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Original research article

Novel ethinyl estradiol-beta-cyclodextrin clathrate formulation does not influence the relative bioavailability of ethinyl estradiol or coadministered drospirenone☆

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Abstract

Background: A new combined oral contraceptive formulation has been developed consisting of a beta-cyclodextrin (betadex) clathrate formulation of ethinyl estradiol in combination with drospirenone (EE-betadex clathrate/drsp). In this novel EE-betadex clathrate/drsp preparation, betadex serves as an inert complexing agent to enhance stability and shelf-life. The study was conducted to investigate the relative bioavailability and pharmacokinetic parameters of EE and drsp after oral administration of EE-betadex clathrate/drsp.

Methods: This was an open-label, randomized, single-dose, three-period, three-treatment, crossover study conducted in 18 healthy postmenopausal women aged 45–75 years. The women received single oral doses of 40 mcg EE/6 mg drsp formulated as EE-betadex clathrate/drsp or EE/drsp (EE as a free steroid) tablets, or as a microcrystalline suspension on three separate occasions. Serum samples were collected for pharmacokinetic analyses.

Results: The relative bioavailability of EE and drsp after EE-betadex clathrate/drsp tablet administration was comparable with that achieved with the EE/drsp tablet (107% and 101%, respectively). In addition, the inclusion of EE in a betadex clathrate does not affect the pharmacokinetics of either EE or drsp. There were no safety concerns with any of the medications.

Conclusion: The betadex clathrate formulation of EE, when combined with DRSP, does not affect the pharmacokinetics and relative bioavailability of either EE or drsp.

Keywords: Drospirenone; Ethinyl estradiol; Bioavailability; Cyclodextrin; Pharmacokinetics

1. Introduction

A new ethinyl estradiol/drospirenone (EE/drsp) formulation has been developed consisting of 20 mcg EE in beta-cyclodextrin (betadex) clathrate in combination with 3 mg DRSP (EE-betadex clathrate/drsp) [1,2]. Betadex consists of seven glucopyranose residues linked by alpha-1,4 glycosidic bonds into a macromolecule which is without biological activity and only poorly absorbed (<4%) from the small intestine following oral administration [3,4]. For oral drug formulations, beta-cyclodextrins may be used to increase drug bioavailability through increased drug dissolution and solubility, modify drug pharmacokinetic profile, decrease mucosal irritation and mask unpleasant taste [5–9]. In addition, beta-cyclodextrin may be used to prolong shelf-life of a drug product, which was the reason for using this excipient in one of the formulations investigated in the present study.

The EE-betadex clathrate/drsp oral contraceptive has been proven to be an effective contraceptive with good safety profile and favorable additional noncontraceptive benefits, based in part on the clinical profile of drospirenone [1,2,10–13]. Drospirenone is the only progestin used in oral contraceptives that, like progesterone, demonstrates clinically relevant antimineralocorticoid and antiandrogenic activities [14–16]. Respectively, when the EE-betadex clathrate/drsp

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oral contraceptive is administered in a novel regimen, with 24 active pills followed by a shortened hormone-free interval of 4 days (24/4 regimen), these properties confer favorable effects on androgen-dependent disorders (e.g., acne) [10,11] and alleviate menstrual symptoms related to sodium and water retention (e.g., bloating and swelling) and, in particular, the emotional and physical symptoms associated with premenstrual dysphoric disorder [12,13].

The objective of the present study was to assess whether oral administration of the innovative EE-betadex clathrate/drsp formulation affects the bioavailability and pharmacokinetics of EE and DRSP. The pharmacokinetic profile of EE and drsp was compared after single oral administration of an EE-betadex clathrate/drsp tablet formulation, a conventional EE/drsp tablet formulation (with EE as a free steroid) and an EE/drsp microcrystalline suspension.

