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Selective progesterone receptor modulators and progesterone antagonists: mechanisms of action and clinical applications

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Since the discovery of the antiprogestin mifepristone, hundreds of similar compounds have been synthesized, which can be grouped in a large family of progesterone receptor ligands. This family includes pure agonists such as progesterone itself or progestins and, at the other end of the biological spectrum, pure progesterone receptor antagonists (PA). Selective progesterone receptor modulators (SPRM) have mixed agonist–antagonist properties, and occupy an intermediate position of the spectrum. These compounds have numerous applications in female health care. Mifepristone is used to terminate pregnancy, and as such is commercially available in many countries. The negative abortion-related image of mifepristone has clearly limited the involvement of the major pharmaceutical companies in the development of PA and SPRM. Many PA and SPRM display direct antiproliferative effects in the endometrium, although with variable actions which seem product- and dose-dependent. This property justifies their use in the treatment of myomas and endometriosis. PA also suppress late follicular development, block the LH surge and retard endometrial maturation, which renders them potential estrogen-free contraceptive drugs. SPRM such as asoprisnil are not as effective in blocking the LH surge and appear to target the endometrium directly and produce amenorrhoea. Interestingly, clinical data show that treatment with these compounds is not associated with hypo-estrogenism and bone loss. The potential clinical applications of these compounds cover a broad field and are very promising in major public health areas. These include emergency contraception, long-term estrogen-free contraception (administered alone, or in association with a progestin-only pill to improve bleeding patterns), myomas (where they induce a marked reduction in tumour volume and produce amenorrhoea) and endometriosis. Further developments might also include hormone replacement therapy in post-menopausal women, as well as the treatment of hormone-dependent tumours.

Key words: contraception/mifepristone/myomas/progesterone receptor antagonists/selective progesterone receptor modulators

Introduction

The reproduction-related targets of progesterone include the uterus, the ovary, the mammary gland, and the hypothalamic–pituitary axis. The physiological effects of progesterone include differentiation of the endometrium, control of implantation, maturation of the mammary epithelium and modulation of GnRH pulsatility. Progesterone also plays an important role in oocyte release from the ovary. These actions have led to major pharmacological applications of progesterone and progestins in contraception, control of uterine bleeding, and HRT. Soon after the discovery of the progesterone receptor (PR) (Sherman *et al.*, 1970; Loosfelt *et al.*, 1986; Misrahi *et al.*, 1987, 1988) it was appreciated that the development of a PR antagonist would have a major therapeutic potential. The first report on mifepristone (RU 486), a progesterone and glucocorticoid receptor antagonist, was published by Philibert *et al.* (1981). Since then, numerous related compounds have been synthesized exhibiting a spectrum of activity ranging from pure progesterone receptor antagonists (PA), to mixed agonists/antagonists. These latter compounds are also known as selective progesterone receptor modulators (SPRM), progesterone receptor modulators (PRM), mesoprogestins or partial agonist–antagonists (Elger *et al.*, 2000;

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Spitz, 2000; Spitz and Chwalisz, 2000). All these molecules, progesterone agonists, PA and SPRM, belong to the large progesterone receptor ligand family, and have many potential clinical applications both in female reproduction, and in the treatment of tumours. There is still a controversy on the classification of these progesterone receptor ligands. Some authors differentiate PA and SPRM while others include antagonists and agonists as part of the SPRM family. In this review the term SPRM will be restricted to compounds with mixed agonist–antagonist activity.

The primary action of progesterone is to maintain pregnancy. This hormone facilitates the LH surge, transforms the endometrium from a proliferative to a secretory state and, together with estradiol, maintains endometrial integrity. Subsequently, progesterone maintains the uterus in a quiescent state by inhibiting myometrial contractility. PA antagonize all these actions. It is therefore not surprising that their first clinical application was to induce termination of pregnancy. Unfortunately, this has delayed the further development of this class of compounds due to the negative image of mifepristone related to abortion, and has kept large companies outside this field of research and development.

This negative perception is, however, scientifically erroneous. In fact, as opposed to PA, the mixed agonist–antagonist SPRM, because of their intrinsic progesterone agonistic activity, have an absent or only a minimal effect on pregnancy termination in animals (Elger *et al.*, 2000). This has been the main justification for a new nomenclature of SPRM to distinguish them from classical PA which have the ability to terminate pregnancy, often at very low doses. Nevertheless, pure PA besides their ability to induce abortion have other very useful indications.

Indeed, the clinical potential of these molecules is very extensive (Table I). This review will highlight the mechanism of action of these compounds with special emphasis on their effects on the uterus. The main gynaecological applications discussed include the treatment of uterine myomas, and endometriosis as well as contraception, emergency contraception and the management of bleeding induced by treatment with progestins. Their potential in the treatment of malignant disorders will also be reviewed. Other applications have been reviewed elsewhere (Grimes, 1997; Ashok and Templeton, 1999; Christin-Maitre *et al.*, 2000; Spitz and Chwalisz, 2000; Spitz, 2003).

Table I. Clinical applications

Short-term (usually single dose) administration of mifepristone
Medical termination of early pregnancy
Medical termination of more advanced pregnancies
Menstrual regulation
Labour induction (not recommended)
Medical management of early fetal demise
Management of fetal death
Emergency contraception
Potential use in IVF programmes
Long-term administration
Uterine myoma (SPRM or PA)
Endometriosis (SPRM or PA)
Contraception (PA), alone or in association with progestin-only pills to control bleeding patterns
Breast cancer (PA)
Non-gynaecological applications of PA
Cushing's syndrome
Glucocorticoid antagonism (potential application in burns, glucocorticoid-dependent hypertension, arthritis, glaucoma, viral diseases possibly including AIDS)
Major depression with psychotic features
Alzheimer's disease
Steroid receptor-containing tumours (breast, ovary, prostate and endometrium as well as in meningiomas, gliomas and leiomyosarcomas)
GeneSwitch® system for ligand-dependent transgene expression

Mifepristone is used for all short-term indications. Selective progesterone receptor modulators (SPRM) cannot be used because of their intrinsic agonist activity. SPRM and progesterone receptor antagonists (PA) have application in other gynaecological and non-gynaecological conditions. [Adapted from Spitz (2003) with permission.]
SPRM = selection progesterone receptor modulators; PA = progesterone receptor antagonists.

Chemical structure

Most PA and SPRM developed for clinical application to date (Table II) are steroid-derived compounds (Figure 1). Mifepristone (RU 38486) [11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-propinyl-4,9-estradiene-3-one] is a beta-aryl-substituted, 19-nortestosterone-derived compound. The substituted radical at position C17 is related to certain progestagens. The substituted radical at position C11 is related to the overall structure of antiestrogens of the triphenylethylene series. The C11 β side chain confers on RU 38486 antagonistic properties to glucocorticosteroid and progestational hormones.

Onapristone (ZK 98 299) [11β-(4-dimethylaminophenyl)-17α-hydroxypropyl-17β-(3-hydropropinyl)-13α-methyl-4,9-gona diene-3-one] shares the same general structure as mifepristone. CDB 2914 (CDB: Contraceptive Development Branch of NICHD) is a 19-norprogesterone derivative, also with 11β-aryl substitutions. CDB 2914 has shown progesterone antagonist without agonist activity in all studies published. The Org 33628 and 31710 compounds are mostly antagonist. Asoprisnil (J 867) is a hydrophobic oxime: benzaldehyde-4-[(11β,17β)-17-methoxy-17-(methoxymethyl)-3-oxoestra-4,9-dien-11-yl]-1-oxime (CAS), with substitutions at the 11 position.

The 'isnil' suffix distinguishes the SPRM from the PA (antagonists, e.g. mifepristone and onapristone). Whereas mifepristone and onapristone (sharing the same 'pristone' suffix), are mainly antagonist PR ligands, asoprisnil has partial PR agonist activity. Non-steroidal PA and SPRM have also been developed (Negro-Vilar, 2000), but are not currently being clinically evaluated, and will not be discussed.

