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Clinical uses and potential clinical uses of antiprogestin : Mifepristone

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Mifepristone เป็นยาสังเคราะห์ที่มีฤทธิ์ต้านโปรเจนเตอร์โรน โดยจับกับโปรเจสเตอร์โรนรีเซฟเตอร์ ที่เยื่อบุมดลูก กล้ามเนื้อมดลูกและเยื่อหุ้มทารก คอเรียน ทำให้โปรเจสเตอร์โรนที่มีหน้าที่ควบคุมไม่ให้มดลูกบีบตัวมาก ออกฤทธิ์ไม่ได้ ดังนั้น เมื่อใช้ในสตรีตั้งครรภ์จึงมีผลทำให้มดลูกบีบตัวมาก และเกิดการแท้งขึ้น ยาตัวนี้ยังมีประโยชน์ในการขับรกและตัวอ่อนออก ในกรณีที่การผสมเทียมเกิดการล้มเหลว ยานี้มีฤทธิ์ทำให้ปากมดลูกขยายตัว จึงมีประโยชน์ในการทำให้การขูดมดลูก การใส่ และถอดห่วงคุมกำเนิดทำได้ง่าย ได้มีการทดลองใช้ยานี้ในการรักษามะเร็งที่เชื่อว่ามีความสัมพันธ์กับโปรเจสเตอร์โรน เช่น มะเร็งเต้านม มะเร็งเยื่อหุ้มสมอง ปรากฏว่าได้ผลดี นอกจากนี้ยังมีผู้พยายามทดลองใช้ยานี้ร่วมกับยาที่ต้านฤทธิ์ GnRH เพื่อจะพัฒนามาเป็นยาคุมกำเนิดที่ใช้เพียงเดือนละครั้ง ซึ่งยังคงต้องรอดูผลกันต่อไป

ABSTRACT

Mifepristone is a synthetic progesterone antagonist acting reversibly at the molecular level of receptor. It blocks progesterone receptors in pregnant myometrium, endometrium and chorion, resulting in pregnancy termination. It is also useful for the expulsion of non viable pregnancy of in-vitro fertilization embryo transfer and gamate intra-fallopian transfer. Mifepristone dilates the cervix of both pregnant and non pregnant women. In preliminary studies, mifepristone has shown a good prospect for treatment of progesterone dependent cancer like breast cancer and meningioma. The possibility of useing mifepristone as once-a-month contraceptive is being studied by a consequent use of GnRH antagonist followed by mifepristone. Mifepristone has just been in clinic shortly, but has shown a number of indications and potential indications.

Introduction

Mifepristone (RU 38486 or RU 486 in short) is a synthetic progesterone antagonist acting reversibly at the molecular level of receptors. It is a 19-norsteroid which has a relative binding affinity 5.3 times higher than that of progesterone (studied on rabbit uterine progesterone receptors)[1]. It is the first antiprogestin working at the receptor site. Following the initial discovery of this drug, some other compounds such as lipopristone (ZK 98734), onapristone (ZK 98299) were developed. As mifepristone is the prototype, most of the studies were on this drug, thus its pharmacology, clinical benefits and potential clinical uses are reviewed here.

Pharmacology

When it enters target cells, mifepristone reaches its receptors which are mostly attached loosely in the nucleus. It is believed that the antiprogestin expresses its antiprogestational activity by binding to the receptors but no gene transcription occcurs, possibly because the receptor does not undergo the conformational change required for optimal DNA binding[2]. The pharmacological activities of mifepristone have been demonstrated in several model systems. In early pregnancy, the decidua, which has high levels of progesterone receptors, is the primmary target for antiprogestin. The rate of increase in hCG (human chorionic gonadotropin) production, which characterizes this stage of pregnancy, slows and once the embryo is detached, levels of hCG decrease sharply[3]. Consequently, the maintenance of ovarian function is withdrawn, resulting in an irreversible luteolytic effect, with corresponding reduction in levels of plasma progesterone and oestrogen[3]. Mifepristone also also acts directly at the progesterone receptor in myometrium, resulting in an increase of uterine contractility[4]. In non-pregnant women, the endometrium is under the influence of progesterone shortly after ovulation. Using mifepristone in the early luteal phase causes a retardation of endometrial development[5]. At mid-luteal and late-luteal phases, mifepristone provokes uterine bleeding and causes decreased LH output[6-7]. Mifepristone also affects the cervix by an unknown mechanism resulting in the softening and dilating of the cervix both in pregnant and non-pregnant women[8-10].

