Influence of domperidone on pharmacokinetics, safety and tolerability of the dopamine agonist rotigotine

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Rotigotine transdermal patch is a new non-ergolinic dopamine agonist developed for the treatment of Parkinson's disease and restless legs syndrome.
- Peripheral dopaminergic side-effects of dopamine agonists such as nausea and vomiting can be prevented by the antiemetic agent domperidone.

WHAT THIS STUDY ADDS

- The study results show no evidence for an interaction of domperidone on bioavailability and steady-state pharmacokinetics of transdermal rotigotine.
- Co-administration of domperidone and rotigotine does not require dose adjustments for rotigotine transdermal patch.

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AIMS

To evaluate the influence of the antiemetic agent domperidone on steady-state pharmacokinetics, safety and tolerability of multiple-dose treatment of the transdermally applied non-ergolinic dopamine agonist rotigotine.

METHODS

Sixteen healthy male subjects (mean age 30.3 years) participated in a randomized, two-way crossover clinical trial. Treatment A consisted of transdermal rotigotine patch (2 mg (24 h)⁻¹, 10 cm², total drug content 4.5 mg) applied daily for 4 days, and concomitant oral domperidone (10 mg t.i.d.) for 5 days. For treatment B, subjects received only transdermal rotigotine treatment (daily for 4 days). Pharmacokinetic variables describing systemic exposure and renal elimination of rotigotine and metabolites, and safety and tolerability of the treatment were assessed.

RESULTS

The primary steady-state pharmacokinetic parameters ($C_{\max,ss}$ and $AUC_{(0-24),ss}$) were similar with or without co-administration of domperidone. Geometric mean ratios were close to 1 and respective 90% confidence intervals were within the acceptance range of bioequivalence (0.8, 1.25): $C_{\max,ss}$ 0.96 (0.86, 1.08) and $AUC_{(0-24),ss}$ 0.97 (0.87, 1.08). $t_{\max,ss}$, $t_{1/2}$, secondary parameters calculated on days 4/5 after repeated patch application ($C_{\min,ss}$, $C_{ave,ss}$, $AUC_{(0-tz)}$) and renal elimination for unconjugated rotigotine and its metabolites were also similar with and without comedication of domperidone. A reduction in the dopaminergic side-effect nausea was seen with domperidone comedication.

CONCLUSIONS

No changes of pharmacokinetic parameters describing systemic exposure and renal elimination of rotigotine were observed when domperidone was administered concomitantly with rotigotine. The lack of pharmacokinetic interactions indicates that a dose adjustment of rotigotine transdermal patch is not necessary with concomitant use of domperidone.

Introduction

Rotigotine is a non-ergolinic dopamine agonist showing agonistic activity for all human dopamine receptor subtypes with the highest affinity for the D₃ receptor followed by the D₂ and D₁ receptors [1]. Its suitable physicochemical characteristics were the basis for the development of a silicone-based matrix-type transdermal delivery system that continuously releases rotigotine over 24 h [2]. Rotigotine is spread evenly in the silicone adhesive matrix of the transdermal system, ensuring a constant drug release per cm² for all patch sizes. Determination of apparent doses has shown that approximately 45% of the total drug content of a patch is released during the 24-h patch-on period (0.2 mg cm⁻² (24 h)⁻¹) [3]. In clinical trials, mean rotigotine plasma concentrations increased dose-proportionally and remained stable throughout a maintenance period of 6 months [4]. The drug is extensively metabolized by conjugation and N-dealkylation involving different cytochrome P450 (CYP) isoforms including CYP 2C19, 1A1, 2D6, 3A4, 1A2 and 2C9 [5]. *In vitro* investigations in human hepatocytes do not indicate relevant liability for CYP-dependent metabolism of rotigotine by inhibition of specific CYP isoforms [6]. The most prominent urinary metabolites are conjugated rotigotine, whereas only traces of rotigotine are eliminated in urine as unconjugated rotigotine. Other main metabolites in urine are conjugates of the N-desalkyl metabolites, N-despropyl- and N-desethienylethyl-rotigotine. Rotigotine has a plasma half-life of 5–7 h. Steady-state plasma concentrations are achieved within 2–3 days of daily dosing [3].

