Translational PKPD modeling in schizophrenia

Pilla Reddy, Venkatesh

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2012

Citation for published version (APA):
Pilla Reddy, V. (2012). *Translational PKPD modeling in schizophrenia: linking receptor occupancy of antipsychotics to efficacy and safety.* s.n.

Scope and Outline of the Thesis

Venkatesh Pilla Reddy

Division of Pharmacokinetics, Toxicology and Targeting,
University of Groningen, Groningen, the Netherlands

CHAPTER 2

SCOPE AND OUTLINE OF THE THESIS

A recent trial watch analysis has indicated that the overall success rates for Phase II and Phase III clinical trials of new drugs conducted between 2007-2010 were in the range of 32-50%.[1,2] Among the unsuccessful trials, about 90% of the failures were related to lack of efficacy (66%) or to safety issues (21%). 32% of the efficacy failures were due to lack of superiority over the placebo treatment. Factors contributing to the failure of a clinical trial can be categorized into disease-, drug-, and trial-related factors, choice of the clinical endpoint and the endpoint analysis. It is currently hypothesized that the problem of Phase II and III trial failures could be reduced to a great extent by applying the knowledge gained by developing pharmacokinetic-pharmacodynamic (PKPD) models early in the drug development process and applying them in support of decision making throughout the different drug development phases.[3] A model-based, including quantitative understanding of disease progression, placebo effect, exposure-response relationships, dropout rates, and sources of variability allows to perform trial simulations to test 'what-if' scenarios and to predict the impact of alternative study designs. Moreover, the sensitivity of the biomarkers and clinical endpoints that were used to measure the severity of illness and drug treatment effects could also be investigated using PKPD tools.

This thesis describes the development of PKPD models for antipsychotic drugs. In this thesis existing clinical trial data were used to develop PKPD models that can be instrumental to improve the conclusions about the effect of the new antipsychotic drugs during clinical studies, taking into account placebo effects, dropout rates, and the influence of trial related factors, and may help to better discriminate between drug- and placebo-effects. These modelling results can later be utilized for optimizing clinical trials of new antipsychotic drugs (according to the so-called "learn and confirm" paradigm).[4] The proposed modelling approach is fundamentally different from the conventional meta-analysis. The latter approach is a statistical practice of combining the results from various trials to understand the effect of the drug in medical practice and does not utilize a learn and confirm paradigm.[4]

Chapter 1 presents an overview of schizophrenia and the concepts of PKPD modelling that are used to characterize the exposure- or biomarker-response relationship of antipsychotics. In addition, a brief introduction about the translational PKPD modelling project in schizophrenia and the research questions of the thesis are presented.

Approximately 50% of recent central nervous system clinical trials failed to show statistical significant superiority of the drug over the placebo, due to the high and highly variable placebo effects (20–70%).[5,6] Therefore, it is crucial to identify true positives (drug effect) or false negatives (due to an inappropriate trial design) as early as possible to avoid exposing the patients to less efficacious drugs/doses and to save costs. Identifying and understanding the factors that

are leading to a high placebo effect may lead to a better design of trials and to increase the chances of identifying truly efficacious compounds. In **Chapter 3,** various empirical to semi-mechanistic models are discussed that have been used to quantify placebo effect and dropout rates in neuropsychiatric drug trials. In addition, factors that lead to a high placebo effect and high dropout rates in schizophrenia trials are summarized.

Subsequently in **Chapter 4** of this thesis the magnitude of the placebo effect in clinical studies testing drugs for schizophrenia is described using historical data collected from 1989 to 2009. The goal was to develop a longitudinal model to describe the effects in placebo-treated subjects, given that data on the longitudinal time course of untreated patients are not easily available. Additionally covariates that are predictive for the placebo effect and the risk of patients dropping out from a trial are described.

Another reason for an unsuccessful trial of a new drug is the lack of differentiation and competitive positioning of a new drug *versus* other existing drugs that are available on the market. Preferably, a new drug should show superior efficacy as an active comparator while demonstrating at least similar safety. The choice of a reliable active comparator, used at optimal dose, is of major importance. In schizophrenia, haloperidol is commonly seen as the comparator drug, but also for haloperidol the dose-effect relation and the best dosage regime is not clearly defined. To the best of our knowledge, there is no literature available on PKPD modelling of haloperidol using PANSS scores that would help in determining the haloperidol dose and dosage regimen. **Chapter 5** characterizes an effective dosing strategy for haloperidol, for an optimal use as a comparator drug in future antipsychotic drug trial. Subsequently these results can be used to analyze the strengths, weaknesses, opportunities, and threats as compared to other antipsychotics.

