Influence of transdermal rotigotine on ovulation suppression by a combined oral contraceptive

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The non-ergolinic dopamine agonist rotigotine was developed for the treatment of Parkinson's disease and restless legs syndrome as a silicone-based matrix-type transdermal system.
- Dopamine agonists have been recommended as initial treatment in young patients with restless legs syndrome which has a higher prevalence in females. It is therefore likely that the rotigotine transdermal patch will be administered to young women taking oral contraceptives.

WHAT THIS STUDY ADDS

- Concomitant administration of 3 mg (24 h)⁻¹ transdermal rotigotine has no impact on the pharmacodynamics and pharmacokinetics of a combined oral contraceptive containing 0.03 mg ethinyloestradiol and 0.15 mg levonorgestrel.
- The study results suggest that application of the transdermal rotigotine patch has no influence on contraceptive efficacy.

AIMS

To assess the influence of the transdermally applied dopamine agonist rotigotine on ovulation suppression by a combined oral contraceptive (0.03 mg ethinyloestradiol and 0.15 mg levonorgestrel) in a randomized, double-blind crossover study in 40 healthy females.

METHODS

Treatment A consisted of the combined oral contraceptive for 28 days plus rotigotine for the first 13 days (2 mg (24 h)⁻¹ on days 1–3, 3 mg (24 h)⁻¹ maintenance dose thereafter). During treatment B, subjects received matching placebo patches instead of rotigotine. Pharmacodynamic parameters (progesterone, oestradiol, luteinizing hormone, and follicle stimulating hormone serum concentrations), pharmacokinetic parameters for ethinyloestradiol/levonorgestrel and rotigotine, and safety and tolerability of the treatment were assessed.

RESULTS

Progesterone serum concentrations remained below 2 ng mL⁻¹ in all subjects during the luteal phase. Median serum concentrations of all other pharmacodynamic parameters were similar during both treatments. Pharmacokinetic parameters $C_{\max,ss}$ and $AUC(0,24 h)_{ss}$ at steady state were similar with or without co-administration of rotigotine for both ethinyloestradiol and levonorgestrel with geometric mean ratios close to 1 and 90% confidence intervals within the acceptance range of bioequivalence (0.8, 1.25): $C_{\max,ss}$ 1.05 (0.93, 1.19), $AUC(0,24 h)_{ss}$ 1.05 (0.9, 1.22) for ethinyloestradiol; $C_{\max,ss}$ 1.01 (0.96, 1.06), $AUC(0,24 h)_{ss}$ 0.98 (0.95, 1.01) for levonorgestrel. Mean plasma concentrations of unconjugated rotigotine remained stable throughout the patch-on period (day 13).

CONCLUSIONS

Concomitant administration of 3 mg (24 h)⁻¹ transdermal rotigotine had no impact on the pharmacodynamics and pharmacokinetics of a combined oral contraceptive containing 0.03 mg ethinyloestradiol and 0.15 mg levonorgestrel, suggesting that the dopamine agonist does not influence contraception efficacy.

Introduction

Rotigotine is a unique non-ergolinic dopamine agonist with activity across D1 through D5 receptors as well as select adrenergic and serotonergic sites [1] which has been developed as a once-daily transdermal patch (Neupro®, Schwarz Biosciences GmbH, UCB-Group, Germany). Transdermal rotigotine has been shown to be efficacious in the treatment of Parkinson's disease [2, 3] and restless legs syndrome [4, 5]. The silicone-based matrix-type transdermal patch avoids first pass effects and ensures a continuous release of rotigotine and relatively stable plasma concentrations over 24 h. Following patch application, approximately half of the administered rotigotine dose is systemically absorbed within 24 h [6] and undergoes extensive metabolism, mainly by conjugation (sulphation and glucuronidation) of the parent compound; a second pathway is the formation of phase 1 metabolites (N-desalkylation) with subsequent conjugation [7]. Several cytochrome P450 (CYP) isoforms including CYP2C19, CYP1A1/2, CYP3A4 and CYP2D6 are involved in rotigotine desalkylation [8]. Rotigotine has no affinity to the drug transporter P-glycoprotein [8]. Excretion of rotigotine metabolites occurs mainly via the kidneys [6]; the main urinary metabolites are conjugated rotigotine and conjugated rotigotine metabolites. Renal elimination of the parent compound is <1%.

