Supplementary material

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Whole body physiologically based pharmacokinetic model to explain a patient with drug-drug interaction between voriconazole and flucloxacillin

Running title: WBPBPK of the DDI of voriconazole & flucloxacillin

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Electronic supplementary material A P P E N D I X I

Model equations

Tissue drug distribution model

A physicochemical drug distribution model was used to predict the total tissue-to-unbound plasma ratio (Kp_u)[18,21,22]. 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). We previously showed that the base model of *Rodgers et al (2006)* provides an adequate tissue distribution prediction for weak basic lipophilic drugs (pKa < 7) at steady state[23]. The relevant psychochemical properties that are used in PBPK modelling of voriconazole and posaconazole can be found in **Table 1**.

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.

Physiologic equations used to describe tissue distribution (Kpu) are:

1) $\text{Intracellular water} = \frac{1+10^{pKa-pH_{iw}}}{1+10^{pKa-pH_p}} * f_{iw}$ *Intracellular water=1+10pKa−pHiw1+10pKa−pHp∗fiw*

2) $\text{Extracellular water} = \frac{1+10^{pKa-pH_{ew}}}{1+10^{pKa-pH_p}} * f_{ew}$

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

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

5) $Ka_{albumin} = \frac{1}{F_{unbound}} - \frac{1 - (P * f_{nl,p} + (0.3P + 0.7) * f_{np,p}}{1+10^{pKa-pH_p}}) * 1 [\text{albumin}]_{\text{plasma}}$

6) $Kp_u =$

$$[(1+10^{pKa-pHiw}1+10^{pKa-pHp}*fiw)+few+(P*Fnl,t+(0.3P+0.7)*Fnp,t1+10^{pKa-pHp})+(Ka_{albumin}*[albumin]_{tissue})]$$

7) $KP=Kp_u*F_{unbound}$ *$KP=Kpu*Funbound$*

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 are presented 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. $F_{unbound}$ is the unbound fraction drug and is used to transform the Kp_u to the KP.

Whole body-PBPK model basis:

The whole body model structure is derived from *Rodgers et al (2006)* and *Elmokadem et al (2019)*[16,18]*.* Organ-specific parameters, such as organ flow (Q) and organ volume (V), were obtained from *Rowland and Tozers* (**Table 1a and Figure 2**)[19]. As voriconazole and posaconazole have renal and hepatic excretion, both were included in the model as described below[20].

Non-eliminating organs:

8) $A_{tissue}=Q_{tissue}*(C_{artery}-C_{tissue}(KP_{tissueBP}/))$

9) $A_{lung}=Q_{lung}*(C_{vein}-C_{lung}(KP_{tissueBP}/))$

10) $A_{vein}=-(Q_{lung}*C_{vein})+\sum Q_{tissue}*C_{tissue}(KP_{tissueBP}/)$

11) $A_{artery}=+(Q_{lung}*C_{lung}(KP_{tissueBP}/))-\sum Q_{tissue}*C_{artery}$

A is the amount of drug in a specific compartment at a specific time point. A is calculated using Q, C, KP, BP. Q represents tissue-specific flow from and to organs. KP is derived by multiplying Rodgers Kp_u with $F_{unbound}$. 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.

Drug absorption organs

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

13) $A_{gut}=+K_{absorption}*dose*F+Q_{tissue}*(C_{artery}-C_{tissue}(KP_{tissueBP}/))$

14) 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 metabolism and elimination

The liver clearance is described by a physiological model. Voriconazole is metabolised using saturable cytochrome P450 iso-enzymes (CYP2C19, CYP2C9 and CYP3A4)[13]. After (saturable) liver metabolism, the minimally active voriconazole metabolites (N-oxide, hydroxide metabolites) are excreted by the kidneys. Only 2% is excreted unchanged via the kidneys. The non-linear-enzymatic metabolism is described by the Michaelis-Menten constant (Km) and maximum velocity (V_{max}) and is shown in equation 14. This is combined with general liver excretion which takes into account the milligrams of microsomal proteins per gram liver (MPPGL), the liver volume (V_{liver}), and the fraction of unbound drug in liver microsomes (fumic)[16].

The total liver clearance is shown in equation 15. Only unbound drug is metabolised and cleared. Bound drug only passes the liver and is described as a non-eliminating organ, the total liver equation is showed in equation 16.

Posaconazole is mainly eliminated by biliary excretion (77%) and a small portion trough real extraction as glucuronide conjugates (13%), population clearance values were used to simulate posaconazole excretion, which is given by CL_{liver} [20].

