ARTICLE

Whole body physiological based pharmacokinetic model to explain the drug-drug interaction between voriconazole and flucloxacillin

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Abstract

Introduction: An intensive care unit (ICU) admitted patient with *Staphylococcus aureus* bacteremia and pulmonary aspergillosis received both flucloxacillin and voriconazole as treatments. After conducting voriconazole therapeutic drug monitoring (TDM), subtherapeutic voriconazole concentrations were observed. After which treatment was switched to posaconazole. The drug-drug interaction was previous described in literature. The lack of knowledge about the mechanism raised the need to explain the drug-drug interaction (DDI) between voriconazole and flucloxacillin mechanistically.
Method: A whole-body pharmacokinetic-pharmacodynamic (WBPBPK) model was applied to predict the DDI. Non-linear liver metabolism was taken into account, as well as non-linear and reversible albumin binding. Protein binding and albumin concentrations as well as elevated CRP levels and decreased CYP-enzymes were used as a surrogate to predict the DDI and simulate an ICU admitted patient. Simulations on four populations with the following characteristics were conducted: healthy (concentration albumin: 40 g/L, normal CRP), ICU-non infected (concentration albumin: 30 g/L, normal CRP), ICU-infected (concentration albumin: 30 g/L, elevated CRP) and DDI (concentration albumin: 2.5 g/L, normal CRP).
Results: The model was able to predict the plasma concentration of both voriconazole and posaconazole over time. A lower albumin concentration resulted in higher voriconazole liver and lung tissue uptake, whereas plasma concentrations decreased. Elevated CRP resulted in a decreased metabolism and increased plasma and tissue concentrations of voriconazole. Posaconazole was not affected by the albumin changes.
Discussion/conclusion: In conclusion, this model describes the effect of the DDI and influence of CRP on voriconazole plasma concentrations. Although, future research is needed to describe the competition between voriconazole and flucloxacillin for the albumin binding pockets and to understand the influence of CYP-enzyme induction and polymorphism.

Keywords: Voriconazole; flucloxacillin; drug-drug interaction; albumin; WBPBPK

INTRODUCTION

Voriconazole and posaconazole are both triazole antifungal agents, used as first and second-line treatment against invasive fungal infections, such as invasive aspergillosis. Invasive aspergillosis is a pulmonary infection caused by *Aspergillus,* a common mold [1,2,3]. It is the most severe form of aspergillosis and has a high mortality rate, therefore adequate and direct treatment is necessary. Patients with weakened immune systems are most susceptible to invasive aspergillosis, and due to their impaired immune system, they are also concomitantly susceptible to bacterial infections, like *Staphylococcus* infections[1–3]. For the treatment of these bacterial infections, flucloxacillin is the preferred wide-used antibiotic[4]. In patients with both invasive aspergillosis and Gram-positive infections, voriconazole and flucloxacillin are combined. A patient with a *Staphylococcus aureus* bacteraemia and pulmonary aspergillosis receiving this drug combination was presented at the intensive care unit (ICU). After conducting therapeutic drug monitoring (TDM) it became clear that voriconazole plasma concentrations were subtherapeutic. TDM is standard of care during voriconazole treatment due to the high inter- and intra-patient variability and toxicity[5]. A literature search showed that multiple other cases of the drug-drug interaction (DDI) between flucloxacillin and voriconazole have been reported, in which subtherapeutic (0.1-0.9 mg/L) voriconazole plasma concentrations were observed, while the therapeutic C_{trough} ranges 1-6 mg/L) [6–8].

Flucloxacillin is highly protein-bound (95%) and binds non-covalent to Sudlow's binding sites I and II of albumin [9,10]. Prior research showed that protein displacement is common between drugs that bind to the same albumin binding pockets with different binding affinity. The binding affinity for a certain binding pocket determines the degree of displacement[9,10]. For example, flucloxacillin can be displaced by the high albumin-bound anti-cancerous agent imatinib (K_d 319 ng/ml), which has a higher affinity for albumin than flucloxacillin (k_d 10200 ng/ml) [9,10,11] Evidence that voriconazole has a lower affinity for albumin compared to flucloxacillin is provided by observed low and highly variable protein binding to albumin (26%)[2].

Another factor that influences protein binding is disease state. Infections are common in intensive care units (ICU). More than 50% of ICU patients have an infection during ICU admission, with an increased risk of infection with longer admission to the ICU [12–14]. At the ICU, critically ill patients undergo complex disease processes, which are associated with significant effects on drug pharmacokinetics (PK). For both

voriconazole and flucloxacillin, these PK changes are related to altered plasma protein binding[10,5,15]. Approximately 40% of critically ill patients develop hypoalbuminemia [12,16]. These ICU patients patients have an albumin concentration between 13.8 to 38.7 g/L, whereas healthy people have an albumin concentration of 40 g/L[5,15]. A second factor correlated to disease state is C-reactive protein (CRP), which is a marker for inflammation. Retrospective studies have shown that elevated CRP values, can increase voriconazole C_{trough} concentrations[17]. The metabolic rate changes during inflammation as a result of the synthesis of pro-inflammatory cytokines during infection and inflammation. These cytokines down-regulate the gene transcription of various CYP iso-enzymes. Hereby, CRP indirectly decreases the amount of CYP-proteins (CYP2C19) and enzyme activity, resulting in a decreased metabolism and increased serum concentrations[5]. Normally CRP levels are around 1 mg/L, however during inflammation they can increase to 500 mg/L[18].

For flucloxacillin, it is known that the unbound concentration and percentage of protein binding (Fu) is significantly associated with albumin concentrations[14]. Furthermore, voriconazole protein binding is variable and ranges between 49-70%. Lower albumin concentrations result in low voriconazole plasma concentrations[5,15]. Therefore, we hypothesize that flucloxacillin may displace voriconazole from the main albumin binding sites, leading to a higher unbound voriconazole fraction[5,15]. This higher unbound fraction is available for hepatic excretion, metabolism and tissue uptake which may result in subtherapeutic voriconazole plasma concentrations[6–8].

Whole-body distribution of drugs can be described by using whole-body PBPK modelling (WBPBPK). A WBPBPK model uses a mechanistic approach to simulate drug distribution and concentrations over time. In this model, each organ is represented as a compartment, the same counts for the veins and arteries. The blood flow (Q), organ volume (V) and tissue-to-plasma partition coefficient (Kp) determine the amount of drug in each compartment over time. Where only unbound and unionized drug can diffuse passively over the cell membranes and be excreted by liver and/or kidneys. Therefore, WBPBPK modelling is be helpful to explore the effects of alterations in any of these processes on whole-body distribution, such as changes in protein binding and unbound drug concentrations as a result of drug-drug interactions[19,20, 21]. In this

study, we applied a WBPBPK model to illustrate the effect of the hypothetical mechanism of the drug-drug interaction between voriconazole and flucloxacillin.

METHODS

Overview

A base model describing whole body drug distribution was built based on previous publications [19–21]. The tissue to blood partitioning (Kp) was predicted using a well-established PBPK-model for weak basic lipophilic drugs[22], as visualized in figure 1. Reversible protein binding was introduced to describe the hypothesis of the drug-drug interaction[9]. To further explore the nonlinearity in albumin binding of voriconazole, affinity (K_d) and albumin concentration were applied in the model. The Michaelis-Menten constant (Km) and maximum velocity (V_{max}) of CYP2C19, CYP2C9, and CYP3A4, were applied to explore non-linear metabolism[17,19]. The final model was evaluated by comparing pharmacokinetic (PK) predictions in tissue and plasma with data from literature. Relevant physicochemical properties used in PKPB-modelling of voriconazole and posaconazole can be found in table 1. An overview of the model is displayed in figure 1 and 2 whereas the equations can be found in supplemental I.

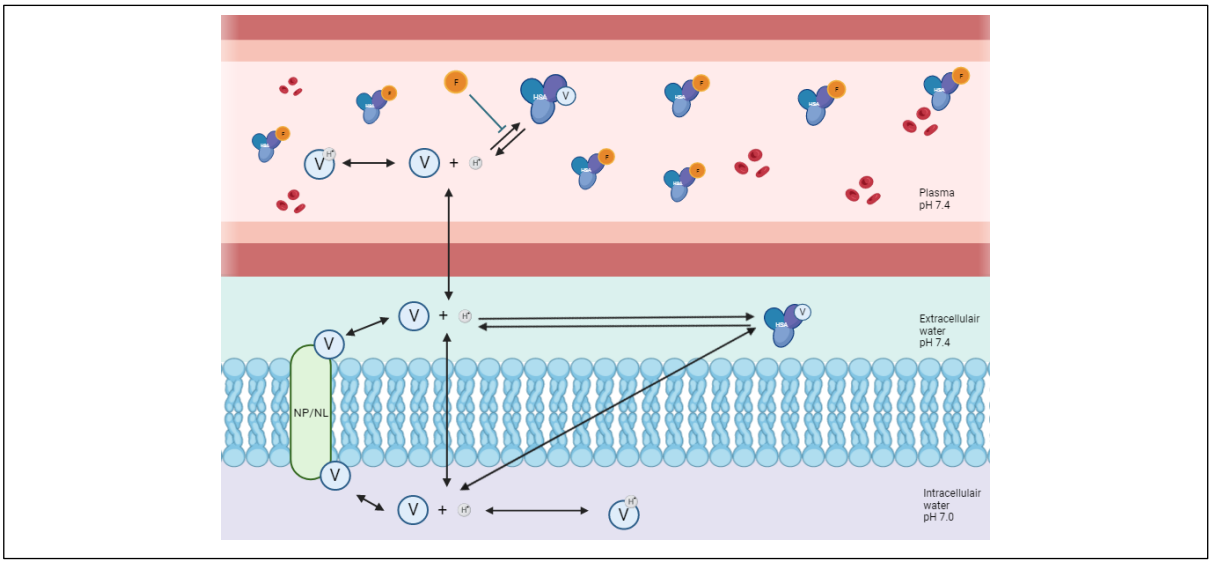
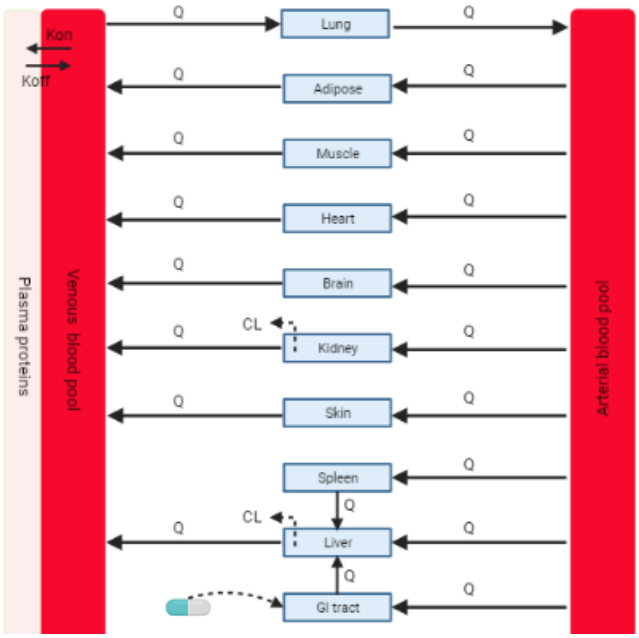


Figure 1 | A schematic overview of the mechanistic PBPK model for voriconazole. The plasma compartment is presented in light pink, extra cellular spaces in green, and intra-cellular space in lilac. Blue circles represent Voriconazole and orange circles flucloxacillin. H+-atoms are visualized with light grey circles and represents protonation when depicted together with voriconazole. The blue lipid bilayer depicts the cell membrane. The green oval visualizes neutral lipids and neutral phospholipids. The proteins in the plasma and extra-cellular space represent albumin, to which voriconazole and flucloxacillin can bind (depicted together). Black arrows visualize processes that are included in the mechanistic PBPK model. pH values of each compartment are given. V = voriconazole, VH+ = protonated voriconazole, F = flucloxacillin, ALB = albumin, NP/NL = neutral lipids/neutral phospholipids, H+ = H+-atoms.

