REVIEW ARTICLE

Ulipristal Acetate- A Selective Progesterone Receptor Modulator

Mohammed Shakeel Mohammed Bashir [1], Kishor A Bansod [2], Tanveer Khan [3]

1- Associate Professor, Department of Pharmacology, Faculty of Dentistry, Taif University, Taif, KSA
2- Associate Professor, Department of Pharmacology, Dr. Punjabrao Deshmukh Medical College, Amravati, MS
3- Professor & Head, Department of Pharmacology, Government Medical College, Rajnandgaon, Chhattisgarh

Abstract

Background: *Unintended pregnancies occur due to unprotected sexual intercourse. To avoid such unplanned pregnancies emergency contraceptives are available. Ulipristal acetate is one such orally active drug which is a selective progesterone receptor modulator. Ulipristal acetate also have promising role in the management of uterine fibroids as it is found that uterine fibroids have progesterone receptors and progesterone activity is responsible for their growth. In this review Ulipristal acetate is reviewed for its action on uterine fibroids and as emergency contraceptive.* ***Methods:*** *Medline database was searched using the keywords like Ulipristal acetate, emergency contraceptives, oral contraceptives, uterine fibroids, menorrhagia to find out the articles related with Ulipristal acetate.* ***Results:*** *The literature indicates that Ulipristal acetate is a good oral emergency contraceptive drug even after 120 hours of unprotected sexual intercourse. Depending upon the menstrual cycle it inhibits ovulation, delays release of ovum, affects ciliar beat frequency and affect endometrial receptivity. It does not have effect on established pregnancy. Ulipristal acetate reduces the uterine fibroid size and also effectively control heavy menstrual bleeding. It does not produce endometrial hyperplasia or any neoplastic changes.* ***Conclusion:*** *Ulipristal acetate is a good emergency contraceptive drug and also useful in the management of uterine fibroids. But still further studies are needed to establish its safety profile.*

Keywords*: Emergency contraceptives, Ulipristal acetate, Uterine fibroids*

Address for correspondence: Dr. Kishore Ambadasrao Bansod, Associate Professor, Department of Pharmacology Dr. Panjabrao Deshmukh Memorial Medical College, Amravati M.S. kishorbansod74@gmail.com

Introduction

Unplanned pregnancies are common throughout the world, although a number of contraceptive methods are available for the prevention of unplanned or unintended pregnancy.[1] A wide variety of highly effective preventive measure are available including condoms etc. still these methods seem to be imperfect. Such unintended pregnancies may be due to lack of contraceptives or contraceptives failure or unprotected sexual intercourse or may be the result of rape. In US around one third of pregnancies occurs among those women which uses contraceptive methods inconsistently, incorrectly or not at all.[2] These pregnancies have great psychological effect on the life of women and leads to millions of abortions each year. In 2005 at United States 1.21 million abortions were reported as per the data of Centers for Disease Control and Prevention.[3] Emergency contraceptive pills are helpful in such situation as emergency contraception is defined as the use of any drug or device after unprotected intercourse to prevent an unwanted pregnancy.[4] Ulipristal acetate is one such drug which can be useful as emergency contraceptive pill.[1] Ulipristal acetate is useful for the prevention of unintended pregnancy even after 5 days of unprotected sexual intercourse.[5]

Uterine fibroids

Uterine fibroids or leiomyoma which occur during the reproductive age are one of the most common benign tumors of uterus with prevalence rate of 70-80% up to the age of 50 years.[6] Prevalence rate among black women is around 80% while it is 70% in white women.[7]It has tremendous negative impact on the quality of life of a woman. The cost of this morbidity is

in billions of dollars worldwide even in US alone it is approximately between 6 to 34 billion dollars annually.[8]

Uterine fibroids are one of the very important cause of female infertility. Uterine fibroids have deleterious effects on endometrium which are responsible for decrease rate of embryo implantation leading to pregnancy failure. Uterine fibroids also affect transport of sperms and uterine contractility, collectively which is responsible for infertility.[9]

Heavy menstrual bleeding (menorrhagia), menstrual periods lasting more than a week are the most common presenting symptoms although most of the uterine fibroids are often asymptomatic and are found during the pelvic examination incidentally. Estrogen and oral contraceptives probably have the roles in stimulating the growth of uterine fibroids. These fibroids shrink after onset of menopause.[10]

