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Bleeding pattern and cycle control with an estradiol-based oral contraceptive: a seven-cycle, randomized comparative trial of estradiol valerate/dienogest and ethinyl estradiol/levonorgestrel☆

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Abstract

Background: This study compared the bleeding pattern, cycle control and safety of an oral contraceptive (OC) comprising estradiol valerate/dienogest (E2V/DNG; administered using a dynamic dosing regimen) with a monophasic OC containing ethinyl estradiol 20 mcg/levonorgestrel 100 mcg (EE/LNG). E2V releases estradiol (E2), which is identical to endogenously produced 17β-estradiol.
Study design: This was a randomized, multicenter, double-blind, double-dummy trial lasting seven cycles in healthy women aged 18–50 years.
Results: Overall, 798 women were randomized and received allocated treatment (399 per group). There were significantly fewer bleeding/spotting days reported by women who received E2V/DNG than those who received EE/LNG [17.3±10.4 vs. 21.5±8.6, respectively, p<.0001, Reference Period 1 (Days 1–90); and 13.4±9.vs. 15.9±7.1, respectively, p<.0001, Reference Period 2 (Days 91–180)]. Through Cycles 1–7, the occurrence of scheduled withdrawal bleeding per cycle was 77.7–83.2% with E2V/DNG and 89.5–93.8% with EE/LNG (p<.0001 per cycle). The duration and intensity of scheduled withdrawal bleeding were reduced with E2V/DNG vs. EE/LNG. The incidence of intracyclic bleeding was similar with E2V/DNG (10.5%–18.6%) and EE/LNG (9.9%–17.1%) (p>.05 per cycle). No unintended pregnancies occurred with E2V/DNG, but there was one unintended pregnancy with EE/LNG. Adverse drug reactions occurred in 10.0% and 8.5% of women taking E2V/DNG and EE/LNG, respectively. Overall, 79.4% of women were satisfied with E2V/DNG and 79.9% with EE/LNG.
Conclusions: A novel OC composed of E2V/DNG is associated with an acceptable bleeding profile that is comparable to that of an EE-containing OC.
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Keywords: Hormonal contraception; Cycle control; Bleeding pattern; Estradiol valerate; Dienogest

1. Introduction

Since their introduction in the 1960s, oral contraceptives (OCs) have become a well-accepted and widely used method of contraception. Despite their undoubted popularity, some women experience side effects while taking OCs, including breast tenderness, headache, nausea and altered libido. In addition, epidemiological studies have suggested an association between the use of OCs and an increased risk of arterial and venous thrombotic events [1]. However, these events are very rare and occur at a rate far less than that associated with pregnancy.

In order to improve their tolerability and to broaden the choice for women using OCs as their method of contraception, OCs have undergone considerable development over the past four decades, including reductions in the dose

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of synthetic estrogen [i.e., ethinyl estradiol (EE)] [2–4] and the incorporation of progestins with more favorable clinical profiles [5]. Additional efforts have included the replacement of synthetic estrogens with 17β-estradiol (E2) [6–20].

Although E2-containing OCs have been shown to effectively inhibit ovulation and provide excellent contraceptive efficacy [6–12,15,18–20], monophasic and biphasic regimens have proved unacceptable in terms of cycle control in clinical trials [6,15,18–20], often resulting in higher rates of premature discontinuation compared with preparations containing EE. Problems identified have included prolonged bleeding [20] an increased number of bleeding/spotting days per cycle [15], spotting and breakthrough bleeding [18,19], and menstrual irregularities [6]. Potential reasons for the bleeding irregularities observed with E2-containing OCs have included an inappropriate estrogen/progestin ratio [6,15,18,20] and suboptimal doses of estrogen [6,19].

In order to improve the unacceptable cycle control observed in clinical studies of E2-containing OCs, an innovative OC has been developed in which estradiol valerate (E2V) has been combined with the progestin, dienogest (DNG), using a dynamic dosing regimen (with an estrogen step-down and a progestin step-up). This regimen provides reliable contraceptive efficacy [21,22] and has been shown to be well tolerated [22], with stable serum E2 levels maintained throughout the cycle [23]. E2V releases E2, which is identical to endogenously produced 17β-estradiol; 1 mg of E2V is equivalent to 0.76 mg of E2, based on molecular weight.

The current study was carried out to compare the bleeding pattern, cycle control and safety of a dynamic dosing regimen of E2V/DNG with that of a monophasic regimen of EE/levonorgestrel (LNG).

2. Materials and methods

2.1. Study design

This was a multicenter, double-blind, double-dummy, randomized study conducted in 34 centers in Germany, the Czech Republic and France, between March 2005 and September 2006 (Protocol No. 304004; ClinicalTrials.gov identifier NCT00185367). The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization-Good Clinical Practice. The study protocol was approved by the local ethics committees in Germany, the Czech Republic and France. Written informed consent was obtained from all study participants prior to entry into the study.

2.2. Study population

Healthy women aged 18–50 years seeking contraception participated in the study. Cigarette consumption of up to 10 per day was permitted in women aged 18–30 years, while women aged >30 years were required to be nonsmokers. The exclusion criteria for this study were consistent with the contraindications and special warnings and precautions for OC use and included the following: pregnancy; lactation; occurrence of <3 menstrual cycles following childbirth, abortion or lactation; current use of an intrauterine device; obesity (body mass index >30 kg/m^2); use of long-acting progestins within 6 months prior to study entry; hypersensitivity to any of the study drug ingredients and known or suspected malignant or premalignant disease. At the beginning of the study, women switching from another OC were to continue OC use until the end of the current cycle pack after randomization. In all other instances, the use of additional sex steroids was prohibited. Normal menstrual cycles were not an inclusion requirement.

2.3. Study treatment

Women were randomized in a 1:1 ratio to receive 28 days of E2V/DNG administered using a dynamic dosing regimen (E2V 3 mg on Days 1–2, E2V 2 mg/DNG 2 mg on Days 3–7, E2V 2 mg/DNG 3 mg on Days 8–24, E2V 1 mg on Days 25–26 and placebo on days 27–28) or EE/LNG (EE 20 mcg/LNG 100 mcg on Days 1–21 and placebo on Days 22–28). Treatment was for seven cycles. Randomization was achieved by means of a computer-generated randomization list using randomization blocks of four.

Treatment started on the first day of menses for new starters or on the first day of withdrawal bleeding for those switching from another combined OC. Women were instructed to take their tablets at the same time each day, and to take any missed tablets as soon as remembered, with the latest being at next administration time (i.e., up to 2 tablets at the same time). If more than one tablet was missed, only the most recently missed tablet (the tablet from the preceding day) was to be taken as soon as remembered. Any remaining tablets in the pack were to be continued and taken at the usual time. If the intake delay was less than 12 h, contraceptive protection was not reduced and no further action was required. If the intake delay was more than 12 h, depending on the cycle day on which the tablets were missed, a nonhormonal method of back-up contraception had to be used.

2.4. Study assessments

Study participants were assessed at screening (Visit 1), baseline (Visit 2), during treatment (Weeks 15–16; Visit 3) and at a final examination (Weeks 29–30 or at premature discontinuation; Visit 4). Throughout treatment, women were required to complete daily diary cards designed to record tablet intake and bleeding events.

2.4.1. Efficacy assessments

The primary efficacy outcomes were bleeding pattern and cycle control parameters.

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