

Investigation of the Hemostatic Effect of a Transdermal Patch Containing 0.55 mg Ethinyl Estradiol and 2.1 mg Gestodene Compared with a Monophasic Oral Contraceptive Containing 0.03 mg Ethinyl Estradiol and 0.15 mg Levonorgestrel: An Open-Label, Randomized, Crossover Study

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Abstract

Background Transdermal delivery of contraceptives offers several advantages over combined oral contraceptives (COCs), including effective absorption and the provision of relatively constant serum concentrations. Ethinyl estradiol (EE) and the progestin gestodene are well-absorbed through the skin and, therefore, well-suited for use in a transdermal contraceptive patch.

Objective The objective of this study was to investigate the impact of a once-weekly transparent, transdermal patch delivering low doses of EE and gestodene equivalent to a COC containing 0.02 mg EE and 0.06 mg gestodene on hemostasis parameters compared with a monophasic COC containing 0.03 mg EE and 0.15 mg levonorgestrel.

Methods In this single-center, open-label, randomized, crossover study, 30 women (aged 18–35 years) received three cycles of each treatment, separated by a two-cycle washout period. The primary outcome measure was the absolute change from baseline in prothrombin fragments 1 + 2 and D-dimer.

Results For both treatments, prothrombin fragments 1 + 2 remained stable during the first treatment period, and increased only slightly in the second period (mean absolute change 0.025 and 0.028 nmol/L in the novel Bayer patch and COC groups, respectively). Increases in D-dimer were

observed in both periods (mean absolute change 107.0 ± 147.2 ng/L for the novel Bayer patch and 113.7 ± 159.0 ng/L for the COC). There were no statistically significant treatment differences in prothrombin 1 + 2 or D-dimer ($p = 0.667$ and $p = 0.884$, respectively) and no statistically significant treatment sequence or period effects.

Conclusion A COC containing 0.03 mg EE and 0.15 mg levonorgestrel and the novel Bayer patch have comparable influence on hemostatic endpoints. Both treatments were well-tolerated by subjects.

1 Introduction

The transdermal application of steroid hormones for systemic use is a well-established method of therapy in postmenopausal women, using patches containing an estrogen alone or in combination with a progestin [1]. Transdermal delivery has also been used effectively for contraception. In Europe, a transdermal contraceptive patch was approved in 2002 that releases ethinyl estradiol (EE) and norelgestromin over the 7-day application period, resulting in systemic exposure comparable to that observed after daily oral administration of a combined oral contraceptive (COC) pill containing 0.034 mg EE and 0.0203 mg norelgestromin [2].¹

More recently, a novel, once-weekly contraceptive patch has been developed with transparent, transdermal technology to deliver low doses of EE and of gestodene that result in the same systemic exposure as observed after oral

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¹ In the USA, a slightly different formulation was approved by the US FDA in November 2001.

administration of a COC containing 0.02 mg EE and 0.06 mg gestodene (Bayer Pharma AG, unpublished data).

While daily oral contraceptives—currently the most common form of contraception used by women in the developed world [3]—are highly efficacious when used correctly, poor compliance is a common problem, and can result in greatly reduced efficacy [4]. Furthermore, oral administration may be associated with rapid and large fluctuations in serum concentrations [5], the bioavailability of EE is low (38–48 %) [6], and the use of COCs can also result in large intra- and inter-individual pharmacokinetic variability in serum levels [7]. Transdermal delivery offers several advantages over the oral administration of hormones, including effective absorption and the provision of relatively constant serum concentrations [5, 8]. These advantages, in conjunction with the convenience of weekly patch application, which may increase compliance, suggest that transdermal hormone delivery may constitute an attractive option for women who previously felt their contraceptive choice was limited.

Both EE and gestodene are hormones that are well-absorbed through the skin. Consequently, they are appropriate for transdermal delivery [5, 8]. At present, EE is the most potent estrogen agonist available [9], and its use in COCs is well-documented. Gestodene is a well-researched progestin, with established efficacy and safety, and has been widely used as a contraceptive agent in Europe for more than 20 years [10–12]. Furthermore, the good skin absorption properties of gestodene [13], and the low absolute dose required for contraceptive efficacy [14], allow for a small patch size (Bayer Pharma AG, unpublished data).

