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

TABLE S1

Supplementary Table 1. Parameters used in model development

Parameter	Value	Source
PHYSICOCHEMICAL PROPERTIES		
Molecular weight	306.27 g/mol	Literature[1]
Effective molecular weight	272.27 g/mol	Literature[1]
pKa value	2.56	Literature[1]
Compound type	weak base	Literature[1]
Lipophilicity	1.10	Optimized value[a]
Protein binding partner	alpha-1 acid glycoprotein	Literature[2,3]
Fraction unbound	0.89	Literature[4]
Solubility	1 μg/mL	Literature[1]
Solubility reference pH	7.0	Literature[1]
Solubility gain per charge	1000	Literature[1]
Blood to plasma ratio	1.0	Literature[2]
ABSORPTION		
Specific intestinal permeability	$2.22e^{-6}$ cm/min	Calculated value[b]
Specific organ permeability	$8.89e^{-4}$ cm/min	Calculated value[c]
DISTRIBUTION		
Partition coefficients	Rodgers & Rowland	Literature[5]
Cellular permeabilities	PK-Sim® Standard	PK-Sim® algorithm[6,7]
METABOLISM		
UGT2B7		
Intrinsic clearance	0.008 L/min	Optimized value[a]
Specific clearance	0.005 1/min	Calculated value[d]
EXCRETION		
GFR fraction	0.30	Optimized value

[a] Lipophilicity and UGT2B7 intrinsic clearance optimization using the prophylaxis study data resulted in very similar values as those optimized in a previous pediatric fluconazole PBPK model, and so the original values were retained.[8]

[b] $266 * \left(MW_{eff} * 10^{9}\right)^{-4.5} * 10^{logP} * 60 * 10^{-1}$; where MW_{eff} is the effective molecular weight and logP is the lipophilicity measure.

[c] $\left(\frac{MW_{eff}*10^{9}}{336}\right)^{-6} * \frac{10^{logP}}{5} * 10^{-5}$; where MW_{eff} is the effective molecular weight and logP is the lipophilicity measure.

[d] $\frac{CL_{int}}{Vol_{liv}*f_{intra,liv}}$; where CL_{int} is the intrinsic clearance, Vol_{liv} is the liver volume, and $f_{intra,liv}$ is the liver intracellular fraction.

UGT2B7:,5'-diphosphoglucuronosyltransferase 2B7; GFR: glomerular filtration rate

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