Mechanism of action of PA and SPRM

Progesterone receptors

The actions of progesterone, as well as of PA and SPRM, in target tissues are mediated mainly by PR which belong to the nuclear receptor family. These receptors are ligand-activated transcription factors and share a similar basic structure (for reviews, see Leonhardt and Edwards, 2002; Giangrande and McDonnell, 1999). The PR exists as two separate isoforms (A and B), expressed from a single gene (Figure 2) with two different transcription initiation sites allowing the transcription of either isoform (Kastner *et al.*, 1990; Leonhardt and Edwards,

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Table II. Main progesterone receptor antagonists (PA) and selective progesterone receptor modulators (SPRM) compounds currently undergoing clinical development

Compound	Company	Trials: phase and field of application
Asoprisnil (J867)	TAP Pharmaceutical Products Inc. (USA)	Phase II–III, leiomyomas
CDB/VA 2914	HRA Pharma (France)	Phase II, contraception, leiomyomas
Org 33628	Organon (The Netherlands)	Phase II, contraception, together with progestins
Mifepristone, Mifegyne®, (RU 38486)	Excelgyn (France) Danco (USA)	Commercially available for medical termination of pregnancy. Ongoing studies: contraception, breast cancer treatment

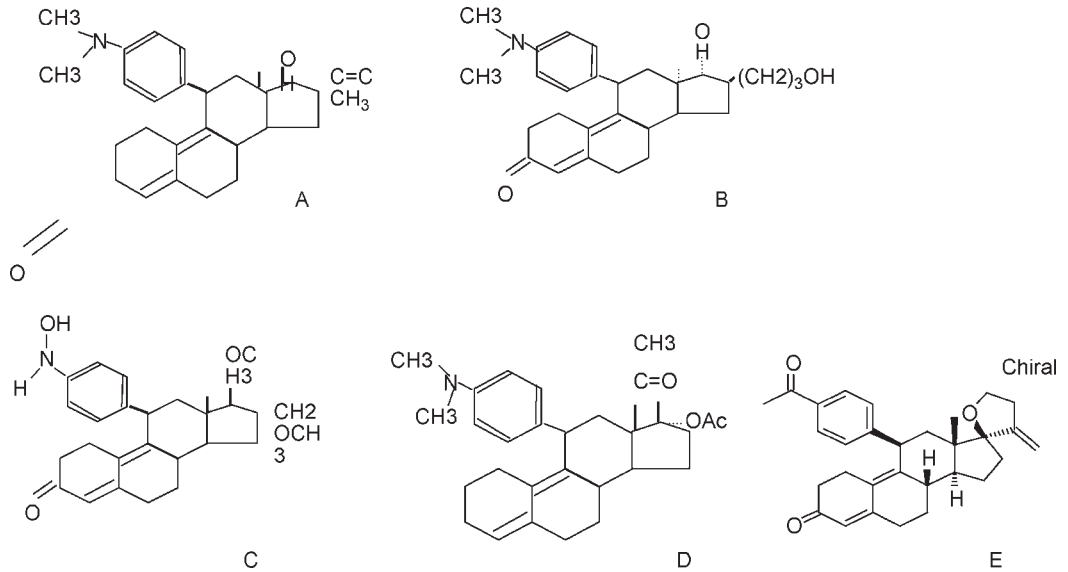

Figure 1. Chemical structures of mifepristone (**A**), onapristone (**B**), asoprisnil (**C**), CDB 2914 (**D**) and Org 33628 (**E**).

2002). The structural configuration of PRA and PRB differs only in the fact that PRB contains an N-terminal fragment of 164 amino acids which is absent from PRA. As a consequence PRB contains three transcription-activating domains (AF-1 AF-2 and AF-3) whereas PRA contains only two (AF-1 and AF-2). The two PR isoforms have similar steroid hormone and DNA binding activities but have distinct functions depending on the cell type and context of the target gene promoter. In general, PRB is a much stronger transcription activator than PRA. Under certain conditions, PRA is inactive as a transcription factor but can function as a ligand-dependent trans-dominant repressor of other steroid receptors including PRB, estrogen receptor (ER), androgen receptor (AR), mineralocorticoid receptor (MR) and glucocorticoid receptor (GR). PRA can act in this repressor mode in response to binding of either progesterone agonists or antagonists (Tung *et al.*, 1993; Vegeto *et al.*, 1993; McDonnell and Goldman, 1994; McDonnell *et al.*, 1994; Leonhardt and Edwards, 2002).

In knock-out models, Mulac Jericevic *et al.* (2000) have shown that PR isoforms can play different roles depending on the tissue. Selective ablation of PRA results in a gain of PRB-mediated proliferative activity in the endometrium. Thus PRB increases whereas PRA decreases estradiol responsiveness in the uterus. The precise effect of these compounds on the endometrium may thus depend on the PRA:PRB ratio. In the breast, PRB appears to control both differentiation and proliferation.

Mechanisms of transcription activation

Once inside a target cell (Figure 3), progesterone induces a conformational change of its receptor, transforming PR from a non-DNA-binding, inactive form, into one that will bind DNA. This transformation is accompanied by a loss of associated heat shock proteins, and dimerization. The activated PR dimer then binds to specific DNA sequences within the promoter region of progesterone-responsive genes, referred to as progesterone response elements (PRE). The agonist-bound PR is believed to activate transcription either by direct action on the general transcriptional machinery or by association with co-activators. This interaction is followed by increases of the transcription rate, producing agonist effects at cellular and tissue levels. Co-activators may be regarded as amplifiers of transcriptional regulation and include, among others, steroid receptor co-activator (SRC) family members and receptor-interacting protein 140 (RIP 140) (Wagner *et al.*, 1998; Liu *et al.*, 2002; Smith and O'Malley, 2004).

PR can also interact with transcription co-repressors such as the nuclear receptor corepressor (NCoR), and the silencing mediator of retinoic acid and thyroid hormone receptor (SMRT).

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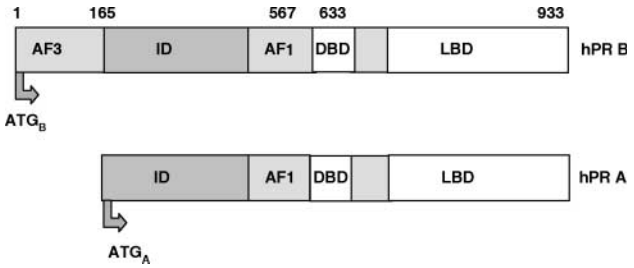

Figure 2. Primary structure of the two main isoforms of the progesterone receptor (PR), hPRA and hPRB. AF = activation function; ID = inhibitory domain; LBD = ligand binding domain; DBD = DNA binding domain; ATG = initiation of transcription codon.

This usually occurs in the presence of an antagonist ligand. Co-repressors, like co-activators, function as part of large protein complexes and may have enzymatic properties including histone deacetylase activity which modulate DNA global shape and transcriptional activity. Their interaction with an antagonist ligand–receptor complex will result in the absence of transcription activation. There appears to be an intracellular equilibrium of co-activators and co-repressors in a tissue-specific manner. This balance can be shifted towards co-repressors by an antagonist. For a review see Smith and O'Malley (2004).

The receptor activation steps of dissociation from heat shock proteins, as well as dimerization and binding to PRE are not impaired by PA and SPRM. The interaction and recruitment of co-regulators (Liu *et al.*, 2002), as well as post-translation modifications of PR and co-regulators (Hermanson *et al.*, 2002; Chauchereau *et al.*, 2003; Smith and O'Malley, 2004) appear to be the main factors determining agonist or antagonist activity. Interactions with other intracellular pathways, especially cAMP, as well as the ratio of PR isoforms in the cell (Gellersen and Brosens, 2003) may also be important. Under *in vitro* conditions, an antagonist may be converted to an agonist depending on the type of model and ligand, the cellular context and the dose and duration of exposure to the ligand (Kahmann *et al.*, 1998).

