Contraceptive efficacy of daily administration of 0.5 mg mifepristone

Lena Marions¹,³, Sandor Viski²,
Kristina Gemzell Danielsson¹, Bela A. Resch²,
Marja-Liisa Swahn¹, Marc Bygdeman¹ and
László Kovács²

¹Department of Woman and Child Health, Division for Obstetrics
and Gynecology, Karolinska Hospital, S-171 76 Stockholm,
Sweden and ²Department of Obstetrics and Gynecology,
Albert Szent-Györgyi, Medical University Szeged, Hungary
³To whom correspondence should be addressed

The antiprogestin mifepristone has shown potential to be used as a contraceptive. If 200 mg mifepristone is administered immediately after ovulation, the endometrium shows sufficient impairment of secretory development to prevent implantation. Low daily doses of mifepristone have been shown to reduce several of the local factors regarded as crucial for implantation in human endometrium. To find out if this regimen is sufficient to prevent pregnancy, 32 women were recruited for a study where 0.5 mg mifepristone was administered daily. A total of 141 cycles were studied. Five pregnancies occurred, which was significantly less than if no contraceptive method had been used. However, the dose chosen did not seem sufficient to act as a contraceptive although it is probably not possible to increase the dose without disturbing ovulation and bleeding pattern.

Key words: antiprogestin/contraception/implantation/mifepristone

Introduction

The 19-norsteroid mifepristone (RU 486; Roussel Uclaf, Paris, France) has a number of effects that could be useful for contraceptive purposes.

Mifepristone interacts with the progesterone receptor, preventing progesterone from expressing its biological effects (Baulieu, 1991). Since progesterone is essential for the formation of the secretory endometrium which is required for nidation of the conceptus (Aitken, 1979), an effect of antiprogestosterone on implantation could be expected.

The effect of antiprogestosterone depends on the time of treatment and the dose given. Administration of high doses of mifepristone in the mid- or late follicular phase delays the luteinizing hormone (LH) surge and postpones ovulation (Liu et al., 1987; Shoupe et al., 1987; Luukkainen et al., 1988), but has no effect on proliferative endometrial morphology (Swahn et al., 1988). However, if 200 mg of mifepristone is administered immediately after ovulation the secretory development of the endometrium is retarded, whilst the plasma concentrations of follicle stimulating hormone (FSH) and ovarian steroids remain unchanged (Swahn et al., 1990). This effect on the endometrium has also been shown to be sufficient to prevent pregnancy (Gemzell Danielsson et al., 1993).

Furthermore, it has been demonstrated that 600 mg mifepristone is sufficient to prevent implantation when given within 72 h of unprotected intercourse (Glasier et al., 1992; Webb et al., 1992). Since a substantial number of women were treated at or after ovulation, the effect of mifepristone must have been due to its inhibitory action on endometrial development and function. This strongly supports the assumption that the endometrial effect of mifepristone is sufficient to prevent pregnancy. Previous studies have shown impaired secretory activity of the endometrium also with low doses of mifepristone daily or weekly. In one study, 5 or 2.5 mg mifepristone was administered once weekly. Ovulation was not inhibited, but it could occasionally be delayed for 6–13 days. A delay in endometrial development occurred associated with an inhibition of the decrease of progesterone receptor concentration, a significant reduction in Dolichus biflorus agglutinin (DBA)–lectin binding and in serum concentration of glycoselin (Gemzell Danielsson et al., 1996). In another study, daily doses of 0.5 or 0.1 mg mifepristone were given during 3 months (Gemzell Danielsson et al., 1997a) and 0.5 mg mifepristone was also shown to affect endometrial secretory activity, with a decrease in endometrial expression of glycoselin as well as decrease in DBA lectin binding during the third month of treatment. However, no significant effect was seen on the progesterone receptor concentration. In none of the volunteers was the duration of the menstrual cycle influenced or any changes in ovarian function demonstrated. It was considered that the effect on the endometrium would be sufficient to prevent implantation and thus a contraceptive method could be developed without an effect on ovulation and the bleeding pattern of the menstrual cycle. To test this possibility, we have recently evaluated the contraceptive effect of administration once weekly of 5 mg mifepristone. Pregnancy rate was significantly reduced but not sufficiently to be used as a regular contraceptive method (Marions et al., 1998a). The aim of the present study was to evaluate the effect of 0.5 mg mifepristone once daily.

