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A historical cycle control comparison of two drospirenone-containing combined oral contraceptives: ethinylestradiol 30 μg/drospirenone 3 mg administered in a 21/7 regimen versus ethinylestradiol 20 μg/drospirenone 3 mg administered in a 24/4 regimen

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ABSTRACT

Objectives: To compare the bleeding patterns and cycle control of an oral contraceptive (OC) containing ethinylestradiol (EE) 30 μg/drospirenone (drsp) 3 mg administered in a 21/7 regimen versus a lower-dose OC containing EE 20 μg/drsp 3 mg administered in a 24/4 regimen, using data from two identically designed studies.

Materials and methods: In the first study, 326 healthy women (18–35 years) received EE 30 μg/drsp 3 mg in a 21/7 regimen. In the second study, 1027 healthy women (17–36 years) received EE 20 μg/drsp 3 mg in a 24/4 regimen. Participants recorded bleeding using daily completed diaries over 13 treatment cycles.

Results: During cycles 1–12, the prevalence of scheduled withdrawal bleeding was lower with EE 20 μg/drsp 3 mg 24/4 than with EE 30 μg/drsp 3 mg 21/7 (82.0–91.7% versus 94.8–100.0% of women, respectively); moreover, a higher proportion of women reported a maximum intensity of light scheduled withdrawal bleeding with EE 20 μg/drsp 3 mg 24/4 than with EE 30 μg/drsp 3 mg 21/7 (30.9–39.0% versus 13.8–20.5% of women, respectively). In cycles 2–13, unscheduled intracyclic bleeding was reported by 7.7–13.8% of EE 20 μg/drsp 3 mg 24/4 recipients and 3.8–7.9% of EE 30 μg/drsp 3 mg 21/7 recipients; these were mainly single bleeding days. During reference periods 1–4, the mean number of bleeding episodes was similar between groups (3.1–3.3 episodes with EE 20 μg/drsp 3 mg 24/4 versus 3.2 episodes with EE 30 μg/drsp 3 mg 21/7).

Conclusions: A low-dose 24/4 regimen OC containing EE 20 μg/drsp 3 mg is generally comparable in terms of bleeding to a higher-dose 21/7 regimen OC containing EE 30 μg/drsp 3 mg. Between-treatment differences in bleeding intensity and unscheduled intracyclic bleeding rates were observed.

1. Introduction

The high contraceptive efficacy of combined oral contraceptives (COCs) has been well established [1]. Nevertheless, a proportion of women discontinue COC use within the first year, even though they have no desire to become pregnant [2,3]. Data suggest that the acceptance of COCs is influenced by the degree of cycle control, such as the frequency of bleeding irregularities [2]. In addition, at least in clinical trials where COC availability is rarely an issue, side effects (e.g. nausea, mood changes, and fluid-related symptoms) can have a profound effect on patient satisfaction. Consequently, recent developments in COCs have focused on minimising these side effects whilst maintaining the desired level of contraceptive efficacy. Such strategies have included reducing the estrogen dosage, changes in the administration regimens to minimise hormone fluctuations, and the introduction of new progestins [1].

Drospirenone (drsp), a spironolactone analogue, is a unique progestin that displays a pharmacological profile similar to that of natural progesterone, with both antimineralcorticoid and antiandrogenic properties [4–7]. Drsp counteracts the aldosterone-stimulating effects of estrogen, thus reducing unwanted fluid-related symptoms such as bloating and breast tenderness.

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Moreover, by binding to and blocking androgen receptors, drsp has beneficial effects on acne and seborrhoea [4].

The objective of this evaluation was to compare the bleeding patterns and cycle control of an EE 30 μg/drsp 3 mg COC, administered in a 21/7 regimen (Yasmin®), and a lower-dose COC containing EE 20 μg/drsp 3 mg administered in a 24/4 regimen (YAZ®), by undertaking a pooled analysis of data from two studies.

2. Methods

2.1. Study design

This was a pooled analysis of data from two multicentre, Phase III, open label studies. The first study enrolled patients from six centres in the USA while the second study was conducted at 35 centres in Austria, Argentina, Brazil, Poland and the USA. Both studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization – Good Clinical Practice Guidelines. The methodology for these studies has been previously published [8,9], but is briefly described below.

2.2. Study participants

Both studies enrolled healthy women aged 18–35 years (inclusive) requesting contraception. The exclusion criteria were consistent with the usual contraindications for COC use. All women provided written, informed consent.

