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Bleeding pattern with drospirenone 3 mg+ethinyl estradiol 20 mcg 24/4 combined oral contraceptive compared with desogestrel 150 mcg+ethinyl estradiol 20 mcg 21/7 combined oral contraceptive

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Abstract

Background: The study was conducted to compare cycle control, bleeding pattern and efficacy of two low-dose combined oral contraceptives.

Study Design: Four hundred fifty-three women were randomized to receive a 24/4 regimen of drospirenone 3 mg/ethinyl estradiol 20 mcg (drsp 3 mg/EE 20 mcg; *n*=230) or a 21/7 regimen of desogestrel 150 mcg/EE 20 mcg (DSG 150 mcg/EE 20 mcg; *n*=223), and recorded bleeding daily over 7 treatment cycles.

Results: The duration [mean 4.7 (SD 1.5)–5.2 (SD 2.2) days in the drsp 3 mg/EE 20 mcg 24/4 group and 5.1 (SD 1.5)-5.4 (SD 2.1) days in the DSG 150 mcg/ EE 20 mcg group] and maximum intensity ("normal bleeding" for >50% of all subjects) of scheduled bleeding in Cycles 1–6 was comparable between treatment groups. The incidence of unscheduled bleeding during Cycles 2–6 was also similar between the two groups (drsp 3 mg/EE 20 mcg, 8.8–17.3%; DSG 150 mcg/ EE 20 mcg, 9.4–16.3%).

Conclusion: Drsp 3 mg/EE 20 mcg 24/4 achieved an acceptable bleeding profile with reliable cycle control, comparable with an established formulation.

Keywords: Bleeding pattern; cycle control; Pearl Index; drospirenone; combined oral contraceptive

1. Introduction

Combined oral contraceptives (COCs) are among the most effective reversible forms of contraception available [1,2]. Acceptance of a hormonal contraceptive method depends largely on the degree of cycle control and the side-effects experienced [3]. Concern about estrogen-related adverse effects has led to progressive reductions in the estrogen dose in COCs. However, COCs with low doses of estrogen have previously been associated with more breakthrough bleeding and spotting [4]. Nonetheless, it is generally accepted that women should use COC formulations with the lowest effective hormone dose in order to minimize hormone-related adverse effects.

The type of progestin and dosing regimen may also affect cycle control [5,6]. Drospirenone (drsp) is a novel progestin with a pharmacological profile different from other progestins; in addition to its progestogenic activity, it has both anti-mineralocorticoid and anti-androgenic properties [7]. A new low-dose COC containing drsp 3 mg/ethinyl estradiol (EE) 20 mcg has been developed that comprises a regimen with 24 active pills and 4 inert pills (24/4) regimen. This COC formulation has reliable contraceptive efficacy, a satisfactory safety profile, an acceptable bleeding pattern, and is approved by the FDA for the treatment of the emotional and physical symptoms associated with premenstrual dysphoric disorder [8–10]. Additionally, drsp 3 mg/EE 20 mcg 24/4 has proven benefits in the treatment of acne and has recently been approved by the FDA for the treatment of moderate acne vulgaris in women who desire an OC for birth control [11–14].

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The present study was undertaken to compare the bleeding pattern, cycle control, contraceptive efficacy and safety of drsp 3 mg/EE 20 mcg 24/4 COC regimen with a low-dose 21/7 preparation containing desogestrel (DSG) 150 mcg and EE 20 mcg. Good cycle control, contraceptive reliability and tolerability with the DSG 150 mcg/EE 20 mcg COC has been reported in other studies making this product a good comparison [15,16].

2. Materials and methods

2.1. Study design

This was a randomized, open, parallel group comparison study carried out at 19 study centers in four European countries (six in Austria, five in Finland, five in Lithuania and three in Estonia) between March 2004 and June 2005. The study was conducted in accordance with the Declaration of Helsinki and the International Conference of Harmonization Good Clinical Practice guidelines. Written informed consent was obtained from the study participants prior to enrollment.