Rotigotine has proven efficacious in the treatment of early and advanced Parkinson's disease (PD) [7, 8] and has been approved for monotherapy of early PD in the USA and for treatment of all PD stages in Europe. Efficacy in the treatment of restless legs syndrome has also been demonstrated [9, 10].

Gastrointestinal side-effects of rotigotine treatment in clinical studies include nausea and vomiting [7–10], typical adverse events resulting from stimulation of dopamine receptors in the gastrointestinal tract and the chemoreceptor trigger zone [11]. The dopamine-receptor antagonist domperidone stimulates upper gastrointestinal tract motility and has antiemetic properties, but does not readily cross the blood–brain barrier [11, 12]. It has been used successfully to prevent peripheral dopaminergic side-effects of levodopa and other dopamine agonists [13]. Domperidone is extensively metabolized, with only 0.4% and 7% of the total dose being recovered as unchanged domperidone in urine and faeces, respectively [14]. N-dealkylation and aromatic hydroxylation are the major routes for domperidone metabolism [14], which may interfere with the metabolism of concomitantly administered drugs. The major CYP isoform for both N-dealkylation and hydroxylation is CYP3A4; CYP1A2, CYP2B6, CYP2C8 and CYP2D6 also hydroxylate

domperidone [15]. Domperidone has a plasma half-life of 7–9 h [16].

This Phase I interaction study investigated a possible influence of domperidone on the pharmacokinetics (PK), safety and tolerability of rotigotine during co-administration of the two compounds.

Methods

Subjects

The study was conducted at a single centre (Aster-Cephac, Paris, France) from December 2001 to February 2002 according to the principles of the Declaration of Helsinki and Good Clinical Practice. The study protocol was reviewed and approved by an independent ethics committee (Comité consultatif de Protection des Personnes dans la Recherche Biomedicale, Broussais-HEGP, France). All subjects were informed about the aim, design and risks of the study and declared their consent in writing. Sixteen healthy male Caucasian subjects between 18 and 45 years of age with a body mass index (BMI) between 20 and 28 kg m⁻² were included in the study. They had to be in good health, with no clinically relevant medical or psychiatric abnormalities. Known or suspected hypersensitivity, in particular to the study medication, a history of atopic eczema and/or an active skin disease, and any concomitant medication within 2 weeks prior to first dosing led to exclusion.

Study design

The investigation was designed as an open-label, randomized, single-site, two-way crossover study; two groups of participants received two different treatments [treatment A, rotigotine transdermal patch (2 mg (24 h)⁻¹, 10 cm², total drug content 4.5 mg rotigotine) applied once daily on days 1–4 and 10 mg domperidone administered orally t.i.d. on days 1–5; treatment B, rotigotine transdermal patch (2 mg (24 h)⁻¹, 10 cm², total drug content 4.5 mg rotigotine) applied once daily on days 1–4] in a randomized sequence (AB and BA) with a wash-out period of ≥7 days between the treatments. A screening examination was carried out 14 to 2 days prior to randomization and eligibility was based on physical examination, vital signs and 12-lead ECG, safety laboratory parameters, medical history, drug and alcohol screening and serology (hepatitis B and C and human immunodeficiency virus) results. Subjects were hospitalized for both treatment periods (day –1 to day 6). Eligibility was confirmed on day –1 of the first period, and subjects were randomized to either treatment sequence using a computer-generated scheme. They remained fasting from at least 22.00 h the night before first dosing on day 1 until 08.30 h for both sequences. Rotigotine transdermal patch (Schwarz Biosciences GmbH, Monheim, Germany) was applied once daily at 08.00 h with a 24-h patch-on period; 10 mg domperidone (Motilium®; Janssen-

