

Effect of Multiple-Dose Dexloxiglumide on the Pharmacokinetics of Oral Contraceptives in Healthy Women

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This study was undertaken to evaluate the effect of dexloxiglumide, a selective cholecystokinin receptor antagonist, on the pharmacokinetics of a combination oral contraceptive (OC). A single-blind, placebo-controlled, 2-period crossover study was conducted in 24 healthy young female subjects who received Ortho Tri-Cyclen containing ethinyl estradiol (EE, 0.035 mg) and norgestimate (NE, 0.180 mg/0.215 mg/0.250 mg per 7-day phase, respectively) for 5 days (days 17-21) concurrently with either 200 mg dexloxiglumide (3 times a day on days 17-20, followed by a single dose on day 21) or matching placebo during 2 consecutive 28-day OC dosing cycles. Plasma was sampled up to 24 hours for the determination of EE, NE, and 17-deacetyl norgestimate (17-DNE, a rapidly formed pharmacologically active metabolite of NE). The geometric mean ratios (GMRs, dexloxiglumide/placebo)

of the plasma concentration-time curve over 24 hours with corresponding 90% confidence intervals (CIs) for EE and 17-DNE were 1.21 (1.17-1.26) and 0.92 (0.89-0.95), respectively. The GMRs (90% CI) of C_{max} for EE and 17-DNE were 1.15 (1.09-1.20) and 0.93 (0.90-0.96), respectively. Coadministration of OC and dexloxiglumide was well tolerated and safe. Comparable systemic exposure of EE and 17-DNE in the presence and absence of dexloxiglumide suggests that dexloxiglumide treatment is unlikely to interfere with the safety and efficacy of oral contraceptives based on the analysis of the resulting pharmacokinetic profile.

Keywords: Dexloxiglumide; pharmacokinetics; oral contraceptives; drug interactions

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Dexloxiglumide, the dextro isomeric form of dloxiglumide, is a potent and selective cholecystokinin subtype-1 (CCK₁) receptor-blocking agent being studied for the treatment of functional gastrointestinal disorders (FGIDs) such as constipation-predominant irritable bowel syndrome, nonulcer dyspepsia, and gastric-emptying disorders.¹ Preclinical studies have demonstrated that dexloxiglumide effectively blocks the actions of both exogenous and endogenous cholecystokinin.¹ Cholecystokinin (CCK), a pep-

tide hormone widely distributed in the small intestine (duodenal I cells and enteric nerves), is secreted in response to meals² and plays a role in regulating gallbladder contraction³ and pancreatic enzyme secretion.^{4,5} The peptide also delays the gastric emptying rate, modulates small bowel transit time, increases colonic transit time, and causes lower esophageal sphincter relaxation in both humans and animals.^{6,7} The biological action of CCK on the exocrine pancreas,⁸ gallbladder,⁹ and gastrointestinal smooth muscle⁹ is mediated by CCK₁ (formerly referred to as CCK_A) receptors. These receptors are located on the target organs, in neurons in the myenteric plexus, and in vagal afferents from the gastrointestinal tract.¹⁰ The ability of dexloxiglumide to block CCK from binding to these receptors is expected to be a key mechanism for its efficacy in the treatment of functional gastrointestinal disorders.

The oral bioavailability of dexloxiglumide in humans is about 48%.¹¹ It is rapidly absorbed and eliminated,

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with peak plasma concentrations (C_{\max}) observed within 1 hour and a terminal elimination half life ($t_{1/2}$) estimated to be approximately 8 hours (data on file). The rate and extent of systemic exposure, as measured by C_{\max} and the area under the plasma concentration-time curve (AUC), respectively, increase in a dose-proportional manner after single and multiple doses of dexloxiglumide in the dose range of 100 to 200 mg.¹² In vitro studies with human liver microsomes and cDNA-expressed P450s have shown that dexloxiglumide is predominantly metabolized by the CYP 2C9 isoform and, to a lesser extent, by the CYP 3A4 isoform.¹³ These 2 isozymes are involved in the conversion of dexloxiglumide to its metabolite, O-demethyl dexloxiglumide, with subsequent oxidation to dexloxiglumide carboxylic acid (data on file).