2. Materials and methods

2.1. Study participants

Healthy postmenopausal women aged between 45 and 75 years were recruited to the study. Postmenopausal status was established by the absence of spontaneous menstrual bleeding for at least 2 years or if bilateral oophorectomy had been performed at least 3 months prior and confirmed by serum hormone levels of estradiol (≤20 pg/mL) and follicular stimulating hormone (≥50 mIU/mL) at screening. Other inclusion criteria included normal gynecological examination and cervical smear, and a body mass index (BMI) between 20 and 29 kg/m^2. Washout periods were required if the women had used systemic or topical medications that have a potential to affect liver enzymes, including antibiotics (8 weeks); oral, transdermal or transvaginal sex hormones (6 weeks); long-acting injectable or implanted sex hormones (6 months); or alcohol (2 days).

2.2. Study design

This was an open-label, randomized (order of treatments), single-dose, three-period crossover study with three treatments and six sequences (Williams design) conducted at a single center in Germany. The study was approved by the appropriate ethics committees and conducted in accordance with the ethical principles of the Declaration of Helsinki (amended in 1996) and guidelines of the International Conference on Harmonization (ICH 1996). All participants gave written and informed consent before enrolment.

2.3. Treatment

The women were randomized using a computer-generated randomization list to a treatment sequence that consisted of two tablets of 20 mcg EE-betadex clathrate/3 mg drsp (EE-betadex clathrate/drsp), two tablets of 20 mcg EE as a free steroid/3 mg drsp (EE/drsp), and an oral dose of a microcrystalline suspension containing 40 mcg EE/6 mg drsp (reference treatment). The microcrystalline suspension was prepared from 328 mg lactose granules containing the respective drug amounts. The granules were dissolved in 100 mL noncarbonated mineral water by 5-min vigorous shaking and swallowed immediately after preparation. The drinking vials were rinsed twice with 70 mL of water which was swallowed immediately afterwards. The tablets were taken with 240 mL of noncarbonated water. There was a 14-day washout phase between each treatment period to prevent any carryover effects — the 14-day washout period far exceeds the half-lives for both EE and drsp. All EE/drsp formulations were manufactured by Bayer Schering Pharma AG.

The women received study medication between 0700 and 0900 hours after an overnight fast of at least 10 h. Set meals were provided from 4 h after drug administration. Volunteers stayed at the study site for 24 h after drug administration in each treatment period. All other measurements were performed on an outpatient basis. Volunteers were permitted their normal diet on outpatient study days, although grapefruit-containing food or beverages were not allowed 2 days before and 2 days after treatment. Other than the noncarbonated water taken with each study drug, fluid intake was not permitted 1 h before and 1 h after drug administration. Women maintained an upright posture (sitting, standing or walking) for at least 4 h after dosing.

2.4. Pharmacokinetic assessments

Blood samples were collected (7.5 mL for EE; 2.7 mL for drsp) via an indwelling cannula into additive-free plastic syringes (Monovette®, Sarstedt, Germany) 0.5 h before administration and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 34, 48 and 72 h after administration of study medication. In addition, EE was measured at 2.5 h post-dose, and drsp was measured at 96 and 120 h post-dose. The serum was separated by centrifugation 30 min after blood sampling and stored between −18°C and −25°C until analysis.

Serum EE concentration was measured at AAI, Germany, by gas chromatography/mass spectrometry (GC/MS) with a lower limit of quantification of 10 pg/mL. Briefly, EE was extracted from acidified serum into toluene. The samples were then evaporated to dryness, reconstituted in dichloromethane and, after two further clean-up steps, stored at 4°C until measurement. Extraction was followed by a derivatization step in order to obtain suitable derivatives for GC/MS analysis, of which 2 μL was injected into the GC/MS system. GC/MS measurements were performed in the chemical ionization mode (negative ions) using ammonia as the reagent gas. The concentration of EE in serum samples was calculated based on reference calibration standards (10.0–500 pg/mL). Quality control samples with nominal EE concentrations of 20, 80 and 400 pg/mL were analyzed in duplicate within each study assay to monitor the precision (inter-assay coefficient of variation) and accuracy of the analyses. Overall, 39 sets of quality control samples were analyzed and the mean precision was determined to be

11.8%, 9.7% and 10.6% at the concentration levels of 20, 80 and 400 pg/mL, respectively. The accuracy was calculated from the ratio of measured concentration to nominal concentration and the mean accuracy based on 39 sets of quality control samples was determined to be 100.2%, 101.2% and 99.7% at the concentration levels of 20, 80 and 400 pg/mL, respectively.