An increased risk of venous thromboembolism (VTE) has been reported with use of COCs. This risk has been attributed predominantly to EE-induced changes in the concentration of coagulatory and fibrinolytic proteins, as well as changes in platelet activity [15]. Using a lower dose of EE may help to ameliorate this risk and reduce the adverse effects associated with the estrogen component of COCs [16]. While there is some evidence that COCs containing lower doses of EE are associated with fewer negative hemostatic effects [17], the role of third-generation progestins constitutes a source of continuing debate. Although there have been attempts to predict VTE risk through the evaluation of changes occurring in the coagulatory system, these surrogate parameters are not generally accepted. However, analysis of these parameters is required by the guidelines for the development of steroidal contraceptives [18]. In general, the effect of third-generation COCs on coagulatory mechanisms appears to be minimal, reflecting a balance between the stimulation of both (pro)coagulant and fibrinolytic factors [19]. Despite

these findings, there are data to suggest that third-generation COCs can have a substantial effect on hemostatic balance, and may result in a prothrombotic state among users. Indeed, there are reports that women using third-generation COCs are significantly less sensitive to activated protein C (APC) than women using second-generation formulations ($p < 0.001$); it could be speculated that these differences may correlate with a higher risk of thrombosis in third-generation COC users [20]. Furthermore, for both third- and second-generation formulations, COC-induced increases in the activity of (pro)coagulatory factors are not always balanced by increased biological levels of coagulation inhibitors [21]. There is some indication that transdermal delivery of hormones may reduce the risk of VTE associated with COC use [22], although the supporting data are limited, and results from clinical trials are conflicting [16, 23–25].

To further investigate the effect of transdermal delivery on hemostatic parameters, we conducted an open-label, randomized, crossover study of the novel Bayer patch in comparison to a monophasic COC containing 0.03 mg EE and 0.15 mg levonorgestrel.

2 Materials and Methods

2.1 Objectives and Study Design

The primary objective of this study was to investigate the impact of the novel Bayer patch (patch size 11 cm²; containing 0.55 mg EE and 2.1 mg gestodene per patch) on hemostasis parameters in a 21-day regimen over a treatment period of three cycles, compared with a standard, monophasic COC containing 0.03 mg EE and 0.15 mg levonorgestrel per tablet (Microgynon[®], Bayer Healthcare AG, Germany). Secondary objectives included assessment of safety, contraceptive efficacy, bleeding pattern, and cycle control.

This was an open-label, randomized, crossover study conducted at a single center in Germany (ClinicalTrials.gov identifier: NCT00933179). The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guideline on Good Clinical Practice, and local laws. The design of the study adheres to the requirements of the European Medicines Agency Committee for Medicinal Products for Human Use guideline on clinical investigation of steroid contraceptives in women (EMEA/CPMP/EWP/519/98 Rev1) [18]. The study protocol was approved by a competent Ethics Committee in Berlin, Germany. Informed consent was obtained from each subject before entry into the study.

2.2 Participants

This study recruited healthy women, 18–35 years of age, who required contraception and who had a normal cervical smear result either at screening or documented in the last 6 months, and a history of regular cyclic menstrual periods. Women were excluded if they were pregnant or lactating, or had fewer than three menstrual cycles since delivery, abortion, or lactation prior to the start of treatment. Other main exclusion criteria included the use of other methods of contraception; undiagnosed abnormal genital bleeding; obesity [body mass index (BMI) >30.0 kg/m²]; known hypersensitivity to any of the study drugs; any disease, condition, or use of medicines that could interfere with the study medication; or any disease or condition that could worsen under hormonal treatment.

2.3 Study Treatment

Subjects were randomized (1:1) into one of two treatment sequences, using a computer-generated randomization list. Treatment sequence A: administration of three cycles of the novel Bayer patch (treatment period 1) followed by two washout cycles and then administration of three cycles of COC (treatment period 2); or treatment sequence B: administration of three cycles of COC (treatment period 1) followed by two washout cycles and then administration of three cycles of the novel Bayer patch (treatment period 2) [Fig. 1].

Treatment with the novel Bayer patch consisted of a 21-day regimen administered as part of each 28-day cycle

(one patch per week for 3 weeks followed by a 7-day, patch-free interval) for three cycles. Each subsequent cycle started immediately after the end of the patch-free interval of the previous cycle and was not triggered by the presence or absence of uterine bleeding. Only one patch was worn at a time and was self-applied by the subject to the outer upper arm, abdomen, or buttocks. Within any given cycle, the three patches were applied to the same application site; subjects were permitted to switch between the left and right side of any chosen application site (e.g., left or right outer upper arms). Application sites could vary from cycle to cycle. For COC use, one tablet was taken daily for 21 consecutive days, with each subsequent pack starting after a 7-day, tablet-free interval. During the washout cycles, subjects were required to use non-hormonal contraception; condoms, spermicide, or diaphragm were permitted, but not the calendar or temperature methods.

