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Endometrial effects of a single early-luteal dose of the selective progesterone receptor modulator CDB-2914

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Abstract

Objective—To test potential contraceptive mechanisms of the selective progesterone receptor modulator CDB-2914 in the early luteal phase.

Design—Prospective randomized clinical trial.

Setting—Clinical Research Center.

Patients—Fifty-six regularly cycling women.

Interventions—Women received a single dose of CDB-2914 (10, 50 or 100 mg) or placebo given after ovulation and within two days of the LH surge. Four to six days later, a transvaginal ultrasound measured endometrial thickness and an endometrial biopsy was obtained.

Main outcome measure(s)—The endometrium was evaluated by thickness and by immunohistochemistry for progesterone-dependent markers; safety laboratory tests, and estradiol and progesterone levels were obtained.

Results—CDB-2914 caused a significant dose-dependent decrease in endometrial thickness, an increase in glandular progesterone receptors, and a decrease in peripheral node addressins. Estradiol and progesterone levels and menstrual cycle timing were not altered. No adverse effects were observed.

Conclusions—The alteration in endometrial thickness and progesterone dependent markers of implantation in the absence of changes in hormone levels and cycle length suggests that CDB-2914 may have contraceptive properties.

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Conflict of interest: None

Capsule: When administered as a single early luteal dose, CDB-2914 decreased endometrial thickness and inhibited progesterone-dependent differentiation markers in cycling women.

Keywords

CDB-2914; endometrium; luteal phase; single dose; selective progesterone receptor modulators

INTRODUCTION

Clinical studies with mifepristone (RU486; Roussel-Uclaf, Romaineville, France), a synthetic steroid with antiprogesterin properties, suggest that this class of compounds has therapeutic utility. A single post-ovulatory dose of 200 mg induces changes in the progesterone-dominated endometrium without affecting menstrual cycle length (1–4). This dose was associated with a delay in secretory differentiation, persistence of follicular phase estrogen and progesterone receptor staining, and a decrease glandular leukemia inhibitory factor (LIF) factor expression. Mifepristone has been shown to be an effective post-coital contraceptive, perhaps because of these endometrial effects (5–7), although an ovarian action cannot be excluded.

CDB-2914 is a selective progesterone receptor modulator (SPRM) developed by the National Institute of Child Health and Human Development (NICHD). Like mifepristone, it has antiprogesterone and antiglucocorticoid activity in animals and monkeys, but with less antiglucocorticoid activity. Normally cycling women given a single mid-luteal dose (up to 200 mg) had no adverse events or antiglucocorticoid effects (8). Early menses consistently occurred at the 200 mg dose, although functional luteolysis, defined as a sustained decrease of estradiol and progesterone to less than 50% of pretreatment values, occurred less commonly.

The present study was undertaken to determine whether early luteal phase CDB-2914 administration would alter endometrial maturation or cause luteolysis, while not altering menses in normally cycling, ovulatory women. Transvaginal ultrasound and endometrial biopsy were performed to evaluate the endometrial effects at the time of expected implantation.

MATERIALS AND METHODS

Subjects

Healthy women, ages 18 to 43, were eligible to participate in the protocol if they had regular menstrual cycles and were within 20% of ideal body weight. Exclusion criteria included current use of an intrauterine device or use of reproductive hormonal medications or glucocorticoids for at least three months before the study, chronic medical problems, abnormal screening blood tests or Pap smears, ovarian masses, symptomatic endometriosis or uterine leiomyomata, or breast-feeding. All women were protected from pregnancy by tubal ligation or vasectomy, or they agreed to abstinence or to the use of barrier contraception. The study was approved by the NICHD IRB and was performed under a Food and Drug Administration Investigational New Drug Application. Written informed consent was obtained from each subject.