Table S1: an overview of the elimination of voriconazole and posaconazole.

Voriconazole				
Renal	2% (unchanged)			
Hepatic	98%			
	Cyp enzyme	K_m	V_{max}	Contribution metabolism
	CYP2C19	9.3 uM	13.9 pmol/min/pmol	85.0%
	CYP3A4	843.7 uM	32.2 pmol/min/pmol	14.5%
	CYP2C9	20 uM	0.056 pmol/min/pmol	0.5%
Posaconazole (83% is excreted unchanged)				
Renal	13 %			
Biliary	77 %			
	Enzyme	contribution		
Hepatic	UGT1A4	17%		

Drug elimination organs

$$15) \text{non linear enzymatic metabolism} = \sum_{ni=1} V_{imax} K_{im} + C_{t,u} n$$

$$16) CL_{liver\ voriconazole} = ((\sum_{ni=1} V_{imax} K_{im} + C_{t,u}) \cdot MPPGL \cdot V_{liver} \cdot 1000 \cdot 60 \cdot 1_{-6}) fumic$$

$$17) A_{liver} = Q_{gu} * (C_{gut}(KP_{gutBP}/)) + Q_{spleen} * (C_{spleen}(KP_{spleenBP}/)) + Q_{hepatic\ arterie} * C_{arterial} - Q_{liver} Aliver = Qgu * CgutKPgutBP + Qspleen * CspleenKPspleenBP + Qhepatic\ arterie * Carterial - Qliver * (C_{liver}(KP_{liverBP}/)) - CL_{liver} * (F_{unbound} * C_{liver}(KP_{liverBP}/)) CliverKPliverBP - CLliver * Funbound * CliverKPliverBP$$

$$18) Akidney = Qkidney * (Carterial - Ckidney(KPkidneyBP/)) - CLkidney * (Funbound * Ckidney(KPkidneyBP/)) Akidney = Qkidney * Carterial - CkidneyKPkidneyBP - CLkidney * Funbound * CkidneyKPkidneyBP$$

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 $F_{unbound}$. CL_{liver} and CL_{kidney} represent the drug elimination rates of the liver and kidney, respectively.