Triphasic oral contraceptives (OCs) constitute the most popular birth control pills as a class. Ortho Tri-Cyclen (Ortho-McNeil, Raritan, NJ) is a combination triphasic OC containing the estrogenic compound ethinyl estradiol (EE, 0.035 mg) and the progestational compound norgestimate (NE, 0.180 mg/0.215 mg/0.250 mg per phase, respectively). EE and NE are well absorbed following oral administration, with mean peak plasma concentrations achieved within 2 hours (0.75-3.0 hours for EE and 0.50-2.0 hours for NE), followed by a rapid decline due to distribution and elimination.¹⁴ The elimination half-life of EE ranges from 6 to 14 hours. The NE serum concentrations following multiple dosing are usually well below assay detection levels within 5 hours; however, a major serum metabolite, 17-deacetyl norgestimate (17-DNE), which exhibits a serum half-life ranging from 12 to 30 hours, appears rapidly in serum with concentrations greatly exceeding that of NE. The 17-DNE metabolite is pharmacologically active with a similar profile to NE.¹⁴ Both EE and NE are extensively metabolized by first-pass mechanisms in the gastrointestinal tract and/or liver and eliminated by renal and fecal pathways.¹⁴ Quantitatively, one of the major metabolic pathways for EE is aromatic hydroxylation and is believed to be mediated by hepatic cytochrome P450 enzymes, primarily the P450 3A4 isozyme.¹⁵

Because a large portion of the patient population suffering from FGIDs are sexually active females of childbearing age, a study designed to evaluate whether a pharmacokinetic interaction exists between dexloxiglumide and an OC medication can provide useful information to female patients relying on OCs for contraception. Dexloxiglumide is a P450 3A4 substrate, similar to EE, and undergoes extensive biliary excretion,¹¹ similar to EE and NE. Therefore, the possibility for a pharmacokinetic interaction between dexloxi-

glumide and OCs exists. An earlier in vitro study¹³ has demonstrated a low potential for a clinically meaningful interaction between dexloxiglumide and CYP3A4 substrate and/or inhibitor. This study was undertaken to evaluate the effects of repeated administration of dexloxiglumide on the pharmacokinetics of EE and 17-DNE following chronic dosing of Ortho Tri-Cyclen with and without (matched placebo) dexloxiglumide during 2 successive menstrual cycles in healthy female subjects.

SUBJECTS AND METHODS

Subjects

Twenty-nine healthy female subjects, aged 19 to 45 years (mean \pm SD, 25.3 \pm 7.1), were enrolled in the study, and 24 subjects, all white women, completed the study. Of the 5 subjects who discontinued the study prematurely, 4 withdrew consent or were lost to follow-up during the run-in phase, and 1 subject dropped out due to an unrelated adverse event (acute bronchitis). All subjects had a body weight \geq 49 kg (mean = 65.0 \pm 9.66), were within 25% of ideal body weight, and were required to document the use of a combination OC for a minimum of 2 dosing cycles (1 cycle = 28 days) prior to screening. All subjects had to agree to use the protocol-specified OC, Ortho Tri-Cyclen, for 3 consecutive cycles (run-in phase + 2 treatment cycles) in addition to using a nonhormonal double-barrier method of contraception as a supplement to the OC during the study. All subjects were required to have a negative serum pregnancy test at screening and a negative serum or urine pregnancy test the day prior to beginning the run-in phase (cycle 1). Subjects also had to have a negative urine drug screen test and no history of alcohol or drug abuse within 5 years of study start. Eligible subjects were required to have no current evidence of cervical dysplasia (as documented by a Papanicolaou test within the past year), a history of regular menstrual cycles with no unusual bleeding during the 3 months prior to study start, and no clinically significant abnormal findings shown by physical examination, medical history, or clinical laboratory results at the screening visit. Subjects had to be nonsmokers for at least 2 years prior to study start and free of any prescription or non-prescription drug treatment (including herbal supplements) within 14 days of study start. Subjects who were nursing or lactating and those who had received an injection of medroxy-progesterone acetate (Depo-Provera, Pharmacia, Kalamazoo, Mich) within 6 months of study initiation were excluded from the study. Placement or removal of levonorgestrel implants