Preparation of CDB-2914

Southwest Foundation for Biomedical Research (San Antonio, Texas) synthesized pure crystalline CDB-2914. The NIH Clinical Center Pharmaceutical Development Service sieved study compound and formulated gelatin capsules containing 10 mg, 50 mg and 100 mg doses of CDB-2914, or inert material (placebo). Initially, only the placebo, 10 mg, and 50 mg doses were studied and randomization was done in two blocks of 6. Subsequently, a

100 mg dose was added, at the time when data from a phase I study were available. Randomization for the next twenty subjects occurred in two blocks of 10 with 4 randomized to the 100 mg dose and 2 subjects each at placebo, 10, and 50 mg. The randomization for the remainder of the subjects was done in four blocks of 8.

Study Design

The study spanned three consecutive menstrual cycles: baseline, treatment, and post-treatment cycle. At study entry, each woman was instructed to use an in-home urinary LH kit and basal body temperature (BBT) chart that included a menstrual calendar and coital log. The urinary LH surge was detected using a self-test or one-step test (OvuQUICK™; Quidel, San Diego, CA). Both assays have a 40 mIU/ml threshold and identify the LH surge the same day as enzyme immunoassay 96% of the time (9). A plasma progesterone level was measured one week after the subjects reported the urine LH surge in the baseline and post-treatment cycles.

After a negative urine hCG test in the second (treatment) cycle, women were seen in the outpatient clinic within two days of a urine LH surge. The occurrence of ovulation was assessed by ultrasonography conducted by one of the investigators (BH, LN, or PS) using a 3.5 MHz transvaginal probe with a real-time scanner (Ultramark 9, Advanced Technologies Laboratories, Bothell, WA). Follicular collapse was defined as an irregularly shaped, collapsing or echogenic follicle in the absence of another follicle greater than 15 mm (10). Women received study drug (CDB-2914 or placebo) on LH +1 or LH +2, only if follicular collapse was documented. If a large follicle was noted on the day of ultrasound, the patient continued LH testing, returned daily for ultrasound until follicular collapse was seen and then received study medication. Endometrial thickness was measured by ultrasound on the day of treatment. Measurements were performed in the sagittal plane, across the upper third of the uterus, from one basal layer to the other, and then the measurement was confirmed in the transverse plane. Blood samples were obtained for estradiol and progesterone measurements.

Blood samples, transvaginal ultrasound, and endometrial biopsy were obtained four to six days after treatment. Blood chemistries, liver function tests, complete blood count, estradiol, and progesterone were measured. Transvaginal ultrasound evaluated endometrial thickness and ovarian cystic structures. To assess ovarian effects, luteal phase cysts were distinguished from corpus luteum. If an echogenic ovarian structure measuring more than 15 mm was noted on vaginal sonography, a limited pelvic transvaginal sonogram and blood hormone measurements were done in the early follicular and mid luteal phase in each subsequent cycle until the presumed cyst resolved. The endometrial biopsy was obtained using a Pipelle endometrial suction curette (Unimar, Wilton, CT) and placed in neutral buffered formalin.

The third study cycle was observed to document ovulation and menstrual cycle length. As in the baseline cycle, ovulation was assessed by serum progesterone measured a week after a reported positive urine LH test. If this cycle was of abnormal length (less than 23 or more than 36 days) or the progesterone was < 4 ng/ml, the woman was observed for another menstrual cycle. For those with a progesterone level < 4 ng/ml after a reported LH surge, a biphasic pattern on the BBT was considered suggestive of ovulation. Because a biphasic BBT is not always present in an ovulatory cycle, only its presence was considered for evaluation of ovulation.

Hormone assays

After centrifugation, plasma was aliquoted and stored at -20°C until radioimmunoassay for estradiol (11,12) and progesterone (13). All intraassay variability was 10% or less, and interassay variability was 15% or less.

Assessment of endometrial development

Endometrial differentiation was assessed morphologically by the criteria established by Noyes (14). A single pathologist (MM) evaluated all endometrial specimens, without knowing which study drug was given, and assigned a postovulatory, 2-day histologic date for the specimen. The endometrial development was considered abnormal if there was greater than 2 days delay of pathological dating compared to the chronologic day of cycle. The chronologic cycle day was determined as the number of days from ultrasound-documented ovulation to biopsy.