Clinically Leiomyomas are termed as uterine fibroids. Uterine fibroids are nothing but the benign tumors of uterine smooth muscle which almost never turn into malignant tumors. These are gray-white sharply circumscribed masses which are scattered within the uterus. These fibroids are composed of bundles of smooth muscle with or without foci of fibrosis, and calcification.[10]

Somatic mutations such as Med12 mutation in myometrial stem cell occurs which leads to conversion of this stem cell into leiomyoma initiating cell. All uterine fibroids are independent as they are originated by different mutagenic event.[11]Estrogen promotes progesterone activity and progesterone directly via progesterone receptors is responsible for increased proliferation, decrease apoptosis and increase in intracellular matrix of the uterine fibroids. Progesterone indirectly by paracrine effects on fibroid stem cells is responsible for more fibroid cells growth.[8]

Management of uterine fibroid includes surgical procedures. Uterine fibroids can be removed by hysterectomy but in future the woman cannot become pregnant. Myomectomy is another method of fibroid removal in which uterus is saved. But unfortunately both hysterectomy and myomectomy have minor and major surgical risk. Myomectomy also have the risk of uterine fibroid recurrence.[5,12]

Medical management includes combined oral contraceptive pills, levonorgestrel intrauterine system, gonadotropin releasing hormone agonists and antagonists, selective estrogen receptor modulators and selective progesterone receptor modulators.

Combined oral contraceptive pills have the disadvantage of limited efficacy and inability to reduce the size of uterine fibroid.[13]Studies indicate conflicting results regarding efficacy of levonorgestrel intrauterine system for controlling uterine bleeding due to uterine fibroids.[8] Gonadotropine releasing hormone (GnRH) decreases symptoms and size of the uterine fibroid but unfortunately have lot of adverse effects such as hot flushes, vaginal dryness, bone demineralization etc.[14] GnRH have better efficacy but have high price and limited evidence about its superiority with GnRH agonist.Selective estrogen receptor modulators like Raloxifene were found to be ineffective for the management of uterine fibroids.[8]

Selective progesterone receptor modulators have mixed agonist and antagonist properties and are tissue and target (Progesterone receptor) specific.[15]These group of drugs minimally affect serum estrogen level hence do not produce adverse effects of estrogen. The drugs included in this group are Mifepristone, Asoprisnil, Onapristone, Ulipristal acetate, Lonaprisan, Vilaprisan, and Telapristone.[8]Mifepristone carries risk of endometrial hyperplasia and does not cause significant decrease in the size of uterine fibroid hence not used for the management of uterine fibroids. Asoprisnil alters endometrial lining while Telapristone increases liver enzymes. Vilaprisan successfully cleared 12-week phase I clinical trial.[8]Recently Ulipristal acetate, the selective progesterone receptor modulator is recommended for the treatment of uterine fibroids in many countries including US, Europe and Canada.[5,8] It is not only used for emergency contraception but also pre-surgical and long term use for uterine fibroids. Hence in this review, Ulipristal acetate is discussed in relation of its role for the management of uterine fibroids and emergency contraception. Medline database was searched using the keywords like Ulipristal acetate, emergency contraceptives, oral contraceptives, uterine fibroids, menorrhagia to find out the papers.

Ulipristal Acetate

Ulipristal acetate a 19-norprogesterone synthetic steroid derivative is a new type of selective progesterone receptor modulator with decreased anti-glucocorticoid activity.[16] US FDA approved it as an oral emergency contraceptive pill in August 2010 as the 1st agent in the novel category of selective progesterone receptor modulator class. It was 1stdeveloped by Laboratoire HRA Pharma/Watson Laboratories.[5] European medicines agency (EMA) approved it in February 2012 for uterine fibroid while health Canada approved it in 2013. Its approval for uterine fibroid is pending with US FDA.[8] Nowadays it is used for the management of uterine fibroid and as emergency contraceptive pill in many countries.