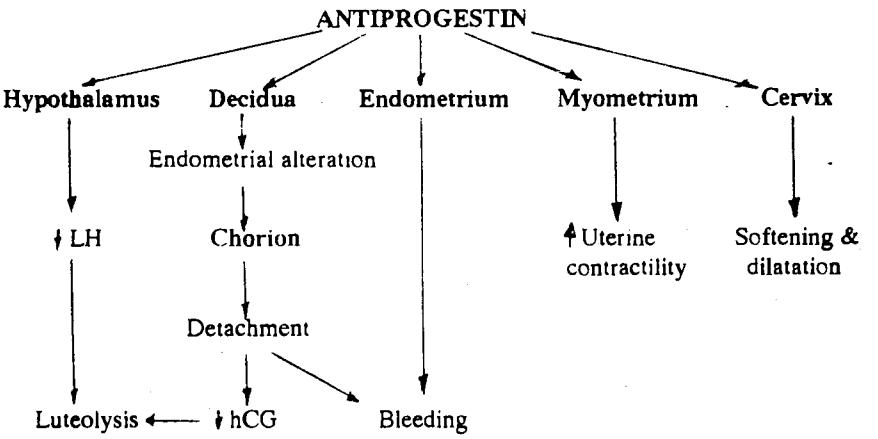

Figure 1 Effects of mifepristone at different sites of action.

In addition to antiprogestational activity, mifepristone also shows antiglucocorticoid activity both *in vitro* and *in vivo* studies[1]. The binding affinity to cytosol glucocorticoid receptors is 3 times higher than dexamethasone[1]. Mifepristone has no affinity to human mineralocorticoid receptors but has weak antiandrogenic activity. It has neither an antioestrogenic nor oestrogenic activity in either human or animals[3].

Pharmacokinetics

Following oral intake, mifepristone is rapidly absorbed and reaches peak levels in approximately 1 h. Thereafter the serum drug concentrations decline gradually with an elimination half life of about 20-24h[11]. The pharmacokinetics of mifepristone are non-linear: within the dose range of 100-800 mg neither the peak

nor the steady state serum level correlates with the dose ingested[11]. The absence of the proportional rise of serum drug concentrations with the increasing doses is believed to attribute to the limited binding capacity of the carrier protein, α-acid glycoprotein. The excess drug pobably binds with low affinity albumin and hence is available for metabolism and extravasation into tissue[12].

Clinical uses and potential clinical uses

Given the mutifaceted role of progesterone in the reproductive system, a compound with antiprogestational activity could have a number of applications.

Pregnancy termination By blocking the progesterone receptors in the pregnant myometrim, endometrium and chorion, mifepristone could, therefore, interrupt the pregnancy. The success of mifepristone used alone for the termination of pregnancy in the first trimester is variable, ranging from 85% in 6 weeks gestation to less than 40% in 9 weeks gestation[13]. There is no correlation between the regimen of mifepristone and the success rate of abortion[12], but the age of gestation and initial β-hCG level appear to be critical factors; higher success rates are achieved in lower β-hCG levels and in earlier pregnancy[13-16]. The complete abortion rate is significantly improved when mifepristone is used in combination with PGE analogue[14-15,17]. Currently, most centres use a single dose of 600 mg mifepristone followed 36-48 h later by either 0.25 mg IM sulprostone or 1 mg vaginal gemeprost. In a recent multicentre trial in the UK. involving 588 women with gestational ages upto 9 weeks, it was shown that 600 mg single oral dose of mifepristone followed by 1 mg vaginal pressary of gemeprost 48h later gave 94% success rate of complete abortion without any need of subsequent surgical procedure[14]. However, since the success rate does not correlate with the dose of mifepristone, the optimal dose of mifepristone and PG analogue, the route and timing of administration remain to be determined.