2.4 Schedule of Visits

The screening visit (visit 1) was performed within 12 weeks prior to the start of the treatment cycle. Before the start of treatment, two washout cycles (1 and 2) were required. Visit 2 took place during washout cycle 2 (days 15–21). Visit 3 took place during treatment cycle 3 (days 15–21) in treatment period 1. Before the next treatment period, another two washout cycles (3 and 4) were required. Visits 4 and 5 took place during washout cycles 3 and 4 (days 15–21), respectively. Visit 6 took place during treatment cycle 6 (days 15–21) in treatment period 2. A follow-up visit took place 21–28 days after the removal of

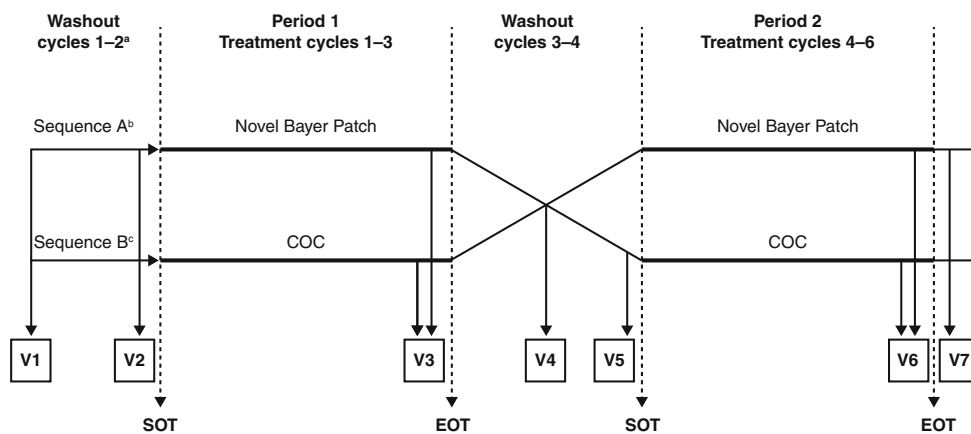


Fig. 1 Study overview. ^a If the subject is a hormonal contraceptive starter (i.e., has not used hormonal contraceptives for a period of 3 months before starting the study), no washout period was necessary; ^b Treatment sequence A: novel Bayer patch containing 0.55 mg EE and 2.1 mg GSD in period 1, COC containing 0.03 mg EE and 0.15 mg LNG in period 2; ^c Treatment sequence B: COC containing 0.03 mg EE and 0.15 mg LNG in period 1, novel Bayer patch containing 0.55 mg EE and 2.1 mg GSD in period 2. COC combined oral

contraceptive, EE ethinyl estradiol, EOT end of treatment, GSD gestodene, LNG levonorgestrel, SOT start of treatment (on the first day of bleeding), V1 screening visit, V2 baseline–washout cycle 2 (days 15–21), V3 treatment period 1–treatment cycle 3 (days 15–21), V4 washout cycle 3 (days 15–21), V5 washout cycle 4 (days 15–21) or baseline for treatment period 2, V6 treatment period 2–treatment cycle 6 (days 15–21), V7 up to 2 weeks after EOT, but at least 2 days after the end of the withdrawal bleeding that follows treatment cycle 6

the last patch or intake of the last tablet (see Fig. 1 for an overview).

2.5 Primary and Secondary Variables

The primary objective of this study was to investigate the impact of the two treatments on hemostasis parameters. The primary variables selected as sensitive activation markers for coagulation status were the absolute changes in prothrombin fragments 1 + 2 and D-dimer following three treatment cycles with the novel Bayer patch and COC, respectively. Laboratory assessment of prothrombin fragments 1 + 2 was made using Enzygnost[®] 1 + 2 (Siemens, Munich, Germany), and D-dimer values were assessed using Asserachrom[®] D-dimer (Roche Diagnostics, Basel, Switzerland).

Secondary variables consisted of (pro)coagulatory parameters (fibrinogen, Factor II, Factor VII, and Factor VIII activity) and anti-coagulatory parameters (anti-thrombin III, protein C, and protein S). APC resistance was determined using COATEST[®] reagents (Haemochrom Diagnostica, Essen, Germany). The APC sensitivity ratio was measured by the method described by Rosing et al. [20]. Blood samples were taken after minimal obstruction of the upper arm and immediate release after venepuncture at the forearm. Subjects were required to rest in a supine position and to adhere to a fasting period of at least 12 h prior to the collection of blood samples.

The numbers of bleeding and spotting, bleeding-only, and spotting-only days were recorded to determine bleeding pattern, and women kept a daily record of menstrual bleeding intensity. To analyze cycle control, menstrual bleeding was classified as withdrawal bleeding (following scheduled treatment withdrawal), application deviation bleeding (following unscheduled treatment withdrawal), or intracyclic bleeding (other).

2.6 Other Efficacy Variables

With regard to the number of unintended pregnancies, all pregnancies that occurred during the study until 7 days after removal of the last patch were recorded.

2.7 Other Safety Variables

Other laboratory assessments conducted include hematology, plasma chemistry, liver enzymes, sex hormone-binding globulin, and carbohydrate and lipid metabolism. Adverse events were assessed throughout the study for each treatment. Other safety parameters included gynecological findings, vital signs, body weight, BMI, and cervical smear results.

2.8 Treatment Compliance

Women were required to record the number of COC tablets (0, 1, or 2) taken each day, the dates new patches were applied, the patch application site, patch application deviations, the reason for patch removal (if applicable), the dates they did not wear a patch, and whether back-up contraception was used. Patch adhesion (e.g., the number of completely and partially detached patches per cycle) was also recorded.

