

Population pharmacokinetic modelling of pimozide and its relation to CYP2D6 genotype

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BACKGROUND

Pimozide is a dopamine receptor antagonist used to treat Gilles de la Tourette's syndrome as well as schizophrenia. Pimozide is mainly metabolised in the liver and metabolism is believed to be mediated mainly by the cytochrome P450 isoenzyme CYP3A4 [1, 2] and to a lesser extent by CYP2D6 [3]; CYP1A2 may also be involved [4]. Significant interindividual variability of pimozide pharmacokinetics has been reported in both adults and children with Tourette's syndrome [5]. Side-effects associated with pimozide administration are QTc prolongation and potentially fatal ventricular arrhythmia [4]. The clinical occurrence of pimozide-induced arrhythmias is dose (concentration) dependent and therefore investigation of the determinants of pimozide exposure is important to reduce the cardiac risk.

OBJECTIVE

The objective of this work is to characterize the population pharmacokinetics of pimozide in healthy male and female volunteers with focus on the role of different CYP2D6 phenotypes in pimozide disposition and on factors affecting inter individual variability in pimozide pharmacokinetics.

STUDY DESIGN AND METHODS

- Open labelled study to investigate the safety and pharmacokinetics of oral pimozide 2mg in 32 healthy volunteers (13M/19F)
- Subjects ranged in age from 18 to 48 years
- 15 plasma samples taken at the following time-points: pre-dose, 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, 120 hours post dose
- plasma samples were analyzed for pimozide using a validated analytical method based on liquid-liquid extraction, followed by HPLC-MS/MS analysis. The lower limit of quantification (LLQ) was 0.05 ng/mL
- Tested covariates were, Age, Sex, Body Weight and CYP2D6 metabolic status
- In order to predict the volunteers' CYP2D6 metabolic status, pharmacogenetic samples were analyzed for CYP2D6 genotype known to alter the enzymatic function. Based on their genotype, the subjects had the following CYP2D6 metabolic status: Extensive - EM (N=26), Intermediate - IM (N=4) and Poor - PM (N=2)
- All modeling efforts were conducted using NONMEM V1 with FOCE-INTERACTION method. Covariate model building made use of stepwise generalized additive modelling (GAM), as implemented in Xpose4

MODEL DEVELOPMENT

Base Model

Based on visual inspection of the individual concentration time profiles as well as from the available literature data [5], a two-compartment model with first-order absorption, and lag-time was implemented for Pimozide as base model (ADVAN4 TRANS4). Inter-individual variability was assumed as log-normal for each pharmacokinetic parameter. The base model was used to identify the best error structure for describing the residual variability σ (mixed proportional and additive error).

Final Model Development

Based on the visual inspection of ETAs vs potential covariates and GAM analyses, the most promising covariate was CYP2D6 metabolic status (MET) on CL/F resulting in a highly significantly improvement in model fit and reduction in interindividual variability. After successful introduction of MET in the model the procedure was repeated for the other potential covariates, but only weight was found to significantly improve model fitting. The following table summarizes the main steps of covariate testing during the final model development

Description	OBJ	η - CL/F (%)	η - V1 (%)	η - V2 (%)	σ Proportional (%)	σ Additive (ng/mL)
Base	-1562	55%	37%	22%	11%	0.1
MET on CL/F	-1612	35%	36%	23%	9%	0.1
WT on V1/F & V2/F	-1629	35%	32%	21%	9%	0.1

RESULTS

The following model was chosen as final:

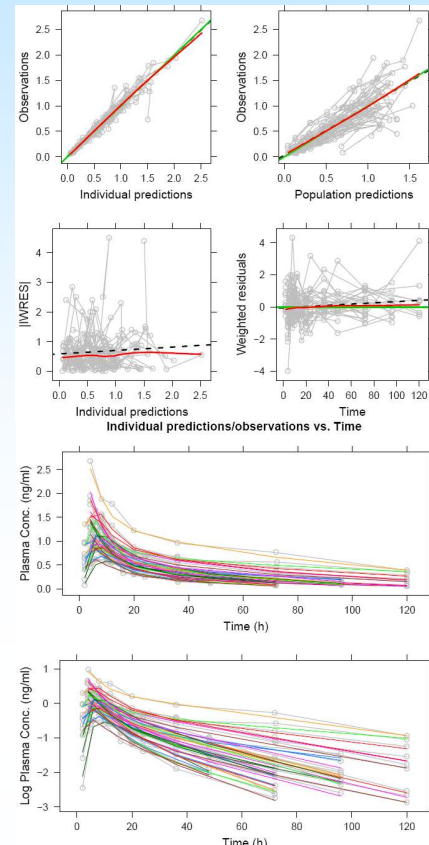
- 2 compartment with 1st order absorption and elimination and lag time
- Metabolic status as covariate of the typical value of oral clearance
- Body weight as covariate of both central and peripheral volume of distribution

Final Model Parameters

Parameter	Final Estimate	η (%)
CL/F (L/h)	14.7 _{PM} 35.8 _{IM} 54.9 _{EM}	35%
V1/F (L)	1240*(WT/70)	32%
V2/F (L)	1040*(WT/70)	21%
CLD/F (L/h)	69.2	20%
Ka (1/h)	0.68	62%
Lag (h)	1.14	18%

The final model provided good fit to the individual as well as population data and was validated using the posterior predictive check.

Goodness of fit plots for the final model



CONCLUSIONS

Our population PK results indicated that

- 1) CYP2D6 metabolic status impacts significantly on the PK of pimozide
- 2) Despite conflicting literature reports CYP2D6 appears at least as important as CYP3A4 in pimozide metabolism (relevant for understanding drug interactions and interpreting adverse events)
- 3) Body weight is linked to pimozide volume of distribution
- 4) Accounting for these covariates may significantly reduce the PK variability of the narrow therapeutic window pimozide

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