Whole-body PBPK model: base model selection

The WBPBPK model structure is derived from *Rodgers et al (2006)* and *Elmokadem et al (2019)*[22,23]. Organ-specific parameters, such as organ flow (Q) and organ volume (V), were obtained from *Rowland and Tozers* (table 1)[24]. The blood flow to each individual organ is comes from the flow of the arterial blood compartment and indirectly the flow of the venous blood compartment after passing the organs. The lungs are opposite, as they receive blood from the venous blood compartment and deliver it to the arterial compartment. As voriconazole and posaconazole have renal as well as hepatic excretion, both are taken into account in the final model, adjusted for (non-)linearity differences between both agents, as described below[25].



$$Q_{tissue} * C_{arterial} - \left(Q_{tissue} * \frac{C_{tissue}}{\left({Kpu_{tissue}}/{BP} \right)/\Phi} \right) \quad \text{Eq 1}$$

$$Q_{lung} * C_{venous} - \left(Q_{lung} * \frac{C_{lung}}{\left({Kpu_{lung}}/{BP} \right)/\Phi} \right) \quad \text{Eq 2}$$

Figure 2 | **Whole body PBPK overview**. Each organ is represented as a compartment, as well as veins and arteries. Reversible protein binding is visualized in pink. Q represents the blood flow from and to the organs. The liver and kidneys are the drug eliminating organs (CL). K_{on} and K_{off} represent the affinity of the drugs for albumin and determine the fraction of unbound drug. Drugs are orally administrated via the GI tract.

Whole-body PBPK model: Liver model – voriconazole

The liver clearance was described by a physiological model. It used saturable cytochrome P450 iso-enzymes (CYP2C19, CYP2C9 and CYP3A4) to describe the metabolism and excretion of voriconazole[20]. After being metabolized by the liver, voriconazole can be excreted. The non-linear-enzymatic metabolism is described by the Michaelis-Menten constant (Km) and maximum velocity (V_{max}) and is shown in equation 3. The non-linear enzymatic metabolism of voriconazole is combined with a general liver equation to take into account the number of liver enzymes (MPPGL), the liver volume (V_{liver}), and the fraction of unbound drug in liver microsomes (fumic)[22]. The total liver clearance equation is shown in equation 4. Not all drug which enters the liver is metabolised and cleared, only unbound drug. The drug which only passes the liver is described as in non-eliminating organs, the total liver equation is showed in equation 5.

As posaconazole is not metabolized by CYP-enzymes, population clearance values were used to simulate posaconazole excretion, which is given by CL_{liver} [25].

As mentioned earlier, it is known that inflammation and elevated CRP values reduce the amount of CYP-enzymes in the liver. To predict the effect of inflammation, V_{max} of CYP2C19 is lowered during ICU-infected patient simulations.

$$Non\ linear\ enzymatic\ metabolism = \sum_{i=1}^{n} \frac{V_{max}^{i}}{K_{m}^{i} + C_{t,u}} \qquad \text{Eq 3}$$

$$CL_{liver\,voriconazole} = \frac{\left(\left(\sum_{i=1}^{n} \frac{V_{max}^{i}}{K_{m}^{i} + C_{t,u}}\right) * MPPGL * V_{liver} * 1000 * 60 * 1^{-6}\right)}{fumic} \qquad \text{Eq 4}$$

$$A_{liver} = Q_{gu} * \left(\frac{C_{gut}}{\left(KP_{gut}/BP\right)/\Phi}\right) + Q_{spleen} * \left(\frac{C_{spleen}}{\left(KP_{spleen}/BP\right)/\Phi}\right) + Q_{hepatic\ arterie} * C_{arterial} - Q_{liver} * \left(\frac{C_{liver}}{\left(KP_{liver}/BP\right)/\Phi}\right) - CL_{liver} * \left(\frac{F_{unbound} * C_{liver}}{\left(KP_{liver}/BP\right)/\Phi}\right) \qquad \text{Eq 5}$$

Physicochemical drug distribution: base model selection

Physicochemical properties can be used to predict tissue-distribution (Kp)[23,26,27]. We previously showed that the base model of *Rodgers et al (2006)* provides an adequate tissue distribution prediction for basic lipophilic drugs at steady state in patients[28]. Therefore, this model can be easily applied for similar compounds such as posaconazole and voriconazole. The relevant psychochemical properties that are used in PBPK modelling of voriconazole and posaconazole can be found in table 1.

Physicochemical drug distribution

The physicochemical drug distribution model predicts the total tissue-to-unbound plasma ratio (Kp_u), at steady state. Predictions of distribution are based on the drug binding to proteins (Fu), the binding to red blood cells, the binding to neutral lipids and neutral phospholipids (NLNP) in the cellular membrane, the binding to albumin (ALB) in the extracellular space, and the drug remaining protonated in the intra- and extracellular spaces (IW & EW). The most important drug specific parameters used are the acid dissociation constant (pKa), partition coefficient (Log P), fraction unbound (Fu), and blood to plasma ratio (B:P). An overview of all physicochemical parameters are displayed in table 1[20,23–25,27,29].

The model predicts the Kp_u by calculating the pH driven distribution of the drug into the cellular components. Tissue-specific parameters are fractional tissue volumes (F_{iw}, F_{ew}, F_{nl}, and F_{np}), pH values, and tissue albumin concentrations. The pH values determine the amount of un-protonated drug, able to diffuse passively over cell membranes. The amount of un-protonated drug bound to albumin in tissue is determined by the relative tissue to plasma albumin concentrations (tissue-to-plasma ratios) and the albumin affinity of voriconazole and posaconazole (Ka), calculated using *Rodgers et al 2006*. The binding affinity of the un-protonated drug for neutral lipids and neutral phospholipids in tissue is predicted by the octanol:water partition coefficient (P). Vegetable oil:water partition coefficient (Pv) is used for adipose tissue. The physicochemical model by Rodgers is based on the following assumptions: only passive transport of drug into tissues occurs, all conditions are non-saturable, and all tissues of interest are well stirred[23]. A schematic overview of the model is given in figure 2. All the equations used in the base model and additional explanations can be found in supplemental I.

Full equation physiochemical drug distribution is given in equation 6. KP values used in the WBPBPK model were obtained by multiplying the Kp_u with the fraction unbound as shown in equation 7 [30].

$$\mathrm{Kpu} = \mathrm{f_{ew}} + \left(\frac{1 + 10^{\mathrm{pKa-pH_{iw}}}}{1 + 10^{\mathrm{pKa-pH_p}}} * \mathrm{f_{iw}}\right) + \left(\frac{\mathrm{P} * \mathrm{f_{nl,t}} + (0.3 * \mathrm{P} + 0.7) * \mathrm{f_{np,t}}}{1 + 10^{\mathrm{pKa-pH_p}}}\right) + \mathrm{K_{a,albumin}} * [\mathrm{ALB}]_{\mathrm{tissue}} \quad \text{Eq 6}$$

$$\mathrm{Kp} = \mathrm{Kp_u} * \mathrm{fu} \quad \text{Eq 7}$$

Table 1 | Tissue and compound-specific input parameters. Parameters were adapted from Table 1 Rodgers et al. (2005), Table 1 Rodgers et al. (2006). * kidney clearance, ** population clearance (liver).

Drug specific parameters		
Parameter	**Voriconazole**[20]	**Posaconazole**[25]
Molecular weight (g/mole)	349.32	700.8
pKa	1.76	2.27
Compound type	Weak base	Weak base
Log $P_{octanol:water}$ (P)	1.8	5.41
Log $P_{vegetable\ oil:water}$ (adipose) (Pv)	0.66	4.68
Fraction unbound	0.42	0.02
Blood:plasma ratio	1	1
K_d albumin (M)	$7.5*10^{-5}$	$2*10^{-6}$
V_{max} (pmole/min/pmole)		N/A
CYP2C19	40	
CYP3A4	32.2	
Km (uM)		N/A
CYP2C19	9.3	
CYP3A4	834.7	
K_{el} (L/h)	0.096 *	195 **
F (%)	96	8

Tissue specific input parameters[23,27]					
Tissue	**F_{nl}**	**F_{np}**	**F_{ew}**	**F_{iw}**	**Albumin tissue to plasma ratio**
Blood cells	$1.7*10^{-3}$	0.0029	n.a.	0.60	n.a.
Plasma	n.a.	n.a.	n.a.	n.a.	n.a.
Adipose	0.0016	0.8530	0.135	0.017	0.068
Bone	0.0174	0.0016	0.100	0.346	0.050
Brain	0.0391	0.0015	0.162	0.620	0.041
Gut	0.0375	0.0124	0.282	0.475	0.141
Heart	0.0135	0.0106	0.320	0.456	0.160
Kidney	0.0121	0.0240	0.273	0.483	0.137
Liver	0.0135	0.0238	0.161	0.573	0.161
Lung	0.0215	0.0123	0.336	0.446	0.168
Muscle	0.0100	0.0072	0.118	0.630	0.059
Spleen	0.0071	0.0107	0.207	0.579	0.207

PK input parameters				
Tissue	**Kp_u Voriconazole**	**Kp_u Posaconazole**	**Tissue volume (L)**[29]	**Blood flow (L/h)**[29]
Adipose	1.76	7.17	18.2	19.5
Bone	0.62	5.44	10.5	19.5
Brain	0.91	3.33	1.45	46.8
Gut	1.06	8.73	0.65 (wall) 0.35 (lumen)	58.8
Heart	1.03	8.57	0.33	25.35
Kidney	1.00	7.35	0.31	74.1
Liver	0.89	5.07	1.8	95.55
Lung	1.08	11.21	0.5	390
Muscle	0.86	3.95	29	66.3
Spleen	0.93	5.64	0.15	11.7
Rest of the body	1.03	7.09	1.15	52.65
Blood	-	-	5.6	-

Extension: protein compartment

To explore the effect of protein binding, it was added to the model based on the equations from *Haouala et al (2019)* [11]. Voriconazole and posaconazole are both protein-bound and have nonlinear binding to albumin, which influences the PK profile of both agents. It is assumed that both posaconazole and voriconazole only bind to one albumin binding pocket. The unbound concentration is described and calculated by equation 8 [31]. In which, C_{total} represent the total concentration of voriconazole/posaconazole in the veins. The K_d is the dissociation constant of voriconazole/posaconazole for albumin. To date, the K_d of voriconazole and posaconazole for albumin are not stated in the literature. Therefore, the K_d of both drugs was calculated by the use of equation 8[11]. The fraction unbound is calculated using the total- and unbound concentration in the veins, as described in equation 9.

$$C_{unbound} = \frac{1}{2} * \left(C_{total} - K_d - [albumin] * \sqrt{(C_{total} - K_d - [albumin])^2 + 4 * C_{total} * K_d}\right) \quad \text{Eq 8}$$

$$Fu = \frac{C_{unbound}}{C_{total}} * 100\% \quad \text{Eq 9}$$

Drug-drug interaction

Since the main research question is the explanation of the drug-drug interaction of voriconazole with flucloxacillin, the following hypothesis was tested. Flucloxacillin may displace voriconazole, with a lower albumin binding affinity, from the albumin binding sites in the blood [9,14,32]. This competition at the albumin binding sites may result in direct changes in protein binding of voriconazole and thereby altering the PK profiles, due to a higher unbound fraction[10] . Unbound voriconazole can be metabolized and excreted and may easily diffuse over the cell membrane into tissues. After passing the cell membrane, unbound voriconazole is available for binding to albumin inside the tissues and for drug metabolism in the liver. The hydrophilic flucloxacillin does not extensively diffuse into tissues, where it is not able to displace voriconazole on albumin in tissues. The effect of the drug-drug interaction (DDI) between voriconazole and flucloxacillin was predicted, by lowering the amount of albumin available in the bloodstream, indicating that albumin is bound by flucloxacillin and not available for voriconazole. A decreased amount of albumin was used to re-estimate Fu of voriconazole and posaconazole in the presence of flucloxacillin, which is subsequently used to recalculate the KP. Finally, in the case of DDI, an additional factor (Φ) was

added to mimic a higher tissue uptake ratio caused by the relatively high availability of albumin to bind to in tissue. Φ is derived by the change in Fu between healthy situation and DDI situation.

During this research, 4 population groups were used of which the dosing and demographic characteristics are listed in table 2. Simulations on each group were performed using different albumin blood concentrations and V_{max} to simulate elevated CRP values. The patients are stated as: healthy, ICU-non infected, ICU-infected and DDI[15,33].

