British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2018) **84** 2317–2324 2317

ORIGINAL ARTICLE

Coadministration of probenecid and cimetidine with mirogabalin in healthy subjects: A phase 1, randomized, open-label, drug–drug interaction study

Correspondence Hamim Zahir, PhD, Daiichi Sankyo Inc., Basking Ridge, NJ, USA. Tel.: +1 908 992 6849; Fax: +1 732 906 5690; E-mail: hzahir@dsi.com

Received 17 January 2018; **Revised** 5 June 2018; **Accepted** 11 June 2018

Masaya Tachibana[1], Naotoshi Yamamura[2], George J. Atiee[3,*], Ching Hsu[4], Vance Warren[4], Ling He[4], Victor Dishy[4] and Hamim Zahir[4]

[1]Clinical Pharmacology Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan, [2]Drug Metabolism and Pharmacokinetics Research Laboratories, Daiichi Sankyo Co., Ltd., Tokyo, Japan, [3]Worldwide Clinical Trials, San Antonio, TX, USA, and [4]Daiichi Sankyo Inc., Basking Ridge, NJ, USA

*Principal investigator.

Keywords drug interactions, pain, pharmacokinetics

AIMS

The primary aim of this study was to assess the individual effects of probenecid and cimetidine on mirogabalin exposure.

METHODS

This phase 1, open-label, crossover study randomized healthy adults to receive three treatment regimens, each separated by ≥5-day washout: a single oral dose of mirogabalin 15 mg on day 2, mirogabalin 15 mg on day 2 plus probenecid 500 mg every 6 h from days 1 to 4, and mirogabalin 15 mg on day 2 plus cimetidine 400 mg every 6 h from days 1 to 4.

RESULTS

Coadministration of mirogabalin with probenecid or cimetidine increased the maximum and total mirogabalin exposure. The geometric mean ratios of C_{max} and $AUC_{(0\text{-}t)}$ (90% CI) with and without coadministration of probenecid were 128.7% (121.9–135.7%) and 176.1% (171.9–180.3%), respectively. The geometric mean ratios of C_{max} and $AUC_{(0\text{-}t)}$ (90% CI) with and without coadministration of cimetidine were 117.1% (111.0–123.6%) and 143.7% (140.3–147.2%), respectively. Mean (standard deviation) renal clearance of mirogabalin (l h^{-1}) was substantially slower after probenecid [6.67 (1.53)] or cimetidine [7.17 (1.68)] coadministration, compared with mirogabalin alone [11.3 (2.39)]. Coadministration of probenecid or cimetidine decreased mirogabalin mean (standard deviation) apparent total body clearance [10.5 (2.33) and 12.8 (2.67) l h^{-1}, respectively, *vs*. 18.4 (3.93) for mirogabalin alone].

CONCLUSIONS

A greater magnitude of change in mirogabalin exposure was observed when coadministered with a drug that inhibits both renal and metabolic clearance (probenecid) *vs*. a drug that only affects renal clearance (cimetidine). However, as the increase in exposure is not clinically significant (>2-fold), no *a priori* dose adjustment is recommended.

DOI:10.1111/bcp.13674

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Mirogabalin is a substrate for organic anion transporters 1 and 3 (OAT1/3), organic cation transporter 2 (OCT2), and multidrug and toxin extrusion (MATE) transporter
- The US Food and Drug Administration guidance for drug interaction studies recommends that *in vivo* human drug–drug interaction studies are performed with probenecid, a uricosuric drug and an OAT1/3 and uridine 5′-diphospho-glucuronosyltransferase inhibitor (UGT); and cimetidine, an H_2-receptor antagonist antihistamine and an OCT2 and MATE inhibitor

WHAT THIS STUDY ADDS

- This study clinically evaluates the effect of a UGT and OAT inhibitor, probenecid and an OCT and MATE inhibitor, cimetidine on mirogabalin pharmacokinetics
- This study demonstrates that a greater magnitude of change in mirogabalin exposure is observed when coadministered with probenecid, a drug that inhibits both metabolic and renal elimination, *vs*. cimetidine, a drug that only affects renal elimination of mirogabalin
- The increase in mirogabalin exposure with cimetidine was similar to the increase observed in patients with mild renal impairment, for whom mirogabalin dose adjustments are not considered necessary. Additionally, the effect of probenecid on mirogabalin was not clinically significant (>2-fold); therefore, a dose adjustment may not be necessary with concomitant administration of a UGT and OAT inhibitor

Introduction

Pain associated with the neurological conditions of diabetic peripheral neuropathic pain (DPNP) and postherpetic neuralgia (PHN) may profoundly impact function and quality of life [1]. DPNP is a common complication of diabetes affecting up to 50% of patients with diabetic neuropathy in the USA [2]. PHN, a common complication of herpes zoster (shingles), affects up to 20% of patients with herpes zoster [3].