The usual method to determine the progestational activity of a given molecule is the McPhail test (McPhail, 1934; Philibert, 1984; Elger *et al.*, 2000) which determines the degree of endometrial proliferation and transformation in immature rabbits initially primed with estradiol and subsequently treated with the test substance. Antagonistic properties may be evaluated by co-administration with progesterone. In this test, mifepristone, onapristone (ZK 98 299) as well as CDB 2914 behave as pure PA and demonstrate no agonist activity. Progesterone and the synthetic progestin R5020 behave as agonists. In contrast, the J compounds (for example asoprisnil) are mixed agonist–antagonists in this model. Even in large doses, these compounds do not display either the potent agonistic activity of progesterone or the antagonistic activity of mifepristone (Elger *et al.*, 2000).

Other models have also been used to evaluate the progestational activity of these compounds. In T47D mammary tumour cell model, mifepristone is converted to a progesterone agonist in the presence of protein kinase A activators (e.g. 8-Br-cAMP), whereas onapristone and CDB 2914 fail to demonstrate any agonist activity (Attardi *et al.*, 2002; Beck *et al.*, 1993; Sartorius *et al.*, 1993). This may be due do different interactions between the different PA and the co-regulators (Wagner *et al.*, 1998; Liu *et al.*, 2002). In T47 D cells, progesterone can induce alkaline phosphatase activity (Wagner *et al.*, 1996). In this model,

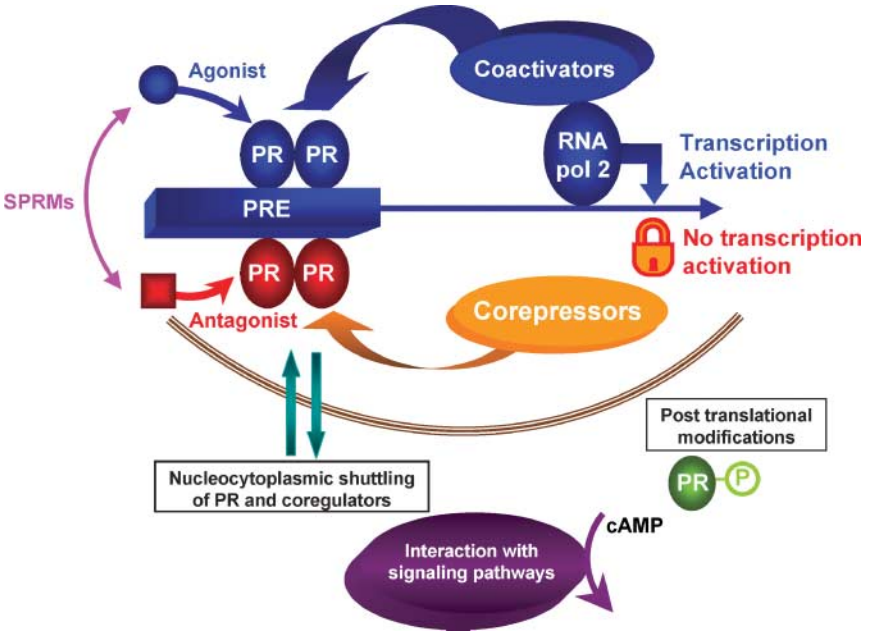

Figure 3. Activation of the progesterone receptor (PR) by progesterone receptor ligands. Binding of progesterone to the inactive receptor complex induces a conformational change, which leads to Heat Shock Protein (HSP) dissociation, receptor dimerization, DNA binding, and recruitment of co-activators [e.g. steroid receptor co-activator (SRC) and CBP] to facilitate communication with the basal transcription apparatus RNA POL2 (RNA polymerase). PRE = progesterone response element. Action of progesterone receptor antagonists (PA): PA compete with the agonist for PR binding and promote the activation steps of dimerization and binding to specific PRE of target DNA. However, PA induce an altered conformation in PR that is transcriptionally inactive, resulting in a non-productive interaction of the receptor with DNA. This is caused by PR recruitment of co-repressors (e.g. nuclear receptor co-repressor (NcoR) and silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) instead of co-activators.

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mifepristone as well as CDB 2914 behave as pure antagonists, without agonist potency (Attardi *et al.*, 2002; Blithe *et al.*, 2003). In the same model, asoprisnil demonstrated less progesterone antagonist activity than mifepristone (DeManno *et al.*, 2003).

Other recent approaches include cellular models where PR is co-transfected with different reporter genes and animal models in which new specific target genes (including complement C3 fraction) are screened to determine the various activities of the compounds (for example C3 variations are correlated to the anti-estrogenic activity of the compounds, (Lundeen *et al.*, 2001). These models are very useful to screen large numbers of potential steroidal and non-steroidal molecules.

Endometrial effects of PA and SPRM

Endometrial PR–co-regulators system

The expression of both PR isoforms as well as of their co-regulators has been described in the endometrium (Figure 4) (Wang *et al.*, 1998; Mote *et al.*, 1999; Gregory *et al.*, 2002). PRB is up-regulated in the stroma and in the glandular epithelium during the follicular phase, and is down-regulated in both cell compartments during the luteal phase. PRA on the contrary is up-regulated in both cell types in the follicular phase and persists in the stromal compartment during the late luteal phase. The sub-nuclear localization of PR isoforms has been shown to vary during the menstrual cycle (Arnett-Mansfield *et al.*, 2004). Although the physiological significance of this phenomenon in the endometrium remains to be determined, PR is expressed in an even manner in the nucleus but may also be localized in discrete nuclear foci. In the proliferative phase, homogeneous localization is dominant and PRA and PRB co-localize. In the secretory phase, the focal localization increases and PRB becomes the predominant isoform in the nuclear foci. This focal nuclear localization is believed to correspond to transcription factor-rich storage domains, lacking RNA polymerase II, in which steroid receptors can be active or not depending on the receptor studied (Grande *et al.*, 1997; Arnett-Mansfield *et al.*, 2004).

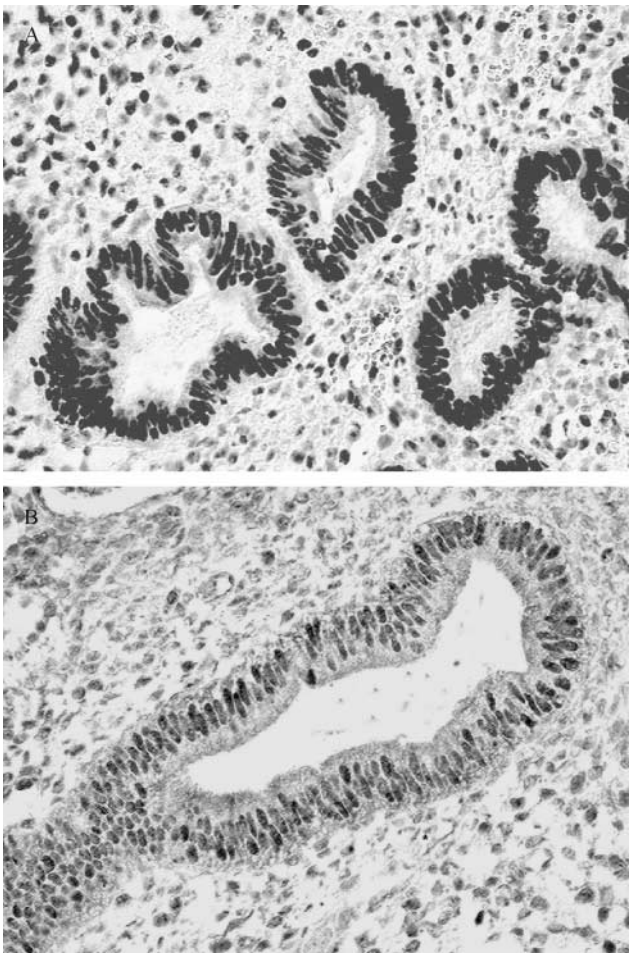

Figure 4. Progesterone receptor (PR) isoform A and B expression in the human endometrial biopsies during the proliferative phase (original magnification ×20). Briefly, after paraffin removal and microwave antigen retrieval, the sections were incubated with Anti PRA (clone PGR 312 Novocastra), Anti PRB (clone LET 126 INSERM U135, le Kremlin Bicêtre France), revealed with a streptavidin–peroxidase immunostaining procedure. Both PR isoforms are expressed in the stromal and glandular cells. (**A**) PRA, (**B**) PRB. (N.Chabbert-Buffet *et al.*, unpublished data.)

