Simulation of midazolam pharmacokinetics after buccal administration
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ABSTRACT SUMMARY:
A physiologically based pharmacokinetic (PBPK) model for simulation of midazolam and its major metabolite 1'-hydroxymidazolam after iv, PO and buccal administration in adult subjects was developed.

INTRODUCTION:
Midazolam belongs to the family of benzodiazepine drugs and is commonly used for treatment of seizures because of its short onset of sedation effects [1]. Its major metabolite 1'-hydroxymidazolam, formed by enzyme CYP3A4 in liver and intestine, has similar therapeutic effects to the parent compound. In vitro and in vivo studies have shown that the metabolism to 1'-hydroxymidazolam accounted for 95% [2] and 75% [3] of the total intrinsic clearance of the parent compound. We developed a PBPK model to simulate the pharmacokinetic profiles of midazolam and 1'-hydroxymidazolam after iv and PO administration in healthy adults. This model was then used in simulations of buccal administration of midazolam in healthy adult subjects. A comparison between the buccal and gastrointestinal absorbed fractions was made based on the simulation results.

EXPERIMENTAL METHODS:
The PBPKPlus™ module of GastroPlus™ (Simulations Plus, Inc.) was used to model the pharmacokinetic distribution and systemic clearance of both compounds. The Advanced Compartmental Absorption and Transit (ACAT™) model described the intestinal absorption. Human physiologies were generated by the program’s internal Population Estimates for Age-Related (PEAR) Physiology™ module. Tissue/plasma partition coefficients for both compounds were calculated using the Lukacova algorithm [4] based on tissue composition and in vitro and in silico physicochemical properties. The biopharmaceutical parameters for both midazolam and 1'-hydroxymidazolam were either obtained from literature data or predicted by ADMET Predictor™ 6.0 (Simulations Plus, Inc.). The metabolism of midazolam to 1'-hydroxymidazolam in gut and liver was modeled by Michaelis-Menten kinetics with in vitro enzyme kinetic parameters (Km = 3.7 µM and Vmax = 850 pmol/min/mg protein [5]) and the GastroPlus built-in expression levels of CYP3A4 in gut and liver. The effective permeability was fitted across three PO solution doses of midazolam: 7.5 mg, 15 mg, and 30 mg [6]. The systemic clearance of 1'-hydroxymidazolam is mainly by UGT metabolism and renal secretion [7]. The enzyme kinetic constants for UGT metabolism of 1'-hydroxymidazolam were fitted against the pharmacokinetic profiles of 1'-hydroxymidazolam after different iv and PO doses of 1'-hydroxymidazolam and midazolam: 8.07 mg iv infusion of 1'-hydroxymidazolam [8] (data not shown here), 5.4 mg iv bolus administration of midazolam (Figure 1) and 30 mg PO solution administration of midazolam (Figure 2). In both figures, midazolam profiles are highlighted in red while 1'-hydroxymidazolam profiles are highlighted in blue. Renal secretion was estimated as the product of fraction unbound in plasma and glomerular filtration rate.

Figure 1. Simulated (lines) and observed (squares) Cp-time profiles after 5.4 mg iv bolus administration of midazolam in healthy volunteers.

Figure 2. Simulated (lines) and observed (squares) Cp-time profiles after 30 mg PO administration of midazolam in healthy volunteers.
The PBPK model accounting for PK of both compounds was then used to simulate their exposure after buccal administration of midazolam [9]. The physiological parameters used to account for oral cavity absorption of midazolam were: saliva production rate = 0.35 mL/min; mucosal volume = 3.5 mL, and saliva baseline volume = 0.85 mL [10]. The only fitted parameter for this dosing route was the effective permeability through the oral mucosa. The results are shown in Figure 3.

RESULTS AND DISCUSSION:

The simulated plasma concentration profiles for both parent and metabolite agreed well with the experimental data after iv infusion of midazolam. The same PBPK model also agreed well with experimental Cp-time data for 3 different PO doses; 7.5 mg, 15 mg and 30 mg, with a fitted Peff = 2*10^-4 cm/s (simulation results for the 30mg dose are shown in Figure 2.).

In the buccal administration study, patients held 2 mL of 5 mg/mL midazolam solution in their mouths for 5 minutes, then spat out the accumulated excessive saliva with its unabsorbed drug. We assumed that the small amount of drug remaining in oral cavity saliva is continuously swallowed as well as absorbed by the buccal tissue after the expectoration. Simulation results for this study also agreed well with observed Cp-time data of midazolam (observed data were not available for 1'-hydroxymidazolam from this study) as shown in Figure 3A. Simulated percents absorbed in each physiological compartment along the gastrointestinal (GI) tract are shown in Figure 3B. Simulations indicated 14% out of 34% the total absorbed amount occurred in the GI tract, resulting from swallowing the drug remaining in the saliva after expectoration.

CONCLUSION:

The GastroPlus PBPK model showed good agreement with observed Cp-time data after iv, PO, and buccal administration of midazolam and its metabolite. Such a model is an important tool for exploring new dosing routes and helping to predict absorption and pharmacokinetics for different doses and different application mechanisms.

REFERENCES:

4. Lukacova V. Poster presentation, AAPS 2008, Atlanta GA

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