Full code description (R)

```
## packages
library(ggplot2) #plots
library(deSolve) #dif equation desolver
library(dplyr) #dataset creation
library(reshape2) #dataset creation



# Tissue specific parameters
##pH values for red blood cells, plasma, intracellular water and hematocrite
pHbc <- 7.22
pHp <- 7.4
pHiw <- 7.0   #Tissue input parameters Rodgers et al 2005
H <- 0.45     #Malcolm & Rowland clinical pharmacokinetics p.503 -> 0.45 #47.3 in Anderson? 0.473

## BLOOD CELL - Schmitt et al.(2019) table 1
Fewbc <- 0 # -> n.a. #fractional tissue volume extracellular water -> wordt niet gebruikt?
Fiwbc <- 0.603       #fractional tissue volume intracellular water
Fnlbc <- 0.0017      #fractional tissue volume neutral lipid
Fnpbc <- 0.0029      #fractional tissue volume neutral phospholipid

## BONE - Schmitt et al.(2019) table 1
Fewb <- 0.1
Fiwb <- 0.346
Fnlb <- 0.017
Fnpb <- 0.0017
ALBb <- 0.100 ##Rodgers et al. table 1 2005/2006 Physiologically Based Pharmacokinetic Modelling
2:Predicting the Tissue Distribution of Acids,very Weak Bases, Neutrals and Zwitterions
tALBb <- 0.001416071



## Adipose
Fewad <- 0.135
Fiwad <- 0.017
Fnlad <- 0.853
Fnpad <- 0.0016
```

```
ALBad <- 0.049
tALBad <- 0.000693875


## Muscle
Fewmu <- 0.118
Fiwmu <- 0.630
Fnlmu <- 0.010
Fnpmu <- 0.0072
ALBmu <- 0.064
tALBmu <- 0.000906285


## Liver - Schmitt et al. (2019) table 1
FewLi <- 0.161
FiwLi <- 0.560
FnlLi <- 0.014
FnpLi <- 0.024
ALBLi <- 0.086       ## Rodgers et al. table 1 (2006)
tALBLi <- 0.001217821


## KIDNEY - Schmitt et al.(2019) table 1
Fewk<- 0.273
Fiwk <- 0.466
Fnlk <- 0.012*3.23
Fnpk <- 0.0242*0.486
ALBk <- 0.130       ##Rodgers et al. table 1 2005/2006 Physiologically Based Pharmacokinetic Modelling 2:Predicting the Tissue Distribution of Acids,very Weak Bases, Neutrals and Zwitterions
tALBk <- 0.001840892


## LUNG - Schmitt et al.(2019) table 1
Fewl<- 0.336
Fiwl <- 0.431
Fnll <- 0.022*0.4       # Rodgers 2007
```

```
Fnpl <- 0.0128*0.238
ALBl <- 0.212
tALBl <- 0.00300207


## BRAIN - Schmitt et al.(2019) table 1
Fewbr <- 0.162
Fiwbr <- 0.606
Fnlbr <- 0.039
Fnpbr <- 0.0015
ALBbr <- 0.048
tALBbr <- 0.000679714


## SPLEEN - Schmitt et al.(2019) table 1
Fews<- 0.207
Fiws <- 0.526
Fnls <- 0.0077*2.77
Fnps <- 0.0113*1.55
ALBs <- 0.097
tABLs <- 0.001373588


## PLASMA - Schmitt et al.(2019) table 1
Fnlp <- 0 # -> n.a.
Fnpp <- 0 # -> n.a.


## Gut  ## schmidt et al (2019) (table I)
FewGu <- 0.282
FiwGu <- 0.475
FnlGu <- 0.038
FnpGu <- 0.0125
```

```
ALBGu <- 0.158  ## rodgers 2006 (table I)
tALBGu <- 0.002237392


## Heart  ## schmidt et al(2019)(table I)
FewHe <- 0.320
FiwHe <- 0.456
FnlHe <- 0.014
FnpHe <- 0.0111
ALBHe <- 0.157  ## rodgers 2006 (table I)
tALBHe <- 0.002223231


## Pancreas  ## schmidt et al (2019)(table I)
FewPa <- 0.120
FiwPa <- 0.664
FnlPa <- 0.041
FnpPa <- 0.0093
ALBPa <- 0.060  ## rodgers 2006 (table I)
tALBPa <- 0.000849642


## Skin  ## schmidt et al (2019)(table I)
FewSk <- 0.382
FiwSk <- 0.291
FnlSk <- 0.060
FnpSk <- 0.0044
ALBSk <- 0.277  ## rodgers 2006 (table I)
tALBSk <- 0.003922516


## Thymus ## schmidt et al (2019)(table I)
FewTh <- 0.150
FiwTh <- 0.626
FnlTh <- 0.017
```

```
FnpTh <- 0.0092
ALBTh <- 0.075  ## rodgers 2006 (table I)
tALBTh <- 0.001062053




## Parameters PBPK model
source("KP voriconazole - posaconazol - Final.V2.R")

## System Parameters
## Tissue volumes (L) ; source: https://www.ncbi.nlm.nih.gov/pubmed/14506981
Vad      = 18.2        ## Adipose
Vbo      = 10.5        ## Bone
Vbr      = 1.45        ## Brain
VguWall  = 0.65        ## Gut wall
VguLumen = 0.35        ## Gut lumen
Vgu      = 1.00        ## Gut
Vhe      = 0.33        ## Heart
Vki      = 0.31        ## Kidneys
Vli      = 1.8         ## Liver
Vlu      = 0.5         ## Lungs
Vmu      = 29          ## Muscle
Vsp      = 0.15        ## Spleen
Vbl      = 5.6         ## Blood




## Cardiac output (L/h)
CA = 6.5 * 60

## Tissue blood flows (L/h); Cardiac output = 6.5 (L/min); source:
https://www.ncbi.nlm.nih.gov/pubmed/14506981
Qad      = 0.05  * CA
Qbo      = 0.05  * CA
Qbr      = 0.12  * CA
Qgu      = 0.15  * CA
Qhe      = 0.04  * CA
```

Qki = 0.19 * CA

Qmu = 0.17 * CA

Qsp = 0.03 * CA

Qha = 0.065 * CA ## Hepatic artery

Qlu = CA ## same as cardiac output

Qco = (5.0/100*CA) ## coronary vessels

bloodflow (A Whole-Body Physiologically Based Pharmacokinetic Model of Gefitinib in Mice and Scale-Up to Humans

Youwei Bi,1 Jiexin Deng,2 Daryl J. Murry,1 and Guohua Ancorresponding author1,2)

