Modelling placebo response in depression using a mechanistic longitudinal approach

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INTRODUCTION

Depression is a common, recurrent and potentially serious illness that is associated with notable chronicity and disability. The WHO ranks major depression as one of the most burdensome diseases in the world. A recent U.S. survey of mental disorders revealed lifetime and 12-month prevalence estimates for Major Depressive Disorder of approximately 16% and 6%, respectively, with women exhibiting higher rates than men. Prevalence estimates for European populations suggest similar rates.

Placebo effect is an important component of the efficiency of antidepressant drug that has to be taken into account when predicting the time course and the variability of the drug effect.

OBJECTIVES

The objective of this investigation was to develop a placebo response longitudinal model in depression as measured with the Hamilton Depression Rating Scale (HDRS) accounting for dropout.

METHODS

Data

Data from 8-week double blind, placebo-controlled study were used. The data file comprises 909 observations in 141 subjects.

HDRS is the most commonly used measure of depression. It consists of 17 items that are summed up to provide a total score.

Hamilton depression scale measurements were obtained before the start of the treatment and at week 1, 2, 3, 4, 6 and 8 during the treatment period.

Modelling

Indirect-response model was used to describe the time course of the Hamilton depression scale. The time course of HDRS is determined as the net resultant of an onset (kin) and a loss rate (kout) process.

Placebo could produce indirect action on either the inhibition of the onset response rate or the stimulation of the loss rate.

Sigmoid Imax and Weibull functions were evaluated to describe the placebo effect.

Responders and non-responders in the population were differentiate either by an a priori selection (drop of HDRS less than 20% from baseline) or using a mixture model.

Data was fitted using NONMEM first order approximation method. Inter-individual variability (exponential model) was introduced on placebo effect parameters and indirect-response parameters. A additive error model was used to model residual variability.

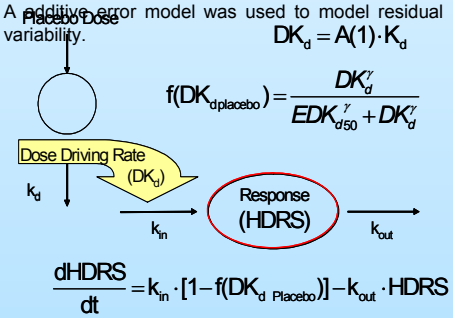

Figure 1. Schematic representation of indirect-response model (Sigmoid Imax) associated with K-PD model

RESULTS

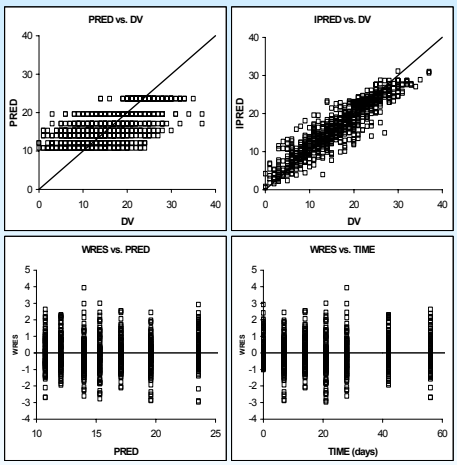

Figure 2. Goodness-of-fit plots of the indirect model for HDRS associated with K-PD model for placebo and a mixture model to select the non-responder.

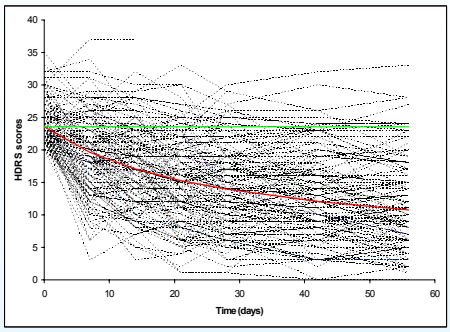

Figure 3: Plot of individual time-course of HDRS and population predicted time-course of HDRS for responders and non responders

The placebo effect produces indirect action on inhibition of the onset response. Initially it was assumed that the placebo effect was identical after each administration. A possible decline of the placebo effect with time was investigated but was not found to be statistically significant.

Sigmoid Imax and Weibull functions adequately described the placebo effect, however the objective function was slightly lower when using the sigmoid Imax function.

Both Dose Driving rate (DK_d) and the response onset account for the delay of the response. It was not possible to estimate both due to identifiability problem. Kin was fixed to 1, Dose Driving Rate could be interpreted as a combination of the equilibration between kinetics between the placebo administration rate and the placebo effect and the response onset.

RESULTS

Table 1. Model parameters with or without mixture model for selection of non-responder

Parameters	Non-responder selected a priori	Non-responder selected by mixture model
K_d	0.000250	0.000197
HDRS baseline	23.1	23.6
Dose Driving Rate leading to 50% inhibition of Kin (EDK_{d50})	0.00799	0.0078
Hill coefficient (γ)	0.913	0.867
Probability of being non-responder		0.122
Inter-individual Variability		
K_d	0.855	0.00557
HDRS baseline	0.0172	0.00794
Dose Driving Rate leading to 50% inhibition of Kin		0.904
Hill coefficient	0.464	0.644
Residual variability		
Additive	10.1	9.92

The K_d and EDK_{d50} were poorly estimated. The precision of the parameters get even worst when introducing the mixture model.

With the a priori selection of the non-responders, 34 subjects (24% of the population) were identified as non-responders. With the model selection of the non-responders, 16 subjects (11%) were identified as non-responders. Figure 4 shows a good correlation between IPRED and DV for the 19 subjects that were a priori selected as non-responder while selected as responder with the mixture model. This indicates that the mixture model seems to adequately selects the non responders.

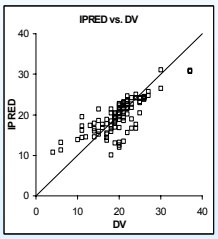

Figure 4. Plot of IPRED vs. DV for the 19 subjects that were a priori selected as non-responder while selected as responder with the mixture model.

CONCLUSIONS

Placebo effect can be characterised by the administration of a "virtual" drug with unknown PK using a K-PD model strategy. This mechanistic approach enables placebo effect to be linked to a dose regimen.

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