Nordette® (Akromed Products Ltd, Republic of South Africa) is a combination oral contraceptive containing 0.03 mg ethinylloestradiol and 0.15 mg levonorgestrel. Levonorgestrel does not undergo first-pass metabolism or entero-hepatic recirculation and its oral bioavailability is almost 100%. Pharmacokinetics are influenced by its strong affinity to steroid hormone binding globulin [9]. Oral bioavailability of ethinylloestradiol is 40–50% [10]. The compound is extensively metabolized and is subject to presystemic (gut) and hepatic first-pass metabolism involving CYP 450, uridine diphosphate-glucuronosyltransferases and sulphotransferases [11]. CYP3A4-mediated 2-hydroxylation is the major oxidative pathway for ethinylloestradiol clearance; a second important contributor is CYP2C9 [11]. Glucuronidation is a minor pathway [12]. Drug interactions at enzyme sites involved in ethinylloestradiol metabolism may impair the efficacy of the oral contraceptive and result in breakthrough bleeding or pregnancy.

As dopamine agonists have been recommended as initial treatment in young patients with restless legs syndrome which has a higher prevalence in females [13], it is likely that the rotigotine transdermal patch will be administered to young women taking oral contraceptives. As both rotigotine and ethinylloestradiol are metabolized by CYP3A4, a possible drug–drug interaction based on CYP3A4 can not be excluded. The present study therefore investigated the potential impact of the transdermal rotigotine patch on the pharmacodynamics and pharmacokinetics of oral hormonal contraceptives.

Methods

Study population and design

This randomized, double-blind, placebo-controlled, cross-over phase I study was carried out at a single South African site from January to June 2006 according to the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by the institutional review board of Pharma-Ethics Ltd, Republic of South Africa. All participating subjects were informed about the aim, design and risks of the study and declared their consent in writing.

Healthy female subjects were enrolled if they were 18–35 years of age with a body mass index of 19–28 kg m⁻² and no tobacco consumption for the past year. Combined oral contraception containing 0.03 mg ethinylloestradiol and 0.15 mg levonorgestrel for at least 2 months prior to screening or willingness to take these oral contraceptives for a run-in period of at least 2 months prior to assignment to a treatment group were also inclusion criteria. In addition, the subjects had to be willing to use an additional barrier contraceptive method during the entire study time. They were excluded if they were pregnant, lactating, climacteric, or menopausal, had previous or current ovarian dysfunction, a coagulopathic condition, or a family history of thromboembolic events related to the intake of oral contraceptives. Further main exclusion criteria were transient ischaemic attack or stroke (within the last 12 months), epilepsy or seizures, symptomatic orthostatic hypotension, cardiac dysfunction or conduction abnormalities, hepatic dysfunction, significant skin hypersensitivity to adhesives or other transdermal products, atopic or eczematous dermatitis, psoriasis and/or active skin disease, or any other medical or psychiatric condition which in the opinion of the investigator could compromise subject safety or result validity. Subjects taking any concomitant medication within 2 weeks prior to start of study were also excluded.

Study medication consisted of rotigotine transdermal patch (2 mg (24 h)⁻¹ [size 10 cm²] and 3 mg (24 h)⁻¹ [size 15 cm²]; Schwarz Biosciences GmbH, UCB-Group, Germany) and a combined oral hormonal contraceptive with 21 active tablets containing 0.03 mg ethinylloestradiol and 0.15 mg levonorgestrel, and seven inert tablets (Nordette®; Akromed Products Ltd. RSA). Following a 2-month run-in period for subjects who had not been taking Nordette® or an equivalent oral hormonal contraceptive for at least 2 months prior to start of study, eligible subjects were randomized to one of two treatment sequences. Each treatment sequence consisted of one 28-day cycle of treatment A and one 28-day cycle of treatment B (sequence AB or BA). In both cycles, subjects received active oral contraceptive tablets on days 1–21 and inert tablets on days 22–28. During treatment A, subjects received rotigotine for the first 13 days of the cycle; the 2 mg (24 h)⁻¹ rotigotine starting dose on days 1–3 was increased to 3 mg (24 h)⁻¹ on day 4. Matching placebo patches were applied on days 1–13 of treatment B. Patches were applied once daily in the

morning to clean dry skin on the right or left lateral abdomen, thigh, hip, flank, shoulder or upper arm according to a randomization schedule defining the sequence of the six application sites, and were left in place for 24 h. The combined oral contraceptive was administered concomitantly. In order to synchronize subjects' menstrual cycles, omission of one–three inert oral contraceptive tablets was permitted prior to commencement of the second treatment cycle. The study medication was administered at the study site during outpatient visits on days 1–12, during an in-house period for pharmacokinetic profiling on day 13 (overnight), and outpatient visits for the determination of hormones on days 19–21. On all other days, study medication was taken at home. Subjects were required to fast for 10 h prior to all laboratory assessments and before dosing on day 13 in both cycles; additionally, they had to fast for 4 h after dosing on day 13. A safety follow-up was performed at least 7 days after the final administration of oral contraceptive tablets.