Cilag, Issy les Moulineaux, France) was administered orally t.i.d. The patch was applied to the abdomen in the morning (before administration of the morning domperidone dose in treatment period A). Subjects had to stay in bed for ≥ 2 h after patch application. A treatment duration of 4 days ensured PK analysis under steady-state conditions for rotigotine in both treatment periods. During confinement, paracetamol up to a maximum daily dose of 2000 mg was the only permitted concomitant treatment. A follow-up visit was performed 5–10 days after the end of the second treatment period and included the recording of adverse events (AEs), physical examination, vital signs and ECG, and safety parameter assessment.

Sampling and drug analysis

Blood samples were collected in both treatment periods into lithium-heparinized Monovettes® by venous puncture or indwelling venous catheter on day 1 prior to first patch application and on days 4/5 at 0, 1, 2, 4, 8, 12, 23.5, 24, 26, 28, 30, 36 and 48 h after last patch application of each treatment. Plasma was separated and stored below -20°C until analysed. Urine samples were collected predose on day 1 and in two intervals on day 4, from 0 to 12 h and 12 to 24 h after patch application. The total amount of urine collected within each interval was accurately determined and an aliquot (30 ml) stored below -20°C until analysed.

Concentrations of rotigotine and its metabolites in plasma and urine were determined by validated liquid chromatography with tandem mass spectrometry (LC-MS/MS). Fentanyl citrate was used as internal standard; overall accuracy and precision for calibration standards and quality controls were well within 10% at all concentrations. The lower limit of quantification (LOQ) in plasma was 10 pg ml^{-1} for unconjugated rotigotine. In urine, LOQ was 10 pg ml^{-1} and 500 pg ml^{-1} for unconjugated and total rotigotine, respectively, 250 pg ml^{-1} and 500 pg ml^{-1} for unconjugated and total N-desethienylethyl-rotigotine, respectively, and 100 pg ml^{-1} and 500 pg ml^{-1} for unconjugated and total N-despropyl-rotigotine, respectively. Total rotigotine concentrations were determined after preincubation with β -glucuronidase (*Helix pomatia*, Sigma, Munich, Germany; 0.1 ml undiluted enzyme preparation per 1 ml plasma) to convert conjugates back into the unconjugated moiety. This enzyme preparation contains both β -glucuronidase and sulphatase activity.

Pharmacokinetic parameters

The primary parameters for PK evaluation of unconjugated rotigotine were the area under the concentration–time curve at steady state ($\text{AUC}_{(0-24),\text{ss}}$), peak plasma concentration at steady state ($C_{\text{max,ss}}$) and time to reach $C_{\text{max,ss}}$ ($t_{\text{max,ss}}$), terminal half-life of unconjugated rotigotine ($t_{1/2}$) and cumulative amount of unconjugated rotigotine excreted into urine (Ae_{0-24}). $C_{\text{max,ss}}$ and $t_{\text{max,ss}}$ were determined directly from the plasma concentration–time curves for unconjugated rotigotine, and $\text{AUC}_{(0-24),\text{ss}}$ was calculated by means

of the linear trapezoidal rule. The terminal rate constant λ_z was determined from 24 h (time of patch removal of the last patch for each treatment) up to the last measurable concentration by log-linear regression. The terminal half-life was calculated by $t_{1/2} = \ln(2)/\lambda_z$. Ae in each sampling interval was determined by multiplying drug concentration and urine volume. Summation of Ae determined in each collection interval resulted in the cumulative amount Ae_{0-24} of unconjugated rotigotine within a 24-h dose interval. The secondary parameters were minimum and average plasma concentrations of unconjugated rotigotine at steady state ($C_{\text{min,ss}}$ and $C_{\text{ave,ss}}$). $C_{\text{ave,ss}}$ was calculated as $\text{AUC}_{(0-24),\text{ss}}$ divided by 24 h. Additional parameters included renal clearance (CL_R) of unconjugated rotigotine (calculated as $\text{Ae}_{0-24}/\text{AUC}_{(0-24),\text{ss}}$) and Ae_{0-24} of total rotigotine and its main metabolites, unconjugated and total N-despropyl-rotigotine and N-desethienylethyl-rotigotine. The peak trough fluctuation of the plasma concentration profile was calculated using the following equation: $\text{PTF}(\%) = [(C_{\text{max,ss}} - C_{\text{min,ss}})/C_{\text{ave,ss}}] \times 100$ with $C_{\text{ave,ss}} = \text{AUC}_{(0-24),\text{ss}}/24$.