until completion of the third cycle of the OC. The total duration of the study was 85 days (including day -1 of cycle 1 to day 28 of cycle 3).

Safety was assessed throughout the study by the monitoring of adverse events, electrocardiograms (ECGs), vital signs, and routine laboratory examinations.

Bioanalytical Assays

Liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods were used to measure the concentrations of EE, NE, and 17-DNE in plasma samples (MDS Pharma Services, Lincoln, Neb). The methods were validated to demonstrate the accuracy, linearity, reproducibility, and precision of the analytical procedures. The limits of quantitation for EE for this assay ranged from 2 pg/mL (lower limit of quantitation, LLOQ) to 500 pg/mL (upper limit of quantitation, ULOQ). The precision and accuracy of EE standards in human plasma were within 5.8% and 3.0%, respectively. The precision and accuracy for EE quality control samples were within 11.7% and 5.5%, respectively. The limits of quantitation for both NE and 17-DNE for the assay ranged from 20 pg/mL (LLOQ) to 2500 pg/mL (ULOQ). The precision and accuracy of NE standards in human plasma were within 9.1% and 4.8%, respectively. The precision and accuracy for NE quality control samples were within 11.6% and 4.4%, respectively. The precision and accuracy of 17-DNE standards in human plasma were within 8.5% and 2.0%, respectively. The precision and accuracy for 17-DNE quality control samples were within 9.2% and 1.5%, respectively.

Pharmacokinetic Analysis

The primary parameters describing the pharmacokinetics of ethinyl estradiol and 17-deacetyl norgestimate were derived from plasma concentrations using noncompartmental analysis. Pharmacokinetic parameters included time of maximum plasma concentration (t_{\max}), maximum plasma concentration (C_{\max}), and area under the plasma concentration-time curve over 24 hours ($AUC_{0-24\text{ h}}$) for EE and 17-DNE.

The C_{\max} for the concentration-time profile was determined by observation as the peak concentration for each subject in each treatment. The t_{\max} was determined as the time corresponding to C_{\max} . Area under the plasma concentration-time curve up to 24 hours ($AUC_{0-24\text{ h}}$) for EE or 17-DNE was calculated by numerical integration using the linear trapezoidal rule.

Pharmacokinetic data analyses were carried out with the program WinNonlin Version 4.0.1 (Pharsight

Corporation, Mountain View, Calif). Plasma concentrations that were below the limit of quantitation (BLOQ values) were treated as zero for all pharmacokinetic calculations.

Statistical Analysis

Estimates of pharmacokinetic parameters (C_{\max} , $AUC_{0-24\text{ h}}$, and t_{\max}) for ethinyl estradiol and 17-deacetyl norgestimate were summarized for each subject group using descriptive statistics. Statistical analyses were performed using the GLM Procedure in Version 6.12 of SAS running on a UNIX operating system.

