

Ulipristal acetate, a progesterone receptor modulator for emergency contraception

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ABSTRACT

Unwanted pregnancy is a global reproductive health problem. Emergency contraception is defined as the use of drug or device after unprotected or underprotected intercourse to prevent an unwanted pregnancy. 1.5 mg of levonorgestrel as a single dose or in two doses with 12 h apart taken within 72 h of unprotected intercourse is the current gold standard emergency contraception regimen. This method is only effective if used as soon as possible after sexual intercourse and before ovulation. A single dose of 30 mg ulipristal acetate, a novel selective progesterone receptor modulator, has recently been proposed for the emergency contraception use up to 120 h of unprotected intercourse with similar side effect profiles as levonorgestrel. Ulipristal acetate could possibly prevent pregnancy when administered in the advanced follicular phase, even if luteinizing hormone levels have already begun to rise, a time when levonorgestrel is no longer effective in inhibiting ovulation.

Key words: Emergency contraception, levonorgestrel, ulipristal acetate

INTRODUCTION

Despite the availability of highly effective methods of contraception, a great number of pregnancies are unintended. Today, levonorgestrel at the dose of 1.5 mg taken within 72 h after unprotected intercourse is the most widely used emergency contraception regimen. The current methods of hormonal emergency contraception are ineffective in preventing follicular rupture when administered in the advanced pre-ovulatory phase and are only effective if used as soon as possible after sexual intercourse and before ovulation.^[1,2] Ulipristal acetate, a selective progesterone receptor modulator,

can be used up to 5 days (120 h) after unprotected sexual intercourse.^[2] Ulipristal acetate developed for emergency contraception has been approved by the European Medicines Agency in May 2009 and by the United States Food and Drug Administration (US FDA) in August 2010.^[3,4] At present, it is not available in India.

Pre-clinical studies

Pre-clinical studies indicate that ulipristal acetate binds to human progesterone and glucocorticoid receptors. Weak and negligible affinity was shown for the androgen, estrogen, and mineralocorticoid receptors, respectively. Ulipristal acetate inhibited progesterone-induced endometrial glandular proliferation in rabbits. The antiovarulatory and antifertility (postcoital) activities of ulipristal acetate have been investigated in rats. The ability of ulipristal acetate to terminate pregnancies was investigated in guinea-pigs and monkeys.^[3]

Mechanism of action

The primary mode of action of ulipristal acetate is thought to be inhibition or delay of ovulation. A single mid-follicular dose

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has been shown to suppress growth of lead follicles. When given prior, or in some cases immediately after the luteinizing hormone (LH) surge, ulipristal acetate inhibited 100% of follicular ruptures. Even on the day of the LH peak, ulipristal acetate could delay ovulation for 24–48 h after administration; unlike levonorgestrel.^[1] Early luteal administration of 10–100 mg ulipristal acetate also results in a reduced endometrial thickness, delayed histological maturation, coupled with alterations in progesterone-dependent markers of implantation, which may subsequently inhibit implantation by rendering the uterus less receptive to the trophoblast.^[5]

Pharmacokinetics

Following oral administration of a single 30 mg dose, ulipristal acetate is rapidly absorbed, with a peak plasma concentration of 176 ± 89 ng/ml occurring approximately 0.5–3 h after ingestion, depending on whether the drug is taken during the fasting state or after a meal. Doses of unmicronized 1, 10, and 50 mg ulipristal acetate exhibit proportional increases in peak serum levels, but serum levels from higher doses, 100 and 200 mg, are not dose-dependent, suggesting saturation of carrier sites.^[6] High level of binding (>98%) occurs to plasma proteins. The compound is extensively metabolized by CYP3A4 in the liver, and the principal metabolites formed are the mono- and di-demethylated derivatives, of which the former, 3877A, is pharmacologically active. The terminal half-life in plasma is 32.4 ± 6.3 h (data on file).^[7]

Adverse effects

The adverse effects commonly associated with ulipristal acetate as evident from the phase II and III comparative studies are mainly mild or moderate, short-lasting, self-limiting, and similar with both ulipristal acetate and levonorgestrel.^[3] Adverse events observed most frequently include headache, nausea, abdominal pain, upper abdominal pain, dysmenorrhea, dizziness, and back pain.^[2]

Drug interactions

Drugs or herbal products that induce enzymes, including CYP3A4, such as carbamazepine, phenytoin, rifampin, St. John's Wort, etc., may decrease the plasma concentrations of ulipristal acetate, and may decrease its effectiveness while CYP3A4 inhibitors such as itraconazole, ketoconazole, etc., may increase plasma concentrations of ulipristal acetate.^[7]

Clinical trials

A controlled, randomized, double-blind, noninferiority phase II trial was carried out by Creinin *et al.*^[8] to compare the efficacy and safety of 50 mg unmicronized ulipristal acetate with levonorgestrel (0.75 mg twice) in 1549 women aged 18 years and over who requested emergency contraception within 72 h of unprotected intercourse and who had a negative pregnancy test (ulipristal acetate, $n = 775$; levonorgestrel, $n = 774$). Results of this study showed that ulipristal acetate

exhibited a trend toward higher efficacy and was statistically noninferior to levonorgestrel (2% noninferiority margin). It was also observed that while a sustained efficacy of ulipristal acetate was demonstrated up to 72 h after unprotected intercourse, efficacy with levonorgestrel decreased over time. The pregnancy rates were 0.9% (7 pregnancies) and 1.7% (13 pregnancies) in the ulipristal acetate group and levonorgestrel group, respectively. In terms of the contraceptive effectiveness, ulipristal acetate and levonorgestrel prevented 85% and 69% of expected pregnancies, respectively.

