Drug-Drug Interaction of Tacrolimus and Voriconazole in Pediatrics with Different Age Groups Compared with Adults

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Abstract

Aim: To evaluate drug–drug interaction (DDI) between tacrolimus (TAC) and different formulations of voriconazole (VRCZ) in adults and pediatrics with different ages. Method: Physiologically based pharmacokinetics (PBPK) models were used to evaluate DDI between oral TAC and different formulations of VRCZ (oral and intravenous (IV) formulations) in adults and pediatrics with different age groups. Both single dose and multiple dose administration were assessed. Multiple dosage regimens were maintained for 7 days. Result: A higher IV dose might lead to a great increase in area under the plasma concentration-time curve (AUC) and maximum concentrations (Cmax) of TAC in both adults and pediatrics. Besides, compared with IV administration, these two PK values of TAC increased more when combined with VRCZ orally. The ratio of two PK values increased with the age growth in pediatrics. And it increased progressively to adult values at the age of 3-8 years. Tacrolimus liposolubility was the most significant parameter on the DDI between TAC and VRCZ. Conclusion: In pediatric population, VRCZ had a less impact on PK of TAC than that in adults. The DDI progressed gradually as the age advances in pediatrics and finally equal to adults. Oral VRCZ increased PK parameters of tacrolimus even more than IV administration. Personalized dosage adjustment should be considered in clinical practice when co-administrated with VRCZ, especially in adults or in oral formulation.

Introduction

Tacrolimus (TAC) was a macrolide immunosuppressant, had proven to be of immense utility in immunosuppression following organ transplant surgery [1, 2]. Its use had revolutionized the future of immunosuppressive regimens in solid organ transplantation and had been associated with better graft survival, a lower incidence of rejection, and improved drug tolerance with fewer side effects [3]. However, its monitoring remained complicated and underexposure increaseed the risk of rejection, whereas overexposure increased the risk of adverse effects, primarily hepatotoxicity and infections [4]. The pharmacokinetic variability of TAC complicated its daily dose assessment, potentially due to its narrow therapeutic window, propensity for clinically drug–drug interactions (DDI), patient age, hepatic dysfunction, concomitant medications as well as interindividual variability in its pharmacokinetic profile or disposition [5]. Among the potential causes for large variability, the high inter-patient pharmacokinetic variability of TAC, especially between adult and pediatric patients, justified dose adjustment based on age grouping [6].

Patients with immune compromise after solid organ transplantation were at risk for serious fungal infections. First-line treatment commonly consisted of the antifungal drug voriconazole (VRCZ) [7]. VRCZ was a potent antifungal agent used for the treatment of invasive fungal infections [8]. It had been reported that VRCZ inhibited the metabolism of TAC and the blood concentration/dose ratio of TAC was significantly correlated with the blood concentration of VRCZ when TAC was intravenously administered [9, 10]. Administration of VRCZ to TAC-treated adult patients resulted in a major DDI characterized by increased exposure to TAC [9-11]. Therefore, therapeutic drug monitoring (TDM) of TAC was essential when combined with VRCZ.

Despite the fact that clinical trials of TAC drug monitoring in organ transplant recipients were reflected in many studies, detailed and practical information on the interaction between TAC and VRCZ in pediatric cases was still scarce. The evidence of association in pediatric patients was not as extensive as adults [12]. Therefore, the aim of the present study was to construct a physiologically based pharmacokinetic (PBPK) model to quantify the DDI between TAC and different formulations of VRCZ in adults and pediatrics with different age groups. To overcome the large pharmacokinetic variability of TAC, optimize efficacy and reduce toxicity, we provide strong insights into the interaction between TAC exposure and VRCZ in pediatric patients and compare it to adults. It could assist the clinical implementation of precision medicine approaches to determine the factors that influence appropriate dosing.

Methods

Study design

The PBPK modeling was conducted in PK-Sim® (version 11.0, part of the Open Systems Pharmacology suite), which has a system- and drug-dependent component. The simulated trials were conducted in virtual healthy adult and pediatric population groups. For adults, healthy volunteers between 18 and 60 years were selected. Virtual pediatric subjects were aged 0-18 years and divided into 5 groups: 0-1 years, 1-3 years, 5-8 years, 8-12years, 12-18 years. All simulations were performed with virtual population of 100 individuals. The proportion of female was the default 0.5 in each simulation. Both p.o. and i.v. administration of VRCZ were simulated in healthy adults and pediatrics.