PR co-regulators have been described in the endometrium, as has their regulation during the menstrual cycle (Mote *et al.*, 1999; Gregory *et al.*, 2002). Steroid receptor co-activator (SRC-1) is up-regulated during the follicular phase and down-regulated during the luteal phase in the glandular epithelium and in the stroma (Gregory *et al.*, 2002; Vienonen *et al.*, 2004). However, the regulation of the co-repressors NCoR and SMRT is less clear. Immunohistochemical studies (Gregory *et al.*, 2002) suggest that NCoR is up-regulated during the follicular phase and down-regulated during the luteal phase in the glandular epithelium and in the stroma, while SMRT protein levels remain rather low and constant during the cycle. On the other hand another study of NCoR and SMRT mRNA levels has shown the opposite finding. SMRT mRNA appears to be regulated while NCoR mRNA remains stable throughout the cycle (Vienonen *et al.*, 2004).

Complexity of endometrial effects of PA and SPRM

Studies in both human and animal endometrium have shown that, in addition to their expected progesterone antagonist properties, these substances may display unanticipated effects. These include proliferative (estrogen-like) and antiproliferative (anti-estrogen). These complex effects depend on, among other things, the hormonal status, the animal model selected, and the dose of PR ligand used (Chwalisz *et al.*, 1998, 2000; Spitz and Chwalisz, 2000).

It is also important to remember that the determination of the endometrial effects of PA and SPRM is based on variable criteria. Earlier studies used histological analysis and studies of enzymes such as estradiol dehydrogenase and DNA polymerase alpha (Gravanis *et al.*, 1985). More recently proliferation markers such as Ki67, anti phosphorylated histone H3 antibody (Phospho H3) and mitotic protein monoclonal antibody 2 (MPM-2) have been used (Brenner *et al.*, 2003). Other methods of evaluation are histological dating as described by Noyes *et al.* (1950), steroid receptor expression levels, apoptosis markers or endometrial differentiation markers (such as glycodelin, Hoxa 10, integrins, leukaemia inhibiting factor, cyclo-oxygenase 2,

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calcitonin). Genomic identification of endometrial PR-regulated pathways, especially during the implantation period (Cheon *et al.*, 2002), has also been used to determine the effects of PA. Obviously, conclusions based on the evaluation of different markers in different species can lead to discrepancies.

Endometrial thickness is usually assessed using vaginal ultrasonography. However, endometrial thickness determined by ultrasound examination is poorly correlated to histologically defined proliferation. This may be related to edematous changes in the myometrium and related connective tissue, to cyst formation, to the collection of fluid in the lumen of dilated glands or to the presence of benign stromal thickening through an increase in collagen production in the stromal cells (Fleischer *et al.*, 1999; Liedman *et al.*, 2000; Baird *et al.*, 2003).

Finally it should be emphasized that the histological changes observed under the effect of PA and SPRM seem to be very specific and do not match to classical histological classification of hyperplasia. At this stage, the evidence that any degree of worrisome proliferation is induced by treatment requires further data. In addition, thus far the histological aspects seem to be comparable regardless of the PR antagonist used (A.Williams, personal communication). However, it should be stressed that only a few studies have been conducted.

Mifepristone

Mifepristone has been the most extensively studied PA to date, and its effects in non-human primates and in women seem to vary according to the hormonal status and the administered dose. In pre-menopausal subjects, low dose mifepristone has an antiproliferative effect while higher doses result in various degrees of hyperplasia.

Antiproliferative effects

In ovariectomized monkeys receiving estradiol treatment without progesterone, low dose (0.1 mg/kg/day) mifepristone induced early endometrial transformation (Hodgen *et al.*, 1994). Higher doses of mifepristone (0.5 mg/kg/day) administered in the absence of progesterone induced endometrial atrophy with stromal compaction and a total abrogation of estradiol induced proliferation.

The endometrium in menstruating women receiving low doses of mifepristone (2 or 5 mg) daily for 4 months is also inactive with a decrease in proliferation markers including Ki67 (Baird *et al.*, 2003). In both women and non-human primates, these low doses of mifepristone are associated with a decrease of menstrual bleeding or even amenorrhoea. This is probably related, at least in part, to the inhibition of ovulation. The threshold doses for ovulation inhibition with mifepristone range from 1 to 2 mg daily (Bygdeman *et al.*, 1997; Croxatto *et al.*, 1998; Brown *et al.*, 2002; Baird *et al.*, 2003).

In post-menopausal women treated with estradiol benzoate and mifepristone at the dose of 100–200 mg/day, secretory transformation of the endometrium was observed, indicating that mifepristone may function as a progesterone agonist (Gravanis *et al.*, 1985). However, in a group treated with both progesterone and mifepristone, mifepristone behaved as a classic progesterone antagonist.

Estrogen-like effects

In contrast to the above observations, it has been shown that mifepristone and other PA may display estrogenic-like activity on the endometrium of rats and rabbits. This is related to the species and maturity of the animals, and to the administered dose of the compound. In immature rats, onapristone and mifepristone markedly increased uterine weights, and onapristone, but not mifepristone, significantly enhanced endometrial luminal epithelial height, a sensitive estrogen parameter. Conversely, in ovariectomized and adrenalectomized rats, neither onapristone nor mifepristone modified uterine weights or endometrial morphology (Chwalisz *et al.*, 1998; Spitz and Chwalisz, 2000).

In women the effect of mifepristone appears to be largely dose-dependent. The endometrial morphology in women treated with mifepristone (50 mg daily for up to 6 months) was dyssynchronous and reminiscent of an unopposed estrogen effect. There was, however, no conclusive evidence of endometrial hyperplasia (Murphy and Castellano, 1994; Murphy *et al.*, 1995a). Some isolated cases of endometrial thickening on vaginal ultrasound have been reported during chronic administration of higher doses of mifepristone (200 mg daily) for the treatment of inoperable meningioma. The reports include a patient who developed an endometrial polyp and some patients with evidence of hyperplasia on endometrial biopsy (Grunberg *et al.*, 1991, 2001; Grunberg, 1994; Martineau and Levental, 2000). In a young girl with Cushing's syndrome treated with mifepristone at the dose of 400 mg/day for ~12 months, marked endometrial enlargement was noted on magnetic resonance imaging and ultrasound. Simple endometrial hyperplasia with no evidence of atypia was observed at histology. The hyperplasia regressed on cessation of mifepristone treatment (Newfield *et al.*, 2001).

The precise mechanism of the hyperplasic effects of mifepristone on the endometrium remains unknown. PA and SPRM bind minimally if at all to ER (Philibert, 1984). The increase in adrenocorticotrophic hormone (ACTH) and cortisol, secondary to the antiglucocorticoid effect observed with high doses of mifepristone, might be associated with an elevation of the adrenal production of androstenedione and testosterone (Lamberts *et al.*, 1991; Heikinheimo *et al.*, 1997, 2000) (Figure 5). It is thus possible that aromatization of these adrenal androgens may enhance the local estrogen levels with resulting hyperplastic effects. However, recent studies have shown that mifepristone is able to inhibit aromatase induction in human breast adipose tissue and in endometrial stromal cells (Tseng *et al.*, 1986; Schmidt and Loffler, 1997).

