



A Physiologically-Based Pharmacokinetic Model of Voriconazole

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Background and Objectives

Background: As first-line anti-fungal therapy, voriconazole exhibits nonlinear pharmacokinetics together with large inter-individual variability but a narrow therapeutic range and markedly inhibits CYP3A4 *in vivo*. This causes difficulties in selecting appropriate dosing regimens of voriconazole and of co-administered CYP3A4 substrates.

Objective: This study aimed to investigate the metabolism of voriconazole in detail to better understand dose- and time-dependent alterations in the pharmacokinetics of the drug, to provide the model basis for safe and effective use according to CYP2C19 genotype, and to assess the potential of voriconazole to cause DDIs with CYP3A4 substrates in more detail.

Methods

Model development: An *in vitro* assay for inhibition of human CYP2C19 and CYP3A4 by voriconazole was carried out to describe mechanism-based inactivation (MBI) of CYP3A4 by voriconazole. These results were combined with 93 published concentration-time curves of voriconazole from clinical trials in healthy volunteers to develop a whole-body physiologically-based pharmacokinetic (PBPK) model in PK-Sim®.

Model evaluation: The model was evaluated with the predicted/observed ratio of AUC and C_{max} , geometric mean fold error (Eq.1), as well as the comparison of predicted with observed concentration-time curves from virtual studies over the full range of dosage regimens. Furthermore, published PBPK models of the CYP3A4 probe substrates midazolam and alfentanil were coupled with the model of voriconazole to assess the inhibitory effects of voriconazole on CYP3A4 *in vivo* and to verify the inhibition model of voriconazole.

$$\text{Eq. 1 } \text{GMFE} = 10^{(\sum |\log_{10}(\text{pred P}/\text{obs P})|)/n}$$

GMFE: geometric mean fold error of all AUC or C_{max} predictions from the respective model, pred P: predicted parameter, obs P: observed parameter, n: number of studies.

Results-model development

MBI: The IC₅₀ shift assay showed that voriconazole had MBI on CYP3A4, with a 16-fold difference in the absence and presence of NADPH. The inactivation kinetic assay gave a K_I of 9.33 (95% CIs: 2.56-34.0) μM and a k_{inact} of 0.0428 (95% CIs: 0.0171-0.107) min^{-1} for CYP3A4, supporting MBI introduced into the PBPK model with Eq. 2. However, the input of k_{inact} of 0.0428 min^{-1} led to overestimation of midazolam exposure for DDI studies. Therefore, k_{inact} was optimized as 0.015 min^{-1} based on the concentration-time profiles with multiple intravenous dosing of voriconazole.

$$\text{Eq. 2 } \frac{dE(t)}{dt} = K_{deg} \times E_0 - K_{deg} \times E(t) - \frac{k_{inact} \times [I]}{K_I + [I]} \times E(t)$$

$E(t)$: amount of active enzyme at time t ; E_0 : original amount of active enzyme; K_{deg} : first-order degradation rate of enzyme in absence of voriconazole; K_I : dissociation rate constant; $[I]$: unbound concentration of voriconazole at enzyme sites; k_{inact} : maximum inactivation rate constant.

Inhibition of CYP3A4 by voriconazole: The time courses of CYP3A4 activity in both the liver and small intestine were assessed during chronic voriconazole treatment. The maximum inhibition was reached at 51.2 h in the liver and 52.5 h in the small intestine (Figure 1). The CYP3A activity was predicted to recover 90% of its baseline 5 days after last voriconazole dose.

Genetic polymorphism of CYP2C19: Based on the concentration-time profiles of CYP2C19 PMs after intravenous voriconazole, V_{max} of CYP3A4 was optimized as 2.12 pmol/min/pmol, assuming that only CYP3A4 mediated the metabolism of voriconazole in PMs. For other genotypes, both CYP2C19 and CYP3A4 mediated pathway were considered in the metabolism of voriconazole. The different CYP2C19 genotypes were integrated into the model for RMs, EMs, IM or PM with the reference CYP2C19 expression values of 0.79, 0.76, 0.40, and 0.01 $\mu\text{mol/L}$, respectively [3].

Results-model verification

The PBPK model verification demonstrated good performance of the model, with 71% of predicted/observed AUC ratios and all C_{max} ratios from 28 verification datasets being within a 2-fold range. For those studies reporting CYP2C19 genotype, 86% of AUC ratios and all C_{max} ratios were inside the 2-fold range of 44 test profiles (Figure 2). When the model was coupled with independently developed CYP3A4 substrate models (midazolam and alfentanil), the predicted/observed AUC of probs change by voriconazole ranged from 0.86 to 1.11, indicating that CYP3A4 inhibition was appropriately incorporated into the voriconazole model (Figure 3).

