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Physiological based pharmacokinetic modeling to estimate *in vivo* Ki of ketoconazole on renal P-gp using human drug-drug interaction study result of fesoterodine and ketoconazole

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ABSTRACT

This study was conducted to estimate *in vivo* inhibition constant (Ki) of ketoconazole on renal P-glycoprotein (P-gp) using human drug-drug interaction (DDI) study result of fesoterodine and ketoconazole. Fesoterodine is a prodrug which is extensively hydrolyzed by non-specific esterases to the active metabolite 5-hydroxymethyl tolterodine (5-HMT). 5-HMT is then further metabolized via Cytochrome P450 (CYP) 2D6 and CYP3A4. It is reported that 5-HMT is a substrate of P-gp whereas fesoterodine is not. Renal clearance of 5-HMT is approximately two-times greater than renal glomerular filtration rate. This suggests the possibility that renal clearance of 5-HMT involves secretion by P-gp. Utilizing the available pharmacokinetic characteristics of fesoterodine and 5-HMT, we estimated *in vivo* Ki of ketoconazole on P-gp at kidney based on DDI study data using physiologically-based pharmacokinetic approach. The estimated *in vivo* Ki of ketoconazole for hepatic CYP3A4 (6.64 ng/mL) was consistent with the reported values. The *in vivo Ki* of ketoconazole for renal P-gp was successfully estimated as 2.27 ng/mL, which was notably lower than reported *in vitro* 50% inhibitory concentration (IC_{50}) values ranged 223–2440 ng/mL due to different condition between *in vitro* and *in vivo*.

1. Introduction

P-glycoprotein (P-gp) is one of the transporter protein which distributes and expresses on gut, blood brain barrier, liver and kidney and affects drug absorption, distribution and excretion. Inhibition of P-gp could lead clinically significant exposure increase when a drug is a P-gp substrate [1]. Therefore accurate drug-drug interaction (DDI) prediction related to P-gp inhibition is important in drug development and also in clinical practice to balance safety and efficacy of a drug. Recently physiologically-based pharmacokinetic (PBPK) model approach provides practical solution to predict human DDI caused by cytochrome P450 (CYP) enzymes [1]. It is vital to have accurate inhibition constant (Ki) of an inhibitor for the prediction, however, prediction based on *in vitro* Ki values often leads over/under estimation compare to observed *in vivo* exposure data. To solve this issue, Kato et al. estimated *in vivo* Kis for CYP3A4 inhibitors and successfully improve *in vivo* pharmacokinetic (PK) profile prediction [2]. CYP3A4 contributes not only to hepatic metabolism but also to absorption on gut. Kato et al. improved the prediction by including the effect of CYP3A4 inhibition on gut by involving the effect in Fraction absorbed (Fa) and intestinal availability (Fg). P-gp also contributes to absorption and also to excretion to bile and urine. For the estimation of *in vivo* parameter of P-gp, it is necessary to model all of these contributions in general but it is difficult. The effect of P-gp on absorption is due to pumping out a drug on gut wall and it cannot be simply involved in FaFg like CYP3A. Regarding bile excretion, it is difficult to measure bile concentration especially in human. Therefore, PBPK modeling in conjunction with a mechanistic absorption model and *in vitro* data for the prediction of DDI between P-gp substrate (digoxin) and inhibitor (verapamil) [3] and simpler static estimation based on *in vivo* [I]/Ki values to predict drug-drug interactions with

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dabigatran etexilate as a substrate [4] had been reported, but there is no report to estimate *in vivo* Ki of P-gp inhibitor thus far.

Fesoterodine fumarate ((E)-but-2-enedioic acid; [2-[(1R)-3-[di(propan-2-yl)amino]-1-phenylpropyl]-4-(hydroxymethyl) phenyl] 2-methylpropanoate, hereafter referred to as "fesoterodine") is a once-daily oral medication for the treatment of overactive bladder. Fesoterodine is a prodrug which rapidly absorbed in humans and immediately and extensively hydrolyzed by nonspecific esterases to the active metabolite 5- hydroxymethyl tolterodine (5-HMT). CYP enzymes do not contribute to fesoterodine metabolism. 5-HMT is further metabolized via CYP2D6 and CYP3A4 [5]. It is reported that 5-HMT is a substrate of P-gp *in vitro* [6] whereas fesoterodine is not a substrate of P-gp. This means CYP3A and P-gp does not affect absorption of the drug. Renal clearance of 5-HMT is approximately two-times greater than renal glomerular filtration rate (GFR) [5]. This suggests the possibility that renal clearance of 5-HMT involves secretion by P-gp. On the other hand, biliary secretion of 5-HMT via P-gp can be ignored because negligible 5-HMT was recovered in feces after intravenous administration of 5-HMT [7]. Therefore, it was considered that when fesoterodine is co-administered with ketoconazole which is a strong dual inhibitor of CYP3A and P-gp, 5-HMT exposure increase is expected to be caused by inhibition of liver CYP3A metabolism and secretion at kidney by P-gp but not related to absorption on gut and excretion to bile via P-gp. DDI study of fesoterodine with ketoconazole was conducted in CYP2D6 extensive metabolizers (EM) and poor metabolizers (PM) [8]. Compared with fesoterodine administration alone, the area under the concentration–time curve (AUC) and observed maximal concentration (Cmax) of 5-HMT increased 2.3 and 2.0 fold in EMs and 2.5 and 2.1 fold in PMs, respectively and renal clearance decreased both in EMs and PMs comparably. These results suggested the contribution of P-gp on renal excretion of 5-HMT.