Structure

The chemical name of Ulipristal acetate is 17α-acetoxy-11β-[4-*N,N*-dimethylaminophenyl-19-norpregna-4,9-diene-3, 20-dione. It is white to yellow crystal insoluble powder with molecular weight of 475.629 g/mol. The molecular formula is $C_{30}H_{37}NO_4$.[1,17]

Role in Emergency Contraception

As far as progesterone is concerned, it is responsible for maintenance of pregnancy. It causes endometrial thickening and alteration of viscosity of cervical mucosa which helps in implantation of fertilized ovum and prevents the exposure of other sperms to fertilized ovum.Progesterone produce such effect by acting on progesterone receptors which are nuclear in nature and mostly distributed in female genital tract. Once progesterone binds to the receptor, the receptor undergoes dimerization, then come in contact of progesterone response element of target genes and then regulates transcription through co-activators. [18]

The action of Ulipristal acetate as agonist or antagonist depends upon the location, the presence of coactivators or coinhibitors of gene expression, and the serum levels of progesterone.[19] Ulipristal acetate has anti-progesterone like action for suppression of ovulation. It acts by binding to progesterone receptors and then either suppress or delays the ovulation and decreases the endometrial thickening.[20]

Ulipristal acetate can inhibit ovulation even if it is given just before ovulation. It is due to selective progesterone receptor modulating property. In the presence of low progesterone, it acts as agonist to progesterone receptor while in the raised level situations acts as antagonist by blocking the rise of LH thus it prevents ovulatory peak. Ulipristal acetate probably suppress expression of progesterone receptor dependent genes which are critical for ovulation, thus prevent ovulation.[19,21]

In fallopian tube, cilia activity and muscular contraction occurs which is responsible for transport of zygote. Too slow are very fast tubal transport may cause failure of pregnancy due to desynchronization.[19]According to Li et al Ulipristal acetate acts on progesterone receptors of fallopian tube as agonist and inhibits ciliar beat frequency and muscular contraction of the fallopian tube in the pharmacological doses and thus prevents pregnancy.[22]But according to Yuan et al, Ulipristal acetate antagonizes the progesterone-induced ciliar beat frequency decrease in dose dependent manner and thus prevent the pregnancy.[23]

Ulipristal is a derivative of 19-norprogesterone which has been developed to improve the specificity at progesterone receptors. Hence it has anti-glucocorticoid and anti-androgen activity approximately 50 times less than the anti-progesterone effects. Moreover, it has ability to inhibit or delay the ovulation and thus prevention of pregnancy even after 120 hours of unprotected sexual intercourse. [24]

The action of Ulipristal differs according to timing of menstrual cycle and the given doses. If Ulipristal acetate is taken before ovulation, the drug is responsible for delayed follicle development and release of the ovum. Decreased estradiol level by the drug might be the reason behind such phenomenon. If it is taken during the LH peak stage, follicular rupture may be delayed. In the later part of the menstrual cycle, drug is responsible for reduced endometrial thickness leading to failure of pregnancy.[24]Ulipristal acetate is responsible for lengthening of the menstrual cycle around 1 to 2 days which is due to delayed ovulatory action of the drug.[1]Ulipristal acetate also prevents pregnancy by acting as antagonist of progesterone, is responsible for suppression of progesterone-induced acrosome reaction,

hyperactivation and calcium concentration in sperms.[25]

Role in the Management of Uterine Fibroid

Progesterone receptors are found in the uterine fibroids. Progesterone activity in the progesterone receptors located on the fibroid is responsible for proliferation of the fibroids. Hence Ulipristal acetate which is a selective progesterone receptor modulator and has tissue-specific mixed agonist/antagonist effects have possible role in the management of uterine fibroids.[26]

Ulipristal has ability to effectively and reversibly block the progesterone receptors located in the genital tract such as uterus, cervix and ovaries. It acts as orally active potent anti-progestin agent which causes substantial reduction in the size of the uterine fibroid with significant reduction in uterine bleeding hence improving the quality of life.[27]

Ulipristal acetate suppresses the expression of growth factors, angiogenic factors such as vascular endothelial growth factor, decreases the cell viability and induces apoptosis. Collectively these actions of Ulipristal acetate is responsible for the suppression of neovascularization, cell proliferation and survival of the fibroid cells. Ulipristal also has the action on metalloproteinases, it decreases the expression of tissue inhibitor of metalloproteinases and increases the expression of matrix metalloproteinases which ultimately reduces the deposition of collagen in the extracellular spaces of fibroids leading to impairment of tissue integrity.[28,29]

