RESEARCH ARTICLE

Assessment of Inter-Individual Pharmacokinetic Variability of Voriconazole Based on Bile Salt Disparities using POP-PK Modeling

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ABSTRACT

Background and Objectives: Voriconazole is a powerful biopharmaceutics classification system (BCS) class II antifungal agent with vast inter-individual pharmacokinetic variability. Bile salts have recently emerged as potential contributors to such variations. Based on population PK modeling and *in-vitro* biorelevant dissolution investigations, the current study intends to evaluate the inter-individual variability of voriconazole in pediatrics.

Methods: All models were developed using PK-Sim software. A simulated population consisting of 100 pediatric individuals was established following the baseline model development. Further, experimentally obtained *in-vitro* dissolution data of voriconazole based on the bile salt differences representing different pediatric age groups were incorporated into a qualified pediatric model. Simulated plasma concentration-time profiles were then evaluated by comparing model-predicted parameters with that of the baseline model to draw inferences.

Result: Each model was created and validated successfully. The pediatric subjects were shown to have larger inter-individual variability than adult subjects. Additionally, simulations based on individual parameter estimations from the final model showed that after administering a 4 mg/kg peroral dose of voriconazole, the anticipated C_{max} values of the adult model were within a two-fold range compared to that of the pediatric model. However, upon comparison, the model-predicted population pk profiles of children, infants, and neonates showed minimal variations in the C_{max} values.

Conclusion: In pediatrics, voriconazole inter-individual variability was significantly influenced by the concentration of gut bile salts. Furthermore, the present research can be carried forward along with population PK modeling and sufficient clinical data for dose recommendations in special populations as well as in diseased conditions.

Keywords: Bile salts, Biorelevant, *In-vitro* dissolution, Inter-individual variability, Pediatric population, PBPK modeling, voriconazole.

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INTRODUCTION

Pharmacokinetics of Voriconazole

Voriconazole is a broad-spectrum antifungal medication that belongs to the Biopharmaceutical Classification System (BCS) class II drugs. For a number of opportunistic invasive fungal infections, including *Aspergillus*, it is regarded as the first line of defense.[1-3] However, the therapeutic window for voriconazole is narrow (1.0–5.5 mg/l).[4] Additionally, elimination and bioavailability between adults and children exhibit considerable discrepancies,[5,6] with clearance values in children being roughly half those in adults,[8] (depicted in Figure 1).[5-8] Voriconazole, however, has a limited therapeutic range (1.0–5.5 mg/l).[4] Due to the substantial inter-individual pharmacokinetic variability of voriconazole, providing tailored therapy can be difficult.[9,10] Additionally, the non-linearity keeps rising more than proportionally as the dosage is increased.[11] Only a few of the variables that could affect a drug's pharmacokinetics are those linked to its formulation, the structure of the gastrointestinal system, and the maturation or expression of enzymes.[12,13] Out of these factors, the maturity and expression of enzymes are major contributors to the pharmacokinetic variability of poorly soluble drugs. Additionally, CYP2C19 contributes significantly to the variability in voriconazole's pharmacokinetics[14-16] among the CYP family. Since CYP3A4 is reported to be

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more active in adults than CYP2C19, this explains the non-linear pharmacokinetics of voriconazole in adults.[17-19] The pharmacokinetics (PK) of voriconazole, despite its extensive and repetitive use in individuals, display considerable intra and inter-subject heterogeneity, in addition to unsuccessful therapies and detrimental outcomes.[20] So far, the variations in gastrointestinal composition particularly related to gut bile salts have not yet been researched as bile salts are potential modifiers of the dissolution behavior of lipophilic drugs.[21] Voriconazole, being lipophilic in nature, can show variations due to fluctuations in bile salts of the GIT. Additionally, bile salt solubilization advances together with the lipophilicity of poorly soluble drugs, and therefore, log *p-values* and molecular weight can be considered as vital parameters for assessing the solubility of drugs in bile salts.[22] Certain drugs ' luminal solubility, especially those belonging to BCS class II, can vary dramatically based on differences in the gut composition between adults and children.[23] Also, compendial media are not favored over bio-relevant media for better *in-vivo* response prediction. Biorelevant media are created based on an individual's age-specific gastrointestinal problems. The earliest years of life, where there are the most variances, are of particular interest.[24-29] The ratios of intestinal bile salt concentrations seen in newborns, infants, and adults in relation to glycine/taurine varied from newborns to infants (7–12 months) to adults in the range of 0.5 to 2.4 to 3.1, respectively.[30]