Utilizing unique PK characteristics of fesoterodine and 5-HMT mentioned above, we estimated *in vivo* Ki value for P-gp at kidney based on the data of fesoterodine – ketoconazole DDI study in healthy subjects using PBPK approach.

2. Materials and methods

2.1. Study design

The PBPK model was constructed using the data of a DDI study with ketoconazole 200 mg BID in 18 Western healthy male volunteers of CYP2D6 EM (n = 12) and PM (n = 6) [8]. Fesoterodine was dosed as sustained release tablet which contains 8 mg fesoterodine fumarate. This was a randomized, open-label, two-way crossover trial with single dose administration of fesoterodine alone or together with an oral pre- and co-treatment of 200 mg ketoconazole twice daily. In co-administration period, fesoterodine 8 mg was dosed with 200 mg ketoconazole after pre-treatment of 4-day oral administration of 200 mg ketoconazole twice daily. Additional administrations of 200 mg ketoconazole were given as single dose 12 h after fesoterodine/ketoconazole administration and twice daily dose on the next day. Subjects received each of the 2 treatments in a randomized order. A wash-out phase of at least 2 weeks between the fesoterodine administrations on Day 1 of each period was mandatory. The study was approved by an Ethics Committee or Institutional Review Board, and was conducted in accordance with the current revision of the Declaration of Helsinki.

2.2. Pharmacokinetic sampling

For the evaluation of plasma 5-HMT concentration, blood was collected at pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, and 48 h post dose. For evaluation of 5-HMT in urine, urine was collected during the following time intervals: predose, 0–6 h, 6–12 h, 12–24 h, and 24–48 h after administration of fesoterodine.

2.3. Bioanalytical methods

The concentrations of plasma and urine 5-HMT were determined by a validated liquid chromatography tandem mass spectrometry as previously described [5]. The lower limit of quantification of 5-HMT was 0.04 ng/mL in plasma and 4 ng/mL in urine. This analysis was performed at Schwarz BioSciences (Monheim, Germany).

2.4. Data analysis

1. Overview of PBPK models

The PBPK model for 5-HMT including both contribution of CYP3A4 on hepatic metabolism and P-gp on renal secretion was constructed using mean plasma concentrations of 5-HMT and amount excreted to urine data of 5-HMT after administration of fesoterodine using Phoenix WinNonlin 6.3 (Certara, St. Louis, MO USA). For ketoconazole, the published PBPK model [2] was used with addition of renal compartment.

For PBPK model for 5-HMT, the following parameters were fixed to the values which had already been reported: Absorption rate (Ka) of 5-HMT was fixed to 0.1 based on the result of population PK analysis [9]. Plasma fraction unbound of 5-HMT (fup) and blood:-serum concentration ratio (Rb) were reported as 0.36 [10] and 0.8 [11], respectively. Tissue:plasma partition coefficients of 5-HMT for liver (Kph) and for kidney (Kpr) were calculated as 6.5 and 3.95, respectively, based on the equation for non-adipose tissue [12] using log P (3.56) and fup of 5-HMT. Physiological parameters were set as follows: volume of liver (Vh) = 1400 mL [2], liver blood flow rate (Qh) = 96600 mL/h [2], volume of kidney (Vr) = 280 mL [13], kidney blood flow rate (Qr) = 74400 mL/h [13], GFR = 7500 mL/h [13]. The model used for the analysis is described by following equations:

$$\frac{dA_{Dept}}{dt} = -A_{Dept} \times Ka$$

$$\frac{dA_{Hepatic}}{dt} = A_{Dept} \times Ka - fup \times \frac{C_{Hepatic}}{Kph} \times \frac{CLh,\mathrm{int}_{CYP3A4}}{1 + \frac{Ci_{Hepatic} \times fupi}{Kphi \times Kih}} - fup \times \frac{C_{Hepatic}}{Kph} \times CLh,\mathrm{int}_{CYP2D6} + Qh \times \left(C_{Blood} - C_{Hepatic} \times \frac{Rb}{Kph}\right)$$

$$\frac{dA_{Blood}}{dt} = -\left(Qr \times \left(C_{Blood} - C_{\mathrm{Renal}} \times \frac{Rb}{Kpr}\right)\right) - \left(Qh \times \left(C_{Blood} - C_{Hepatic} \times \frac{Rb}{Kph}\right)\right)$$

$$\frac{dA_{\mathrm{Renal}}}{dt} = Qr \times \left(C_{Blood} - C_{\mathrm{Renal}} \times \frac{Rb}{Kpr}\right) - fup \times \frac{C_{\mathrm{Renal}}}{Kpr} \times \frac{CL\ \mathrm{sec,int}}{1 + \frac{Ci_{\mathrm{Renal}} \times fupi}{Kpri \times Kir}} - \frac{fup}{Rb} \times GFR \times C_{Blood}$$

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