Materials and methods

Subjects

Between February and June 1997, 32 healthy, fertile and sexually active women with regular menstrual cycles (median 28 days; SD 2.6, range 21–42 days) were recruited for the study from two centres;
Szeged, Hungary and Stockholm, Sweden. The mean age was 31 years (range 21–42) and all had been pregnant before (mean number of pregnancies 2.5; range 1–6). Several women in the study had previously used oral contraceptives and preferred for various reasons an oestrogen-free contraceptive method. The subjects were treated with 0.5 mg mifepristone daily (Roussel Uclaf, Paris, France; batch no. CT-0339, expired date September 1999), starting on cycle day 2, for up to 6 months. No other contraceptive method was used. A follow-up examination was performed once a month at the expected time of menstruation. Human chorionic gonadotrophin (HCG) in plasma was then determined using non-competitive immunassay (Immulite system, DPC, Los Angeles, CA, USA). The detection limit of the assay was 1.1 mIU/ml. The antibody used was highly specific for HCG with low cross-reactivity to other glycoprotein hormones present in patient samples, according to the manufacturer. Information was also collected through diary cards and interviews, concerning pill intake time, side-effects, vaginal bleeding, time of onset, duration and amount of menstrual bleeding and acts of intercourse. The subjects were also asked to return the pill packages at the end of the study.

If HCG was negative (β-HCG <10 mIU/ml if pregnancy was defined as HCG >10 mIU/ml) the treatment was continued. If HCG was positive, the woman was referred for pregnancy termination (our recommendation) or continued the pregnancy depending on her own choice. All subjects were informed about the limited knowledge of the effects of mifepristone on fetal development and the risk of teratogenic effects, before entering the study. The study was approved by the drug regulatory authorities and by the local ethics committee in both countries. A prerequisite for the approval was that the study was interrupted if more than two pregnancies in each centre occurred.

Statistical analysis

The χ² test was used to compare the number of pregnancies observed with the expected number of pregnancies if no contraceptive method had been used.

Results

The intention at the start of the study, was to recruit 40 women, 20 from each centre, to be treated for 6 months. Since five pregnancies occurred prior to that, the study was interrupted when 32 women had been treated for 1–6 months for a total of 141 cycles. Figure 1 illustrates the distribution of treatment cycles among the subjects. Fifty percent of the women (16 subjects) completed the 6 month study period. All but five women were treated for 3 months or more (median 5.5 months, SD 1.8 months). Five pregnancies occurred during the study, all of which were terminated by medical or surgical abortion. No histological analyses were performed other than for confirmation of the pregnancy. One pregnancy occurred in the first treatment month, one in the second, two in the third and one in the fifth treatment month.

The mean frequency of intercourse was 2.0 per week. Assuming that ovulation occurred 14 days before the onset of menstruation, at least one act of intercourse would have occurred during the period 3 days before to 1 day after ovulation in 122 cycles, which would give a probability of pregnancy of 0.04. According to Wilcox and co-workers (Wilcox et al., 1995), the expected number of pregnancies would have been 40 when calculated from the day of intercourse in each cycle. In cycles where more than one act of intercourse occurred during the fertile period of the cycle, only the one with the highest probability factor was used.

The median duration of the menstrual cycles was slightly prolonged from 28 days (SD 2.6 days, range 21–42) to treatment to a median of 31 days (SD 11.2 days, range 19–69 days) during treatment. Light intermenstrual bleeding (heavy bleeding not exceeding 2 days) occurred in two cycles and spotting (light bleeding not requiring sanitary napkins) in two other cycles. One subject discontinued after one cycle because of prolonged menstrual bleeding (21 days). Seven treatment months without bleeding were reported. The median duration of the menstrual bleeding was unchanged, 5 days (SD 1.0, range 4–8). No differences in the bleeding pattern were reported from the subjects who became pregnant.

No other side-effects other than bleeding disturbances which could be related to the treatment were found.