2.9 Statistical Analyses

All treatment variables were analyzed using descriptive statistical methods. The primary analyses of this study were performed on the absolute changes from corresponding baseline values for the two primary variables (prothrombin fragments 1 + 2 and D-dimer). A normal distribution was assumed for the absolute change in each parameter.

The treatment effect in either variable was investigated using an ANOVA model to test for a treatment difference for each variable. Bonferroni correction was used to account for multiple testing; therefore, for each of the two primary hemostatic parameters, a 97.5 % two-sided confidence interval was derived for the treatment difference. For the secondary variables, descriptive analyses of the absolute and relative changes from corresponding baseline values were conducted.

While a sample size of 30 women was chosen without formal statistical power considerations, this number is commonly used for metabolic studies on contraceptives. All women who received study drug, and for whom data from any treatment period were available, were included in the full analysis set (FAS). The primary analysis of this study was based on the FAS; this population was also used for evaluation of safety data.

3 Results

3.1 Subject Disposition and Demographics

A total of 48 women were enrolled onto the study. Of these women, 18 did not pass the screening process, and 30 were randomized for treatment (Fig. 2). In total, 15 women were assigned to each of treatment sequences A and B. One woman chose to withdraw from the study prior to treatment (sequence B), and 29 women either started treatment or, for those who had used a method of hormonal contraception prior to screening, performed the first washout phase and then started treatment period 1. For five women in treatment sequence A and three women in treatment sequence B, previous use of hormonal contraception was reported

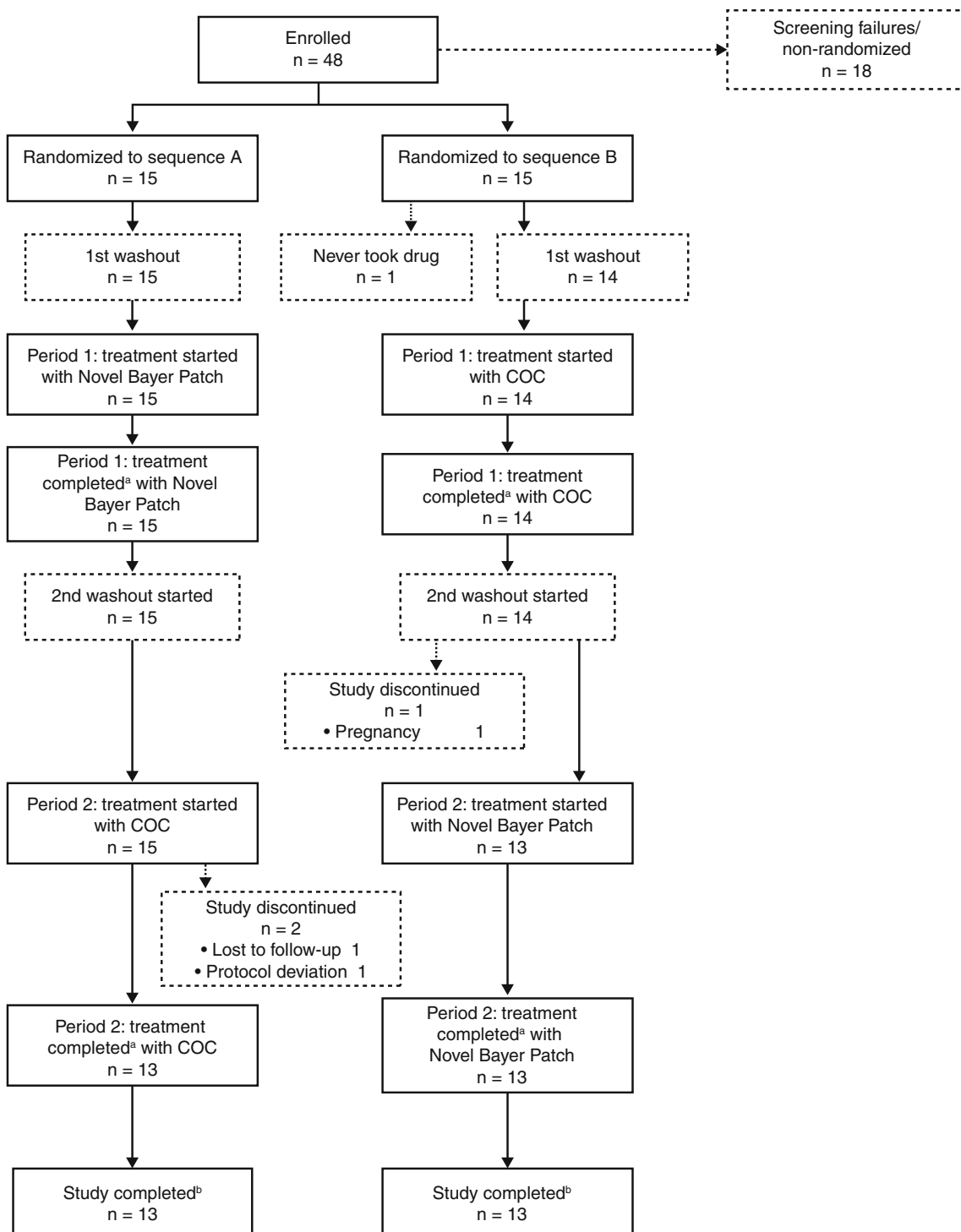


Fig. 2 Disposition of subjects. ^a Subjects using the novel Bayer patch were regarded as having completed treatment if there were ≥ 77 days between “Last day patch removed” and “First day patch worn”

