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

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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 of three clinical Phase 3 studies.

Data: Efficacy end points (PANSS) and plasma drug levels were subject to concentration-response analysis using a recently proposed indirect response efficacy model [1]. Two different antipsychotic drugs were used in the study (Drug A and Drug B). Overall, 1544 patients were randomized into 7 groups, to receive either placebo or either one dose of Drug A or Drug B. Five doses (3, 6, 9, 12 and 15 mg) of Drug A and one dose of Drug B (10 mg) were evaluated simultaneously over 7 weeks of treatment.

A substantial number of patients dropped out before the trial end (Figure 1), so dropout was a factor to be implemented in the model.

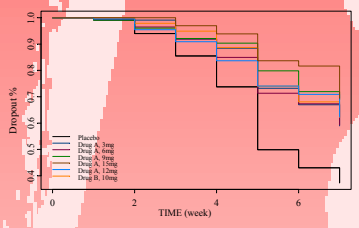

Figure 1. Dropouts vs. time

Methods:

PK model: 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 analysed 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 "tolerance" (Figure 3).

The model describes the patient's clinical status as a balance between deterioration (rD) and amelioration (rA) processes. The nature of these processes cannot be described as of yet, so the model is empirical. However, some mechanistically sound elements can be added.

$$dR/dt = rD - rA \quad (1)$$

Initial conditions are: R(0) = R0 ("baseline"). Several assumptions have been made to apply the general model (1) to clinical data. rA is assumed to be proportional to the current value of R; the proportionality coefficient being the equilibration rate constant (K). It is assumed that rD is reduced by the drug/placebo effect, and can be expressed as follows: rD = K*RP, where RP is the asymptotic value (ultimate score) when t -> inf. For further explanation see [2]. Substituting rD and rA into Eq 1 gives:

$$dR/dt = K*(RP - R) \quad (2)$$

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.

$$RP = 180*\exp(\text{logit}(R0)+DP+EFF+TT)/(1+\exp(\text{logit}(R0)+DP+EFF+TT))+30 \quad (3)$$

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 R smetimes 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.

PK Parameter	Typical value	Interindividual variability, %
K (1/day)	0.0237	83.84
RO	93.3	49.19
DP	-2.10	97.26
EP	-5.01	>150
Emax Drug A	-22.5	-
Emax Drug B	-59.6	-
C50 (ng/mL)	139	>150
KLO (1/day)	-0.091	-
KT (1/day)	0.167	-

Table 1. Population parameters of indirect efficacy model

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

$$E = Emax*Css/(C50 + Css) \quad (4)$$

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).

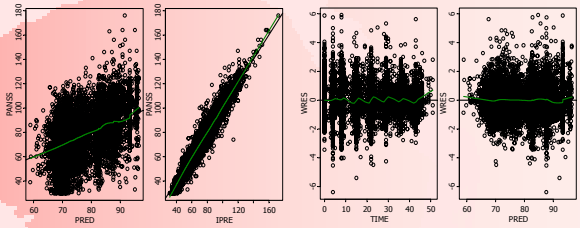

Figure 2. Goodness-of-fit plots

According to the model, the equilibration rate constant (K) was 0.0237/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 = -59.6), 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 (KLO=-0.0910/day), participates to the global effect, deteriorating the overall response that results 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) .

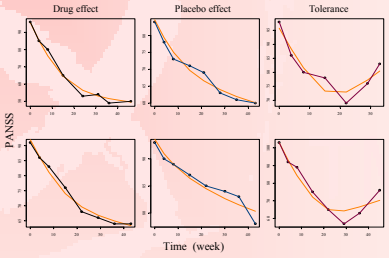

Figure 3. Typical temporal profiles of PANSS score in 6 individuals

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

References:

[1] Piotrovsky V. Drug efficacy analysis as an exercise in dynamic (indirect-response) population pk-pd modeling. 11th PAGE Meeting, Paris, France, 2002.
[2] Piotrovsky V. Indirect-response model for the analysis of concentration-effect relationships in clinical trials where response variables are scores. 14th PAGE Meeting, Pamplona, Spain, 2005.