Development of a Population Model to Describe Diurnal and Chronokinetic Variation in Cilostazol Pharmacokinetics

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OBJECTIVES

Diurnal variation, characterized by higher C_{max} and shorter T_{max} after the morning dose in oral twice-a-day treatment, has been reported in many lipophilic drugs, which is known to occur due to higher gastrointestinal perfusion rates and faster gastric emptying times in the morning. [1-3] The primary purpose of this study was to investigate such variation in cilostazol pharmacokinetics (PK) , and assess seasonal or chronokinetic variation of the drug also. The secondary purpose was to explain the pharmacokinetic relationship between the parent drug (cilostazol, OPC-13013) and its potent active metabolite, OPC-13015.

METHODS

A total of 1,856 plasma concentrations ware obtained from 2 PK studies recently conducted in healthy Korean subjects, Study 1 conducted in 26 subjects in February (winter), and Study 2 conducted in 37 subjects in August (summer). A population model was developed using NONMEM 7. To model diurnal variation, the circadian rhythm consisting of cosign functions with various periods were incorporated into the absorption rate constant (KA). Study effect was described as a covariate influencing the typical value of PK parameters. On the assumption that the PK of OPC13015 doesn't affect the PK cilostazol, the model building for the metabolite was conducted after completing the modeling for the parent drug. The central volume of metabolite was fixed to 1. The developed model was then validated using visual predictive check (VPC) using 1000 simulated datasets.

RESULTS

Part 1. Model Building for the Parent Drug

A two compartment model with first order absorption was selected for fixed effect, and proportional models for inter and intra-individual errors, allowing for a lag time. The final estimated values (RSE%) of KA, oral clearance (CL/F), central volume (Vc/F), inter-compartment clearance(Q/F), peripheral volume (Vp/F) and lag time (LAG) were 0.249 hr^{-1} (25.2%), 13.8 L·hr^{-1} (6.61%), 30.7 L (31.4%), 15.0 L·hr^{-1} (13.2%), 88.0 L (10.2%), and 0.443 hr (12.8%) , respectively. The circadian rhythm was best described by the combination of periods of 24 and 12 hrs, yielding estimated values (RSE%) of amplitude and acrophase for 24 hour rhythm being 0.185 (16.1%) and 1.50 (48.4%), and those for 12 hour rhythm being 0.337 (17.3%) and 7.24 (5.62%), which decreased OFV by 356.658 Study differences were found significant in CL/F and KA2M ($p<0.001$), yielding 9.43 L·hr^{-1} and 8.80 hr in Study 1 versus 13.8 L·hr^{-1} and 7.24 hr in Study 2, respectively.

Table 1. Final Parameter Estimates of the Parent Drug Model with Circadian and Chronokinetic Variation

Parameter (units)	Definition	Value	RSE(%)	CV(%)	RSE(%)
KA (hr^{-1})	Absorption rate	0.249	25.2%	29.0%	22.7%
CL (L/hr)	Clearance (CL/F) for Study 2	13.8	6.61%	28.6%	21.4%
CL_STUDY	Study effect on CL	-0.317	19.6%		
CL_STUDY1	Clearance for Study 1 = CL * (1 + CL_STUDY)	9.43			
V2 (L)	Central volume (Vc/F)	30.7	31.4%		
Q3 (L/hr)	Intercompartmental clearance (Q/F)	15.0	13.2%	17.8%	146%
V3 (L)	Peripheral volume (Vp/F)	88.0	10.2%	53.3%	19.9%
ALAG1 (hr)	Lag time (LAG)	0.443	12.8%		
KA1	Amplitude for 24-hour rhythm	0.185	16.1%	71.1%	35.0%
KA1M (hr)	Acrophase for 24-hour rhythm	1.50	48.4%		
KA2	Amplitude for 12-hour rhythm	0.337	17.3%	25.1%	69.7%
KA2M (hr)	Acrophase for 12-hour rhythm for Study 2	7.24	5.62%		
KA2M_STUDY	Study effect on KA2M	0.216	23.8%		
KA2M_STUDY1	Acrophase for 12-hour rhythm for Study 1 = KA2M * (1 + KA2M_STUDY)	8.80			
Proportional Residual Error				31.5%	3.63%

Figure 1. Basic Model (upper) vs. Final Model (lower)