2.3. Treatments

In the first study, 326 women received EE 30 μg/drsp 3 mg in a 21/7 regimen (i.e. each treatment cycle consisted of 21 consecutive days of active treatment followed by a 7-day placebo period). In the second study, 1027 women received EE 20 μg/drsp 3 mg in a 24/4 regimen (i.e. each treatment cycle consisted of 24 consecutive days of active treatment followed by a 4-day placebo period). The overall treatment duration was 13 cycles (12 months) without a break between cycles.

Women were instructed to take their first tablet on the first day of their menstrual cycle (i.e. the first day of menses for new starters of OCs or the first day of withdrawal bleeding for those switching from another OC). Tablets were required to be taken once daily exactly as directed and at intervals not exceeding 24 h.

2.4. Study assessments

In both studies, cycle control and bleeding patterns were assessed as secondary outcomes. Diary cards were completed by participating women on a daily basis and completed diaries were collected and reviewed at each study visit. For the current pooled analysis, the cycle control and bleeding patterns of EE 30 μg/drsp 3 mg in a 21/7 regimen and EE 20 μg/drsp 3 mg in a 24/4 regimen were compared.

2.5. Cycle control analysis

For the current analysis, time to onset, duration and intensity of scheduled withdrawal bleeding and unscheduled intracyclic bleeding episodes were identified in both studies and compared between treatments according to the guidelines developed by Gerlinger et al. [10].

A scheduled withdrawal bleeding episode was defined as the first bleeding/spotting episode that started following intake of the last active tablet in the current treatment cycle up to five days before withdrawal of active treatment in the subsequent cycle (i.e. from day 22 of one cycle to day 17 of the subsequent treatment cycle for the 21/7 regimen, or from day 25 to day 20, respectively, for the 24/4 regimen). The one exception to this rule was any bleeding/spotting episode which started before (but not earlier than 3 days before) intake of the last active tablet and was still ongoing on the first day of the hormone-free period; this ongoing bleeding/spotting episode was also considered to be a scheduled withdrawal bleeding episode.

Unscheduled intracyclic bleeding was defined as all other (unexpected) bleeding episodes that did not fit the criteria for scheduled withdrawal bleeding. If no bleeding occurred until five days before the next episode of progestin withdrawal (i.e. day 17 for the 21/7-day regimen and day 20 for the 24/4-day regimen), this was assessed as absence of withdrawal bleeding in the previous treatment cycle. A bleeding and/or spotting episode was defined as such, provided that it was preceded and followed by at least two bleed-free days. On this basis, a bleeding-free interval of at least two days had to occur before one bleeding episode was considered to be separate from another.

In the first study with EE 30 μg/drsp 3 mg in a 21/7 regimen treatment, women classified the intensity of all bleedings as none, light, normal, or heavy. In the second study with EE 20 μg/drsp 3 mg in a 24/4 regimen treatment, bleedings were classified as: none; spotting; light; normal; or heavy. For the current analysis, bleeding that was described as spotting in the second study was mapped to light, to enable comparisons between treatments. In this manner, traditional spotting data were not separated out, but were merged into the light bleeding category. Bleeding intensities were defined as follows: spotting, less than that associated with normal menstruation relative to the subject's experience with no need for sanitary protection (except for panty liners); light bleeding, less than that associated with normal menstruation relative to the subject's experience with the need for sanitary protection; moderate bleeding, normal menstruation relative to the subject's experience; and heavy bleeding, more than normal menstruation relative to the subject's experience.

2.6. Bleeding pattern analysis

For the current analysis, the mean total number of bleeding days and the mean number, mean length, maximum length and range of all bleeding episodes were identified. Based on the data obtained from subject diary cards, bleeding patterns were characterised using 90-day reference periods, as defined by the World Health Organization (WHO) [11]. Reference periods 1–4 were analysed and compared between treatments.

2.7. Data analysis

Analyses were performed in the full analysis set (FAS) which comprised all women who took at least one tablet of study medication (study 1; EE 30 μg/drsp 3 mg 21/7) and all women who took at least one tablet of study medication and for whom at least one observation after dosing was available (study 2; EE 20 μg/drsp 3 mg 24/4). Cycle control and bleeding pattern parameters were summarised using descriptive statistics and no formal hypothesis testing was performed. Data from all 13 treatment cycles and 4 reference periods were analysed. For scheduled withdrawal bleeding, data from cycle 13 were not included in the evaluation as documentation in this cycle was incomplete and therefore could not be adequately reported (e.g. bleeding that was ongoing at the end of cycle 13 was not documented in a subsequent follow-up cycle). For unscheduled intracyclic bleeding, data were assessed between cycles 2 and 13 because data in the first treatment cycle were distorted by changes to the menstrual cycle through the