Table 2 |Concentrations of albumin used in the simulations stated as healthy, ICU-infected, ICU-non-infected and DDI. Infected ICU patients have an elevated CRP value which decreases the amount of CYP-enzyme represented by V_{max}. Combined with the dosing and demographic characteristics of the 4 typical patients.

	Case patient (ICU &DDI)	Healthy patient	ICU-non-infected patient	ICU infected patient	DDI patient
Observed albumin concentrations (value included in the model)	30 g/L	33 – 52 g/L (40g/L)	13.8 to 38.7 g/L (30g/L)	13.8 to 38.7 g/L (30g/L)	unknown (2.5 g/L)
Weight	50 kg	70 kg	70 kg	70 kg	70 kg
CRP mg/L	33	Non elevated	Non elevated	Elevated	Non elevated
V_{max} CYP2C19 (pmole/min/pmole)	20	40	40	20	40
Voriconazole dosing	Loading dose: 400 mg twice every 12 hours Maintenance dose: 200 mg every 12 hours	Loading dose: 400 mg twice every 12 hours Maintenance dose: 200 mg every 12 hours	Loading dose: 400 mg twice every 12 hours Maintenance dose: 200 mg every 12 hours	Loading dose: 400 mg twice every 12 hours Maintenance dose: 200 mg every 12 hours	Loading dose: 400 mg twice every 12 hours Maintenance dose: 200 mg every 12 hours
Posaconazole dosing	Loading and maintenance dose: 300 mg every 12 hours	Loading and maintenance dose: 300 mg every 12 hours	Loading and maintenance dose: 300 mg every 12 hours	Loading and maintenance dose: 300 mg every 12 hours	Loading and maintenance dose: 300 mg every 12 hours
Plasma concentrations (C_{trough})	Voriconazole < 0.1 mg/L Posaconazole 2,35 mg/L 5,21 mg/L	1.5 mg/L[34]	0.5 – 8.7 mg/L[15]	2.32 mg/L[35]	0.2 mg/L[7]

Statistics and software

The simulations of the PBPK- and WBPBPK models were performed with R software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria). Data from literature and blood samples from the case report were used to evaluate the PBPK- and WBPBPK models. Voriconazole plasma literature was

derived from *Purkins et al (2002*), which reported voriconazole plasma concentrations in healthy volunteers using a multiple dosing regimen[34]. Lung and liver tissue concentrations were derived from *Weiler et al (2011),* who performed tissue concentration measurements on eight deceased patients[36]. Posaconazole simulations were compared to plasma concentrations reported in the posaconazole review by *Chen et al. (2020)*[25]*.* Lung and liver tissue simulations of posaconazole were compared to tissue concentrations reported *by Blennow et al (2014)* who performed data/sample collection on deceased patients[37]. Tissue concentration evaluation was conducted using the mean prediction error (PE) of the observed tissue concentrations over one dose at steady state and literature values mentioned above.

$$PE = \left(\frac{predicted - observed}{Mean\ (predicted + observed)}\right) * 100\% \qquad \text{Eq 10}$$

RESULTS

A whole-body PBPK model was built to predict the voriconazole and posaconazole concentration-time profiles in plasma and tissues and to explore the mechanism of action of the drug-drug interaction between voriconazole and flucloxacillin. The WBPBPK model-predicted concentration-time profiles of voriconazole and posaconazole administered as oral (PO) single agents at a steady-state and standard dosing in plasma and liver and lung tissue (figure 3A and 3D). The plasma-PK profile was similar to the plasma-PK of patients described in the literature and resulted in concentrations within the therapeutic window for voriconazole[25,36–38]. Oral dosing simulations however, resulted in an over-prediction compared to literature PO data (figure 3B). whereas, voriconazole IV dosing simulations correspond to the literature (figure 3C). Furthermore, posaconazole plasma prediction corresponded the patient data of the earlier mentioned case-report (figure 3F). Oral posaconazole simulations yielded an over-prediction compared to literature (figure 3E).

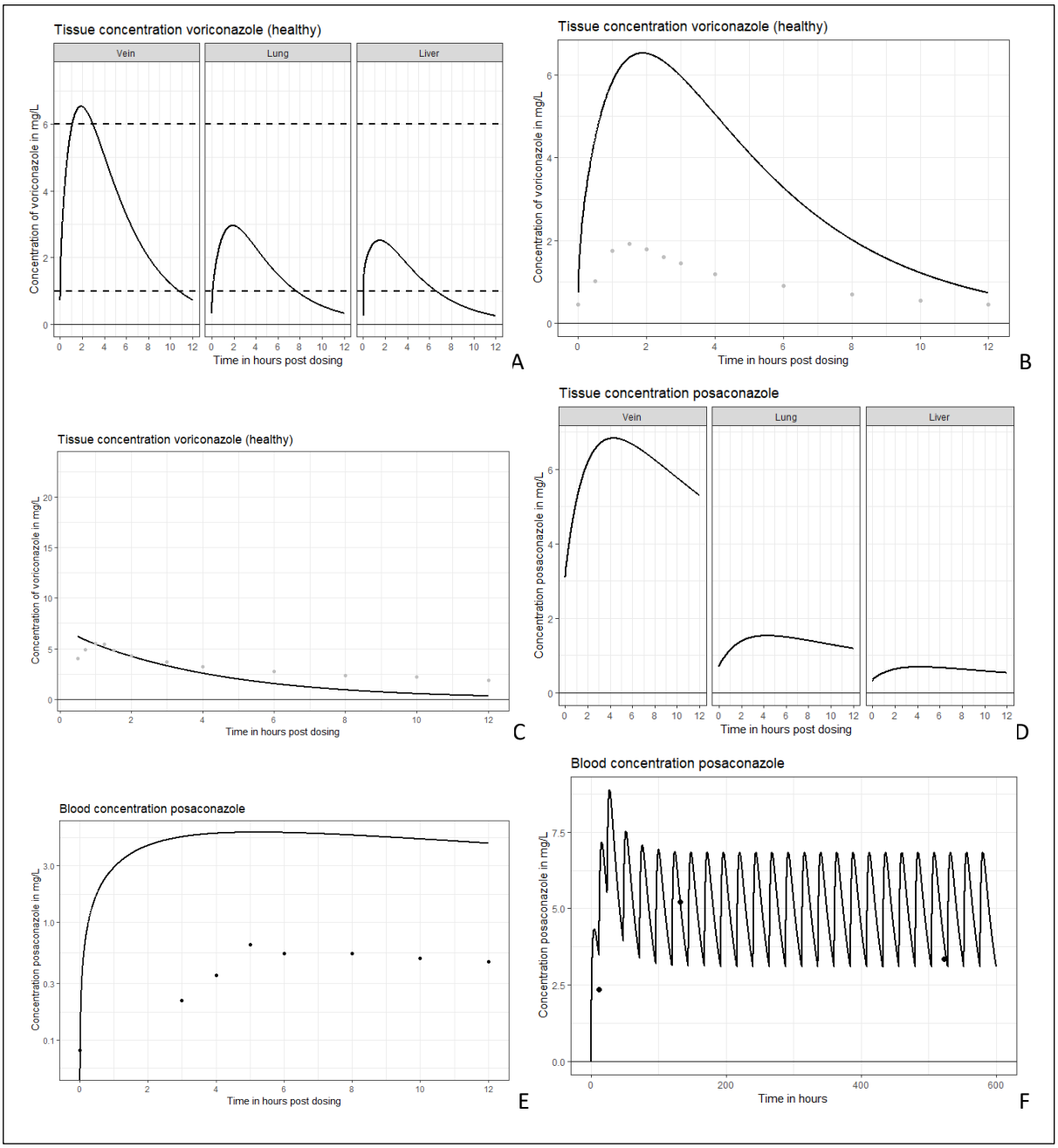


Figure 3 | Simulations of voriconazole and posaconazole in healthy patients, as one dose at a steady state. A) Voriconazole concentrations after oral administration in the vein, lung, and liver. The dotted black line represents TDM reference concentrations (1-6 mg/L). B) Magnification of voriconazole venous blood concentrations after oral administration (solid black line) and literature plasma concentration values (grey dots). C) Expansion of voriconazole venous blood concentrations after IV dosing (solid black line) and literature plasma concentration values (grey dots). D) Posaconazole concentrations after oral administration in the vein, lung and liver. E) Enlargement of posaconazole venous blood concentrations after oral administration (solid black line) and literature plasma values (black dots). F) Blood concentration time profile of posaconazole with case dosing regimen. Blood samples taken from the patient during treatment are visualized as black dots.

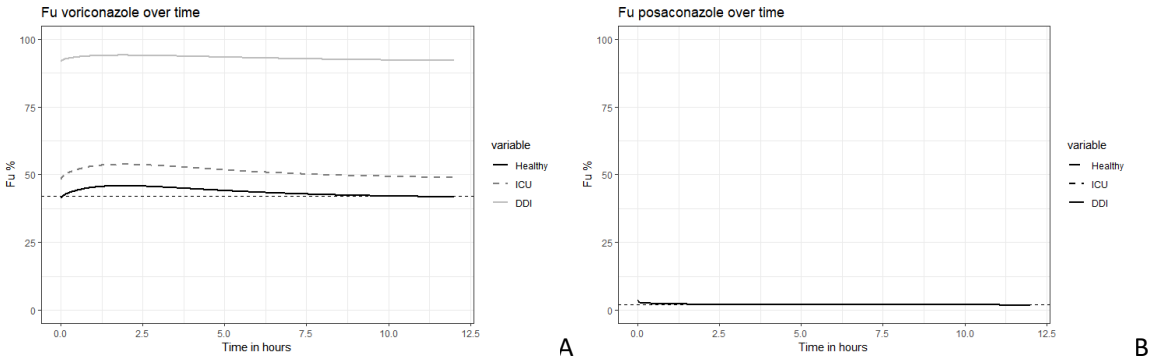
The lung and liver tissue predictions of voriconazole and posaconazole were compared to literature data. All tissue samples in literature were taken from deceased patients. The mean prediction error (PE) was used to evaluate lung and liver drug uptake predictions. The PE of all simulations fell within a 2-fold range (table 3). It was observed that posaconazole liver and lung uptake was well predicted with an PE of 94.44%

and -29.29% respectively. With corresponding liver and lung prediction errors of voriconazole 168.46% and 131.89% respectively.

Table 3| Mean predicted values, mean observed values and mean prediction error of both voriconazole and posaconazole in liver and lung tissue. Mean predicted values were based on one dose at steady state in healthy situation. Mean observed values were obtained from literature and were collected from deceased patients. All predictions fell within an 2-fold change with the observed values.

	Voriconazole			Posaconazole		
	Mean prediction value	Mean observed value	Mean prediction error	Mean prediction value	Mean observed value	Mean prediction error
Lung	1.54 mg/L	7.53 mg/L	131.89%	1.360 mg/L	1.01 mg/L	- 29.29%
Liver	1.28 mg/L	14.96 mg/L	168.46%	0.617 mg/L	1.83 mg/L	94.44%

Changes in albumin concentration affected the fraction of unbound voriconazole in critically ill patients (ICU admission) and the DDI in veins (figure 4A). The fraction unbound increased from 42% (healthy) to 50% during ICU admission and 95% for drug-drug interaction. To confirm that posaconazole blood concentrations are not affected by co-treatment with flucloxacillin, as no case reports have been reported. Simulations with a change of albumin were conducted on posaconazole. Despite the albumin changes during ICU admission and flucloxacillin, the fraction unbound posaconazole remained 2% (figure 4B). no change was observed in whole body posaconazole distribution over time (data not shown).



	Healthy	ICU	DDI
Concentration albumin	33 – 52 g/L	13.8 to 38.7 g/L	-
Concentration albumin used in simulations	40 g/L	30 g/L	2.5 g/L
Fu voriconazole	0.42	0.50	0.95
Fu posaconazole	0.02	0.02	0.02
Albumin tissue:blood factor (Φ)	1	1	2.26

Figure 4| Fraction unbound voriconazole (A) and posaconazole (B) simulated with three different albumin concentrations declared as healthy, ICU, and DDI, respectively, and stated in the table above. A) Fraction unbound voriconazole in three different situations. Healthy (solid black line), ICU (solid grey line) and DDI (dotted grey line). The fraction unbound in healthy people was about 42%, similar to literature. In ICU patients, albumin decreases, which resulted in an increased fraction unbound of 50%. The DDI simulation showed the highest unbound fraction of 95%. B) The fraction unbound posaconazole in the same three situations. Posaconazole was not affected by albumin changes and stays around 2%.