The equivalence of the pharmacokinetic parameters $AUC_{0-24\text{ h}}$ and C_{\max} for ethinyl estradiol and 17-deacetyl norgestimate was measured between 2 treatment groups: Ortho Tri-Cyclen plus dexloxiglumide (test) and Ortho Tri-Cyclen plus placebo (reference). These were tested using Schuirmann's 2 one-sided test procedure.¹⁶ Analysis of variance (ANOVA) was performed on log-transformed data for $AUC_{0-24\text{ h}}$ and C_{\max} with sequence, treatment, and period as fixed factors and subject nested within sequence as a random factor in the model. A 5% level of significance was used for within-subject comparisons. Ninety percent confidence intervals for the ratios of the geometric means for pharmacokinetic (PK) parameters between 2 treatment groups were calculated using the least squares means and standard error obtained from ANOVA. The t_{\max} for EE and 17-DNE was compared nonparametrically using the Wilcoxon signed-rank test based on the matched pairs.

RESULTS

Subjects

Twenty-nine subjects were enrolled into this study, and 24 subjects completed it. Four subjects withdrew/discontinued from the study during the run-in phase (cycle 1) and did not receive any treatments. Another subject, randomized to receive placebo treatment in cycle 2, dropped out of the study during cycle 2 due to an adverse event (acute bronchitis) and was not exposed to dexloxiglumide. The mean age of 25 subjects who started cycle 2 was 25.3 years (range, 19-45 years), mean weight was 65.0 kg (range, 49-93 kg), and mean height was 166.8 cm (range, 154.9-175.3 cm).

Pharmacokinetics

Comparable ethinyl estradiol plasma concentration-time profiles were observed following repeated admin-

Table I Pharmacokinetic Parameters (Mean \pm SD) of Ethinyl Estradiol After Coadministration of Oral Contraceptive With Dexloxiglumide or Placebo in Healthy Young Female Subjects

Parameter	OC + Dexloxiglumide/OC + Placebo			
	OC + Placebo	OC + Dexloxiglumide	Geometric Mean Ratio	90% CI or P Value
C_{\max} , pg/mL	173 \pm 53	197 \pm 59	1.15	1.09-1.20
$AUC_{0-24\text{ h}}$, pg•h/mL	1314 \pm 357	1600 \pm 456	1.21	1.17-1.26
t_{\max} , h	1.2 \pm 0.4	1.3 \pm 0.6	1.08 ^a	.188 ^b
	1.0 (0.75-2.0) ^c	1.0 (0.75-3.0) ^c		

OC, oral contraceptive; CI, confidence interval.

a. Ratio of arithmetic means.

b. Based on nonparametric Wilcoxon signed-rank test for the matched pairs.

c. Median (range).

istration of 200 mg dexloxiglumide or placebo with OCs in healthy young female subjects (Figure 2). The average (\pm SD) EE peak plasma concentration following administration of OC with dexloxiglumide was 197 \pm 59 pg/mL compared to 173 \pm 53 pg/mL after administration of OC in the presence of placebo (Table I). The mean (\pm SD) $AUC_{0-24\text{ h}}$ for EE was 1600 \pm 456 pg•h/mL in the presence of dexloxiglumide compared to 1314 \pm 357 pg•h/mL in the presence of placebo. The EE geometric mean ratio of C_{\max} for EE was estimated to be 1.15 with a 90% confidence interval of 1.09 to 1.20, whereas the ratio of $AUC_{0-24\text{ h}}$ was 1.21 with a confidence interval of 1.17 to 1.26 (Table I). These data indicated that, on average, nearly equivalent exposure of EE was observed following chronic administration of OC in the presence and absence of dexloxiglumide. The mean EE t_{\max} values were 1.3 and 1.2 hours for the OC/dexloxiglumide and OC/placebo treatments, respectively, and no significant difference between the treatments was evident ($P = .19$).

Following once-daily dosing of Ortho Tri-Cyclen containing EE (0.035 mg) and NE (0.180-0.250 mg) for 21 days, plasma concentrations of norgestimate were below the limit of quantitation within 2 hours after the morning dose on day 21, which is in line with the known literature on norgestimate dosing.¹⁴ However, a major serum metabolite of norgestimate, 17-DNE, appeared in the plasma rapidly, with concentrations greatly exceeding those of norgestimate. The 17-deacetylated metabolite is pharmacologically active, and the pharmacologic profile is similar to that of norgestimate.¹⁴ Therefore, pharmacokinetic parameters of 17-DNE were calculated and used instead of NE pharmacokinetic parameters because 17-DNE concentrations were representative of NE concentrations.