Sample collection and analytical methods

Blood samples (4 ml) were collected pre-dose (if applicable) in both treatment cycles for progesterone on days 19–21, for oestradiol on days 10, 13, 14, 19–21, and for luteinizing hormone (LH) and follicle stimulating hormone (FSH) on days 10, 13, 14. Following centrifugation within 30–60 min after collection for 5 min at 2000 *g* and 4°C, serum was divided into two aliquots of 1 ml each and stored at –20°C. Serum hormone concentrations were determined using two types of AutoDELFIA assays (Wallac Oy, Turku, Finland): fluoroimmunoassays (FIA) for progesterone and oestradiol, and immunofluorometric assays (IFMA) for LH and FSH. Accuracy and precision for calibration standards and quality controls were within 20% at all concentrations. Lower limit of quantification (LOQ) was 0.408 ng ml^{–1} for progesterone, 13.6 pg ml^{–1} for oestradiol, 0.62 U l^{–1} for LH and 1.00 U l^{–1} for FSH.

For the pharmacokinetic profiling of ethinyloestradiol and levonorgestrel, 7 ml blood samples were collected in both treatment cycles pre-dose on day 1 (baseline value), and then at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after medication intake on day 13. Samples were drawn into polypropylene tubes containing dry heparin and centrifuged for 10 min at 1600 *g* at 4°C within 30 min after collection. The plasma was then aliquoted (2.5 ml and balance) into two polypropylene tubes and stored at –20°C. Plasma concentrations of both compounds were determined by validated liquid chromatography with tandem mass spectrometry (LC-MS/MS). 17 α -Ethinyloestradiol-2,4,16,16-d₄ and ¹³C₂-norethindrone were used as internal standards for ethinyloestradiol and levonorgestrel, respectively; overall accuracy and precision for calibration standards and quality controls were within 15% at all concentrations. Lower LOQ was 3.0 pg ml^{–1} for ethinyloestradiol and 50 pg ml^{–1} for levonorgestrel.

For the pharmacokinetic profiling of rotigotine, 10 ml blood samples were collected pre-dose on day 1 (baseline value), and then at 0 (pre-dose), 4, 6, 9, 16, and 24 h after patch application on day 13 for both treatments. Samples were drawn into lithium-heparinized tubes and centrifuged for 10 min at 1600 *g* at 4°C within 20 min after collection. The plasma was then aliquoted (3 ml in one polypropylene tube and the rest into a second tube) and stored at –20°C. Concentrations of unconjugated and total (unconjugated and conjugated) rotigotine were determined by validated LC-MS/MS. Oxybutynin chloride was used as internal standard; overall accuracy and precision for calibration standards and quality controls were within 10% at all concentrations. For both unconjugated and total rotigotine the lower LOQ was 10 pg ml^{–1}. Total rotigotine concentrations were determined after pre-incubation with β -glucuronidase (*Helix pomatia*, Sigma; 0.1 ml undiluted enzyme preparation per 1 ml plasma) to convert conjugates back into the unconjugated moiety. This enzyme preparation contained both β -glucuronidase and sulphatase activity.

Apparent dose values for rotigotine were evaluated by a validated method for patches applied on day 13 in both treatment cycles. The amount of rotigotine was quantified by high pressure liquid chromatography (HPLC) in used patches treated with an organic solvent mixture. The apparent dose as an estimate of the drug amount released within 24 h was calculated as the difference between initial drug content (6.75 mg) in the patches and the residual drug amount in the used patches.

Pharmacokinetic analysis

The following pharmacokinetic parameters were calculated for ethinyloestradiol, levonorgestrel, unconjugated and total rotigotine using noncompartmental methods: area under the plasma concentration–time curve from 0 to 24 h at steady state (AUC(0,24 h)_{ss}); maximum plasma concentration at steady state (C_{max,ss}); and time to reach C_{max,ss} (t_{max,ss}). For unconjugated and total rotigotine AUC(0,24 h)_{ss} and C_{max,ss} were additionally normalized by apparent dose.

Safety and tolerability assessments

Safety laboratory parameters, vital signs, 12-lead ECG and physical examinations were assessed throughout the study. All adverse events (AE) were recorded and monitored. Pregnancy tests were performed at screening, on day 1 of each treatment cycle and at safety follow-up. Skin assessments using an international scoring system [14] were carried out on days 7, 13 and 14 within 50–60 min after patch removal. The scoring system evaluated dermal response on a 0–7 scale: 0 (no evidence of irritation), 1 (minimal erythema/barely perceptible), 2 (definite erythema/readily visible or minimal oedema or minimal papular response), 3 (erythema and papules), 4 (definite oedema), 5 (erythema, oedema and papules), 6 (vesicular

eruption), and 7 (strong reactions spreading beyond the test site). An additional alphabetical code (A-H) was used to describe further the physical appearance of skin with A (slight glazed appearance), B (marked glazing), C (glazing with peeling and cracking), F (glazing with fissures), G (film of dried serous exudates covering all or part of the patch site), and H (small petechial erosions and/or scabs). Patch adhesiveness was assessed by the investigator or designee prior to each patch removal on days 2–14 using a score from 0 ($\geq 90\%$ adhesion or no lift) to 4 (complete detachment of patch). Subject diary entries together with the return of oral contraceptive empty blister packs were used to assess compliance during outpatient periods.