As shown in figure 5, the decrease in albumin in ICU patients and DDI patients resulted in a decrease of the total venous blood concentrations, compared to healthy patients. DDI patients showed the lowest C_{max} and C_{trough} concentrations (figure 5A and 5B). This resulted in voriconazole blood concentrations below the therapeutic window (<0.2 mg/L, grey dotted horizontal line), also described in literature and our case patient (figure 5B). On the contrary, the tissue concentrations in lung and liver increased as a result of a lower albumin plasma concentration due to the DDI. The peak concentration in liver tissue differt in DDI patients compared to infected ICU-patients (figure 5C). Non infected ICU patients had similar liver concentrations compared to healthy people and had the lowest liver tissue concentrations. The elevated CRP value had a negligible influence on liver concentrations (figure 5C). The highest peak dose in lung tissue was observed in infected ICU patients. Lung tissue concentrations in ICU patients without elevated CRP were similar to that in the healthy population (figure 5D). The DDI resulted in a higher peak concentration compared to non-infected ICU patients, but was lower compared to infected ICU patients (figure 5D).

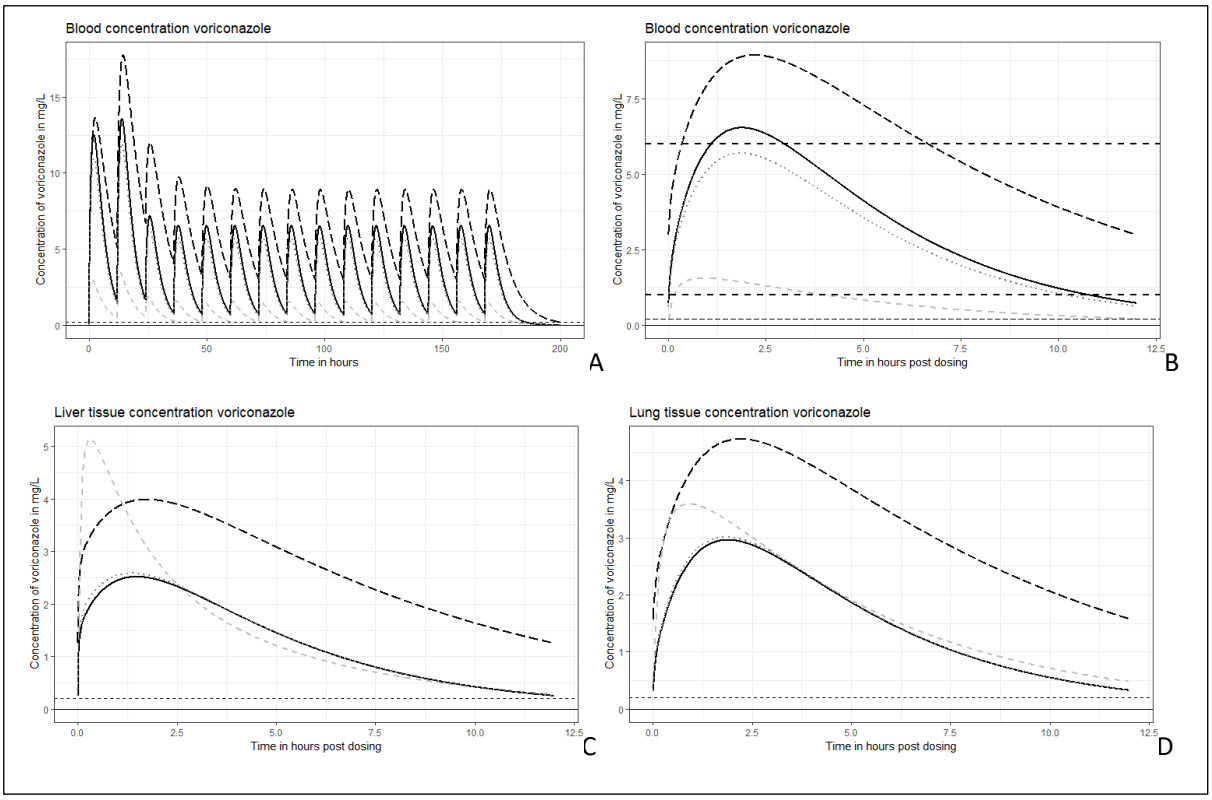


Figure 5| Simulation of voriconazole concentrations with three different albumin concentrations (healthy (solid black), ICU-non-infected (grey solid), DDI (grey dotted) and one CRP elevated patient (black long-dashed)), TDM detection limit is shown as a grey dotted horizontal line at 0.2 mg/L. A) Concentration voriconazole in venous blood compartment with dosing every 12 hours. C_{max} and C_{trough} concentrations of the CRP elevated patient simulations were the highest, followed by healthy/ICU-non-infected and DDI. Where DDI has a C_{trough} of 0.2 mg/L. B) Expansion of one dose at steady state, simulated in hours post-dosing in four different situations. Horizontal black dashed lines represent TDM ranges of 1-6 mg/L. C) Concentration voriconazole in liver tissue in three situations (healthy, ICU-non-infected, ICU-infected, DDI). The liver uptake in healthy and ICU-non-infected are similar. However, liver uptake is increased as a result of DDI an elevated CRP compared to healthy. D) Concentration voriconazole in lung tissue in four situations (healthy, ICU-non-infected, ICU-infected, DDI). The lung uptake in healthy and ICU-non-infected patients are similar. Lung tissue uptake is increased as a result of DDI. ICU-infected patients reached the highest C_{max} concentrations.

The WBPBPK model was applied to predict the posaconazole exposure in our case. The model was able to predict the posaconazole plasma concentrations as shown in figure 1FThe plasma concentrations corresponded to the patient blood concentrations.

DISCUSSION

The model was able to predict whole body distribution of voriconazole and posaconazole over time. Both oral dosing and IV dosing simulations showed similar profiles to literature data[7,15,34,35]. However, oral dosing simulations were over-predicted, this might be due to the absorption rate and bio-availability which could be attributed to both drugs. Voriconazole and posaconazole have a high variability in absorption and

bio-availability, in particular for posaconazole, with a highly variable bioavailability ranging from 8 to 50%[25,39]. Deviations in lung and liver concentrations might be explained by the fact that the decedent patients were all critically ill[36,37]. As our study used the model based on a healthy populations to evaluate the model, we cannot directly compare this to the used literature data. Besides, sample collection in both studies varied in time post dosing and post dying, which might have influenced the tissue concentrations. Nevertheless, all tissue prediction errors fell within the 2-fold ranges.

The four different simulations performed with the whole body PBPK model showed the results matching the hypothesis. The elevated CRP resulted in an increase in total plasma and tissue concentrations. This was expected due to its reducing effect on CYP2C19 iso-enzymes, and therefore a reduced metabolism and clearance. The DDI simulated as a decrease in albumin showed subtherapeutic C_{trough} values in the blood, and an elevated tissue concentration. This was the result of a higher unbound fraction which was able to be metabolized and cleared by the liver and to penetrate tissues where it could bind to albumin, as hypothesized.

In general, only highly protein-bound drugs (>95%) are affected by fluctuating plasma proteins[4]. Voriconazole is a drug with relatively low protein binding (58%)[10]. Therefore, albumin displacement is not expected to have a major clinical impact[10]. However, voriconazole is metabolized mainly by CYP2C19, CYP3A4, and CYP2C9, which are saturable[5,15,20]. As a result, it has non-linear metabolism and non-linear kinetics caused by the lower available albumin to bind to[5,15,20]. Due to the non-linearity of voriconazole and the fact that only unbound drug can be cleared, increased the amount of unbound drug in the body.

During this research, only the effect of albumin binding and CRP on PK were taken into account. Prior studies show that the protein binding rate of voriconazole is influenced by alfa-1-acid glycoprotein (AAG) and albumin binding and by CYP2C19 and CYP3A4 polymorphism[2,5]. Normally, 4.8% of voriconazole binds to AAG, which ranges between 50 to 100 mg/dL in healthy patients, a fraction of the albumin concentrations. However, AAG increases during infection up to 200 mg/dL[2,5]. Besides AAG, CRP also elevates during infection. Studies have shown that elevated CRP levels increased voriconazole C_{trough} values[17]. To wit, CRP causes the synthesis of pro-inflammatory cytokines during infection and inflammation. These cytokines down-regulate gene transcription of CYP2C19. Concequently, the amount

of liver enzymes and their activity is decreased. This results in a decreased metabolism and hence an increase in serum concentrations[5].

Another theory that might explain part of the DDI-mechanism is provided by *Shukla et al*[40]. The article states that subtherapeutic voriconazole concentrations could be cause by the ability of flucloxacillin to induce the pregnane X receptor (PXR). PXR is a nuclear receptor in the gut and the liver and is an important regulator for drug metabolism and efflux. Flucloxacillin binds to PXR and reaches the nucleus, where it co-activates a complex of PXR and retinoid X receptor (RXR). This complex binds to the xenobiotic-responsive enhancer molecule/PXR responsive element (XREM/PXRE) enhancer, which causes upregulation of the CYP3A4 enzymes[41]. This upregulation of CYP3A4 could lead to rapid metabolisation of voriconazole, and might explain the subtherapeutic effects. However, upregulation of the CYP3A4 enzyme usually takes one to two weeks[40]. As the effect of flucloxacillin starts within approximately two days, it is unlikely that the subtherapeutic blood concentrations are caused by this mechanism. Additionally, even if the mechanism was caused by upregulation of enzymes, a peak dose should still be detectable in blood concentrations. Furthermore, other drugs that are concomitantly used and metabolized by CYP3A4 enzymes, remain unchanged during flucloxacillin treatment[7]. It is therefore unlikely that flucloxacillin causes subtherapeutic blood concentrations by the induction of CYP3A4 enzymes.

Studies on CYP3A4 genotyping and the influence on voriconazole concentrations provided by *He et al (2015)* showed that the genotype rs4646437 was related to increased voriconazole plasma concentrations[42]. rs4646437 has the phenotype of poor metabolizer[42–45]. On the other hand, this might indicate that induced CYP3A4 metabolism could result in decreased voriconazole plasma concentrations. About 25% of the European population has this CYP3A4 polymorphism[43]. This might also explain why *Muilwijk et al (2017)* reported that the DDI only occurred in half of the investigated population[7]. The up-regulation of CYP3A4 by the induction of PXR by flucloxacillin and its influence on voriconazole pharmacokinetics should be further investigated.

The lack of experimental data on binding affinity and drug displacement is a limitation of this study. It is currently unknown to which albumin drug-binding pockets posaconazole and voriconazole bind. Moreover, the affinity (K_a/K_d) of both drugs for albumin is unknown. As a consequence, K_d values of voriconazole and

posaconazole were predicted based on albumin concentrations, which makes the model less accurate. In vitro experiments to determine binding places and binding affinity should be conducted to confirm our hypothesis. Currently, it is unknown whether the drugs compete with each other at the same binding pocket. Mostly, drugs with similar physicochemical characteristics can compete with each other to bind to plasma proteins[11]. Voriconazole and flucloxacillin are dissimilar. Flucloxacillin is a hydrophilic drug with a low distribution volume of 17L and is mainly present in the blood compartment. On the contrary, voriconazole is a lipophilic drug with a relatively high distribution volume and therefore high tissue penetration[4,39].

Due to these limitations in the current model, the DDI was simplified by reducing the amount of available albumin to bind to voriconazole and posaconazole. The influence of infection and inflammation, common situations on the ICU, on voriconazole clearance was taken into account by lowering V_{max} of CYP2C19. Future experiments and extension of the mechanistic model to describe the competition for the albumin binding pocket and to describe the CYP3A4 upregulation would contribute to more accurate DDI predictions.