The expression of progesterone-dependent markers of luteal phase differentiation was assessed by immunohistochemical analysis of estrogen and progesterone receptors and peripheral node addressins (PNAds), using the antibody MECA-79. Formalin-fixed paraffin embedded tissue was used for immunohistochemical analysis. Five-micron tissue sections were cut onto silanated slides, deparaffinized, cleared, and stripped of endogenous peroxidase. Sections were hydrated through graded alcohols and distilled water, and treated with monoclonal antibodies to estrogen receptor (ER) (Coulter-Immunotech, Miami, FL), progesterone receptor (PR) (BioGenex, San Ramon, CA) or MECA-79 (BD Biosciences, San Jose, CA) all at 1:50 dilution, using avidin-biotin immunoperoxidase technique. Pretreatment antigen retrieval was used routinely. For ER and PR antigen retrieval, the slides were placed in citrate buffer at a pH of 6.0 and then heated in a pressure cooker for 5 minutes. Antigen retrieval for MECA-79 was performed with 0.5% trypsin for 30 minutes at 37°C and 2.5% normal horse serum was used as a blocking agent.

Slides were developed with diaminobenzidine, counterstained with Mayer's hematoxylin, and subjected to qualitative and quantitative visual assessment of both glands and stroma. ER and PR were graded as negative when 0 percent of the nuclei stained, 1+ if 10 percent were positive, 2+ if 20 to 50 percent were positive, 3+ if 60 to 80 percent were positive, and 4+ if 90 percent or more were positive. MECA staining intensity (i) from 0 (none) to 3 (strong) was scored by two observers. An H score $=\sum \text{Pi}(i+1)$ was calculated for each biopsy, where Pi is the percentage of cells for each intensity, varying from 0 to 100%. Positive and negative controls were used for each antibody.

Cycle Characterization

A menstrual cycle was defined as the number of days from the first day of menses to the beginning of the next menses, with the follicular phase comprising the number of days from the first day of menses to the reported positive urinary LH test. The luteal phase was defined as day LH surge +1 until the next menses. In the treatment cycle, the number of days from the urinary LH surge until follicular collapse was calculated. Women were observed for a baseline cycle to confirm ovulation and normal cycle length. The baseline menstrual cycle length was considered ovulatory if it ranged from 23 to 36 days with at least two of the following: a luteal phase at least 11 days in length, a luteal phase plasma progesterone measurement $> 4 \text{ ng/ml}$ and/or a biphasic basal body temperature pattern.

Statistical analyses

Analyses were performed using SAS 9.1 and Enterprise Guide 4.1 (SAS Institute; Cary, NC). Descriptive statistics including means, standard deviations, medians, frequencies, proportions, and graphical displays were analyzed to determine whether parametric

distributional assumptions were valid. Those not meeting these assumptions were analyzed using non-parametric methods. The treatment groups were compared by ANOVA to establish whether the groups behaved similarly and in cases in which significant differences existed between groups, post-hoc tests were performed using the Bonferoni method or Dunnett's test. For analysis, the placebo group was compared to those receiving CDB-2914 (10 mg, 50 mg, or 100 mg). Confirmatory analyses compared groups using the Jonckheere-Terpstra non-parametric test for trend or linear regression for dose-related effects. Changes in baseline, treatment, and post-treatment follicular, luteal, and total cycle length were compared across groups using generalized linear models. Two-tailed p-values were reported and $p=0.05$ was considered significant. Safety was evaluated by the frequency of adverse events and laboratory abnormalities.

RESULTS

Demographics

Seventy-one healthy non-pregnant women were admitted into the study. Six dropped out voluntarily before receiving study drug. Four were excluded in the treatment cycle because of long follicular phase ($n = 3$) or new hypertension ($n = 1$). Of the sixty-one women who received treatment, five were excluded from analysis because of inadvertent dosing during the follicular phase, inferred from continued follicular growth, proliferative phase endometrium, and a low progesterone at the time of biopsy; three of these five women also had a long treatment cycle. Fifty-six women were included in the analysis (15 given placebo, 13 at 10 mg, 14 at 50 mg and 14 at 100 mg). One woman with insufficient biopsy material for analysis was included in the safety and hormone analysis only. Despite oral and written instructions to use barrier contraception or abstain from intercourse, one woman who received a 10 mg dose became pregnant in the treatment cycle after mid-cycle, unprotected intercourse. As a result, there were no data for cycles 2 and 3. Her pregnancy was uneventful.