Total rotigotine (or total metabolites) is the sum of unconjugated and conjugated rotigotine (or metabolites). Apparent rotigotine doses were evaluated from the last 24-h patches removed (day 5) as the difference between initial drug content of the patch and the residual drug amount in the used patches.

Safety and tolerability assessments

Safety and tolerability were evaluated at regular intervals throughout the study by vital signs measurements (supine blood pressure and pulse rate), 12-lead ECG, physical examination, clinical laboratory tests and skin assessments. AEs were recorded and monitored.

Patch adhesiveness was documented 24 h after application before each patch removal and was assessed according to a scoring system with a range from 1 (no lift) to 6 (80–100% lift). Skin assessment was performed 3 h and 24 h after patch removal on day 4 (patch 3) and day 5 (patch 4) of each period. It was evaluated with an erythema score from 0 (no reddening), 1 (slight reddening), 2 (evident reddening), 3 (papular reaction) to 4 (vesiculation) and an oedema score from 0 (no visible reaction), 1 (marginal oedema/barely recognizable), 2 (slight oedema/area well defined by a recognizable elevation), 3 (evident oedema/elevation up to 1 mm) to 4 (severe oedema/elevation >1 mm and extending to outside of patch area).

Statistical analysis

Owing to the exploratory nature of the study, no formal sample size calculation was undertaken. Data analysis was carried out using WinNonlin software (version 3.3; Pharsight, Mountain View, CA, USA) and SAS® software (version 8; SAS Institute, Cary, NC, USA). Calculations of peak trough fluctuation were done by SAS® version 8.2. Descriptive statistics were performed by SAS® procedure SUMMARY.

All treated subjects with complete data, sufficient patch adhesiveness and without major protocol deviations who completed the study were included in the analysis of the PK parameters (PK set). The primary variables were evaluated statistically to derive treatment ratios or differences between rotigotine treatment with and without domperidone comedication. Log-transformed $AUC_{(0-24),ss}$, $C_{max,ss}$ and $t_{1/2}$ data for unconjugated rotigotine were subjected to an analysis of variance (ANOVA) with sequence, subject within sequence group, period and treatment effect using general linear models. The residuals of ANOVA were examined for a normally distributed random error. For the log-transformed parameters geometric mean ratios (rotigotine plus domperidone to rotigotine alone) and corresponding 90% confidence intervals (CIs) were calculated for comparison. Nonparametric Wilcoxon signed rank test was used to compare differences in $t_{max,ss}$. Secondary PK parameters were analysed using descriptive statistics without a formal statistical comparison between treatments.

All subjects who received at least one patch application of rotigotine were included in the safety and tolerability analysis. AEs were encoded according to a modified World Health Organization Adverse Reaction Terms dictionary (1993). Safety and tolerability data were assessed descriptively.

Results

All 16 enrolled subjects completed the study and were included in the PK and safety/tolerability analysis. All subjects were Caucasian males with a mean age of 30.3 ± 7.8 years (range 21–44 years), mean weight of 73 ± 7.1 kg (range 59.5–85.2 kg) and mean BMI of 23.5 ± 1.8 kg m⁻² (range 21.2–26.9 kg m⁻²). No relevant previous or concomitant diseases or treatments were reported; one subject had a urinary tract infection and was treated with sulfamethoxazole and trimethoprim for 5 days (treatment started after the two treatment periods including the respective PK sampling days had been completed).