Neuropathic pain has been linked to the upregulation of the $\alpha_2\delta$-1 subunit of **voltage-dependent calcium channels** in the central nervous system [4]. In addition to a pore-forming α1 subunit, voltage-dependent calcium channels are composed of an intracellular β subunit, a disulfide-linked dimer of α_2 and δ subunits ($\alpha_2\delta$), and a transmembrane γ subunit in some types [5]. Ligands of the **$\alpha_2\delta$-1 subunit** exert analgesic effects by preventing its trafficking to presynaptic terminals, decreasing presynaptic calcium influx, and thereby, reducing neurotransmitter release [4]. Mirogabalin monobenzenesulfonate (referred to herein as mirogabalin; Daiichi Sankyo Co., Ltd., Tokyo, Japan) is a preferentially selective $\alpha_2\delta$-1 ligand that is intended for the treatment of DPNP and PHN (NCT02318706, NCT02318719).

In a phase 2 study in patients with DPNP, mirogabalin was well tolerated in doses of up to 30 mg day^{-1}, and significantly reduced average daily pain scores compared with placebo when administered at 15 mg day^{-1}, 20 mg day^{-1} or 30 mg day^{-1} [6]. Mirogabalin is eliminated primarily as the parent drug through renal excretion after oral administration in animals and humans; approximately 20% is eliminated by glucuronidation, followed by generation of a lactam metabolite (A204–4455; unpublished data on file, Daiichi Sankyo). The US Food and Drug Administration (FDA) guidance for drug interaction studies recommends that investigational drugs with significant renal clearance are evaluated to determine whether they are a substrate of renal transporters—namely organic anion transporters 1 and 3 (OAT1/3)—and organic cation transporter 2 (OCT2) [7]. *In vitro* data indicate that mirogabalin is a substrate for OAT1/3, OCT2, and the multidrug and toxin extrusion (MATE) transporter (unpublished data on file, Daiichi Sankyo) [8–10]. The FDA guidance for drug interaction studies further recommends that *in vivo* human drug interaction studies are performed with probenecid, a uridine 5′-diphospho-glucuronosyltransferase (UGT) inhibitor for drugs which are metabolized by the UGT pathway. Probenecid is also an OAT1/3 inhibitor. Additionally, cimetidine is the recommended OCT2 and MATE inhibitor [7, 11–13]. Therefore, a drug–drug interaction study was conducted in healthy subjects to determine the effects of probenecid and cimetidine on mirogabalin pharmacokinetics (PK). The primary objective of this study was to assess the individual effects of probenecid and cimetidine on mirogabalin exposure. The secondary objectives of this study were to assess the safety and tolerability of mirogabalin and additional PK parameters of mirogabalin when administered alone or with probenecid or cimetidine. The PK of a lactam metabolite of mirogabalin (A204–4455) was also evaluated, since this is a measure of UGT-mediated metabolism of mirogabalin and, therefore, its exposure may be altered by the coadministration of UGT inhibitor probenecid.

Methods

Study design

This was a phase 1, randomized, open-label, three-period, crossover study in which healthy adults received the following three treatments: a single oral dose of mirogabalin 15-mg tablet on day 2 (treatment A), mirogabalin 15 mg on day 2 plus probenecid 500-mg tablet every 6 h from days 1 to 4 (treatment B), mirogabalin 15 mg on day 2 plus cimetidine 400-mg tablet every 6 h from days 1 to 4 (treatment C); each separated by a ≥5-day washout period (Figure 1). Subjects fasted overnight for at least 10 h prior to mirogabalin administration and for at least 4 h after dosing. Mirogabalin was administered with approximately 240 ml of water. Subjects

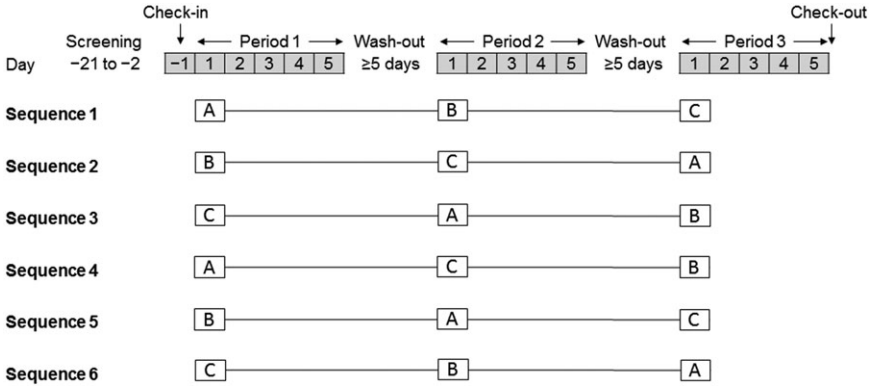

Figure 1

Study design. Treatment A (a single oral dose of mirogabalin 15 mg on day 2), Treatment B (mirogabalin 15 mg on day 2 plus probenecid 500 mg every 6 h from days 1–4), Treatment C (mirogabalin 15 mg on day 2 plus cimetidine 400 mg every 6 h from days 1–4). Treatment regimens were separated by a ≥5-day washout period

received one of six possible treatment sequences (i.e. ABC, ACB, BAC, BCA, CAB or CBA).

The study was approved by an Institutional Review Board and was performed in accordance with the Declaration of Helsinki and International Conference on Harmonization guidelines. All subjects provided written informed consent before participation.

