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A randomized study on pharmacodynamic effects of vaginal rings delivering the progesterone receptor modulator ulipristal acetate: research for a novel estrogen-free, method of contraception☆,☆☆,★,★★,☆☆☆,★★★,☆☆☆☆

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Abstract

Objective: To determine whether a 3-month contraceptive vaginal ring (CVR) delivering ulipristal acetate (UPA) can inhibit ovulation in 90% of cycles.

Study Design: This was a randomized dose-finding parallel group clinical trial. Fifty-five healthy women with normal ovulation at baseline were randomized to receive a low-dose (1500 μg/day) or a high-dose (2500 μg/day) UPA-CVR for two consecutive 12-week treatment periods, followed by a recovery cycle. A subgroup of women received levonorgestrel (LNG) 1.5 mg orally twice (at the end of both 12-week ring periods) or once (at the end of the 24-week treatment). The primary outcome was ovulation suppression assessed by transvaginal ultrasound and hormone levels. Secondary outcomes included endometrial safety and bleeding patterns.

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★★★ Dr. Diana Blithe is a principal investigator on the Collaborative Research and Development Agreement (CRADA) of the NICHD with HRA Pharma for the development of ulipristal acetate for therapeutic indications. Inventions under research in the CRADA are joint property of NICHD and HRA Pharma. Funds from the CRADA were not used in the conduct of this research; however, the company supplied the drug for the studies.

☆☆☆☆ Other authors have nothing to declare and their disclosures are also reported separately on appropriate forms.

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Results: All subjects showed normal ovulation at baseline and recovery. Ovulation suppression was seen in 81.8% (95% CI: 73.3%, 88.5%) and 86.1% (95% CI: 78.1%, 92%) of treatment cycles with low and high-dose, respectively. Benign progesterone receptor modulator associated endometrial changes (PAEC) were seen during treatment; 78.8% at week 24, but resolved at recovery cycle. A few cases of heavy bleeding occurred near the end of the 24-week treatment, but a single dose of LNG every 12 weeks reduced the increase in endometrial thickness during the second treatment period and prevented excessive bleeding.
Conclusion: The 3-month UPA-CVR may become an effective long-acting, user-controlled estrogen-free contraceptive. The greatest suppression of ovulation was seen with the 2500-μg/day ring.
Implications: The 3-month CVR delivering UPA 2500 μg/day can become an effective user-controlled estrogen-free contraceptive method. Benign PAEC during treatment returns to normal after discontinuation. The prevention of occasional excessive withdrawal bleeding, either by a progestin or by using higher UPA levels to increase follicle suppression may permit prolonged treatment.

Keywords: Ulipristal acetate; Contraception; Pharmacodynamics; Endometrium; Vaginal ring

1. Introduction

High rates of unintended pregnancy resulting from non-use of contraception or failure of existing methods indicate the need for novel methods with better safety and acceptability [1]. An estrogen-free, long-acting, user-controlled, vaginal ring with a simplified continuous regimen, may improve compliance and contraceptive safety and efficacy.

The progesterone receptor modulators (PRMs) exert contraceptive action through a variety of mechanisms including inhibition of ovulation. Prevention of follicular rupture occurs by blockade of gonadotropin-surge mediated events which are PR dependent [2]. Ulipristal acetate (UPA), also known as CDB/VA-2914, is a PRM initially developed by the National Institutes of Child Health and Human Development (NICHD) and then by HRA pharma [3,4]. UPA was developed for gynecological applications, and is currently approved as an oral emergency contraceptive in Europe (EU) and in the USA, for use up to 5 days after unprotected intercourse [5], and for treatment of heavy menstrual bleeding due to uterine fibroids (EU) [6]. Oral doses of 5 or 10 mg/day suppress ovulation in about 80% of subjects and induce amenorrhea in 81% and 90% of subjects, respectively [7]. UPA metabolism is predominantly mediated by cytochrome P450 isoenzymes (CYP450) 3A4 with the mono-demethylated derivative (CDB-3877) being the main metabolite. This derivative is pharmacologically active but less than its parent compound [4].

A 3-month UPA contraceptive vaginal ring (UPA-CVR) designed for continuous use is under development for contraception by The Population Council (PC). In earlier studies, rings releasing 800 μg/day UPA, suppressed ovulation in 68% of cycles, when UPA levels reached >7 ng/mL [8,9]. End of treatment endometrial biopsies (EB) showed benign glandular changes, described as PRM-associated endometrial changes (PAECs) [10], in a background of inactive or weakly proliferative endometrium. Results from these preliminary studies demonstrate tolerability of UPA-CVR and indicate UPA levels at ≥7 ng/ml, as threshold for efficacy.

We report here pharmacodynamic results of a dose-finding study testing two new UPA-CVRs releasing 1500 or 2500 μg/day. We hypothesized that by increasing the delivery dose of UPA, subjects using the new rings would achieve higher serum levels of UPA than seen with the prior UPA-CVR [9]. Therefore the main objective was to determine the dose capable of suppressing ovulation in 90% of cycles.

2. Materials and methods

2.1. Study design

This randomized, parallel-group dose-finding and safety study was conducted at three clinics in Chile (Clinic 2), Dominican Republic [(DR) Clinic 3], and Portland [(OR) Clinic 17], in accordance with ICH Guidelines and the Declaration of Helsinki. Approval was granted by each clinic's Ethics Committee and PC's Institutional Review Board.

Eligible subjects were 21–40 years old, with regular menstrual cycles, a body mass index (BMI) ≤30 kg/m^2 and not at risk for pregnancy. Exclusion criteria included breastfeeding, contraindications to hormonal contraceptives, and current use of hormones or intrauterine device. A baseline ovulatory cycle was required.

Eligible subjects were randomized to the first treatment period on day 2–5 of the next cycle to a low-dose (1500 μg/day) or a high-dose (2500 μg/day) vaginal ring to determine the lowest-effective dose to block ovulation in 90% of cycles. Staff members in clinics 2 and 3, or pharmacists in clinic 17 dispensed either dose of vaginal rings according to a computer generated randomization list (See description in supplemental material section).

The UPA-CVRs made of micronized UPA mixed in a silicone elastomer matrix designed to achieve a first-order release profile of the steroid over 3 months [11]. Each ring was used continuously for 12 consecutive weeks. After 12 weeks (Treatment Period-1), the ring was changed for a new ring of same dose used for 12 additional weeks (Treatment Period-2). A post-treatment recovery cycle followed.

Transvaginal ultrasound (TVUS) and serum hormone levels were used to evaluate ovarian activity. For safety evaluation of the endometrial effect of treatment, an EB was