The concentration of drsp in serum was measured by a specific, validated radioimmunoassay using methods described elsewhere [17], with minor modifications (specific activity of the tracer was 3.714 GBq/mg; antiserum was diluted 1:11000). The lower limit of quantification was 0.2 to 0.5 ng/mL, depending on the accuracy of quality control results in individual assays. The precision (inter-assay coefficient of variation) and accuracy of the analyses were monitored by sixfold measurements within each assay using quality control samples with nominal drospirenone concentrations of 0.2, 0.5, 1.0 and 3.0 ng/mL, and determined to be 3.9–10.6% and 102–113%, respectively.

2.5. Pharmacokinetic evaluation

The observed maximum serum drug concentration (C_{max}) and time to reach this concentration (t_{max}) were taken directly from individual concentration vs. time graphs. The terminal half-life ($t_{1/2}$) of drsp was determined from the terminal rate constant (λ_z) which was calculated by means of regression analysis from the linear part of the concentration–time curve in a semi-logarithmic plot using at least five data points within a time range covering at least two half-lives. The resulting $t_{1/2}$ was calculated as $t_{1/2}=\ln 2/\lambda_z$. The area under the concentration–time curves up to the last measurable time point ($AUC_{(0-tlast)}$) was calculated using the linear trapezoidal rule. The AUC value was calculated by extrapolation according to the following equation:

$$AUC = AUC_{(0-tlast)} + C_t / \lambda_z$$

with C_t as the concentration at last data point.

AUC values were not accepted if appropriate calculation of the terminal half-life was not possible or if the extrapolated area was greater than 20%.

2.6. Safety and tolerability assessments

General physical examinations (including body weight and vital signs), electrocardiogram and clinical laboratory testing (blood chemistry, hematological and urinalysis measurements) were performed prior to receiving the first study medication. Clinical laboratory measurements were repeated at the end of the study.

Adverse events were recorded up to 14 days after the last drug was given. All adverse events were coded and classified by the study investigators as to their intensity and to their relationship to study medication.

2.7. Statistical analysis

The planned sample size was 18 participants, which was not based on any biometrical consideration.

The $AUC_{(0-tlast)}$ was considered the primary target variable; all other pharmacokinetic parameters were considered secondary target variables. All pharmacokinetic data from women with no relevant protocol deviations were

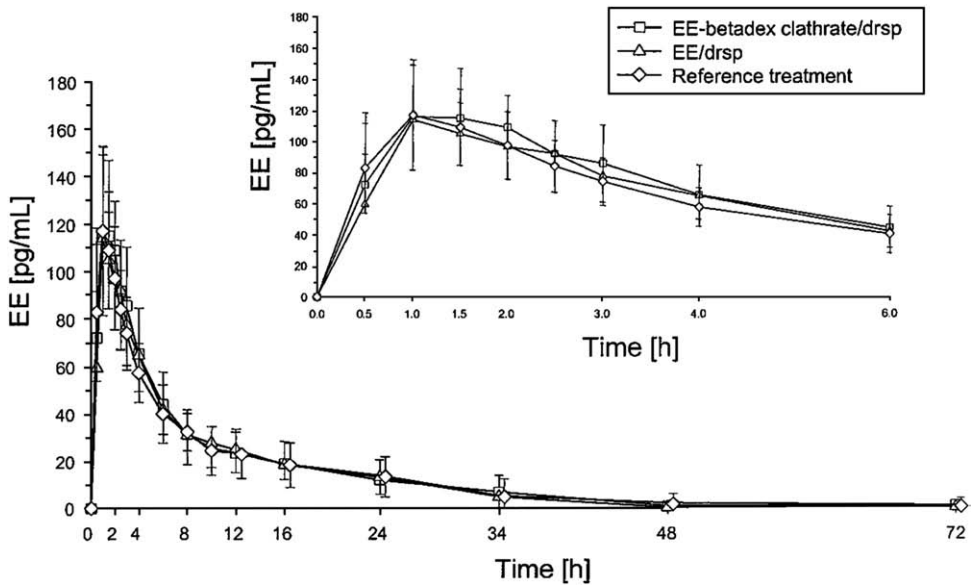

Fig. 1. Mean (±SD) EE serum concentration vs. time curves determined after treatment with EE 40 mcg/drospirenone 6 mg (EE/drsp) given as EE-betadex clathrate/drsp tablets, EE/drsp tablets with EE as a free steroid or an EE/drsp microcrystalline suspension (reference treatment) in 18 healthy postmenopausal women.