PBPK model establishment and validation of TAC

General physiochemical properties (molecular weight, LogP, compound type, pKa) of TAC and in vitro data from blood, plasma protein were utilized for building the PBPK model [13-15]. System-dependent physiological parameters (organ volumes, blood flow rates, hematocrit, etc.) were provided in PK-Sim(r) with the small molecule model. The input parameters for specific intestinal permeability were optimized using the PK profiles of single 5mg TAC in healthy subjects. According to the clinical routine drug regimens, a simulation of TAC was performed at a single dosage of 2 mg for adults. The predictive performance was evaluated by visually comparing predicted concentration-time data with the observed data from the literature for initial verification

[16]. Predicted concentration-time profiles were obtained using the developed PBPK model of TAC. Observed concentration–time data were obtained in graphical form using GetData Graph Digitizer version 2.25.0.32. The ratio of predicted to observed pharmacokinetics (PK) values was used to evaluate model performance. Next, the quantitative assessment was conducted by calculating the mean fold error (MFE) of PK parameters such as the area under the plasma concentration-time curve (AUC) and maximum concentrations (Cmax), expressed as the ratio of predicted to observed mean values. The model was acceptable if it met the 0.5- to 2.0-fold limit. After model validation, the adult PBPK model was scaled to children (pediatric PBPK model). Drug-specific parameters defined in the adult PK data were kept constant for the pediatric PBPK model. The physiological parameter values for pediatric individuals were taken from the PK-Sim population database. The PBPK model performance in pediatrics was evaluated using the quantitative verification described in adult model verification[17].

PBPK model establishment and validation of VRCZ

Drug-specific physicochemical properties were obtained from the literature [18, 19]. Organ-plasma partition coefficients were determined using Poulin and Theil's method based on the literature [20]. The model was verified with clinical data of adults and pediatrics in different formulations[21, 22]. The PBPK model performance in children was evaluated using the quantitative verification described in TAC model verification.

DDI simulations of TAC and VRCZ in adults and pediatrics

The DDI of TAC combined with VRCZ in different formulations and different dosing regimens were simulated in adults and pediatrics. Verified PBPK models were used to predict the DDI using PK-Sim(r). The dosage

and dosing interval of TAC and VRCZ were prescribed on the basis of the clinical routine drug regimens. The detailed dosage regimens are shown in Table 1. DDI simulations were performed in turn following these dosing schedules.

Sensitivity Analysis

Sensitivity of the DDI between TAC and oral VRCZ to single parameters (local sensitivity analysis) was calculated as relative change of AUC using the Sensitivity Analysis tool implemented in PK-Sim(r). Sensitivity analysis was performed applying a relative perturbation of 1000 % (variation range 10.0, maximum number of 9 steps). Parameters selected for the sensitivity analysis fulfilled one of the

following criteria: (1) optimized; (2) related to optimized parameters; (3) a strong influence in the model. Sensitivity to a parameter was calculated as the ratio of the relative change of the simulated AUC to the relative variation of the parameter around its value used in the final model according to the Eq. (1):

$$S = \frac{AUC}{\mathrm{AUC}} \bullet \frac{P}{P}$$

where S = sensitivity of the simulated AUC0–24 to the examined model parameter value, [?]AUC= change of the simulated AUC0–24, AUC = simulated AUC0–24 with the original parameter value, [?]p = change of the examined parameter value, p = original parameter value. A sensitivity value of +1.0 means that a 10% change in the examined parameter causes a 10% alteration of the predicted AUC.

Results

PBPK model and verification of TAC

The input parameters describing the PBPK model of TAC are listed in Table 1. With the optimization of specific intestinal permeability, the resulting TAC model was able to capture the PK profile of single 5mg TAC dose in healthy volunteers (Supplement Figure 1). The simulated and observed plasma concentration–time profiles of TAC are shown in Figure 1. There was a good match between predicted and observed data in both adults and pediatrics. The predicted and observed PK parameters are all summarised in Table 3. The accuracy of simulation was measured by calculating the fold error between simulated and observed, described as Eq. (1). Predicted PK parameters were reasonably consistent (0.5- to 2.0-fold) with observed clinical values which indicated that the prediction accuracy of the developed PBPK models were acceptable and could be used to simulate the different dosing regimens.

PBPK model and verification of VRCZ

The input parameters describing the PBPK model of TAC are listed in Table 2. The simulated and observed plasma concentration–time profiles of VRCZ are shown in Figure 2. Simulated plasma concentration–time profiles of TAC in both adults and pediatrics corresponded well with the observed profiles. The pharmacokinetic parameters of VRCZ were all within 2.0-fold error (Table 3).