Statistical analysis

Statistical analysis including the calculation of pharmacokinetic parameters was carried out using the SAS program (SAS Institute, Cary, NC, USA, version 8.2). No formal sample size determination was performed; it was planned to include 42 subjects into the study. Three analysis sets were defined in the protocol: the safety set included all randomized subjects who received at least one patch application; the pharmacodynamic set included all subjects valid for safety without major protocol deviations with respect to pharmacodynamic assessment and with complete serum concentration data for progesterone on days 19–21; the pharmacokinetic set included all subjects valid for safety without major protocol deviations with respect to pharmacokinetic assessment and who had a sufficient number of valid bioanalytical assessments to calculate reliable estimates for ethinylloestradiol and levonorgestrel pharmacokinetic parameters. Pharmacodynamic results are presented for the pharmacodynamic set, and pharmacokinetic results are presented for the pharmacokinetic set.

The primary variable for this study was progesterone serum concentrations on days 19–21 of each treatment cycle, summarized by descriptive statistics. Absolute and relative frequencies for the number of subjects with ovulation suppression (defined as progesterone serum concentrations $<2 \text{ ng ml}^{-1}$) were calculated for each treatment.

Secondary variables were serum concentrations of oestradiol, LH and FSH, and plasma concentrations of ethinylloestradiol, levonorgestrel, and unconjugated and total rotigotine, all summarized descriptively.

For all analyses, values below LOQ were substituted by zero for calculation of the mean; means at any time were only calculated if at least two out of three of the individual data were measured and were above LOQ.

Log-transformed $\text{AUC}(0,24 \text{ h})_{\text{ss}}$ and $C_{\text{max,ss}}$ of ethinylloestradiol and levonorgestrel were analyzed using an analysis of variance (ANOVA). The ANOVA model included the factors sequence, subject within sequence, treatment and period. Point estimates (LS means) and 90% confidence intervals (CI) for the ratio of A:B (A = with rotigotine patch; B = with placebo patch) were calculated by re-transformation of the logarithmic data using the root

mean square error (MSE) of the ANOVA. To demonstrate the appropriateness of the multiplicative model, the ANOVA residuals of the log-transformed parameters were shown graphically and tested for normality by means of the Shapiro-Wilk test (at a type-I error level of 5%) for the null hypothesis that the residuals are normally distributed. In case of a significant deviation from the normality assumption ($P < 0.05$, Shapiro-Wilk test), the corresponding nonparametric analysis was also performed. Nonparametric point estimators for the ratios of expected medians of the ratio A:B (based on the Hodges-Lehmann estimator for the difference of the log transformed data) and the corresponding nonparametric 90% CI were calculated based on Wilcoxon-Mann-Whitney statistics using log-transformed data.

Safety and tolerability data were summarized descriptively. Adverse events were coded using version 9.0 of the Medical Dictionary for Regulatory Activities (MedDRA®).

Results

A total of 43 healthy females were included in the run-in period to account for potential drop-outs during this period. These subjects were randomly assigned to treatment sequences AB ($n = 21$) or BA ($n = 22$); 37 (86%) completed the study. Three of the 43 subjects discontinued during the run-in period and did not receive any patches. One of these subjects withdrew consent and two subjects were withdrawn due to AEs (hepatic enzymes increased and influenza). These three subjects were not included in any analysis because they did not receive any rotigotine treatment. One subject was withdrawn due to an AE (see below) while on rotigotine, and one subject in each treatment sequence did not commence the second cycle. The majority of subjects (92.5%) in the safety analysis set ($n = 40$) were Caucasian; three subjects were of mixed race. Mean age and mean body mass index of the study population were 27.1 ± 5.2 years and $23.6 \pm 3.2 \text{ kg m}^{-2}$, respectively. Data from one subject who completed the study were not included in the pharmacodynamic and pharmacokinetic calculations due to repetitive episodes of vomiting and diarrhoea on days 16 and 18 of cycle 1 which could have affected absorption of the combined oral contraceptive. Both the pharmacodynamic and pharmacokinetic set were therefore comprised of 36 subjects (18 per treatment sequence).