Table 1
Pharmacokinetic parameters of EE after single oral administration of EE 40 mcg/drsp 6 mg given as EE-betadex clathrate/drsp tablets, EE/drsp tablets with EE as a free steroid or an EE/drsp microcrystalline suspension (reference treatment) to 18 healthy postmenopausal women

Formulation	C_{max} (pg/mL)	t_{max} (h)	$AUC_{(0-tlast)}$ (pg h/mL)
EE-betadex clathrate/drsp	125 (22.8%)	1.5 (1.0–3.0)	862 (44.8%)
EE/drsp	120 (22.9%)	1.0 (0.5–2.5)	843 (31.7%)
Reference treatment	123 (27.2%)	1.0 (0.5–2.0)	866 (37.8%)

Results are presented as geometric mean (geometric coefficient of variation)
* except for t_{max} which is given as median (range).
* The geometric mean estimates the distribution median of a log-normal distribution. The geometric coefficient of variation estimates the distribution coefficient of variation of a log-normal distribution.

included in the statistical analysis; however, women with missing data which prevented reliable calculation of the primary variable were excluded. All target variables were described using descriptive statistics. Analyses were performed using SAS software (version 6.12).

The primary target variables were evaluated with an analysis of variance. It was assumed that the pharmacokinetic parameters are log-normally distributed. Therefore, the logarithms (base e) were analyzed using subject as a random factor, and period, treatment and first-order carryover as fixed factors. The relative bioavailabilities of EE and drsp between the formulations, including the corresponding confidence intervals, were derived from the parameter estimations and confidence intervals in the analysis of variance by antilogarithmic transformation.

3. Results

3.1. Study participants

Of 54 volunteers screened, 18 healthy postmenopausal women were recruited and completed the study according to the study protocol. The reasons for nonparticipation in the study included abnormal laboratory assessments (n=12), logistical reasons (n=9), withdrawal of consent (n=6), use of co-medication excluded by protocol (n=5), not postmenopausal (n=2), abnormal medical history (n=l) and failure to return to study center (n=1). Each participant took one dose of EE-betadex clathrate/drsp, EE/drsp and the reference medication. Protocol violations consisted of diet errors (eight subjects did not eat all of the standard meals) and inclusion/exclusion criteria violations (one subject consumed alcohol 2 days before dosing). These protocol deviations were considered to be minor and to have little impact on drug pharmacokinetics.

The mean (range) demographic characteristics of the volunteers were as follows: age, 59.8 (48–75) years; height, 165.8 (153–178) cm; weight, 69.2 (52–93) kg; BMI, 25.1 (20.3–29.4) kg/m^2.

3.2. Pharmacokinetic parameters

The mean serum concentration–time curve for EE following a single oral dose of each EE/drsp study medication is shown in Fig. 1. For all study medications, EE was rapidly absorbed reaching mean peak serum concentrations of 120–125 pg/mL within a median time of 1.0–1.5 h. Overall,