DDI simulations between TAC and VRCZ in adults and pediatrics

The plasma concentration–time curves of single oral TAC at baseline and following both single IV and oral dose of VRCZ in adults and pediatrics are shown in Figure 3. Model-predicted Cmax and AUC of TAC combined with VRCZ (IV and oral) were obtained (supplement Table 1). These results indicated that a higher IV dose might lead to a great increase in Cmax and AUC of TAC in both adults and pediatrics. Besides, compared with IV administration, these two PK values of TAC increased more when combined with VRCZ orally. The ratio of Cmax and AUC

in multidose simulation (IV and oral) was presented in Figure 4. The ratio of two PK values increased with the age growthin the pediatrics. And it increased progressively to adult values at the age group of 3-8.

Sensitivity Analysis

A sensitivity analysis was performed based on the simulation of the therapeutic single oral dosing regimen (TAC oral 0.05mg/kg and VRCZ oral 400mg) to assess the impact of the parameters on the DDI between TAC and VRCZ. Sensitivity analysis (Figure 5) revealed that the DDI between TAC and VRCZ was sensitive to the values of TAC liposolubility, VRCZ liposolubility, TAC fraction unbound in plasma, CYP2C19 kcat and reference concentrition , CYP3A4 kcat and km, as well as intestinal permeability. The most impactful drug parameters in the model were TAC liposolubility.

Discussion

This was the first study to explore the DDI between TAC and different formulations of VRCZ in adults and pediatrics with different age groups using PBPK models. The results indicated that IV and oral VRCZ both had a significant effect on PK of TAC in two population. However, for pediatrics at the age of 0-1, VRCZ presented a relatively unremarkable effect on the PK of TAC compared with adults, and DDI was more pronounced when VRCZ was administered orally. Besides, TAC liposolubility was the most significant parameter on the DDI between TAC and VRCZ.

Predicted values of the PBPK model established in this study were highly close to the clinical observed values, indicating that the results predicted by DDI model were credible. Firstly, it has shown that in pediatrics at the age of 0-1, the DDI between TAC and VRCZ was inapparent compared with adults. Besides, the DDI progressed gradually as the age advanced and was finally equal to adults. That might be due to enzyme inhibition of VRCZ was dose dependent[23]. Our study also showed the same result that 6mg IV single dose showed more obvious interaction compared with 4mg IV single dose. Pediatrics had faster metabolism of VRCZ and lower accumulation of VRCZ than adults, and thus the interaction in pediatrics was less pronounced than that in adults[24]. Besides, many studies illustrated that compounds which were mainly metabolized by CYP3A4 were likely to be mainly metabolized by CYP3A7 in neonates and young infants[25-27]. The activity of CYP3A4 was extremely weak or absent in the fetus and began to rise after birth to reach 30–40% of the adult activity after 1 month[28]. There are also studies that show that CYP3A4 levels from the 5–15 year age-group that were only 25% of the average CYP3A4 value obtained from the adult samples[29]. In our study, for the age dependent hepatic clearance, default CYP3A4 ontogeny information was described in the online PK-Sim Ontogeny Database Open Systems Pharmacology (2018). The activity of CYP3A4 increased after birth and reached the adult level over approximately 4 years. Therefore, the DDI in pediatrics at the age of 3-8 years was basically at the same level compared with adults.

In the present study, it also illustrated that compared with IV administration, both Cmax and AUC of TAC increased more when combined with VRCZ orally. Previous research has also shown that the AUC of oral midazolam increases by 885 %, and the AUC of intravenous midazolam increases by 261 % on administration of 400 mg of oral VRCZ [30]. The metabolism of TAC was known to be mainly mediated by CYP3A family, which was most relevant in the intestinal and liver[31, 32]. In the gut wall, members of the CYP3A subfamily are the predominant enzymes, accounting for 82 % of total intestinal CYP[23, 33]. Since VRCZ was known to strongly inhibit CYP3A activity [34, 35], oral VRCZ might not only inhibit the metabolism of TAC in liver, but also inhibit the absorption and transport of TAC in intestinal which could explain the more prominent interaction when orally VRCZ[36]. Besides, there had been some study illustrated that oral administration of VRCZ had a stronger impact on CYP3A activity than intravenous administration. This was expected because CYP-containing enterocytes would be exposed to higher drug concentrations during duodenal and jejunal passage of orally administered VRCZ compared with the lower concentrations reaching enterocytes from the blood compartment[23].