CONCLUSION

In conclusion, the WBPBPK model was able to predict the voriconazole concentration-time profiles in four different patient populations. It showed that voriconazole displacement by flucloxacillin at the albumin binding sites influenced the plasma PK. Higher unbound drug fractions led to increased tissue drug uptake and a decreased plasma concentrations. The model elucidates on the drug-drug interaction mechanism, which has not been reported elsewhere before.

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SUPPLEMENTAL I

Model equations

Rodgers base model

Physiologic equations used to describe physicochemical parameters (Kpu)

1) $\text{Intracellular water} = \frac{1+10^{\text{pKa}-\text{pH}_{\text{iw}}}}{1+10^{\text{pKa}-\text{pH}_{\text{p}}}} * \text{f}_{\text{iw}}$

2) $\text{Extracellular water} = \frac{1+10^{\text{pKa}-\text{pH}_{\text{ew}}}}{1+10^{\text{pKa}-\text{pH}_{\text{p}}}} * \text{f}_{\text{ew}}$

3) $\text{Albumin binding} = \text{Ka}_{\text{alb}} * \frac{[\text{albumin}]_{\text{tissue}}}{[\text{albumin}]_{\text{plasma}}}$

4) $\text{Lipid binding} = \frac{\text{P}*\text{f}_{\text{nl}}+(0.3\text{P}+0.7)*\text{f}_{\text{np}}}{1+10^{\text{pKa}-\text{pH}_{\text{p}}}}$

5) $\text{Ka}_{\text{albumin}} = \left[\frac{1}{\text{F}_{\text{unbound}}} - 1 - \left(\frac{\text{P}*\text{f}_{\text{nl,p}}+(0.3\text{P}+0.7)*\text{f}_{\text{np,p}}}{1+10^{\text{pKa}-\text{pH}_{\text{p}}}}\right) * \frac{1}{[\text{albumin}]_{\text{plasma}}}\right]$

6) $\mathrm{Kp_u} = \left[\left(\frac{1+10^{\mathrm{pKa-pHiw}}}{1+10^{\mathrm{pKa-pHp}}} * \mathrm{fiw}\right) + \mathrm{few} + \left(\frac{\mathrm{P*Fnl,t+(0.3P+0.7)*Fnp,t}}{1+10^{\mathrm{pKa-pHp}}}\right) + (\mathrm{Ka_{albumin}} * [\mathrm{albumin}]_{\mathrm{tissue}})\right]$

7) $\mathrm{KP} = \mathrm{Kp_u} * \mathrm{F_u}$

f_{iw}, f_{ew}, f_{nl} and f_{np} represent fractional tissue volumes of intracellular water, extracellular water, and neutral lipids/phospholipids, respectively. Distribution is pH driven by the use of pH_{iw} and pH_{ew} relative to pH_p, pH intra-cellular, pH extra-cellular, and pH plasma. Which predicts the fraction available un-protonated drug diffusion into cellular parts. pH and f values can be found in table 1. Both octanol:water petition coefficient (P) and vegetable oil:water partition coefficient (Pv) are included for binding affinity to neutral lipids and neutral phospholipids for all tissues and adipose, respectively. A 70% hydrophilic and 30% lipophilic ratio was assumed for neutral lipids and phospholipids, therefore P and Pv are weighted with 0.3. Tissue albumin binding is predominant in tissue distribution and is calculated using the albumin association constant (Ka) and tissue-specific albumin tissue-to-plasma ratio. F_u is the unbound fraction drug and is used to transform the Kp_u to the KP.

WBPBPK model is built using basic PBPK model equations:

Non-eliminating organs:

8) $\mathrm{A_{tissue}} = \mathrm{Q_{tissue}} * \left(\mathrm{C_{artery}} - \frac{\mathrm{C_{tissue}}}{\left(\mathrm{KP_{tissue}}/_{\mathrm{BP}}\right)/\Phi}\right)$

9) $\mathrm{A_{lung}} = \mathrm{Q_{lung}} * \left(\mathrm{C_{vein}} - \frac{\mathrm{C_{lung}}}{\left(\mathrm{KP_{tissue}}/_{\mathrm{BP}}\right)/\Phi}\right)$

10) $\mathrm{A_{vein}} = -\left(\mathrm{Q_{lung}} * \mathrm{C_{vein}}\right) + \sum \mathrm{Q_{tissue}} * \frac{\mathrm{C_{tissue}}}{\left(\mathrm{KP_{tissue}}/_{\mathrm{BP}}\right)/\Phi}$

11) $\mathrm{A_{artery}} = + \left(\mathrm{Q_{lung}} * \frac{\mathrm{C_{lung}}}{\left(\mathrm{KP_{tissue}}/_{\mathrm{BP}}\right)/\Phi}\right) - \sum \mathrm{Q_{tissue}} * \mathrm{C_{artery}}$

A is the amount of drug in a specific compartment at a specific time point. A is calculated using Q, C, KP, BP, and Φ. Q represents tissue-specific flow from and to organs. KP is derived by multiplying Rodgers Kp_u with F_u. C is the concentration in tissue, artery, or vein, calculated by dividing the amount of drug through the organ volume. BP is the blood to plasma ratio and Φ is the tissue to plasma albumin correction factor.

Drug absorption organs

12) $\mathrm{A_{Gutlumen}} = -\mathrm{K_{absorption}} * \mathrm{Dose} * \mathrm{F}$

13) $\mathrm{A_{gut}} = + \mathrm{K_{absorption}} * \mathrm{dose} * \mathrm{F} + \mathrm{Q_{tissue}} * \left(\mathrm{C_{artery}} - \frac{\mathrm{C_{tissue}}}{\left(\mathrm{KP_{tissue}}/_{\mathrm{BP}}\right)/\Phi}\right)$

The drug is orally administered, represented by the gut lumen after which it is distributed to the gut and the rest of the body. Where $K_{absorption}$ is the absorption rate constant, the dose is the administered dose and F is the bio-availability.

Drug elimination organs

$$14)\ A_{liver} = Q_{gu} * \left(\frac{C_{gut}}{\left(KP_{gut}/_{BP}\right)/\Phi}\right) + Q_{spleen} * \left(\frac{C_{spleen}}{\left(KP_{spleen}/_{BP}\right)/\Phi}\right) + Q_{hepatic\ arterie} * C_{arterial} - Q_{liver} * \left(\frac{C_{liver}}{\left(KP_{liver}/_{BP}\right)/\Phi}\right) - CL_{liver} * \left(\frac{F_u * C_{liver}}{\left(KP_{liver}/_{BP}\right)/\Phi}\right)$$

$$15)\ CL_{liver_{voriconazole}} = \frac{\left(\left(\sum_{i=1}^{n} \frac{V_{max}^{i}}{K_m^i + C_{t,u}}\right) * MPPGL * V_{liver} * 1000 * 60 * 1^{-6}\right)}{fumic}$$

$$16)\ A_{kidney} = Q_{kidney} * \left(C_{arterial} - \frac{C_{kidney}}{\left(KP_{kidney}/_{BP}\right)/\Phi}\right) - CL_{kidney} * \left(\frac{F_u * C_{kidney}}{\left(KP_{kidney}/_{BP}\right)/\Phi}\right)$$

The drug is eliminated from the body via the liver and kidneys. Only unbound drug is cleared by both liver and kidney. Therefore, the concentration in the eliminating organ is multiplied by F_u. CL_{liver} and CL_{kidney} represent the drug elimination rates of the liver and kidney, respectively.

Protein binding

$$17)\ C_{unbound} = \frac{1}{2} * \left(C_{total} - K_d - [albumin]_{blood} * \sqrt{(C_{total} - K_d - [albumin]_{blood})^2 + 4 * C_{total} * k_d}\right)$$

$$18)\ F_{unbound} = \frac{C_{unbound}}{C_{total}} * 100\%$$

$$19)\ \Phi = \frac{F_{unbound,healthy}}{F_{unbound,DDI}}$$

The concentration of unbound drug in the vein is calculated by the use of C_{total}, total drug concentration in the vein, K_d, the dissociation constant of the drug for albumin, and the blood albumin concentration. $C_{unbound}$ is used to calculate the fraction of unbound drugs in the vein. Φ is the factor used as a correction factor for voriconazole which can bind to albumin in the tissues. As flucloxacillin does not penetrate tissues, albumin displacement will only take place in the plasma. Therefore, higher unbound fractions lead to more diffusion of voriconazole into tissues, in which it can bind to a higher extent to albumin, for which a factor is used.