Hyperplastic endometrial effects have been observed with lower doses of mifepristone. A high incidence of simple endometrial hyperplasia (28%) was observed in women receiving 5 or 10 mg mifepristone daily for 6 months, for the treatment of myoma (Eisinger *et al.*, 2003). Data from this study have since been re-evaluated and a 25% incidence of hyperplasia has been confirmed, exclusively in the 10 mg dose group. None of the patients in the 5 mg dose group had endometrial hyperplasia (Steinauer *et al.*, 2004). Administration of 1 mg mifepristone daily for 5 months was associated with increased endometrial thickness and dilated glands in 25 and 43% of the monophasic cycles respectively (Croxatto *et al.*, 1998). These 'estrogenic' effects of mifepristone are not completely understood and might

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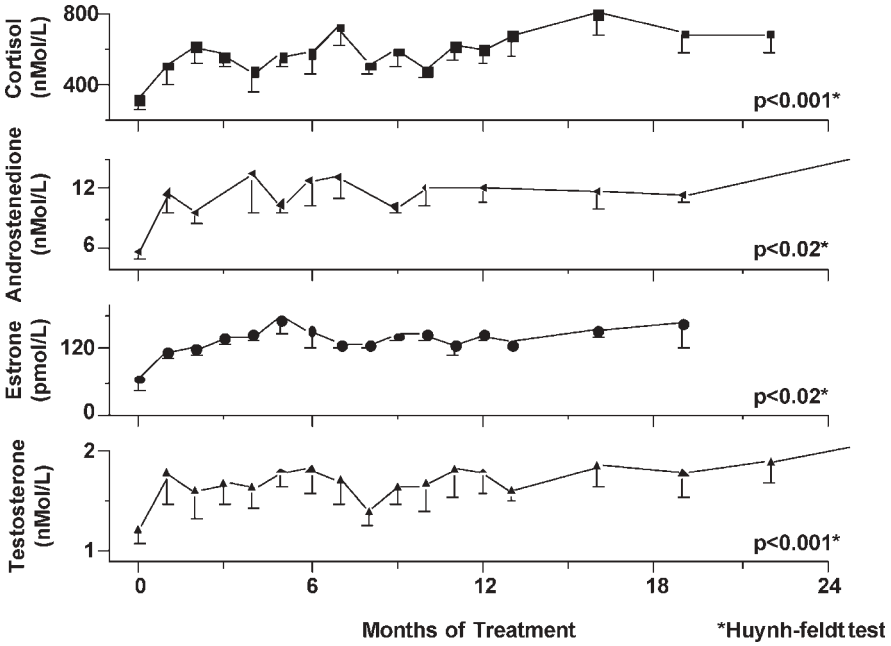

Figure 5. Cortisol, androstenedione, estrone, and testosterone responses to mifepristone 200 mg/day in post-menopausal women with non-resectable meningioma. The increase in adrenocorticotrophic hormone (ACTH) and cortisol secondary to the antiglucocorticoid effect of mifepristone produces an elevation of androstenedione and testosterone. Aromatization of these adrenal androgens in the endometrium may enhance the estrogen levels in this tissue. (I.M.Spitz *et al.*, unpublished data.)

imply an antagonist effect of mifepristone on the β estrogen receptor (ERβ) leaving the ERα proliferative effect unopposed (Hall and McDonnell, 1999; Zou *et al.*, 1999; Weihua *et al.*, 2000).

Further studies are required to determine the risk of endometrial hyperplasia under mifepristone treatment, in particular at low doses. There is still a need to investigate the endometrial morphological changes induced by mifepristone, and particularly the glandular changes such as benign cystic hyperplasia (Murphy *et al.*, 1995a).

Onapristone

The clinical development of onapristone has been interrupted due to liver toxicity. In post-menopausal women, this molecule acts as a pure progesterone antagonist. Daily administration of onapristone (1 or 10 mg/day for 56 days) to estradiol-treated (2 mg/day of oral estradiol) post-menopausal women did not induce endometrial hyperplasia. However, proliferative activity was histologically evident in every endometrial specimen. Many biopsies also showed inactive cystically dilated glands. The proliferation marker Ki67 was positive in every biopsy with no difference between the 1 mg dose group and the 10 mg dose group (Cameron *et al.*, 2003). This is in marked contrast to mifepristone. Thus, onapristone is devoid of any progestogenic or antiproliferative effects on the endometrium of post-menopausal women. These results may be related to the fact that onapristone acts as a pure PA and has no progesterone agonistic effects in all models tested. It might also reflect pharmacological differences between the two molecules, including the shorter half-life of onapristone, or differences in PR binding. Histological evidence of estrogenic stimulation of the endometrium has also been observed in intact adult rats receiving long-term onapristone administration. This was interpreted as an effect of unopposed endogenous estrogen (Rumpel *et al.*, 1993). Nevertheless, in the immature ovariectomized rodent uterus, onapristone exhibited mild estrogenic activity and acted as a weak estrogen agonist. This effect was antagonized by tamoxifen (Bigsby and Young, 1994).

CDB 2914

CDB 2914 is a potent progesterone antagonist in the McPhail test and in other cellular models. This molecule also appears to act as a progesterone antagonist in the post-menopausal endometrium, and is currently being evaluated in pre-menopausal women. A single study, reported as an abstract, describes a group of post-menopausal women treated with oral estradiol 1 mg/day plus either placebo, 2.5 mg medroxyprogesterone (MPA), 10 mg CDB 2914, or 50 mg CDB 2914 orally for 6 weeks. Endometrial hyperplasia was more frequent in the CDB group (11 out of 20 patients) than in the MPA group (no hyperplasia) (Christian *et al.*, 2002). Thus, CDB 2914 seems to increase estradiol-induced endometrial proliferation and thickening in post-menopausal women. These data remain to be confirmed.

Asoprisnil

Asoprisnil differs from the previously described compounds in its partial progesterone agonist activity. Asoprisnil treatment in cynomolgus monkeys resulted in endometrial atrophy with stromal compaction and inhibition of endometrial gland proliferation (DeManno *et al.*, 2003). This molecule reversibly suppressed menstruation at doses >10 mg per day irrespective of the effect on ovulation in regularly cycling volunteers (Chwalisz *et al.*,

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2002). Sixty pre-menopausal women received different doses (5 mg/day once daily, 5 mg/day twice daily, 10 mg once daily, 25 mg twice daily, 50 mg twice daily, $n = 8$ per group) of asoprisnil for 28 days starting on day 1 to 4 of the cycle. Except for the 5 mg once daily group, which was not statistically significantly different from the placebo group, all subjects had longer cycles. Cycle length ranged from 39.6 for the 5 mg twice daily group to 60.4 days for the 50 mg twice daily group. Thus cycle length increased proportionally to the increase of the asoprisnil dose. Unlike mifepristone, the effects on ovulation inhibition were inconsistent and lacked dose dependency. This suggests that the endometrial effect of asoprisnil is specific and is independent of ovulation inhibition. To date, no endometrial proliferative effects have been reported with this compound.

