Population pharmacokinetic model of sildenafil describing first-pass effect to its metabolite

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BACKGROUND

Although sildenafil is an old drug, its population PK has been rather neglected. This PK modeling was performed to investigate the PK characteristics of sildenafil (Viagra®) using data from several different comparative PK studies in healthy male Korean subjects. The major active metabolite (N-desmethyl sildenafil, NDS) was also modeled.

METHODS

Non-linear mixed effect analysis (NONMEM ver 7.2) was performed using a total of 6,130 observations (3,065 for each chemical entity) from 223 subjects (27.5 observations / subject) obtained after single 50-100 mg sildenafil citrate dose in 5 PK studies. The samples were collected just before and 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 12 and 24 hours after dosing. First-order conditional estimation method with interaction option was used for all applicable minimization process.

RESULTS

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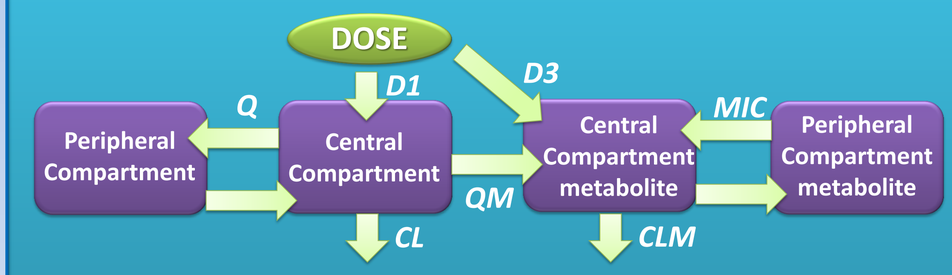
A two-compartment first-order elimination model was finally chosen for both sildenafil and NDS. The absorption of sildenafil and the first-pass metabolism to NDS were best with zero-order process. The population PK parameter estimates are summarized in the table.

FINAL MODEL STRUCTURE



GOODNESS OF FIT PLOT

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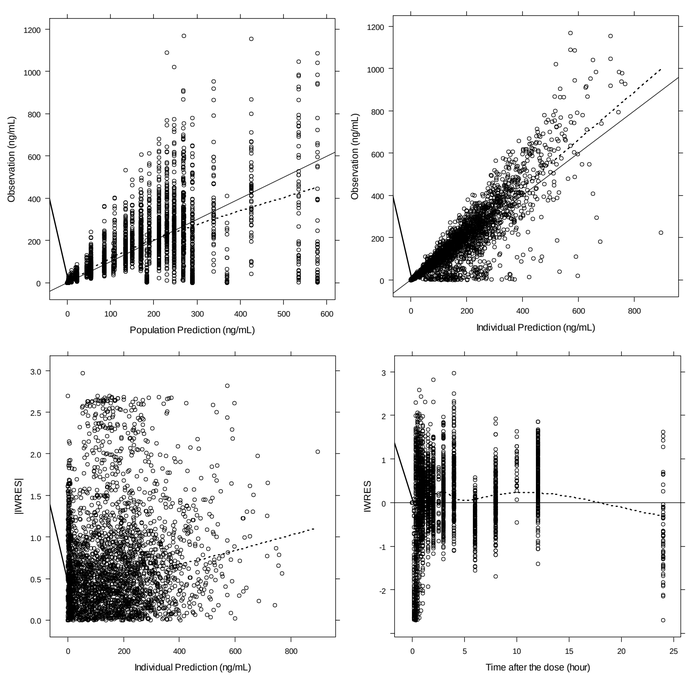
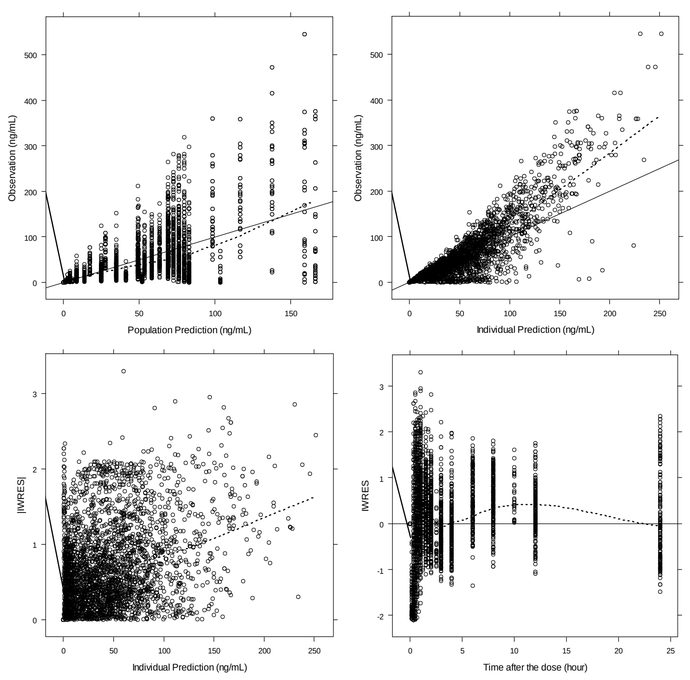


