Development and evaluation of a population pharmacokinetic model for cilobradine, an I_f channel blocker

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Background

The I_f channel blocker cilobradine belongs to a class of bradycardic agents selectively decreasing heart rate by reducing the diastolic depolarisation rate in the sinus node. Hence, cilobradine might be beneficial in the treatment of cardiovascular diseases, e.g. ischemia.

Objectives

To describe the population pharmacokinetics (PopPK) of cilobradine based on data of 6 clinical phase I trials with different formulations (development data set)

To identify covariates in the development data set (study, laboratory and demographic characteristics) influencing the pharmacokinetics of cilobradine

To evaluate the predictive performance of the developed PopPK model using data of a different clinical trial with cilobradine (phase Ib; evaluation data set)

Data and Methods

Study design

The development data set included PK profiles of 162 healthy male subjects with 2733 plasma samples over a dose range of 0.6-40 mg, three different formulations (p.o. solution, p.o. capsule, i.v. infusion), single and multiple dosing, laboratory and demographic characteristics [Table 1; Table 2].

The evaluation data set contained PK profiles of 76 healthy subjects (70 males/6 females) with 1713 plasma concentrations of p.o. solution over a dose range of 0.25-5 mg [Table 1].

Table 1. Study characteristics

	Subjects	Observations	Formulation	Dose range [mg]	Dosing
development data set					
Study A	42	344	p.o. solution	1.25, 2.5, 5, 10, 20, 30, 40	SD [b]
Study B	23	264	i.v. infusion	2.5, 5, 10, 15	SD
Study C	18 [a]	903	p.o. solution p.o. capsule i.v. infusion	10	SD x 3 (cross-over)
Study D	30	882	p.o. capsule	5, 10, 20	MD [c] (qd, 7 d)
Study E	24	236	p.o. capsule	10, 20	SD
Study F	25	104	p.o. capsule	0.6, 1.25, 2.5	MD (qd, 15 d)
evaluation data set					
Study G	76	1713	p.o. solution	0.25, 0.5, 1, 2, 5	MD (qd, 14 d)

[a] Corresponding to 53 different plasma profiles
[b] Single dosing
[c] Multiple dosing

Table 2. Laboratory and demographic characteristics of the development data set

Laboratory characteristics	Median (range)
Heart rate at rest [min^{-1}]	64 (48-93)
BP_{syst} at rest [mmHg]	131 (105-160)
BP_{diast} at rest [mmHg]	75 (51-90)
Creatinine Clearance [mL/min]	114.8 (76.4-175.2)
AST [U/L]	10.9 (5-24)
ALT [U/L]	11 (2-25.6)
GGT [U/L]	13 (4.4-52.6)
AP [U/L]	104.4 (45-175.2)
LDH [U/L]	129 (93.4-208)

Demographics	Median (range)
Age [years]	29 (18-54)
Height [cm]	180 (164-192)
Weight [kg]	76 (57-102)

BP_{syst}: systolic blood pressure
BP_{diast}: diastolic blood pressure
AST: aspartate aminotransferase
ALT: alanine aminotransferase
GGT:gamma-glutamyl transferase
AP: alkaline phosphatase
LDH: lactate dehydrogenase

Pharmacokinetic data analysis

NONMEM, version V, level 1.1 with FOCE INTERACTION estimation method was used for data analysis. Covariates were tested by forward inclusion (p=0.05 with 1 df) and backward deletion (p=0.001 with 1 df) techniques. The predictive performance of the final PopPK model was evaluated by estimating its fixed and random effects parameters using the evaluation data set and by simulations (n=500) of the evaluation data set based on the final PopPK model.

Results

A 3-compartment model with first-order absorption and elimination (ADVAN 12, TRANS 4) provided the best fit to the data. The first distribution process revealed administration route-dependent characteristics; after i.v. dosing the initial distribution phase was faster than after p.o. dosing. Therefore, V2, V3 and Q3 were separately estimated for i.v. or p.o. data. Figure 1 represents the structural model of cilobradine. Covariate analysis revealed a statistically significant relation between KA and dose which was best described by a positive saturation function. Results of estimated parameters of the final PopPK model of cilobradine are listed in Table 3, goodness of fit plots are given in Figure 2.

