APPLICATION OF THE SIMCYP PBPK/PD MODEL TO SIMULATE PK AND PD OF NIFEDIPINE IN JAPANESE AND CAUCASIAN POPULATIONS

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Objective

The recent success in application of systems approach in the area of predicting pharmacokinetics (PK) has led many to believe a similar strategy for the prediction of pharmacodynamic (PD) aspects should be adopted and popularised [1]. Although the fundamentals of mechanism-based PD (MBPD) are not new, integration of these into platforms with a user-friendly interface has not taken place up until now.

The aim of this study is to assess the ability of the PD modules within the Simcyp Simulator V.11 to predict PK and PD profiles of nifedipine in *Healthy* Japanese and Caucasian populations. It is assumed that the PK and PD in the healthy populations are the same as those in the hypertensive patients, although no PD effect has been constantly observed in healthy volunteers.

Model structure

Via an effect compartment, Simcyp Mini-PBPK is linked to various Simcyp PD modules, both of which are characteristic of user-friendliness and flexibility in model selection. Besides the classical Hill function model, a semi-mechanistic PD model is available to describe the receptor-binding stimulus-response mechanism. The latter further includes the empirical, operational and/or intrinsic transduction models, all of which have been incorporated in Simcyp Population-based Simulator V.11.

As shown in Figure 1, the systemic concentration-time profile of nifedipine simulated by the Mini-PBPK model is used to drive the Simcyp PD modules to generate the PD response, which is the change in the systolic blood pressure in this study, by using various PD models and parameter settings.

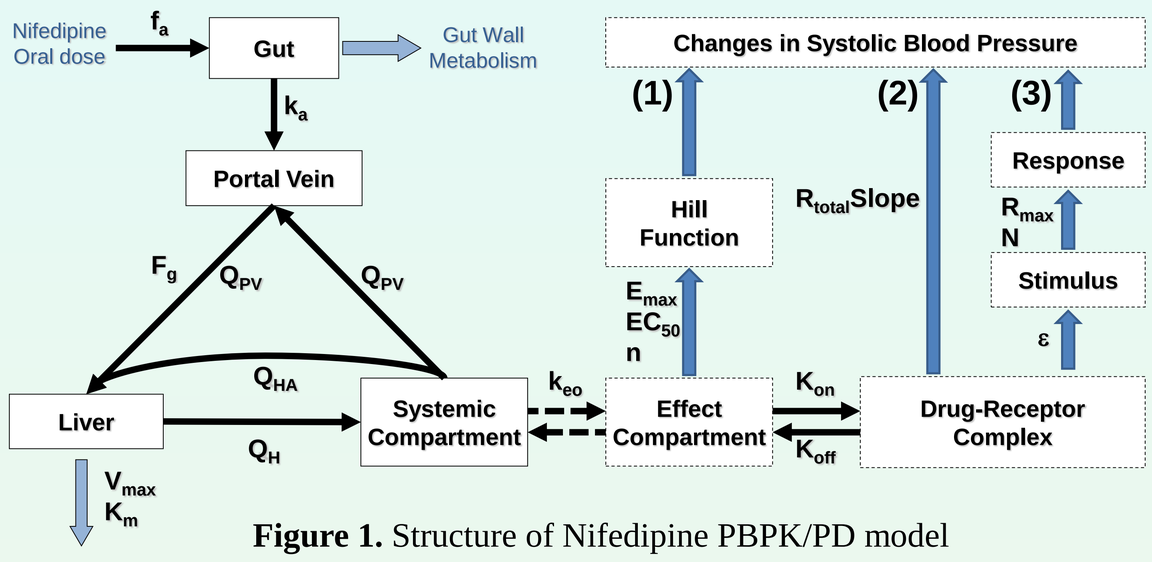


Figure 1. Structure of Nifedipine PBPK/PD model

(1: Hill function; 2: Empirical transduction; 3: Operational transduction)

Parameters for nifedipine PBPK/PD

Various PK/PD parameters of nifedipine used in this study are summarized in Table1. Mainly, all the PK data are default values of nifedipine compound in Simcyp Simulator, while the PD data are collated from Shimada *et al*. [2].

In addition to the drug-specific data, various system-specific data (such as blood flow rates, enzyme abundance etc) has been provided for various populations, including Caucasian, Japanese and Chinese in Simcyp Simulator. The current study will use these default drug- and system-related data to simulate nifedipine PK and PD in virtual *Healthy* Japanese and Caucasian populations.

