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.

Response = \( \frac{E_{\text{max}} \cdot \tau}{\left( K_0 + C \cdot \tau + \text{tau} \cdot C^2 \right)} \), \( \tau = \frac{c}{K_1} \)

Equation 1. Response as defined by the operational model of agonism. Drug and system specific parameters are shown in blue and red, respectively. \( E_{\text{max}} \): maximal system response; \( \tau \): transducer ratio; \( K_0 \): equilibrium binding dissociation constant; \( C \): drug concentration; \( n \): slope; \( c \): intrinsic efficacy of the drug; \( K_1 \): 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 \( \alpha_1 \) 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. \( K_0 \) 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, \( E_{\text{max}} \) 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 (\( k_0 \)) and operational model parameters \( E_{\text{max}} \) and \( n \) and \( \tau \) were obtained based on average data from 4 studies [6-9] (Table 1).

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Subjects</th>
<th>( E_{\text{max}} )</th>
<th>( n )</th>
<th>( \tau )</th>
<th>( k_0 ) (h(^{-1}))</th>
<th>( \text{OFV} )</th>
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<td>13</td>
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<td>0.50</td>
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<tr>
<td>3 (M)</td>
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<td>1.32</td>
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<td>1.44</td>
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<td>1.03</td>
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<tr>
<td><strong>Weighted Mean</strong></td>
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<td><strong>0.85</strong></td>
<td><strong>3.58</strong></td>
<td><strong>6.92</strong></td>
<td><strong>0.45</strong></td>
</tr>
</tbody>
</table>

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](image1.png)

Figure 1. The estimated values for the operational model parameters and \( K_0 \) (1nM) were used to simulate the response to 0.125 mg and 0.25 mg oral triazolam in the absence 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 \( K_0 \) value consistent with the literature (Figure 2). The simulated/observed ratios for \( R_{\text{max}} \) 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](image2.png)

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 \( K_0 \) (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