After having characterized the placebo effects, drop-out rates and the PKPD of haloperidol, the data of clinical trials of a range of antipsychotic drugs were modelled. In **Chapter 6**, a PKPD model was developed that describes the longitudinal changes in the total PANSS score in patients treated with a range of compounds, using individual-level data and accounting for various predictors of the placebo effect (normalized placebo effect) and the dropout rates. In addition, a clinical utility criterion is proposed using the efficacy of the drug and dropout rates. In the subsequent **Chapter 7,** the developed PKPD model from **Chapter 6** is utilized to quantify the efficacy of antipsychotics using each of the three different PANSS subscales separately with the aim to investigate the hypothesis that atypical antipsychotics show better negative symptom control than conventional antipsychotics. Moreover, we explored to what extent the developed exposure-response relationships using the PANSS total scores apply to the three different sets of sub-items (subscales) of the PANSS total scale (e.g. related to positive, negative, and general psychopathology). In addition, in this chapter the

relationship between clinical efficacy, *in vitro* receptor pharmacology profiles, and the dopamine or serotonin receptor occupancy (D_2RO or $5\text{-}HT_{2A}\text{-}RO$ levels) is discussed.

From a psychiatric drug-development perspective, the question is not only to establish the relationship between the mechanism of action (e.g., D_2 receptor occupancy) and the clinical response, but also to ensure that the clinical scales are sufficiently sensitive to differentiate between treatment effects. Rating scales may be suitable and reliable but may lack sensitivity in discriminating between the effects of active treatment and placebo.[7] In **Chapter 8**, the sensitivity of the PANSS individual items and their contribution to the success rate of antipsychotic trials are investigated using different statistical methods and a pharmacometric approach.

Another major problem in the treatment of schizophrenic patients with the current antipsychotic drugs, mainly acting as dopamine D_2 receptor antagonists, is the occurrence of side effects such as extrapyramidal symptoms (EPS). In **Chapter 9,** a PKPD model is developed describing the probability and time course of EPS severity levels as a function of dose, individual steady-state plasma concentration of drug (C_{ss}) or predicted D_2RO using a compartment-based probability model with Markov elements.

Integrating not only drug exposure, but also biomarker information related to the disease state or the drug effect (e.g., D_2RO) in the evaluation of clinical endpoints helps to better understand the requirements for their use in clinical research. **Chapter 10** focuses on modelling the treatment effects by accounting for the interaction of antipsychotics with the central D_2 receptor. In this chapter, receptor occupancy data of different compounds, from separate PET studies, and predicted receptor occupancy based on pre-clinical translational work is linked to clinical outcome data. Most of the D_2 blocking antipsychotics interact with a range of receptor subtypes other than the D_2 receptor. These interactions could influence the efficacy or safety profile, and therefore, it is important to be able to characterize the time course of receptor occupancy also at other receptor subtypes, in particular the $5\text{-}HT_{2A}$ receptors. $5\text{-}HT_{2A}$ receptors are important in view of its role in achieving low EPS incidence rates and improvement in the negative symptoms. In this chapter, we also account for the influence of the $5\text{-}HT_{2A}$ receptor occupancy on the release of endogenous dopamine and the effect of endogenous dopamine D_2 receptor binding on the efficacy and safety of antipsychotic drugs.

In **Chapter 11,** the barriers, challenges that are observed in psychiatric trials are summarized and recommendations based on our experience and some future perspectives for the current research are discussed.

Finally, in **Chapter 12** the results of the various investigations are summarized.

REFERENCES

1. Arrowsmith J. TRIAL WATCH Phase III and submission failures: 2007-2010. Nat Rev Drug Discov 2011; 10(2):1.

2. Arrowsmith J. Phase II failures: 2008-2010. Nat Rev Drug Discov 2011; 10(5):1.

3. Powell JR, Gobburu JVS. Pharmacometrics at FDA: Evolution and impact on decisions. Clin Pharmacol Ther 2007; 82(1):97-102.

4. Sheiner LB. Learning versus confirming in clinical drug development. Clin Pharmacol Ther 1997; 61(3):275-291.

5. Storosum JG, Elferink AJ, van Zwieten BJ. Schizophrenia: do we really need placebo-controlled studies? Eur Neuropsychopharmacol 1998; 8(4):279-286.

6. Fava M, Evins AE, Dorer DJ, et al. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. Psychother Psychosom 2003; 72(3):115-127.

7. Della Pasqua O, Santen GW, Danhof M. The missing link between clinical endpoints and drug targets in depression. Trends Pharmacol Sci 2010; 31(4):144-152.

2