Qli = (Qgu + Qsp + Qha) ## Bloodflow liver

Qre = (Qlu - (Qli + Qki + Qbo + Qhe + Qmu + Qad + Qbr)) ## blood flow rest compartment

other parameters

Weight = 73 ## (kg)

in vitro hepatic clearence parameters; source: : https://pubmed.ncbi.nlm.nih.gov/28159656/ & http://dmd.aspetjournals.org/content/38/1/25.long

fumic = 0.711 ## Fraction of unbound drug in microsomes

MPPGL = 30.3 ## Adult mg microsomal protein per g liver (mg/g)

VmaxH = 40 ## Adult hepatic Vmax (pmol/min/min) CYP2C19

KmH = 9.3 ## Adult hepatic Km (uM) CYP2C19

Renal clearance; source: https://link.springer.com/article/10.1007%2Fs40262-014-0181-y

CL_ki = 0.096 ## (L/h) renal clearance

MAIN

Additional Volume derivations

Vve = (0.705*Vbl) ## Venous blood

Var = (0.295*Vbl) ## Arterial blood

Vre = (Weight - (Vli + Vki + Vsp + Vhe + Vlu + Vbo + Vbr + Vmu + Vad + VguWall + Vbl)) ## Volume rest of the body compartment

Vtot = (Vad + Vbo + Vbr + VguWall + Vhe + Vki + Vli + Vlu + Vmu + Vsp + Vbl + Vre) ## Total body volume

Additional blood flow derivation

Qli = (Qgu + Qsp + Qha) ## Blood flow liver

Qre = (Qlu - (Qli + Qki + Qbo + Qhe + Qmu + Qad + Qbr)) ## blood flow rest compartment

intrinsic hepatic clearance calculation

CL_Li = (((VmaxH/KmH)*MPPGL*Vli*1000*60*1e-6) / fumic)   ## (L/h) hepatic clearance

##

Voriconazole pharmacokinetic parameters ----

Drug Parameters> sources: https://doi.org/10.1080/10408347.2018.1468728, Anderson 1985 EJCP 27:713-19, Malcolm & Rowland clinical pharmacokinetics p.503

##

PV <- 1.8

P_voV <- 1.115*PV-1.35

pKaV <- 1.76

bpV <- 1 # uitzoeken

FuV <- 0.42 ## normale vrije fractie

KaV <- 0.849

FV <- 0.96## fraction absorped

fup   = 0.42   ## fraction unbound drug in plasma (voriconazole)

fup_icu = 0.49   ## fraction unbound drug increased, due to lower albumin concentrations

fup_ddi = 0.42   ## fraction unbound drug does not increase, due to lower albumin concentrations (DDI flucloxacillin)

Liver clearance Fang Qi et al

Vmax_2C19 = 40   #pmol/min/pmol

Km_2C19   = 9.3   # uM

Vmax_2C9 = 0.056 #pmol/min/pmol

Km_2C9   = 20   # uM

Vmax_3A4 = 32.2 #pmol/min/pmol

Km_3A4   = 834.7 # uM

Km_2C19_mRNA = 3.72

Km_2C9_mRNA = 13.33

Km_3A4_mRNA = 181.45

contribution

CYP2C19 <- 0.85

CYP2C9 <- 0.005

CYP3A4 <- 0.145

##

Posaconazole

---- pharmacokinetic parameters ----

PP <- 5.41

P_voP <- 1.115*PP - 1.35

pKaP <- 2.77

bpP <- 1 # uitzoeken

FuP <- 0.02 ## normale vrije fractie

KaP<-0.795 ## absorption rate constant (/h) --> Population pharmacokinetics of a posaconazole tablet formulation in transplant adult allogeneic stem cell recipients - Diego Pena-Lorenzo

FP<-0.08 ## fraction absorped (SMPC)

Pos_CL_pop = 8.02/FP# not from L/h --> /H door * Vli ## Median table 1: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7183491/ and 8.02 (L/h) --> Population pharmacokinetics of a posaconazole tablet formulation in transplant adult allogeneic stem cell recipients - Diego Pena-Lorenzo

---- Protein compartment ----

Pos_Kd = (2e-06) ## (M-1) goede waarde nog invullen --> voor nu Kd van fluxloc.(a) A meta-analysis of protein binding of flucloxacillin in healthy volunteers and hospitalized patients; E. Wallenburg, R. Bruggemann, J. Roberts, N. Jager, M. Ulldemolins, S. Wilkes, J. Schouten, P. Chin, R. ter Heine

