Introduction

Simcyp Rat 2009: A physiologically based pharmacokinetic (PBPK) model used to predict the disposition of drugs in a standard 250g Male Sprague Dawley Rat. Using In Vitro In Vivo Extrapolation (IVIVE) the model is capable of predicting:
- Plasma concentration-time profiles & pharmacokinetic parameters
- Various organ/tissue concentration-time profiles of drugs.

Routes of Administration: Simcyp Rat can handle various IV and Oral Dosages such as Intravenous Bolus + Infusions, Oral Drug Solutions, Immediate Release (IR), Enteric-Coated Granules/Tablets and Controlled/Modified Release formulations.

Prediction of Vss & Tissue Concentration-Time Profiles: Vss (Apparent Volume of Distribution at Steady State) following IV administration, is a primary descriptive term that relates the amount of drug in body to the concentration of drug in the measured compartment. Prediction is based on a PBPK model developed by Rodgers et al² using drug physicochemical parameters and in vitro experimental data.

Purpose

To evaluate the performance of Simcyp Rat 2009 to predict the Vss and Tissue Concentration-Time Profiles for four Benzodiazepines.

Methods

Simcyp Rat 2009, was used to predict the Vss and Tissue (Liver, Adipose, Kidney) Concentration-Time profiles for Alprazolam (Alp), Diazepam (Diaz), Midazolam (Midz) and Triazolam (Trz). Simulations were performed using a virtual Male Sprague Dawley Rat (250g) without variability following a 5 minute IV infusion of 1 mg for all four substrates. Vss values & Tissue Concentration-Time profiles were predicted from Tissue-Plasma Partition coefficients (Kp) using a PBPK model developed by Rodgers et al² incorporated in Simcyp Rat 2009. Experimental values of Vss and tissue concentration-time profiles were used as published by Gueorguieva et al² using NONMEM. Performance evaluation of Simcyp Rat 2009 was undertaken by comparing the predicted Vss and tissue concentration-time profiles with experimentally determined data.

Results & Discussion

The Vss (L/kg) values predicted by Simcyp Rat 2009 are shown in Table 1 and Figure 1. Vss values determined using predicted Kp¹ and experimental Kp² were within 3 fold and 2 fold of observed Vss values respectively. The largest differences were found for Midazolam (5.64 L/kg) and Triazolam (2.8 L/kg).

Simcyp predicted values (Kp²) were within two fold of the observed values. Observed Vss values for Alprazolam (1.22; 1.29) and Triazolam (1.23; 1.1) were in close agreement with Simcyp predicted values (Table 1 & Figure 1).

Conclusions: Physiological parameters and the model structure used in Simcyp Rat 2009 provide a reasonable estimate for the prediction of Vss and specific organ concentration-time profiles for the four benzodiazepines using physicochemical and in vitro data. Such a PBPK model can be used to reduce, replace and refine the use of preclinical species in an early drug discovery setting.