Nieman LK et al found the good control over uterine bleeding, reduced uterine fibroid size and improved quality of life when Ulipristal acetate was given for 3 to 6 months.[27]Courtoy GE et al with Ulipristal acetate observed decreased proliferation, stimulated cell death and decreased extracellular matrix in uterine fibroids in comparison to placebo in their retrospective study of tissue collected form women preoperatively treated with the drug.[30]Levy G et al[31] did not observed any evidence of endometrial hyperplasia in regular biopsy of a case of uterine fibroid treated with Ulipristal acetate over the period of 5 years.

Donnez J et al in their study in 2012, treated symptomatic uterine fibroids cases pre-surgically for 13 weeks with Ulipristal acetate. 96 patients received Ulipristal acetate 5mg/day while another 98 patients received 10mg/day. 48 patients received placebo. It was found that Ulipristal acetate reduced the size of the uterine fibroid and effectively controlled excessive uterine bleeding in comparison to placebo.[32]

Donnez J et al compared efficacy and safety profile of Ulipristal acetate with Leuprolide acetate during the treatment of symptomatic uterine bleeding due to uterine fibroids before surgical removal. 95 patients received Ulipristal acetate 5mg/day while another 100 patients received 10mg/day. Leuprolide acetate 3.75 mg/month was received by 95 patients. Treatment course was for 3 months. Both the doses of Ulipristal acetate were superior to Leuprolide acetate once monthly dose in controlling the uterine bleeding. There were significantly less adverse effects such as hot flushes with Ulipristal acetate in comparison to leuprolide acetate.[33]

Donnez J et al in their another study investigated efficacy and safety of Ulipristal acetate during the treatment of symptomatic uterine fibroids. Treatment with 10mg Ulipristal acetate was given for 3 months daily. This course of treatment was immediately followed by 10-day double-blind treatment with 10mg per day norethisterone acetate (progestin) or placebo. Such 4 cycles were repeated. Ulipristal acetate reduced the size of the uterine fibroids and also significantly reduced the uterine bleeding without uterine hyperplasia. 10 days' progestin course was responsible for return of menstrual bleeding during the off period with less magnitude of flow.[34]

Donnez J et al in their study, two 12 week courses of Ulipristal acetate were intermittently given for the treatment of symptomatic uterine fibroids and efficacy and safety were evaluated. 5mg daily dose for 12 weeks of Ulipristal acetate was given to 451 patients while 10mg daily dose was given to 223 patients. The two repeated courses were separated by a drug free interval. With both the doses bleeding was well controlled, fibroid size decreased, pain controlled and quality of life improved. In the extension of the trial two more repeated courses of drug were given in which the same efficacy was observed. Laboratory finding was favorable

and endometrial thickening was also at the safety level.[35,36]

De Milliano I et al in their systematic review of endometrial changes during Ulipristal acetate use did not observed any non- reversible premalignant lesions in uterus (endometrium). The follow up was seen up to a maximum four weeks in most of the studies. Although a transient increase is observed in endometrial thickening which was reversed to normal level after initial few weeks of Ulipristal acetate discontinuation. The endometrial thickening was attributed to unopposed action of estrogen on the endometrium leading to endometrial thickening due to antagonistic effects of progesterone receptor modulator, Ulipristal acetate. They felt the need of more long term intermittent studies to finally conclude the safety of the drug.[37]

Whitaker et al studied the endometrium (histological and molecular analysis) of women suffering from uterine fibroids and treated with 5mg daily dose of Ulipristal acetate for 9 to 12 weeks prior to hysterectomy. They found that Ulipristal acetate acting as progesterone receptor antagonist, made changes in endometrial morphology and gene expression but without increasing the rate of endometrial cell proliferation.[38]