Pharmacodynamics

Mean progesterone serum concentrations in the luteal phase (days 19–21, primary variable) were similar after rotigotine and placebo treatment (Table 1). Maximum individual concentrations were 1.16 ng ml^{-1} following rotigotine, and 1.21 ng ml^{-1} following placebo treatment, both on day 20. In all subjects, progesterone concentrations remained below 2 ng ml^{-1} during the luteal phase.

Secondary variables oestradiol, LH, and FSH serum concentrations are listed in Table 2. As less than two thirds of the data were >LOQ, only median (range) was summarized. All oestradiol, LH and FSH values were within the normal range for non-ovulatory females [15] and comparable between rotigotine and placebo treatment.

Pharmacokinetics

Ethinylestradiol At 1.5 h after administration of the combined oral contraceptive, mean ethinylestradiol plasma concentrations increased from trough values of 36.8 ± 112.0 pg ml⁻¹ after rotigotine and 21.7 ± 20.8 pg ml⁻¹ after placebo to maximum concentrations of 102.2 ± 91.7 after rotigotine and 88.6 ± 25.3 pg ml⁻¹ after placebo. Mean plasma concentrations then continuously decreased to trough values of 29.4 ± 61.7 pg ml⁻¹ (rotigotine) and 21.0 ± 12.7 pg ml⁻¹ (placebo) after 24 h. The concentration–time profile showed slightly higher mean ethinylestradiol plasma concentrations during concomitant treatment with rotigotine (Figure 1A). Interindividual variability of

ethinylestradiol plasma concentrations was substantially higher after rotigotine than placebo (as expressed by higher SD values) but median values were very similar indicating a deviation from normal distribution of the individual data. The increased variability was the result of one individual who showed an unexpected pharmacokinetic profile with only linearly decreasing plasma concentrations on a very high level compared with all other subjects on day 13 after rotigotine treatment (689 pg ml⁻¹ at 0 h decreasing to 387 pg ml⁻¹ at 24 h, Figure 1B). After placebo, the subject showed a typical pharmacokinetic profile with similar plasma concentrations for ethinylestradiol compared with the other subjects (12.4 pg ml⁻¹ at 0 h, a maximum of 58.7 pg ml⁻¹ at 1 h, decreasing to 11 pg ml⁻¹ at 24 h, Figure 1B). Mean ethinylestradiol plasma concentrations after rotigotine calculated without this individual's data were 18.1 ± 6.9 pg ml⁻¹ at 0 h, 87.5 ± 24.6 pg ml⁻¹ after 1.5 h (maximum concentration), and 19.2 ± 7.1 pg ml⁻¹ after 24 h, and similar to placebo (Figure 1C).

Statistical analysis including the data from the above mentioned outlier showed no effect of rotigotine on $C_{\max,ss}$ and $AUC(0,24\text{ h})_{ss}$ for ethinylestradiol: the ratio of geometric means for both parameters was close to 1 with 90% CIs within the acceptance range of bioequivalence of 0.80, 1.25 (Table 3). As deviation from normality was observed for both parameters, a nonparametric analysis was performed which showed the same results. Median $t_{\max,ss}$ was also comparable between treatments (Table 3).

Levonorgestrel Mean plasma concentration–time profiles of levonorgestrel were similar with and without concomitant rotigotine (Figure 2). Maximum mean concentrations of 6.80 ± 2.48 ng ml⁻¹ after rotigotine and 6.72 ± 2.5 ng ml⁻¹ after placebo were reached 1 h after adminis-

Table 1

Mean progesterone serum concentrations (ng ml⁻¹) during combined oral contraceptive administration and concomitant treatment with rotigotine or placebo (pharmacodynamic set, $n = 36$)

	Contraceptive plus rotigotine	Contraceptive plus placebo
Day 19	0.46 ± 0.30 (0.0–1.0)	0.46 ± 0.29 (0.0–1.0)
Day 20	0.45 ± 0.32 (0.0–1.16)	0.48 ± 0.28 (0.0–1.21)
Day 21	0.46 ± 0.31 (0.0–1.09)	0.46 ± 0.3 (0.0–1.02)

Data are mean $\pm$ SD (range).