in period 2; ^b The study was completed only if the subject had completed the treatment period and had performed the follow-up visit. COC combined oral contraceptive

and a first washout phase required. All 29 women completed treatment period 1 and the second washout phase; these 29 women constitute the FAS. During the second washout phase, after treatment with the COC, one woman

in treatment sequence B became pregnant and discontinued the study. The remaining 28 women started treatment period 2, which was completed by a total of 26 subjects: 13 subjects (86.7 %) in treatment sequence A and 13 subjects

(92.9 %) in treatment sequence B. Two subjects discontinued this period prematurely: one was lost to follow-up, and the other discontinued following a protocol deviation.

The key demographic characteristics of the FAS population are summarized in Table 1. Overall, characteristics were very similar between the treatment groups.

3.2 Primary Hemostasis Parameters

With regard to prothrombin fragments 1 + 2, no statistically significant differences were observed between the treatment groups in either treatment period. While little change was observed in the first treatment period, an increase of prothrombin fragments 1 + 2 was seen in the second treatment period for both groups (baseline values 0.099 and 0.109 nmol/L in the novel Bayer patch and COC groups, respectively; absolute changes 0.025 and 0.028 nmol/L in the novel Bayer patch and COC groups, respectively). Over both treatment periods, the overall mean absolute change was 0.008 ± 0.042 nmol/L for the novel Bayer patch group and 0.013 ± 0.043 nmol/L for the COC group; the treatment difference of 0 (two-sided 97.5 % CI -0.032 to 0.022) was not statistically significant ($p = 0.667$). There were no statistically significant treatment sequence or period effects.

Slight differences in D-dimer concentrations were observed between the treatment groups in both treatment periods; however, these were not statistically significant. Over both treatment periods, the overall mean absolute change was 107.0 ± 147.2 ng/L for the novel Bayer patch group and 113.7 ± 159.0 ng/L for the COC group. The treatment difference of -6.19 (two-sided 97.5 % CI -103.00 to 90.92) was not statistically significant ($p = 0.884$).

3.3 Secondary Variables

A summary of the absolute changes in the secondary coagulation parameters is shown in Table 2. None of these changes was of clinical or functional significance.

3.4 Other Efficacy Variables

3.4.1 Cycle Control

In the FAS, withdrawal bleeding was experienced by 86.7–100 % of women in all treatment cycles using the novel Bayer patch, and by 83.3–100 % of women using the COC, while intracyclic spotting/bleeding was reported by 6.7–30.8 and 7.1–25.0 % of women in all treatment cycles, respectively.

3.4.2 Contraceptive Efficacy

Although subjects were well-informed and confirmed that they would use non-hormonal methods of contraception (condoms were offered and distributed throughout the study), one woman became pregnant during the second washout phase following treatment period 1, during which the woman had taken the COC. All other pregnancy test results during the course of the study were negative.

3.5 Safety

Due to the crossover design of the study, adverse events were recorded per treatment regardless of treatment sequence. At least one treatment-emergent adverse event was reported by 21 women (72.4 %) using the novel Bayer

Table 1 Subject demographics and baseline characteristics (full analysis set) for treatment sequence A ($n = 15$), treatment sequence B ($n = 14$), and in total ($n = 29$)

	Treatment sequence A ^a	Treatment sequence B ^b	Total
Characteristic [mean \pm SD (range)]			
Age (years)	26.9 \pm 5.3 (18–35)	27.2 \pm 3.8 (18–32)	27.0 \pm 4.6 (18–35)
Height (cm)	167.3 \pm 4.5 (161–174)	166.8 \pm 7.2 (148–178)	167.1 \pm 5.8 (148–178)
Body weight (kg)	62.6 \pm 7.0 (51–78)	62.5 \pm 9.0 (44–78)	62.6 \pm 7.9 (44–78)
BMI (kg/m ²)	22.4 \pm 2.4 (19–26)	22.4 \pm 2.8 (19–29)	22.4 \pm 2.6 (19–29)
Race [n (%)]			
Caucasian	14 (93.3)	13 (92.9)	27 (93.1)
Asian	1 (6.7)	1 (7.1)	2 (6.9)

BMI body mass index, COC combined oral contraceptive, EE ethinyl estradiol, GSD gestodene, LNG levonorgestrel, SD standard deviation