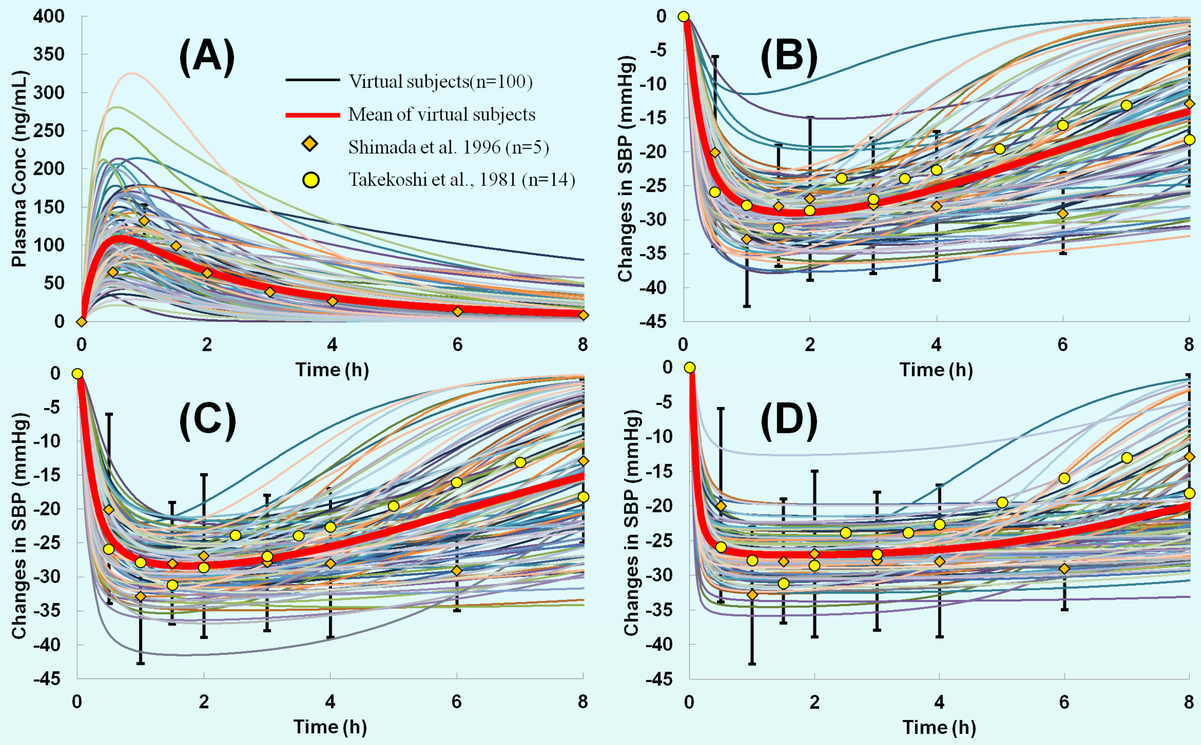
In order to verify the Simcyp predictions, nifedipine PK/PD profiles in essential hypertensive patients in Japanese and Caucasian populations [3, 4], which are reported from various clinical studies and have not been used by Shimada *et al.* in generating nifedipine PD parameters, are abstracted and used to compare to simulation results.

Table 1. Parameters of Nifedipine PBPK/PD model

Parameters0.0	Unit	Value	CV	References
f_a	-	1	30%	Simcyp default
k_a	1/h	3.67	30%	Simcyp default
F_g	-	0.68	-	Simcyp default
V_{ss}	L/kg	0.57	30%	Simcyp default
$V_{max\text{-}3A4}$	μL/min/mg	22	-	Simcyp default
$K_{m\text{-}3A4}$	μM	10.95	-	Simcyp default
$V_{max\text{-}3A5}$	μL/min/mg	3.5	-	Simcyp default
$K_{m\text{-}3A5}$	μM	31.9	-	Simcyp default
k_{eo}	1/h	0.88	32%	Shimada *et al.*
E_{max}	mmHg	-35	14%	Shimada *et al.*
EC_{50}	μM	0.035	49%	Shimada *et al.*
n	-	1	-	Shimada *et al.*
K_{on}	1/μm/h	19	40%	Shimada *et al.*
K_{off}	1/h	0.47	36%	Shimada *et al.*
K_d (=K_{off}/K_{on})	μM	0.025	-	Shimada *et al.*
R_{total}*Slope	mmHg	-33	10%	Shimada *et al.*
R_{max}	mmHg	-33	10%	Shimada *et al.*
N	-	1	-	Shimada *et al.*
τ (=f(ε, R_{total}))	-	6	30%	Assumed

