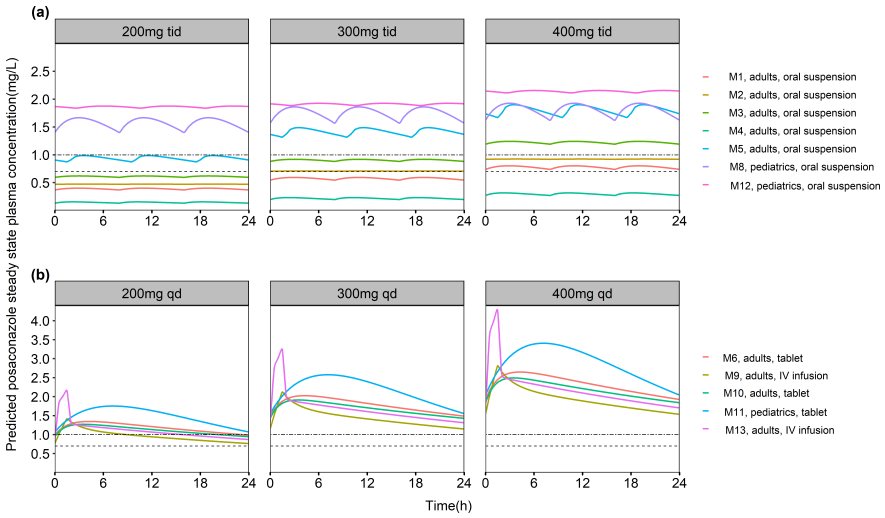

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