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REVIEW ARTICLE

Mifepristone in Obstetrics and Gynaecology

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ABSTRACT

Mifepristone acts by antagonising the biological action of progesterone acting as competitive receptor antagonist. Medical abortion with mifepristone and prostaglandin is an effective method. Continuous administration of mifepristone in a dose of 2mg/day for 30 days inhibits ovulation and delays menstruation. It has also been used in a dose of 600 mg as post-coital contraception within 72 hours. It has marked effect on cervical dilatation and myometrial contractility and therefore justifies its future trial for use in induction of labour. It can be used for the treatment of ectopic pregnancy and endometriosis but further verification is needed by randomized controlled trials. Mifepristone reduces BCL-2, decreases EGF expression in uterine fibroid cells and increases TNF and thereby reducing fibroid size and volume. Recent cochrane study revealed that mifepristone reduces heavy menstrual bleeding and improved fibroid specific quality of life but does not reduce fibroid volume significantly and further studies are required for recommendation for treatment.

Keywords: Mifepristone, progesterone, abortion, leomyoma.

Mifepristone was invented in France by Dr Etienne - Emile Beaulieu in 1980. It was named RU 486 from the initials of the pharmaceutical company Roussel Uclaf and an arbitrary lab serial number. They were investigating compounds that would block glucocorticoid receptors and noticed that some of the compounds bound strongly to the similarly shaped progesterone receptor and blocked the action of progesterone. In 1982 the potential of RU486 as an abortifacient was introduced when "Effect of an antiprogesterone in women, interruption of menstrual cycle and of early pregnancy" was presented before French Academic des Sciences.[1]

In 1988, the French Ministry of Solidarity, Health and Social Welfare announced that mifepristone would soon be approved for marketing and distribution.[2] Strong, largely American anti-abortion forces targeted Roussel-Uclaf and its parent farm, German Manufacturer Hoechst for protest. Analogies were made between RU 486 and the poison gas that had been produced by Hoescht's corporate predecessor, I G. Farben, for Nazi gas chambers in World- war II. An active campaign of picketing, threats, boycotts and hostile letters were rapidly undertaken and therefore the company announced that it would not distribute the medicine. French Government, which owned a share in the company ordered resumption of plan to distribute the drug or else the company would face transfer of licence to distribute mifepristone to other manufacturers. The Ministry of Solidarity, Health and Social Welfare declared that this action was taken in the interest of public health and that RU486 was "the moral

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property of women, not just the property of the drug company".

With government intervention, company resumed plans for distribution. Anti-abortion groups challenged the governments ruling in the courts and the state council ruled that the government did not have the authority to order Roussel-Uclaf to distribute the drug. But the company did not withdraw it from the market.

The use of mifepristone for termination of pregnancy was approved by French authorities with several conditions [3]. It can only be prescribed in centres registered for pregnancy termination, the control of medication must be similar to narcotic control, and the patient must sign consent that she is aware that the method is not risk free and does not ensure cent percent success rate. Termination can only be done up to 7 weeks gestation, and there is a mandatory 1 week waiting period between decision to terminate the pregnancy and actual ingestion of drug. There is also mandatory clinic visit at 8-19 days after RU 486 intake.

The introduction of mifepristone was less dramatic in Britain and in 1991, 10 months after an application for licensing was submitted, it was approved for use up to 9 weeks of gestation. Other condition included its use in non-smoking women who were younger than 35 years, and multiple visit to abortion centre were required. The requirement of the British abortion law would have to be satisfied; including approval of physicians and the medication could not be prescribed by family planning clinics or general practitioners. In 1991, private abortion clinics were approved, allowing alternative to use in public hospitals. Requirement for the clinic included having an overnight bed available for every patient, and providing services only for women who lived within 1 hour of medical abortion and 2 hours for surgical abortion.

In the Unites states laboratory and clinical researchers studied mifepristone until 1989 and in 2000 it was approved for clinical use.

In 1981 first abstract on antiprogestins at endocrine society in San Francisco was presented and the first clinical study was conducted in 1984-86. In 1999 it was approved for clinical use in 10 European countries and Israel. In 1992 mifepristone was approved for clinical use in China.

