Introduction

Esmirtazapine is the S(-)-enantiomer of mirtazapine—a well-known antidepressant. In addition to the antidepressant effect, preclinical and clinical studies have also revealed sleep-promoting effects of mirtazapine. The S(-)-enantiomer has a shorter half-life than the R(-)-enantiomer and making it useable for the S(-)-enantiomer or the racemate for the treatment of insomnia. The malevolent side of esmirtazapine is a stable pharmaceutical formulation that is currently under clinical development. Esmirtazapine is metabolized by cytochrome P450 CY2D6 in the liver. The subjects were therefore genotyped with regard to CY2D6.

Methods

The studies included in this analysis are:

- Study 1
  - Design: Randomized, open-label, phase I, parallel design
  - Subjects: 20 healthy adult volunteers (18 – 45 years)
  - Assessments: Blood samples for esmirtazapine plasma concentrations up to 72 h post-dose
  - Sampling scheme: Rich (16 samples per subject on average)

- Study 2
  - Design: Randomized, open-label, phase II, parallel design
  - Subjects: 24 PM (4 subjects by genotype and 20 subjects by phenotype), and 34 IM, 64 EM and 2 UM, all of which were included on clearance and relative bioavailability.
  - Assessments: Blood samples for esmirtazapine plasma concentrations up to 72 h post-dose
  - Sampling scheme: Rich (16 samples per subject on average)

A pharmacometric model was developed using NONMEM VI with FCDE (first order conditional estimation) as the estimation method. The NONMEM output was coded as an integer representing the number of the mutations in the CY2D6 gene (the subjects from Study 1 resulting esmirtazapine maleate after paroxetine were included as poor metabolizers).

Results

In total 104 healthy volunteers contributed to 2910 esmirtazapine plasma concentration samples. The dataset contained 24 PM (7 subjects by genotype and 17 subjects by phenotype), and 34 IM, 64 EM and 2 UM, all of which were by genotype.

Structural model: The pharmacokinetics of esmirtazapine was best described by a two-compartment first-order absorption model with lag-time. Inter-individual variability (IV) was assumed to be log-normally distributed. Residual variability was additive with the log-transformed data (thus proportional on a linear scale).

Covariates:

Previous non-compartmental analysis showed that CY2D6 polymorphism had an effect on exposure of esmirtazapine (PMs had approximately doubled exposure in comparison to EM). An effect of CY2D6 polymorphism was expected a priori, so CY2D6 genotypic polymorphism was included in the model as a structural covariate. The effect of CY2D6 polymorphism was manually tested first on the base model since we also wanted to test multicollinearity (SCM is a univariate search algorithm). Clearance was found to depend on CY2D6 polymorphism in a linear fashion (gene-dose). Relative bioavailability was also found to depend on CY2D6 polymorphism: a linear relationship was tested but did not yield successful covariance step; categorical relationships were tested, and the difference between two categories, PM/EM and EM/UM, was included in the final model.

The covariates investigated for their effect on the PK parameters with SCM (sex, age, body weight, dose and study), the effects of doses on clearance and study on peripheral volume were selected by SCM. However, the final model chosen by SCM was unstable. Dose-proportionality has been previously demonstrated in the dose-range 1.5 – 18 mg/day. The effect of dose on clearance was small (corresponding to changes < 2% in the typical value of CL) and thus not clinically relevant.

In the final model only the effect of CY2D6 genotypic polymorphism was included on clearance and relative bioavailability.

Model performance:

Model performance was robust as indicated by bootstrapping: all PK parameters were normally distributed around their typical value. The final model was run with the nonparametric estimation method and the IV estimates were similar to those obtained with the first order conditional estimation method. This indicates that the log-normal assumption for the distribution of the IV was correct and no over- or under-dispersion was observed. Shrinkage was moderate to large indicating that diagnostic plots based on individual parameter estimates might be less adequate for detecting model misspecification.

Graph:

Model performance was adequate as shown by simulations (after single dose administration and at steady state) and the effect of the genotype was well captured by the model (see Figure 5). The uncertainty in the PK parameters is visualized by simulating 1000 samples from the parameter space, based on the variance-covariance matrix (see Figure 2). The dose-proportionality assumption was checked with box-plots of dose vs. clearance, dose vs. bioavailability, median clearance in the 4.5 mg dose was slightly above the medians for the other dose groups (see Figure 3), likely due to a study difference rather than dose-nonlinearity.

Table 1. Pharmacokinetic model parameters

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Typical value</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>L(CL)</td>
<td>9.6 to 11.9</td>
<td>7.5 to 10.5</td>
</tr>
<tr>
<td>L(AUC)</td>
<td>19.8 to 17.1</td>
<td>16.2 to 20.0</td>
</tr>
<tr>
<td>V</td>
<td>44.8 to 79.1</td>
<td>32.4 to 84.2</td>
</tr>
<tr>
<td>CL</td>
<td>29.8 to 13.3</td>
<td>16.8 to 13.1</td>
</tr>
<tr>
<td>V</td>
<td>0.68 to 0.47</td>
<td>0.60 to 0.48</td>
</tr>
<tr>
<td>V</td>
<td>50.0 to 40.0</td>
<td>44.0 to 40.0</td>
</tr>
</tbody>
</table>

Conclusions

A pooled population PK model successfully described the data of three Phase I trials. CY2D6 polymorphism (PM exposure approximately 2-fold higher than EM) was identified as relevant covariate. Good concordance agreement was observed between this approach and noncompartmental analysis. This model provides a sound basis to explore the exposure-response relationship with efficacy data obtained in Phase III.

Reference