Mifepristone is also value in the second trimester abortion as the mean induction time for abortion in women receiving 600 mg mifepristone 24 h before receiving extra-amniotic PGE_2 instillation, was significantly lower than that induced by PGE_2 alone[18]. However, giving mifepristone 36 h or 48 h prior to PG instillation was of no advantage compared to administration of mifepristone 24 h prior to the PG instillation[18-19]. The further value of mifepristone in the second trimester abortion was demonstrated by lower dose of PG required to induce abortion[19-20].

Expulsion of dead fetus Retention of dead fetus in the uterus constitutes a risk of disseminated intravascular coagulation, a dangerous complication, and this leads most clinicians to induce fetal expulsion when possible. Mifepristone has been tested for this purpose in women whose gestational ages were > 16 weeks. Mifepristone, 200 mg three times daily for 2 days, induced the expulsion of dead fetus within 72 h in 63% of patients as compared to 17.4% in the placebo group[21]. Since prostaglandins, the drugs for the management of intrauterine fetal death, are not well tolerated and their use is limited by classical contraindications e.g. hypertension, scarred uterus, pelvic inflammatory disease, asthma, peptic ulcer and diabetes mellitus, mifepristone could, therefore, be a treatment of choice in these cases. Further investigation may reveal whether administration of mifepristone with lower dose prostaglandin will be of benefit for the expulsion of the dead fetus.

Mifepristone has also been tried for the management of non-viable pregnancy in women undergoing in-vitro-fertilization-embryo-transfer (IVF-ET) and gamate-intra-fallopian-transfer (GIFT)[22]. According to the clinical registry report of American Fertility Society, about 25% of IVF-ET and GIFT are eventually resulted in an early pregnancy loss[23]. The non-

viable conceptus is sometimes expelled spontaneously, but frequently, secondary to hormonal support from multiple corpora lutea, in cases of controlled ovarian hyperstimulation they remain in the uterus for an extended period of time. A few case reports of using 600 mg mifepristone single dose in these non-viable pregnancies at about 50 days after IVF-ET or GIFT showed succesful outcome of expulsion of the gestational sac[22].

Cervical ripening and cervical dilatation In several instances, investigators using mifepristone for pregnancy interuption have noted some degree of cervical softening and dilatation which eased subsequent vacuum aspiration in cases where the drug failed to terminate the pregnancy. In a study using mifepristone for the cervical preparation in first trimester pregnancy termination by vacuum aspiration, it was found that mifepristone significantly increased the degree of cervical dilatation by an average of between 0.9-1.2 mm[8]. There was no significant difference in degree of cervical dilatation between using 25, 50 or 100 mg mifepristone twice at 24 h and 12 h before vacuum aspiration. The maximum effect was achieved in 24 h and no further therapeutic benefit was gained, in term of the degree of cervical dilatation, by extending the period of pretreatment beyond 24h[8]. Furthermore, one study showed that the increase in cervical dilatation was significantly greater in patients with gestational age between 10-12 weeks than in those with gestational age $<$ 10 weeks[9]. The mechanism by which mifepristone exerts its effect on the cervical tissue is not known. It could be that by countering progesterone activity resulting in the increasing activity of oestrogen : progesterone ratio thus increase in cervical collagenase and/or prostaglandin synthetase activity[24]. However, Radestad *et al* (1990) demonstrated that mifepristone did not enhance or qualitatively alter the bioconversion of arachidonic acid to prostaglandins in the cervix of the first trimester women[25].

Mifepristone has also been shown to dilate the cervix of non-pergnant women[10]. This would facilitate many out-patient procedures such as intra-uterine contraceptive device insertion and removal, endometrial sampling, laser ablation of dysplastic lesions in the cervical canal and in in-patient procedures such as dilatation and curettage.