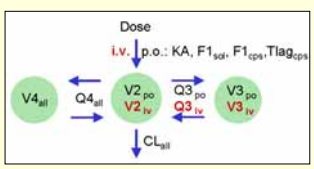

Figure 1. Schematic structural model of cilobradine

Table 3. Results of estimated parameters of the final PopPK model of cilobradine based on the development data set or on the evaluation data set

Model parameter		Development data set		Evaluation data set	
		EST [a]	RSE [b]	EST	RSE
CL	[L/h]	21.5	6	18.7	9
V2	[L]	9.10 (p.o.) / 24.5 (i.v.)	24 / 8	9.03	14
V3	[L]	33.8 (p.o.) / 52.9 (i.v.)	13 / 7	52.6	9
V4	[L]	52.9	12	85	16
Q3	[L/h]	6.61 (p.o.) / 99.8 (i.v.)	16 / 6	8.07	14
Q4	[L/h]	1.34	7	0.997	18
KA_{max}	[h^{-1}]	0.43	5	0.408 [c]	5
$Dose_{KA50}$	[mg]	1.00	15	0.0000 [c]	> $7 \cdot 10^7$
$Tlag_{cps}$	[h]	0.154	52	n.a.	n.a.
F1	[%]	34 (sol) / 43 (cps)	6 / 7	34 [d]	n.a.
Inter-individual variability					
ω CL	[%CV]	25	15	28	30
ω F1	[%CV]	34 [e]	16	39	22
ω KA	[%CV]	15	26	15	30
ω $V2_{iv}$	[%CV]	46	19	n.a.	n.a.
$Covariance_{CL/V2iv}$		0.0306	28	n.a.	n.a.
Residual error					
σ proportional	[%CV]	26	7	20	7

[a] Population estimate
[b] Relative standard error in percent (standard error divided by population estimate *100; for the random effects parameters RSE is related to the corresponding variance scale)
[c] Without covariate relation the objective function value did not change
[d] Fixed parameter
[e] Same variance of F1 for p.o. solution and p.o. capsule coded as SAME BLOCK
n.a.: not applicable

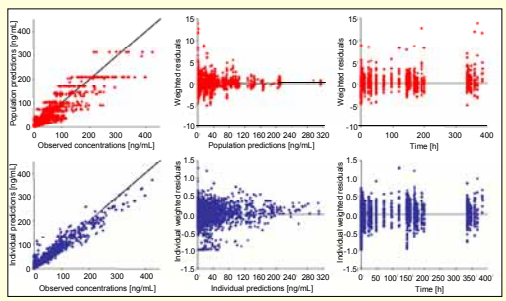

Figure 2. Goodness of fit plots of the final PopPK model based on the development data set

The estimates of the evaluation data set based on the final PopPK model were very similar to those of the development data set except of the covariate relation which was not supported by the evaluation data set [Table 3]. Simulations of the evaluation data set based on the final PopPK model but without the covariate relation revealed that almost all observed concentrations of the evaluation data set were covered by the 90% prediction interval of the simulated concentrations [Figure 3].

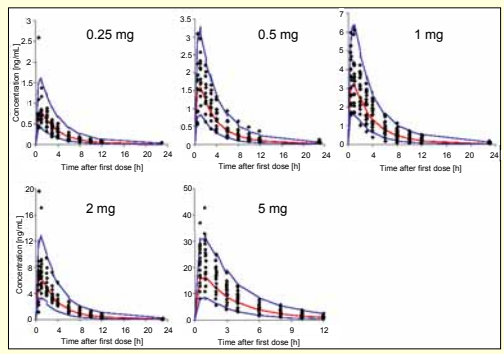

Figure 3. 5th (lower blue line), 50th (red line) and 95th percentiles (upper blue line) of the simulated concentration-time profiles and observed concentrations (black dots) of the evaluation data set of the first dosing occasion

Conclusions

- A PopPK model has been successfully developed describing the plasma concentration-time course of cilobradine after administration of different formulations.
- As the covariate relationship found in the development data set was based on a limited number of data in the low dose range and could not be confirmed in the evaluation dataset it should be revisited in a larger population, preferentially in the target patient population.
- The PopPK model was suitable to sufficiently predict concentrations of a different study design. Therefore, the model can serve as a tool to simulate and evaluate different dosing regimens for further clinical trials.