Prediction of Vss and Tissue Concentration-Time Profiles for Four Benzodiazepines Using Physicochemical, *in vitro* and Experimental Data in Rat using a Mechanistic PBPK Model.

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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)[1] 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 al*[2] 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 al*[2] incorporated in Simcyp Rat 2009. Experimental values of Vss and tissue concentration-time profiles were used as published by Gueorguieva *et al*[3] 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 Kp[1]** and **experimental Kp[2]** 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).

	Comparison of Vss (L/kg) values		
Substrate	Obsd. In vivo[2]	Simcyp using Predicted Kp[1]	Simcyp using Expt. Kp[2]
Alp	1.22	1.44	1.29
Diaz	4.29	3.08	5.12
Midz	2.16	5.64	1.16
Trz	1.23	2.8	1.10

Table 1. Vss (L/kg): Expt. Observed and Predicted using Simcyp Rat 2009.

Simcyp predicted values (Kp[2]) 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).

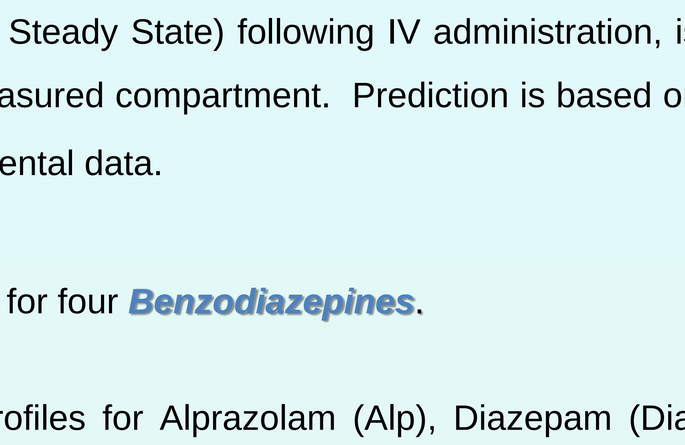

Fig1: Vss (L/kg) Predicted using Simcyp vs. Observed.