Results

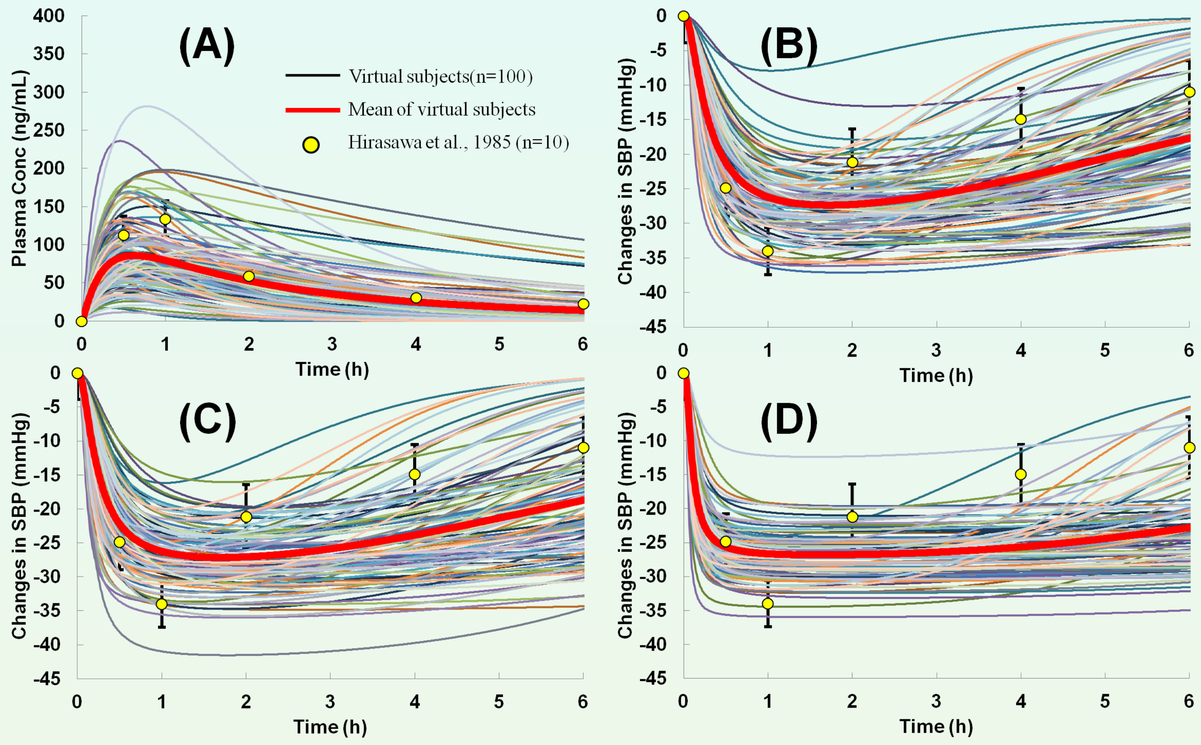
- PK/PD profiles of nifedipine in a Japanese population



(A) PK profile based on Mini-PBPK
(B) PD profile based on Hill function
(C) PD profile based on empirical transduction
(D) PD profile based on operational transduction

Figure 2. Comparison of simulated PK/PD profiles to clinical data in Japanese hypertensive patients

- PK/PD profiles of nifedipine in a Caucasian population



(A) PK profile based on Mini-PBPK
(B) PD profile based on Hill function
(C) PD profile based on empirical transduction
(D) PD profile based on operational transduction

Figure 3. Comparison of simulated PK/PD profile to clinical data in Caucasian hypertensive patients

Discussion

As shown in Figures 2 and 3, both PK and PD profiles were successfully simulated in Japanese and Caucasian populations, producing results consistent with reported clinical studies. It was observed that including an effect compartment in the PD module could improve the prediction of PD profiles. Whilst all the PD modules could describe the observed data, the operational transduction model could be considered a more mechanistic account of nifedipine pharmacological response.

Encouragingly Shimada *et al.* [2] have shown a nice relationship between the *in vivo* equilibrium dissociation constants (K_d) of various calcium channel blockers including nifedipine and their respective affinity binding constants obtained from *in vitro* binding studies. Similar to the IVIVE of PK, various data from *in vitro* binding assays could be used to predict *in vivo* PD response, via the mechanism-based PK/PD models implemented within the Simcyp Simulator.

Conclusions and further development

- Implemented PK/PD models within the Simcyp Simulator are able to simulate both the PK and PD profiles of nifedipine in Japanese and Caucasian populations.
- Further applications could be envisaged which are facilitated by the new PBPK/PD link models.
- Various information obtained from *in vitro* binding assays will benefit the mechanism-based IVIVE in PD.

References

[1] Atkinson & Lyster, *Clin Pharmacol Ther* (2010) 88: 3-6.
[2] Shimada *et al.*, *Biol Pharm Bul* (1996) 19: 430-437.
[3] Takekoshi *et al.*, *Jpn Circ J* (1981) 45: 852-860.
[4] Hirasawa *et al.*, *Eur J Clin Pharmacol* (1985) 28: 105-107.