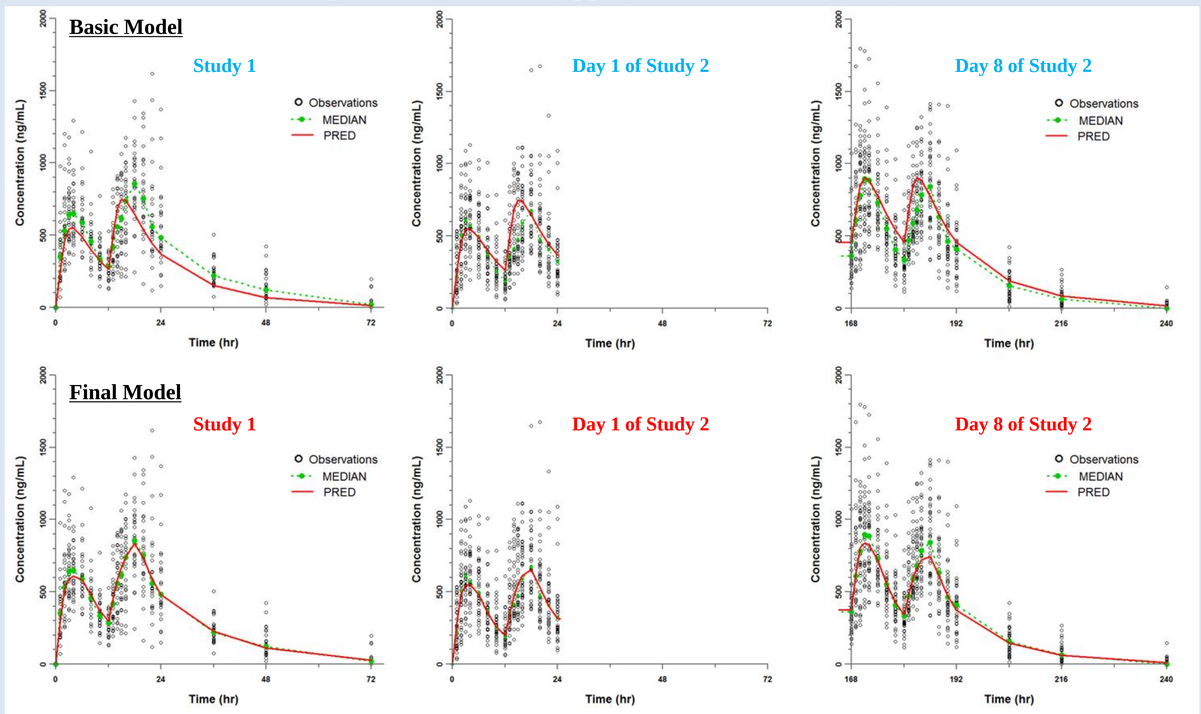


Figure 2. Goodness of Fit Plots of the Basic Model (upper plots) and the Final Model (lower plots)

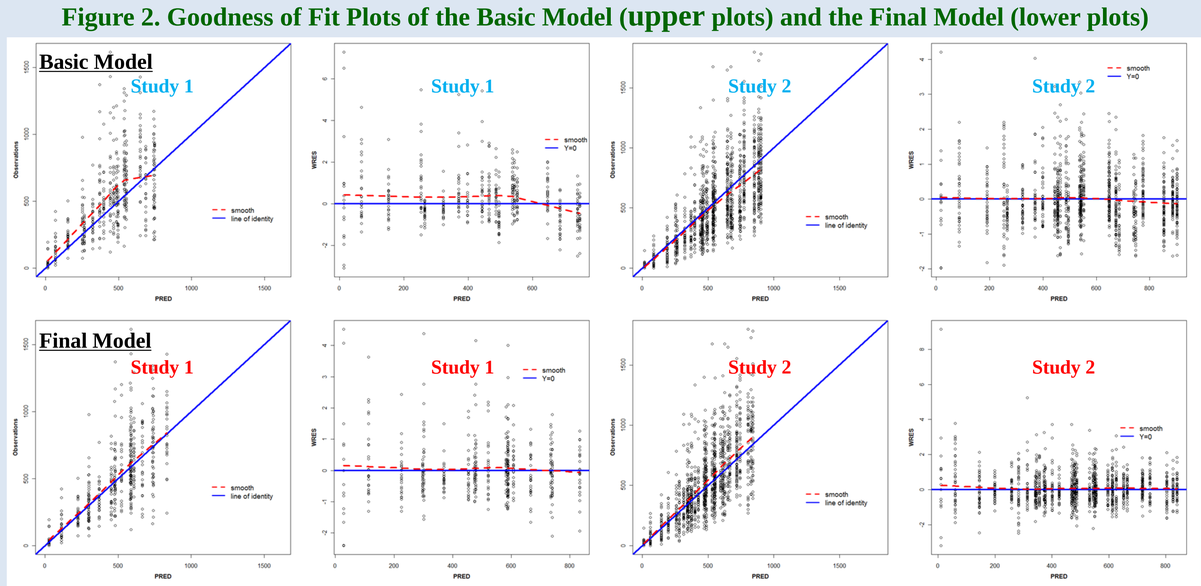
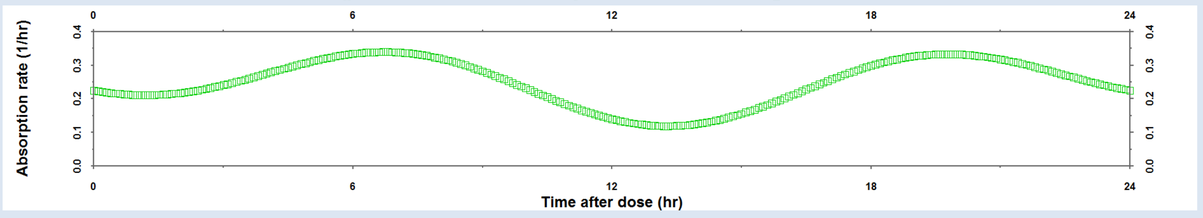


