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Efficacy and safety of 17α-hydroxyprogesterone caproate in hormone replacement therapy

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Abstract
The aim of the present study was to evaluate the efficacy (in terms of induction of uterine bleeding) and safety (in terms of absence of endometrial hyperplasia) of 17α-hydroxyprogesterone caproate (17α-HPC) in a therapeutic regimen for hormonal replacement after menopause. Fifty postmenopausal patients received hormone replacement therapy (HRT) for 24 weeks. The treatment regimen consisted of standard estrogen replacement therapy at commonly prescribed doses for the prevention of climacteric symptoms and 341 mg of 17α-HPC every 30 days. Enrolled women were told to expect withdrawal bleeding 7–10 days after the administration of 17α-HPC. Forty-eight patients completed the trial. In 91.7% of cases, patients experienced the expected pattern, i.e., strict withdrawal bleeding exclusive of any other form of bleeding. Breakthrough bleeding and/or other forms of abnormal bleeding affected only four women. At the 6th month none of the endometrial samplings motivated by endometrial thickness >10 mm and evidence of heterogeneous echogenicity (two cases) was positive for carcinoma. No biopsies had to be performed at the end of the 12th month of treatment. No serious adverse effect where recorded during the study period. In conclusion, our data show the efficacy and safety of 17α-HPC in HRT.

Keywords: *17α-hydroxyprogesterone caproate, menopause, hormone replacement therapy, uterine bleeding*

Introduction

17α-hydroxyprogesterone caproate (17α-HPC) was first patented by Kaspar and colleagues in 1956, and was prepared via the esterification of hydroxyprogesterone with caproic anhydride in the presence of *p*-toluenesulfonic acid [1]. One year before Davis and Wied had published their clinical observations on 17α-HPC administration to three castrated women, who had been treated with an injection of estradiol valerate 2 weeks before [2]. In the following years, when 17α-HPC became available for clinical use, the potential of this steroid ester in the management of pregnancy complications was suggested by four characteristics of the compound [3]. First, its high potency; second, its prolonged action; third, its high solubility in oil, which permits one to administer high doses of the drug; and finally the negligible local irritation following the injection of even large quantities of the compound. Moreover, 17α-HPC has an estimated half-life of about 6 days [4], i.e., four times longer than that of progesterone [5]. Sas and associates demonstrated that administration of 250 mg of 17α-HPC results in a rise in body temperature which lasts 8–10 days, changes vaginal cytology and initiates secretory transformation of the endometrium within 48 h [6].

It is widely documented that hormone replacement therapy (HRT) may prevent postmenopausal symptoms [7,8]. Furthermore, epidemiological data from studies performed in past decades suggest that HRT may also lower the increase in cardiovascular morbidity and mortality associated with menopause [9,10] even if recent studies have questioned the long-term safety of HRT [11,2]. Currently, diverse sex steroids are under investigation in order to design more appropriate HRT regimens for the individual woman [13]. Moreover, since the long-term use of unopposed estrogens causes endometrial disorders, progestogens have been added in various formulations and administered in sequential or continuous therapeutic regimens.

The aim of the present study was to evaluate the efficacy (in terms of uterine bleeding occurrence) and

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safety (in terms of absence of endometrial hyperplasia) of 17α-HPC combined with estrogens in HRT.

Materials and methods

Fifty healthy postmenopausal volunteer women (mean age 54.1 ± 4.6 years, mean body mass index 25.5 ± 2.4 kg/m^2) with menopausal symptoms (hot flushes, established osteoporosis on X-ray/bone mineral density measurements, high urinary calcium/creatinine) and not responsive to treatments other than HRT were recruited. Inclusion criteria were intact uterus, non-smokers, normotensive, normocholesterolemic, free of chronic disease, menopausal for at least for 12 months (26 ± 9.0 months) and with follicle-stimulating hormone level >40 IU/l. Frequent use of alcoholic beverages and administration of hormones in the previous 3 months were considered as exclusion criteria.

The treatment regimen consisted of standard estrogen replacement therapy at doses commonly prescribed for the prevention of climacteric symptoms: an oral preparation, e.g., conjugated equine estrogen 0.625 mg/day (Premarin®; Wyeth Lederle, Aprilia, Italy) or transdermal estradiol patches (systems delivering 50 μg/day) (Estraderm MX 50®; Novartis Farma, Origgio, Italy). In all cases, estrogen therapy was prescribed continuously. Moreover, every 30 days, 341 mg of 17α-HPC (Lentogest®; Amsa Farmaceutici, Rome, Italy) was administered intramuscularly. Patients were told to expect withdrawal bleeding 7–10 days after the 17α-HPC administration; they were also asked to record the day of the beginning of the withdrawal bleeding and to inform us of any dysfunctional uterine bleeding occurring at any time, so that we could perform a clinical evaluation. All the enrolled women were treated with estrogens and 17α-HPC for 24 weeks.