Finally, our study showed that TAC liposolubility was likely a most contributing factor to the DDI between TAC and VRCZ. We also attempted to simulate the DDI between TAC and VRCZ in different levels liposolubility of TAC, and found that increasing the liposolubility of TAC significantly reduced the degree of interaction with VRCZ. A rapid initial distribution phase was followed by a plasma clearance phase whose t1/2 depended on the physical chemistry characteristics of drugs[37]. Lipid-soluble agents had lower plasma concentrations[38-40], perhaps because a more lipid soluble drug might result in more-extensive tissue uptake, a larger volume of distribution, lower plasma clearance values and a longer terminal half-life[41]. This

then could lead to a relatively less significant interaction.

There were actually some limitations in our present study. Because of the insufficient information of our existing population data, the object of this study is only a virtual healthy population. The physiological complications of transplant patients and changes during post-operative period might affect the PK of TAC and VRCZ and influence their interaction. In addition, previous researchers found that CYP2C19 polymorphism as a major metabolizing pathway of VRCZ might influence the extent of drug interaction in healthy volunteers [42, 43]. Since VRCZ blood concentrations in slow metabolizers of CYP2C19 may be higher than fast metabolizers, which might result in more significant drug interaction. The specific changes in CYP2C19 activity were not considered in our models. The effects of CYP450 polymorphism on the interaction and the specific changes in CYP2C19 activity would be considered in our further researches.

Conclusion

An optimized PBPK model of TAC was successfully established in adults to evaluate DDI between TAC and VRCZ with different administration. Furthermore, the adult PBPK model had been successfully scaled to pediatrics population with different age groups for assessment of DDI between TAC and VRCZ. Both IV and oral VRCZ had a significant effect on PK of TAC in two population. For pediatrics at the age of 0-1, VRCZ presented a relative unremarkable effect on the PK of TAC compared with adults, and DDI was more pronounced when VRCZ was administered orally. The DDI progressed gradually as the age advances and finally equal to adults. Besides, TAC liposolubility was the most significant parameter on the DDI between TAC and VRCZ. In clinical practice, the concentration monitoring and dosage adjustment of TAC should be emphasized when co-administrated with VRCZ, especially in adult or in oral formulation.

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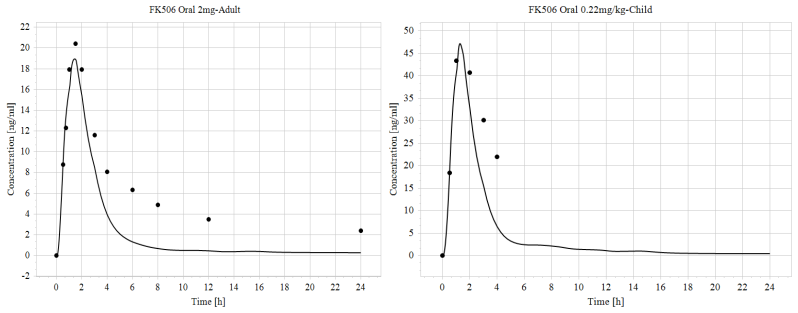

