Asoprisnil: A selective progesterone receptor modulator

Progesterone is a hormone that is secreted by the corpus luteum, placenta, and in minimal quantities by the testis and adrenal cortex. The important function of progesterone is to sustain pregnancy. Large doses of progesterone inhibit LH surge and potentiate the inhibitory effect of estrogen on hypothalamus–pituitary axis, preventing ovulation. Therefore, synthetic substances which are agonist at progesterone receptor called “progestins” were developed, and these substances became an essential constituent of oral contraceptive pills. Progestins are mitogenic for breast epithelium and increase mammographic shadow. Clinical trials have shown that progestins and estrogens, and not estrogen alone, cause an increased incidence of breast cancer in postmenopausal women.[10,11] Progesterone receptor antagonist,mifepristone was then developed, which is now used for post-coital contraception and termination of early pregnancy. There was a constant need for a drug with the beneficial effects of progestins and progesterone antagonists, and at the same time will not affect the estrogen secretion, thereby retaining the protective effect of estrogen on the bone and cardiovascular system. This necessity led to the discovery of a new group of partial agonist–antagonist at the progesterone receptor called the “selective progesterone receptor modulators” [SPRMs]. These drugs are also known as “mesoprogestins”. Asoprisnil is the first selective progesterone receptor modulator.

Mechanism of tissue selectivity

Progestins, progesterone antagonists, and SPRMs all act through the Progesterone receptor (PR). The PR exists as two isoforms – PR-A and PR-B. These isoforms play different roles depending on the tissue where it is present. PR-A decreases estradiol responsiveness in the tissues. PR-B is responsible for the proliferation of endometrium, differentiation and proliferation of breast tissue.

Generally, PR exists in the DNA non-binding state. When progestins/ progesterone antagonists/SPRMs bind to PR, it undergoes dimerization and a conformational change, thereby converting it into a DNA-binding form. This form binds to progesterone response elements (PRE) present in DNA of the target tissue. This receptor-DNA complex recruits molecules which regulate transcription known as co-regulators. Co-regulators may either be co-activators which activate transcription, or co-repressors which inhibit transcription.[12] The agonist-receptor-DNA complex will recruit co-activators and the antagonist-receptor-DNA complex will recruit co-repressors. The tissue selective actions of the SPRMs depend on the relative concentrations of co-activators and co-repressors in the target tissue.[13] Transcription activation leads to protein synthesis and subsequent effects on the target tissue.

Pharmacological actions

Selective progesterone receptor modulators are partial agonist–antagonist at progesterone receptors. Asoprisnil has an antagonistic effect on progesterone receptors. Asoprisnil has an antagonistic effect on progestosterone receptors. It has no effect or partial agonistic effect on myometrium of pregnant uterus, whereas in myometrium of leiomyoma it acts as an antagonist.

On endometrium

The selective progesterone receptor modulators cause atrophy of the endometrium. Both selective progesterone receptor modulators and progesterone antagonists make the blood vessels that supply blood to the endometrium robust, whereas they become fragile with progestins. Both progesterone antagonists and SPRMs cause amenorrhea. But the way in which both these group of drugs cause amenorrhea is different. The Progesterone antagonists cause amenorrhea by causing anovulation, whereas the SPRMs have a direct inhibitory effect on endometrium.

On ovary

The most important aspect of selective progesterone receptor modulators on the ovary is that they do not affect the estrogen secretion from ovary. So the beneficial effects of estrogen on the bone and cardiovascular system are well maintained. Also, they have no or minimal inhibitory effect on the ovarian progesterone secretion. The progestins and progesterone antagonists inhibit ovulation, whereas the selective progesterone receptor modulators may only partially inhibit it.

On pregnant uterus

Another advantageous effect of SPRMs is that they do not affect the myometrial contractility of the pregnant uterus. They do not also affect the cervix of the pregnant uterus. This is in strong contrast to the progesterone antagonists which are used for termination of early pregnancy.

On breast

As already discussed, the progestins have a drawback of increasing the proliferation of the epithelium of breast. This effect is not seen with selective progesterone receptor modulators which decrease the proliferation of breast tissue.