Table 2

Median serum concentrations of oestradiol, luteinising hormone, and follicle stimulating hormone in subjects receiving combined oral contraceptive treatment and concomitant rotigotine or placebo (pharmacodynamic set, $n = 36$)

	Contraceptive plus rotigotine		Contraceptive plus placebo	
	$n > \text{LOQ}$	Serum concentration	$n > \text{LOQ}$	Serum concentration
Oestradiol (pg ml⁻¹)				
Day 10	22	14.5 (0.0–51.1)	21	14.0 (0.0–22.3)
Day 13	20	14.0 (0.0–20.8)	16	0.0 (0.0–19.7)
Day 14	22	14.3 (0.0–19.9)	17	0.0 (0.0–18.9)
Day 19	11	0.0 (0.0–19.7)	16	0.0 (0.0–20.7)
Day 20	13	0.0 (0.0–20.3)	15	0.0 (0.0–21.0)
Day 21	13	0.0 (0.0–17.6)	13	0.0 (0.0–19.2)
Luteinising hormone (U l⁻¹)				
Day 10	31	2.93 (0.0–12.8)	28	1.98 (0.0–7.09)
Day 13	23	0.99 (0.0–7.07)	21	0.72 (0.0–5.24)
Day 14	21	0.95 (0.0–6.53)	17	0.88 (0.0–8.61)
Follicle stimulating hormone (U l⁻¹)				
Day 10	28	1.76 (0.0–5.11)	24	1.48 (0.0–4.8)
Day 13	21	1.10 (0.0–5.09)	18	0.55 (0.0–4.14)
Day 14	17	0.0 (0.0–4.69)	17	0.0 (0.0–4.24)

LOQ, lower limit of quantification; LOQ values were 13.6 pg ml⁻¹ for oestradiol, 0.62 U l⁻¹ for LH, and 1.00 U l⁻¹ for FSH. Values < LOQ were replaced by zero. As less than two thirds of the data were >LOQ, median (range) was calculated.

Figure 1

Mean ethinyloestradiol plasma concentration–time profile on cycle day 13. **A.** Concomitant administration of combined oral contraceptive and rotigotine (▲; +SD) and of combined oral contraceptive and placebo (○; -SD); pharmacokinetic set, $n = 36$. **B.** Pharmacokinetic profile of subject 80038 with unexpectedly high ethinyloestradiol plasma concentrations after combined oral contraceptive and rotigotine treatment (▲) in comparison with combined oral contraceptive and placebo (○). **C.** Concomitant administration of combined oral contraceptive and rotigotine, pharmacokinetic set excluding subject 80038 (▲; -SD) and of combined oral contraceptive and placebo (○; +SD), pharmacokinetic set

tration of the combined oral contraceptive and then concentrations continuously declined to mean trough concentrations of 2.69 ± 1.24 ng mL⁻¹ (rotigotine) and 2.81 ± 1.36 ng mL⁻¹ (placebo) at 24 h. Median $t_{\max,ss}$ for levonorgestrel was identical with comparable ranges for both treatments (Table 3). Statistical analysis showed geometric mean ratios for $C_{\max,ss}$ and $AUC(0, 24)_{ss}$ close to 1 and 90% CI

within the accepted bioequivalence range of 0.80, 1.25 for both parameters (Table 3). As deviation from normality was observed for $AUC(0, 24)_{ss}$ a nonparametric analysis was performed which showed the same result.

Rotigotine Mean apparent rotigotine doses ranged from 3.23 ± 0.63 mg ($47.8 \pm 9.3\%$) following application to the thigh to 4.14 ± 0.50 mg ($61.3 \pm 7.4\%$) following application to the flank with an overall mean apparent dose of 3.59 ± 0.74 mg ($53.2 \pm 11\%$).

Mean plasma concentrations of unconjugated and total rotigotine remained stable under steady state conditions ranging from 0.43 ± 0.2 ng mL⁻¹ to 0.56 ± 0.27 ng mL⁻¹ for unconjugated rotigotine, and from 1.63 ± 0.75 ng mL⁻¹ to 1.76 ± 0.8 ng mL⁻¹ for total rotigotine. Pharmacokinetic parameters are summarized in Table 4. Mean maximum concentrations at steady state ($C_{\max,ss}$) of 0.58 ng mL⁻¹ were reached at a median 16 h for unconjugated rotigotine. For total rotigotine, a $C_{\max,ss}$ of 2.01 ng mL⁻¹ was reached after a median 6 h.

Safety and tolerability

The majority of subjects receiving rotigotine (92.3%, $n = 36$) reported adverse events with at least a possible relationship to the study medication. After placebo, AEs considered 'at least possibly drug-related' by the investigator occurred in eight subjects (21%). All reported AEs were mild to moderate in intensity and had resolved by the end of the study. The most common drug-related side-effects, reported at least once during the whole treatment period, were nausea (in 74% of rotigotine vs 8% of placebo treated subjects), skin irritation (44% vs 3%), vomiting (41% vs 0%), headache (36% vs 8%), dizziness (36% vs 3%), and insomnia (21% vs 3%), which all occurred with a higher incidence during treatment with rotigotine. They were reported more frequently during titration (days 1–3) than during the dose maintenance phase (days 4–13). The majority of skin irritations (53%) occurred at the patch application site and were described as 'itching' by the subjects. No serious AEs were reported. One subject was withdrawn due to an AE of moderate intensity (anaemia) which was observed during rotigotine treatment. The following laboratory values were determined: haemoglobin 107 g L⁻¹ (baseline 115 g L⁻¹), MCV 78 fL (baseline 86 fL), MCH 1.55 fmol (baseline 1.8 fmol). This AE was assessed as unrelated to the study medication by the investigator but possibly related to iron deficiency. The AE had resolved at safety follow-up.

