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Original research article

Bleeding pattern and cycle control of a low-dose transdermal contraceptive patch compared with a combined oral contraceptive: a randomized study☆,☆☆,★

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Abstract

Objective(s): The aim of this study was to investigate the bleeding pattern and cycle control of a contraceptive patch containing 0.55 mg ethinyl estradiol (EE) and 2.1 mg gestodene (GSD) compared with a combined oral contraceptive (COC) containing 0.02 mg EE and 0.1 mg levonorgestrel (LNG).

Study design: In this phase III, randomized, controlled, double-blind, double-dummy, multicenter trial, healthy women aged 18–45 years (smokers aged 18–35 years) received either the EE/GSD patch and a placebo tablet (n=171), or a placebo patch and the COC (n=175) for seven 28-day cycles. Bleeding control was assessed in two 90-day reference periods.

Results: Mean number of bleeding/spotting days was comparable across treatment groups in both reference periods (p>.05). Mean number of bleeding/spotting episodes was also comparable in reference period 1; however, there were fewer bleeding/spotting episodes for COC in reference period 2 (3.4 versus 3.1; p=.01). Mean length of bleeding/spotting episodes was comparable across treatment groups for both reference periods (p>.05). Withdrawal bleeding occurred consistently in both groups over the entire treatment period, but its absence was more common in the COC group in cycles 4 and 6 of reference period 2 (p<.01). Intracyclic bleeding was comparable between groups.

Conclusion(s): Bleeding pattern and cycle control with the EE/GSD patch was comparable to an EE/LNG-containing COC.

Implications statement: The findings suggest that bleeding patterns with the EE/GSD patch are similar to an EE/LNG-containing COC, except for absence of withdrawal bleeding, which was less common in patch users. The EE/GSD patch may constitute an additional contraceptive option for women.

Keywords: Transdermal; Female contraception; Contraceptive patch; Bleeding pattern; Cycle control

1. Introduction

Daily use of oral contraceptives is the most common means of female contraception in the developed world [1]; however, poor compliance has been reported due to the daily dosing schedule [2]. Further issues with this method of contraception include low bioavailability of ethinyl estradiol (EE; 38–48%) [3], the tendency for serum concentrations of estrogens and progestins to fluctuate widely [4], and large intra- and interindividual pharmacokinetic variations of serum hormone levels due to oral administration [5].

In comparison with oral contraceptives, data from transdermal contraceptive patch technology suggest effective drug

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absorption and delivery of relatively constant serum hormone concentrations [4,6]. The need to apply three transdermal patches (rather than taking 21 tablets) per cycle may be beneficial in terms of perceived convenience and compliance [7].

Both EE and gestodene (GSD) are effectively absorbed into the systemic circulation through the skin and are therefore suitable hormones for use in transdermal contraceptives [4,8]. The use of both hormones in combined oral contraceptives (COCs) is well documented, with EE being the most potent estrogen agonist currently available [9] and GSD being a well-researched progestin with an established safety and efficacy profile, and more than two decades of use in Europe [10–12]. An additional advantage of GSD is the low absolute dose required for contraceptive efficacy [13], which allows for a small patch size.

A problem associated with hormonal contraceptives is unscheduled and prolonged uterine bleeding – one of the often-cited reasons that women stop using these agents [14]; thus, studies evaluating their effect on bleeding patterns and cycle control can provide clinically useful data for any new hormonal contraceptive.

An additional transdermal option – a once-a-week contraceptive patch – has been developed with transparent, transdermal technology delivering low doses of EE and GSD. This patch provides the same systemic exposure as observed after oral administration of a COC containing 0.02 mg EE and 0.06 mg GSD, based on an analysis of relative bioavailability [15]. The primary objective of the present study was to investigate, and reliably describe, the bleeding pattern and cycle control parameters of the EE/GSD patch in comparison with a COC containing EE and levonorgestrel (LNG).

2. Materials and methods

2.1. Study design

This was a phase IIIa, double-blind, double-dummy, randomized, controlled, parallel-group, multicenter trial conducted at 28 centers in the United States. The main objective was to investigate the bleeding pattern and cycle control parameters of a patch containing 0.55 mg EE and 2.1 mg GSD in comparison with a COC containing 0.02 mg EE and 0.1 mg LNG. Additional objectives of the study were to investigate the contraceptive efficacy and safety profile of the EE/GSD patch. Compliance and subjective user assessments were also evaluated.

The conduct of this clinical study met all local legal and regulatory requirements in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization Guideline E6: Good Clinical Practice. The protocol was reviewed and approved by each study site's internal ethics committee or review board, and written informed consent was obtained from each participant before the start of the study.

2.2. Study population

Participants were healthy women, 18–45 years of age (18–35 years, if smokers), who were seeking contraception. When asked about contraceptive use in the 28 days prior to screening, 50.0% of women (n=173) reported having used hormonal contraception, 36.1% (n=125) had used barrier methods, 12.7% (n=44) had not used contraception, and 1.2% (n=4) had used 'other' methods, for example, vasectomy. Percentages were similar in both groups. Key exclusion criteria included pregnancy and lactation (fewer than three menstrual cycles since delivery or abortion, or cessation of lactation); any disease or condition that could affect the pharmacokinetics of the study drug or worsen during hormonal treatment; undiagnosed abnormal genital bleeding; abuse of alcohol, drugs, or medicines; and medical contraindications to hormonal contraception. Women with a presence or history of venous or arterial thrombotic/thromboembolic events (e.g., deep venous thrombosis, pulmonary embolism, myocardial infarction), or conditions that could increase their risk (e.g., hereditary predisposition), were also excluded. No participant was excluded on the basis of body mass index (BMI). At the suggestion of the FDA, at least a third of the women should not have been using hormonal contraceptives within 3 months before their study start date to eliminate any carryover effect.

2.3. Study treatment

Women were randomized (1:1) to one of two parallel groups, receiving either the EE/GSD patch and a placebo tablet, or the COC tablet and a placebo patch. For each of the seven 28-day cycles, all women applied one patch (either the EE/GSD patch or a placebo) on days 1, 8, and 15 to the outer upper arm, abdomen, or buttocks. The third patch was removed on day 22, and no patch was worn on days 23–28. In parallel, all women also took one tablet daily (either the placebo tablet or the COC tablet) for 21 days at the same time of the day (±2 h), followed by a 7-day, tablet-free interval. The application of the patch and ingestion of the tablet were to occur at the same time.

If a patch was detached for less than 24 h, the patch was to be reapplied; if no longer adhesive, a replacement patch was to be applied. In either case, the patch was to be worn until the next scheduled change. If a patch became detached for 24 h or more, or the participant was unsure about how long the patch was detached, they were to restart the current cycle by applying a new patch. Restarting meant the application of three patches during the subsequent 3 consecutive weeks followed by a 7-day, patch-free interval.

The study included a screening visit, admission visit, treatment visits and final visit. Study visits took place during treatment cycles 3 and 7, with the final examination after cycle 7. Self-reported outcome measures, assessed using diary cards, were the primary method of evaluating bleeding pattern, cycle control, and compliance.