Pos_MW = 700.8 ## g/mol

##

Protein compartment (for liver metabolism vori only)

Kd = ((0.000075)) ## (M-1) ## Kd of Mexiletine, a drug with 55% protein binding 0.29*10^3 -> ((1/(0.29*10^3))/2)

PROThealthy = 40/67000

PROTicu = 30/67000

PROTddi = 2.5/67000

ConcAlbhealthy = PROThealthy / Vbl

ConcAlbicu = PROTicu / Vbl

ConcAlbddi = PROTddi / Vbl

ConcAlbPos = PROThealthy / Vbl

```
#dataframes for manuscript:
 Clearance_dataframe <- data.frame(
  "CYP enzymes" = c("CYP2C19", "CYP3A4", "CYP2C9"),
  "Km" = c(Km_2C19, Km_3A4, Km_2C9),
  "Vmax" = c(Vmax_2C19, Vmax_3A4, Vmax_2C9),
  "contribution" = c(CYP2C19, CYP3A4, CYP2C9)
)

Parameters <- data.frame(
  "Tissue" = c("Blood cells", "adipose", "bone", "brain", "gut", "heart", "kidney", "liver",
               "lung", "muscle", "pancrease", "skin", "spleen", "thymus"),
  "Fnl" = c(Fnlbc, Fnlad, Fnlb, Fnlbr, FnlGu, FnlHe,  Fnlk, FnlLi,  Fnll, Fnlmu, FnlPa, FnlSk, Fnls, FnlTh),
  "Fnp" = c(Fnpbc, Fnpad, Fnpb, Fnpbr, FnpGu, FnpHe,  Fnpk, FnpLi,  Fnpl, Fnpmu, FnpPa, FnpSk, Fnps, FnpTh),
  "Few" = c(NA, Fewad, Fewb, Fewbr, FewGu, FewHe,  Fewk, FewLi,  Fewl, Fewmu, FewPa, FewSk, Fews,
FewTh),
  "Fiw" = c(Fiwbc, Fiwad, Fiwb, Fiwbr, FiwGu, FiwHe,  Fiwk, FiwLi,  Fiwl, Fiwmu, FiwPa, FiwSk, Fiws, FiwTh),
  "ALB" = c(NA, ALBad, ALBb, ALBbr, ALBGu, ALBHe,  ALBk, ALBLi,  ALBl, ALBmu, ALBPa, ALBSk, ALBs, ALBTh),
  "tALB"= c(NA, tALBad, tALBb, tALBbr, tALBGu, tALBHe, tALBk, tALBLi, tALBl, tALBmu, tALBPa, tALBSk, tABLs,
tALBTh),
  "logPV"= c(PV, P_voV, PV, PV, PV, PV, PV, PV, PV, PV, PV, PV, PV, PV),
  "logPP" = c(PP, P_voP, PP, PP, PP, PP, PP, PP, PP, PP, PP, PP, PP, PP),
  "Q" = c(NA, Qad, Qbo, Qbr, Qgu, Qhe, Qki, Qlu, Qli, Qmu, NA, NA, Qsp, NA)

)

# Parameters without Bloodcells
Parameters2 <- Parameters %>%
  filter(!Tissue == "Blood cells")
 ##############################################################################################
# Model Voriconazole
IWV       <- (((1+10^(pKaV-pHiw)) * Parameters2[,"Fiw"]) / (1+10^(pKaV-pHp)))
EWV       <- (Parameters2[,"Few"])
NLNPV     <- ((Parameters2[,"logPV"] * Parameters2[,"Fnl"] + (0.3 * Parameters2[,"logPV"] + 0.7) *
Parameters2[,"Fnp"]) / (1+10^(pKaV-pHp)))
AlbuminV  <- abs((((1/FuV)     -1-((Parameters2[,"logPV"] * Fnlp + (0.3 * Parameters2[,"logPV"] + 0.7) * Fnpp) /
(1+10^(pKaV-pHp))) ) * (Parameters2[,"ALB"])))
```

```
# Model posaconazole

IWP      <- (((1+10^(pKaP-pHiw)) * Parameters2[,"Fiw"]) / (1+10^(pKaP-pHp)))

EWP      <- (Parameters2[,"Few"])

NLNPP    <- ((Parameters2[,"logPP"] * Parameters2[,"Fnl"] + (0.3 * Parameters2[,"logPP"] + 0.7) * Parameters2[,"Fnp"]) / (1+10^(pKaP-pHp)))

AlbuminP  <- abs((((1/FuP)    -1-((Parameters2[,"logPP"] * Fnlp + (0.3 * Parameters2[,"logPP"] + 0.7) * Fnpp) / (1+10^(pKaP-pHp))) ) * (Parameters2[,"ALB"])))



Kpu <- Parameters2 %>%
 mutate(
  Kpu_V  =  (IWV + EWV + NLNPV + AlbuminV),
  Kpu_P  =  (IWP + EWP + NLNPP + AlbuminP)
 ) %>%
 select(Tissue | Kpu_V | Kpu_P)


TBR <- Kpu %>%
 mutate(
  TBR_V =  (Kpu_V * (FuV/bpV)),
  TBR_P =  (Kpu_P * (FuP/bpP))
 )



## contribution KPU
Contribution_healthy <- TBR %>%
 mutate("%Fiw" = (IWV/Kpu_V)*100) %>%
 mutate("%Few" = (EWV/Kpu_V)*100) %>%
