A Preliminary PBPK Model for the Echinocandin Antifungal, Mycamine® (Micafungin Sodium)

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BACKGROUND

Micafungin (mycamine®) is a semi-synthetic antifungal drug belonging to the novel echinocandin class.[1,2] As its absorption is very poor, micafungin is only available as an intravenous (iv) formulation.

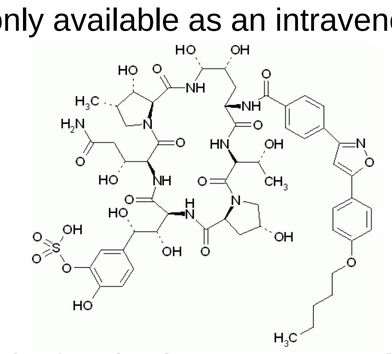

Figure 1 – Chemical structure of micafungin.

Micafungin is **not extensively metabolised** and renal clearance **does not constitute** a major pathway (Figure 2)[2]. Hepatobiliary clearance seems to be the main route of elimination for this compound – indicating a key role of transporters in it's disposition – with hepatic uptake occurring primarily via **NTCP** and to a lesser extent via **OATP(s)** and biliary excretion occurring primarily via **BSEP**[3].

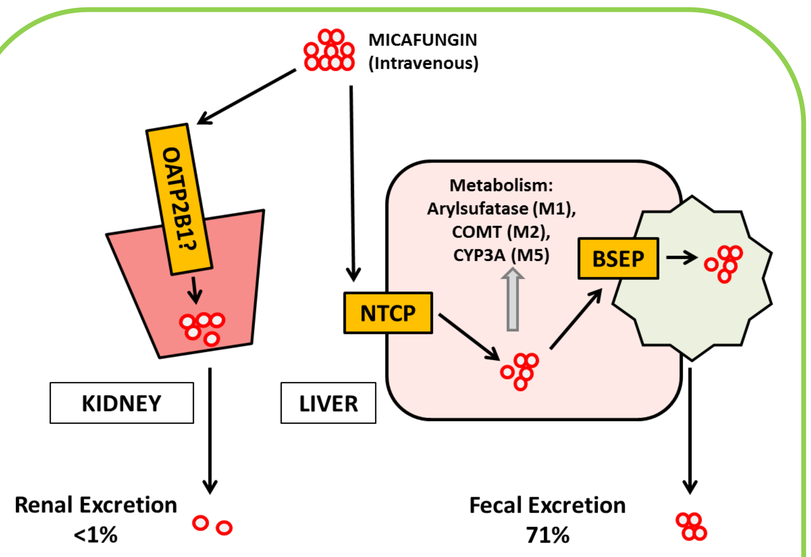

Figure 2 – The elimination pathway of micafungin. Pharmacokinetics studies have demonstrated that 71% of the administered dose is eliminated via biliary clearance, whereas urinary excretion is a minor route of elimination[1,2].

OBJECTIVE

To develop a preliminary physiologically-based pharmacokinetic (PBPK) model, to be used in the prediction of micafungin disposition in different populations.

METHODS

Physicochemical information and *in vitro*/*in vivo* data[4,5] on the clearance of micafungin were used in a full PBPK model, implemented in the Simcyp Population-based Simulator (V13r2), as follows:

Parameters	Model I Top-down	Model II Retrograde
Absorption	----	----
Distribution	V_{ss} prediction - Method 2: Rogers & Roland[4], using: • kp scalar and • Hepatic uptake scalar of 1.6	V_{ss} prediction - Method 2: Rogers & Roland[4], using: • kp scalar and • Hepatic uptake scalar of 1.6
Clearance	CL_{iv} (in vivo[5,6])	CL_{met} (CYPs (20%) /other enzymes (2%)) CL_{Renal} (1%) CL_{Bile} (71%)

Concentration-time profiles of micafungin were simulated in healthy volunteers (HVs) following 100 mg single-dose (SD) iv administration to assess pharmacokinetic parameters compared to observed data.