In addition, crucial components of the "patient-centric drug development" process are thought to include *in-vitro* dissolution studies conducted in age-specific biorelevant media coupled with physiologically based pharmacokinetic (PBPK) models.[31] With the goal of reducing the requirement for animal and human research, *in-vitro* biorelevant dissolution studies linked with PBPK modeling have fast become recognized as a viable and trustworthy technique to support the pharmaceutical drug development process.[32] The PBPK model is created based on the incorporation of system-related parameters (expression of metabolizing enzymes, blood flow, volume of a particular organ, organ clearance, etc.) and drug-related parameters (molecular weight, pKa, logP, fraction unbound, etc.) alongside mathematical computational techniques to forecast the pk profiles of the drug in a quantitative manner.[33]

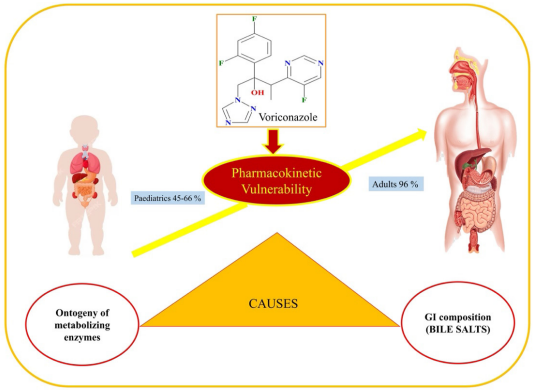

Figure 1: Factors affecting pharmacokinetic variability of voriconazole[5-8]

Therefore, the objectives of the present study were: 1) to develop the population pk models based on experimentally obtained *in-vitro* dissolution data in biorelevant media for various age groups of pediatrics and then compare the simulated adult pop-pk profiles with the pediatric PK profiles following the same dosage administration.

Subsequently, comparing the simulated PK profiles of different age groups of pediatrics following the same dosage administration of voriconazole to draw inferences on the role of bile salts in affecting the inter-individual variability of voriconazole.

MATERIALS AND METHODS

The list of the chemicals procured for carrying out the solubility and *in-vitro* dissolution studies was given in detail in the previously accepted manuscript.[34] Further, the media preparation and the solubility studies were conducted as per pharmacopoeial methods and published literature.[34-36] *In-vitro* dissolution studies in biorelevant and compendial buffers were also conducted based on pharmacopoeial methods. The details of the studies were mentioned in the accepted manuscripts.[34,36-41]

PBPK Model Development

All the models were created using the PK-Sim® software. On the basis of pertinent inputs, including drug-related parameters (LogP, Pk_a, solubility-pH profile, molecular weight, etc.) retrieved from literature, the baseline models were initially developed. The preliminary models and the models based on utilizing the *in-vitro* dissolution data were developed and qualified by comparing the model-predicted values with the values reported in the literature. A detailed overview of preliminary model development along with the incorporation of *in-vitro* dissolution data into the baseline models, was already mentioned in the manuscript under communication.[41]

Once the individual models were qualified. Then the virtual population of 100 individuals was created for both adults and pediatrics. The dose and dosing trials for adult and pediatric PBPK model development were based on published literature. The model development does not alter system-related features. The models were further evaluated by comparing them with the observed data available in the literature.[5,6,21,41-43] Subsequently, population models of both adults and pediatrics were created using *in-vitro* dissolution estimates obtained in biorelevant medium with age-specific bile salt concentrations. The simulated pop-pk profiles of pediatrics were then compared with the adult profiles and with the pop-pk profiles of different pediatric age groups (neonates and infants).

RESULT

The results of solubility as well as *in-vitro* dissolution, are not shown in the present study (Detailed in the accepted manuscript).[34] All the simulated population pk profiles were created utilizing the *in-vitro* dissolution data extracted in bio-pertinent medium with age-specific bile salt concentrations. For the pop-pk model development, analysis of the population simulated profiles of children revealed large inter-individual variability in comparison to the adults. Additionally, the plasma

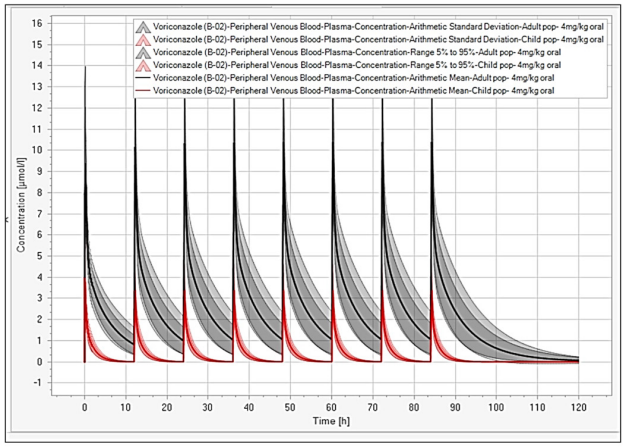

Figure 2: Comparison of model-predicted pop-pk profiles of children with adults following 4 mg/kg peroral administration of voriconazole.[5,6]

