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Effect of a combination of ethinylestradiol 30 μg and drospirenone 3 mg on tolerance, cycle control, general well-being and fluid-related symptoms in women with premenstrual disorders requesting contraception

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Abstract

Purpose: Positive effects on premenstrual symptoms have been observed with low-dose oral contraceptives. Drospirenone is a synthetic progestogen with antiandrogenic and antimineralocorticoid effects. This open-label, multicenter study evaluated the effects of a combination of ethinylestradiol 30 μg and drospirenone 3 mg on safety, cycle control, general well-being and fluid-related symptoms in women with premenstrual disorders requesting contraception.

Materials and methods: A total of 241 healthy volunteers with symptoms of premenstrual disorder was enrolled in the study. Of the final sample, 203 completed the six-cycle treatment and were included in the efficacy analysis whereas 236 were included in the tolerability analysis. The subjects recruited to the study were required to fill up the Psychological General Well-Being Index (PGWBI).

Results: There was no significant change in body weight or blood pressure throughout the treatment. Adverse events reported by patients during treatment consisted of those already known to be associated with oral contraceptive use. PGWBI scores were significantly higher after six cycles of treatment compared with baseline values ($p<.0001$). A total of 198 (84.2%) subjects reported a great improvement in premenstrual symptoms.

Conclusions: The results of this study confirm that oral use of a combination of ethinylestradiol 30 μg and drospirenone 3 mg provides good cycle control, is well tolerated and has a positive impact on symptoms of premenstrual disorder.

Keywords: Contraceptive efficacy; Cycle control; Drospirenone; Oral contraceptive; Premenstrual disorders

1. Introduction

Low-dose combined oral contraceptives are generally well tolerated and represent an excellent reversible form of contraception for most women. Improving the safety and tolerability of oral contraceptives without affecting their efficacy has been a major research goal for more than three decades. Developing new progestogens and low-dose compounds has been considered a means of achieving this goal [1]. Depending on their chemical structure, progestogens may also have estrogenic, androgenic or antiandrogenic activity [2]. None of the currently available progestogens displays the clinically relevant levels of antimineralocorticoid activity of natural progesterone; therefore, they are unable to

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counteract the sodium-retaining effect of the ethinylestradiol component of combined oral contraceptive preparations [3].

Drospirenone is a novel progestogenic compound and is the first potent synthetic progestogen to exhibit both antiandrogenic and antimineralocorticoid characteristics at pharmacologically relevant doses [4–6]. The compound is devoid of any additional estrogenic or glucocorticoid property [4,7,8]. Progesterone exerts a natriuretic effect by competing with mineralocorticoids for their receptors, as demonstrated by an increase in plasma renin activity and in plasma aldosterone during the luteal phase [6,9]. As both natural estrogens and ethinylestradiol induce salt and water retention, an ideal progestogen would possess the antimineralocorticoid activity of natural progesterone, counteracting estrogenic side effects. Drospirenone has a pharmacological profile very similar to that of natural progesterone and a high binding affinity to the mineralocorticoid receptor [10,11]. Due to its antimineralocorticoid effects, which are approximately eightfold those of spironolactone, drospirenone can be expected to reduce certain estrogen-induced side effects in women [12].

Weight gain, in addition to menstrual irregularities, is a major reason for women to discontinue or avoid oral contraceptive pill use, and only half to two thirds of women who start using oral contraceptives still use them 1 year later [13,14]. Side effects associated with oral contraceptive use include symptoms associated with fluid retention such as weight gain, breast tenderness, increased blood pressure and mood swings.

It has already been established that prospective assessment of premenstrual symptoms is essential to correct for confounding variables such as women's beliefs and expectations concerning menstruation [15,16]. In addition, the calendar of premenstrual experiences method permits successful distinction between patients with premenstrual syndrome and control subjects [17]. The present study was therefore designed to assess the tolerance and cycle control of a contraceptive containing ethinylestradiol 30 μg and drospirenone 3 mg and its effects on well-being and fluid-related symptoms in healthy women with premenstrual disorder requesting use of oral contraception.

2. Materials and methods

2.1. Study design and population

Six sites in Brazil participated in this multicenter, open-label study. The study was approved by the National Committee for Ethics in Research and by the institutional review board of each participating center. Informed consent forms were signed by all subjects prior to enrollment. Two hundred forty-one healthy volunteers [aged between 18 and 40 years (between 18 and 35 years in the case of smokers)] requesting use of oral contraception were enrolled in the study. To be included in the study, women had to have regular menstrual cycles and psychological/behavioral and somatic symptoms of premenstrual disorder. These symptoms had to have a pattern of occurring at the beginning of the second half of the menstrual cycle and improving with the onset of menstruation. At least one psychological or behavioral symptom and one somatic symptom had to have been present in at least two of the three cycles preceding screening.

Exclusion criteria consisted of the usual contraindications to oral contraceptive use such as pregnancy or lactation; vascular or metabolic diseases; liver or renal dysfunction; obesity; hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg); use of diuretics, anxiolytics, antidepressants, sedatives, hypnotics or any other medication that could affect the efficacy of oral contraceptives; use of any preparation for treating premenstrual syndrome; and the use of any hormonal contraception during the 3 months prior to enrollment. In addition, the subjects recruited to the study were required to complete the Psychological General Well-Being Index (PGWBI), a questionnaire designed to obtain information on psychological symptoms in daily life, and to obtain a baseline score of 60–95 points.

A complete medical, gynecological and obstetric history was obtained from each patient. Concomitant use of medication, adverse events, vital signs and body mass index were registered at all visits. Physical and gynecological examinations, including breast examination and Papanicolaou smear, were carried out at screening and at the final visit at the end of Cycle 6. Five office visits were scheduled: enrollment, pretreatment and at the end of Cycles 1, 3 and 6 each.

Volunteers received a preparation containing ethinylestradiol 30 μg and drospirenone 3 mg that was to be taken orally for 21 days followed by a 7-day tablet-free interval. Treatment was evaluated with respect to contraceptive efficacy, cycle control, adverse events and symptoms of premenstrual disorder. The influence of the menstrual-related symptoms on daily life was assessed using the PGWBI questionnaire, answered onsite during all scheduled visits. The analysis of psychological/behavioral parameters included assessment of mood swings, fatigue, lack of energy, irritability, aggressiveness, anger, depressive mood, social withdrawal, poor concentration, increased appetite and food craving. The presence and intensity of fluid-related symptoms (breast tenderness, abdominal bloating and extremity edema) were assessed using a diary specifically provided for this purpose.

Cycle control was evaluated using a menstrual diary in which patients recorded bleeding patterns and tablet intake. Data on the intensity and duration of bleeding were collected at all visits. Intermenstrual bleeding was classified as either spotting (scanty bleeding) or breakthrough bleeding (normal/excessive bleeding).

2.2. Statistical methods

Descriptive analysis was carried out on continuous data. Contraceptive efficacy was calculated using the Pearl Index