The mean age of study participants included in the analysis was 30.8 ± 9.8 years. Thirty-one were Caucasian, 20 were Black, two were Hispanic, and three were Asian. Thirty-three had been previously pregnant. The mean body mass index was 23.8 ± 2.9 kg/m² (range 17.4 to 28.7 kg/m²). There was no significant difference in race, age, body mass index, weight, gravidity, or parity among the treatment groups.

Fifty-four women experienced a normal ovulatory pattern in the treatment cycle, as assessed by a urine LH surge, growth and collapse or filling in of a lead follicle, and a progesterone level greater than 4 ng/ml within one week of ovulation. Usually the time from reported LH surge to documented follicular collapse was less than 2 days. Nine women (two women at placebo, 10 mg and 50 mg, and three at 100 mg) ovulated three or four days after reporting an LH surge.

Effect on cycle length and hormone levels

There were no significant differences among the treatment groups in the length of the luteal phase, or the length of the baseline, the treatment, or the post-treatment menstrual cycles (Table). Mid-luteal phase progesterone and estradiol concentrations four to six days after treatment also were similar among the groups (Table). Three women, one each at 10 mg, 50 mg and 100 mg, had abnormally short treatment cycles of 20 or 21 days. One woman with a baseline cycle of 36 days had a treatment cycle of 37 days; all other treatment cycles were normal length. All post-treatment cycle lengths were normal, except for two at 100 mg (20 and 21 days) and one on placebo (38 days). For these subjects, the subsequent cycle was of a normal length.

All 52 women who used the kit detected the LH surge in the post-treatment cycle. Of the other four, one was pregnant (10 mg) and the other three had received placebo. Of the latter three, BBT was biphasic in the one woman who provided information. Eight of 56 women had inadequate information to judge corpus luteum function: four did not have a progesterone measurement (3 on placebo and 1 at 100 mg), and four had progesterone values < 4.0 ng/mL (one at 10 and 50 mg and two at 100 mg). Their cycle length was normal except for one woman (placebo group) with a cycle length of 38 days.

Endometrium

Of the 56 endometrial biopsies performed, 55 had sufficient tissue for histologic dating. Using the cycle day of biopsy calculated from the day of follicular collapse, 11 biopsies (placebo: 2, 10 mg: 1, 50 mg: 5, 100 mg: 4) demonstrated an endometrial maturation delay of >2 days; 10 of these women had progesterone levels > 4 ng/mL on the day of the biopsy. Among those receiving CDB-2914 (50 or 100 mg), there was no significant increase in delayed endometrial maturation when compared to placebo (OR: 2.2; 95%CI: 0.4–11.3; $p = 0.36$). Additionally, there was no statistically significant evidence of increasing delay in endometrial maturation with escalating doses of CDB-2914; however, with a larger sample size, the impact of increasing dose on endometrial delay might become evident (Jonckheere-Terpstra test, $p=0.06$). One biopsy (at 50 mg) was reported to have complex proliferative architecture consistent with endometrial hyperplasia. A follow-up luteal phase biopsy performed two months after treatment noted only stromal glandular dysynchrony.

Baseline treatment cycle endometrial thickness was similar between groups (Table). The endometrial thickness on the day of biopsy ranged as follows: placebo: 5.8 – 18.7 mm; 10 mg: 8.4 – 12.6 mm; 50 mg: 6.1 – 11.7 mm; and 100 mg: 5.9 – 12.6 mm. There was a significant reduction in endometrial thickness among those subjects receiving CDB-2914 (10, 50 or 100 mg) compared to those receiving placebo (Table).

