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Editorial

Mifepristone - beyond Medical Termination of Pregnancy

Introduction

Mifepristone, primarily known as "abortion pill", is an orally active, synthetic steroid with potent antiglucocorticoid, antiprogestogen and a weak antiandrogen used for the termination of pregnancy. Recently, other medical applications of mifepristone include cervical ripening at term, induction of labor in late pregnancy, regular long term use as an oral contraceptives, treatment of uterine fibroids, endometriosis, breast cancer, ovarian cancer, prostate cancer, meningioma, Cushing's Syndrome, and major depression with psychotic features. Mifepristone acts as a competitive receptor antagonist at the progesterone receptor in the presence of progesterone, and acts as partial agonist in the absence of progesterone. Mifepristone at doses greater or equal to 1mg/kg antagonize the endometrial and myometrial effects of progesterone. Antiglucocorticoid effect of mifepristone is manifested at doses greater or equal to 4.5 mg / kg and antiandrogenic effect in animals is seen with prolonged administration of very high doses of 10 to 100 mg / kg [1].

In late pregnancy, the uterus is sensitized by mifepristone to prostaglandins and promotes cervical dilatation which induces labor. p receptors in the placenta are also blocked by mifepristrone effectively, resulting in the termination of pregnancy . In 2000, Wing DA et al [2] in their study reported that 54 percent normal women given 200 mg Mifepristone daily for two consecutive days went into labor within 72 hours compared with only 18.2 percent of those given a placebo. Thus, Mifepristone appears to be efficacious, safe and adds valuable alternatives to the cervical ripening and labor induction. However, further studies are necessary to determine optimal doses, administration regimes, the incidence of complications or side effects and benefit – cost analyses.

Mifepristone, a novel estrogen free contraceptive when administered in low doses daily (2 to 10 mg), it inhibits ovulation, menstruation and significantly suppresses effects on the endometrium. However, due to continuation of variable degree of follicular development, unopposed estrogen can cause hyperplastic or malignant changes in the endometrium. But in 2003, Baird ST et al [3], in their study reported that mifepristone <10 mg per day neither caused endometrial hyperplasia nor the significant effect on the HPA-axis. Mifepristone also maintained bone density, lipids & sense of well being. Mifepristone as a postcoital contraceptive inhibits ovulation, blocks implantation by causing a delay in maturation of endometrium and causes regression of the corpus luteum in the majority of women when given in the middle or late lutal phase. Two randomized trial have compared 600 mg of mifepristone with the Yuzpe regimen. In these trials single dose of 600 mg of mifepristone given within 72 hours of unprotected intercourse was 100 percent effective as an emergency contraceptive [4]. Once a month administration of mifepristone alone at the end of the luteal phase of menstrual cycle is not an effective method for menstrual induction.

For safe and effective non-surgical treatment of symptomatic fibroids, high – dose progestin therapy and GnRh agonists have been shown to decrease overall uterine volume by 50 percent at the end of 3 months therapy. So far no therapy has been used on a long term basis, therefore, the effect of medical therapy is temporary. On a long term basis, mifepristone blocks progesterone dependent growth factors, reduces blood supply due to vascular changes and decreases inhibition of progesterone estrogen receptor gene transcription by the progesterone receptor A isoform, these are some of the mechanisms causing the antiproliferative activity of mifepristone. In 1998, Zeng C et al [5]. compared mifepristone 12.5 mg daily for 3 months with

gonadotrophin releasing hormone (GnRh) agonists in the treatment of fibroids and found comparable shrinkage, rates of amenorrhoea and resolution of anemia. In 2003, Steven H et al [6] studied 5 mg and 10 mg mifepristone (low dose) administered daily for 6 months in 40 women with large and symptomatic fibroids. Mean uterine volume shrank by 50 percent in both groups and fibroid related symptoms were comparably reduced in both groups. Simple endometrial hyperplasia was comparable in both groups but the incidence of hot flashes increased significantly over baseline in the 10 mg groups but not in 5 mg groups. Thus, Mifepristone can be used in uterine fibroids as alternative to GnRh anlogues in the preoperative application and if the safety of long term low dose mifepristone is established, perimenopausal women with large, symptomatic fibroid could avoid hysterectomies by using mifepristone till menopause.

Mifepristone through anitoxidant property does not allow endometriosis to proliferate. It also preserves follicular phase levels of estradiol. In a first experiment, Ana A et al [7] administered 100 mg of mifepristone for 3 months to six women with severe endometriosis. During the treatment all of them had significant improvement in their pelvic pain and were amenorrhic but resulted into antiglucocorticoid effects. In a follow up experiment 50 mg of mifepristone was given and had comparable clinical efficacy in reducing pain. Bone mineral density measurements of the lumbar spine & femur revealed no adverse effect. No antiglucocorticoid effect was noted but side effects included transient, mild increased in liver transaminase which returned to normal with in one month. In a third experiment, 5 mg (low dose) was used with comparable efficacy but with significant irregular bleeding hence, the study was terminated. Thus, 5 mg dose does not stabilize the endometrium and hence needs a dose of 50 mg daily. However, the use of mifepristone for the treatment of endometriosis requires additional studies.