A slight increase in heart rate was observed after rotigotine compared with placebo (change from baseline in mean heart rate up to 11 beats min⁻¹ with rotigotine compared with up to 8 beats min⁻¹ with placebo). Overall, there were no clinically relevant changes from baseline in clinical laboratory parameters, vital signs or ECGs.

Skin tolerability and patch adhesiveness were good. Most subjects had either no evidence of dermal response

Table 3

Pharmacokinetic parameters for ethinyloestradiol and levonorgestrel at steady state after combined oral contraceptive and concomitant rotigotine or placebo treatment (Day 13, pharmacokinetic set, $n = 36$)

	Contraceptive plus rotigotine	Contraceptive plus placebo	Ratio (90% CI)	ANOVA CV
Ethinyloestradiol				
$C_{max,ss}$ (pg ml ⁻¹)	93 (45%)	89 (28%)	1.05 (0.93,1.19)	32.0%
$AUC(0,24\ h)_{ss}$ (pg ml ⁻¹ h)	926 (57%)	883 (39%)	1.05 (0.90,1.22)	40.2%
$t_{max,ss}$ (h)*	1.5 (0.0–2.0)	1.25 (0.5–4.0)		
Levonorgestrel				
$C_{max,ss}$ (ng ml ⁻¹)	6.76 (33%)	6.71 (36%)	1.01 (0.96,1.06)	13.2%
$AUC(0,24\ h)_{ss}$ (ng ml ⁻¹ h)	81.8 (40%)	83.67 (44%)	0.98 (0.95,1.01)	8.6%
$t_{max,ss}$ (h)*	1.00 (0.5–3.0)	1.00 (0.5–2.0)		

Data are geometric mean and geometric coefficient of variation (%). CI, confidence interval; ANOVA, analysis of variance. *Median (range).

Table 4

Pharmacokinetic parameters for unconjugated and total rotigotine at steady state (pharmacokinetic set, $n = 36$)

	Unconjugated rotigotine	Total rotigotine
$C_{max,ss}$ (ng ml ⁻¹)	0.58 (38%)	2.01 (38%)
$C_{max,ss,norm}$ (ng ml ⁻¹ mg ⁻¹)	0.16 (32%)	0.56 (34%)
$AUC(0, 24\ h)_{ss}$ (ng ml ⁻¹ h)	10.62 (46%)	37.69 (44%)
$AUC(0,24\ h)_{ss,norm}$ (ng ml ⁻¹ h mg ⁻¹)	2.98 (35%)	10.57 (36%)
$t_{max,ss}$ (h)*	16.0 (0–24)	6.0 (0–24)

Data are geometric mean and geometric coefficient of variation (%); norm, normalized by apparent dose. *Median (range).

Figure 2

Mean levonorgestrel plasma concentration–time profile on cycle day 13 during concomitant administration of combined oral contraceptive and rotigotine (▲; +SD) or combined oral contraceptive and placebo (○; –SD); pharmacokinetic set, $n = 36$

or minimal erythema at all assessment days. Definite erythema was reported more frequently with the rotigotine than the placebo patch (29% vs 13% on day 14). ‘Erythema and papules’ occurred only in one subject taking rotigotine on day 7 in cycle 1. No other application effects (dermal scores 4–7, additional scores A–H) were

reported during the study. Patch adhesiveness was rated $\geq 90\%$ for the majority of the assessed patches.

Discussion

Concomitant administration of the transdermal dopamine agonist rotigotine at a concentration of 3 mg (24 h)⁻¹ did not influence ovulation suppression by a combined oral contraceptive of ethinyloestradiol and levonorgestrel in young healthy females. Both pharmacodynamic and pharmacokinetic measurements showed no evidence for drug–drug interactions.