Advanced breast cancer Studies in the *in vitro* human breast cancer cell lines showed that mifepristone had the ability to block the production of progestin regulated proteins[26]. Mifepristone possesses very potent progesterone receptor mediated antiproliferative effects in animal experimental models of mammary carcinomas[27-28]. The antitumor mechanism of antiprogestin in these models is believed to be a direct progesterone receptor mediated antiproliferative effect with the following evidence. (a) the antitumor activity was not found in various progesterone receptor negative cell lines, but was related to progesterone receptor concentrations[26], (b) the antitumor activity of the progesterone antagonist depended on the availability of a sufficient number of unoccupied progesterone receptors, since the antitumor activity disappeared when the progesterone receptors were blocked or occupied by an increased number of progesterone molecules[28]. The morphological analysis also established the concept that antiprogestin trigers an antiproliferative effect in these mammary carcinomas by the induction of differentiation of the mitotically active polygonal cell to the terminal differentiation stage, leading to termminal cell death[28]. In a preliminary clinical trial using mifepristone in advanced breast cancer which was unresponsive to several medical therapies (tamoxifen or other endocrine therapy, chemotherapy, radiotherapy), 12 out of 22 oophorectomized or postmenopausal women with metastatic breast cancer receiving 100 mg mifepristone twice daily showed some degree of metastses regression or stabilization[30]. Eight of these patients responded for 4-6 weeks

and 4 patients responded for more than 12 weeks[30]. Although this preliminary trial shows low percentage of response, one should, however, bare in mind that the antiprogestin was given as a third line treatment when patients did not respond to other therapies. Further studies are required before a conclusion could be made whether mifepristone should be an additional and complementary endocrine therapy of breast cancer.

Mifepristone also showed a good propective in the treatment of meningioma, a carcinoma which is believed to be progesterone dependent. Treating the unresectable meningiomas with 200 mg/day mifepristone for periods of 2-31 months showed signs of objective response in 5 out of 14 patients (reduced tumor size and improved visual field examination)[41]. The value of antiprogesterone in the treatment of unresectable benign meningioma is still needed further validation.

Luteal contraception? Mifepristone induces uterine bleeding in luteal phase women irrespective of circulating progesterone levels, demonstrating a direct impact on the endometrium[5-7]. Additionally, both LH pulse amplitude and frequency are reduced after a single oral dose of mifepristone given at late luteal phase[6-7], an effect which may have facilitated the ongoing luteolytic process since corpus luteum function is LH dependent. Therefore, mifepristone has been tried as a late postcoital contraception and once-a-month contraception[31]. but this contraceptive method can have failure rates as high as 20%[32]. A women with a regular sex life has a 20% chance of pregnancy for unprotected intercourse[32]. The overall 4% (20% × 20%) failure rate of this luteal contraception is still far to high to accept as a routine contraception. In one long term study using 600 mg mifepristone single dose one day before the expected day of menses in 12 regular cycling women, it was found that of 137 cycles, 22 pregnancies occurred (16%) and 4 (18%) were not interruped by the second dose of mifepristone[31]. Nevertheless, it is still worth investigating the possibility of using antiprogestin as once-a-month contraception based on the concept of using anti-GnRH follow by antiprogestin. Whereas the GnRH antagonist primarily enhances ongoing luteolysis, the consequence of which is withdrawal of hormone support to the endometrium, antiprogestin will exert its predominant effect on endometrium and may also inhibit gonadotropin secretion. Thus the combination of these two antagonists with complementary luteolytic and endometriolytic effects may lead to once-a-month contraception in the future. Roseff *et al* (1990) have already demonstrated this good pospect by consequently using the GnRH antagonist followed by progesterone antagonist in luteal phase women and found the accelerated ongoing luteolysis and promt onset of uterine bleeding without functional alterations of the subsequent cycle[33].

