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A new paradigm for low-dose oral contraception

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Cycle control, safety and efficacy of a 24-day regimen of gestodene 60 µg/ethinylestradiol 15 µg and a 21-day regimen of desogestrel 150 µg/ethinylestradiol 20 µg

Gestodene Study Group 324

ABSTRACT

Objective This multicenter, open-label study was conducted to compare the cycle control, efficacy and safety of a 24-day regimen of a new ultra-low-dose oral contraceptive containing gestodene (GTD) 60 µg/ethinylestradiol (EE) 15 µg and a 21-day regimen of desogestrel (DSG) 150 µg/EE 20 µg.

Methods Healthy women at least 18 years of age who had had regular menstrual cycles for the prior 3 months were randomly assigned to treatment for six cycles.

Results Data from 1074 women were included in the analyses. Overall, 65% of cycles were normal with GTD/EE and 78% with DSG/EE. The overall incidence of breakthrough bleeding and/or spotting was 29% with GTD/EE and 20% with DSG/EE, with absence of bleeding occurring in 6% of cycles in the GTD/EE group and 1% of cycles in the DSG/EE group. The GTD/EE group had a significantly shorter length of bleeding episodes (4 vs. 5 days, $p < 0.001$), a significantly lower intensity of bleeding ($p < 0.01$) and a significantly shorter time for onset of withdrawal bleeding than the DSG/EE group ($p < 0.001$). Safety profiles for the two treatment groups were similar. Significantly more subjects in the DSG/EE group withdrew because of breast pain ($p = 0.03$) and nausea or vomiting ($p = 0.05$). One pregnancy occurred in each treatment group.

Conclusions The 24-day regimen of GTD 60 µg/EE 15 µg provided good efficacy, acceptable cycle control and a favorable safety profile compared with DSG/EE. This ultra-low-dose formulation offers unique advantages in efficacy and safety for oral contraception.

KEY WORDS Oral contraceptives, Desogestrel, Gestodene, Ethinylestradiol

INTRODUCTION

Oral contraceptive (OC) development has focused on lowering both estrogen and progestogen doses over the past 30 years in an effort to reduce the risk of complications, while maintaining contraceptive efficacy[1]. Low-dose OC products containing gestodene (GTD) 75 µg plus ethinylestradiol (EE) 30 µg or 20 µg have been shown to provide effective contraception with favorable cycle control and a low incidence of side-effects[2].

In an effort to improve safety and tolerability further while maintaining efficacy, an ultra-low-dose formulation of GTD 60 µg and EE 15 µg has been

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developed with a 24-day regimen of active pills and 4 days of placebo. To ensure that efficacy was maintained at this lower dose, the number of active pill days was increased from 21 to 24, thereby shortening the placebo period, when most 'escape' ovulations develop. The objective of this study was to compare the cycle control, safety and efficacy of this 24-day regimen of GTD 60 µg and EE 15 µg with those of a 21-day regimen of a currently marketed product that contains desogestrel (DSG) 150 µg and EE 20 µg (Mercilon®).

METHODS

This multicenter, open-label, randomized, comparative study was conducted at 61 sites in Europe (Belgium, France, Italy, the Netherlands and Switzerland). The study was conducted in accordance with the provisions of the Declaration of Helsinki and its amendments. The study protocol was approved by appropriate ethics committees, and written informed consent was obtained from all subjects before enrolment.

Subjects

Healthy women, at least 18 years old, were eligible if they had had regular menstrual cycles (21 to 35 days) for the 3 preceding months. Women who had recently had an abortion or given birth and were not breast-feeding were eligible if they had had at least one normal cycle before the start of study medication. There was no upper age limit for women who smoked fewer than ten cigarettes per day, but women who smoked ten or more cigarettes per day were enrolled only if they were younger than 36 years of age.

Subjects were excluded from the study if there was a history or presence of any thromboembolic or clotting disorder, cardiovascular or cerebrovascular disease, malignancy, or any other medical condition that could interfere with the conduct of the study. Also excluded were women with known or suspected pregnancy. In addition, women were ineligible for enrolment if they were breast-feeding or had a positive Papanicolaou (Pap) test result. Women who used any other estrogens, progestins, or androgens, or other forms of contraception except as recommended in the study or any other concomitant medications that could interfere with study assessments were also ineligible for enrolment.