Combined oral contraceptives act by inhibiting pituitary production and secretion of the gonadotropins FSH and LH, particularly on the mid-cycle surge of the two hormones; ovarian oestradiol secretion is markedly reduced and progesterone synthesis suppressed [16]. Concentrations of these four endogenous hormones can therefore serve as indicators for ovulation suppression. Progesterone concentrations remained stable during the luteal phase (days 19–21) and did not increase with concomitant rotigotine treatment. Serum concentrations remained below 2 ng ml⁻¹ for all subjects at all time points measured indicating that ovulation did not occur. LH, FSH and oestradiol serum concentrations remained below LOQ for more than one third of all data collected; median concentrations instead of mean concentrations were therefore calculated. Serum concentrations of LH, FSH and oestradiol were within the normal range for nonovulatory females [15] and were sufficiently suppressed at all time points measured to suggest absence of ovulation with concomitant rotigotine treatment. These results point to a lack of influence of rotigotine on pharmacodynamic effects of the oral contraceptive as no midcycle increase was observed for LH, FSH or oestradiol on days 13 and 14, nor was an increase in oestradiol concentration evident in the luteal phase.

The pharmacodynamic findings are supported by the pharmacokinetic data obtained in this study. The statistical

analysis (including all subject data) showed geometric mean ratios for $C_{\max,ss}$ and $AUC(0,24\text{ h})_{ss}$ (with vs without rotigotine co-administration) close to 1 for both ethinylloestradiol and levonorgestrel, and the corresponding 90% confidence intervals were within the acceptance range for bioequivalence of 0.80, 1.25. This indicates no relevant differences in rate and extent of absorption of both hormone derivatives in the presence or absence of rotigotine.

Mean plasma concentrations of ethinylloestradiol were slightly higher during concomitant rotigotine treatment; the variability was much higher as well. This finding was the result of one subject with an unexpected pharmacokinetic profile showing only linearly decreasing plasma concentrations on an exceptionally high concentration during rotigotine treatment. No reason was identified for this finding. Serum concentrations of progesterone, oestradiol, LH, and FSH were similar between both treatment periods for this subject. Furthermore, rotigotine plasma concentrations observed in this subject were even lower compared with the respective mean values.

Drug–drug interactions affecting the efficacy of oral contraceptives are predominantly based on pharmacokinetic interactions with ethinylloestradiol. In contrast to levonorgestrel which has not been shown to undergo enterohepatic circulation, ethinylloestradiol is extensively metabolized by sulphation in the gut wall, and by hydroxylation and glucuronidation in the liver, and undergoes significant enterohepatic recirculation [12]. CYP3A4-mediated hydroxylation is the major oxidative pathway for ethinylloestradiol clearance [11].

Previous studies using human hepatocytes and monkey liver have already shown the lack of a significant induction or inhibition of CYP isoforms by rotigotine [8]. Ethinylloestradiol has shown inhibitory activity on CYP enzymes and an inductive effect on glucuronidation [11]. Rotigotine metabolism involves conjugation (sulphation >> glucuronidation), and N-desalkylation mediated by several CYP isoforms [8]. Absorption of rotigotine (as determined by apparent dose) was comparable with previous studies [6, 17]. Unconjugated rotigotine plasma concentrations remained relatively stable during concomitant administration of the combined oral contraceptive under steady state conditions. Plasma concentrations and derived pharmacokinetic parameters were in accordance with data previously observed for rotigotine in healthy volunteers (data on file). These data suggest that there is no relevant influence of ethinylloestradiol/levonorgestrel on the pharmacokinetics of rotigotine.

There are no published data about drug–drug interaction studies with oral contraceptives and oral non-ergolinic dopamine agonists. Ropinirole has the potential to interact with other drugs via the CYP enzyme system whereas pramipexole has not [18]. Population pharmacokinetic investigations found that clearance of oral ropinirole was reduced by 33% in females on hormone replacement therapy compared with females not taking

oestrogens ($P < 0.005$). This resulted in an increase in the elimination half-life of the drug [19].

Overall, the rotigotine transdermal patch was well tolerated at a maintenance dose of 3 mg (24 h)^{-1} which represents the upper end of the therapeutic dose range for the indication restless legs syndrome [4, 5]. None of the side-effects was severe. Most were consistent with dopaminergic stimulation or the use of a transdermal delivery system. It should be noted that the titration rate was faster than normal; instead of a 1 mg (24 h)^{-1} starting dose and a weekly dose increment of 1 mg (24 h)^{-1} , this study used a starting dose of 2 mg (24 h)^{-1} rotigotine increasing to 3 mg (24 h)^{-1} after 3 days. This might account for the higher AE incidences after rotigotine compared with previous studies [4, 5].

In conclusion, co-administration of 3 mg (24 h)^{-1} transdermal rotigotine had no impact on the pharmacodynamics and pharmacokinetics of a combined oral contraceptive containing 0.03 mg ethinylloestradiol and 0.15 mg levonorgestrel, suggesting that the drug does not influence contraception efficacy.

Competing interests

M.B., J.-P.E., J.-O.A. and R.H. are employees of Schwarz Biosciences, UCB-Group.

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