Discussion

The optimal contraceptive method disturbs endometrial development enough to prevent implantation without affecting ovulation and thus the bleeding pattern. Several studies have confirmed disturbances in the endometrium during the implantation window following treatment with mifepristone in both animals and humans. Once weekly administration of 5 or 10 mg of the antiprogestin onapristone to bonnet monkeys did not inhibit ovulation but caused atrophic changes in endometrial glands as well as in the stroma. The same group also demonstrated this effect to be sufficient to prevent implantation (Ishwad et al., 1993; Katkam et al., 1995). In humans the individual differences seem to be greater, influencing the effect of antiprogestins. In any case, it is difficult to compare results from different species.

Daily administration of 1 mg mifepristone consistently inhibits endometrial development in humans, but will occasionally also suppress ovulation (Batista et al., 1992; Croxatto et al., 1993). When 21 women were treated with 1 mg of mifepristone daily for 5 months, endometrial development was disrupted in all subjects (Croxatto et al., 1998). However, bleeding cyclicity was altered in 57% of cases, suggesting that an even lower dose might still affect endometrial maturation without preventing ovarian cyclicity. In the present study, the dose was reduced to 0.5 mg mifepristone daily to avoid an effect on ovarian sex hormone secretion and to evaluate if the endometrial alteration previously reported (Gemzell Danielsson et al., 1997a) would be sufficient to prevent implantation. Five pregnancies occurred, which is significantly fewer than

Figure 1. Distribution of treatment cycles among subjects.
expected \((n = 40)\) according to studies (Wilcox et al., 1995) in fertile and sexually active females, indicating that the effect of mifepristone on the endometrium at least disturbs the implantation process. It is possible that a higher dose of mifepristone would be more effective. However, in this study several cycles were amenorrhoeic and, in agreement with a previous report (Croxatto et al., 1998), it is likely that an increase in dose would cause an unacceptable frequency of cycle disturbances. Furthermore, early luteal phase treatment with 200 mg mifepristone on the second day after the LH surge \((\text{LH} + 2)\) has been shown to be an effective contraceptive method and might be an attractive alternative when more reliable and cheaper self tests for detection of ovulation become available.

Several markers for endometrial receptivity have been proposed. Lessey and co-workers (Lessey et al., 1994) have suggested members of the integrin family to be such markers. Consistent with their findings, we previously found expression of \(\alpha_\beta\) and \(\alpha_\beta\beta\) integrin during the putative implantation window. After treatment with both high \((200 \text{ mg monthly})\) and low \((0.5 \text{ mg daily}, 2.5 \text{ mg or } 5 \text{ mg weekly})\) doses of mifepristone the expression of \(\alpha_\beta\) and \(\beta_\beta\) integrin was significantly reduced, while the expression of \(\alpha_\beta\beta\beta\) integrin remained unaffected (Marions et al., 1998b). Leukaemia inhibitory factor (LIF) has also been suggested as an important factor during the receptive phase (Stewart et al., 1992) and was also inhibited with both high \((200 \text{ mg monthly})\) and low \((0.5 \text{ mg daily}, 2.5 \text{ mg or } 5 \text{ mg weekly})\) doses of mifepristone (Gemzell Danielsson et al., 1997b). However, a high dose of mifepristone had a more pronounced effect on endometrial morphology. In addition to a significant decrease in number of glands and glandular diameter, which could also be demonstrated following low doses of mifepristone, an increased frequency of glandular and stromal mitosis was found after treatment with 200 mg mifepristone on cycle day LH + 2. Mifepristone 200 mg administered immediately after ovulation (Gemzell Danielsson et al., 1993) seems to have a higher contraceptive effect than both 5 mg mifepristone once a week and 0.5 mg mifepristone daily. Normal endometrial receptivity appears to be strongly associated with the down-regulation of epithelial progesterone receptor levels during the luteal phase, an effect that is prevented by 200 mg mifepristone in the post-ovulatory period but not (or not to the same extent) during treatment with lower doses, i.e. 0.5 mg daily, 2.5 mg or 5 mg weekly. Thus the contraceptive efficacy of mifepristone might be related to the effect on progesterone receptor concentration.

We conclude that 0.5 mg mifepristone daily significantly decreases pregnancy rate, but not enough to be used on a regular basis.

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