Mechanism of the antiproliferative effects of PA and SPRM

Since mifepristone as well as other PA and SPRM bind minimally, if at all, to ER (Philibert, 1984), their antiproliferative effect has been defined as non-competitive (Hodgen *et al.*, 1994). Even in primates, it is tissue specific and is absent in bone and the oviduct (Slayden and Brenner, 1994; Grow *et al.*, 1996). Several hypotheses have been formulated to account for these observations (Spitz and Chwalisz, 2000). The antiproliferative effects might be secondary to an inhibition of the estrogen receptor gene transcription by the PRA isoform (McDonnell and Goldman, 1994). Other potential explanations include a reduced endometrial blood supply due to atrophy of spiral arteries (Zelinski Wooten *et al.*, 1998; Chwalisz *et al.*, 2000), blockade of progesterone-dependent growth factors (Koji *et al.*, 1994), inhibition of angiogenesis (Greb *et al.*, 1997; Grow *et al.*, 1998), apoptosis modulation via growth factors such as NKκB (Slayden *et al.*, 1993; Han and Sidell, 2003) and cell cycle blockade (Heikinheimo *et al.*, 1996). This antiproliferative effect on the endometrium is accompanied by an increase in ER and PR (Neulen *et al.*, 1996), suggesting that the endometrial antiproliferative effect is due to progesterone antagonism. In addition, administration of PA is also associated with an increase in androgen receptor (AR) (Slayden and Brenner, 1994; Brenner *et al.*, 2002) which could also produce these antiproliferative effects since androgens suppress estrogen-induced endometrial proliferation (reviewed by Brenner *et al.*, 2002). This hypothesis is further supported by the fact that treatment with the pure antiandrogen flutamide blocks the antiproliferative effects of PA in the endometrium (Slayden and Brenner, 2003; Narvekar *et al.*, 2004).

Treatment of uterine leiomyoma

Both ER and PR (and their mRNA) are more abundant in leiomyoma cells than in the adjacent myometrium (Brandon *et al.*, 1993; Englund *et al.*, 1998) suggesting that uterine myomas are sex-steroid-dependent tumours. Estradiol seems to stimulate myoma cell growth either directly or through the mediation of growth factors such as epidermal growth factor (EGF) and insulin-like growth factor I (IGF-I) (Huet-Hudson *et al.*, 1990; Murphy and Ghahary, 1990). Progestins have been used in myoma treatment in the attempt to counteract estradiol effects. Although a beneficial effect on bleeding has been reported (Coutinho, 1990), myoma growth has also been observed (Harrison-Woolrych and Robinson, 1995).

Table III. Main clinical studies on mifepristone treatment for uterine myomas

Mifepristonedose (mg)	No. of patients	Volume decrease[a] (%)	Amenorrhoea (%)	References
5	9	26	100	Murphy *et al.*, 1995b
12.5	45	74	100	Zeng *et al.*, 1998
25	11	56	100	Murphy *et al.*, 1995b
50	10	49	100	Murphy *et al.*, 1993
5	16	48	61	Eisinger *et al.*, 2003
10	16	49	55	Eisinger *et al.*, 2003
10	28	27	100	Yang *et al.*, 1996
20	15	33	100	Yang *et al.*, 1996
25	8	32	NA	Reinsch *et al.*, 1994

The duration of treatment was of 3 months for all studies, except for Eisinger's (6 months).
[a]The indicated volume is the leiomyoma volume in the first four studies and the total uterine volume in the remaining five studies.
Adapted from (Steinhauer *et al.*, 2004) with permission.

At the cellular level, progesterone seems to induce leiomyoma cell growth, as suggested by the increased expression of proliferation markers in myomas during the luteal phase. Progesterone action might be mediated by EGF or IGF-I as well as through estradiol receptor signalling. Progesterone also inhibits apoptosis in cultured leiomyoma cells (Maruo *et al.*, 2003) and might even contribute to myoma growth.

These data have been confirmed by clinical trials suggesting the potential of low dose mifepristone treatment in myoma management (Steinhauer *et al.*, 2004) (Table III). A total of 30 women received 5, 25 or 50 mg of mifepristone daily for 3 months (Yen, 1993; Murphy and Castellano, 1994). A significant decrease in myoma volume was observed in patients treated with the two highest doses, but no sustained effect was evident with the lowest dose (Yen, 1993; Murphy and Castellano, 1994). Other investigators administered 10 and 20 mg mifepristone daily for 3 months to 43 women with myoma. Myoma volume decreased 40% with both doses, with improvement of abdominal pain and anaemia (Yang *et al.*, 1996). In a more recent study, doses of 5 and 10 mg of mifepristone were administered to two groups of 20 patients with uterine myomas for 6 months (Eisinger *et al.*, 2003). Both doses resulted in comparable myoma regression. In another Chinese study, a dose of 12.5 mg of mifepristone was administered to 45 women and their response compared to that of a second group of patients receiving a GnRH analogue. Over 90% of patients from both groups achieved a 20% reduction in tumour volume. However, the recurrence rate after cessation of treatment was 40% after GnRH analogue and only 17.8% after mifepristone (Zeng *et al.*, 1998).

Doses of 5, 10 and 25 mg of asoprisnil and placebo were administered for 12 weeks to women with myomas. Asoprisnil reduced the intensity and duration of uterine bleeding in a dose-dependent manner (Chwalisz *et al.*, 2003). The rate of unscheduled bleeding decreased to 9.4% in the 5 mg group, 18% in the 10 mg group and 13% in the 25 mg group. The rate of amenorrhoea increased with the dose of asoprisnil, reaching 83.3% in

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the 25 mg group. In women with menorrhagia at baseline (76%), the menstrual blood loss reverted to normal or amenorrhoea was induced after 3 months (5 mg group: 78%; 10 mg group: 88%; 25 mg group: 100%; compared to placebo: 26%). All doses of asoprisnil significantly increased haemoglobin concentrations after 3 months. Additionally leiomyoma volume decreased (median decrease 36.1% after 12 weeks of treatment) in association with a diminution of tumour-associated symptoms such as bloating and pelvic pressure.

The initial studies with mifepristone and the more recent studies with asoprisnil have proven the efficacy of these agents for the treatment of leiomyoma. In view of the 25% incidence of endometrial hyperplasia reported by Eisinger *et al.* (2003), further studies are required to document their safety. Long-acting GnRH analogues are also used to treat endometriosis and uterine myoma. Their main drawbacks are the profound estrogen deficiency and decrease in bone mineral density (Dodin *et al.*, 1991) up to 6–7% after 6 months of treatment. In marked contrast, mifepristone treatment is not associated with a decrease in bone mineral density (Yen, 1993).

PA and SPRM may certainly be used as a rapidly effective alternative to GnRH analogues to prepare women before surgical removal of leiomyomas. Immediate re-growth has been documented on cessation of GnRH analogue treatment. One small Chinese study suggested that myoma re-growth might not be as rapid after mifepristone as after GnRH analogues (Zeng *et al.*, 1998). Further studies are required. PA and SPRM may be used to avoid surgery in peri-menopausal women with symptomatic myomas. Further studies will show if their long-term use is also possible.

PA might be used as contraceptives in pre-menopausal women. In this context, mifepristone (and perhaps other PA) may have an advantage over asoprisnil (and other mixed agonist–antagonist compounds) since PA, in the dose range tested for myoma treatment, inhibit ovulation. On the other hand, an unopposed estrogen effect is less likely to occur with a SPRM in view of its progesterone agonist activity. Ultimately the effect of PA and SPRM on the endometrium will indicate which compound should be used.

Treatment of endometriosis

The effects of these compounds in the treatment of endometriosis are difficult to predict since the physiopathology of this disorder remains unclear. Additionally the effects of PA and SPRM may be different in the endometriotic tissue from those in the eutopic endometrium which have different steroid metabolism and enzyme physiology. For example, in endometriotic tissue, aromatase activity is increased and 17β-hydroxysteroid dehydrogenase activity is decreased, resulting in increased *in situ* estradiol concentrations. The effect of mifepristone in endometriosis may be related to its antiproliferative effect, since endometriosis is an estrogen-dependent condition, as well as to its apoptosis-promoting effect (Han and Sidell, 2003).