Glandular progesterone receptor staining differed among treatment groups (Fisher's exact test; $p=0.02$) with those receiving higher CDB-2914 doses demonstrating greater staining as evidenced by immunohistochemistry (Jonckheere-Terpstra test; $p=0.01$). For example, 8 of 15 specimens (53%) in the placebo group had little to no glandular progesterone receptor staining (≤ 2), whereas 86% of those treated with 100 mg of CDB-2914 demonstrated progesterone receptor staining >2. There were no differences noted between the groups for stromal progesterone receptor or estrogen receptor in either the glands or stroma (data not shown). MECA-79 staining was similar in the placebo (median: 3.8) and 10 mg (median: 3.5) groups, but was significantly reduced in the 50 mg (median: 2.1) and 100 mg groups (1.5) ($p<0.001$) with a notable linear decline in the staining with increasing CDB-2914 dosage (point estimate: -0.019 ; 95%CI: -0.023 , -0.015 ; $p<0.001$) (Figure).

Ovarian cysts

At the time of biopsy, ten of the 56 women from all dose groups ($n = 3$ placebo, 4 at 10 mg, 2 at 50 mg, 1 at 100 mg) had ovarian cysts between 12 and 24 mm in maximum diameter. Of the five women followed by ultrasound, four had complete resolution by 3 weeks to 3 months, and the fifth had diminished size at 6 weeks. Of the other five women, four did not return for follow-up ultrasounds, and one woman became pregnant.

Safety

CDB-2914 was tolerated well at all doses with no symptoms being reported. Apart from the endometrial abnormality noted above, all post-treatment laboratory values were normal.

DISCUSSION

A single post-ovulatory dose of up to 100 mg of the antiprogesterin CDB-2914 significantly increased glandular progesterone receptors and decreased endometrial thickness. Treatment did not alter corpus luteal function, as assessed by a single mid-luteal estradiol and progesterone measurement, and the length of the luteal phase or menstrual cycle. CDB-2914 appeared to inhibit endometrial development while sparing menstrual rhythm. The current study was the first dose-ranging study to document significant endometrial effects with low doses of CDB-2914 given in the early luteal phase. Similar endometrial effects have been observed among those receiving mifepristone (200 mg) (1,3,4); however, these endometrial effects were present at lower doses (10 mg) (15). Whether there is a difference in potency between mifepristone (200 mg) and CDB-2914 (100 mg) is not known. In addition, these agents might differ in their tissue specificity (16). For example, CDB-2914 and/or its metabolites might affect binding of the progesterone receptor to the progesterone response elements in a different way than mifepristone and its metabolites.

CDB-2914 inhibited progesterone-dependent markers of luteal phase differentiation. Both CDB-2914 and early luteal phase doses of 200 mg of mifepristone prevent the expected luteal phase decrease in glandular progesterone receptor staining (1,2,4). CDB-2914 also was associated with decreased expression of peripheral node addressins (PNAds), which are important L-selectin ligands found on the surface of endothelial cells. Recent studies have shown that L-selectin ligands are up-regulated during the implantation window, making the uterus more receptive to the trophoblast (17,18).

Other markers of normal secretory phase endometrial maturation are inhibited by mifepristone. When given in the early luteal phase, mifepristone prevents 17 β hydroxysteroid dehydrogenase expression (4,19), alters integrin distribution (19,20), reduces Dolichos biflorus agglutinin lectin binding (20), and reduces endometrial leukaemia inhibitory factor expression (1) assessed during the implantation window.

In this study, determining ovulation by combining the urine LH surge with an ultrasound evaluation was a more rigorous and accurate assessment of cycle day than using the urine LH alone, as daily serum measurements were not planned. As others have noted, we found that about one-fifth of study subjects ovulated 3 or more days after the urine LH surge (21).

Mid-luteal endometrium was significantly thinner in the high dose groups. Gu *et al.* reported a mid-luteal endometrial measurement of 8 to 19 mm in normal women, similar to the range of 6 to 19 mm observed in this study (22). Dose-dependent endometrial effects of endometrial atrophy and persistence of proliferative endometrium in the luteal phase of the cycle were observed less frequently. Endometrial atrophy defined as scant tissue on biopsy and a thin endometrium (6 mm) occurred in only one subject (at 100 mg). Proliferative endometrium despite normal ovarian luteal function (progesterone greater than 4 ng/ml) was observed in four subjects at the higher doses of CDB-2914. One of these women had hyperplasia that resolved within two months; it is very unlikely that hyperplasia developed within a few days of a single dose of CDB-2914. Although a thicker endometrium might be expected in those with continued endometrial proliferation after an antiprogesterin, in this study, women with proliferative endometrium on mid-luteal biopsy did not have a thicker endometrium. Either effect of CDB-2914, endometrial atrophy or continued proliferation, however, may hamper implantation.