Pharmacokinetics

Asoprisnil is given orally in a dose range of 5 to 25 mg once daily. It is well absorbed orally. It is metabolised in the liver by the cytochrome P450 enzymes. The metabolite is found to have weaker agonist and stronger antagonist effects than asoprisnil. But its exact role in the pharmacological effect of asoprisnil is still not known. The elimination half-life of asoprisnil is 4-5 h.[14]

Uses

Uterine fibroids

Uterine fibroids (leiomyoma) are the most common benign tumour in females. In the past, estrogen was considered to play an important role in the growth of myomas. But now
studies have shown that there is an increased concentration of progesterone receptors in leiomyoma tissue than the normal myometrium. Two randomized controlled trials have shown that progestins when used as add-back therapy in combination with GnRH agonists, attenuate or reverse the inhibitory effects of GnRH agonists on leiomyoma. On the basis of these evidences, and on the fact that asoprisnil is a progesterone antagonist at uterine myometrium, it is used in the treatment of uterine fibroids in the dose range of 5 to 25 mg/day. Phase II trials have shown promising results and phase III trials are underway.

Endometriosis

Endometriosis is a disease that is characterized by the presence of functional endometrial tissue outside the uterus. The main presenting features are pelvic pain and infertility. The medical management of pain involves progestins in the form of oral contraceptive pills, androgenic progestins like danazol and GnRH agonists. But on chronic use, these have undesirable side effects such as hypoestrogenic state (GnRH agonists), acne, hirsutism and voice change (Danazol). Because asoprisnil inhibits endometrial proliferation without compromising the systemic beneficial effects of estrogen, it has the potential to become the favored medical treatment for endometriosis.

Side effects

Asoprisnil is generally well tolerated in a dose of 5-25 mg. Minor side effects such as headache and abdominal pain were reported and were self-limiting. There has been no report of any drug-related serious adverse effects. As the drug is still undergoing phase III trials, the ongoing trials and vigorous post-marketing surveillance can bring out any adverse effect, which is not known now.

Clinical trials

In a double blind dose escalation study, Chwalisz K, et al. evaluated the effects of asoprisnil in 60 regularly cycling premenopausal women at doses ranging from 5 to 100 mg/day for 28 days. Asoprisnil consistently prolonged the menstrual cycle at doses of 10 mg/day, even though the effects on luteal phase progesterone, an indicator of luteinization, were inconsistent and independent of the dose. Asoprisnil suppressed periovulatory estradiol but not below follicular phase levels. There were no considerable changes in cortisol and prolactin levels.

In phase II multicenter, double-blind, placebo-controlled trial conducted in patients with uterine fibroid, asoprisnil (5, 10 and 25 mg) was administered orally once daily for 12 weeks. The results suggested a significant dose-dependent suppression of both duration and intensity of uterine bleeding in the asoprisnil group, and also an increased haemoglobin concentration compared with the placebo group. Other effects were a dose-dependent induction of amenorrhoea during the entire treatment period, reduction in uterine volume and volume of leiomyoma, and suppression of pressure symptoms. Asoprisnil did not decrease ovarian estrogen production in subjects with leiomyomata during the 12 week treatment period.

The results of phase III trials in patients with menorrhagia associated with uterine fibroids are awaited.

A randomized placebo-controlled, dose-finding phase II trial was done with asoprisnil in subjects with a laparoscopic diagnosis of endometriosis, exhibiting moderate or severe pain. Asoprisnil was given in doses of 5, 10 and 25 mg for 12 weeks. There was a considerable reduction in the average daily combined scores of non-menstrual pelvic pain and dysmenorrhea in all dose regimens compared with placebo. No serious drug-related adverse events were reported.

Conclusion

Asoprisnil is the first drug of the novel group – the selective progesterone receptor modulators. It is a partial agonist–antagonist that has the advantages of both the progestins and progesterone antagonists while retaining the beneficial effect of estrogen on the bone and cardiovascular system. Phase III clinical trials are underway to study its use in treating uterine leiomyoma and endometriosis. It is premature to conclude anything at this time, and watchful waiting is needed to see whether this group of drugs comes up as a promising medical therapy for uterine leiomyoma and endometriosis.

References