PA have been shown to reduce endometriotic lesions in animal models. In surgically induced endometriosis in rats, onapristone (ZK 98 299, 2 mg/day for 1 month) induced a 40–50% reduction of lesions while ZK 136 799 (another PA, 2 mg/day) induced a 63–75% reduction (Stoeckemann *et al.*, 1995). In monkeys, surgically induced endometriotic lesions were reduced from 1.8 to 0.05 cm^2 after 9 months of mifepristone treatment, from 1.7 to 0.6 cm^2 after 9 months of GnRH analogue treatment, and from 1.2 to 0.15 cm^2 after mifepristone + GnRH analogue treatment of the same duration. Thus in this model mifepristone appeared to have a great capacity to reduce endometriotic lesions. Mifepristone alone was even more efficient than in combination with a GnRH analogue or than a GnRH analogue alone, suggesting a direct effect of this compound in endometriotic explants, independent of hormone levels (Grow *et al.*, 1996).

Three small clinical trials have been reported using three different dose schedules of mifepristone (5 mg or 50 mg per day for 6 months or 100 mg per day for 3 months) (Kettel *et al.*, 1993, 1996, 1998). There was an improvement in symptoms in all treated patients independently of the dose and a 55% mean regression of visible endometriosis after 6 months of treatment was observed following the 50 mg dose (Kettel *et al.*, 1993, 1996, 1998). Mifepristone appears to be very promising for the treatment of endometriosis, since it does not induce the severe estrogen deficiency associated with aromatase inhibitors.

Contraception

Mifepristone and other PA also have contraceptive potential (Spitz *et al.*, 1996, 2000; Bygdeman *et al.*, 1999). They may act by several mechanisms (Table IV). At low doses they inhibit ovulation by blocking the LH surge. Low doses also retard endometrial development by virtue of their antiproliferative action. As a consequence, the endometrium cannot support implantation. Higher doses can even block follicular maturation and induce follicular atresia. Finally PA induce endometrial bleeding when administered in the late luteal phase, thus preventing implantation (Croxatto, 2003). Mifepristone may also hinder tubal function, male gamete as well as oocyte maturation and fertilization (Gemzell-Danielsson *et al.*, 2003). The progestin levonorgestrel may also delay or inhibit ovulation if administered early enough in the follicular phase. However, once fertilization has taken place, levonorgestrel is not efficient in

Table IV. Potential targets of progesterone receptor antagonists (PA) used for contraception

Target	Alterations	References
Follicular development	Delay in the late follicular phase by low dose mifepristone	Croxatto *et al.*, 1995; Permezel *et al.*, 1989
Ovulation	High dose mifepristone induced collapse of the dominant follicle (related to FSH levels decrease, LH surge delay)	Croxatto *et al.*, 1995
Oocyte maturation	No evidence	Messinis and Templeton, 1988
Tubal function	Indirect evidence of modulation of tubal cilia by progesterone	Mahmood *et al.*, 1998
Corpus luteum	Induction of luteolysis	Ottander *et al.*, 2000
Sperm	Decrease of basal intracellular calcium (*in vitro*, not confirmed *in vivo*)	Yang *et al.*, 1994
Endometrium	See text	

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preventing ongoing pregnancy. Ortiz *et al.* (2004) has recently shown that post-coital levonorgestrel does not interfere with post-fertilization events in monkeys. This may not occur with PA, which not only block ovulation but also affect implantation.

Long-term contraceptive potential

Daily doses of 2–10 mg mifepristone suppress follicular development, block the LH surge and delay ovulation (Croxatto *et al.*, 1993; Cameron *et al.*, 1996). In a recent study, no pregnancies were reported after 200 months of exposure in 50 women who received either 2 or 5 mg of mifepristone daily as their only method of contraception (Brown *et al.*, 2002).

The threshold dose of mifepristone capable of inducing ovulation inhibition is of 2 mg daily. With a dose of 1 mg daily, ovulation usually occurs (Croxatto *et al.*, 1998). Although this dose does not inhibit the LH surge, it delays endometrial maturation and the appearance of progesterone-dependent markers (Spitz *et al.*, 1996; Bygdeman *et al.*, 1999; Sarkar, 2002). These results raise the prospect of endometrial contraception, i.e. prevention of endometrial maturation without disruption of ovulation. This approach is effective in monkeys (Borman *et al.*, 2003). However, mifepristone at a very low dose (0.5 mg/day or 5 mg once weekly) administered to women not using contraception, did not prevent pregnancy, notwithstanding a delay in endometrial maturation and in appearance of progesterone-dependent markers (Marions *et al.*, 1998, 1999; Bygdeman *et al.*, 1999).

Luteal phase contraception (Croxatto, 2003) is another potential application of PA although this strategy has not been precisely formulated. One of the main difficulties of this type of treatment is the timing of administration, since there is no prospective, reliable and non-invasive way to detect the beginning of the luteal phase. Administration of mifepristone in the early luteal phase in an attempt to prevent embryo implantation (200 mg mifepristone administered 48 h after the LH surge) has minimal or no effect on ovulation and bleeding patterns, and is an effective contraceptive (Gemzell Danielsson *et al.*, 1993; Bygdeman *et al.*, 1999; Hapangama *et al.*, 2001).

Administration of mifepristone in the late luteal phase produces menstrual bleeding. When administered together with prostaglandins, it has been shown to be an effective menses regulator (World Health Organization Task Force on Post-Ovulatory Methods of Fertility Regulation, 1995). A single dose of mifepristone either alone or together with prostaglandins has been administered to women between the implantation period and the expected menses as a monthly alternative to regular oral contraception. This treatment failed to induce bleeding in a significant number of women and induction of bleeding did not necessarily terminate an ongoing pregnancy. This treatment is thus not effective in preventing pregnancy (Spitz *et al.*, 1996, 2000; Swahn *et al.*, 1999).

Management of irregular bleeding induced by progestin-only contraception

Bleeding is one of the main drawbacks of estrogen-free contraception, and may lead to treatment discontinuation in 15–25% women. Mifepristone and other PA may also be used to reduce the occurrence of bleeding irregularities induced by progestin-only contraceptive methods (Spitz *et al.*, 2000; Gemzell-Danielsson *et al.*, 2002). Org 31710 (a PA) administered monthly (150 mg) to women using the desogestrel-only contraceptive pill (75 μg/day) permitted the restoration of a regular bleeding pattern, with a significantly lower frequency of irregular, prolonged or frequent bleeding (Gemzell-Danielsson *et al.*, 2002). However, since then, different schemes and doses of Org 31710 or Org 33628 associated with desogestrel have failed to maintain a normal bleeding pattern or to provide sufficient long-term ovulation inhibition (Verbost PM, Hanssen RGJM, Korver GHV, Mulders TMT, unpublished data).

In women using levonorgestrel-releasing subdermal contraceptive implants, bleeding has been correlated to vascular fragility, and is independent of circulating estradiol or progesterone levels. In a double-blind placebo-controlled study (Cheng *et al.*, 2000), women using a levonorgestrel-releasing contraceptive implant were treated with 50 mg mifepristone once every 4 weeks. Although the number of bleeding episodes tended to decrease independently of treatment in all women over the 360 days of the study, the duration of bleeding episodes decreased significantly more rapidly in the mifepristone group. Women using mifepristone were also more likely to comply with the treatment (Cheng *et al.*, 2000). The precise mechanism of action of mifepristone in this context has not been established and might include a direct effect on the endometrium or, less likely, on ovulation induction. This effect might hinder the contraceptive efficacy of progestagen-only contraception. However, in the study by Cheng *et al.* (2000), 300 cycles were followed and no pregnancy occurred.

Emergency contraception

Several clinical trials comparing the effectiveness of mifepristone to other established methods of emergency contraception including danazol, levonorgestrel, an intrauterine contraceptive device and the classical Yuzpe method (ethinylestradiol, 100 μg, with levonorgestrel, 500 μg, repeated after 12 h) (Glasier *et al.*, 1992; Webb *et al.*, 1992; Ashok *et al.*, 2001, 2002; von Hertzen *et al.*, 2002) have been conducted (Table V). Different doses of mifepristone have also been compared (World Health Organization Task Force on Postovulatory Methods of Fertility Regulation, 1999; Xiao *et al.*, 2002). In all these studies the number of expected pregnancies has been determined by the probabilities of conception by cycle day from established conception rates (Wilcox *et al.*, 1995; Trussell *et al.*, 1998). All methods (with the exception of danazol), resulted in a marked decrease in the number of expected pregnancies.

