New option for reversible suppression of menstruation

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Two new types of antiprogestins have been shown to reversibly suppress menstruation, and could provide a reliable method of menstrual control for women. Scientists at the Oregon Regional Primate Research Center (ORPRC; Beaverton, OR, USA) have recently published preclinical data[1] in rhesus macaques identifying the different doses of antiprogestins (progesterone antagonists; PAs) that can block menstruation and, depending on the dose, also block ovulation, in a reversible manner. The rhesus macaque is a useful model of menstruation because it is one of the only animals that regularly menstruates, and its hormonal control of menstruation is similar to that in women.

A reliable method of menstrual suppression could greatly enhance the quality of life for many women, particularly those who suffer from excessive bleeding (which often requires treatment by hysterectomy) or in stressful occupations such as the military. Although the combined oestrogen and progesterone contraceptive pill can serve this purpose, it is not suitable for all women because of health risks such as increased blood-clotting and breast cancer, and is often associated with unfavourable side-effects.

Normal menstruation

The term menstruation describes the bleeding and sloughing of the uterine endometrium, which consists of two distinct layers: the basal layer (stratum basale) and the functional layer (stratum functionale). The basal layer undergoes little cyclic change, whereas the functional layer arises from the basal layer during each menstrual cycle in response to hormonal stimuli, and is shed in the absence of a fertilized egg (menstruation).

The development and subsequent shedding of the endometrium occurs in three distinct phases, during which the levels of several reproductive hormones vary. First, during the proliferative phase, the cells of the functional layer grow in response to high oestrogen levels. Second, progesterone levels peak and stimulate the secretory phase during which egg implantation would occur; and third, in the menstrual phase, the absence of human chorioid gonadotrophin (hCG) secreted by an embryo causes progesterone levels to drop. The highly specialized vasculature of the functional layer, known as spiral arteries, then constricts in response to reduced progesterone levels, causing hypoxia, ischaemia and subsequent tissue breakdown, which results in menstruation.

Antiprogestin action

PAs block the action of progesterone, which is the predominant hormone in the second half of the menstrual cycle that induces the development of the functional layer of the endometrium. If, therefore, PAs are administered before the functional layer fully develops, then no menstruation will occur. Similarly, if PAs are administered at a dose that is sufficient to block ovulation, then the ovary will not produce the progesterone required to build up the endometrium.

Brenner and colleagues at the ORPRC have carried out three different studies in macaque monkeys[1]. First, using two recently identified antiprogestins, ZK137316 and ZK230211, which are type II and type III antiprogestins, respectively, they established the dose range that would block progesterone action directly on the endometrium in artificially cycled, spayed macaques. Second, they studied the histological effects of ZK230211 on the endometrium; and third, they determined whether reversible menstruation could be achieved in normal, cycling rhesus monkeys after chronic administration of both ZK137316 and ZK230211 at doses that suppress endometrium development.

Dose studies

Two dose-finding studies were carried out in ovariectomized rhesus macaques during hormonally regulated, artificial menstrual cycles: (1) to determine the dose of PA given chronically throughout one menstrual cycle that would block menstruation on progesterone withdrawal, and (2) to determine the dose that would induce menstruation when given acutely at the end of a menstrual cycle.

Brenner and colleagues found that ZK230211 was three–fivefold more potent than ZK137316 at inducing bleeding in the menstruation induction study. Histological observations, such as reduced mitotic and elevated apoptotic indices, endometrial shrinkage (Fig. 1), stromal compaction, glandular atrophy and hyalinizating degeneration of the spiral artery wall showed that ZK230211 was also approximately threefold more potent than ZK137316 at suppressing the proliferation of the functional layer of the endometrium in oestradiol and progesterone-primed animals.

In another experiment, immunocytochemistry was used to measure the

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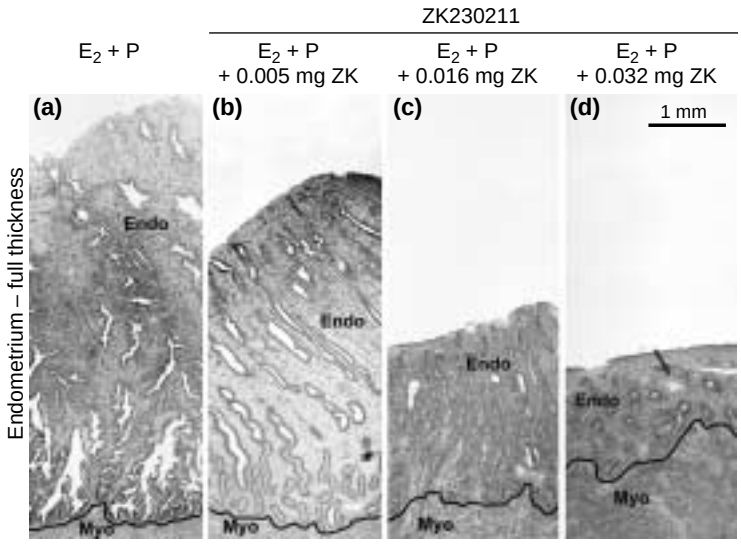

