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Pharmacokinetic drug interaction study between overactive bladder drugs mirabegron and tolterodine in Japanese healthy postmenopausal females

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ABSTRACT

Mirabegron, the first selective β_3-adrenoceptor agonist for the treatment of overactive bladder (OAB), inhibits cytochrome P450 isozyme CYP2D6. This study was performed in healthy postmenopausal female volunteers to assess any pharmacokinetic drug interaction between mirabegron and tolterodine, another OAB drug and a sensitive substrate of CYP2D6. Tolterodine 4 mg was orally administered from Days 1–7 and co-administered with mirabegron 50 mg from Days 8–14. Mirabegron 50 mg increased maximum concentration (C_{max}) and area under the concentration-time curve from zero to 24 h after dosing (AUC_{24h}) of tolterodine by 2.06-fold (90% confidence interval [CI] 1.81, 2.34) and 1.86-fold (90% CI 1.60, 2.16), respectively, and increased C_{max} and AUC_{24h} of the metabolite 5-hydroxymethyl tolterodine by 1.36-fold (90% CI 1.26, 1.47) and 1.25-fold (90% CI 1.15, 1.37), respectively. This suggested a weak pharmacokinetic drug interaction between mirabegron and tolterodine. Mean change from baseline of Fridericia's QT correction formula (ΔQTcF) was slightly higher on Day 14 than on Day 7. No subject had QTcF >480 msec or ΔQTcF >60 msec. All the treatment-emergent adverse events were mild. Mirabegron 50 mg was considered to be safe and well tolerated when coadministered with tolterodine 4 mg in healthy postmenopausal female volunteers.

1. Introduction

Mirabegron is the first selective β_3-adrenoceptor agonist, approved for the treatment of overactive bladder (OAB) symptoms of urge urinary incontinence, urgency, and urinary frequency in Japan (July 2011), the United States (June 2012), and Europe (December 2012). Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis [1]. *In vitro* studies suggest a role for cytochrome P450 (CYP) 2D6 and CYP3A4 in the oxidative metabolism of mirabegron [2] and *in vivo* results indicate that these isozymes play a limited role in the overall elimination [3]. Mirabegron was shown to be a time-dependent inhibitor of CYP2D6 in human liver microsomes [4]. In an *in vivo* study, mirabegron increased the exposure of the sensitive CYP2D6 substrates metoprolol (by 1.90-fold for maximum concentration (C_{max}) and 3.29-fold for area under the curve (AUC) from the time of dosing extrapolated to time infinity ($AUC_{0-\infty}$) with 160 mg/day of mirabegron) and desipramine (by 1.79-fold for C_{max} and 3.41-fold for $AUC_{0-\infty}$ with 100 mg/day of mirabegron) [5]. The results of a thorough QT/QTc (TQT) study showed that mirabegron did not have any clinically significant effects on the QT interval, which is from the beginning of the QRS complex to the end of the T wave, at its clinical dose (25–50 mg/day) but prolonged the QTcI interval, which was used as individual subject-specific correction formulae for QTc, at the 200 mg supratherapeutic dose (upper one-sided 95% CI > 10 msec) in females [6].

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Another OAB drug, tolterodine, is an antimuscarinic agent. While tolterodine itself has no detectable effect on CYP2D6, CYP3A4, CYP2C19 and CYP1A2 [7], it is known to be a sensitive substrate of CYP2D6. Tolterodine is eliminated primarily by metabolism involving CYP2D6 and CYP3A4 [8,9] and undergoes metabolism to form the 5-hydroxymethyl tolterodine (5-HMT) derivative [10,11], a major metabolite which is pharmacologically active and has equivalent antimuscarinic potency to tolterodine *in vitro* [12]. Serum concentrations of tolterodine were higher in CYP2D6 poor metabolizers (PMs) than in extensive metabolizers (EMs), and the AUC of tolterodine was increased by 4.8-fold in CYP2D6 EM with fluoxetine 20 mg, which is known as a potent CYP2D6 inhibitor [13]. Exposure to the pharmacologically active moiety in EM (sum of unbound tolterodine and 5-HMT) and PM (unbound tolterodine) is comparable regardless of metabolic phenotype [14], given protein binding of tolterodine and 5-HMT (unbound fractions of 3.7% and 36%, respectively) [15]. An *in vitro* study of the effects of tolterodine on cardiac ion channels showed that it was a potent inhibitor of both human ether a-go-go-related gene (hERG) cardiac potassium and L-type calcium channels [16]. In a TQT study tolterodine immediate release (IR) tablet did not have a clinically significant effect on QTc interval but numerically prolonged it at a dose of 4 mg twice daily [17]. However, a TQT study of fesoterodine, a prodrug of 5-HMT, indicated that fesoterodine is not associated with QTc prolongation or other electrocardiogram (ECG) abnormalities at either therapeutic (4 mg) or supratherapeutic (28 mg) doses [18]. The C_{max} of tolterodine and 5-HMT with tolterodine extended release (ER) capsules are approximately 61% and 67% lower, respectively, than with IR tablets [19].