Figure 1 Performance of voriconazole PBPK model in DDI with CYP3A4 substrates

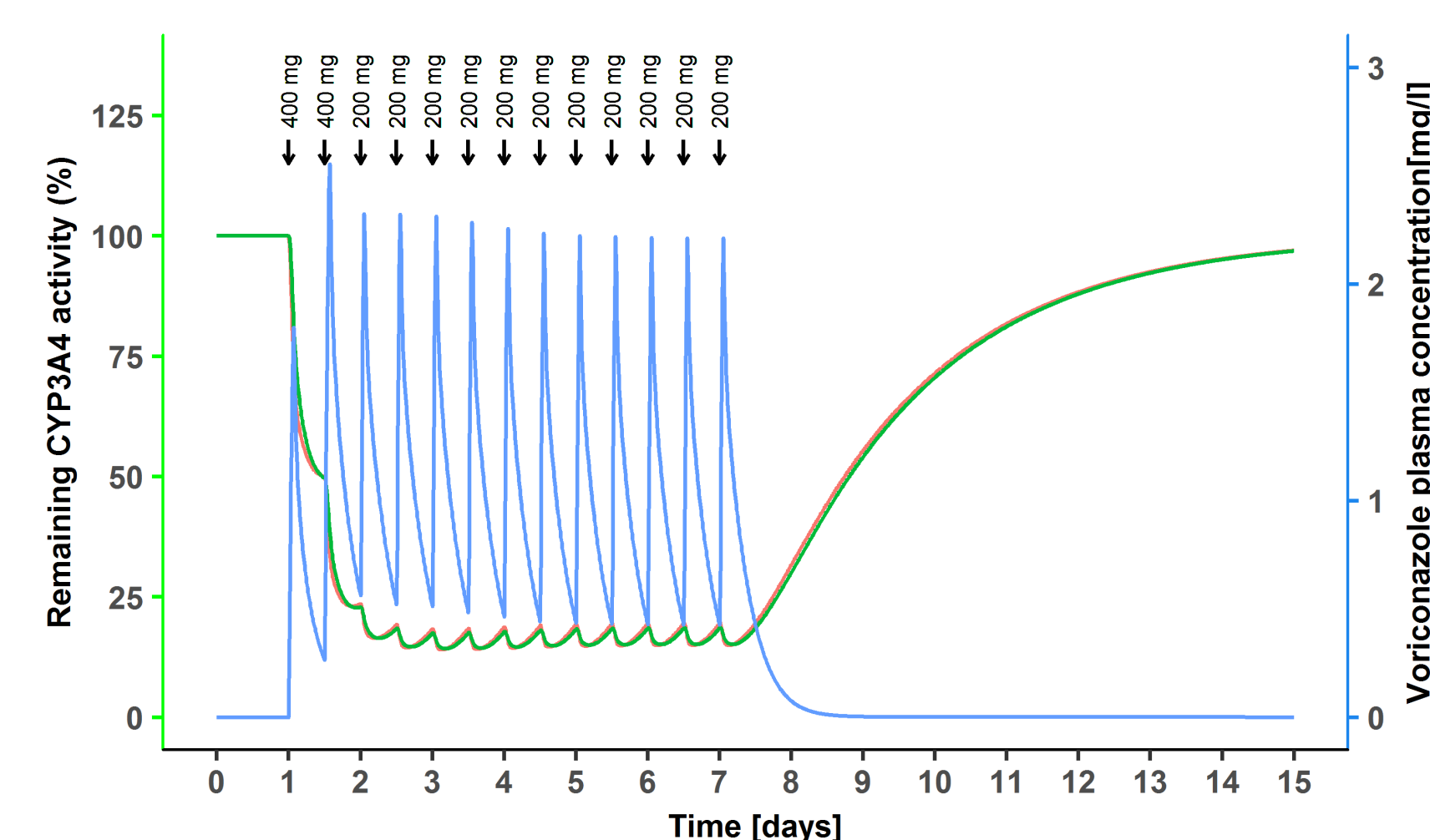


Figure 2 Goodness of fit plot of the PBPK model of voriconazole

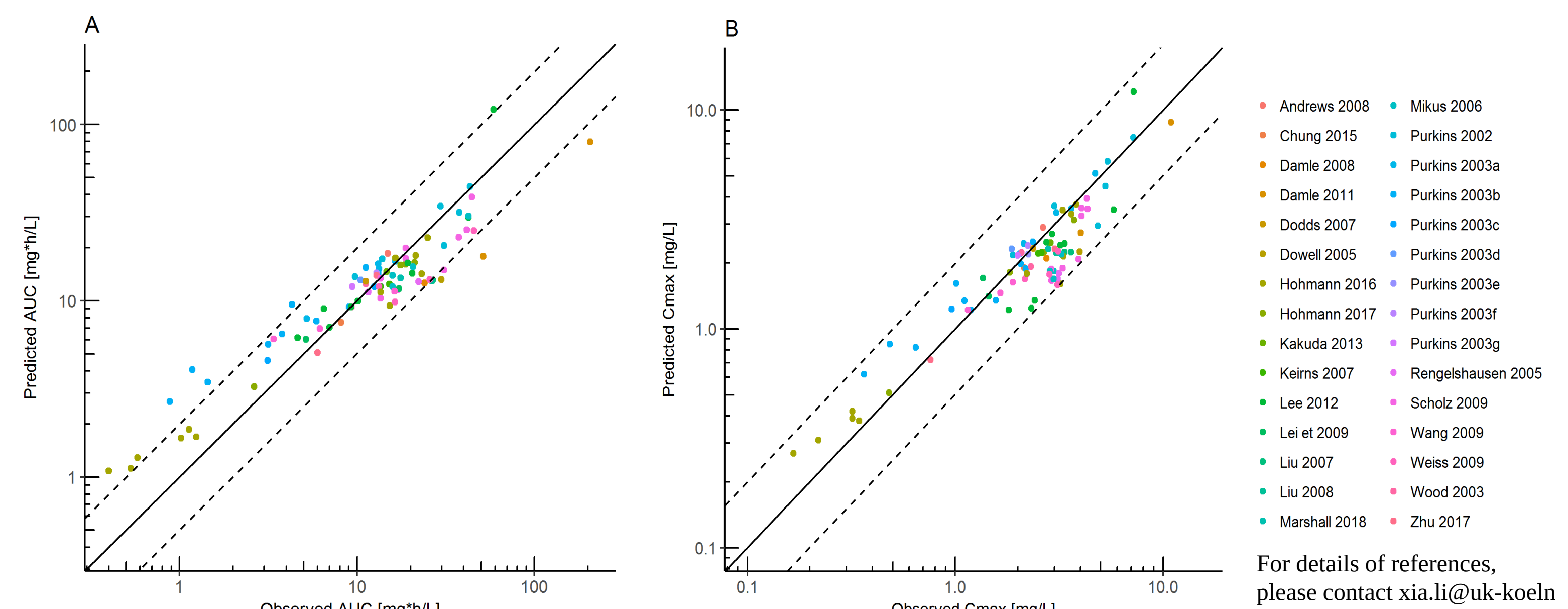
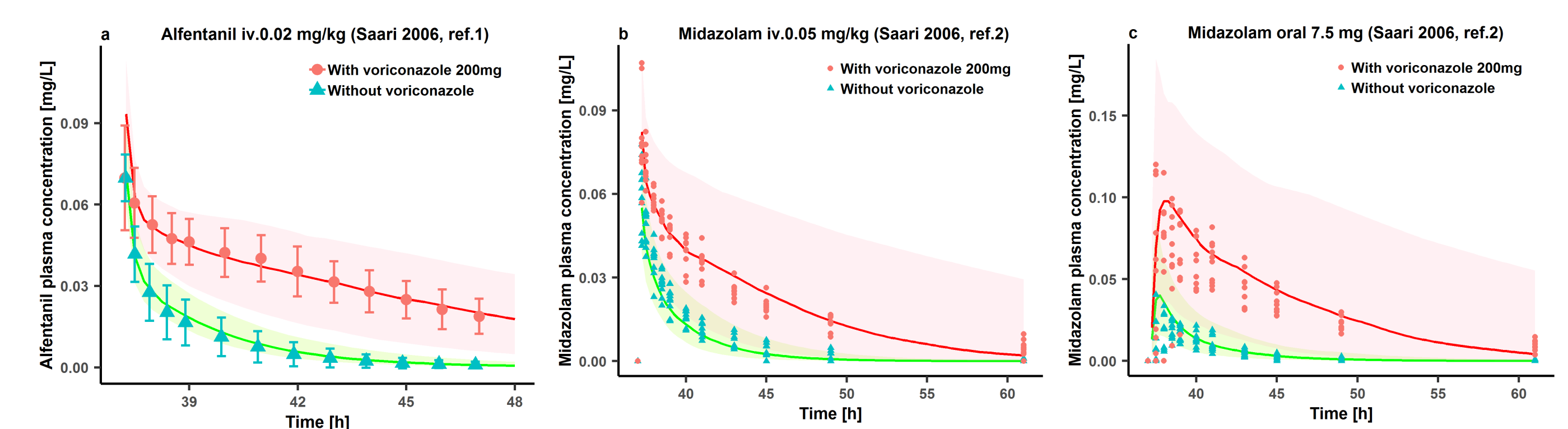


Figure 3 Performance of voriconazole PBPK model in DDI with CYP3A4 substrates



Conclusion

MBI of CYP3A4 by voriconazole is an important pharmacokinetic characteristic of the drug and needs to be taken into account along with CYP2C19 genotype to predict the exposure of voriconazole properly. By incorporating these elements, a PBPK model of voriconazole was developed which could accurately capture the time- and dose-dependent alterations of voriconazole pharmacokinetics as well as DDIs caused by voriconazole inhibitory effects on CYP3A4. This model could support individual dose optimization of voriconazole as well as DDI risk management.

References

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