SUPPLEMENTAL II - Rscript

```
rm(list=ls())
setwd("M:/Onderzoek/PKPD.NONMEM.IB/imaging.TKI.PK/studenten/Julia/_4 R studio/Voriconazol")

## source PBPK model parameters
source("Final_Parameters_Voriconazole_Posaconazole.R")

## packages
library(tidyverse)
library(ggplot2)
library(deSolve)
library(dplyr)
```

```
library(reshape2)
library(gridExtra)
library(patchwork)
library(zoo)

## bron equations: Elmokadem et al

## Load parameters into the model

parameters <- parameters_base

## PBPK model has initial values
## Set initial values = 0
state <- unlist(c(data.frame(
  A_VEN        = 0,
  A_ART        = 0,
  A_LUNG       = 0,
  A_ADIPOSE    = 0,
  A_HEART      = 0,
  A_BRAIN      = 0,
  A_BONE       = 0,
  A_MUSCLE     = 0,
  A_KIDNEY     = 0,
  A_GUT        = 0,
  A_GUTLUMEN   = 0,
  A_SPLEEN     = 0,
  A_REST       = 0,
  A_LIVER      = 0

)))


  ## ----- VORICONAZOLE ---- ##

## PBPK model met eigen KPU waarden
PBPK_Model_Voriconazole_healthy <- function(t, state, parameters){
  with(as.list(c(state, parameters)),{

    ## ODE
    ## Calculation of tissue drug concentrations (mg/L) -> wordt niet gebruikt
    Clung     = A_LUNG     / Vlu
    Cadipose  = A_ADIPOSE  / Vad
    Cheart    = A_HEART    / Vhe
    Cbrain    = A_BRAIN    / Vbr
    Cbone     = A_BONE     / Vbo
    Cmuscle   = A_MUSCLE   / Vmu
    Ckidney   = A_KIDNEY   / Vki
    Cgut      = A_GUT      / VguWall
    Cgutlumen = A_GUTLUMEN / VguLumen
    Cspleen   = A_SPLEEN   / Vsp
    Crest     = A_REST     / Vre
    Carterial = A_ART      / Var
    Cvenous   = A_VEN      / Vve
    Cliver    = A_LIVER    / Vli
```

```
  ## LIver clearance Fang QI et al
  CL_int_QI  = ((Vmax_2C19/(Km_2C19 +( (A_LIVER / Vli) * fup))) + (Vmax_3A4/(Km_3A4 + ( (A_LIVER /
Vli) * fup))) + (Vmax_2C9/(Km_2C9 + ( (A_LIVER / Vli) * fup))))
  CL_pb_QI   = (BP * Qli * ((CL_int_QI)/(CL_int_QI+(Qli*BP/fup))))
  CL_Li_new  = (((CL_int_QI)*MPPGL*Vli*1000*60*(1*10^-6)) / fumic)          ## (L/h) hepatic clearance


  ##ODE
  dA_LUNG    = ((Qlu * (A_VEN / Vve)) - (Qlu * ((A_LUNG    / Vlu)  /(KPlu/BP))))
  dA_ADIPOSE  = ((Qad * (A_ART / Var)) - (Qad * ((A_ADIPOSE / Vad)  /(KPad/BP))))
  dA_HEART   = ((Qhe * (A_ART / Var)) - (Qhe * ((A_HEART   / Vhe)  /(KPhe/BP))))
  dA_BRAIN   = ((Qbr * (A_ART / Var)) - (Qbr * ((A_BRAIN   / Vbr)  /(KPbr/BP))))
  dA_BONE    = ((Qbo * (A_ART / Var)) - (Qbo * ((A_BONE    / Vbo)  /(KPbo/BP))))
  dA_MUSCLE  = ((Qmu * (A_ART / Var)) - (Qmu * ((A_MUSCLE  / Vmu)  /(KPmu/BP))))
  dA_SPLEEN  = ((Qsp * (A_ART / Var)) - (Qsp * ((A_SPLEEN  / Vsp)  /(KPsp/BP))))
  dA_REST    = ((Qre * (A_ART / Var)) - (Qre * ((A_REST    / Vre)  /(KPre/BP))))


  dA_GUTLUMEN = ((0.96*(A_GUTLUMEN))* - 0.849)
  dA_GUT     = (+(Qgu * (A_ART / Var)) - (Qgu * ((A_GUT / VguWall) / (KPgu/BP)))  + ((0.849*
(A_GUTLUMEN / VguWall))))


  dA_LIVER   = ((+ Qgu * ((A_GUT / VguWall)/(KPgu/BP))) +  (Qsp *((A_SPLEEN / Vsp)/(KPsp/BP))) +
(Qha*(A_ART / Var)) - (Qli*((A_LIVER / Vli)/(KPli/BP))) - (CL_Li_new * ( ((A_LIVER / Vli) * fup)/(KPli/BP))))
  dA_KIDNEY  = ((Qki * (A_ART / Var)) - (Qki * ((A_KIDNEY  / Vki)  /(KPki/BP)))   - (CL_ki * (((A_KIDNEY /
Vki)*fup)/(KPki/BP))))


  dA_VEN     = (- (Qlu * (A_VEN     / Vve))
           + (Qad * ((A_ADIPOSE / Vad)   /(KPad/BP)))
           + (Qhe * ((A_HEART   / Vhe)   /(KPhe/BP)))
           + (Qbr * ((A_BRAIN   / Vbr)   /(KPbr/BP)))
           + (Qbo * ((A_BONE    / Vbo)   /(KPbo/BP)))
           + (Qmu * ((A_MUSCLE  / Vmu)   /(KPmu/BP)))
           + (Qki * ((A_KIDNEY  / Vki)   /(KPki/BP)))
           + (Qli * ((A_LIVER   / Vli)   /(KPli/BP)))
           + (Qre * ((A_REST    / Vre)   /(KPre/BP))))

  dA_ART     = (+ (Qlu * ((A_LUNG    / Vlu)   /(KPlu/BP)))
           - (Qad * (A_ART / Var))
           - (Qhe * (A_ART / Var))
           - (Qbr * (A_ART / Var))
           - (Qbo * (A_ART / Var))
           - (Qmu * (A_ART / Var))
           - (Qki * (A_ART / Var))
           - (Qgu * (A_ART / Var))
           - (Qsp * (A_ART / Var))
           - (Qha * (A_ART / Var))
           - (Qre * (A_ART / Var)))


  ## Table
```

```
  capture_CP = Cvenous/BP

  list(c(
   dA_VEN,
   dA_ART,
   dA_LUNG,
   dA_ADIPOSE,
   dA_HEART,
   dA_BRAIN,
   dA_BONE,
   dA_MUSCLE,
   dA_KIDNEY,
   dA_GUT,
   dA_GUTLUMEN,
   dA_SPLEEN,
   dA_REST,
   dA_LIVER
  ))
 })
}



PBPK_Model_Voriconazole_icu <- function(t, state, parameters){
 with(as.list(c(state, parameters)),{

  ## ODE
  ## Calculation of tissue drug concentrations (mg/L) -> wordt niet gebruikt
  Clung     = A_LUNG     / Vlu
  Cadipose  = A_ADIPOSE  / Vad
  Cheart    = A_HEART    / Vhe
  Cbrain    = A_BRAIN    / Vbr
  Cbone     = A_BONE     / Vbo
  Cmuscle   = A_MUSCLE   / Vmu
  Ckidney   = A_KIDNEY   / Vki
  Cgut      = A_GUT      / VguWall
  Cgutlumen = A_GUTLUMEN / VguLumen
  Cspleen   = A_SPLEEN   / Vsp
  Crest     = A_REST     / Vre
  Carterial = A_ART      / Var
  Cvenous   = A_VEN      / Vve
  Cliver    = A_LIVER    / Vli

  ## LIver clearance Fang QI et al
  CL_int_QI = ((Vmax_2C19/(Km_2C19 +( (A_LIVER / Vli) * fup_icu))) + (Vmax_3A4/(Km_3A4 + ( (A_LIVER
/ Vli) * fup_icu))) + (Vmax_2C9/(Km_2C9 + ( (A_LIVER / Vli) * fup_icu))))
  CL_pb_QI  = (BP * Qli * ((CL_int_QI)/(CL_int_QI+(Qli*BP/fup_icu))))
  CL_Li_new  = (((CL_int_QI)*MPPGL*Vli*1000*60*(1*10^-6)) / fumic)          ## (L/h) hepatic clearance

  ##ODE
  dA_LUNG    = ((Qlu * (A_VEN / Vve)) - (Qlu * ((A_LUNG    / Vlu)  /(KPlu_icu/BP))))
  dA_ADIPOSE  = ((Qad * (A_ART / Var)) - (Qad * ((A_ADIPOSE / Vad)  /(KPad_icu/BP))))
  dA_HEART    = ((Qhe * (A_ART / Var)) - (Qhe * ((A_HEART   / Vhe)  /(KPhe_icu/BP))))
  dA_BRAIN    = ((Qbr * (A_ART / Var)) - (Qbr * ((A_BRAIN   / Vbr)  /(KPbr_icu/BP))))
```

```
  dA_BONE    = ((Qbo * (A_ART / Var)) - (Qbo * ((A_BONE    / Vbo)  /(KPbo_icu/BP))))
  dA_MUSCLE  = ((Qmu * (A_ART / Var)) - (Qmu * ((A_MUSCLE  / Vmu)  /(KPmu_icu/BP))))
  dA_SPLEEN  = ((Qsp * (A_ART / Var)) - (Qsp * ((A_SPLEEN  / Vsp)  /(KPsp_icu/BP))))
  dA_REST    = ((Qre * (A_ART / Var)) - (Qre * ((A_REST    / Vre)  /(KPre_icu/BP))))


  dA_GUTLUMEN = ((0.96*(A_GUTLUMEN))* - 0.849)
  dA_GUT     = (+(Qgu * (A_ART / Var)) - (Qgu * ((A_GUT / VguWall) / (KPgu_icu/BP)))  + ((0.849*
(A_GUTLUMEN / VguWall))))


  dA_LIVER   = ((+ Qgu * ((A_GUT / VguWall)/(KPgu_icu/BP))) +  (Qsp *((A_SPLEEN / Vsp)/(KPsp_icu/BP)))
+ (Qha*(A_ART / Var)) - (Qli*((A_LIVER / Vli)/(KPli_icu/BP))) - (CL_Li_new * ( ((A_LIVER / Vli) *
fup_icu)/(KPli_icu/BP))))
  dA_KIDNEY  = ((Qki * (A_ART / Var)) - (Qki * ((A_KIDNEY  / Vki)  /(KPki_icu/BP)))   - (CL_ki * (((A_KIDNEY
/ Vki)*fup_icu)/(KPki_icu/BP))))


  dA_VEN     = (- (Qlu * (A_VEN     / Vve))
           + (Qad * ((A_ADIPOSE / Vad)   /(KPad_icu/BP)))
           + (Qhe * ((A_HEART   / Vhe)   /(KPhe_icu/BP)))
           + (Qbr * ((A_BRAIN   / Vbr)   /(KPbr_icu/BP)))
           + (Qbo * ((A_BONE    / Vbo)   /(KPbo_icu/BP)))
           + (Qmu * ((A_MUSCLE  / Vmu)   /(KPmu_icu/BP)))
           + (Qki * ((A_KIDNEY  / Vki)   /(KPki_icu/BP)))
           + (Qli * ((A_LIVER   / Vli)   /(KPli_icu/BP)))
           + (Qre * ((A_REST    / Vre)   /(KPre_icu/BP))))

  dA_ART     = (+ (Qlu * ((A_LUNG    / Vlu)   /(KPlu_icu/BP)))
           - (Qad * (A_ART / Var))
           - (Qhe * (A_ART / Var))
           - (Qbr * (A_ART / Var))
           - (Qbo * (A_ART / Var))
           - (Qmu * (A_ART / Var))
           - (Qki * (A_ART / Var))
           - (Qgu * (A_ART / Var))
           - (Qsp * (A_ART / Var))
           - (Qha * (A_ART / Var))
           - (Qre * (A_ART / Var)))


  ## Table
  capture_CP = Cvenous/BP

  list(c(
   dA_VEN,
   dA_ART,
   dA_LUNG,
   dA_ADIPOSE,
   dA_HEART,
   dA_BRAIN,
   dA_BONE,
   dA_MUSCLE,
   dA_KIDNEY,
```

```
    dA_GUT,
    dA_GUTLUMEN,
    dA_SPLEEN,
    dA_REST,
    dA_LIVER
   ))
  })
}



PBPK_Model_Voriconazole_CRP <- function(t, state, parameters){
  with(as.list(c(state, parameters)),{

   ## ODE
   ## Calculation of tissue drug concentrations (mg/L) -> wordt niet gebruikt
   Clung     = A_LUNG     / Vlu
   Cadipose   = A_ADIPOSE  / Vad
   Cheart     = A_HEART    / Vhe
   Cbrain     = A_BRAIN    / Vbr
   Cbone      = A_BONE     / Vbo
   Cmuscle    = A_MUSCLE   / Vmu
   Ckidney    = A_KIDNEY   / Vki
   Cgut       = A_GUT      / VguWall
   Cgutlumen  = A_GUTLUMEN / VguLumen
   Cspleen    = A_SPLEEN   / Vsp
   Crest      = A_REST     / Vre
   Carterial  = A_ART      / Var
   Cvenous    = A_VEN      / Vve
   Cliver     = A_LIVER    / Vli

   ## LIver clearance Fang QI et al
   CL_CRP     = (((Vmax_2C19/2)/(Km_2C19 +( (A_LIVER / Vli) * fup_icu))) + (Vmax_3A4/(Km_3A4 + (
(A_LIVER / Vli) * fup_icu))) + (Vmax_2C9/(Km_2C9 + ( (A_LIVER / Vli) * fup_icu))))

   CL_LI_CRP  = (((CL_CRP)*MPPGL*Vli*1000*60*(1*10^-6)) / fumic)

   ##ODE
   dA_LUNG     = ((Qlu * (A_VEN / Vve)) - (Qlu * ((A_LUNG    / Vlu)  /(KPlu_icu/BP))))
   dA_ADIPOSE  = ((Qad * (A_ART / Var)) - (Qad * ((A_ADIPOSE / Vad)  /(KPad_icu/BP))))
