Prediction of the Hypnotic Effects of Zolpidem by Extrapolation of a Mechanism-Based PKPD Model Developed for Triazolam in Healthy Volunteers

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Background

The recent success in application of systems approach in the area of predicting pharmacokinetics has led many to believe a similar strategy for prediction of PD aspects should be adopted and popularised [1]. The operational model of agonism [2] (Equation 1) is a mechanism-based PD (MBPD) model that incorporates drug specific parameters, available from *in vitro* experiments, and system specific parameters that can be estimated using *in vivo* data. In principle, once the operational model has been established for a drug in a particular system and linked to a mechanistic PBPK model, the PD response for a drug that shares the same mechanism of action can be predicted in the same system (e.g. healthy volunteers) by changing only the drug specific parameters. Although the fundamentals of MBPD are not new, integration of these into platforms with a user-friendly interface has not taken place up until now.

$$\text{Response} = \frac{E_{max}.\text{tau}^n.C^n}{(K_D+C)^n+\text{tau}^n.C^n}; \qquad tau = \frac{\epsilon}{K_E}$$

Equation 1. Response as defined by the operational model of agonism. Drug and system specific parameters are shown in blue and red, respectively. E_{max}: maximal system response; tau: transducer ratio; K_D: equilibrium binding dissociation constant; C: drug concentration; n: slope; ϵ: intrinsic efficacy of the drug; K_E: stimulus resulting in 50% effect

Objectives

To establish a MBPD model to describe the hypnotic effects of triazolam, as measured by change in beta-EEG amplitude, using recently developed PD modules within the Simcyp Simulator.

To combine the MBPD developed for triazolam with the PBPK modelling capabilities of Simcyp to predict the hypnotic response to zolpidem since the hypnotic effects of both drugs are mediated via the α_1 subunit containing $GABA_A$ receptors.

Methods

Simulations of triazolam and zolpidem PK and PD were performed using the Simcyp simulator v11.1 using the Sim-Healthy Volunteers population and default Sim-Triazolam and Sim-Zolpidem compound files, with the first order absorption and minimal PBPK models. Unbound plasma concentration was used as the input to the PD model.

K_D values for triazolam (1nM) and zolpidem (53nM) and relative intrinsic efficacy (1) were identified from published *in vitro* data [3-6].

The Simcyp Parameter Estimation module (WLS and Nelder-Mead methods) was used to determine the values of tau, E_{max} and n using 4 published studies, and the mean estimated values were used in simulations [7-10].

The quality of these parameter estimates to predict the PD response to triazolam was tested by their ability to predict the PD response following interaction with the CYP3A inhibitor ketoconazole before predicting the response to zolpidem.

Results

1. Parameter Estimation Parameter estimates for the effect compartment elimination rate (keo) and operational model parameters Emax, n and tau were obtained based on average data from 4 studies [6-9] (Table 1).

Study	No. Subjects	Emax	n	Tau	keo (h^{-1})	OFV
1	18	14.31	0.54	1.10	1.46	1.92
2	24	20.78	0.55	0.55	2.97	0.39
3 (F)	13	32.77	0.71	0.50	10.44	0.45
3 (M)	10	21.67	1.32	1.32	1.05	2.86
4	7	24.03	1.70	1.44	1.98	1.03
Weighted Mean		**21.76**	**0.80**	**0.85**	**3.58**	
SD		6.92	0.45	0.38	3.77	

Table 1. Parameter estimates for the system specific parameters of the operational model

2. Prediction of response to triazolam The resulting operational model using the average parameter estimates was able to predict the PD response to 0.125 mg and 0.25 mg triazolam with and without ketoconazole DDI reasonably well, although the PD response was underestimated at the highest plasma concentrations of triazolam (Figure 1).