Study population

Healthy participants were eligible to enroll if they were aged 18 to 60 years and with a body mass index (BMI) of 18 to 30 kg m^{-2}. Healthy participants were determined by medical history, physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and clinical laboratory tests at screening. Women were either of nonchildbearing potential or of childbearing potential and using nonhormonal methods of contraception for at least 3 months prior to study. Men agreed to use barrier contraception and spermicide, and not to donate sperm. All subjects agreed to abstain from caffeinated drinks and foods; alcohol; grapefruit, apple or orange juice; vegetables from the mustard green family; and charbroiled meats from 7 days prior to the first dose until the end of the study. Exclusion criteria included a history of any surgical treatment that may impair the oral absorption of drugs, creatinine clearance of <90 ml min^{-1}, and use of tobacco- or nicotine-containing products within the preceding 6 months.

Sample collection and bioanalytic methods

Blood samples were collected to assess the PK of mirogabalin and inactive lactam metabolite over days 2 to 5 of each treatment period at predose (h 0) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, 24, 30, 36, 48, 54, 60 and 72 h postdose. Urine samples were collected for the assessment of mirogabalin and its lactam metabolite over days 2 to 5 of each treatment period at predose (h 0) and at 0 to 6 h, 6 to 12 h, 12 to 24 h, 24 to 48 h and 48 to 72 h postdose. Blood samples were collected to assess the PK of cimetidine and probenecid on day 1, prior to the morning dose and prior to the doses at 6, 12 and 18 h; on day 2, prior to the morning dose, at 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4 h after the morning dose, and prior to the doses at 6 and 12 h; on days 3 and 4, prior to the morning dose and prior to the doses at 6 and 12 h; and on day 5, 6 h after the last dose.

Plasma concentrations of free-base mirogabalin were analyzed at Celerion (Lincoln, NE, USA) using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method. Plasma samples containing analyte and internal standard (d_5-mirogabalin, A206–04632; Daiichi Sankyo Pharma Development, Basking Ridge, NJ, USA) were extracted using an Oasis® HLB solid-phase extraction plate (Waters Inc., Milford, MA, USA). Extracted samples were analyzed on a Zorbax 300-SCX column (50 mm length, 3.0 mm internal diameter, 5 μm particle size; Agilent Technologies, Santa Clara, CA, USA) at ambient temperature with a mobile phase of 80:20 (v/v) acetonitrile: 20 mmol l^{-1} ammonium formate, pH 2.5 with formic acid, at a flow rate of 1.0 ml min^{-1}. Mirogabalin and internal standard were detected using an AB Sciex API 4000™ triple quadrupole mass spectrometer (Sciex, Framingham, MA, USA). The calibration curves for mirogabalin (1/concentration squared-weighted linear regression) ranged from 1 to 500 ng ml^{-1}. The intra- and interassay precision (coefficient of variation, CV) values in validation were within 1.1% to 14.6% and 2.0% to 11.7%, respectively; the intra- and interassay accuracy values were –16.3% to 3.1%, and –7.1% to 1.9%, respectively. Dilution integrity was verified at a concentration up to 20 000 ng ml^{-1}.

The plasma concentrations of probenecid were analyzed using a validated LC–MS/MS method by Worldwide Clinical Trials (Austin, TX, USA). Plasma samples (50 μl) were mixed with internal standard (probenecid-d14, SynFine Research, Richmond Hill, ON, Canada). Samples were extracted via methanol-mediated protein precipitation. The 100 μl sample was removed and diluted with 0.800 ml of 20% acetonitrile in water. Up to 10 μl of extracted sample was injected onto an Onyx C-18, 2.0 × 500 mm (Phenomenex, Inc., Torrance, CA, USA), which was connected to an API 4000 triple quadrupole mass spectrometer (Sciex). Analyte was eluted using a gradient mobile phase comprised of water, formic acid, ammonium acetate (1000:0.5:0.385) and 2-propanol, acetonitrile, formic acid, ammonium acetate (200:800:0.5:0.385). The flow rate was 0.500 ml min^{-1} with a total run time of

4.5 min. Quantitation was performed using weighted linear least squares (LS) regression analyses generated from calibration standards prepared fresh daily. The method was validated for a range of 0.200 to 200 μg ml^{-1} probenecid. The intra- and interassay precision and accuracy CV values were within 13.2% and 9.7%, respectively, at lower limit of quantification (LLOQ); the intra- and interassay accuracy values were within 8.1% and 5.9%, respectively, at other concentrations.

The plasma concentrations of cimetidine were also analyzed using a validated LC–MS/MS method by Worldwide Clinical Trials (Austin, TX, USA). Plasma samples (50 μl) were mixed with the internal standard (cimetidine-d3, SynFine Research; Richmond Hill, ON, Canada). Samples were extracted via acetonitrile-mediated protein precipitation. Up to 5 μl of the extracted sample was injected onto a Kinetex PFP, 2.6 μm, 2.1 × 50 mm (Phenomenex, Inc.), which was connected to an API 5000 triple quadrupole mass spectrometer (Sciex). The analyte was eluted using a gradient mobile phase comprised of 5 mmol l^{-1} ammonium formate in water and acetonitrile in water (900:100). The flow rate was 0.400 ml min^{-1} with a total run time of 2.6 min. Quantitation was performed using weighted linear LS regression analyses generated from calibration standards prepared fresh daily. The method was validated for a range of 10 to 10 000 ng ml^{-1} cimetidine. The intra- and interassay precision and accuracy (CV) values were within 7.2% and 8.5%, respectively, at LLOQ; the intra- and interassay accuracy values were within 4.2% and 5.3%, respectively, at other concentrations.