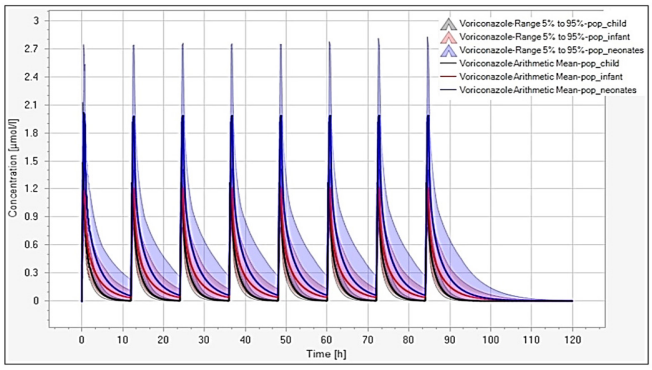

Figure 3: Population simulated profiles of children, infants, and neonates based on *in-vitro* dissolution conducted in biorelevant media with corresponding bile salt concentrations.[5]

concentrations and C_{max} values for pediatrics were found to be higher in comparison to the adults. The C_{max} values for pediatrics were found to be nearly two folds lower than the adults with C_{max} values of 10.39 and 3.97 µmol/ L for adults and pediatrics, respectively (as depicted in Figure 2.).[5,6]

Further, the results inferred that when the same dosage was administered to the different age groups, it showed wide variability in the individual pharmacokinetics. This could be attributed to the bile salt concentrations present in the gut which primarily alter the disposition of poorly soluble drugs.

Further, upon comparing the pop-pk profiles of children with the infants and neonates showed higher plasma concentrations for neonates with C_{max} of 2.02 µmol/l in comparison to infants and children with C_{max} values of 1.22 and 1.48 µmol/l, respectively (as depicted in Figure 3).[5]

Although neonates have lower bile salt concentrations, the results showed higher plasma concentrations for neonates, which seems contrary to what we are proposing. Additionally, when the same dosage was administered to the different age groups in the pediatric population, it revealed significant inter-individual variability. However, based on the findings, it is possible to hypothesize that the pediatric inter-subject variability and the elevated plasma levels of voriconazole in neonates compared to children and infants may be linked to the development and maturity of specific enzymes that are predominant in the initial phases of life.[44-54]

DISCUSSION

As anticipated, disparities in bile salt levels between different age groups might contribute to the inter-individual heterogeneity of voriconazole. The population pharmacokinetic model of adults showed significantly higher inter-individual variation in comparison to pediatrics, which is consistent with the assumption.

Furthermore, the model predicted C_{max} values for pediatrics, which were found to be nearly two-fold lower than the adults'. The results inferred that when the same dosage was administered to the different age groups, it showed wide variability in the individual pharmacokinetics. This could be attributed to the concentrations of bile salts in the gut, which primarily influence the rate and extent to which poorly soluble drugs are eliminated by rendering them more soluble or by making membranes more permeable to lipophilic molecules. However, different age groups in pediatrics showed minimal differences in the plasma concentrations, C_{max}, and AUC values. Furthermore, the results showed higher C_{max} values for neonates than children due to the fact that a few hepatic enzymes are completely developed and active throughout the neonatal phases of life, which may not be the case with children of older age groups.

Additionally, population PBPK modeling is essential for comprehending inter-individual variability. It is necessary to do further research with adequate clinical data to draw conclusions about the potential significance of variations in bile salt concentration on the inter-individual pharmacokinetic variability of voriconazole, especially in difficult-to-reach populations.[44-47]

CONCLUSION

Age-related developmental changes particularly associated with the bile salt variations might be one of the prominent contributors to the inter-individual pharmacokinetic variability of voriconazole. Additionally, based on the findings, bile salts are found to be significant contributors along with the maturity and expression of hepatic enzymes, which are anticipated to be the primary and dominant factor responsible for significant pk variations in different age groups. However, the theory could be further supported and validated with sufficient clinical data on the pediatric population. Additionally, the PBPK approach encourages the possibility of foreseeing the influence of bile salt discrepancies on the pharmacokinetics for numerous BCS class II and IV medications. This possibility may be helpful during the drug development process to develop safe and effective dosing, particularly in special populations or disease states, as well as lower the cost of *in-vivo* pharmacokinetic studies.

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