   dA_HEART    = ((Qhe * (A_ART / Var)) - (Qhe * ((A_HEART   / Vhe)  /(KPhe_icu/BP))))
   dA_BRAIN    = ((Qbr * (A_ART / Var)) - (Qbr * ((A_BRAIN   / Vbr)  /(KPbr_icu/BP))))
   dA_BONE     = ((Qbo * (A_ART / Var)) - (Qbo * ((A_BONE    / Vbo)  /(KPbo_icu/BP))))
   dA_MUSCLE   = ((Qmu * (A_ART / Var)) - (Qmu * ((A_MUSCLE  / Vmu)  /(KPmu_icu/BP))))
   dA_SPLEEN   = ((Qsp * (A_ART / Var)) - (Qsp * ((A_SPLEEN  / Vsp)  /(KPsp_icu/BP))))
   dA_REST     = ((Qre * (A_ART / Var)) - (Qre * ((A_REST    / Vre)  /(KPre_icu/BP))))


   dA_GUTLUMEN = ((0.96*(A_GUTLUMEN))* - 0.849)
   dA_GUT      = (+(Qgu * (A_ART / Var)) - (Qgu * ((A_GUT / VguWall) / (KPgu_icu/BP)))  + ((0.849*
(A_GUTLUMEN / VguWall))))
```

```
   dA_LIVER    = ((+ Qgu * ((A_GUT / VguWall)/(KPgu_icu/BP))) +  (Qsp *((A_SPLEEN / Vsp)/(KPsp_icu/BP)))
+ (Qha*(A_ART / Var)) - (Qli*((A_LIVER / Vli)/(KPli_icu/BP))) - (CL_LI_CRP * ( ((A_LIVER / Vli) *
fup_icu)/(KPli_icu/BP))))
   dA_KIDNEY   = ((Qki * (A_ART / Var)) - (Qki * ((A_KIDNEY  / Vki)  /(KPki_icu/BP)))   - (CL_ki * (((A_KIDNEY
/ Vki)*fup_icu)/(KPki_icu/BP))))


   dA_VEN     = (- (Qlu * (A_VEN      / Vve))
              + (Qad * ((A_ADIPOSE / Vad)   /(KPad_icu/BP)))
              + (Qhe * ((A_HEART   / Vhe)   /(KPhe_icu/BP)))
              + (Qbr * ((A_BRAIN   / Vbr)   /(KPbr_icu/BP)))
              + (Qbo * ((A_BONE    / Vbo)   /(KPbo_icu/BP)))
              + (Qmu * ((A_MUSCLE  / Vmu)   /(KPmu_icu/BP)))
              + (Qki * ((A_KIDNEY  / Vki)   /(KPki_icu/BP)))
              + (Qli * ((A_LIVER   / Vli)   /(KPli_icu/BP)))
              + (Qre * ((A_REST    / Vre)   /(KPre_icu/BP))))

   dA_ART     = (+ (Qlu * ((A_LUNG    / Vlu)   /(KPlu_icu/BP)))
              - (Qad * (A_ART / Var))
              - (Qhe * (A_ART / Var))
              - (Qbr * (A_ART / Var))
              - (Qbo * (A_ART / Var))
              - (Qmu * (A_ART / Var))
              - (Qki * (A_ART / Var))
              - (Qgu * (A_ART / Var))
              - (Qsp * (A_ART / Var))
              - (Qha * (A_ART / Var))
              - (Qre * (A_ART / Var)))


   ## Table
   capture_CP = Cvenous/BP

   list(c(
    dA_VEN,
    dA_ART,
    dA_LUNG,
    dA_ADIPOSE,
    dA_HEART,
    dA_BRAIN,
    dA_BONE,
    dA_MUSCLE,
    dA_KIDNEY,
    dA_GUT,
    dA_GUTLUMEN,
    dA_SPLEEN,
    dA_REST,
    dA_LIVER
   ))
  })
}


PBPK_Model_Voriconazole_icu <- function(t, state, parameters){
```

```
 with(as.list(c(state, parameters)),{

   ## ODE
   ## Calculation of tissue drug concentrations (mg/L) -> wordt niet gebruikt
   Clung      = A_LUNG     / Vlu
   Cadipose   = A_ADIPOSE  / Vad
   Cheart     = A_HEART    / Vhe
   Cbrain     = A_BRAIN    / Vbr
   Cbone      = A_BONE     / Vbo
   Cmuscle    = A_MUSCLE   / Vmu
   Ckidney    = A_KIDNEY   / Vki
   Cgut       = A_GUT      / VguWall
   Cgutlumen  = A_GUTLUMEN / VguLumen
   Cspleen    = A_SPLEEN   / Vsp
   Crest      = A_REST     / Vre
   Carterial  = A_ART      / Var
   Cvenous    = A_VEN      / Vve
   Cliver     = A_LIVER    / Vli

   ## LIver clearance Fang QI et al
   CL_int_QI = ((Vmax_2C19/(Km_2C19 +( (A_LIVER / Vli) * fup_icu))) + (Vmax_3A4/(Km_3A4 + ( (A_LIVER
/ Vli) * fup_icu))) + (Vmax_2C9/(Km_2C9 + ( (A_LIVER / Vli) * fup_icu))))
   CL_pb_QI  = (BP * Qli * ((CL_int_QI)/(CL_int_QI+(Qli*BP/fup_icu))))
   CL_Li_new  = (((CL_int_QI)*MPPGL*Vli*1000*60*(1*10^-6)) / fumic)          ## (L/h) hepatic clearance

   ##ODE
   dA_LUNG     = ((Qlu * (A_VEN / Vve)) - (Qlu * ((A_LUNG    / Vlu)  /(KPlu_icu/BP))))
   dA_ADIPOSE  = ((Qad * (A_ART / Var)) - (Qad * ((A_ADIPOSE / Vad)  /(KPad_icu/BP))))
   dA_HEART    = ((Qhe * (A_ART / Var)) - (Qhe * ((A_HEART   / Vhe)  /(KPhe_icu/BP))))
   dA_BRAIN    = ((Qbr * (A_ART / Var)) - (Qbr * ((A_BRAIN   / Vbr)  /(KPbr_icu/BP))))
   dA_BONE     = ((Qbo * (A_ART / Var)) - (Qbo * ((A_BONE    / Vbo)  /(KPbo_icu/BP))))
   dA_MUSCLE   = ((Qmu * (A_ART / Var)) - (Qmu * ((A_MUSCLE  / Vmu)  /(KPmu_icu/BP))))
   dA_SPLEEN   = ((Qsp * (A_ART / Var)) - (Qsp * ((A_SPLEEN  / Vsp)  /(KPsp_icu/BP))))
   dA_REST     = ((Qre * (A_ART / Var)) - (Qre * ((A_REST    / Vre)  /(KPre_icu/BP))))


   dA_GUTLUMEN = ((0.96*(A_GUTLUMEN))* - 0.849)
   dA_GUT      = (+(Qgu * (A_ART / Var)) - (Qgu * ((A_GUT / VguWall) / (KPgu_icu/BP)))  + ((0.849*
(A_GUTLUMEN / VguWall))))


   dA_LIVER    = ((+ Qgu * ((A_GUT / VguWall)/(KPgu_icu/BP))) +  (Qsp *((A_SPLEEN / Vsp)/(KPsp_icu/BP)))
+ (Qha*(A_ART / Var)) - (Qli*((A_LIVER / Vli)/(KPli_icu/BP))) - (CL_Li_new * ( ((A_LIVER / Vli) *
fup_icu)/(KPli_icu/BP))))
   dA_KIDNEY   = ((Qki * (A_ART / Var)) - (Qki * ((A_KIDNEY  / Vki)  /(KPki_icu/BP)))   - (CL_ki * (((A_KIDNEY
/ Vki)*fup_icu)/(KPki_icu/BP))))


   dA_VEN      = (- (Qlu * (A_VEN      / Vve))
               + (Qad * ((A_ADIPOSE / Vad)   /(KPad_icu/BP)))
               + (Qhe * ((A_HEART   / Vhe)   /(KPhe_icu/BP)))
               + (Qbr * ((A_BRAIN   / Vbr)   /(KPbr_icu/BP)))
               + (Qbo * ((A_BONE    / Vbo)   /(KPbo_icu/BP)))
               + (Qmu * ((A_MUSCLE  / Vmu)   /(KPmu_icu/BP)))
```

```
            + (Qki * ((A_KIDNEY  / Vki)   /(KPki_icu/BP)))
            + (Qli * ((A_LIVER   / Vli)   /(KPli_icu/BP)))
            + (Qre * ((A_REST    / Vre)   /(KPre_icu/BP))))

  dA_ART     = (+ (Qlu * ((A_LUNG    / Vlu)   /(KPlu_icu/BP)))
            - (Qad * (A_ART / Var))
            - (Qhe * (A_ART / Var))
            - (Qbr * (A_ART / Var))
            - (Qbo * (A_ART / Var))
            - (Qmu * (A_ART / Var))
            - (Qki * (A_ART / Var))
            - (Qgu * (A_ART / Var))
            - (Qsp * (A_ART / Var))
            - (Qha * (A_ART / Var))
            - (Qre * (A_ART / Var)))


  ## Table
  capture_CP = Cvenous/BP

  list(c(
    dA_VEN,
    dA_ART,
    dA_LUNG,
    dA_ADIPOSE,
    dA_HEART,
    dA_BRAIN,
    dA_BONE,
    dA_MUSCLE,
    dA_KIDNEY,
    dA_GUT,
    dA_GUTLUMEN,
    dA_SPLEEN,
    dA_REST,
    dA_LIVER
  ))
 })
}


PBPK_Model_Voriconazole_ddi <- function(t, state, parameters){
 with(as.list(c(state, parameters)),{

  ## ODE
  ## Calculation of tissue drug concentrations (mg/L) -> wordt niet gebruikt
  Clung     = A_LUNG     / Vlu
  Cadipose  = A_ADIPOSE  / Vad
  Cheart    = A_HEART    / Vhe
  Cbrain    = A_BRAIN    / Vbr
  Cbone     = A_BONE     / Vbo
  Cmuscle   = A_MUSCLE   / Vmu
  Ckidney   = A_KIDNEY   / Vki
  Cgut      = A_GUT      / VguWall
  Cgutlumen = A_GUTLUMEN / VguLumen
```

```
  Cspleen    = A_SPLEEN   / Vsp
  Crest      = A_REST     / Vre
  Carterial  = A_ART      / Var
  Cvenous    = A_VEN      / Vve
  Cliver     = A_LIVER    / Vli

  ## LIver clearance Fang QI et al
  CL_int_QI = ((Vmax_2C19/(Km_2C19 +( (A_LIVER / Vli) * fup_ddi))) + (Vmax_3A4/(Km_3A4 + ( (A_LIVER
/ Vli) * fup_ddi))) + (Vmax_2C9/(Km_2C9 + ( (A_LIVER / Vli) * fup_ddi))))
  CL_pb_QI  = (BP * Qli * ((CL_int_QI)/(CL_int_QI+(Qli*BP/fup_ddi))))
  CL_Li_new  = (((CL_int_QI)*MPPGL*Vli*1000*60*(1*10^-6)) / fumic)          ## (L/h) hepatic clearance

  ##ODE
  dA_LUNG    = ((Qlu * (A_VEN / Vve)) - (Qlu * ((A_LUNG    / Vlu)  /(kplu/BP)/ Co_Fa )))
  dA_ADIPOSE  = ((Qad * (A_ART / Var)) - (Qad * ((A_ADIPOSE / Vad)  /(kpad/BP)/ Co_Fa )))
  dA_HEART   = ((Qhe * (A_ART / Var)) - (Qhe * ((A_HEART   / Vhe)  /(kphe/BP)/ Co_Fa )))
  dA_BRAIN   = ((Qbr * (A_ART / Var)) - (Qbr * ((A_BRAIN   / Vbr)  /(kpbr/BP)/ Co_Fa )))
  dA_BONE    = ((Qbo * (A_ART / Var)) - (Qbo * ((A_BONE    / Vbo)  /(kpbo/BP)/ Co_Fa )))
  dA_MUSCLE  = ((Qmu * (A_ART / Var)) - (Qmu * ((A_MUSCLE  / Vmu)  /(kpmu/BP)/ Co_Fa )))
  dA_SPLEEN  = ((Qsp * (A_ART / Var)) - (Qsp * ((A_SPLEEN  / Vsp)  /(kpsp/BP)/ Co_Fa )))
  dA_REST    = ((Qre * (A_ART / Var)) - (Qre * ((A_REST    / Vre)  /(kpre/BP)/ Co_Fa )))


  dA_GUTLUMEN = ((0.96*(A_GUTLUMEN))* - 0.849)
  dA_GUT     = (+(Qgu * (A_ART / Var)) - (Qgu * ((A_GUT / VguWall) / (kpgu/BP)/ Co_Fa ))  + ((0.849*
(A_GUTLUMEN / VguWall))))


  dA_LIVER   = ((+ Qgu * ((A_GUT / VguWall)/(kpgu/BP)/ Co_Fa )) +  (Qsp *((A_SPLEEN / Vsp)/(kpsp/BP)/
Co_Fa)) + (Qha*(A_ART / Var)) - (Qli*((A_LIVER / Vli)/(kpli/BP)/ Co_Fa)) - (CL_Li_new * ( ((A_LIVER / Vli) *
fup_ddi)/(kpli/BP))))
  dA_KIDNEY  = ((Qki * (A_ART / Var)) - (Qki * ((A_KIDNEY  / Vki)  /(kpki/BP)/ Co_Fa ))  - (CL_ki *
(((A_KIDNEY / Vki)*fup_ddi)/(kpki/BP))))


  dA_VEN     = (- (Qlu * (A_VEN     / Vve))
           + (Qad * ((A_ADIPOSE / Vad)  /(kpad/BP)/ Co_Fa))
           + (Qhe * ((A_HEART   / Vhe)  /(kphe/BP)/ Co_Fa))
           + (Qbr * ((A_BRAIN   / Vbr)  /(kpbr/BP)/ Co_Fa))
           + (Qbo * ((A_BONE    / Vbo)  /(kpbo/BP)/ Co_Fa))
           + (Qmu * ((A_MUSCLE  / Vmu)  /(kpmu/BP)/ Co_Fa))
           + (Qki * ((A_KIDNEY  / Vki)  /(kpki/BP)/ Co_Fa))
           + (Qli * ((A_LIVER   / Vli)  /(kpli/BP)/ Co_Fa))
           + (Qre * ((A_REST    / Vre)  /(kpre/BP)/ Co_Fa)))

  dA_ART     = (+ (Qlu * ((A_LUNG    / Vlu)  /(kplu/BP)/ Co_Fa))
           - (Qad * (A_ART / Var))
           - (Qhe * (A_ART / Var))