The plasma concentrations of the lactam metabolite of mirogabalin were analysed at Celerion using a validated LC–MS/MS method. Plasma samples containing analyte and internal standard (d5-labeled analyte, A212–6230; Daiichi Sankyo Pharma Development) were mixed with equal-volume ammonium acetate (250 mmol l^{-1}) and extracted with n-butyl chloride in a 96-well plate. Extracted samples were analyzed on an ACE C18 column (50 mm length, 3.0 mm internal diameter, 5 μm particle size; Advanced Chromatography Technologies, Aberdeen, UK) at ambient temperature, with a mobile phase of 40:60:0.1 (v/v) acetonitrile: water: formic acid and a flow rate of 1.0 ml min^{-1}. The lactam metabolite of mirogabalin and internal standard were detected using an AB Sciex API 4000™ triple quadrupole mass spectrometer. The calibration curve for the analyte (1/$concentration^2$ weighted linear regression) ranged from 0.1 to 50 ng ml^{-1}. The intra- and interassay precision (CV) values in validation were 1.9% to 17.3% and 3.4% to 14.2%, respectively; the intra- and interassay accuracy values were –9.2% to 10.0%, and –4.7% to 1.3%, respectively. Dilution integrity was verified at a concentration of 200 ng ml^{-1}.

Pharmacokinetic assessments

Pharmacokinetic parameters were computed using Phoenix™ WinNonlin® (version 6.3, Certara, Princeton, NJ, USA). PK assessments included maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (t_{max}), area under the plasma concentration-time curve from time 0 to the last quantifiable dose ($AUC_{[0-t]}$), terminal elimination half-life ($t_{½}$), apparent total body clearance (CL/F), fraction of the administered dose excreted in urine (fe), percentage of dose excreted in urine (Ae, % dose) and renal clearance (CL_R).

Safety assessments

Safety assessments included treatment-emergent adverse events (TEAEs), physical examination findings, vital signs, 12-lead ECGs and clinical laboratory tests. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 18.0 (McLean, VA, USA).

Statistical analysis and planned sample size

Differences between treatments, when mirogabalin was administered alone or with probenecid or cimetidine were calculated by ratios of geometric LS mean and their 90% confidence intervals (CIs). For PK parameters C_{max}, $AUC_{(0-t)}$ and AUC, an analysis of variance model with treatment, sequence, period, and subject nested within sequence as a fixed effects model was performed on the natural log transformed data.

Assuming an equal randomization ratio, a type I error rate of 0.05, no-effect equivalence limits of 80% to 125%, an expected ratio of geometric LS mean of 1.05, and an intrasubject CV of 22%, a total of 24 subjects (i.e. four subjects per treatment sequence) provided an 80% power to conclude absence of an interaction. Therefore, a total of 30 subjects were planned to be enrolled in the study (i.e. five subjects per treatment sequence).

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [14], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [15].

Results

Patient demographics and characteristics

All 30 subjects randomly assigned to one of three treatment sequences completed the study. Approximately 46.7% (14/30) of subjects were women and the subjects were predominantly White (56.7%; 17/30) or Black or African American (40.0%; 12/30). Mean (standard deviation, SD) age was 37.8 (7.81) years and mean (SD) BMI was 26.4 (2.56) kg m^{-2} in this study population. Demographics were similar among patients in all treatment sequences.

Effects of probenecid and cimetidine on the single-dose pharmacokinetics of mirogabalin

The arithmetic mean (SD) concentration–time profiles of mirogabalin, when administered alone or in combination with probenecid or cimetidine, are shown in Figure 2A and 2B. The PK parameters of mirogabalin are summarized in Table 1, and a comparison between treatments administered mirogabalin alone or in combination with probenecid or cimetidine are shown in Table 2.

Coadministration of mirogabalin and probenecid or cimetidine resulted in an increase in maximum and total

