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PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING & SIMULATION USING SIMCYP TO PREDICT DRUG-DRUG INTERACTION WHEN MIRABEGRON IS CO-ADMINISTERED WITH FESOTERODINE

Hypothesis / aims of study

Fesoterodine (4 or 8 mg once daily (QD)), an antimuscarinic (1), and mirabegron (25 or 50 mg QD), a β_3-agonist (2), are indicated for the treatment of overactive bladder. Mirabegron is a moderate competitive and time-dependent inhibitor of cytochrome P450 (CYP) 2D6 (Table 1) and a weak inhibitor of CYP3A. Administration of mirabegron 160 mg QD with a single dose of 100 mg metoprolol (CYP2D6/3A substrate) increased metoprolol Cmax and AUC by 90% and 229%, respectively. Administration of mirabegron 100 mg QD for 18 days with a single dose of 50 mg desipramine (CYP2D6 substrate) increased desipramine Cmax and AUC by 79% and 241%, respectively. The active metabolite of fesoterodine, 5-hydroxymethyl tolterodine (5-HMT), is further metabolized to inactive metabolites *via* two major pathways involving CYP2D6 and CYP3A4, and excreted unchanged in urine (~16% of dose). In CYP2D6 poor metabolizers (PMs), representative of complete inhibition of CYP2D6 by a potent CYP2D6 inhibitor, 5-HMT Cmax and AUC increased by 70% and 100%, respectively, which does not require any adjustment in dosing recommendations for fesoterodine. Coadministration of fesoterodine with a potent CYP3A4 inhibitor, ketoconazole, increased 5-HMT Cmax and AUC by 110% and 150%, respectively, whereas a moderate CYP3A4 inhibitor, fluconazole, increased 5-HMT Cmax and AUC by only 19% and 27%, respectively. Based on these prior results and due to multiple elimination pathways of 5-HMT, a moderate CYP2D6 inhibitor is not expected to significantly increase 5-HMT exposure.

Physiologically-based pharmacokinetic (PBPK) modeling and simulation (M&S) has been used for the assessment of drug-drug interactions (DDIs) prior to or in place of clinical studies (3). Simcyp® is a computerized PBPK M&S program that integrates physicochemical properties, *in vitro* metabolism and *in vivo* pharmacokinetic data and applies fundamental scaling and PBPK concepts for the prediction of drug interactions. A PBPK modeling M&S study using Simcyp® was undertaken to estimate the effect of coadministration of the moderate CYP2D6 inhibitor mirabegron with fesoterodine on 5-HMT exposures.

Study design, materials and methods

PBPK models for mirabegron and 5-HMT were developed using Simcyp® (version 14 release 1; Simcyp Ltd, a subsidiary of Certara LLC). Table 1 contains the key input parameters that were used in the mirabegron and fesoterodine PBPK models.