Single doses of CDB-2914 given to normally cycling women at other times of the cycle have yielded effects similar to mifepristone's on the endometrium, ovary, and menstrual cycle. In the luteal phase, a single 200 mg mid-luteal dose of CDB-2914 caused early menses and less frequently functional luteolysis (8), as did 200 mg mifepristone (23). Lower

amounts of mifepristone (10 mg) given twice in the mid-luteal phase induced stromal edema and delayed glandular development without changes in the cycle length (24). With a single late-follicular dose, luteal phase endometrial maturation was delayed in 70% of biopsies at each dose of CDB-2914 (10, 50, and 100 mg) compared with 17 % in the placebo group (25). A delay in ovulation and suppression of estradiol levels was less frequently observed and was dose-dependent. Similarly, 100 mg mifepristone given from days 10 to 17 delayed both ovulation and endometrial maturation (26).

This study has some limitations. The women were not overweight and the generalizability of these findings to an overweight or obese population remains to be tested. While a larger sample size may have revealed a statistically significant dose-dependent trend for delayed endometrial maturation, recent studies suggest that endometrial dating does not correlate well with fertility (27). In contrast to histologic dating, molecular markers of implantation and progesterone action and endometrial thickness were reduced by CDB-2914 in a dose dependent fashion.

In summary, decreased endometrial thickness and decreased L-selectin ligands expression may be the earliest features of the antiprogesterone effect of CDB-2914 in the luteal phase, heralding other endometrial changes. In our studies, endometrial maturation appeared to be more vulnerable to a small, single dose given in the follicular phase than with a single dose given either in early or mid-luteal phase. Whether this is a direct endometrial effect or secondary to an ovarian effect is not known. Taken together, these endometrial effects in the absence of ovarian and menstrual cycle effects suggest mechanisms by which CDB-2914 might be effective as an emergency contraceptive (28).

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Figure 1.
Representative endometrial MECA-79 immunohistochemistry in biopsies from women receiving placebo (PL) and 10, 50 and 100 mg CDB-2914. The H score was significantly reduced in the 50 and 100 mg groups compared to placebo ($p < 0.001$).

Table

The effect of CDB-2914 administration compared to placebo on outcome measures.

	Placebo	CDB-2914 (10 mg, 50 mg, 100 mg)	
	Mean $\pm$ s.d.	Mean $\pm$ s.d.	<i>p</i> -value
<i>Cycle length</i>			
Baseline cycle length (days)	28.3 $\pm$ 2.2	27.8 $\pm$ 2.8	0.52
Treatment cycle length (days)	28.2 $\pm$ 2.0	27.1 $\pm$ 3.2	0.23
Luteal phase length during treatment (days)	12.5 $\pm$ 2.5	13.3 $\pm$ 2.4	0.32
Post-treatment cycle length (days)	29.6 $\pm$ 3.5	28.2 $\pm$ 3.9	0.23
<i>Mid-luteal phase (treatment cycle)</i>			
Progesterone (ng/mL)	12.5 $\pm$ 5.6	16.1 $\pm$ 8.5	0.13
Estradiol (pg/mL)	136.1 $\pm$ 67.6	165.3 $\pm$ 64.8	0.15
<i>Ultrasound endometrial thickness (treatment cycle)</i>			
Baseline (mm)	10.2 $\pm$ 3.2	10.3 $\pm$ 2.3	0.93
At biopsy (mm)	11.5 $\pm$ 4.1	9.7 $\pm$ 1.8	0.03
Change in thickness (mm)	1.3 $\pm$ 2.3	-0.6 $\pm$ 2.2	0.007