Average plasma concentration-time profiles of 17-DNE after coadministration of OC with either multiple-dose 200-mg dexloxiglumide or placebo were compa-

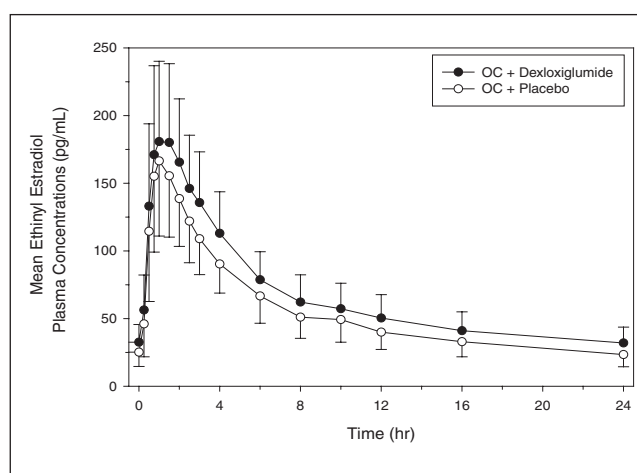


Figure 2. Mean (\pm SD) ethinyl estradiol plasma concentrations after administration of placebo or dexloxiglumide in the presence of oral contraceptive (OC) treatment in healthy female subjects.

table in healthy young female subjects (Figure 3). The average (\pm SD) 17-DNE peak plasma concentration following administration of OC with dexloxiglumide was 2.08 \pm 0.44 ng/mL compared to 2.23 \pm 0.42 pg/mL after administration of OC in the presence of placebo (Table II). The mean (\pm SD) $AUC_{0-24\text{ h}}$ for 17-DNE was 15.62 \pm 3.72 ng•h/mL in the presence of dexloxiglumide compared to 16.96 \pm 3.82 ng•h/mL in the presence of placebo. The 17-DNE C_{\max} geometric mean ratio was estimated to be 0.93 with a 90% confidence interval of 0.90 to 0.96, whereas the 17-DNE $AUC_{0-24\text{ h}}$ ratio was 0.92 with a confidence interval of 0.89 to 0.95, with both confidence intervals within the target interval of 0.80 to 1.25 for equivalent exposure (Table II). The mean 17-DNE t_{\max} values were 1.4 and 1.3 hours for the OC/dexloxiglumide and OC/placebo treatments, respectively, and no significant difference between the treatments was evident ($P = .64$).

Table II Pharmacokinetic Parameters (Mean \pm SD) of 17-Deacetyl Norgestimate After Coadministration of Oral Contraceptive With Dexloxiglumide or Placebo in Healthy Young Female Subjects

Parameter	OC + Dexloxiglumide/OC + Placebo			90% CI or P Value
	OC + Placebo	OC + Dexloxiglumide	Geometric Mean Ratio	
C_{max} , pg/mL 0.90-0.96	2233 \pm 423		2080 \pm 438	0.93
AUC _{0-24 h} , pg•h/mL 0.89-0.95	16 961 \pm 3821		15 615 \pm 3724	0.92
t_{max} , h .639 ^b	1.3 \pm 0.4		1.4 \pm 0.5	1.07 ^a
	1.5 (0.75-2.0) ^c	1.5 (0.75-2.5) ^c		

OC, oral contraceptive; CI, confidence interval.