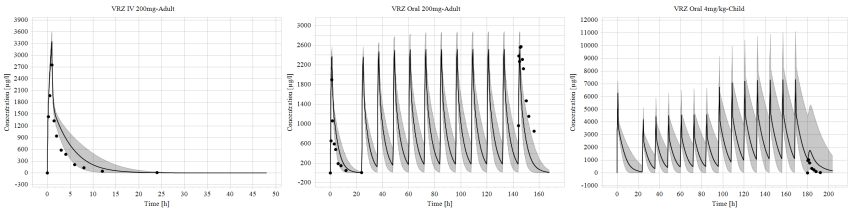

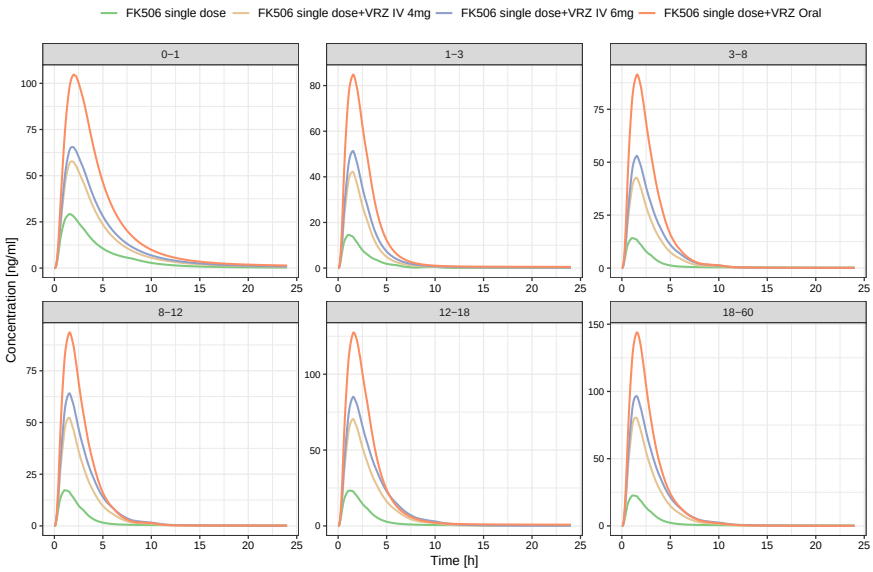

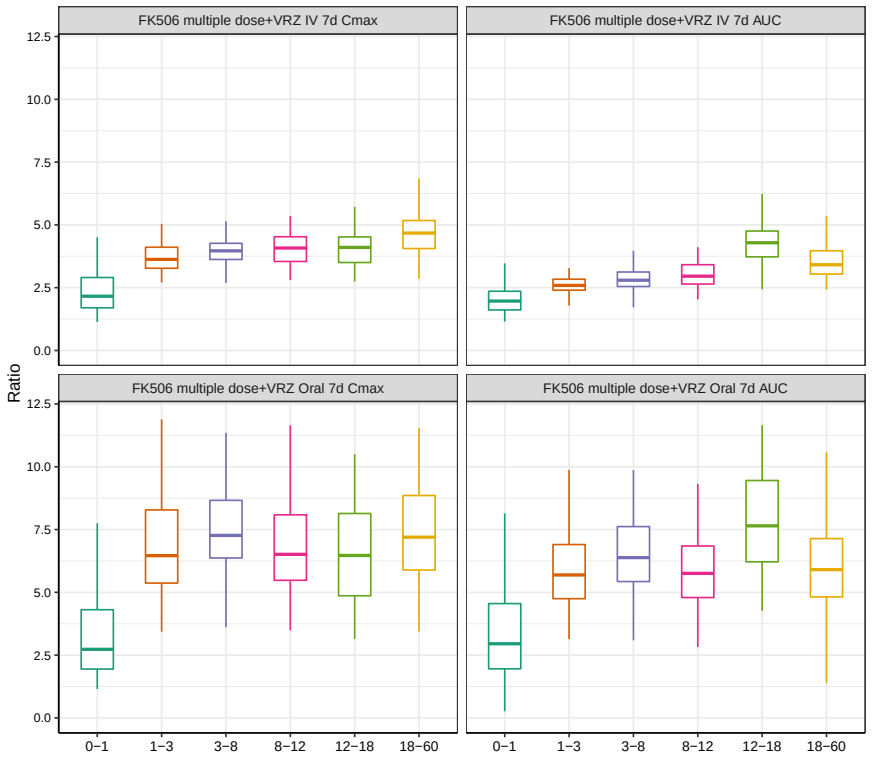

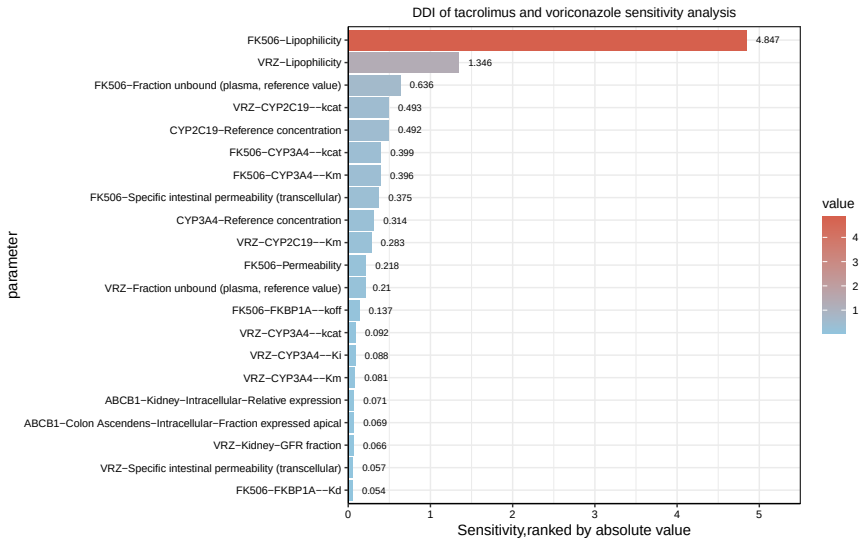

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