As additional validation of the model, concentration-time profiles were simulated in:

- Simcyp Japanese population at doses of 50, 75, and 150 mg - pharmacokinetic profile was compared to observed data.
- Simcyp renal-impaired population (GFR < 30 mL/min) at a dose of 100 mg - pharmacokinetic profile was compared to observed data.

RESULTS

PBPK Model I

Simcyp-Healthy Volunteer

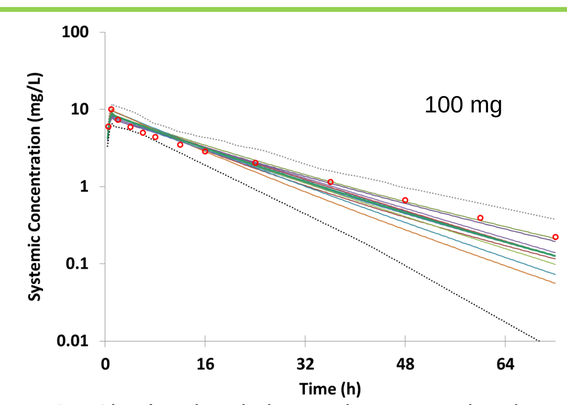

Figure 3 – Simulated and observed concentration-time profiles of micafungin in HVs at a dose of 100 mg, single-dose, intravenous (iv) infusion for 1 hour. Simulations were performed in 80 subjects (10 trials x 8 subjects, 63% male). Age-range: 18-65 years. Average weight: 75 kg. Red circles represent the observed mean values from respective clinical study[6]. Grey dotted lines represent the 5th and 95th percentile confidence intervals. Transporter kinetics and individual clearance pathways were not included in this simulation, however, contribution of general hepatic uptake was taken into account using the hepatic uptake factor in Simcyp.

The simulated profiles of micafungin in HVs indicated were in agreement with previously reported clinical values at the dose simulated[6].

Validation: PBPK Model I

Simcyp-Japanese

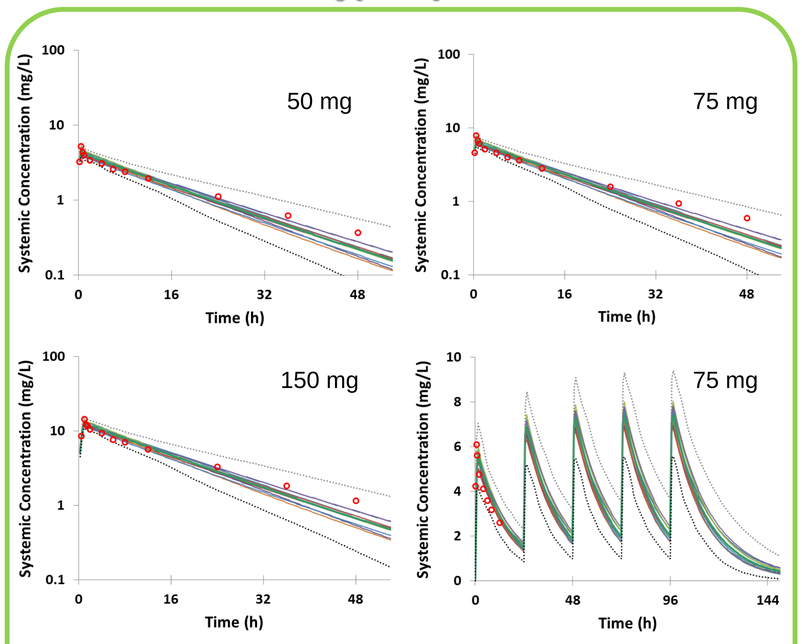

Figure 4 – Simulated and observed concentration-time profiles of single-dose (50, 75 and 150 mg – iv infusion) and multiple-dose (75 mg iv infusion – 7 days) micafungin in Japanese individuals. Simulations were carried out in 250 male-only subjects (10 trials x 25 subjects). Age-range: 20-31 years. Average weight: 65 kg. Red circles represent the observed mean values from the respective clinical study of micafungin[7].

Simulated micafungin profiles in the Japanese population agreed with previous findings by Azuma, 2002[7] and dose proportionality was observed over the dose range analysed.

Differences observed in the PK profile of Japanese subjects have been attributed to smaller body size[2], which is accounted for within the Simcyp Simulator.