Pharmacokinetics

Mean apparent rotigotine dose after treatment B was 2.01 mg (range 1.30–3.24 mg), indicating that approximately 45% of total drug rotigotine content in the transdermal patch was absorbed through the skin during the patch-on period of 24 h. Mean apparent dose was not influenced by domperidone co-administration (mean 2.08 mg, range 1.14–3.51 mg). Mean plasma concentration–time profiles of unconjugated rotigotine are shown in Figure 1. The profile was similar with and without comedication with domperidone. Just before application of the last patch on day 4, mean steady-state concentrations of unconjugated rotigotine were 201.8 ± 85.4 pg mL⁻¹ with and 222.8 ± 103.3 pg mL⁻¹ without domperidone co-administration.

Figure 1
Mean plasma concentration–time profiles of unconjugated rotigotine at steady state (0 h before last patch application on day 4 to 24 h after last patch removal). Rotigotine with Domperidone (—●—); Rotigotine (—■—)

Table 1
Primary steady–state pharmacokinetic parameters for unconjugated rotigotine in plasma after rotigotine patch application with or without domperidone comedication (n = 16)

Parameter	With domperidone	Without domperidone	Ratio (90% CI) [95% CI]
$C_{max,ss}$ (pg mL ⁻¹)	263 (59)	274 (53)	0.96 (0.86, 1.08) [0.84, 1.10]
$AUC_{(0-24),ss}$ (pg h ⁻¹ mL ⁻¹)	5147 (61)	5302 (56)	0.97 (0.87, 1.08) [0.84, 1.11]
$t_{1/2}$ (h)	5.3 (37)	5.1 (34)	1.05 (0.93, 1.18) [0.91, 1.21]
$t_{max,ss}$ (h)*	17.8 (0–24)	17.8 (0–24)	NS†

Data are presented as geometric mean and geometric coefficient of variation (%). *Median and range. †Wilcoxon signed rank test. CI, confidence interval; NS, not significant.

After a slight decrease due to the lag time of the newly applied patch, rotigotine plasma concentrations reached a plateau at 8 h after patch application, which remained in a stable range for the remaining duration of the patch application. Maximum mean concentrations with and without domperidone were 269.3 ± 149.4 pg mL⁻¹ and 283.0 ± 148.1 pg mL⁻¹, respectively, at 12 h. After removal of the last patch of each treatment, the plasma concentration of unconjugated rotigotine declined with mean $t_{1/2}$ of 5.6 ± 1.7 h with and 5.3 ± 1.6 h without domperidone. Statistical analysis showed no effect of domperidone on any of the evaluated parameters: the ratio of geometric means for $AUC_{(0-24),ss}$ and $C_{max,ss}$ between the treatments was close to 1 with 90% CIs within the acceptance range of bioequivalence of 0.80–1.25 (Table 1). There was also no difference between treatments A and B with respect to median $t_{max,ss}$ (17.8 h for both treatments). Secondary PK parameters for unconjugated rotigotine were also similar between treatments (Table 2). The peak trough fluctuation of the plasma

concentration profile was $54.9 \pm 20.4\%$ with and $60.7 \pm 16.8\%$ without domperidone treatment.

Renal clearance of unconjugated rotigotine was similar with and without concomitant treatment with domperidone (4.56 ± 3.12 and 4.31 ± 2.10 ml min⁻¹, respectively) (Table 3). The mean amount of unconjugated rotigotine excreted in urine (Ae) was also comparable between treatment with and without domperidone comedication with values of 1.51 ± 1.10 µg and 1.44 ± 0.86 µg, respectively. Urine concentrations of unconjugated N-despropyl- and N-desthienylethyl-rotigotine were below LOQ for most samples. Mean amount excreted in urine within 24 h of total N-desthienylethyl-rotigotine was 49 ± 42 µg with domperidone comedication and 48 ± 25 µg without dom-

peridone. Higher amounts of total N-despropyl-rotigotine were excreted into urine during both treatments, with mean values of 131 ± 68 µg and 122 ± 52 µg with and without domperidone, respectively (Table 3).