It is possible that mirabegron and tolterodine might be taken simultaneously in a clinical situation for treatment of OAB. In this scenario, the exposure of tolterodine is expected to be increased with mirabegron. The current study was conducted to assess the effect of multiple doses of mirabegron 50 mg on the pharmacokinetics (PK) of tolterodine and its metabolite. A secondary objective of this study was to evaluate safety, including the effect of co-administration of mirabegron and tolterodine on QTc.

To evaluate the maximum inhibitory effect of mirabegron in a clinical setting, postmenopausal female subjects were selected as the target population for the following reasons: The PK of mirabegron is higher in females than in males with no clear safety differences between sexes [20,21]; there are no clear age differences regarding the PK of mirabegron [20,21]; the prevalence of OAB increases with age; the target population of OAB mainly consists of elderly patients [22,23]. Mirabegron 50 mg was selected because it is the standard and maximum clinical dose. Tolterodine ER 4 mg was selected because it is the standard clinical dose. There are no clear sex or age differences regarding the PK of tolterodine [24].

2. Materials and methods

This study was conducted in accordance with the ethical principles based on the Declaration of Helsinki and Good Clinical Practice, as defined by the Ministerial Ordinance concerning the standards for the implementation of clinical studies on pharmaceutical products, and the regulations stipulated in the Japanese Pharmaceutical Affairs Law. The study was conducted at one center and approved by its institutional review board. All subjects provided written informed consent before screening.

2.1. Subjects

Subjects enrolled in this study were healthy postmenopausal females aged 45–70 years, with a body weight of 40 to <70 kg and a body mass index (BMI) of 17.6 to <26.4 kg/m^2. Eligible subjects were of good health (no clinically significant deviation from normal in physical examination, standard 12-lead ECG, vital signs, QT/QTc interval corrected for heart rate (time from R wave to R wave: RR interval), according to Fridericia's formula (QTcF) evaluation, and clinical laboratory tests) and had no clinically significant medical history. Normal range of QT/QTcF evaluation were time from P wave to QRS complex (PR interval) of 120 to <200 msec, QRS interval of <120 msec, and QTc interval corrected for RR interval according to Bazett's formula (QTcB) and QTcF interval of <450 msec.

2.2. Study design

This single-center, open-label, multiple dose, single-sequence, drug–drug interaction study was designed to assess the effect of mirabegron on the PK of tolterodine and to evaluate the safety under steady state of concomitant use of mirabegron and tolterodine.

The sample size was set at a total of 24 subjects as this was the number deemed necessary to assess the PK of this study, taking the feasibility of enrollment of healthy postmenopausal adult female subjects into consideration. No formal statistical sample size calculation was performed.

After giving written informed consent, subjects were screened within 26 days to ascertain their eligibility for the study according to the inclusion and exclusion criteria. Subjects were admitted to the clinical unit, Medical Co. LTA Sumida Hospital, from Day − 2 to Day 15. A clinical dose of tolterodine ER 4 mg was administered orally once daily after breakfast from Days 1–7 (mono dosing period) and both tolterodine ER 4 mg and a mirabegron oral controlled absorption system (OCAS®) tablet (mirabegron OCAS) 50 mg were administered once daily after breakfast from Days 8–14 (combination dosing period). The periods were established as a sufficient length of time for the plasma concentration of each drug to reach steady state. Subjects were discharged on Day 15 provided that there were no medical reasons for a longer stay. An end-of-study visit took place on Day 22. Concomitant medication (use of drugs and therapies other than the study drugs) was not allowed during the study period, except for treatment of adverse events (AEs).

Safety was assessed based on physical examinations, vital signs (axillary body temperature, supine blood pressure, and supine pulse rate), clinical laboratory tests (biochemistry, hematology and urinalysis), standard 12-lead ECGs, time-matched QT/QTc assessments and AE monitoring. Clinically significant adverse changes in any safety assessment including symptoms and signs, vital signs, ECGs and clinical laboratory tests were considered AEs. AEs were collected from the time of admission to the study site until the end of the study.

Time-matched QT/QTc assessments were performed at screening, 24, 23, 22, 20, 17, 12 and 0 h before dosing on Day 1 as the baseline, at pre-dose, 1, 2, 4, 7, 12 and 24 h after dosing on Days 7 and 14, and at the time of discontinuation. The12-lead ECG records for QT assessment were forwarded to eResearchTechnology, Inc., Pennsylvania, USA, for analysis, and the PR interval, RR interval, QRS interval, and QT interval were calculated to evaluate multiple-dose and steady-state QTc effects of tolterodine ER 4 mg with/without mirabegron OCAS 50 mg.

Blood sample for genotyping was collected on Day 2 to explore the contribution of CYP2D6 to the PK of tolterodine and 5-HMT.Mutated alleles CYP2D6*2, *4, *5, *10, *14,*18, *21, *36 and duplication (x N) of each allele were selected for the genotyping in this study based on the frequencies of PMs in the Japanese population [25,26]. Genotyping for the CYP2D6 alleles was performed by allele-specific polymerase chain reaction-based assays, and CYP2D6*18 allele by sequence-based assay at Hokkaido System Science, Inc., Hokkaido, Japan. Subjects who carried mutant alleles

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