Mifepristone inhibits ovarian cancer cells growth by inducing G1 cell cycle arrest and blocking the G1-S phase transition without causing cell death. This growth arrest is observed by a decline in cyclin – dependent kinase 2 (cdk2) protein level and activity. In 2003, Xu M et at [8] reported that ovarian cancer cells expressed glucocorticoid receptors. Mifepristone may drives it anticancer action by binding to glucocorticoid receptors with an affinity similar to that for progesterone receptors and as an antioxidant to drive G1 arrest through a p53 independent p21. In 2000, Rocereto TF [9] et al in their small trial conducted with 44 patients suffering from recurrent epithelial ovarian cancer whose tumors had become resistant to standard chemotherapy, mifepristone administration showed desirable effects against some of the tumors. Thus, mifepristone is a single agent potent blocker of ovarian cancer growth, however, the feasibility of using mifepristone to enhance the efficacy of conventional chemotherapy for ovarian cancer requires further investigations.

Approximately thirty percent of unselected patients and fifty to eighty percent of estrogen and progesterone – receptor – positive metastatic breast cancer patients have some degree of benefit from a variety of endocrine interventions. These patients may improve temporarily in response to these endocrine interventions but they are not cured. It has been observed that estrogen and progesterone in low doses stimulates breast cancer growth but in high doses both inhibit breast cancer growth. Tamoxifen, the antiestrogen, remains the first line therapy for advanced estrogen – receptor – positive tumor because of its efficacy, safety and convenience. Antiestrogen (Tamoxifen) and antiprogestin produce tumor regression but either agent alone only produces tumor stasis. Tamoxifen down regulates the estrogen receptor but it favors agonists activities and therefore up regulates the progesterone receptor. Mifepristone down regulates both estrogen and the progesterone receptors. The finding suggests that tamoxifen can not inhibit the progestin – mediated growth – stimulatory effects. Thus, addition of mifepristone to tamoxifen effectively reestablishes tamoxifen growth inhibition It has been observed that eventually all advanced breast cancer become hormone independent and increasingly resistant to any subsequent therapy as a result there is limitation in potential utility of antiprogestin and other endocrine therapies for the treatment of advanced disease.

In 1993, Corroll RS et al [10] in their series revealed that 64 percent of patients had functional progesterone receptors. In the initial clinical trial in 24 patients with recurrent meningioma following surgery or radiotherapy were administered mefipristone 200 mg daily for more than one year reported that 25 percent had decrease in tumor size on CT Scan or MRI & improvement in visual symptoms or headache [11].

Chronic exposure to excessive corticosteroids in Cushing's Syndrome leads to the development of multiple metabolic abnormalities such as glucose intolerance, dyslipidemia, hypertension, oestoporosis

and weight gain. In 2001, Dwight FM et al [12] reported that extremely ill patient with CS, treated initially unsuccessfully by a combination of conventional surgical, medical and radiotherapeutic approaches responded extremely well up to 25 mg / kg / day, long term mifepristone, glucocorticoid receptor antagonist therapy. Treatment efficacy was confirmed by the normalization of all biochemical glucocorticoid – sensitive measurements, significant reversal of the patient's heart failure, the resolution of the psychotic depression and usual return of his HPA axis to normal.

Mifepristone is contraindicated in the presence of an intrauterine device (IUD),ectopic pregnancy, adrenal failure, hemorrhagic disorders, inherited porphyria and anticoagulant or long term corticosteroid therapy.
Side effects of short term use include abdominal pain, cramping, nausea, vomiting and headache which are dose and treatment duration dependant. Antiglucocorticoid side effects in long term use are rarely observed when daily doses of mifepristone ranges from 5 to 100 mg. Clinically adrenal insufficiency is manifested as episodes of severe nausea prostration and marked hypotension and concomittent gloucocorticoid replacement therapy can be given. Risk of endometrial carcinoma in relation to long term treatment with mifepristone is low. Inspite of this, regular vaginal ultrasound is necessary to rule out endometrial hyperplasia. Long term administration of mifepristone is associated with low serum potassium levels, a slight increase in serum creatinine levels ,moderate increased in hepatic enzymes and significant increased in thyrotrophins (TIH) levels.

Mifepristone is currently used with Government approval in Medical Termination of Pregnancy. Apart from this, there are variety of applications during pregnancy, progesterone dependent gynecological diseases, breast cancer and other medical diseases and the results are encouraging. Thus, mifepristone appears to be efficious, safe and to add valuable alternatives to the progesterone dependent obstetrical, gynecological and medical diseases armamentarium.

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Dr. Purandare Chittaranjan N.

Purandare Griha,
31/C, Dr. N. A. Purandare Marg,
Mumbai - 400 007.
Email : dr.c.n.purandare@gmail.com
Mobile : 98200 88183