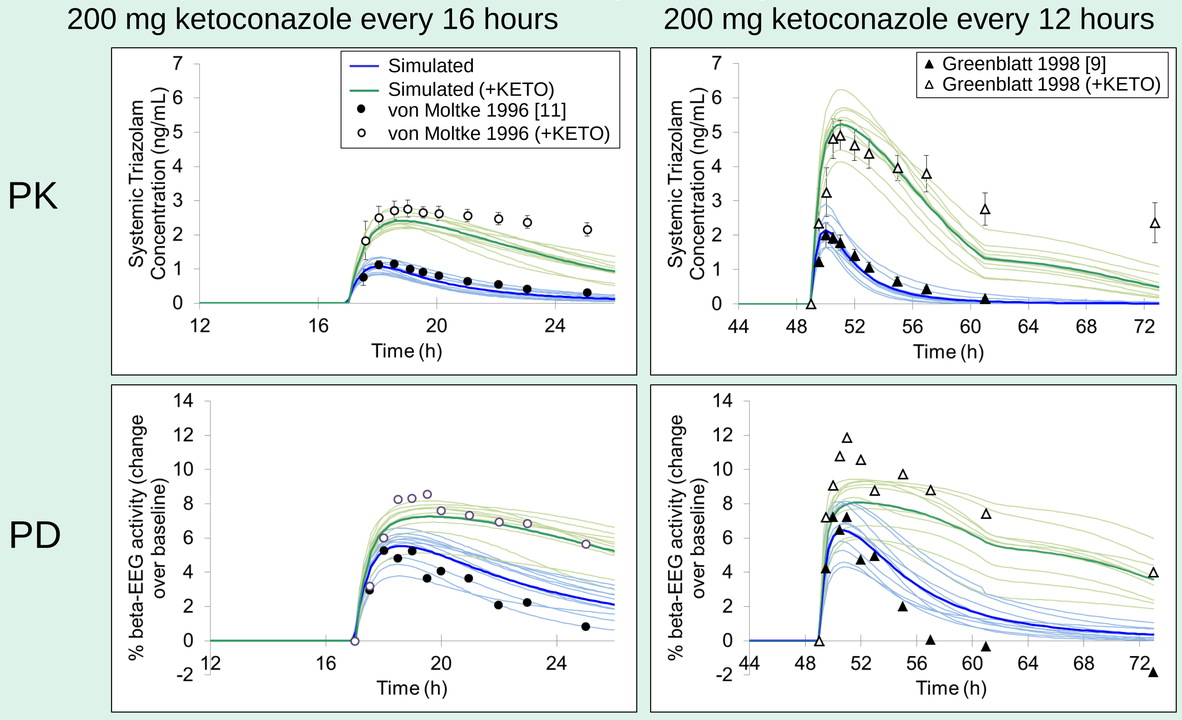

Figure 1. The estimated values for the operational model parameters and *in vitro* K_D (1nM) were used to simulate the response to 0.125 mg and 0.25 mg oral triazolam in the absence of and following pre-dosing with ketoconazole (+KETO). Simulated data are shown as the mean of 10 individual trials and the overall mean of 10 simulated trials (bold). Error bars show the standard error of the observed data, where reported.

3. Prediction of the response to zolpidem The maximal response to zolpidem was predicted well by changing only the PBPK model input to the operational model and the K_D value consistent with the literature (Figure 2). The simulated/observed ratios for Rmax are 0.86 for the 5 mg dose [12] and 0.86 and 0.91 for two studies of 10mg zolpidem [7,13]. However, the duration of response was overestimated (Figure 2).