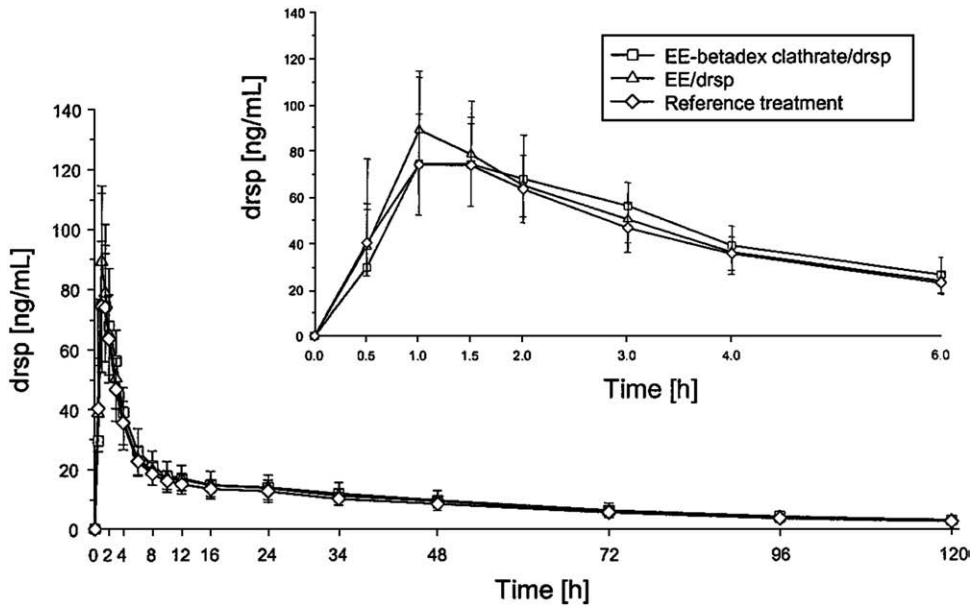

Fig. 2. Mean (±SD) drospirenone (drsp) serum concentration vs. time curves determined after treatment with ethinyl estradiol 40 mcg/drsp 6 mg (EE/drsp) given as EE-betadex clathrate/drsp tablets, EE/drsp tablets with EE as a free steroid or an EE/drsp microcrystalline suspension (reference treatment) in 18 healthy postmenopausal women.

Table 2
Pharmacokinetic parameters of drsp after single oral administration of EE 40 mcg/drsp 6 mg (EE/drsp) given as EE-betadex clathrate/drsp, EE/drsp with EE as a free steroid or an EE/drsp microcrystalline suspension (reference treatment) to 18 healthy postmenopausal women

Formulation	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{(0-tlast)}$ (ng h/mL)	AUC (ng h/mL)
EE-betadex clathrate/drsp	87.1 (30%)	1.0 (1.0–4.0)	36.6 (22%)[a]	1207 (24%)	1299 (25%)[a]
EE/drsp	92.1 (27%)	1.0 (0.5–2.0)	34.4 (18%)[b]	1171 (23%)	1242 (26%)[b]
Reference treatment	82.7 (22%)	1.3 (1.0–2.0)	34.3 (28%)[b]	1091 (16%)	1186 (15%)[b]

Results are presented as geometric mean (geometric coefficient of variation)* except for t_{max} which is given as median (range).
*See footnote to Table 1.
[a] n=16.
[b] n=14.

the pharmacokinetic parameters of EE after administration of EE-betadex clathrate/drsp tablets were similar to those after the administration of either conventional EE/drsp tablets or the EE/drsp microcrystalline suspension reference medication (Table 1). Serum EE concentrations were quantifiable in all subjects for at least 8 h (up to 72 h in some women). Fig. 2 shows the mean serum concentration–time curve for drsp following a single oral dose of each EE/drsp formulation. For all study medications, drsp was rapidly absorbed reaching t_{max} between 1.0 and 1.3 h (medians) and with corresponding mean C_{max} values between 83 and 92 ng/mL. Overall, the pharmacokinetic parameters of drsp after administration of EE-betadex clathrate/drsp tablets were similar to those after the administration of either EE/drsp tablets or reference medication (Table 2). Serum drsp concentrations were quantifiable in all subjects for the entire 120-h post-dose sampling period.

When compared with the reference medication, the relative bioavailability of EE and drsp with EE-betadex clathrate/drsp tablets was 97% and 107%, respectively. Similar relative bioavailability results were found for EE/drsp tablets vs. the reference treatment (Table 3). In addition, the relative bioavailability of EE and drsp after administration of EE-betadex clathrate/drsp was comparable with that of the EE/drsp tablet formulation.

3.3. Safety and tolerability

All EE/drsp formulations were generally well tolerated. None of the laboratory assessments or other physical medical assessments gave rise to any safety concerns. No unexpected or serious adverse events were reported. All adverse events were transient and none of the volunteers withdrew prematurely from the study.

