

Prediction of sildenafil concentrations in the central nervous system with physiologically based pharmacokinetic modelling

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BACKGROUND

Sildenafil is widely used in the treatment of erectile dysfunction and pulmonary hypertension (1).

It crosses the blood-brain barrier and may have **neuroprotective and neurorestorative effects**. Therefore, it is a promising **candidate for drug repurposing** in neurological disorders such as Alzheimer's disease and Leigh syndrome (1).

Sildenafil is a **substrate of the efflux transporter P-glycoprotein (P-gp)**, which is expressed at the blood-brain barrier and reduces the concentration of sildenafil in the brain (2). This makes sildenafil an interesting compound for studying and predicting its distribution in the brain.

AIM

Our aim was to **establish and validate** a physiologically based pharmacokinetic model (PBPk) for sildenafil and its main active metabolite, N-desmethyl sildenafil (DMS).

In addition, the **concentration ratios** of the unbound interstitial concentration of sildenafil in the brain to the unbound plasma concentration were predicted and compared with the ratios measured in macaques (*M. fascicularis*) (3).

METHODS

MODEL DEVELOPMENT

The PBPk model was developed in **PK-Sim®**, version 12.0 (Open Systems Pharmacology).

Twenty clinical studies were used for the modelling of sildenafil, four of them for model development and others for model validation.

Fifteen clinical studies were used for the modelling of DMS, three of which were used for model development and others for model validation.

The physicochemical and pharmacokinetic properties of sildenafil and DMS (Table 1) were obtained from **the literature, optimised or estimated**.

The dosage in the clinical studies ranged **from 10 mg to 200 mg**. Sildenafil was administered **intravenously** in three studies and **orally** in the other studies.

Virtual individuals and **virtual populations** were created based on the demographic data reported in the clinical studies.

Sildenafil was modelled as a substrate for **CYP3A4**, **CYP2C9** and **P-gp**, while DMS was modelled as a substrate for **CYP3A4**.

Table 1: Physicochemical and pharmacokinetic properties of sildenafil and DMS.

Parameter	Sildenafil	DMS
Lipophilicity	3.03 log units	2.45 log units
Fraction unbound	0.04 (alpha-1-acid glycoprotein)	0.04 (alpha-1-acid glycoprotein)
Molecular weight	474.58 g/mol	460.55 g/mol
pKa1, pKa2	6.78 (base), 9.12 (acid)	7.16 (base), 11.14 (acid)
Water solubility	3.5 mg/mL	0.419 mg/mL
Blood-to-plasma ratio	0.64	/
Partition coefficient	Rodgers and Rowland	Rodgers and Rowland
Cellular permeability	PK-Sim Standard	PK-Sim Standard
kcat, Km of CYP3A4	34.44 min ⁻¹ , 15 μM	/
Vmax, Km of CYP2C9	78 pmol/min/mg, 27 μM	/
Vmax, Km transport of P-gp	114 pmol/min/pmol, 23.2 μM	/
Reference concentration of P-gp	0.077 μM	/
Specific clearance by CYP3A4	/	4.09 min ⁻¹

MODEL VALIDATION

The PBPk model was validated using the **mean relative deviation (MRD)** of all predicted plasma concentrations and the **geometric mean fold error (GMFE)** of all AUC_{inf} and C_{max}.

MODEL PREDICTION OF BRAIN CONCENTRATIONS

Two virtual populations of 100 adults (50 % female, age 30.0 years) were created based on a typical 30-year-old European. One population **expressed P-gp**, while the other did **not**.

The ratio of the **unbound interstitial concentration in the brain** to the **unbound plasma concentration** of sildenafil was determined for these two virtual populations at **0.5 h, 1.0 h, 1.5 h, 2.0 h and 2.5 h** after oral administration of **50 mg** sildenafil tablet.

The predicted ratios were compared with the measured ratios in macaques (3) at the same time points after administration using a **two-tailed t-test**.

RESULTS

MODEL DEVELOPMENT

The **sink metabolites** of sildenafil were not included in the model, as the model assumed that sildenafil is mainly **metabolised to DMS**. DMS was further metabolised to sink metabolites.

For the **P-gp reference concentration**, default settings were used for all tissues (Human Gene Expression Database), except in the intestinal mucosa, where the relative expression was multiplied by a factor of 3.57 (4).

