Concentration-response analysis of antipsychotic drug effects using an indirect response model

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Advanced PK/PD modeling & Simulation

Background: Antipsychotic drugs are used to treat schizophrenia. The effect of antipsychotics is typically assessed using various scales, which reflect the clinical status of patients. The Positive and Negative Syndrome Scale (PANSS) is the scale most often used. Scores are typically ordered as categorical variables, however, when the number of categories is large enough they can be considered as being continuous, though they should be constrained between lower and upper limits. In the case of PANSS scores, the lower and upper limits are 30 and 210, respectively.

Objective: The aim of our analysis was to link the response to two different antipsychotic drugs with their steady-state plasma concentrations using data from three clinical Phase 3 studies.

Methods: Population pharmacokinetics (PK) modeling was performed and individual predictions of steady-state plasma concentrations (Css) were obtained to be used in further PK efficacy modeling.

Indirect response model: Drug A and Drug B were analyzed simultaneously. During analysis, some typical elements of antipsychotic response were taken into account and included into the model: drug effect, placebo effect and a reduction of the effect with time that will be called "amelioration (rA)". The nature of these processes cannot be described as of yet, so the model is empirical, however, some mechanistically sound elements can be added.

\[ \frac{dR}{dt} = rD - rA \] (1)

In the absence of treatment, Eq 2 describes disease progression, and K controls the rate of spontaneous changes of the score. Treatment should reduce RP, and to be efficacious, the drug effect must exceed that of placebo. RP becomes thus a composite parameter incorporating various (fixed and random) effects that contribute additively in the model. These effects are considered in the logit domain to keep RP within the PANSS score boundaries.

\[ RP = 180 \times \exp(\logit(R0) + DP + EFF + TT) + \exp(\exp(\logit(R0) + DP + EFF + TT)) \times 30 \] (3)

DP, EFF and TT stand for disease progression, placebo and drug effects, and the effect of the time to last observation (TTLO), respectively. Graphical analysis of mean scores versus time shows that after initial decrease due to drug/placebo effect it sometimes increases, and this may indicate the gradual weakening of one or both effects. It was assumed that both placebo effect and drug effect decreased, and this was implemented as an exponential decay governed by a rate constant KT. EFF = (EP + E) *exp(-KT *T), where EP is the placebo effect, E is the drug effect, and T is time.

The steady-state plasma concentration of the drug, Css, was used as a predictor of the drug effect through an Emax model:

\[ E = Emax\times\frac{C_{ss}}{C_{50} + C_{ss}} \] (4)

where Emax is the maximal drug effect in the logit domain, and C50 is the plasma concentration corresponding to half-maximal effect. A different Emax was estimated for each drug included in the study, C50 was the same for both drugs.

TTLO was included in the data set as a patient covariate, and TT was expressed as - KLO*(TTLO - 51), where KLO is a slope parameter and 51 is the maximum trial duration (in days). The model incorporated individual random effects on K, R0, DP, EP and C50. The normal distribution and constant variance model were postulated for logit(R0), DP and EP. In the case of K and C50 the exponential variance model was assumed. The residual error model assumed a constant variance. The model was fitted using the NONMEM V software and the first-order method.

Results: The model provides a good fit as confirmed by the plot of observations versus population and individual predictions (Figure 2).

According to the model, the equilibration rate constant (K) was 0.033/day and PANSS at baseline (R0) was 93.3. The placebo effect was estimated (EP = -5.01) and the drug effect was defined by a similar C50 for both drugs but by a different Emax (C50 = 139 ng/mL and Emax: Drug A = -22.5, Drug B = -25.0), both of them reducing ultimate PANSS. The diseases progression (DP) was -2.1. On the other hand, the effect of the time to last observation (TTLO=0.995/day), participates to the global effect, deteriorating the overall results that occurs in dropouts. Finally, due to "tolerance" (KT = 0.167/day) both the placebo and the drug effect diminish with time, and an increase in the PANSS score can be observed at the end of the study. These results and the interindividual variability are showed in Table 1.

The model correctly predicts the individual PANSS temporal profile of drug effect or placebo effect in treated patients. It also predicts the reduction of the effect observed in some patients at the end of the trial ("tolerance") (Figure 3).

The model presents a platform for analysis and simulation of clinical efficacy trials in schizophrenia. It provides unaquevalical parameters that could potentially be related to biomarker responses thereby enabling early prediction of clinical efficacy.

References:

Figure 2. Goodness-of-fit plots

Figure 3. Typical temporal profiles of PANSS score in 6 individuals

Table 1. Population parameters of indirect efficacy model

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Typical value</th>
<th>Interindividual variability, %</th>
</tr>
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<tbody>
<tr>
<td>R0</td>
<td>93.3</td>
<td>40.19</td>
</tr>
<tr>
<td>DP</td>
<td>-2.10</td>
<td>97.26</td>
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<tr>
<td>EP</td>
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<tr>
<td>Emax Drug A</td>
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<tr>
<td>Emax Drug B</td>
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<tr>
<td>C50 (mg/mL)</td>
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<td>&gt;180</td>
</tr>
<tr>
<td>(1/day)</td>
<td></td>
<td>(0.09)</td>
</tr>
<tr>
<td>KT (1/day)</td>
<td>0.167</td>
<td></td>
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