Ethinyl estradiol and 17-DNE attained steady state by day 21, as trough plasma levels obtained prior to dosing on days 19 through 21 were found to be relatively constant over the 3-day period (Figure 4), as observed in other similar studies.^{17,18} Although plasma concentrations of dexloxiglumide were not determined in this study, steady state was expected to have been achieved by day 21 following tid dosing for the previous 4 days, considering the half-life for dexloxiglumide to be around 8 hours.

Clinical Safety

There were no serious adverse events reported during this study. One subject dropped out of the study due to an adverse event (acute bronchitis) during cycle 2 after receiving placebo treatment and was not exposed to dexloxiglumide. Although adverse event data were collected for all 3 cycles of the study, only those adverse events that were recorded during cycles 2 and 3 were considered as treatment-emergent adverse events. Nineteen subjects reported at least 1 treatment-emergent adverse event during the course of the study. There were a total of 43 adverse events reported for the duration of the study (in cycles 2 and 3), out of which 40 were considered mild in severity, whereas 3 events (acute bronchitis and 2 incidences of headache) were considered moderate in severity. Overall, the proportion of subjects reporting at least 1 adverse experience in the dexloxiglumide plus oral contraceptive group (50%) was similar to that reported in the placebo plus oral contraceptive group (56%). Thirst (reported a total of 6 times by 6 different subjects) and headache (reported a total of 5 times by 5 different subjects, all in the placebo-treated group) were the most common complaints. All reported adverse events were transient.

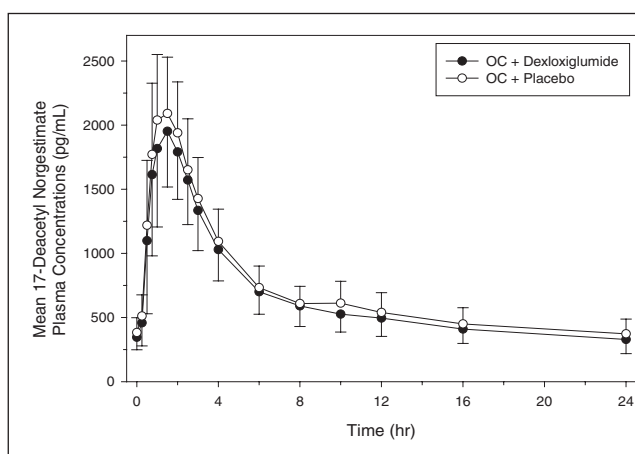


Figure 3. Mean (\pm SD) 17-deacetyl norgestimate plasma concentrations after administration of placebo or dexloxiglumide in the presence of oral contraceptive (OC) treatment in healthy female subjects.

Concomitant administration of dexloxiglumide with oral contraceptives did not change the adverse event profile as compared to administration of placebo with oral contraceptives. There were no clinically relevant changes observed for electrocardiograms or vital signs, and there were no clinically important trends noted in the laboratory findings during the study.

DISCUSSION

Ethinyl estradiol is extensively metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.¹⁴ One of the major pathways of ethinyl estradiol metabolism involves 2-hydroxylation by the CYP3A4 enzyme. Therefore, the pharmacokinetics of EE can be altered as a result of induction and inhibition of CYP3A4. Extensive literature^{15,19} describes drug in-