Metabolite



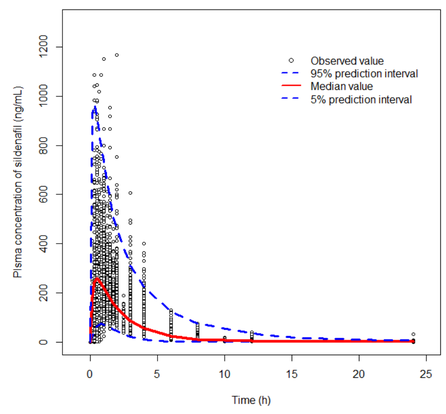
PATIENT DEMOGRAPHICS

Variable[a]	Mean (range)
Age (years)	24.5 (20 – 41)
Sex (male/female)	223 / 0
Weight (kg)	68.4 (50.5 – 92.9)
Bilirubin	0.874 (0.32 – 1.74)
AST	20.3 (12 – 37)
ALT	19.2 (7 –53)

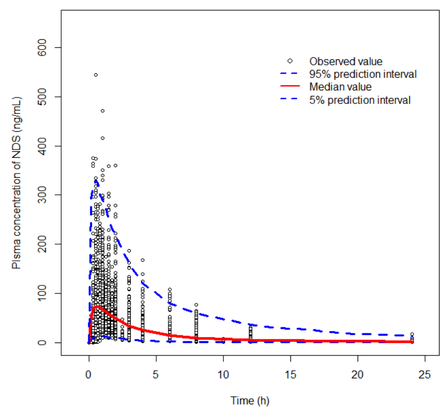
[a]Mean (range) for continuous variables and actual number of subject for categorical variables were presented

VPC PLOT

Parent



Metabolite



FINAL PARAMETER ESTIMATES

Parameter	Description (units)	Estimate
Fixed Effects		
CL	*Clearance (L/h)*	10.3
V1	*Volume of central compartment (L)*	124
D1	*Duration for central compartment (h)*	0.28
V2	*Volume of peripheral compartment (L)*	272
Q	*Inter-compartmental clearance (L/h)*	6.01
QM	*Inter-compartmental clearance, patrent-metabolite (L/h)*	40.8
CLM	*Clearance, metabolite (L/h)*	126
MIC	*Inter-compartmental clearance, metabolite (L/h)*	46.4
F1	*Bioavailability for central compartment*	0.78
Inter-individual variability (Estimates presented in CV%)		
ω_{CL}^2	*BSV of CL*	32.5
ω_{V1}^2	*BSV of V1*	12.8
ω_{D1}^2	*BSV of D1*	95.4
ω_{QM}^2	*BSV of QM*	11.2
ω_{CLM}^2	*BSV of CLM*	21.8
ω_{MIC}^2	*BSV of MIC*	10.5
Intra-individual variability		
Σ_1^2	*Residual error (proportional)*	0.371
Σ_3^2	*Residual error (proportional, metabolite)*	0.476

RSE : Relative standard error
95% CI : 95% Confidence interval

CONCLUSION

The first pass effect model successfully described the time-concentration profile of sildenafil and its major metabolite in this population PK model.

REFERENCE

1. Peter A. Milligan, Scott F. Marshall, Mats O. Karlsson(2002) 'A population pharmacokinetic analysis of sildenafil citrate in patients with erectile dysfunction', British Journal of Clinical Pharmacology, 53: 1, 45 – 52
2. Donald J. Nichols, Gary J. Muirhead, Jane A. Harness(2002) 'Pharmacokinetics of sildenafil after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality', British Journal of Clinical Pharmacology, 53: 1, 5 – 12
3. D. K. Walker, M. J. Ackland, G. C. James, G. J. Muirhead□D. J. Rance, P. Wastall, P. A. Wright(1999) 'Pharmacokinetics and metabolism of sildenafil in mouse, rat, rabbit, dog and man', XENOBIOTICA, 29: 3, 297 – 310
4. Gary J. Muirhead, Keith Wilner, Wayne Colburn, Gertrude Haug-Pihale, Bernhard Rouviex(2002) 'The effects of age and renal and hepatic impairment on the pharmacokinetics of sildenafil citrate', British Journal of Clinical Pharmacology, 53: 1, 21 – 30