^a Treatment sequence A = transdermal patch containing 0.55 mg EE and 2.1 mg GSD in period 1, COC containing 0.03 mg EE and 0.15 mg LNG in period 2

^b Treatment sequence B = COC containing 0.03 mg EE and 0.15 mg LNG in period 1, transdermal patch containing 0.55 mg EE and 2.1 mg GSD in period 2

Table 2 Summary of absolute changes in secondary coagulation parameters (full analysis set)

Parameters	Novel Bayer patch ^a			COC ^b		
	<i>n</i> ^c	Mean	SD	<i>n</i> ^c	Mean	SD
<i>Primary hemostasis parameters</i>						
<i>Prothrombin fragments 1 + 2 (nmol/L) [reference range 0.07–0.23 nmol/L]^d</i>						
Period 1: baseline	15	0.1	0.0	14	0.1	0.0
Period 1: treatment cycle 3	15	0.1	0.1	14	0.1	0.1
Period 1: absolute change (baseline to cycle 3)	15	0.0	0.0	14	0.0	0.1
Period 2: baseline	13	0.1	0.0	14	0.1	0.0
Period 2: treatment cycle 3	13	0.1	0.1	13	0.1	0.0
Period 2: absolute change (baseline to cycle 3)	13	0.0	0.0	13	0.0	0.0
Both periods together: absolute change (baseline to cycle 3)	28	0.0	0.0	27	0.0	0.0
<i>d-dimer (nmol/L) [reference range 0.0–500 nmol/L]^e</i>						
Period 1: baseline	15	174.1	55.4	14	164.2	66.2
Period 1: treatment cycle 3	15	269.5	185.4	14	268.0	179.6
Period 1: absolute change (baseline to cycle 3)	15	95.3	172.8	14	103.8	150.2
Period 2: baseline	13	145.5	85.7	14	164.9	47.7
Period 2: treatment cycle 3	13	265.9	146.4	13	289.5	180.5
Period 2: absolute change (baseline to cycle 3)	13	120.5	116.6	13	124.4	173.5
Both periods together: absolute change (baseline to cycle 3)	28	107.0	147.2	27	113.7	159.0
<i>Thrombin and fibrin turnover (activation marker)</i>						
<i>Prothrombin (Factor II) (%) [reference range 70–120 %]</i>						
Period 1: baseline	15	99.9	10.0	14	113.4	13.2
Period 1: treatment cycle 3	15	117.2	8.4	14	114.9	11.3
Period 1: absolute change (baseline to cycle 3)	15	17.3	11.7	14	1.5	13.5
Period 2: baseline	13	101.2	15.6	14	101.4	10.1
Period 2: treatment cycle 3	13	118.1	11.6	13	110.5	13.2
Period 2: absolute change (baseline to cycle 3)	13	16.9	15.0	13	9.0	7.2
Baseline (both periods together)	28	100.5	12.7	28	107.4	13.1
Absolute change (both periods together)	28	17.1	13.1	27	5.1	11.4
<i>(Pro)coagulatory parameters</i>						
<i>Fibrinogen (g/L) [reference range 1.8–3.5 g/L]</i>						
Period 1: baseline	15	2.7	0.5	14	2.7	0.5
Period 1: treatment cycle 3	15	2.7	0.6	14	3.0	1.0
Period 1: absolute change (baseline to cycle 3)	15	0.0	0.7	14	0.2	0.9
Period 2: baseline	13	2.4	0.6	14	2.3	0.5
Period 2: treatment cycle 3	13	2.7	0.8	13	2.5	0.4
Period 2: absolute change (baseline to cycle 3)	13	0.3	0.7	13	0.2	0.4
Baseline (both periods together)	28	2.6	0.5	28	2.5	0.5
Absolute change (both periods together)	28	0.2	0.7	27	0.2	0.7
<i>Factor VII activity (%) [reference range 70–120 %]</i>						
Period 1: baseline	15	90.5	18.9	14	109.1	19.6
Period 1: treatment cycle 3	15	112.0	16.6	14	105.9	17.6
Period 1: absolute change (baseline to cycle 3)	15	21.5	15.5	14	−3.2	16.8
Period 2: baseline	13	92.9	17.6	14	96.9	17.1
Period 2: treatment cycle 3	13	118.4	17.2	13	97.7	16.3
Period 2: absolute change (baseline to cycle 3)	13	25.5	12.2	13	3.4	7.9
Baseline (both periods together)	28	91.6	18.0	28	103.0	19.1
Absolute change (both periods together)	28	23.3	14.0	27	0.0	13.5