Initial studies of mifepristone attempted to find out the optimal dose and dosing schedule to achieve acceptable rate of expulsion. The outcome of oral therapy was no different within a dose range of 50-400mg daily in single or divided doses over 4 days. Among women more than 49 days gestation, complete expulsion occurred in approximately 60-80% cases, incomplete abortion occurred in 6-30% and pregnancy continued in 7-40% [4 - 9]. At best 80% of women treated with mifepristone alone during early pregnancy had complete abortion, a rate not clinically acceptable. Investigators therefore began to add small doses of uterotonic agents on the last day of mifepristone treatment in an attempt to increase complete abortion rates. In 1985 investigators reported that adding small doses of prostaglandin analogue increased the efficiency of the drug as an abortifacient to nearby 100% [4, 8].

The metabolic clearance rate of mifepristone is 30L / day [10]. Because of its slow rate of removal from circulation it can be administered in a single oral dose for medical abortion. Serum drug concentration increases progressively after oral doses ranging from 50-100mg but no further increase occur after doses of 100-800mg. At present the standard dose is 200mg.

It acts by antagonising the biological action of progesterone at the receptor level acting as competitive receptor antagonist. It causes decrease of estrogen and progesterone receptors [11] in deciduas which may be related to prolonged uterine bleeding after its use for medical abortion.

Clinical use of Mifeptistone

Abortion

The total dose of mifepristone administered to induce abortion ranged from 140-1600mg given for a period of 1-7 days upto 9 weeks of amenorrhoea [12, 13]. When it was used alone, the success rate for less than 7 weeks ranged from 64-85%, no vaginal bleeding occurred in 1-10% and in 10-30% cases had incomplete abortion. The most likely lack of response could be due to inadequate increase in either in endogenous accumulation of PGF_2 alfa or in uterine contractility which was subsequently overcome by the use of prostaglandins. Medical abortion with sequential administration of mifepristone and prostaglandin is a safe effective well tolerated acceptable method of termination of early first trimester and second

trimester of pregnancy. The major side effect with this regimen is gastrointestinal and is commonly related to prostaglandin analogue and these are self limiting.

Contraception

Given in first 3 days of menstrual cycle, it has no effect on the cycle, length of follicular phase, LH surge or luteal phase length. The administration of 200-800mg of mifepristone after a dominant follicle has been demonstrated by USG inhibits the surge of LH as well as further follicular growth and ovulation. Thereafter, follicular growth resumes and ovulation occurs [14 - 16]. Continuous administration of mifepristone in a dose of 2mg/day for 30 days inhibits ovulation and delays menstruation [17, 18.]. More prolonged use results in low serum estradiol level, the periodic use of progestin leads to secretory transformation of the endometrium [19]. This regime produces well controlled bleeding, but does not always block ovulation. Administration of mifepristone each month during luteal phase to induce menstruation whether or not pregnancy has occurred [14,15,20, 21,22] . Failure rate were 17-19% in addition to low efficacy and because of its limitation like disruption of cycle rhythm it use is not popular. It has also been used in a dose of 600mg as post-coital contraception within 72 hours which remains effective longer than the combination of oestrogen and progesterone, which is effective for 72 hrs.

Cervical dilatation

Because of its marked effect on cervical dilatation and myometrial contractility it is useful for the preoperative preparation of women for surgical abortion in late first trimester and in second trimester pre treatment with it reduces the interval between expulsion and prostaglandin administration.

Induction of labour

It is used to induce labour after intra uterine foetal demise [23]. This has also been tried for induction of labour in third trimester and in a randomised double blind study of women at term, 50% of those who received mifepristone had spontaneous labour, as compared to 25% women who received placebo [24]. Cochrane study in 2009 after analysing 10 trials concluded that there is insufficient data to support the use of misoprostol for induction. However available data showed less chances of failed induction leading to Caesarean section in cases where mifepristone is used and therefore probably justify its future trial for use in induction of labour [25].