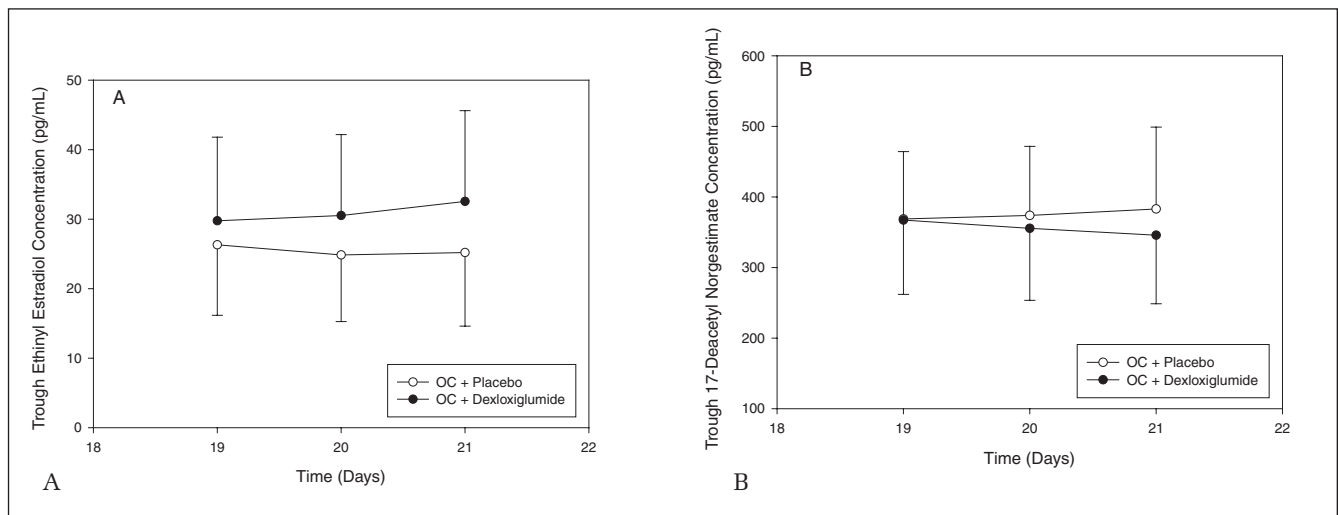


Figure 4. Mean (\pm SD) trough plasma concentrations of (A) ethinyl estradiol and (B) 17-deacetyl norgestimate to show attainment of steady state by day 21. OC, oral contraceptive.

teractions with oral contraceptives; a number of them are related to loss of effectiveness of oral contraceptives, causing breakthrough bleeding and unplanned pregnancy. This effect is often due to interference with EE exposure as a result of enhanced metabolism by the CYP3A4 isozyme. On the other hand, due to the availability of multiple alternative metabolic routes for ethinyl estradiol, inhibition of CYP3A4 is less likely to produce an increase in ethinyl estradiol exposure, causing enhancement of the contraceptive efficacy. Potent inducers of CYP3A4 such as rifampin have been associated with contraceptive failure, in which EE AUCs were decreased by 40% to 50%.^{15,20} The present study was carried out to investigate that EE systemic exposure was not lower after dexloxiglumide administration, which is often associated with contraceptive failure. As expected, the results from this study demonstrated a lack of induction potential of dexloxiglumide toward EE metabolizing enzymes such as CYP3A4. Instead, the data demonstrated a marginal increase in C_{max} and $AUC_{0-24 h}$ of EE, indicating a weak inhibitory effect on EE metabolism. The confidence intervals for both EE C_{max} and $AUC_{0-24 h}$ do not include unity, implying that small increases of 15% and 21% in the rate and extent of EE absorption may occur with the coadministration of dexloxiglumide. No observed change in the short-term safety profile in the presence of dexloxiglumide compared to placebo in this group of young healthy women provided assurance that this change in EE exposure is unlikely to be of clinical significance.

In contrast to EE, 17-DNE average C_{max} and $AUC_{0-24 h}$ both decreased in the presence of repeated administration of dexloxiglumide by 7% and 8%, reporting confidence intervals that did not include unity but within the 0.80 to 1.25 bioequivalence criterion. This indicates lack of a clinically significant interaction, despite a slight numerical trend toward a decrease in 17-DNE systemic exposure.

In conclusion, concurrent administration of multiple-dose 200-mg dexloxiglumide tablets with combination OC such as Ortho Tri-Cyclen was not associated with clinically relevant alterations in the plasma concentrations of the OC components EE and NE/17-DNE. Any change in the safety and efficacy of the contraceptive regimen as they relate to systemic exposure is therefore not anticipated.

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