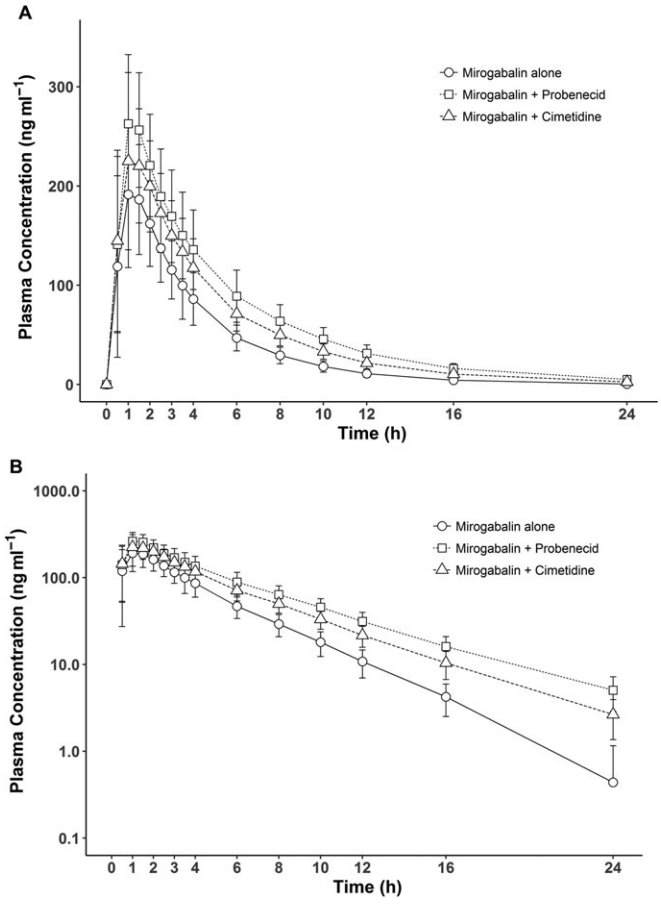

Figure 2

Mean (standard deviation) plasma mirogabalin concentration–time profiles after administration of mirogabalin alone or when coadministered with probenecid or cimetidine: (A) linear scale; (B) semilogarithmic scale. Plasma mirogabalin concentrations that are below the lower limit of quantification were not included in the plots

mirogabalin exposure: the geometric mean ratios of C_{max} and $AUC_{(0\text{-}t)}$, coadministered with and without probenecid were 128.7% (90% CI, 121.9–135.7%) and 176.1% (90% CI, 171.9–180.3%), respectively. The geometric mean ratios of C_{max} and $AUC_{(0\text{-}t)}$ coadministered with and without cimetidine were 117.1% (90% CI, 111.0–123.6%) and 143.7% (90% CI, 140.3–147.2%), respectively (Table 2). Median t_{max} of mirogabalin occurred at 1 h after dose, irrespective of the treatment (Table 1). Mean percentage of dose of mirogabalin excreted in the urine (Ae, % dose) was similar after probenecid coadministration (63.6%) and was slightly lower after cimetidine coadministration (55.9%), compared with mirogabalin alone (61.5%; Table 1). Mean (SD) CL_R for mirogabalin was substantially slower after probenecid [6.67 (1.53) l h^{-1}] or cimetidine [7.17 (1.68) l h^{-1}] coadministration, compared with mirogabalin alone [11.3 (2.39) l h^{-1}; Table 1]. Reduction in total clearance of mirogabalin when coadministered with probenecid was much larger than when mirogabalin was coadministered with cimetidine.

Mean plasma concentrations of the lactam metabolite of mirogabalin were lower with probenecid than when mirogabalin was administered alone. By contrast, mean plasma concentrations of the lactam metabolite of mirogabalin were slightly higher when mirogabalin was coadministered with cimetidine than with mirogabalin alone (Figure 3). Based on geometric means, C_{max} and $AUC_{(0\text{-}t)}$ of the lactam metabolite of mirogabalin decreased by approximately 46% and 33%, respectively, in the presence of probenecid, compared with mirogabalin alone. C_{max} and $AUC_{(0\text{-}t)}$ of the lactam metabolite of mirogabalin increased by approximately 24% and 58%, respectively, in the presence of cimetidine compared with mirogabalin alone. However, based on AUC, when coadministered with probenecid, the mean metabolite to parent ratio (MPR%) reduced by >50% (alone: 15.4% *vs.* coadministered with probenecid: 6.1%). There was only a small increase in mean MPR%, when coadministered with cimetidine (alone: 15.4% *vs.* coadministered with cimetidine: 17.2%).

Steady state was attained for both probenecid and cimetidine before mirogabalin administration and during coadministration of mirogabalin and probenecid or cimetidine (Figures S1 and S2).

Safety

There were no clinically significant changes in vital signs or ECGs. There were no deaths, serious AEs or TEAEs that led to discontinuation. Thirteen subjects (43.3%) reported 23 TEAEs during the study. All TEAEs were mild to moderate and resolved without sequelae. Constipation was the most common TEAE, reported by one subject (3.3%) in the mirogabalin alone group, one subject (3.3%) in the mirogabalin + probenecid group, and four subjects (13.3%) in the mirogabalin + cimetidine group. Dizziness, headache and somnolence were each reported by two subjects (6.7%) following mirogabalin and probenecid coadministration; dizziness was also reported by one subject (3.3%) in the mirogabalin alone group and two subjects (6.7%) following mirogabalin and cimetidine coadministration.