Drug administration

Women were randomly assigned to either GTD/EE from days 1 to 24 followed by placebo pills for 4 days, or DSG/EE from days 1 to 21 followed by a 7-day pill-free interval. Treatment was continued for six cycles. GTD/EE and DSG/EE were dispensed in 28-day and 21-day blister packs, respectively. All women began taking study medication on the first day of menses at cycle 1. In case of a missed active pill less than 12 h late, women were told to take the missed pill at once, continue taking the remaining pills at the usual time on subsequent days, and start the next blister pack as normally indicated. If one or more pills were missed for more than 12 h, women were told to take the last missed pill at once, and additional contraception (barriers or spermicides) was recommended for the remainder of the cycle.

Study assessments

Complete medical, obstetric and gynecological histories were obtained at the prestudy screening visit. Complete physical and gynecological examinations were conducted during the prestudy screening and at the post-treatment visit. Clinical laboratory determinations were obtained under fasting conditions between days 15 and 24 of the prestudy screening cycle and cycle 6. Cervical cytological smears (Papanicolaou or Bethesda system) were obtained at prestudy screening and post-treatment. A serum or urine β-human chorionic gonadotropin pregnancy test was performed within 15 days before the start of study medication. Sitting systolic and diastolic blood pressures and body weight were measured at the prestudy screening, baseline, cycle 3 and post-treatment evaluations.

Cycle-control analysis was performed to assess menstrual pattern irregularities and cycle characteristics for the description of withdrawal bleeding. Cycles were excluded from analysis if three consecutive pills were missed, or five or more pills were missed at any time during the cycle. Also excluded were cycles that were started 3 or more days early. Bleeding episodes were reported on diary cards. Cycles were classified as normal, as having breakthrough bleeding/spotting, or as having no bleeding during the entire cycle. Analysis of cycle control characteristics also included determination of cycle length and the withdrawal bleeding episode

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length, mean intensity and latent period. Spotting was defined as very slight bleeding that required no sanitary protection, whereas breakthrough bleeding required sanitary protection. A cycle was classified as 'normal' if withdrawal bleeding started during the 7-day period after the last day of active pill intake, the withdrawal bleeding did not extend beyond 11 days after the last active pill and the rest of the cycle was without spotting or breakthrough bleeding. A withdrawal bleeding episode was defined as a sequence of one or more days of spotting, breakthrough bleeding or both during the 7-day period after the last day of active pill intake, bounded by 2 consecutive non-bleeding days. Bleeding intensity was rated daily and was classified by use of the following scale: 0 = none, 1 = spotting, 2 = light bleeding, 3 = moderate bleeding and 4 = heavy bleeding.

The safety assessment was based on signs or symptoms detected during physical examinations and clinical evaluations, as well as changes in laboratory and vital sign measurements from prestudy screening or baseline evaluations. Treatment-emergent adverse events were new adverse events, not present at screening, or adverse events present at the prestudy screening that worsened during treatment.

Efficacy was assessed from the total number of pregnancies in each treatment group. The Pearl index was calculated by use of the following formula: total number of pregnancies × 1300/total cycles of exposure. Life-table analysis was carried out to assess the cumulative termination rates between treatments.

Statistical analysis

An intent-to-treat analysis was conducted, which included all subjects who were randomly assigned to treatment and took at least one pill. Bleeding classification was compared between treatment groups at each cycle by the Mantel–Haenszel test. Cycle-control characteristics were compared at each cycle by an analysis of variance (ANOVA) with treatment, investigator and treatment by investigator as factors in the model. The 95% confidence intervals were also calculated. Fisher's exact test was used for comparisons of treatment groups with respect to the incidence of adverse events. For routine laboratory data, vital signs and body weight, comparisons between treatment groups were performed by analysis of covariance (ANCOVA) with treatment, investigator and treatment by investigator as factors and the screening value as covariate. Within-group changes from screening were assessed by use of a paired *t* test. All statistical tests were two-sided at an alpha level of 0.05.

RESULTS

Study population

A total of 1074 women were randomly assigned to treatment and took at least one dose of study medication (539 GTD/EE subjects and 535 DSG/EE subjects). All subjects were included in efficacy and safety analyses. At baseline, the two groups were comparable with regard to demographic and clinical characteristics (Table 1). There were no clinically important differences between the two treatment groups in menstrual and obstetrical history or gynecological examination findings. A total of 475 subjects (88%) in the GTD/EE group and 484 subjects (90%) in the

Table 1 Baseline demographic and clinical characteristics of the study population

Characteristic	*GTD/EE* (*n* = 539)	*DSG/EE* (*n* = 535)
Age (years)		
Mean (SD)	27.6 (6.7)	27.4 (6.6)
Range	16–50	17–47
Weight (kg)		
Mean (SD)	60.3 (10.5)	59.7 (9.6)*
Range	40.4–108.4	40.0–108.0
Body mass index (kg/m²)*		
Mean (SD)	21.9 (3.2)	21.9 (3.2)
Contraceptive status (*n*)		
Switcher	345 (64%)	325 (61%)
Recent user	25 (5%)	25 (5%)
Former user	109 (20%)	106 (20%)
New user	60 (11%)	79 (15%)
Cigarette smoker (*n*)	189 (35%)	194 (36%)
Cigarettes/day		
Mean (SD)	9.4 (6.1)	9.2 (5.4)
Range	1–30	1–25