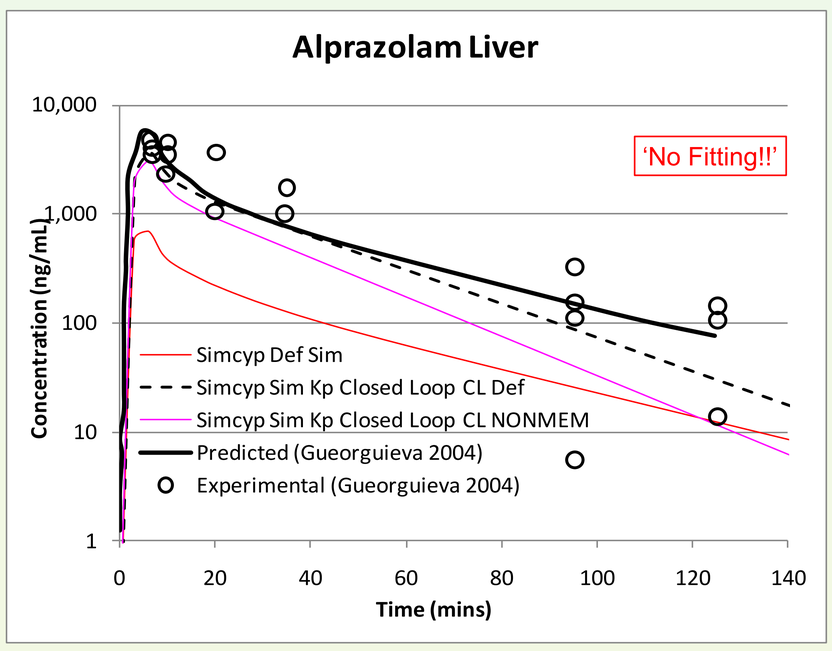

Fig 2: Tissue Concentration-Time Profiles of Alprazolam in Liver

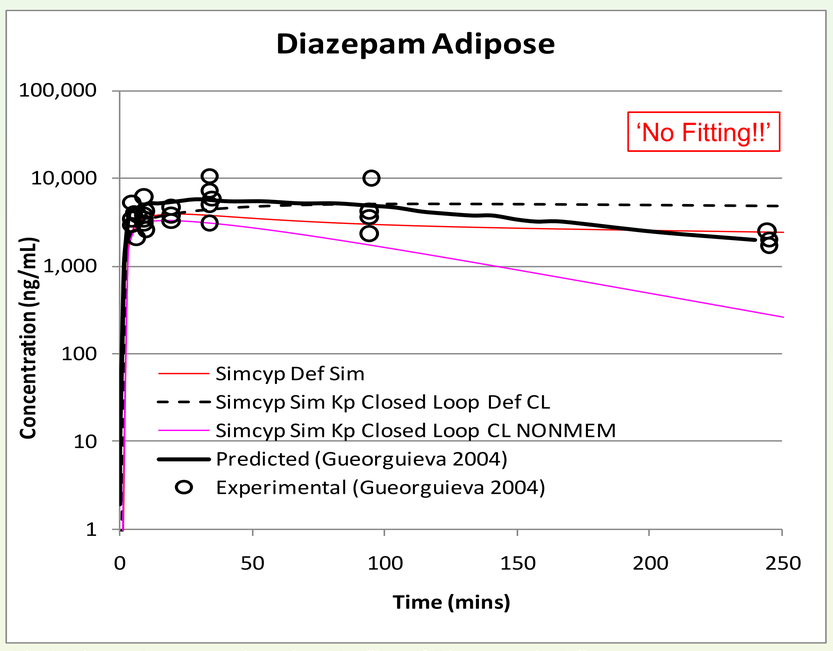

Fig 3: Tissue Concentration-Time Profiles of Diazepam in Adipose

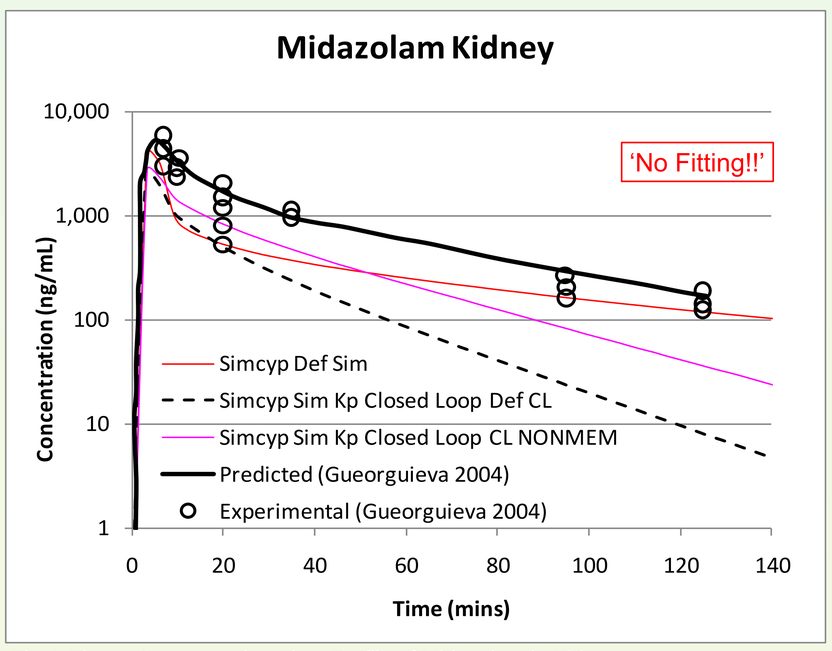

Fig 4: Tissue Concentration-Time Profile of Midazolam in Kidney

Figure 2, 3 and 4 show the experimental (Gueorguieva *et al*) and predicted (Simcyp Rat) liver, adipose and kidney concentration-time profiles for Alprazolam, Diazepam and Midazolam respectively following: 1) Simcyp simulation with Simcyp default values; 2) Simcyp simulation with Expt. Kp (Closed Loop) (Gueorguieva et al); 3) Simcyp simulation with Expt. Kp (Closed Loop) and CL_{iv} (Gueorguieva et al.); 4) Predicted profiles by Gueorguieva et al.; 5) Experimental profiles by Gueorguieva et al.

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.

References: **(1)** Gibson G. G. & Rostami-Hodjegan. *Xenobiotica*. 2007 Oct-Nov; 37 (10-11): 1013-1014. **(2)** Rodgers T. *et al*. *J Pharm Sci.* 2007 Nov; 96(11):3151-2 & 96(11): 3153-4. **(3)** Gueorguieva I. *et al*. *J PKPD*. 2004 Dec; 32(5-6): 655-8.