Table 2 continued

Parameters	Novel Bayer patch ^a			COC ^b		
	<i>n</i> ^c	Mean	SD	<i>n</i> ^c	Mean	SD
<i>Factor VIII activity (%) [reference range 70–150 %]</i>						
Period 1: baseline	15	90.1	9.9	14	88.7	17.6
Period 1: treatment cycle 3	15	99.0	9.5	14	96.4	22.5
Period 1: absolute change (baseline to cycle 3)	15	8.9	11.3	14	7.7	11.8
Period 2: baseline	13	90.9	18.4	14	89.4	12.8
Period 2: treatment cycle 3	13	96.0	21.4	13	94.5	13.7
Period 2: absolute change (baseline to cycle 3)	13	5.1	9.8	13	4.2	10.2
Baseline (both periods together)	28	90.5	14.2	28	89.1	15.1
Absolute change (both periods together)	28	7.1	10.6	27	6.0	11.0
<i>Anti-coagulatory parameters</i>						
<i>Anti-thrombin III activity (%) [reference range 75–125 %]</i>						
Period 1: baseline	15	97.2	9.3	14	97.6	10.2
Period 1: treatment cycle 3	15	98.8	7.5	14	99.6	7.0
Period 1: absolute change (baseline to cycle 3)	15	1.6	7.8	14	2.0	6.8
Period 2: baseline	13	98.9	6.3	14	99.6	4.4
Period 2: treatment cycle 3	13	96.8	8.5	13	96.9	6.1
Period 2: absolute change (baseline to cycle 3)	13	−2.1	4.7	13	−1.9	5.7
Baseline (both periods together)	28	98.0	7.9	28	98.6	7.8
Absolute change (both periods together)	28	−0.1	6.7	27	0.1	6.5
<i>Protein C activity (%) [reference range 70–150 %]</i>						
Period 1: baseline	15	102.4	17.8	14	106.1	15.5
Period 1: treatment cycle 3	15	106.1	13.3	14	111.9	17.0
Period 1: absolute change (baseline to cycle 3)	15	3.7	10.6	14	5.7	11.4
Period 2: baseline	13	101.9	19.5	14	97.7	11.0
Period 2: treatment cycle 3	13	114.0	20.7	13	103.2	12.3
Period 2: absolute change (baseline to cycle 3)	13	12.1	8.4	13	7.3	10.2
Baseline (both periods together)	28	102.2	18.3	28	101.9	13.9
Absolute change (both periods together)	28	7.6	10.4	27	6.5	10.6
<i>Protein S activity (%) [reference range 52–118 %]</i>						
Period 1: baseline	15	80.9	11.7	14	74.6	11.8
Period 1: treatment cycle 3	15	77.7	10.1	14	81.2	9.0
Period 1: absolute change (baseline to cycle 3)	15	−3.1	6.9	14	6.6	12.8
Period 2: baseline	13	79.7	9.0	14	82.6	9.2
Period 2: treatment cycle 3	13	70.6	10.6	13	82.9	10.4
Period 2: absolute change (baseline to cycle 3)	13	−9.1	5.4	13	−0.3	9.3
Baseline (both periods together)	28	80.3	10.3	28	78.6	11.2
Absolute change (both periods together)	28	−5.9	6.8	27	3.3	11.6
<i>APC resistance (ratio) [reference range 2.0–5.0]</i>						
Period 1: baseline	15	3.1	0.3	14	3.2	0.5
Period 1: treatment cycle 3	15	3.0	0.4	14	3.0	0.4
Period 1: absolute change (baseline to cycle 3)	15	−0.1	0.4	14	−0.2	0.3
Period 2: baseline	13	3.3	0.6	14	3.2	0.3
Period 2: treatment cycle 3	13	2.9	0.4	13	3.1	0.4
Period 2: absolute change (baseline to cycle 3)	13	−0.4	0.2	13	−0.1	0.2
Baseline (both periods together)	28	3.2	0.5	28	3.2	0.4
Absolute change (both periods together)	28	−0.2	0.3	27	−0.1	0.3

Table 2 continued

Parameters	Novel Bayer patch ^a			COC ^b		
	<i>n</i> ^c	Mean	SD	<i>n</i> ^c	Mean	SD
<i>APC sensitivity (ratio) [reference range 0.9–2.2]</i>						
Period 1: baseline	15	2.0	0.9	14	2.4	1.3
Period 1: treatment cycle 3	15	3.7	1.1	14	4.5	1.4
Period 1: absolute change (baseline to cycle 3)	15	1.7	0.6	14	2.1	1.0
Period 2: baseline	13	2.3	1.4	14	1.8	0.9
Period 2: treatment cycle 3	13	4.8	1.4	13	3.3	1.2
Period 2: absolute change (baseline to cycle 3)	13	2.6	0.8	13	1.4	0.8
Baseline (both periods together)	28	2.1	1.2	28	2.1	1.2
Absolute change (both periods together)	28	2.1	0.8	27	1.8	1.0

APC activated protein C, *COC* combined oral contraceptive, *EE* ethinyl estradiol, *GSD* gestodene, *LNG* levonorgestrel, *SD* standard deviation

^a Novel Bayer patch = 0.55 mg EE and 2.1 mg GSD

^b COC = 0.03 mg EE and 0.15 mg LNG

^c *n* = total number of subjects who received treatment. Note: subjects treated in period 1 are different from those treated in period 2