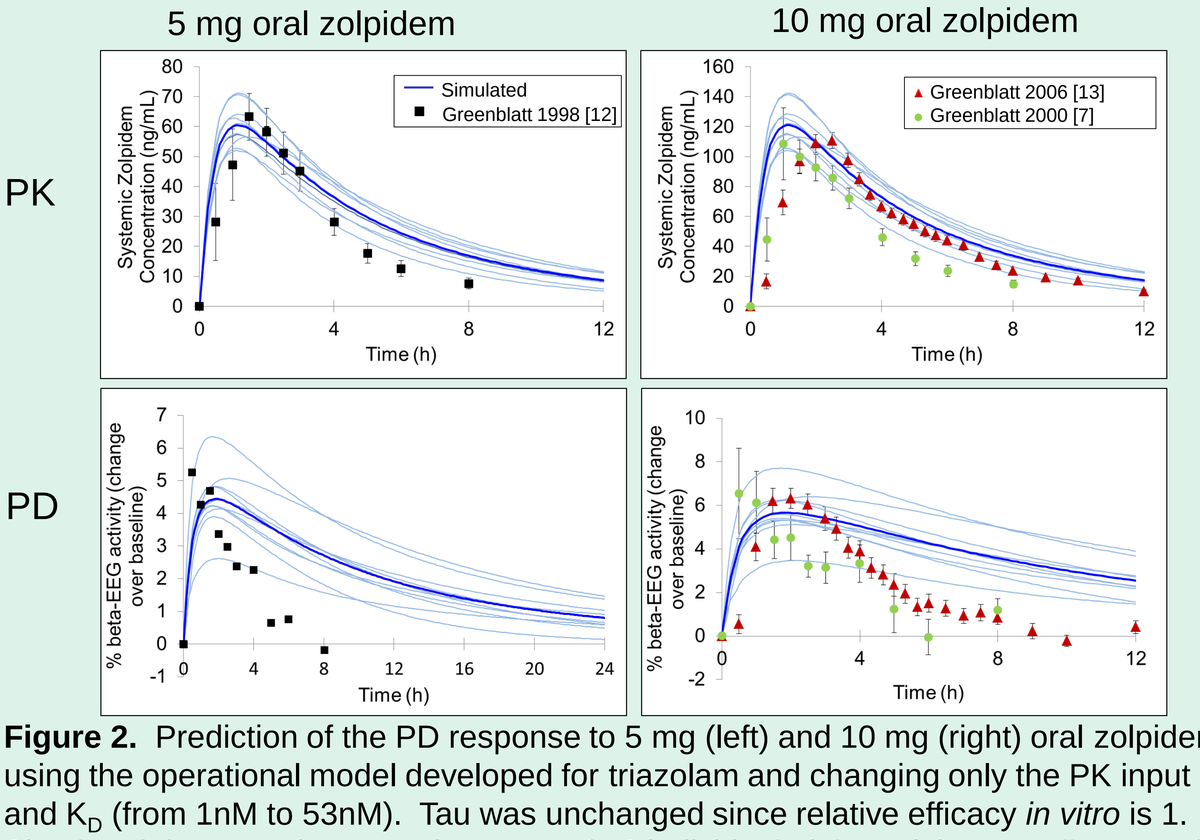

Figure 2. Prediction of the PD response to 5 mg (left) and 10 mg (right) oral zolpidem using the operational model developed for triazolam and changing only the PK input and K_D (from 1nM to 53nM). Tau was unchanged since relative efficacy *in vitro* is 1. Simulated data are shown as the mean of 10 individual trials and the overall mean of 10 simulated trials (bold). Error bars show the standard error of the observed data, where reported.

Conclusions

The operational agonism PKPD model developed for triazolam was reasonably successful when predicting the maximal EEG response to zolpidem. Error in the model prediction may relate to acute tolerance effects to zolpidem, as has previously been proposed [14]. Mechanism-based PKPD models may be useful in the prediction of the dose of a drug candidate that produces equivalent clinical efficacy to a well studied drug with the same mechanism of action.

References

[1] Atkinson and Lyster (2010) Clin Pharmacol Ther 88: 3-6; [2] Black and Leff (1983) *Proc R Soc Lond B* 220: 141-62; [3] Hadingham *et al.,* (1993) Mol Pharmacol 43: 970-5; [4] Sancar *et al.,* (2007) Mol Pharmacol 71: 38-46; [5] Wingrove *et al.,* (1997) Mol Pharmacol 52: 874-81; [6] Smith *et al.,* (2001) Mol Pharmacol 59: 1108-18; [7] Greenblatt *et al.,* (2000) J Pharmacol Exp Ther 293: 435-43; [8] Greenblatt *et al.,* (1994) Clin Pharmacol Ther 56: 100-11; [9] Greenblatt *et al.,* (1998) Clin Pharmacol Ther: ,: 237-247; [10] Greenblatt *et al.,* (2004) Clin Pharmacol Ther 76: 467-79; [11] von Moltke *et al.,* (1996) J Pharmacol Exp Ther 276: 370-9; [12] Greenblatt *et al.,* (1998) Clin Pharmacol Ther 64: 661-71; [13] Greenblatt *et al.,* (2006) J Clin Pharmacol 46: 1469-80; [14] de Haas *et al.,* (2010) J Psychopharmacol 24: 1619-29