           - (Qbr * (A_ART / Var))
           - (Qbo * (A_ART / Var))
           - (Qmu * (A_ART / Var))
           - (Qki * (A_ART / Var))
           - (Qgu * (A_ART / Var))
           - (Qsp * (A_ART / Var))
```

```
            - (Qha * (A_ART / Var))
            - (Qre * (A_ART / Var)))


  ## Table
  capture_CP = Cvenous/BP

  list(c(
   dA_VEN,
   dA_ART,
   dA_LUNG,
   dA_ADIPOSE,
   dA_HEART,
   dA_BRAIN,
   dA_BONE,
   dA_MUSCLE,
   dA_KIDNEY,
   dA_GUT,
   dA_GUTLUMEN,
   dA_SPLEEN,
   dA_REST,
   dA_LIVER
  ))
 })
}



 ## ---- SIMULATIONS ---- ##

## Simulation in moles
## set time regimen   time is in minutes
time <- seq(0, 500, by = 0.01)
LoadingDose <- data.frame(var = "A_GUTLUMEN",    ## location of drug drop
                  time = c(0, 12),       ## time regimen
                  value = (0.400/349.3) , ## dose in mole
                  method = "add")        ## add method
Dose       <- data.frame(var = "A_GUTLUMEN",
                  time = c(24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168),
                  value = (0.200/349.3),
                  method = "add")
dosing     <- rbind(LoadingDose, Dose)          ## combining loading dose and dose
dosing     <- dosing[order(dosing$time),]       ## setting right order
Events     <- list(data=dosing)               ## as list, as event



#Simulation Voriconazole
Simulation_moles <- ode(y= state, times = time, func = PBPK_Model_Voriconazole_healthy, parms =
parameters, events = Events)   ## Simulation
Simulation_moles <- as.data.frame(Simulation_moles)   # ODE uitkomsten als dataframe

simulation <- Simulation_moles[,c(-12)]             # Data-frame without gutlumen
```

```
Simulation_moles$A_tot_body <- rowSums(Simulation_moles[2:15])  # addition of a total body colum to sum up total body amount



## Simulation in miligrams Voriconazole

timeMG <- seq(0, 500, by = 0.01)
LoadingDoseMG <- data.frame(var = "A_GUTLUMEN",
                  time = c(0, 12),
                  value = (400) ,  ## 6 mg/kg at 0 and 12 h (438)
                  method = "add")
DoseMG       <- data.frame(var = "A_GUTLUMEN",
                  time = c(24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168),
                  value = (200),   ## 4 mg/kg every 12 h (292)
                  method = "add")
dosingMG     <- rbind(LoadingDoseMG, DoseMG)
EventsMG     <- list(data=dosingMG)

# simulation
Simulation_mg <- ode(y= state, times = timeMG, func = PBPK_Model_Voriconazole_healthy, parms = parameters, events = EventsMG)   ## Simulation in MG
Simulation_mg <- as.data.frame(Simulation_mg)              # ODE uitkomsten als dataframe

simulation_mg <- Simulation_mg[,c(-12)]                    # Dataframe without gutlumen
Simulation_mg$A_tot_body <- rowSums(simulation_mg[2:14])      # dataframe with total body (with gutlumen)
Simulation_mg$A_tot_body_Gut <- rowSums(Simulation_mg[2:15])  # dataframe with total body without gutlumen



## simulation ICU
Simulation_ICU <- ode(y= state, times = timeMG, func = PBPK_Model_Voriconazole_icu, parms = parameters, events = EventsMG)   ## Simulation in MG
Simulation_ICU <- as.data.frame(Simulation_ICU)

## simulation DDI
Simulation_DDI <- ode(y= state, times = timeMG, func = PBPK_Model_Voriconazole_ddi, parms = parameters, events = EventsMG)   ## Simulation in MG
Simulation_DDI <- as.data.frame(Simulation_DDI)

## Simulation CRP
Simulation_CRP <- ode(y= state, times = timeMG, func = PBPK_Model_Voriconazole_CRP, parms = parameters, events = EventsMG)   ## Simulation in MG
Simulation_CRP <- as.data.frame(Simulation_CRP)



    ## -----  POSACONAZOLE  ----- ##
```

```
## PBPK model met eigen KPU waarden
PBPK_Model_Posaconazole <- function(t, state, parameters){
  with(as.list(c(state, parameters)),{

    ## ODE
    ## Calculation of tissue drug concentrations (mg/L)
    Clung      = A_LUNG     / Vlu
    Cadipose   = A_ADIPOSE  / Vad
    Cheart     = A_HEART    / Vhe
    Cbrain     = A_BRAIN    / Vbr
    Cbone      = A_BONE     / Vbo
    Cmuscle    = A_MUSCLE   / Vmu
    Ckidney    = A_KIDNEY   / Vki
    Cgut       = A_GUT      / VguWall
    Cgutlumen  = A_GUTLUMEN / VguLumen
    Cspleen    = A_SPLEEN   / Vsp
    Crest      = A_REST     / Vre
    Carterial  = A_ART      / Var
    Cvenous    = A_VEN      / Vve
    Cliver     = A_LIVER    / Vli



    ##ODE
    dA_LUNG     = ((Qlu * (A_VEN / Vve)) - (Qlu * ((A_LUNG    / Vlu)/(KPluPos/BP))))
    dA_ADIPOSE  = ((Qad * (A_ART / Var)) - (Qad * ((A_ADIPOSE / Vad)/(KPadPos/BP))))
    dA_HEART    = ((Qhe * (A_ART / Var)) - (Qhe * ((A_HEART   / Vhe)/(KPhePos/BP))))
    dA_BRAIN    = ((Qbr * (A_ART / Var)) - (Qbr * ((A_BRAIN   / Vbr)/(KPbrPos/BP))))
    dA_BONE     = ((Qbo * (A_ART / Var)) - (Qbo * ((A_BONE    / Vbo)/(KPboPos/BP))))
    dA_MUSCLE   = ((Qmu * (A_ART / Var)) - (Qmu * ((A_MUSCLE  / Vmu)/(KPmuPos/BP))))
    dA_KIDNEY   = ((Qki * (A_ART / Var)) - (Qki * ((A_KIDNEY  / Vki)/(KPkiPos/BP))))
    dA_SPLEEN   = ((Qsp * (A_ART / Var)) - (Qsp * ((A_SPLEEN  / Vsp)/(KPspPos/BP))))
    dA_REST     = ((Qre * (A_ART / Var)) - (Qre * ((A_REST    / Vre)/(KPrePos/BP))))

    dA_GUTLUMEN = (- 0.56 * (A_GUTLUMEN*0.08))
    dA_GUT      = ((Qgu * (A_ART / Var)) - (Qgu * ((A_GUT / VguWall)      /(KPguPos/BP))) +
(0.56*(A_GUTLUMEN / VguLumen)*0.08))
    dA_LIVER    = ((+ (Qgu * ((A_GUT / VguWall)      /(KPguPos/BP))) + (Qsp * ((A_SPLEEN / Vsp)
/(KPspPos/BP)))) + (Qha*(A_ART / Var)) - (Qli*((A_LIVER / Vli)/(KPliPos/BP))) - ( Pos_CL_pop * (((A_LIVER /
Vli)*Pos_fup)/(KPliPos/BP))))

    dA_VEN      = (- (Qlu * (A_VEN / Vve))
                + (Qad * ((A_ADIPOSE / Vad)/(KPadPos/BP)))
                + (Qhe * ((A_HEART   / Vhe)/(KPhePos/BP)))
                + (Qbr * ((A_BRAIN   / Vbr)/(KPbrPos/BP)))
                + (Qbo * ((A_BONE    / Vbo)/(KPboPos/BP)))
                + (Qmu * ((A_MUSCLE  / Vmu)/(KPmuPos/BP)))
                + (Qki * ((A_KIDNEY  / Vki)/(KPkiPos/BP)))
                + (Qli * ((A_LIVER   / Vli)/(KPliPos/BP)))
                + (Qre * ((A_REST    / Vre)/(KPrePos/BP))))

    dA_ART      = (+ (Qlu * ((A_LUNG / Vlu)/(KPluPos/BP)))
                - (Qad * (A_ART / Var))
                - (Qhe * (A_ART / Var))
```

```
            - (Qbr * (A_ART / Var))
            - (Qbo * (A_ART / Var))
            - (Qmu * (A_ART / Var))
            - (Qki * (A_ART / Var))
            - (Qgu * (A_ART / Var))
            - (Qsp * (A_ART / Var))
            - (Qha * (A_ART / Var))
            - (Qre * (A_ART / Var)))


  ## Table
  capture_CP = Cvenous/BP

  list(c(
    dA_VEN,
    dA_ART,
    dA_LUNG,
    dA_ADIPOSE,
    dA_HEART,
    dA_BRAIN,
    dA_BONE,
    dA_MUSCLE,
    dA_KIDNEY,
    dA_GUT,
    dA_GUTLUMEN,
    dA_SPLEEN,
    dA_REST,
    dA_LIVER
  ))
 })
}


 ## ---- SIMULATIONS ---- ##

# setting events in moles
timePos <- seq(0, 500, by = 0.01)
LoadingDosePos <- data.frame(var = "A_VEN",
                  time = c(0, 12),
                  value = (0.3/700.8) ,
                  method = "add")
DosePos      <- data.frame(var = "A_VEN",
                  time = c(24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288),
                  value = (0.3/700.8),
                  method = "add")
dosingPos    <- rbind(LoadingDosePos, DosePos)
EventsPos    <- list(data=dosingPos)


#Simulation Posaconazole moles
Simulation_moles_Pos <- ode(y= state, times = timePos, func = PBPK_Model_Posaconazole, parms =
parameters, events = EventsPos)   ## Simulation in mole
Simulation_moles_Pos <- as.data.frame(Simulation_moles_Pos)   # ODE uitkomsten als dataframe
simulation_Pos <- Simulation_moles_Pos[,c(-12)]             # dataframe without gutlumen
```

```
Simulation_moles_Pos$A_tot_body <- rowSums(Simulation_moles_Pos[2:15])  # dataframe with total body


## Simulation in miligrams posaconazole
timeMGPos <- seq(0, 600, by = 0.01)
LoadingDoseMGPos <- data.frame(var = "A_GUTLUMEN",
                  time = c(0, 12),
                  value = (400) ,
                  method = "add")
DoseMGPos       <- data.frame(var = "A_GUTLUMEN",
                  time = c(24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408,
432, 456, 480, 504, 528, 552, 576, 600),
                  value = (400),
                  method = "add")
dosingMGPos     <- rbind(LoadingDoseMGPos, DoseMGPos)
EventsMGPos     <- list(data=dosingMGPos)


# simulation Posaconazole MG
Simulation_mg_Pos <- ode(y= state, times = timeMGPos, func = PBPK_Model_Posaconazole, parms =
parameters, events = EventsMGPos)    ## simulation in MG
Simulation_mg_Pos <- as.data.frame(Simulation_mg_Pos)   # ODE uitkomsten als dataframe
simulation_mg_Pos <- Simulation_mg_Pos[,c(-12)]        # dataframe without gutlumen
Simulation_mg_Pos$A_tot_body <- rowSums(simulation_mg_Pos[2:14]) # dataframe with total body
(with gutlumen)
Simulation_mg_Pos$A_tot_body_gut <- rowSums(Simulation_mg_Pos[2:15]) # dataframe with total body
(without gutlumen)
```