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Original research article

A comparison of bleeding patterns and cycle control using two transdermal contraceptive systems: a multicenter, open-label, randomized study☆,☆☆,★,★★

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Abstract

Objective(s): To investigate the bleeding pattern and cycle control parameters of a contraceptive patch containing 0.55 mg ethinyl estradiol (EE) and 2.1 mg gestodene (GSD) compared with a patch containing 0.6 mg EE and 6 mg norelgestromin (NGMN).
Study design: In this phase III, open-label, randomized, parallel-group trial, healthy women aged 18–35 years (smokers aged 18–30 years) received either the EE/GSD patch (n=200) or the EE/NGMN patch (n=198). Treatment consisted of one patch per week for 3 weeks followed by a 7-day, patch-free interval for seven cycles. Bleeding control was assessed in two 90-day reference periods.
Results: In reference period 1, mean number of bleeding/spotting days was comparable across treatment groups ($p>0.05$). However, in reference period 2, there were fewer bleeding/spotting days in the EE/GSD patch group (15.7 versus 18.4; $p<0.0001$). Mean number of bleeding/spotting episodes was comparable across groups for both reference periods, but bleeding/spotting episodes were shorter for the EE/GSD patch than the EE/NGMN patch during reference period 1 (5.13 days versus 5.53 days, respectively; $p<0.05$) and reference period 2 (5.07 versus 5.66; $p=0.0001$). Both treatment groups showed a similar frequency of withdrawal bleeding episodes; however, across all seven cycles, the length of these episodes was consistently shorter with the EE/GSD patch ($p<0.01$). There were no notable treatment differences in intracyclic bleeding.
Conclusion(s): Bleeding pattern and cycle control achieved with the EE/GSD patch was similar to that of the EE/NGMN patch.
Implications statement: The paper presents data on the bleeding pattern and cycle control parameters of an investigational transdermal contraceptive patch containing EE and GSD compared with an approved contraceptive patch containing EE and NGMN. This descriptive study found that bleeding patterns associated with the EE/GSD patch were similar to those of an EE/NGMN patch providing higher EE exposure.

Keywords: Transdermal contraceptive patch; Bleeding pattern; Cycle control; Ethinyl estradiol; Gestodene; Tolerability

1. Introduction

Daily oral contraceptives – presently the most common means of contraception in the developed world [1] – are highly effective when used correctly; however, poor compliance is common and can result in greatly reduced efficacy [2]. Moreover, oral contraceptives can be associated with rapid and large fluctuations in serum concentrations [3], large intra- and inter-individual pharmacokinetic variations in serum levels [4], and low bioavailability of ethinyl estradiol (EE; 38–48%) [5]. Transdermal contraceptives afford the user a number of advantages over oral administration of hormones, including

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effective absorption and the provision of relatively constant serum concentrations [3,6].

Both EE and gestodene (GSD) are effectively absorbed into the systemic circulation via the transdermal route and are, therefore, suitable hormones for delivery through the skin for contraceptive purposes [3,7]. The use of EE in combined oral contraceptives (COCs) is well documented, and it is the most potent estrogen agonist currently available [8], while GSD is a well-researched progestin that has established safety and efficacy, with more than two decades of use in the European market for the purposes of birth control [9–11]. An additional advantage of GSD is the low absolute dose required for contraceptive efficacy [12], which allows for a small patch size.

One of the major reasons women discontinue use of hormonal contraceptives is abnormal uterine bleeding [13]. Therefore, it is essential that any new hormonal contraceptive entering the market is evaluated for its effect on both bleeding patterns and cycle control. The primary objective of the present study was to investigate, and reliably describe, these parameters for an investigational, transdermal contraceptive patch containing EE and GSD compared with an approved transdermal contraceptive patch containing EE and norelgestromin (NGMN).

2. Materials and methods

2.1. Study design

This study was a phase IIIa, multicenter, open-label, randomized, parallel-group trial conducted at 24 centers in three countries (Austria, Czech Republic and the Netherlands). The objective was to evaluate the bleeding pattern and cycle control parameters of two transdermal contraceptives: an 11 cm^2 EE/GSD patch (0.55 mg EE/2.1 mg GSD; Bayer Pharma AG, Berlin, Germany) resulting in the same systemic exposure as after oral intake of a COC containing 0.02 mg EE and 0.06 mg GSD [14] and a 20 cm^2 EE/NGMN patch (0.6 mg EE/6.0 mg NGMN; EVRA®, Janssen-Cilag Ltd, High Wycombe, UK) resulting in the same systemic exposure as after oral intake of 0.0339 mg EE and 0.203 mg NGMN [15].

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 aged 18–35 years (18–30 years, if smokers) who were seeking contraception. When asked about contraceptive use in the 28 days prior to screening, 82.2% of women overall (n=327) reported having used hormonal contraception, 7.5% (n=30) had used barrier methods and 10.3% (n=41) had not used contraception; percentages were similar in both treatment groups. Key exclusion criteria included pregnancy (fewer than three menstrual cycles since delivery, abortion or lactation before start of treatment), obesity (BMI > 30.0 kg/m^2), any disease or condition that could affect the pharmacokinetics of the study drug or worsen during hormonal treatment, undiagnosed abnormal genital bleeding, or abuse of alcohol, drugs or medicines. 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.

2.3. Study treatment

There were two parallel groups receiving either the EE/GSD patch or the EE/NGMN patch, and participants were randomized (1:1) into one of these groups by means of an interactive voice response system. Before the start of the study, a computer-generated randomization list was produced, and each random number was assigned to either treatment group using randomization blocks of four.

In each study group, treatment consisted of a 21-day regimen per 28-day cycle (one patch per week for 3 weeks followed by a 7-day, patch-free interval) for seven cycles. Patches were applied to the outer upper arm, abdomen or buttocks. Application site could be changed between cycles, but all three patches within a single cycle were to be applied to a different location within the same general area (i.e. abdomen, buttocks or upper arm). Participants used diaries to record the dates new patches were applied, the application site, application deviations, the reason for patch removal (including complete or partial detachment), the dates they did not wear a patch, and whether back-up contraception was used.

If a patch was detached for less than 24 hours, it 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 hours 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, four treatment visits (two visits during cycle 3 and two visits during cycle 7) and a final visit (after cycle 7, 21–28 days after removal of the last patch). Self-reported outcome measures with diary cards were the primary tool used to assess bleeding pattern and cycle control.

2.4. Study assessments

2.4.1. Efficacy assessments

Bleeding pattern was described in terms of number of bleeding/spotting days and episodes in each of two 90-day