Discussion

Plasma exposure to mirogabalin was increased when a single 15-mg dose of mirogabalin was administered in combination with either probenecid or cimetidine, compared with mirogabalin alone. This increase was more pronounced with probenecid compared with cimetidine. When coadministered with probenecid, a known OAT1/3 and UGT inhibitor, mirogabalin C_{max} and $AUC_{(0\text{-}t)}$ increased by approximately 29% and 76%, respectively. When coadministered with cimetidine, a known OCT2 and MATE inhibitor, mirogabalin C_{max} and $AUC_{(0\text{-}t)}$ values increased by approximately 17% and 44%, respectively. Mean renal clearance for mirogabalin was substantially slower after probenecid or cimetidine coadministration compared with mirogabalin alone. Therefore, the observed increases in mirogabalin exposure with reduced renal clearance are likely a result of reduced renal secretion of mirogabalin caused by cimetidine-induced inhibition of renal transporters (OCT2 and/or MATE) or probenecid-induced inhibition of renal transporters (OAT1/3). Additionally, probenecid decreased total clearance of mirogabalin (–7.9 l h^{-1}) more than it did renal clearance (–4.6 l h^{-1}; Table 1), suggesting that it decreases not only

Table 1

Plasma and urinary pharmacokinetic parameters of mirogabalin alone and in combination with probenecid or cimetidine

	Mirogabalin 15 mg Alone (n = 30)	Mirogabalin 15 mg + probenecid 500 mg (n = 30)	Mirogabalin 15 mg + cimetidine 400 mg (n = 30)
Plasma parameters			
C_{max} (ng ml^{-1})	227 (55.0)	290 (58.9)	265 (60.3)
Geometric mean (CV%)	221 (25.5)	284 (21.4)	259 (22.6)
t_{max} (h)			
Median (min, max)	1.00 (0.50, 2.50)	1.00 (0.50, 3.00)	1.00 (0.50, 2.00)
$AUC_{(0\text{-}t)}$ (ng·h ml^{-1})	840 (178)	1480 (306)	1200 (239)
Geometric mean (CV%)	822 (21.6)	1450 (21.5)	1180 (20.5)
$t_{½}$ (h)	2.93 (0.486)	4.62 (0.726)	3.92 (0.569)
CL/F (l h^{-1})	18.4 (3.93)	10.5 (2.33)	12.8 (2.67)
Urinary parameters			
fe	0.615 (0.044)	0.636 (0.055)	0.559 (0.056)
Ae, % dose	61.5 (4.37)	63.6 (5.54)	55.9 (5.60)
CL_R (l h^{-1})	11.3 (2.39)	6.67 (1.53)	7.17 (1.68)

Shown as arithmetic mean (standard deviation), unless otherwise noted
Ae, percentage of drug in urine; $AUC_{(0\text{-}t)}$, area under the plasma concentration *vs*. time curve from time 0 to the last quantifiable dose; CL/F, apparent total body clearance; CL_R, renal clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; fe, fraction of dose excreted in urine; $t_{½}$, terminal elimination half-life; t_{max}, time to reach maximum plasma concentration

Table 2

Statistical analyses of pharmacokinetic parameters of mirogabalin alone and in combination with probenecid or cimetidine

Pharmacokinetic parameters	Geo LS mean mirogabalin + probenecid (Treatment B)	Geo LS mean mirogabalin alone (Treatment A)	Ratio (%; B/A) (90% CI)
C_{max} (ng ml^{-1})	284	221	129 (122–136)
$AUC_{(0\text{-}t)}$ (ng·h ml^{-1})	1448	822	176 (172–180)
AUC (ng·h ml^{-1})	1458	834	175 (171–179)
Pharmacokinetic parameters	**Geo LS mean mirogabalin + cimetidine (Treatment C)**	**Geo LS mean mirogabalin alone (Treatment A)**	**Ratio (%; C/A) (90% CI)**
C_{max} (ng ml^{-1})	259	221	117 (111–124)
$AUC_{(0\text{-}t)}$ (ng·h ml^{-1})	1181	822	144 (140–147)
AUC (ng·h ml^{-1})	1192	834	143 (140–146)

AUC, area under the plasma concentration *vs*. time curve at infinity; $AUC_{(0\text{-}t)}$, area under the plasma concentration *vs*. time curve from time 0 to the last quantifiable dose; CI, confidence interval; C_{max}, maximum plasma concentration; Geo LS mean, geometric least squares mean

renal but also nonrenal (i.e., metabolic) clearance of mirogabalin. These results are consistent with the decreased level of lactam metabolite of mirogabalin (which originates from a glucuronide metabolite) in the presence of probenecid. As probenecid inhibits both UGT and OAT1/3, this observation is specific to dual inhibition of OAT1/3 and UGT by probenecid. This also explains the greater increase in mirogabalin exposure when coadministered with probenecid—due to the inhibition of both metabolic and renal clearance of mirogabalin—as compared with mirogabalin coadministered with cimetidine, which inhibits only the renal clearance of mirogabalin.

The unbound plasma concentration of cimetidine attained in this study was approximately 9.1 μmol l^{-1}, with approximately 20% of cimetidine bound to human plasma protein [16]. The FDA guidance for drug interaction studies recommends that *in vivo* human drug–drug interaction studies are performed with cimetidine for OCT2 [7]; however, comparison of the inhibition constant (K_i) values of cimetidine previously reported for OCT2 (K_i = 95–146 μmol l^{-1}), MATE1 (K_i = 1.1–3.8 μmol l^{-1}) and MATE2-K (K_i = 2.1–6.9 μmol l^{-1}) with the observed maximum unbound plasma concentration (9.1 μmol l^{-1}) suggests that the inhibition of MATE1 and/or MATE2-K, and not OCT2, is the likely