Clinical evaluation and baseline ultrasound examination were performed on all patients before starting the study. The baseline ultrasound scan documented the absence of uterine and/or ovarian pathology. Uterine fibroids did not cause exclusion if they were <5 cm in size and/or not symptomatic and/or submucosal. These examinations were repeated after 6 and 24 months of therapy. Biopsies were performed if endometrial thickness values at ultrasound examination were between 5 and 10 mm and if there was evidence of heterogeneous echogenicity. In any case, a biopsy was performed if endometrial thickness was >10 mm.

Results

Only 48 patients completed the study. One patient dropped out for personal reasons after 3 weeks of therapy; the other decided to terminate the therapy because of moderate pain at the injection site after the seventh administration of 17α-HPC. Consequently, data concerning their endometrial characteristics and bleeding pattern were not considered in the analysis. The bleeding patterns and endometrial thickness as evaluated at ultrasound examination of the women who completed the study are reported in Tables I and II.

In 91.7% of cases patients experienced the expected pattern, i.e., strict withdrawal bleeding exclusive of any other form of bleeding. Breakthrough bleeding and/or other forms of abnormal bleeding affected four women in at least one of the treatment cycles during the trial (Table I). In >90% of the menstrual cycles considered, bleeding started within 10 days from 17α-HPC administration (data not shown).

Endometrial thickness measured by ultrasound at baseline and after 6 and 12 months of treatment is reported in Table II. At the 6th month, none of the endometrial samplings motivated by endometrial thickness > 10 mm and evidence of heterogeneous echogenicity (two cases) was positive for carcinoma. No biopsies had to be performed at the end of the 12th month of treatment. No serious adverse events were reported.

Discussion

During the past few decades several studies have demonstrated the long-term benefits of HRT, including decreases in osteoporosis and in coronary heart disease risk [7,8]. Consequently, HRT has been extensively proposed in the treatment of symptoms associated with the aging process in perimenopausal women. Recent evidence has questioned the use of HRT due to growing concern about the occurrence of side-effects (small but substantial increase in breast cancer risk, slight increase in the incidence of adverse cardiovascular events) [11,12,14]. Notwithstanding this, many women in menopause still request HRT, mainly to reduce the

Table I. Bleeding patterns ($n = 48$) during the 12-month treatment with estrogens and 17α-hydroxyprogesterone caproate.

Withdrawal only	44/48 (91.7%)
Breakthrough and/or other abnormal bleeding in at least one treatment cycle	4/48 (8.3%)

Table II. Endometrial thickness ($n = 48$; mm) on ultrasound examination (mean ± standard deviation) at baseline and after 6 and 12 months of treatment with estrogens and 17α-hydroxyprogesterone caproate.

Baseline	5.1 ± 1.5
After 6 months of treatment	5.2 ± 2.6
After 12 months of treatment	4.5 ± 0.5

estrogen deficiency-associated symptomatology (i.e., hot flushes, depression, symptoms of genital ageing, osteoporosis) that may adversely affect quality of life. This is one of the reasons why new administration routes and novel hormone regimens are currently under evaluation. In fact, these new therapies for hormonal replacement in menopause might have different impact on breast cancer risk and cardiovascular-associated adverse events because of differences in their metabolic and pharmacodynamic effects [13].

The efficacy of estrogens in relieving menopausal symptoms in the majority of patients is counteracted by the occurrence of side-effects at endometrial level (hyperplasia and carcinoma) that has to be counterbalanced by the administration of a progestogen. Unfortunately, the addition of a progestogen reduces the endometrial adverse effects but may cause unacceptable symptoms, i.e., bleeding and spotting, which can affect adherence to therapy [15]. Our results demonstrated that HRT performed with estrogens and 17α-HPC provides a satisfactory control of uterine bleeding. Cyclical administration of 17α-HPC (341 mg intramuscularly every 30 days) resulted in a remarkably predictable withdrawal bleeding. In >90% of the menstrual cycles considered, bleeding started within 10 days from 17α-HPC administration. Considering the remaining patients who experienced breakthrough bleeding, a fraction (3/4) presented a pre-existing anatomical cause (submucosal fibroids) at clinical examination. All these conditions were corrected by surgery.

In conclusion, our data show the safety and efficacy of 17α-HPC in HRT. Furthermore, the improved predictability of withdrawal bleeding achieved with the cyclical administration of 17α-HPC indicates that this progestogen may find a place among HRT options and be instrumental in improving long-term compliance of menopausal patients to hormonal therapy.

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