Figure 1. Photomicrographs of haematoxylin-stained sections of full-thickness endometrium. **(a–d)** show the decreasing thickness of the endometrium with increasing doses of ZK230211. The black line indicates the endometrial–myometrial border. The arrow in **(d)** points to a dilated vein. Abbreviations: E_2, oestradiol; P, progesterone; ZK, ZK230211; Endo, endometrium; Myo, myometrium. Reproduced, with permission, from Ref. 1.

levels of progesterone and oestrogen receptors (PR and ERα, respectively). Administration of the PAs had blocked the suppressive effect of progesterone on both the PR and ERα. Furthermore, the anti-progesterone activity of ZK230211 was sufficient to block the progesterone-dependent growth of the basal endometrial layer, which, in rhesus macaques, contributes to overall endometrial growth during the second half of the cycle. The suppressive effects of progesterone on oviductal growth and differentiation were also blocked by PA treatment. These are the first data that demonstrate low-dose modulation of the endometrium and oviduct by ZK230211 in spayed, cycling macaques.

Menstrual suppression

From the previous dose-finding studies, Brenner and colleagues were able to choose doses at which to study the ability of PAs to suppress menstruation in ovarian-intact animals undergoing normal menstrual cycles. Two studies (40-day and 100-day) were conducted with ZK137316 and one study (60-day) with ZK230211, to mimic cases where women might want to block either one or several menstrual periods.

Treatment with ZK137316 at either 0.05 mg kg^{-1} or 0.10 mg kg^{-1} blocked menstruation in all animals and suppressed ovulation in ~50% of the animals. In animals that ovulated, ZK137316 antagonized progesterone-dependent endometrial development, as shown by the absence of menstrual bleeding. By contrast, ZK230211 was found to be far more potent than ZK137316 because a dose of 0.016 mg kg^{-1} completely suppressed both ovulation and menstruation. Interestingly, Brenner and colleagues noted a significant suppression of luteinizing hormone (LH), which suggests that ZK230211 is exerting its anti-ovulatory actions via the hypothalamic–pituitary axis[2].

The difference in action and potency between the two PAs suggests that ZK230211 is a pure PA, that is, it has no agonist activity for the progesterone receptor. By contrast, the anti-ovulatory and anti-endometrial effects of ZK137316 were dissociated, and other data[3] suggest that this compound might act as a partial agonist. There is a potential, therefore, for two separate therapeutic approaches with these compounds depending on whether blockade of ovulation is required.

Brenner described important aspects of this type of therapy as follows: first, the ovulatory blockade induced by PAs was accompanied by normal levels of circulating oestradiol, which would favour normal oestradiol action in the skeletal and vascular systems; for example, hot flushes would not occur. Second, PA treatment should, through its endometrial antiproliferative effect, prevent the risk of endometrial cancer resulting from unopposed oestrogen action.

David Baird from the Department of Reproductive Biology at the University of Edinburgh (Edinburgh, UK) thinks this research is encouraging. His research group have used very low doses of mifepristine (RU486, known as the abortion pill) to induce amenorrhoea in 90% of the women studied. He said, '[Menstrual suppression] is an area that we are particularly interested in, in our capacity of trying to develop new methods of contraception, and a number of us have felt for a long time that there's room for a method of contraception which induced amenorrhoea. We've just completed quite a big international survey including women in Edinburgh, two centres in Africa, and in Asia, to see how acceptable a method of induced amenorrhoea would be and whether women would welcome it. The data is still under analysis, but the bottom line is that the majority of women in each of these centres say that, yes, they would like induced amenorrhoea. For example, in Edinburgh [this majority] was ~65%.' He continued, 'So, I think this is a very encouraging development, the use of compounds that induce a degree of atrophy of the endometrium…the health benefits are really quite substantial, [as well as] the social convenience of not menstruating'.

Are antiprogestins safe?

After treatment, the menstrual cycles of the animals were observed to be normal, demonstrating the lack of any residual effect and the complete reversibility of menstrual suppression. Research is now needed in women to establish whether PA-mediated menstrual suppression is safe, and whether it might affect fertility in the long term. However, Brennan pointed out that women currently use intra-uterine devices (IUDs) that suppress menstruation for years without ill effect, and rhesus macaques given antiprogestin in a one-year unpublished ORPRC study showed no ill effect after treatment, and a complete return to normal fertility. He adds that, 'When we conducted these studies, we had in mind women in the military, the space program or in other stressful jobs where a short-term suppression of menses would be useful. Not all women can use the pill to accomplish this. We also felt that suppression of excessive bleeding would be an aid to the clinical management of menorrhagia and perhaps reduce the need for hysterectomies, most of which are done to reduce excessive bleeding.'

Brenner is uncertain as to when clinical trials of antiprogestins could begin, but predicts that it might be within a few years depending on the interests of patient populations, clinicians and the pharmaceutical industry. He and his colleagues are now working on how antiprogestins induce their specific antiproliferative effects in the endometrium.

References

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