2.2. Study population

Healthy women aged 18–35 years were recruited into the study. Smokers over the age of 30 years were precluded due to the age-dependent increased risk of arterial thrombosis among smokers using oral contraceptives. The exclusion criteria were consistent with the accepted contraindications for COC use and included pregnancy, obesity (body mass index >30 kg/m^2), lactation or abortion within the last 3 months before start of treatment; hypersensitivity to any of the study drug ingredients; suspicious cervical smear result within last 6 months prior to start of treatment; use of DSG or drsp-containing COCs or intrauterine device/system within the last cycle before start of treatment; and use of depot contraception within last six cycles before start of treatment.

Women with irregular menstrual cycles, breakthrough bleeding or amenorrhea were not excluded from the study. Moreover, *Chlamydia* screening was not performed; therefore, *Chlamydia* was not included in the exclusion criteria.

2.3. Treatment

Participating subjects were randomized to receive either drsp 3 mg/EE 20 mcg for 24 consecutive days of active treatment followed by 4 days of a daily hormone-free pill (24/4 regimen) or DSG 150 mcg/EE 20 mcg for 21 consecutive days of active treatment followed by a 7-day pill-free period (21/7 regimen) for seven cycles. Computer-generated randomization was performed in blocks balanced for each treatment. The distribution of women to each treatment group was 1:1. Treatment started on the first day of menses for COC starters or scheduled bleeding for switchers.

2.4. Clinical assessments

Subjects were assessed at Visit 1 (initial screening), Visit 2 (admission to treatment and randomization), Visits 3 and 4 (Days 12–19 of the respective cycle) and finally at Visit 5 (10–17 days after last tablet intake). At Visit 1, physical and gynecological examinations (including cervical smear and breast palpation) were performed and medical, surgical and medication history were assessed to ensure study eligibility. At Visit 2, the subjects were assigned their medication and asked to undergo a pregnancy test before first pill intake. Subjects were also given diary cards to record pill intake and intensity of vaginal bleeding. At Visits 3 and 4, completed diary cards and used blister packs were collected and adverse events (AEs) were documented. Vital signs (heart rate and blood pressure) and body weight were assessed at each visit. A final physical and gynecological examination was performed at Visit 5. In order to monitor compliance, the participating women were requested to record tablet intake daily on their diary cards and return all used, partly used, or unused blister packs to the investigator at Visit 5.

The participating women were requested to start their bleeding record with first pill intake at the onset of regular bleeding. Bleeding intensity classifications were defined as follows: none, absence of any vaginal bleeding; spotting, less than associated with normal menstruation relative to the volunteer's experience with no need for sanitary protection (except for panty liners); light, less than associated with normal menstruation relative to the volunteer's experience with need for sanitary protection; normal, like normal menstruation relative to the volunteer's experience; and heavy, more than normal menstruation relative to the volunteer's experience.

2.5. Efficacy assessments

Cycle control, bleeding patterns and unintended pregnancies were the primary variables. For cycle control analysis, time to onset, duration and intensity of scheduled bleeding and unscheduled bleeding episodes were identified. Scheduled bleeding was defined as a bleeding or spotting episode that began during the hormone-free period or started not more than 4 days before the last tablet intake (i.e., not before Day 17 or 20, respectively) in any cycle that continued through into the hormone-free interval. It is possible that scheduled bleeding may start during the hormone-free interval and last until the first few days of the next blister pack of tablets.

All other bleeding episodes besides scheduled bleeding were defined as unscheduled bleeding. Consequently, the bleeding episode at the beginning of the treatment in Cycle 1 was regarded as unscheduled bleeding. A bleeding/spotting episode was defined as a number of days with bleeding/spotting proceeded by at least two bleeding-free days. A bleed-free interval consisted of at least 2 days without bleeding/spotting preceded and followed by at least 1 day of bleeding/spotting.

For bleeding pattern analysis, the mean total number bleeding/spotting days and mean length of all bleeding/spotting episodes were identified. The bleeding pattern was characterized using 90-day reference periods as recom-