Safety and tolerability

No serious AE occurred during the study; all 41 reported treatment-emergent AEs were of mild or moderate intensity. Of these, 46% were reported during co-administration with domperidone compared with 54% experienced without domperidone treatment. The most common AEs were reddening and pruritus at the patch application site in both treatment periods. A difference between treatments was observed for the number of subjects experiencing nausea, which was lower during domperidone comedication (one subject with nausea episode vs. four subjects with nausea in the treatment period without domperidone). Vomiting only occurred once in each treatment group. One AE, a urinary tract infection, required treatment for 5 days, but was considered as not related to the study medication. All other AEs were classified as probably or possibly related to the study medication and were reported as resolved/recovered at the end of the study. One subject experienced a syncope (reported term vagal faint) on day 5 of treatment A (after removal of patch; medication domperidone t.i.d.), which was judged by the investigator as mild and possibly related to trial medication. The AE was resolved after 5 min.

Local tolerability was good, as shown by the results of the skin assessment after patch removal in Table 4. Only one case of evident reddening and one case of slight oedema were observed after removal of the third rotigotine transdermal patch (monotherapy). A reduction in the number of cases with slight reddening 24 h compared with 3 h after patch removal indicates a transient erythema, probably due to the mechanical stress of patch removal.

Patch adhesiveness in general was good; 68% of subjects had a patch lift of <20%; two subjects (12.5%, one in each treatment group) presented a patch lift of >80% on one occasion (not affecting PK profile days). There were no

Table 2

Secondary steady-state pharmacokinetic parameters of unconjugated rotigotine in plasma after rotigotine patch application with or without domperidone comedication ($n = 16$)

Parameter	With domperidone	Without domperidone
$C_{min,ss}$ (pg ml ⁻¹)	144 (53)	138 (54)
$C_{ave,ss}$ (pg ml ⁻¹)	214 (61)	221 (56)
$AUC_{(0-12)}$ (pg h ⁻¹ ml ⁻¹)	6487 (58)	6632 (55)

Data are presented as geometric mean and geometric coefficient of variation (%).

Table 3

Renal clearance and cumulative amount of rotigotine and metabolites excreted in urine within 24 h

Parameter	With domperidone	Without domperidone
CL_R (ml min ⁻¹)	4.6 (3.1)	4.3 (2.1)
Ae_{0-24} (µg)		
unconjugated rotigotine	1.51 (1.10)	1.44 (0.86)
total rotigotine	437.3 (213.6)	423.7 (163.0)
total N-despropyl-rotigotine	131.2 (67.8)	121.5 (52.3)
total N-desthienylethyl-rotigotine	49.0 (42.3)	48.4 (24.7)

Data are presented as arithmetic mean (SD). Ae, amount excreted; CL_R , renal clearance.

Table 4

Skin erythema assessments after patch removal

Group	Time point	No reddening		Slight reddening		Evident reddening	
		n	%	n	%	n	%
With domperidone	3 h after removal – patch 3	15	93.8	1	6.3	0	0
	24 h after removal – patch 3	16	100	0	0	0	0
	3 h after removal – patch 4	10	62.5	6	37.5	0	0
	24 h after removal – patch 4	14	87.5	2	12.5	0	0
Without domperidone	3 h after removal – patch 3	13	81.3	3	18.8	0	0
	24 h after removal – patch 3	14	87.5	1	6.3	1	6.3
	3 h after removal – patch 4	13	81.3	3	18.8	0	0
	24 h after removal – patch 4	15	93.8	1	6.3	0	0

clinically relevant mean changes from baseline in vital signs, ECG or laboratory values.