^d Treatment difference = 0.0, two-sided 97.5 % CI: 0.0–0.0, *p* value of test for treatment difference = 0.667

^e Treatment difference = –6.2, two-sided 97.5 % CI: –103 to 90.9, *p* value of test for treatment difference = 0.884

patch and 18 (62.1 %) using the COC; these were most frequently nasopharyngitis [13 (44.8 %) and 12 (41.1%) women, respectively] and headache [4 (13.8 %) and 3 (10.3 %) women, respectively]. Twelve events were considered to be treatment related, and were experienced by five women (17.2 %) in the novel Bayer patch group and two (6.9 %) in the COC group. All were mild to moderate in intensity. No women discontinued the study prematurely due to adverse events and no serious adverse events or deaths were reported.

3.6 Treatment Compliance

Overall, compliance with the novel Bayer patch was good, with women wearing the patch an estimated 99.9 % (±0.38; range 98.5–100.0) of the required 21 days. Compliance with COC treatment was also good, with an estimated 98.6 % of women (±2.50; range 90.5–100.0) taking the expected 63 tablets over three cycles.

4 Discussion

The aim of this crossover study was to examine the impact of the novel Bayer patch and a COC on prothrombin fragments 1 + 2 and D-dimer in healthy women over two treatment periods, each comprising three treatment cycles. The aforementioned hemostasis parameters were selected because they are sensitive indicators of coagulation and fibrinolysis activation; the comparator COC was chosen as a gold-standard, reference monophasic COC to comply with the European Medicines Agency Committee for

Medicinal Products for Human Use guideline on clinical investigation of steroid contraceptives in women, which states that a product containing levonorgestrel and EE (150/30 µg) or desogestrel and EE (150/30 µg) is appropriate as a comparator where VTE risk has been established in observational studies [18].

While prothrombin fragment 1 + 2 levels were stable (first treatment period) or slightly increased (second treatment period) in response to both treatments, increases in D-dimer were observed under both treatments and in both treatment periods; however, the differences in the changes between treatment groups were neither statistically nor clinically significant. The observed increase for D-dimer in both treatment periods, and for prothrombin fragments 1 + 2 in the second period, implies that the overall balance between the different factors influencing hemostasis was maintained on an increased level.

With regard to changes in the secondary hemostasis parameters, both treatments showed a slight increase in activation marker levels; however, in most cases, these increased values did not exceed their upper reference limits. There were no, or minimal, changes in (pro)coagulatory factors with either treatment, except for Factor VII activity, which increased in both treatment periods with the novel Bayer patch. In both treatment sequences, the balance of the coagulatory system appeared to be maintained at an increased level for both the pro- and the anti-coagulatory parameters. This is consistent with an increase in fibrin turnover.

It is difficult to correlate changes in individual hemostasis parameters with the clinical endpoint of VTE. Comparative pharmacodynamics data may indicate possible

differences between products, but there are no generally accepted surrogate endpoints for the risk of VTE [18]. As expected, the evaluation of both the primary and secondary parameters in this study shows that individual hemostasis parameters are changed by both treatments. This has been well-documented for other low-dose combined hormonal contraceptives [26–28]. Overall, the simultaneous changes in pro- and anti-coagulatory parameters seen in this study do not suggest a difference in VTE rate for the novel Bayer patch compared with currently marketed low-dose COCs.

The profile of adverse events recorded during the course of the study indicated that both treatments were well-tolerated. In addition, no safety events of clinical significance were observed, and bleeding pattern and cycle control were, in general, comparable between the two treatments. Both the novel Bayer patch and the COC showed good contraceptive efficacy in this study, with no pregnancies occurring during either treatment. One pregnancy occurred during the second washout phase of this study; however, this occurred after intake of the last COC tablet.

Despite these favorable results, caution should be taken when interpreting these findings with the aim of predicting VTE risk among users of different hormonal contraceptives. Although comparative pharmacodynamic data may be used to indicate possible differences between products, there are no generally accepted surrogate endpoints. In addition, it should also be noted that the inability of this study to find any differences between treatments may be a reflection of its small sample size and relatively short treatment duration. In addition lipid metabolism was not assessed in the present study. However, study data have shown that low-density lipoprotein cholesterol levels (LDL-C) decrease and triglyceride and high-density lipoprotein cholesterol (HDL-C) levels increase from baseline levels after treatment with a contraceptive preparation that contains gestodene and EE. These changes resulted in an increased HDL-C/LDL-C ratio, demonstrating that the contraceptive had an anti-atherogenic effect [29].

5 Conclusion

The results of this crossover, comparative study demonstrate that both the novel Bayer patch delivering low doses of EE and gestodene and a low-dose, monophasic COC containing EE and levonorgestrel have comparable influence on hemostatic endpoints. Both treatments were well-tolerated by subjects, and no clinically significant laboratory changes were observed.

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