 mutate("%NLNP" = (NLNPV/Kpu_V)*100) %>%
 mutate("%Albumin" = (AlbuminV/Kpu_V)*100) %>%
 mutate("Total%" = (`%Albumin`+`%Fiw`+`%Few`+`%NLNP`))



## Tissue-to-plasma partition coefficients (Kp values) of voriconazole calculated using Rodgers et al (see R-script KP voriconazole)
KPad    = Kpu[1,"Kpu_V"] * fup

KPbo    = Kpu[2,"Kpu_V"] * fup

KPbr    = Kpu[3,"Kpu_V"] * fup

KPgu    = Kpu[4,"Kpu_V"] * fup
```

```
KPhe    = Kpu[5,"Kpu_V"] * fup
KPki    = Kpu[6,"Kpu_V"] * fup
KPli    = Kpu[7,"Kpu_V"] * fup
KPlu    = Kpu[8,"Kpu_V"] * fup
KPmu    = Kpu[9,"Kpu_V"] * fup
KPpa    = Kpu[10,"Kpu_V"] * fup
KPsk    = Kpu[11,"Kpu_V"] * fup
KPsp    = Kpu[12,"Kpu_V"] * fup
KPth    = Kpu[13,"Kpu_V"] * fup
KPre    = sum(KPad, KPbo, KPbr, KPgu, KPhe, KPki, KPli, KPlu, KPmu, KPpa, KPsk, KPsp, KPth)/13


## KP ICU
KPad_icu    = Kpu[1,"Kpu_V"] * fup_icu
KPbo_icu    = Kpu[2,"Kpu_V"] * fup_icu
KPbr_icu    = Kpu[3,"Kpu_V"] * fup_icu
KPgu_icu    = Kpu[4,"Kpu_V"] * fup_icu
KPhe_icu    = Kpu[5,"Kpu_V"] * fup_icu
KPki_icu    = Kpu[6,"Kpu_V"] * fup_icu
KPli_icu    = Kpu[7,"Kpu_V"] * fup_icu
KPlu_icu    = Kpu[8,"Kpu_V"] * fup_icu
KPmu_icu    = Kpu[9,"Kpu_V"] * fup_icu
KPpa_icu    = Kpu[10,"Kpu_V"] * fup_icu
KPsk_icu    = Kpu[11,"Kpu_V"] * fup_icu
KPsp_icu    = Kpu[12,"Kpu_V"] * fup_icu
KPth_icu    = Kpu[13,"Kpu_V"] * fup_icu
KPre_icu    = sum(KPad_icu, KPbo_icu, KPbr_icu, KPgu_icu, KPhe_icu, KPki_icu, KPli_icu, KPlu_icu, KPmu_icu,
KPpa_icu, KPsk_icu, KPsp_icu, KPth_icu)/13


## kp DDI Model
kpad    = Kpu[1,"Kpu_V"] * fup_ddi
kpbo    = Kpu[2,"Kpu_V"] * fup_ddi
kpbr    = Kpu[3,"Kpu_V"] * fup_ddi
kpgu    = Kpu[4,"Kpu_V"] * fup_ddi
kphe    = Kpu[5,"Kpu_V"] * fup_ddi
kpki    = Kpu[6,"Kpu_V"] * fup_ddi
```

```
kpli    = Kpu[7,"Kpu_V"] * fup_ddi
kplu    = Kpu[8,"Kpu_V"] * fup_ddi
kpmu    = Kpu[9,"Kpu_V"] * fup_ddi
kppa    = Kpu[10,"Kpu_V"] * fup_ddi
kpsk    = Kpu[11,"Kpu_V"] * fup_ddi
kpsp    = Kpu[12,"Kpu_V"] * fup_ddi
kpth    = Kpu[13,"Kpu_V"] * fup_ddi
kpre    = sum(kpad, kpbo, kpbr, kpgu, kphe, kpki, kpli, kplu, kpmu, kppa, kpsk, kpsp, kpth)/13


 ## ---- KP values posaconazole---- ##

## ---- Tissue-to-plasma partition coefficients (Kp values) of posaconazole calculated using Rodgers et al (see R-script KP posaconazole) ---- ##
KPadPos   = Kpu[1,"Kpu_P"]  * FuP
KPboPos   = Kpu[2,"Kpu_P"]  * FuP
KPbrPos   = Kpu[3,"Kpu_P"]  * FuP
KPguPos   = Kpu[4,"Kpu_P"]  * FuP
KPhePos   = Kpu[5,"Kpu_P"]  * FuP
KPkiPos   = Kpu[6,"Kpu_P"]  * FuP
KPliPos   = Kpu[7,"Kpu_P"]  * FuP
KPluPos   = Kpu[8,"Kpu_P"]  * FuP
KPmuPos   = Kpu[9,"Kpu_P"]  * FuP
KPpaPos   = Kpu[10,"Kpu_P"] * FuP
KPskPos   = Kpu[11,"Kpu_P"] * FuP
KPspPos   = Kpu[12,"Kpu_P"] * FuP
KPthPos   = Kpu[13,"Kpu_P"] * FuP
KPrePos    = sum(KPadPos, KPboPos, KPbrPos, KPguPos, KPhePos, KPkiPos, KPliPos, KPluPos, KPmuPos, KPpaPos, KPskPos, KPspPos, KPthPos)/13


#List all Parameters for simulations
parameters_base <- unlist(c(data.frame(
  Vad, Vbo, Vbr, VguWall,  VguLumen, Vgu, Vhe,  Vki, Vli, Vlu, Vmu, Vsp, Vbl, Vtot,
  Qad, Qbo, Qbr, Qli, Qgu, Qhe, Qki, Qmu, Qsp, Qha, Qlu, Qre,
  kpad, kpbo, kpbr, kpgu, kphe, kpki, kpli, kplu, kpmu, kpsp, kpre,