Pharmacokinetic Properties

Ulipristal acetate is rapidly absorbed when given by oral route in the dose of 30mg. Peak plasma concentration (176 ± 89 ng/mL) is achieved around 0.5 to 3 hours after taking the drug. The peak plasma concentration level of the drug depends upon whether it is taken at fasting stage or after a meal.[1,20] It has active metabolite (mono-demethyl-ulipristal acetate), which has peak plasma level of 69 ± 26 ng/mL.[5] Absorption is pH dependent and better absorbed in acidic pH. It has high plasma protein binding (98%). It binds to albumin, $alpha_1$-acid glycoprotein, and high-density lipoprotein-cholesterol.[1]

Ulipristal acetate is extensively metabolized in liver by cytochrome P450 3A4 (CYP3A4) and by lesser extent with CYP 1A2. The active metabolite is mono-demethyl-ulipristal acetate, another metabolite di-demethyl-ulipristal acetate in inactive. The plasma half-life of a single dose of 30 mg is approximately 32.4 ± 6.3 hours.[1,5]It is mainly excreted by feces although less than 10% is also eliminated by urine.[8]

Adverse Effects

Ulipristal acetate is well tolerated drug. Commonly observed adverse effects are lower abdominal pain, nausea, headache, hot flushes, fatigue, dizziness, dysmenorrhea, functional ovarian cysts, acne and sweating. These events are mild to moderate in severity and usually resolved spontaneously. It may can cause delayed onset of next menstrual cycle but subsequent cycles are unaffected.[39]

Contraindications and precautions

Ulipristal acetate is contraindicated in pregnancy because of non-availability of data regarding its teratogenicity potential. It should be avoided in nursing mothers and if given to breast-feeding mothers, breast feeding should be avoided in the 36 hours following use of Ulipristal acetate. Drug is also contraindicated before menarche and in postmenopausal women. Hypersensitivity to Ulipristal or any other active substance is also contraindication for its use.[1,5]

Dosage

For emergency contraception the dose of Ulipristal acetate is 30mg oral tablet taken within 120 hours of unprotected sexual intercourse. It can be taken irrespective of food intake and menstrual cycle. In case of its use as emergency contraceptive, if vomiting occurs within 3 hours of its intake then another dose of Ulipristal should be taken to avoid pregnancy.[1,5] Recommended dose of Ulipristal acetate for uterine fibroids is 5mg once daily for 3 months, one more cycle of 3 months was recommended in 2014 by European medicines agency.[8,40]

Drug Interactions

Ulipristal acetate is metabolized by CYP3A4, hence any drug which induces CYP3A4 isoenzyme will be responsible for decrease action of the drug as its plasma concentration will be low. Barbiturate, Dexamethasone, Carbamazepine, Felbamate, Griseofulvin, Oxacarbazepine, Phenytoin, Rifampicin and Topiramate decreases activity of Ulipristal acetate as they are CYP3A4 isoenzyme inducers. Combined oral contraceptives pills and progestin only pills also increases its metabolism hence may reduce its therapeutic

efficacy[4,5] Ketoconazole, Itraconazole, Erythromycin increases plasma concentration of Ulipristal acetate as they inhibit CYP3A4 isoenzyme which is responsible for its metabolism.[1,5]

Drugs such as proton pump inhibitors, histamine$_2$-receptor antagonists, and antacids are responsible for increase gastric pH and since Ulipristal is better absorbed in acidic pH, these drug decreases it absorption from stomach.[5]

Conclusion

Ulipristal acetate is a selective progesterone receptor modulator. It can be used as emergency contraceptive pill even after 120 hours of unprotected sexual intercourse. It delays the follicle development and release of the ovum and also inhibit the ovulation. It affects ciliar beat frequency and muscular contraction of the fallopian tube and also decreases the receptivity of endometrium for implantation.

Progesterone receptors are found in the uterine fibroids. Progesterone activity is responsible for proliferation of the fibroids. Ulipristal acetate has tissue-specific mixed agonist/antagonist effects. It has ability to effectively and reversibly block the progesterone receptors and causes substantial reduction in the size of the uterine fibroid with significant reduction in uterine bleeding. Ulipristal acetate suppresses the neovascularization, cell proliferation and survival of the fibroid cells. It makes changes in endometrial morphology and gene expression but without endometrial hyperplasia or any neoplastic changes. It is well tolerated drug with mild to moderate degree of adverse effects. Still further studies are needed to establish its safety profile.

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