GTD, gestodene; EE, ethinylestradiol; DSG, desogestrel; SD, standard deviation; *body mass index was unknown for one subject in each group

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Table 2 Reasons for premature discontinuation

	GTD/EE (n = 539)		DSG/EE (n = 535)	
Reason	n	%	n	%
Subject request	6	1	11	2
Other medical event	30	6	18	3
Lost to follow-up	8	1	12	2
Protocol violation	9	2	5	1
Other*	11	2	5	1
Total withdrawn	64	12	51	10

GTD, gestodene; EE, ethinylestradiol; DSG, desogestrel; *included pregnancy, desire for pregnancy, investigator choice, release from study, terminated by sponsor

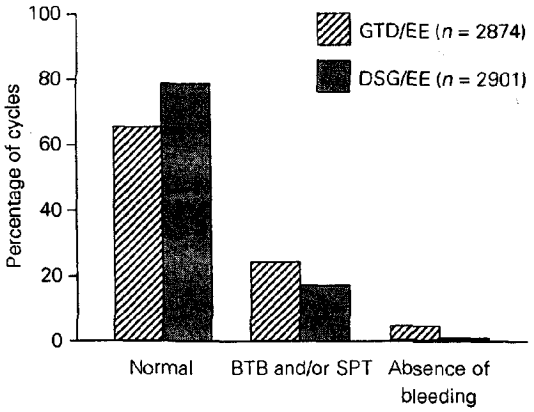

Figure 1 Bleeding classification in percentage of total number of cycles. BTB, breakthrough bleeding; SPT, spotting; GTD, gestodene; EE, ethinylestradiol; DSG, desogestrel

DSG/EE group completed six cycles of treatment. Sixty-four (12%) women in the GTD/EE group and 51 (10%) women in the DSG/EE group were withdrawn prematurely, most commonly because of a medical event (Table 2).

During the study, there was no significant difference between treatment groups in the number of subjects who took some form of concomitant therapy. The number of subjects in the DSG/EE group (36 subjects) who used additional methods of contraception was significantly ($p = 0.045$) greater than in the GTD/EE group (22 subjects). Overall, there were 349 (12%) cycles of GTD/EE and 346 (11%) cycles of DSG/EE in which subjects missed at least one pill. A total of 61 subjects failed to take three or more pills: 31 (6%) subjects in the GTD/EE group and 30 (6%) subjects in the DSG/EE group.

Efficacy

One pregnancy occurred in each treatment group. The pregnancy in the GTD/EE group occurred during cycle 6 after five non-consecutive pills were missed during cycle 5. The pregnancy in the DSG/EE group occurred post-treatment. The cumulative termination rate for accidental pregnancy was 0.004 for GTD/EE and 0 for DSG/EE. The cumulative termination rates per woman were 0.339 for GTD/EE and 0.308 for DSG/EE; no significant differences were noted between treatments. The Pearl index was 0.44 for GTD/EE and 0 for DSG/EE.

Cycle control

The cycle-control analysis was based on 2874 cycles of GTD/EE (157 were excluded) and 2901 of DSG/EE use (118 cycles were excluded). Overall, the total percentage of normal cycles was lower in the GTD/EE group (65%) than in the DSG/EE group (78%; Figure 1). The proportion of normal cycles increased from 56% at cycle 1 to 70% at cycle 6 in the GTD/EE group, and from 68% at cycle 1 to 83% at cycle 6 in the DSG/EE group. The incidence of breakthrough bleeding/spotting was higher in the GTD/EE group than in the DSG/EE group. Absence of bleeding was reported in 6% of cycles with GTD/EE and in 1% of cycles with DSG/EE ($p < 0.001$). The incidence of spotting alone was 14% in the GTD/EE group and 11% in the DSG/EE group.

Cycle-descriptive analysis was based on 2611 cycles of GTD/EE (420 cycles excluded) and 2780 cycles of DSG/EE (239 cycles excluded). Withdrawal bleeding episode length and latent period were significantly ($p < 0.001$) reduced with GTD/EE compared with DSG/EE at cycles 1–5 (Figure 2).

Safety

Adverse events were reported by 398 (74%) subjects in the GTD/EE group and 367 (69%) subjects in the DSG/EE group (Table 3), but this difference was not

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