Physiologically-Based Pharmacokinetic (PBPK) Modeling of Fluconazole Using Plasma and Cerebrospinal Fluid Samples from Preterm and Term Infants

SUPPLEMENTARY MATERIAL S2 – PBPK Model Building Process and Input Parameters

Model Building Process

1. Create the healthy adult model in PK-Sim®. See Compound File and Healthy Adult Individual and Population files below.
2. Scale the healthy adult model to infants in PK-Sim. See Infant Individual and Population files below.
    a. In the Infant Population file, change the alpha-1 acid glycoprotein ontogeny based on the Maharaj et al equation:

$$AAG_{OF} = \frac{PNA^{0.735}}{11.53^{0.735} + PNA^{0.735}}$$

    where AAG_{OF} is the ontogeny factor for alpha-1 acid glycoprotein and PNA is the postnatal age in days.
3. For all simulations, a standard deviation of 0.2225, equal to 25% of the mean of 0.89, was included for fraction unbound under User Defined Variability.

Reference

1. Maharaj, A. R., Gonzalez, D., Cohen-Wolkowiez, M., Hornik, C. P., & Edginton, A. N. Improving pediatric protein binding estimates: An evaluation of α1-acid glycoprotein maturation in healthy and infected subjects. *Clin. Pharmacokinet.* **57**, 577-589 (2018).

FLUCONAZOLE COMPOUND FILE	
Basic Physico-chemistry	
Is small molecule	Yes
Lipophilicity	1.10
Fraction unbound	
Binds to	α1-acid-glycoprotein
Fraction unbound	0.89
Species	Human
Molweight	
Molecular weight	306.271 g/mol
Has halogens	Yes (2 F)
Effective molecular weight	272.27 g/mol
Compound type / pKa	
Compound type	Base
pKa	2.56
Solubility	
Solubility at reference pH	1.00 µg/mL
Solubility reference pH	7.00
Solubility gain per charge	1000
Absorption	
Specific intestinal permeability	$2.22e^{-6}$ cm/min
Distribution	
Distribution Calculation	
Calculation methods	
Partition coefficients	Rodgers and Rowland
Cellular permeabilities	PK-Sim Standard
Specific organ permeability	$8.89e^{-4}$ cm/min
Metabolism	
Metabolizing Enzymes	
UGT2B7	
Species	Human
Process type	Intrinsic clearance – First Order
Volume (liver)	2.36 L
Fraction intracellular	0.67
Intrinsic clearance	$8.00e^{-3}$ L/min
Specific clearance	$5.09e^{-3}$ 1/min
Transport & Excretion	
Renal Clearances	
Species	Human
Process type	Glomerular filtration
GFR fraction	0.30
Advanced Parameters	
Default values	

HEALTHY ADULT INDIVIDUAL FILE	
Biometrics	
Species	Human
Population	European (ICRP, 2002)
Gender	Male
Calculation methods	
Body surface area	Mosteller
Endothelial surface areas	Organ vascularization
Age	30 years
Weight	73 kg
Height	176 cm
BMI	23.57 kg/m^2
Anatomy & Physiology	
Default values	
Expression	
Metabolizing Enzymes	
UGT2B7	PK-Sim® Gene Database, default values
Data Transfer Overview	RT-PCR

HEALTHY ADULT POPULATION FILE	
Demographics	
Number of individuals	500
Proportion of females	50%
Age range	18-55 years
Expression	
Metabolizing Enzymes	
UGT2B7	PK-Sim® Gene Database, default values

INFANT INDIVIDUAL FILE	
Biometrics	
Species	Human
Population	Preterm
Gender	*
Age	*
Weight	*
Height	*
BMI	*
Anatomy and physiology	
Default values	
Expression	
Metabolizing Enzymes	
UGT2B7	PK-Sim® Gene Database, default values
Data Transfer Overview	RT-PCR

* This value was set to match each infant's individual value for the prophylaxis and PPRU studies.

INFANT POPULATION FILE – PROPHYLAXIS STUDY	
Demographics	
Number of individuals	1000
Proportion of females	63%
Age range	2 – 6 days
Gestational age range	24 – 29 weeks
Weight range	0.35 – 0.85 kg
Expression	
Metabolizing Enzymes	
UGT2B7	PK-Sim® Gene Database, default values

INFANT POPULATION FILE – PPRU STUDY	
Demographics	
Number of individuals	100
Proportion of females	54
Age range	1 – 79 days
Gestational age range	24 – 40 weeks
Weight range	0.45 – 7.13 kg
Expression	
Metabolizing enzymes	
UGT2B7	PK-Sim® Gene Database, default values