A new CNS active drug and its metabolite: a population pharmacokinetic analysis

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Background and Objectives

A population pharmacokinetic (PK) model for a new CNS active drug in clinical development and its metabolite was to be developed. In addition, the model development was intended to include an initial screening for covariates that might influence the PK characteristics of the drug and/or its metabolite.

Subjects and Methods

Study characteristics

Plasma concentration-time profiles of 119 subjects of four phase I and two phase IIa studies [Tables 1 and 2, Figure 1] consisting of 1819 parent compound and 1333 metabolite concentrations were included in the population PK analysis.

Table 1. Study characteristics

Study	Clinical Phase	Dose Route	Dosing	Population	Number of Subjects	Number of Samples* Parent Compound	Metabolite
A	I	intravenous	single dosing	healthy	21	409	21
B	I	oral	single dosing	healthy and renally impaired	30	498	454
C	I	oral	multiple dosing	healthy	12	315	297
D	I	oral	multiple dosing	healthy	12	240	220
E	IIa	oral	multiple dosing	patient	24	115	106
F	IIa	oral	multiple dosing	patient	20	242	235

*concentrations above LOQ

Table 2. Subject demographics

		Median	Mean	Minimum	Maximum
Age	[years]	62	55.4	21	80
Weight	[kg]	80	80.7	54	120
Height	[cm]	174	173.7	147	190
Body mass index	[kg/m^2]	25.9	26.7	20.4	39.4
Serum creatinine	[µmol/L]	88.4	112.8	53.04	607.9
Creatinine clearance*	[mL/min]	86.6	86.1	13.98	148.2

Number of Subjects	
Sex	
men	83
women	36
Smoker	
non-smoker	85
former	16
current	18

*calculated by Cockcroft-Gault formula

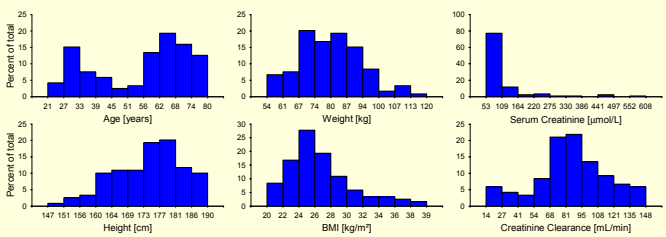

Figure 1. Distribution of continuous covariates

Pharmacokinetic data analysis

The structural model was developed in a stepwise manner, starting with a one-compartment model for parent compound and metabolite, respectively. Initially all interindividual variability was modeled using an exponential random effect model. Residual variability was modeled using proportional or combined error models.

Influence of covariates was investigated using a predefined forward inclusion and backward elimination process. All analyses were performed using the software NONMEM, version V, level 1.1; ADVAN 5 subroutine; the FOCE INTERACTION estimation method was applied.

Results

Base Model

Plasma concentration-time profiles were best described by a two compartment model for the parent compound as well as for the metabolite [Figure 2]. Metabolic formation was accounted for by a transfer constant (K_{MET}) between the central compartments of both compounds. K_{MET} was fixed to a value reflecting the recovery of the metabolite in urine (7%). The parameter estimates for parent drug and metabolite [Table 3] revealed large volumes of distribution and low clearances resulting in long half-lives. Moderate to high interindividual variability was determined for the PK parameters CLP, CLM, V_2, V_4 and F1. A proportional error model was included for the parent compound and the metabolite to describe the residual variability.

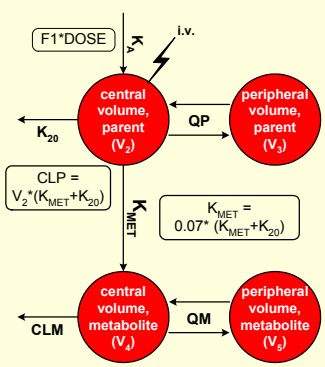

Figure 2. Schematic PK model

Covariate Screening

During initial covariate screening women were found to have an 35% increased bioavailability compared to men. Creatinine clearance (CLCR) and study were found to have a statistically significant influence on the central volume of the metabolite (V_4). No other covariates revealed a statistically significant influence on the PK properties.