Validation: PBPK Model I

Simcyp-Renal Impaired (GFR < 30 mL/min)

Table 1 – Simulated and observed PK parameters of micafungin in renal-impaired subjects at a dose of 100 mg (1 hour iv infusion) in 80 subjects. Age-range: 20-65 years. Average weight: 70 kg.

Description	C_{max} (mg/L)	AUC (mg/L.h)	CL (L/h)
Predicted - Trial 1	7.9	125.14	0.82
Predicted - Trial 2	8.2	138.7	0.75
Predicted - Trial 3	7.9	142.7	0.75
Predicted - Trial 4	8.3	132.5	0.79
Predicted - Trial 5	8.9	137.5	0.75
Predicted - Trial 6	9.3	134	0.76
Predicted - Trial 7	8.1	131.5	0.78
Predicted - Trial 8	9.2	147.8	0.72
Predicted - Trial 9	8.1	142.5	0.75
Predicted - Trial 10	8.2	123.6	0.85
Overall Predicted	**8.4 ± 1.3**	**135.6 ± 30.6**	**0.77 ± 0.16**
Observed	**8.2 ± 1.4**	**120.9 ± 16.7**	**0.85 ± 0.14**

RESULTS (cont'd)

The simulated concentration-time profile of micafungin (100 mg – iv) indicated no effect of renal impairment on micafungin PK parameters, which is consistent with findings that CL_{Renal} is a minor elimination pathway[5].

PBPK Model II

Retrograde Clearance Breakdown

To further develop this PBPK model, *in vivo* clearance was divided into the separate pathways involved in micafungin clearance:

CL_{Met}, CL_{Renal} and $CL_{Biliary}$

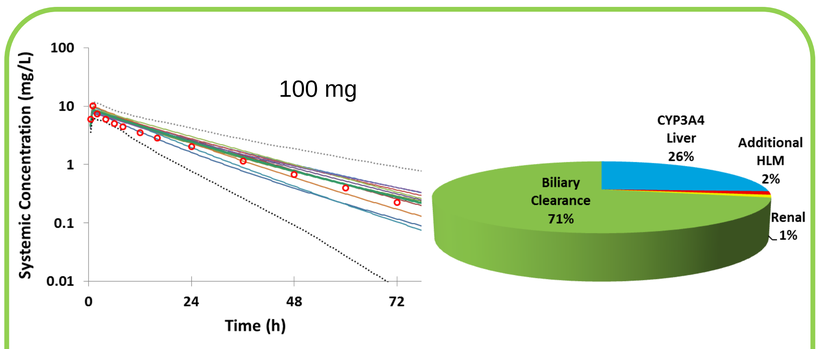

Figure 5 – Simulated and observed concentration-time profiles of micafungin in HVs for a dose of 100 mg iv infusion for 1 hour, and the predicted contribution of each pathway to micafungin clearance. Simulations were performed in 80 subjects (10 trials x 8 subjects, 63% male). Age-range: 18-65. Red circles represent the observed mean values[6].

The concentration-time profile and the relative contribution of each pathway to micafungin disposition were predicted through retrograde calculation and were consistent with observed data.

To obtain a more **mechanistic model of micafungin** disposition, the **permeability-limited liver (PerL) model** will need to be utilized, including specific transporter information.

CONCLUSION

The preliminary PBPK model for micafungin simulates concentration-time profiles consistent with *in vivo* observations in HV, Japanese and renal-impaired populations.

To refine this model to include the contribution of all pathways involved in the disposition and clearance of micafungin - important data are still largely missing:

1. Contribution of each transporter pathway to the uptake and excretion of micafungin in hepatocytes – as well as contribution of passive transport, if at all.
2. Specific transporter kinetics (K_m, J_{max}) for the excretion of micafungin by BSEP.
3. Percent contribution of each metabolic pathway to the metabolism of micafungin (f_m)

To allow extrapolation of *in vivo* values from *in vitro* transporter kinetic data, relative expression factors (REF) and relative activity factor (RAF) for the liver vs. *in vitro* systems largely remain to be determined for BSEP and NTCP.

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