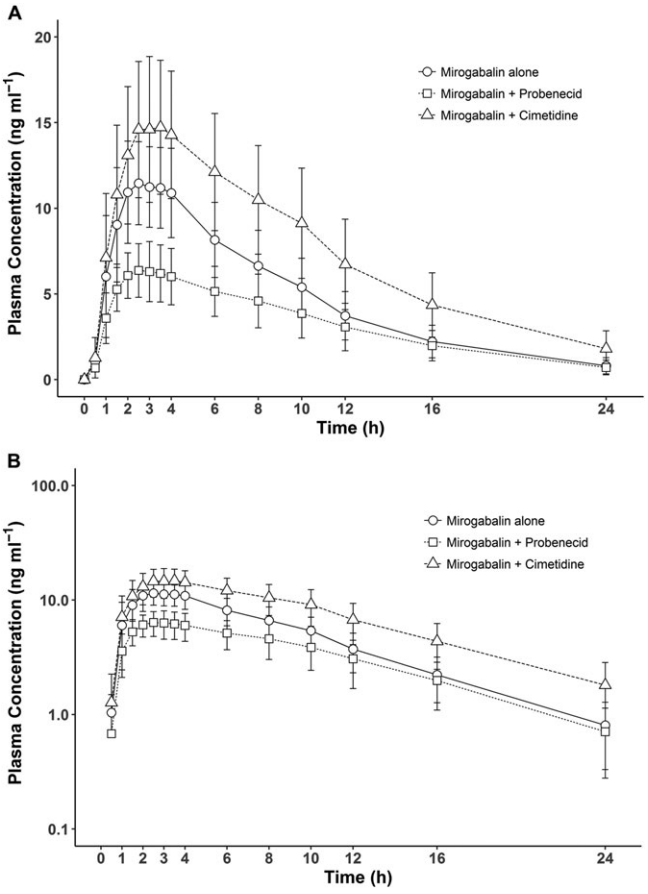

Figure 3

Mean (standard deviation) plasma mirogabalin lactam metabolite concentration–time profiles after administration of mirogabalin alone or when coadministered with probenecid or cimetidine: (A) linear scale; (B) semilogarithmic scale. Plasma mirogabalin lactam metabolite concentrations that are below the lower limit of quantification were not included in the plots

mechanism underlying the drug–drug interaction between mirogabalin and cimetidine [17]. Similarly, comparison of the K_i value of probenecid previously reported for OAT1/3 (<4 μmol l^{-1}) with the observed maximum unbound trough plasma concentration of 28 μmol l^{-1} just before dosing of mirogabalin is consistent with the hypothesis that the inhibition of OAT1/3 is the mechanism underlying the drug–drug interaction between mirogabalin and probenecid.

A single 15-mg dose of mirogabalin was well tolerated with no serious AEs, or AEs leading to discontinuation when administered alone or in combination with probenecid or cimetidine.

A limitation of this study is that the inhibitors tested in combination with mirogabalin affect multiple transporters. This is due to lack of inhibitors specific for each transporter. Therefore, the results of this study should be evaluated cautiously, and future studies or physiologically-based PK modelling are needed to determine the effects of specific transporters. Another limitation of this study is that it did not evaluate the effects of these drug–drug interactions in the target patient population. Diabetes is frequently complicated by renal and hepatic impairment [18, 19]. Since the metabolism and clearance of drugs may be different in patients with renal and hepatic impairment, future studies are needed to evaluate the PK and safety of mirogabalin coadministered with probenecid or cimetidine in these patients.

Finally, although this was a single-dose study, no significant accumulation of mirogabalin was observed over multiple therapeutic doses and mirogabalin has a linear PK [20, 21]. Therefore, effect of probenecid and cimetidine on mirogabalin PK from this study can be utilized for multiple dose settings.

Conclusion

There was a greater magnitude of change in mirogabalin exposure when coadministered with a drug that inhibits both renal and metabolic clearance (probenecid) *vs*. a drug that only affects renal clearance (cimetidine). The increase in mirogabalin exposure with cimetidine is similar to the increase observed in patients with mild renal impairment, for whom mirogabalin dose adjustments are not considered necessary [22]. Additionally, since the effect of probenecid on mirogabalin is not significant (>2-fold), mirogabalin dose adjustments may not be necessary with concomitant probenecid. Future studies or analyses should explore the combined effects of physiological changes, organ impairment, and drug interactions in the target population.

Competing Interests

M.T., N.Y., C.H., V.W., L.H. and H.Z. are full-time employees of the Sponsor, Daiichi Sankyo. V.D. was a full-time employee of Daiichi Sankyo at the time of the study.

The authors wish to thank the Worldwide Clinical Trials (Austin, TX, USA) bioanalytical laboratories. Medical writing and editorial support was provided by Senem Kurtoglu, PhD, of AlphaBioCom, LLC, King of Prussia, PA, USA, and funded by Daiichi Sankyo, Inc., Basking Ridge, NJ, USA.

Contributors

M.T., C.H. and H.Z. designed the present studies. M.T., G.J.A., L.H., V.W. and V.D. conducted the research. M.T., N.Y., G.J.A., C.H. and H.Z. analysed the data. All authors critically revised the manuscript and the final version of the manuscript was approved by all authors.