Another phase II noninferiority study designed to assess the efficacy and safety of ulipristal acetate 10 mg micronized *versus* 50 mg unmicronized, in 400 women >18 years of age, showed that the 10 mg micronized formulation was nonsignificantly inferior to the 50 mg unmicronized formulation. The prevented fraction was 52.38% in unmicronized compared with 76% in micronized formulation. The trial was subsequently used to identify an appropriate dosing formulation of ulipristal acetate.^[3] The US FDA approval of ulipristal acetate was based on an open label trial in which 1241 healthy female subjects who requested emergency contraception 48 to 120 h after unprotected intercourse received ulipristal acetate 30 mg orally. Statistically significant reduction in the pregnancy rate, from an expected rate of 5.5% to an observed rate of 2.1% (26 pregnancies), was associated with ulipristal acetate. In addition, pregnancy rates were 2.3%, 2.1% and 1.3% for intervals of 48–72 h, more than 72–96 h and more than 96–120 h, respectively, indicating no decrease in efficacy over time.^[9]

The US FDA approval of ulipristal acetate was also based on a randomized, single-blind comparative, multicentric, noninferiority trial in which 2221 women were randomly assigned to receive a single, supervised dose of 30 mg ulipristal acetate or 1.5 mg levonorgestrel orally. In the efficacy-evaluable population, 1696 women received emergency contraception within 72 h of sexual intercourse (ulipristal acetate, $n = 844$; levonorgestrel, $n = 852$). The pregnancy rate was 1.8% (15 pregnancies) in the ulipristal acetate group compared with 2.6% (22 pregnancies) in the levonorgestrel group. Further, the number of pregnancies in women taking emergency contraception between 72 and 120 h after unprotected intercourse was 0 in 97 women in the ulipristal group and 3 in 106 women in the levonorgestrel group. A meta-analysis using this study and study by Creinin *et al.*^[8] showed that during 0–72 h time, there were 22 pregnancies (1.4%) in 1617 women in the ulipristal acetate group and 35 pregnancies (2.2%) in 1625 women in the levonorgestrel group ($P = 0.046$).^[2]

There is one more study in the support of the above-mentioned efficacy studies of ulipristal acetate. A double-blind, crossover, randomized, placebo-controlled study was designed to

determine the capacity of ulipristal acetate to block follicular rupture when administered with a follicle of ≥ 18 mm. In this study, 35 women contributed with oral ulipristal acetate 30 mg and a placebo cycle. Follicular rupture failed to occur for at least 5 days following ulipristal acetate administration in 20/34 cycles (59%), whereas rupture took place in all cycles within 5 days of placebo intake. When ulipristal acetate was administered before the onset of the LH surge, or after the onset but before the LH peak, follicle rupture had not occurred within 5 days in 8/8 (100%) and 11/14 (78.6%) cycles, respectively. In contrast, when ulipristal acetate was given after the LH peak, follicle rupture inhibition was only observed in 1/12 (8.3%) cycles. Overall, this study demonstrated that ulipristal acetate can significantly delay follicular rupture when given immediately before ovulation and could possibly prevent pregnancy when administered in the advanced follicular phase, even if LH levels have already begun to rise, a time when levonorgestrel emergency contraception is no longer effective in inhibiting ovulation.^[11] On the other side, it has also been reported that as ulipristal has no proven advantages, postcoital contraception should continue with a better-assessed drug levonorgestrel.^[10]

Other indications

In addition to the approved use of ulipristal acetate as an emergency contraception, it has also been found to be effective in the treatment of uterine fibroids. A study by Nieman *et al.* concluded that administration of ulipristal acetate for 3–6 months controls bleeding, reduces fibroid size, and improves quality of life without serious adverse events.^[11] In the PEARL I study, ulipristal acetate demonstrated statistically significant superior efficacy to placebo in reducing excessive uterine bleeding and also showed superior efficacy to placebo in correcting anemia caused by uterine fibroids and suppressing fibroids-related pain.^[12] In the PEARL II study, ulipristal acetate has been found to be at least as efficacious as leuporelin in reducing excessive uterine bleeding caused by uterine myomas and demonstrated a safety and tolerability profile statistically superior to leuporelin.^[13] A multicentric phase III clinical trial with ulipristal acetate *versus* placebo in uterine myomas has been reported as part of a global study PEARL I in the Clinical Trials Registry—India (CTRI) of Indian Council of Medical Research.^[14] In addition, CTRI also reports of a bioequivalence study of ulipristal acetate 30 mg tablets in healthy Indian female subjects.^[15] However, the detailed results of these Indian studies are not available.

To sum up, currently available data from the clinical trials suggests ulipristal acetate would be an effective alternative to

currently available methods for emergency contraception after unprotected intercourse.

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