Ectopic pregnancy

It is suggested for the treatment of ectopic pregnancy. In a recent meta-analysis of 23 randomised study of 1706 patients indicated that showed better outcome of ectopic pregnancy with combination of mifepristone and misoprostol. Combination of methotrexate and mifepristone increases the success rate especially if the progesterone level is higher [26 - 28]. But the conclusion needs further verification by randomized, double-blind, and controlled trials with larger sample size and more rigorous trial design.

Endometriosis

As antiprogesterone it also inhibits estradiol stimulated endometrial growth but the mechanism is unknown. It may partly due to upregulation of endometrial androgen receptors in both gland and stromal cells and this enhanced endometrial androgen receptor expression could play a role in their antiproliferative, antiestrogenic effect. This effect of endometrial cells receptors occurs both in ectopic and utopic endometrium which is the theoretical basis of treatment of endometriosis. It was used in endometriosis for 3 months. Pelvic pain improved in low dose of 5mg for 3 months, but no change in the extent of the disease was found by follow-up laparoscopy [29]. Kettel et al. published a series of studies of administration of different doses of mifepristone in women with endometriosis. A minimum dose of 50 mg mifepristone for six months demonstrated a significant regression in visible endometriotic lesions and a decrease in clinical symptoms [30]. Another study recently has shown its effect in alleviating symptoms as well as combined therapy with minimal invasive surgery improved the reproductive outcome [31].

Leiomyomas

Recent evidence suggests that progesterone is essential for the maintenance and growth of leiomyomas [32]. Beta cell lymphoma 2 is a protein which inhibits apoptosis in uterine fibroid cells, epidermal growth factor increases angiogenesis in uterine fibroid cells, tumour necrosis factor inhibits fibroid cell proliferation and induce apoptosis and progesterone increases BCL-2 protein, EGF expression and reduces TNF expression in uterine fibroid

cells [33]. It was proposed that growth enhancement of leiomyoma cells by progesterone was mediated via bcl-2 induction. Mifepristone reduces BCL-2, decreases EGF expression in uterine fibroid cells and increases TNF and thereby reducing fibroid size and volume [34]. Reduction in the size may be due to its direct effect on progesterone receptors. Increase androgen receptors may also contribute its effect on the reduction of the size of fibroid. As it inhibits ovulation it may produce amenorrhoea. It has a direct suppressive effect on endometrial vasculature and reduces stromal VEGF causing less menstrual blood loss [35-38]. Cochrane study in 2012 concluded that mifepristone reduces heavy menstrual bleeding and improved fibroid specific quality of life but does not reduce fibroid volume significantly and further studies are required for recommendation for treatment. The initial studies with mifepristone suggested lesser efficacy with doses <10 mg and also concluded that an effective dose to cause a clinically significant (50%) decrease in leiomyoma volume was 25 mg daily. Mifepristone therapy when used in uterine leiomyoma there was a 49% reduction in tumour volume after 3 months [39]. In a study by ICMR in AIIMS it was concluded that there is 90% reduction in menstrual blood loss with both 10 and 25 mg Mifepristone for 3 months in fibroids of more than 5cm to 15 cm size [38]. But 25 mg dose has significantly greater reduction in the size of myoma than 10 mg and there was no endometrial atypia. This can be an optional treatment for younger patients who want to avoid surgery, in pre-menopausal patients as well as an adjunct to surgery for size reduction. There is chance increased endometrial hyperplasia without atypia which is reversible but no risk of decrease in BMD and osteoporosis.

Other uses

Other than this obstetric and gynaecological use this molecule is also been tried in progesterone receptor positive breast cancers, meningioma, hypercorsolism, lowering of intraocular pressure in glaucoma and prevention of viral disease in human.

Conclusion

Presently the most widely use of mifepristone is in combination with misoprostol for medical abortion because of its affectivity and safety that has resulted in increased access and options for reproductive health care throughout the world. Effective use in other indications in obstetrics and gynaecology will need further evaluation although the present studies are also having shown some encouraging results.

Conflict of interest: None. **Disclaimer:** Nil.

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