Mifepristone has the distinct advantage of being effective up to 120 h after unprotected intercourse whereas other methods are usually restricted to the initial 72 h (World Health Organization Task Force on Postovulatory Methods of Fertility Regulation, 1999; Ashok *et al.*, 2001; von Hertzen *et al.*, 2002; Xiao *et al.*, 2002). Moreover side-effects such as nausea, vomiting, headache and breast tenderness were significantly less frequent among women given mifepristone than other compounds (Glasier *et al.*, 1992; Webb *et al.*, 1992; Ashok *et al.*, 2002). In one study, 19% of women taking mifepristone complained of excess bleeding as compared to 31% of the women taking levonorgestrel (von Hertzen *et al.*, 2002).

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Table V. Main clinical trials comparing mifepristone to other emergency contraception agents

	No. of women evaluated	No. (%) of observed pregnancies	No. (%) of expected pregnancies	References
Mifepristone 600 mg	195	0	11.7 (6)	Webb *et al.*, 1992
vs Yuzpe	191	5 (2.6)	11.3 (5.9)	
vs Danazol	193	9 (4.7)	11.7 (6.1)	
Mifepristone 600 mg	347	0	23 (6.6)	Glasier *et al.*, 1992
vs Yupze[a]	346	4 (1.2)	23 (6.7)	
Mifepristone 100 mg	487	3 (0.6)	39 (8)	Ashok *et al.*, 2002
vs Yupze[a]	471	17 (3.6)	39 (8)	
Mifepristone 10 mg	1359	21 (1.6)	108 (8)	von Hertzen *et al.*, 2002
vs LNG 1.5 mg administered once	1356	20 (1.5)	111 (8.2)	
vs LNG 0.75 mg administered twice, 12 h apart	1356	24 (1.8)	106 (7.8)	
Mifepristone 200 mg	155	1 (0.7)	6.7 (4.3)	Ashok *et al.*, 2001
vs IUD	14	0	0.34 (2.4)	
Mifepristone 10 mg	2065	(1.3)	77% pregnancies avoided	Hamoda *et al.*, 2004
vs LNG 0.75, administered 12 h apart		(2)	64% pregnancies avoided	
Meta-analyses of 12 RCT evaluating mifepristone 10 mg	6083	101 (1.7)	83.4% pregnancies avoided	Piaggio *et al.*, 2003b

[a]100 μg ethinylestradiol with 500 μg levonorgestrel, repeated after 12 h.
IUD = intrauterine device; LNG = levonorgestrel; RCT = randomized controlled trials.

In a large multicentre randomized trial, the number of ongoing pregnancies was similar in women given 10, 50 or 600 mg mifepristone (World Health Organization Task Force on Postovulatory Methods of Fertility Regulation, 1999). Another trial compared the response to 10 and 25 mg mifepristone administered within 120 h of an unprotected intercourse. The results were identical with both dose schedules (Xiao *et al.*, 2002). Thus, lowering the dose of mifepristone did not compromise effectiveness. Similar results were reported in the meta-analysis by Piaggio *et al.* (2003b) who compared doses of mifepristone from 5 to 600 mg. In the low dose range, efficacy did appear to be reduced: pregnancy rate increases by 1.6-fold if 10 mg RU 486 is used versus 25 mg. However, as stated by the authors, 'in terms of the number of women needed to treat, using 10 mg in the place of 25 mg implies having one extra pregnancy every 146 women requesting emergency contraception, which might be a low cost compared to the benefit of more women having access to treatment'.

More women using mifepristone have a delay in the expected onset of their next menstrual period as compared to other methods. This is a drawback since the onset of menses reassures the woman who has used emergency contraception on the successful termination of pregnancy. The use of mechanical contraception is therefore required until the next menstruation. This menstrual delay is a dose-dependent phenomenon and is greater with mifepristone doses of 600 and 100 mg than doses of 25 mg or 10 mg (World Health Organization Task Force on Postovulatory Methods of Fertility Regulation, 1999; Xiao *et al.*, 2002). Since the success rates are similar with all doses, the lowest dose of mifepristone is recommended. Lower doses are also more economical, which may compensate for the slight decrease in efficacy.

Despite the proven effectiveness of mifepristone as an emergency contraceptive agent, to date China is the only country to have licensed and approved mifepristone for this indication. It is hoped that other countries will shortly make this preparation available.

Treatment of tumours

Both PR isoforms are expressed in reproductive tissues but their ratios vary depending on the developmental and hormonal status (Mangal *et al.*, 1997). Most importantly their expression may be altered during carcinogenesis. A higher incidence of endometrial cancer has been reported in women bearing a PR gene polymorphism favouring the PRB isoform expression (De Vivo *et al.*, 2002). In endometrial cancer, abnormal PRA:PRB ratios have been observed (Arnett Mansfield *et al.*, 2001) and down-regulation of PRB has been described in poorly differentiated human endometrial cancer cells (Kumar *et al.*, 1998). Over-expression of the PRB isoform has been correlated with more aggressive endometrial ovarian and endometrial cancers (Fujimoto *et al.*, 1995). Alterations in the subnuclear localizations of PR isoforms are observed in endometrial cancer cells (Arnett Mansfield *et al.*, 2004) and may result in altered intranuclear modulation of progesterone action. The PRB isoform is able to down-regulate cellular adhesion molecules in human endometrial cancer cells (Arnett Mansfield *et al.*, 2004). PRB over-expression has been described in ovarian epithelial tumours and the PRB labelling index may be a prognostic marker (Akahira *et al.*, 2000; Li *et al.*, 2003). Thus, a PRB antagonist might also play a role in the treatment of steroid receptor-expressing tumours. Depending on the type of isoform present in a tumour, tailor-made PA directed specifically to the PRA or PRB may be required.

In the breast, PRA and PRB distribution is similar in proliferative disease without atypia and atypical ductal hyperplasia, while PRA expression is decreased compared to that of PRB in ductal carcinoma *in situ* and invasive ductal carcinoma (Ariga *et al.*, 2001). The loss of normal co-expression of both isoforms of PR may be involved in the early process of carcinogenesis (Mote

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et al., 2002). Preliminary studies suggest that PA may be of value in the treatment of breast cancer, alone or in association with anti-estrogens and/or GnRH analogues (Romieu *et al.*, 1987; Perraut *et al.*, 1996; Koide, 1998; Klijn *et al.*, 2000). However, further studies must be performed.

Conclusions

Studies on PA and SPRM are finally being conducted despite the initial lack of interest of major pharmaceutical companies. To date, no serious untoward effects of PA and SPRM have been reported. The outstanding issue to be resolved mainly relates to the endometrial effects of these compounds. The balance between the proliferative (estrogenic) and antiproliferative (anti-estrogenic) activity of these compounds on the endometrium is clearly of importance in any long-term treatment with these agents. These effects may vary with the dose and the administered molecule. Long-term treatment with SPRM possessing agonist activity may give better results than with pure PA. The intrinsic agonist activity of a SPRM may prevent endometrial proliferation. Since selective activation of PRA in mice (Mulac Jericevic *et al.*, 2000) decreases proliferation of the endometrium, it is possible that in the future selective PRA agonists may also play an important role in the prevention of endometrial hyperplasia.

Different indications seem to be readily available for PA and SPRM in the future: the treatment of menorrhagia and the reduction of tumour volume in leiomyomas, and estrogen-free contraception. Other future developments may include the treatment of endometriosis, hormone-dependent cancers and the development of selective ligands to the PR isoforms.

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