  bpV, bpP, KPad, KPbo, KPbr, KPgu, KPhe, KPki, KPli, KPlu, KPmu, KPsp, KPsk, KPth, KPpa, KPre,
  KPad_icu, KPbo_icu, KPbr_icu, KPgu_icu, KPhe_icu, KPki_icu, KPli_icu, KPlu_icu, KPmu_icu,
  KPsp_icu, KPsk_icu, KPth_icu, KPpa_icu, KPre_icu,
```

```
  Weight, KaP, KaV,  fup,  fup_ddi,  fup_icu,  fumic, MPPGL,  VmaxH,  KmH,  CL_ki,  Vve,  Var,  Vre,  CL_Li,  FP,FV,
Vmax_2C19, Vmax_2C9,  Vmax_3A4,  Km_2C19, Km_2C9,  Km_3A4,  Kd,  KaP,  FuP,

  Pos_CL_pop,  Pos_Kd,  Pos_MW,  KPadPos,  KPboPos,  KPbrPos,  KPliPos,  KPguPos,  KPluPos,

  KPhePos,  KPkiPos,  KPmuPos,  KPpaPos,  KPskPos,  KPspPos,  KPrePos,  KPthPos,

  PROThealthy,  PROTicu,  PROTddi,  ConcAlbPos, ConcAlbhealthy,  ConcAlbicu,  ConcAlbddi

)))
```

```
## 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


)))
```

```
#############################################################################################
#start differentatials equations
 ## - Voriconazole - ##

## (1) DDI -->
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




      if (t < 24) {
        ## 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  = (bpV * Qli * ((CL_int_QI)/(CL_int_QI+(Qli*bpV/fup_ddi))))
       CL_Li_new  = (((CL_int_QI)*MPPGL*Vli*1000*60*(1*10^-6)) / fumic)          ## (L/h) hepatic clearance
      } else {
       CL_int_QI = ((Vmax_2C19/(Km_2C19_mRNA +( (A_LIVER / Vli) * fup_ddi))) + (Vmax_3A4/(Km_3A4_mRNA
+ ( (A_LIVER / Vli) * fup_ddi))) + (Vmax_2C9/(Km_2C9_mRNA + ( (A_LIVER / Vli) * fup_ddi))))
       CL_pb_QI  = (bpV * Qli * ((CL_int_QI)/(CL_int_QI+(Qli*bpV/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/bpV) )))
dA_ADIPOSE  = ((Qad * (A_ART / Var)) - (Qad * ((A_ADIPOSE / Vad)  /(kpad/bpV) )))
dA_HEART    = ((Qhe * (A_ART / Var)) - (Qhe * ((A_HEART   / Vhe)  /(kphe/bpV) )))
dA_BRAIN    = ((Qbr * (A_ART / Var)) - (Qbr * ((A_BRAIN   / Vbr)  /(kpbr/bpV) )))
dA_BONE    = ((Qbo * (A_ART / Var)) - (Qbo * ((A_BONE    / Vbo)  /(kpbo/bpV) )))
dA_MUSCLE   = ((Qmu * (A_ART / Var)) - (Qmu * ((A_MUSCLE  / Vmu)  /(kpmu/bpV) )))
dA_SPLEEN   = ((Qsp * (A_ART / Var)) - (Qsp * ((A_SPLEEN  / Vsp)  /(kpsp/bpV) )))
dA_REST    = ((Qre * (A_ART / Var)) - (Qre * ((A_REST    / Vre)  /(kpre/bpV) )))

dA_GUTLUMEN  = (-  KaV * (A_GUTLUMEN) * FV )
dA_GUT     = (+(Qgu * (A_ART / Var)) - (Qgu * ((A_GUT / VguWall) / (kpgu/bpV) ))  + (KaV*
A_GUTLUMEN)*FV)

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

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

dA_ART     = (+ (Qlu * ((A_LUNG    / Vlu)   /(kplu/bpV)))
          - (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

Voriconazole_DDI_1          <- ode(y= state, times = timeMG, func = Voriconazole_DDI, parms = parameters,
events = EventsMG)          ## Simulation in MG
## data frames

Voriconazole_DDI_1 <- as.data.frame(Voriconazole_DDI_1)  ## dataframe
Voriconazole_DDI_1 <- Voriconazole_DDI_1[,c(-12)]
Voriconazole_DDI_1 <- Voriconazole_DDI_1[,c(1:14)]
```

```
Voriconazole_DDI_1$vein <- Voriconazole_DDI_1$A_VEN /Vve
Voriconazole_DDI_1$Lung <- Voriconazole_DDI_1$A_LUNG /Vlu
Voriconazole_DDI_1$Liver <- Voriconazole_DDI_1$A_LIVER /Vli

## -----  POSACONAZOLE  ----- ##

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