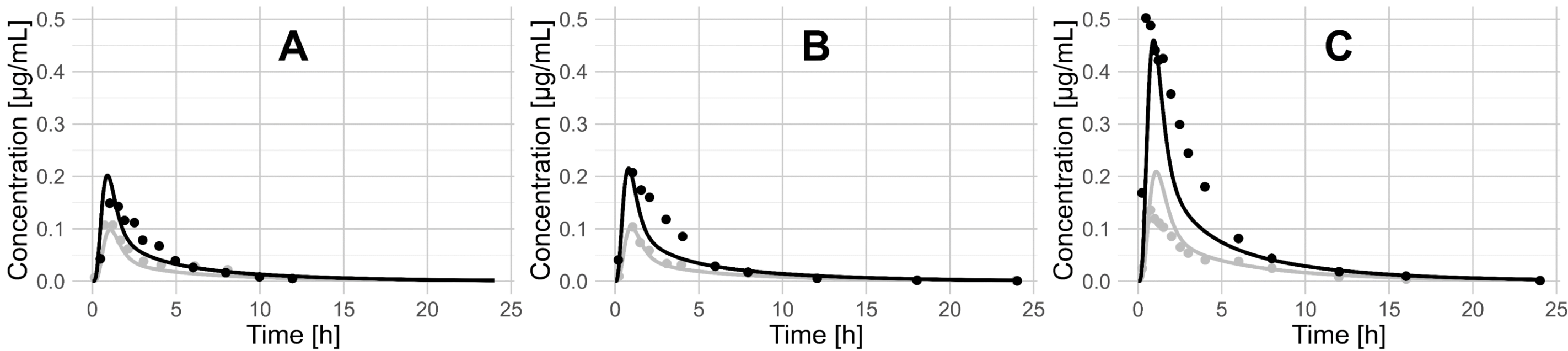


Figure 1: Predicted (solid line) and measured (dots) concentrations of sildenafil (black) and DMS (grey) after oral administration of 50 mg (A, B) and 100 mg (C) sildenafil as tablet (A, C) and oral solution (B) for the three clinical studies used for model development.

MODEL VALIDATION

The model was validated as the MRD and GMFE values were less than 2. The MRD values for sildenafil and DMS were **1.89** and **1.99**, respectively. The GMFE of AUC_{inf} for sildenafil and DMS were **1.22** and **1.35**, respectively. The GMFE of C_{max} for sildenafil and DMS were **1.47** and **1.61**, respectively.

MODEL PREDICTION OF BRAIN CONCENTRATIONS

The predicted concentration ratios were **above 0.1** at all measured time points, which corresponds to the threshold for drug crossing the blood-brain barrier (3).

In the population with P-gp expression, the predicted concentration ratios decreased over time after administration, from **0.69 at 0.5 h** to **0.51 at 2.5 h**.

Similarly, in the population without P-gp expression, the concentration ratios decreased over time after administration, from **1.21 at 0.5 h** to **0.89 at 2.5 h**.

Furthermore, **no significant differences** were observed between the predicted concentration ratios in the virtual population with P-gp expression and the measured concentration ratios in macaques (Fig. 2A; p-values between 0.347 and 0.919).

On the other hand, **significant differences** were observed between the predicted concentration ratios in the virtual population without P-gp expression and the measured concentration ratios in macaques at 2.0 h and 2.5 h after administration (Fig. 2B; p-values 0.012 and 0.020, respectively).

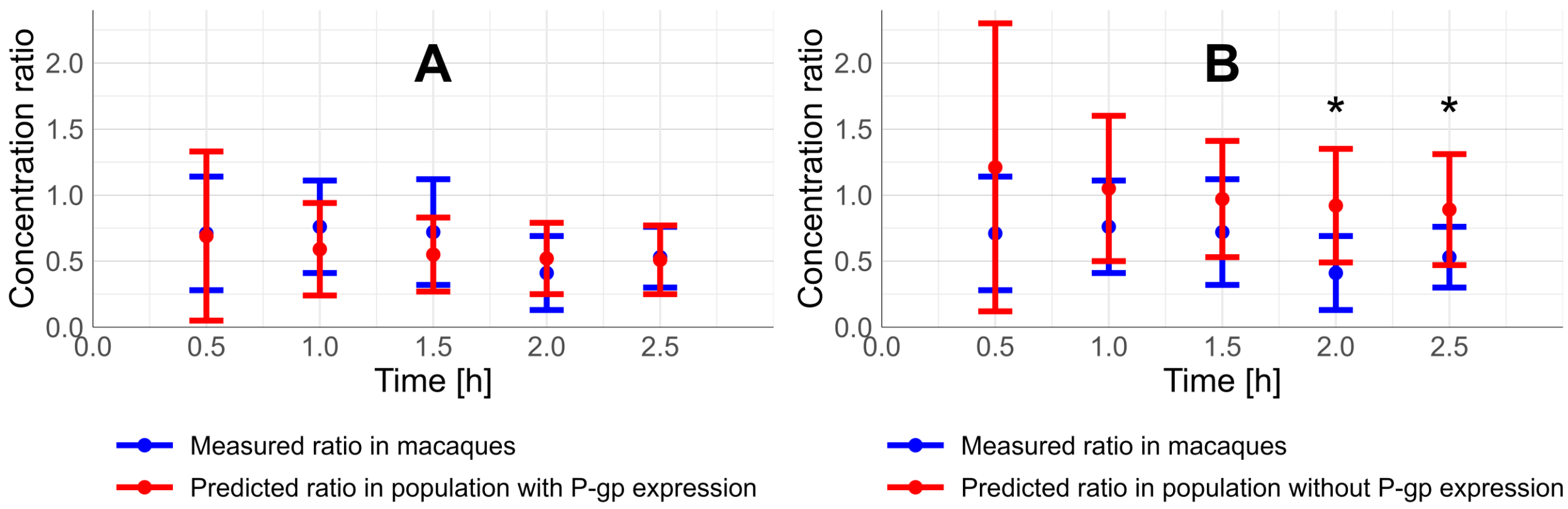


Figure 2: Measured concentration ratios of sildenafil (mean ± SD) of the unbound interstitial concentration in the brain to the unbound plasma concentration at various time points after oral administration in macaques (3) and simulated in virtual populations with P-gp expression (A) and without P-gp expression (B). * p < 0.05

CONCLUSIONS

The PBPk was **successfully developed** for sildenafil and DMS.

The inclusion of the P-gp transporter was found to be **appropriate**, as the predicted concentration ratios are closer to the values measured in macaques than when P-gp is not included.

Understanding the distribution of sildenafil in the brain enables prediction of **optimal dosing regimens** for the potential treatment of neurological disorders.

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