References

1 Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. Neurology 2007; 68: 1178–82.

2 Veves A, Backonja M, Malik RA. Painful diabetic neuropathy: epidemiology, natural history, early diagnosis, and treatment options. Pain Med 2008; 9: 660–74.

3 Mallick-Searle T, Snodgrass B, Brant JM. Postherpetic neuralgia: epidemiology, pathophysiology, and pain management pharmacology. J Multidiscip Healthc 2016; 9: 447–54.

4 Bauer CS, Nieto-Rostro M, Rahman W, Tran-Van-Minh A, Ferron L, Douglas L, *et al*. The increased trafficking of the calcium channel subunit alpha2delta-1 to presynaptic terminals in neuropathic pain is inhibited by the alpha2delta ligand pregabalin. J Neurosci 2009; 29: 4076–88.

5 Catterall WA. Voltage-gated calcium channels. Cold Spring Harb Perspect Biol 2011; 3: a003947.

6 Vinik A, Rosenstock J, Sharma U, Feins K, Hsu C, Merante D, *et al*. Efficacy and safety of mirogabalin (DS-5565) for the treatment of diabetic peripheral neuropathic pain: a randomized, double-blind, placebo- and active comparator-controlled, adaptive proof-of-concept phase 2 study. Diabetes Care 2014; 37: 3253–61.

7 FDA Guidance for Industry. Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations 2012. Available at https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf (last accessed 11 July 2017).

8 Daiichi Sankyo Europe GmbH study no. TCRM-DMPK-2014-05.2015.

9 Daiichi Sankyo Co., Ltd. Protocol no. AM14-H0055-P01. 2015.

10 Solvo biotechnology protocol no. DS-16-19Nov2015. 2015.

11 Uchaipichat V, Mackenzie PI, Guo XH, Gardner-Stephen D, Galetin A, Houston JB, *et al*. Human udp-glucuronosyltransferases: isoform selectivity and kinetics of 4-methylumbelliferone and 1-naphthol glucuronidation, effects of organic solvents, and inhibition by diclofenac and probenecid. Drug Metab Dispos 2004; 32: 413–23.

12 Takeda M, Narikawa S, Hosoyamada M, Cha SH, Sekine T, Endou H. Characterization of organic anion transport inhibitors using cells stably expressing human organic anion transporters. Eur J Pharmacol 2001; 419: 113–20.

13 Tsuda M, Terada T, Ueba M, Sato T, Masuda S, Katsura T, *et al*. Involvement of human multidrug and toxin extrusion 1 in the drug interaction between cimetidine and metformin in renal epithelial cells. J Pharmacol Exp Ther 2009; 329: 185–91.

14 Harding SD, Sharman JL, Faccenda E, Southan C, Pawson AJ, Ireland S, *et al*. The IUPHAR/BPS guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. Nucl Acids Res 2018; 46: D1091–106.

15 Alexander SP, Striessnig J, Kelly E, Marrion NV, Peters JA, Faccenda E, *et al*. The Concise Guide to PHARMACOLOGY 2017/18: Voltage-gated ion channels. Br J Pharmacol 2017; 174 (Suppl 1): S160–94.

16 Somogyi A, Gugler R. Clinical pharmacokinetics of cimetidine. Clin Pharmacokinet 1983; 8: 463–95.

17 Ito S, Kusuhara H, Yokochi M, Toyoshima J, Inoue K, Yuasa H, *et al*. Competitive inhibition of the luminal efflux by multidrug and toxin extrusions, but not basolateral uptake by organic cation transporter 2, is the likely mechanism underlying the pharmacokinetic drug-drug interactions caused by cimetidine in the kidney. J Pharmacol Exp Ther 2012; 340: 393–403.

18 Bell DS, Ketchum CH, Robinson CA, Wagenknecht LE, Williams BT. Microalbuminuria associated with diabetic neuropathy. Diabetes Care 1992; 15: 528–31.

19 Bhatt HB, Smith RJ. Fatty liver disease in diabetes mellitus. Hepatobiliary Surg Nutr 2015; 4: 101–8.

20 Brown K, Kumagae Y, Ohwada S, Warren V, Zahir H, Dishy V. A multiple ascending-dose study to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of mirogabalin in healthy elderly subjects. Arthritis Rheumatol 2015; 67: Abstract 1443.

21 Brown K, Ohwada S, Warren V, Zahir H, Dishy V. A single ascending-dose study of mirogabalin in healthy subjects: safety, tolerability, pharmacokinetic, and pharmacodynamic results. J Pain 2016; 17: S76.

22 Kato M, Tajima N, Shimizu T, Sugihara M, Furihata K, Harada K, *et al*. Pharmacokinetics and safety of a single oral dose of Mirogabalin in Japanese subjects with varying degrees of renal impairment. J Clin Pharmacol 2018; 58: 57–63.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13674/suppinfo

Figure S1 Mean (standard deviation) plasma probenecid concentration-time profiles after coadministration of mirogabalin and probenecid. (A) Linear scale; (B) semilogarithmic scale

Figure S2 Mean (standard deviation) plasma cimetidine concentration-time profiles after coadministration of mirogabalin and cimetidine. (A) Linear scale; (B) semilogarithmic scale