Further exploration by simulation studies showed that the sex effect on bioavailability might have a clinically significant influence on the plasma concentration-time profiles, influences of CRCL and study on V_4, however, were negligible.

Table 3. Parameter estimates of PK model

Model Parameter	Units	Population Estimate	Relative Standard Error %
K_A	[h^{-1}]	0.32	9.9
V_2	[L]	213	23.6
QP	[L/h]	201	16.8
V_3	[L]	564	5.5
CLP	[L/h]	2.19	6.4
V_4	[L]	24.1	19.5
QM	[L/h]	6.77	11.6
V_5	[L]	141	10.1
CLM	[L/h]	0.42	7.4
F1	[%]	117	7.4
Interindividual variability			
IIV CLP	[%CV]	25.0	13.0
Corr (ω^2_{CLP}, ω^2_{CLM})		0.801	14.5
IIV CLM	[%CV]	41.4	13.7
IIV V2	[%CV]	43.9	35.1
IIV V4	[%CV]	115.3	19.3
IIV F1	[%CV]	24.3	20.2
Residual error			
σ prop. parent	[%CV]	14.1	7.0
σ prop. metabolite	[%CV]	14.3	9.0

Corr: correlation coefficient

ω^2: diagonal elements of the Ω variance-covariance matrix

Discussion

Base Model

A population PK model has successfully been developed describing adequately the plasma concentration-time profiles of the parent compound and its metabolite [Figures 3 and 4]. All parameters were estimated with good precision.

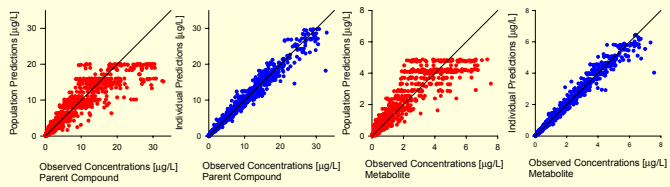

Figure 3. Goodness of fit plots; population (red) and individual (blue) predictions respectively versus observed plasma concentrations of parent compound (left) and metabolite respectively (right)

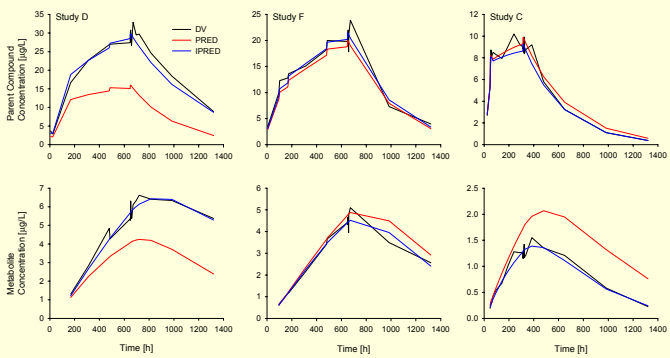

Figure 4. Individual parent compound (upper panel) and metabolite (lower panel) plasma concentration time profiles of randomly selected subjects; DV: observed plasma concentration; PRED: population prediction; IPRED: individual prediction

Covariate Screening

Initial covariate screening showed a higher bioavailability for women compared to men. As sex and weight were highly correlated more data is needed to clearly differentiate between these two covariates. In study A with intravenous administration only men were included. To confirm that the difference in exposure is due to bioavailability differences in women and men and not due to clearance differences data after intravenous administration in women would be helpful. Influence of covariates will be further evaluated in a larger number of subjects presumably exhibiting wider distributions of covariates.

Summary

- A population PK model has successfully been developed describing the plasma concentration-time profiles of the parent compound and its metabolite
- Interindividual variability was determined for CLP, CLM, V_2, V_4 and F1
- Women were found to have an increased bioavailability compared to men
- No other covariates were found to have a clinically relevant influence on the PK characteristics of parent compound and metabolite
- Influence of covariates will be further evaluated in a larger number of subjects presumably exhibiting wider distributions of covariates
- The model developed might serve as a tool to simulate and evaluate different dosing regimens for further clinical trials