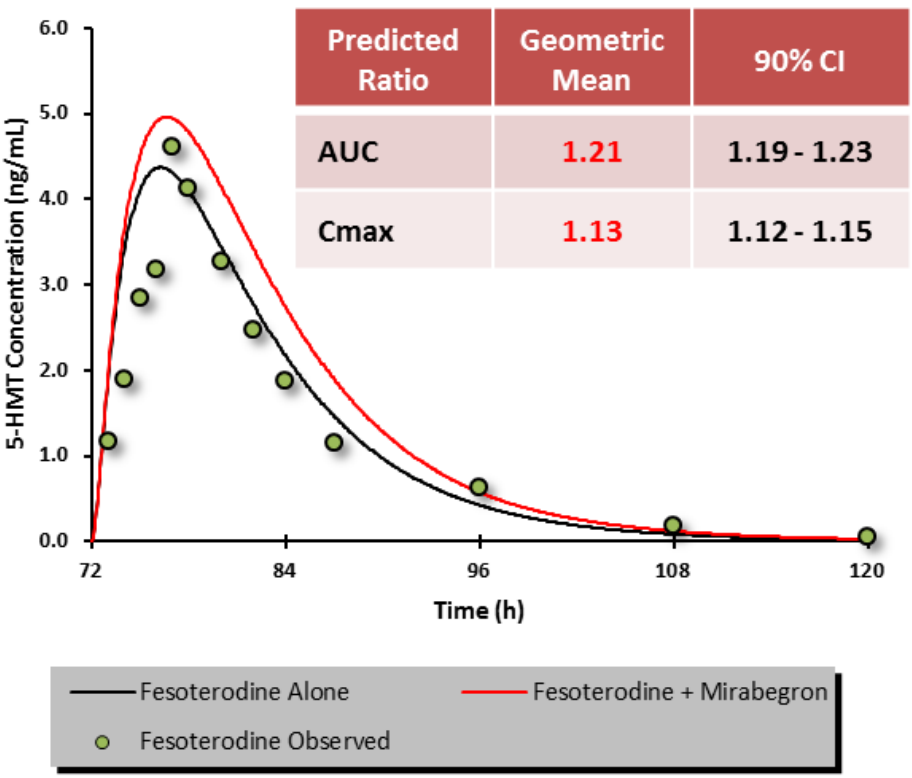
The PBPK models for mirabegron and 5-HMT were verified by comparing the predicted and observed PK profiles from single and multiple dose studies. The models were also used to predict DDIs between mirabegron and desipramine, as well as between fesoterodine (5-HMT) and ketoconazole and compared to the observed clinical data. After successfully predicting the PK of mirabegron and 5-HMT, the models were used to simulate the potential DDI between mirabegron and fesoterodine in 10 trials of 10 subjects each.

Table 1: Simcyp Input Parameters for Mirabegron and 5-Hydroxymethyltolterodine (5-HMT)

Parameter	Compound Mirabegron	5-HMT	Parameter	Compound Mirabegron	5-HMT
Physicochemical					
MW	396.16	341.5	pKa	NA	10.47
Log P	1.32	3.7	B/P	1	1
Compound type	neutral	base	f_u (plasma)	0.29	0.49
Absorption					
F_a	1	0.70	Tlag (h)	1.5	NA
k_a (h^{-1})	0.25	0.17			
Distribution					
V_{ss} (L/kg)	20	2.06	V_{sac} (L/kg)	17	NA
Elimination					
CL_{po} (L/h)	155	NA	CL_{int} CYP2D6 (µL/min/pmol)	NA	2.06
CL_Q (L/h)	262	NA	CL_{int} CYP3A4 (µL/min/pmol)	NA	0.12
CL_r (L/h)	13	14.4			
Drug Interaction – Reversible inhibition					
CYP2D6 K_i (µM)	2.3	NA	CYP3A4 K_i (µM)	23	NA
Drug Interaction – Time-dependent Inhibition					
CYP2D6 K_I (µM)	8.18	NA	CYP2D6 k_{inact} (h^{-1})	6.6	NA

Results

Fig 1: Steady-State 5-HMT PK Profiles Following Fesoterodine 8 mg QD Administered Alone or Fesoterodine 8 mg QD Co-administered with Mirabegron 50 mg QD.



Interpretation of results

Mirabegron and 5-HMT PK were accurately described with the PBPK models developed using Simcyp®. Application of the Simcyp® input parameters for mirabegron predicted a 60% and 203% increase in desipramine Cmax and AUC, respectively, following co-administration with mirabegron, accurately predicting the observed clinical study results (2). Administration of fesoterodine on day 4 following administration of mirabegron to steady state for 5 days predicted a 13% and 21% increase in 5-HMT Cmax and AUC, respectively, which is not considered to be a clinically relevant DDI for fesoterodine.

Concluding message

Based on this PBPK M&S analysis, concomitant administration of mirabegron 50 mg QD with fesoterodine 8 mg QD is estimated to increase 5-HMT Cmax and AUC by <25%, which is not considered clinically relevant for any adjustment in dosing recommendations for fesoterodine.

References

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Disclosures

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