Figure 3. Circadian Rhythm of the Absorption rate



Part 2. Model Building for the Metabolite

A two compartment model was selected for fixed effect in the metabolite model, and proportional models for individual errors. The final estimated values (CV%) of Q4, CLM, V5, and Q5 were 1.12 L·hr^{-1}, 3.30 L·hr^{-1} (18.4%), 8.84 L (30.9%), and 15.0 L·hr^{-1} (21.5%), respectively.

Figure 4. Pharmacokinetic model for cilostazol and OPC-13015

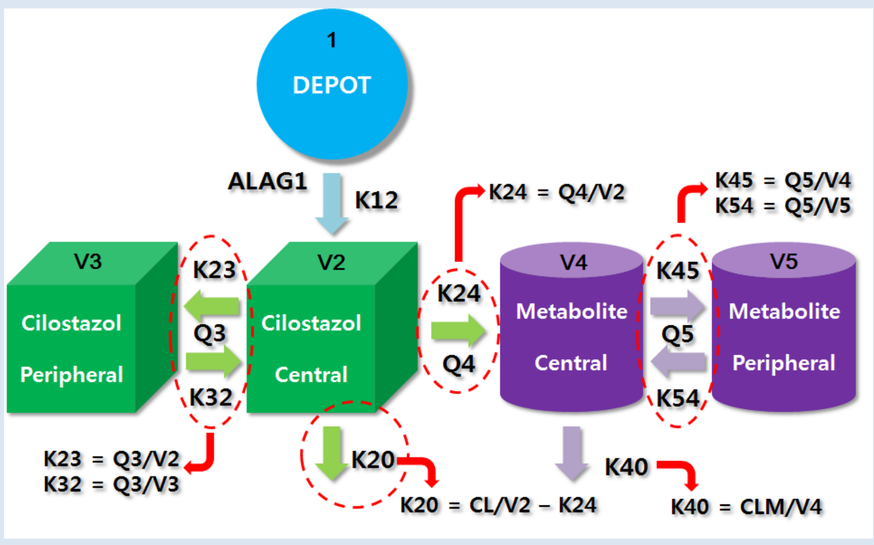


Figure 5. Prediction (upper) and Goodness of Fit (lower) plots of the Metabolite Model