4. Discussion

The inclusion of an EE-betadex clathrate with drsp in an oral tablet formulation does not affect the pharmacokinetics and relative bioavailability of either EE or drsp compared with oral administration of conventional EE/drsp tablets (with EE as a free steroid), or a microcrystalline suspension of EE/drsp in healthy postmenopausal women. The relative bioavailability of EE and drsp after the administration of EE-betadex clathrate/drsp was comparable with that achieved with EE/drsp or a reference suspension. Therefore, complete in vivo release of EE and drsp was achieved in healthy postmenopausal women following oral administration of EE-betadex clathrate/drsp tablets.

As this was a single-dose, intra-individual crossover study to determine the performance of the different formulations in vivo, postmenopausal women were recruited to this study instead of the target population for oral contraceptives. This selection was decided because fewer bleeding disturbances would be expected in this population. Nonetheless, the pharmacokinetics of EE and drsp following single oral dosing of the three EE/drsp formulations in this study is consistent with published reports, typically involving healthy young women. For EE, a similar pharmacokinetic profile has been reported following single oral doses (30 mcg) in combination with drsp. In general, ethinyl estradiol drug levels increase linearly within the dose range of about 20–100 mcg [17–19]. Moreover, the large inter-subject variability in EE levels observed in our study is well known [18]. The pharmacokinetics of drsp is dose proportional (from 1 to 10 mg) after single oral doses [14,20]. The median t_{max} (1–1.3 h) and $t_{1/2}$ (~35 h) of drsp reported

Table 3
Relative ratios of EE and drsp following administration of EE 40 mcg/drsp 6 mg as EE-betadex clathrate/drsp tablets (Test 1), EE/drsp tablets with EE as a free steroid (Test 2) or an EE/drsp microcrystalline suspension (reference treatment, RT) to 18 healthy postmenopausal women

Pharmacokinetic parameter	Comparison		
	Test 1 vs. RT[a]	Test 2 vs. RT[a]	Test 2 vs. Test 1[a]
EE, C_{max}	100.9 (89.6–113.6)	105.8 (94.0–119.2)	104.9 (93.2–118.1)
EE, $AUC_{(0-tlast)}$	97.2 (85.3–110.7)	104.3 (91.6–118.8)	107.3 (94.2–122.3)
drsp, C_{max}	102.7 (93.5–112.9)	111.9 (101.8–122.9)	108.9 (99.1–119.6)
drsp, $AUC_{(0-tlast)}$	107.0 (98.7–116.1)	108.2 (99.8–117.4)	101.1 (93.2–109.7)

[a] Data presented as mean ratio (%) with 90% confidence interval in parentheses.

here are also consistent with previous findings. Our results suggest that the pharmacokinetics of single doses of EE and drsp is comparable between postmenopausal women and women of reproductive potential.

The dose of EE (40 mcg) and drsp (6 mg) administered in this study was double the contraceptive dose and was chosen to ensure appropriate analytic sensitivity for pharmacokinetic evaluation. The safety and tolerability of these higher hormone doses were not expected to be an issue as there is extensive experience with long-term use of EE used at daily doses of up to 50 mcg. In addition, evidence from several Phase I trials showed that doses of drsp up to 100 mg, including daily administration of 10 mg to postmenopausal women for 5 days, did not affect laboratory or physical medical variables. Moreover, beta cyclodextrin can be considered to be practically nontoxic due to their lack of absorption through the gastrointestinal tract [9].

The use of betadex clathrate and other cyclodextrin complexes to stabilize drug formulations is an established pharmaceutical procedure [5,9]. However, this is the first time that this technology has been applied to develop a hormone formulation containing EE and drsp. Current real-time stability data support a shelf-life of 5 years for this drug product.

5. Conclusion

A betadex clathrate formulation of EE, when combined with drsp, did not influence the relative bioavailability of EE or drsp, or alter the pharmacokinetic profile of these hormones. The adverse events with EE-betadex clathrate/drsp were mild and typical of a combined oral contraceptive. None of the safety assessments gave rise for concern.

Acknowledgments

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