Discussion

Co-administration of the peripheral dopamine antagonist domperidone did not influence systemic exposure or steady-state PK of transdermally applied rotigotine. On average, approximately 45% of the total drug content of the patch was absorbed by the skin within the patch application period of 24 h. After a slight decrease during the first 2 h after application of a new patch due to the known lag time, mean steady-state rotigotine plasma concentrations remained stable throughout the patch application period of 24 h. The statistical comparison of primary PK parameters showed no evidence for an interaction of domperidone on the bioavailability of rotigotine: geometric mean ratios for $AUC_{(0-24),ss}$ and $C_{max,ss}$ (with vs. without comedication with domperidone) were close to unity, and the corresponding 90% CIs were within the acceptance range of bioequivalence. There were also no relevant changes in $t_{max,ss}$ or terminal half-life. Comparison of secondary PK parameters supported these findings. These data are in line with the low drug–drug interaction liability of rotigotine with multiple metabolic pathways (conjugation and N-dealkylation) and a CYP-dependent metabolism involving several isoenzymes [6]. In addition, no data on CYP induction or inhibition by domperidone are available in the public domain.

There was considerable interindividual variability in rotigotine plasma concentrations and PK parameters that was independent of domperidone comedication. This may reflect individual differences in the amount of drug absorbed through the skin, as indicated by a large range in apparent dose values.

Concomitant treatment with domperidone has also been shown not to alter PK of the oral non-ergoline dopamine agonist ropinirole [17].

The administration of maximum effective doses of drugs with direct or indirect dopaminergic action is often prevented by side-effects. Domperidone holds a unique position in preventing peripheral dopaminergic side-effects in patients on antiparkinsonian medication [18–20], while maintaining or increasing the central therapeutic effects of levodopa and dopamine agonists [21–23]. Domperidone has a high affinity to gastrointestinal tissue, but does not readily cross the blood–brain barrier [11, 12]. The drug antagonizes the inhibiting effects of dopamine on the upper gastrointestinal tract and its activity at D_2 -receptors in the chemoreceptor trigger zone, resulting in suppression of nausea and vomiting [11]. In the present clinical trial, there was a reduction in the dopaminergic side-effect nausea when subjects were treated with domperidone (one subject experienced nausea under combined treatment with rotigotine and domperidone

compared with four subjects during monotherapy with rotigotine). Vomiting occurred in only one subject during both treatments. Comedication of domperidone with the dopamine agonist pergolide also reduced nausea in elderly PD patients and permitted a quicker and easier titration schedule of pergolide [24].

Immediately after patch removal (24 h), mean plasma concentrations of rotigotine decreased with a terminal half-life of approximately 5 h that was not altered by comedication with domperidone.

Rotigotine undergoes extensive metabolism by conjugation of the parent compound and N-dealkylation with subsequent conjugation [5]. The most prominent urinary metabolites are rotigotine conjugates (total rotigotine minus unconjugated rotigotine), whereas only traces of rotigotine are eliminated in urine as unconjugated rotigotine. Other main metabolites in urine are conjugates of the N-desalkyl metabolites, N-despropyl- and N-desethienylethyl-rotigotine. Domperidone undergoes rapid and extensive biotransformation by hydroxylation and oxidative N-dealkylation with CYP3A as the major catalyst [15]. The main metabolites recovered in urine are conjugated metabolites [14]. Renal elimination of rotigotine and its metabolites was not changed by cotreatment with domperidone, indicating that domperidone does not interfere with the biotransformation of rotigotine.

In this study, domperidone was safely co-administered with non-ergoline transdermal rotigotine. There was no evidence for an interference of domperidone with systemic exposure and steady-state PK of transdermal rotigotine. These results indicate that dose adjustment of rotigotine transdermal patch is not necessary with concomitant use of the antiemetic agent domperidone.

Competing interests

MB, WC, HB and RH are employees of Schwarz Biosciences.

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