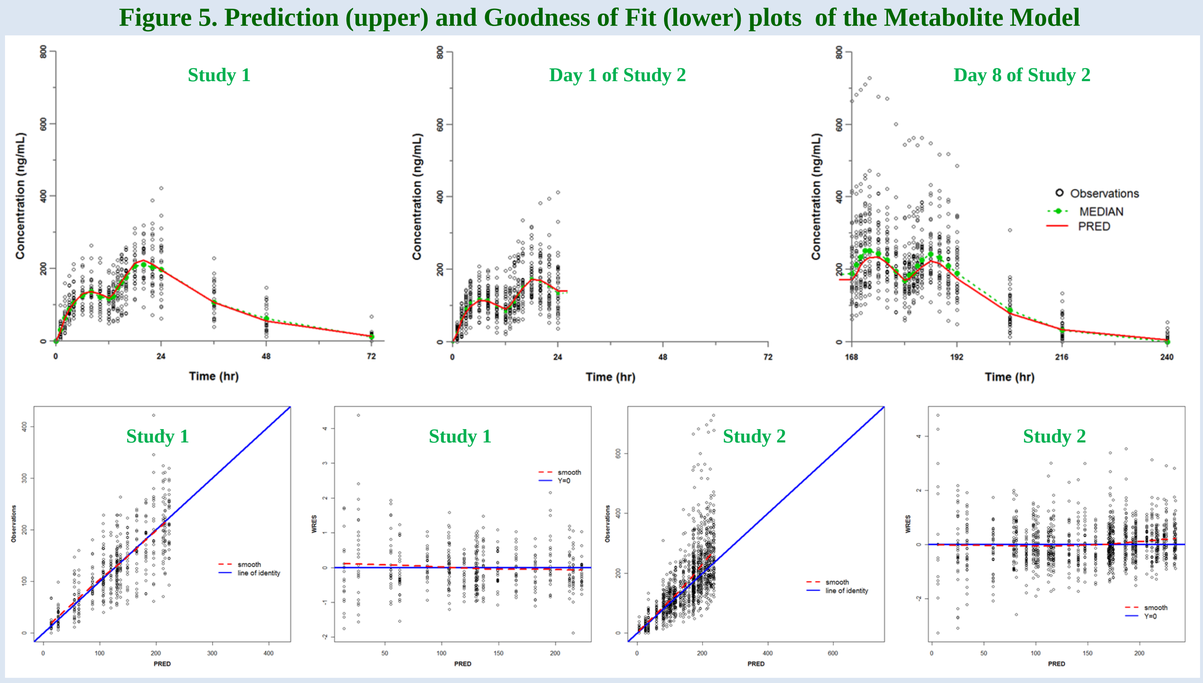
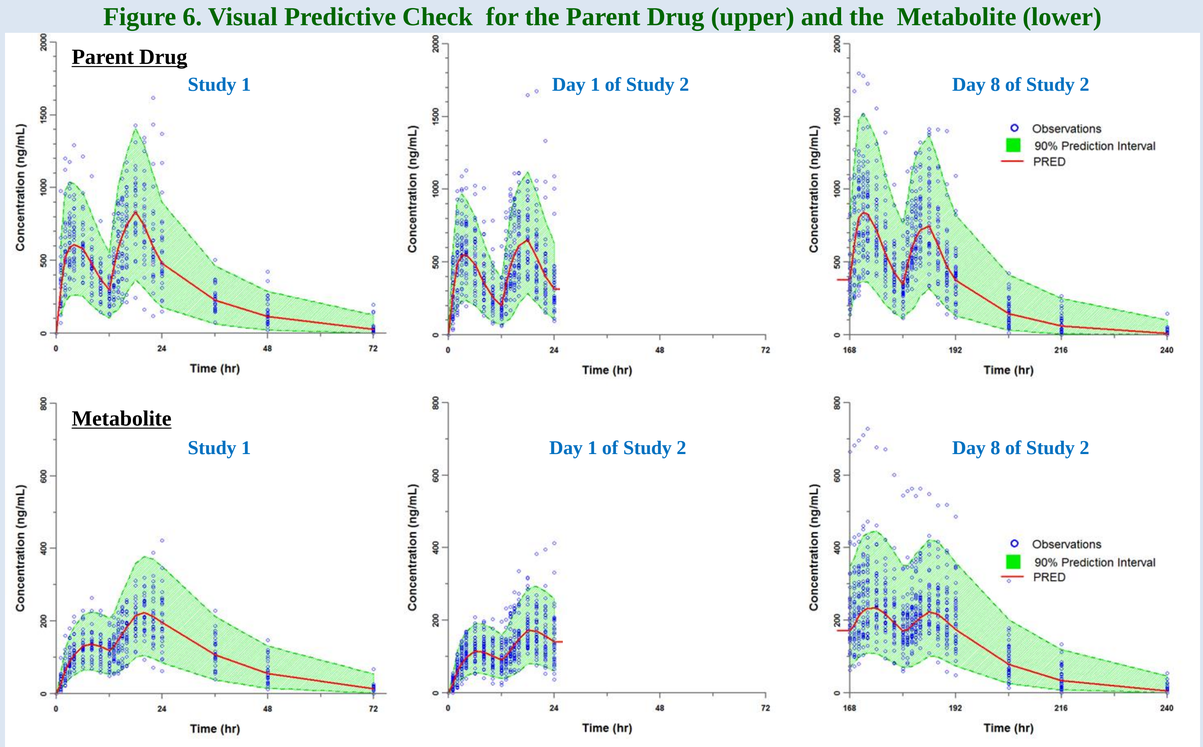


Figure 6. Visual Predictive Check for the Parent Drug (upper) and the Metabolite (lower)



CONCLUSIONS

These results show that cilostazol PK in Korean population are influenced not only by diurnal variation but also by seasonable variation, indicating the importance of considering such variations in optimal drug therapy of this drug. To validate our results, further study with more patients will be necessary.

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