```
  dA_GUTLUMEN  = (- KaP * (A_GUTLUMEN) * FP )


  dA_GUT     = ((Qgu * (A_ART / Var)) - (Qgu * ((A_GUT / VguWall) / (KPguPos/bpP)))  + ((KaP*
(A_GUTLUMEN)*FP)))
  dA_LIVER    = ((+ (Qgu * ((A_GUT / VguWall)      /(KPguPos/bpP))) + (Qsp * ((A_SPLEEN / Vsp)
/(KPspPos/bpP)))) + (Qha*(A_ART / Var)) - (Qli*((A_LIVER / Vli)/(KPliPos/bpP))) - ( Pos_CL_pop * (((A_LIVER /
Vli)*FuP)/(KPliPos/bpP))))


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


  dA_ART     = (+ (Qlu * ((A_LUNG / Vlu)/(KPluPos/bpP)))
            - (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/bpP


  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 miligrams posaconazole
timeMGPos <- seq(0, 600, by = 0.01)
LoadingDoseMGPos <- data.frame(var = "A_GUTLUMEN",
                        time = seq(0, 12, by = 12),
                        value = (300) ,
                        method = "add")
DoseMGPos       <- data.frame(var = "A_GUTLUMEN",
                        time = seq(24, 588, by = 24),
                        value = (300),
                        method = "add")
dosingMGPos     <- rbind(LoadingDoseMGPos, DoseMGPos)
EventsMGPos     <- list(data=dosingMGPos)


# simulation Posaconazole
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 as 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)

 Simulation_mg_Pos$Vein <- Simulation_mg_Pos$A_VEN /Vve
```