Cushing's syndrome

As mifepristone has an affinity to bind to glucocorticoid receptors, therefore it should also be value for the treatment of Cushing's syndrome. There are case reports of using mifepristone to treat Cushing's syndrome caused by the ectopic secretion of ACTH. In these patients, a gradually increasing dose of mifepristone over 9 weeks abolished the somatic features of the syndrome (cervical fat pad,central obesity, moon facies), reduced the high blood pressure and reduced plasma glucose to normal levels[34-35]. However, since there is no practical way, at the present, to evaluate an extent of glucocorticoid blockage which might bring to an adrenal insufficiency conditions in long term use of drug. Therefore the drug should not yet be considered as a routine for the treatment of Cushing's syndrome[36].

For Cushing's disease, which pituitary ACTH overproduction is the cause of adrenal hyperplasia, cortisol hypersecretion, and cortisol negative feed back mechanism still exists, the use of mifepristone had been

reported to subsequently increase cortisol overproduction[36]. It is hard to know the balance at the target organ between the peripheral action of mifepristone and subsequently increasing cortisol production, the use of mifepristone in Cushing's disease is, again, not recommended[36].

As a pharmacological tool As a competitive antagonist to the progesterone receptor, without doubt, the availability of antiprogestins offers important new avenues for research into the physiological role and into the mechanism of action of progesterone at cellular level and probably for clinical investigation of progesterone dependent diseases and conditions in the future. Also as a glucocorticoid antagonist, the drug could be used to block the glucocorticoid receptors for the exploration of the hypothalamus-pituitary-adrenal system. These pospectives are out of the scope of this review and are not mentioned in detail.

Adverse drug reactions and drug safety

Mifepristone was first introduced in a clinical trial in 1982, which is still a relatively short period of clinical use, but so far the reports of adverse drug reactions are considered to be low. In large scale monitoring in multicentre trials, a small percentage of patients experienced headache, nausea vomitting and diarrhoea are reported after ingesting mifepristone[14,21]. Patient self assessment of abdominal pain 24-48 h after taking a single dose drug for pregnancy termination revealed that 2% had severe pain, 14% had moderate pain, 33% had mild pain and 51% had no pain at all[14]. No significant changes in haemoglobin, haematocrit, platelets, prothrombin or partial thromboplastin time ratio after using the drug were observed although some patients had experienced heavy uterine bleeding[14,37].

In chronic use of mifepristone in the preliminary trial for advanced breast cancer, 200 mg mifepristone daily caused a significant decrease in plasma potassium during the first month of treatment, and an increase in cortisol about 2 fold but without clinical hypo or hypercorticism[30]. Plasma LH, FSH and PRL were also significantly modified by chronic use[30]. In a study using 10 mg/kg-day for 14 days in healthy volunteers, it was reported that 8 out of 11 volunteers developed generallized exanthem (diffuse maculo-papular erythematous cutaneous eruption distributed over the entire body) all of which spontaneously resolved within 6 days of discontinuing the drug. One patient developed symptoms of adrenal insufficiency (extreme weakness, malaise, myalgias, arthralgias, headache, orthostatic hypotension, nausea and anorexia) the symptoms resolved after mifepristone was discontinued and 8 mg dexamethasone was given for 2 days[38].

Transplacental passage of mifepristone and long term effect on the fetus and teratogenicity of the drug are other points of consideration because there is still a small percentage of population who do not respond to the drug as an abortifacient. Also some women change their minds and decide to continue the pregnancy after the drug has already been taken. Mifepristone is transfered through placenta and an exponential increase in drug concentrations in the fetus with time was demonstrated[39], and fetal aldosterone levels were significantly elevated after the mother ingested the drug[40].

Conclusion

With the indispensibility of progesterone for the establishment and maintenance of pregnancy, the discovery of a drug with antiprogestational activity has brought a new era for the management of fertility regulation. So far, the drug has been shown to be useful for the pregnancy termination and for cervical dilatation. The drug also has several other potential benefits; once-a-month contraception, expulsion of dead fetus and progesterone-mediated breast cancer, which still required further investigations before clinical indications can be established.

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