Ulipristal acetate and its role in emergency contraception: a comment

Panagiotis Peitsidis
Department of Obstetrics and Gynecology “Helena Venizelou” Hospital, Athens, Greece

The use of selective progesterone modulators (SRMs) has been investigated extensively over the last few years. Ulipristal acetate (UPA) is an selective progesterone receptor modulator (SPRM) which has been in use since 2010 as an effective alternative emergency contraception (EC) regimen to Levonorgestrel (LNG). It acts by inhibiting ovulation and delaying implantation. Its effectiveness is active up to 120 h after sexual intercourse. UPA is safe and has a good tolerability profile. Health care practitioners should inform women of all reproductive ages that UPA is an effective alternative agent for those who are dissatisfied with other means of EC, and its activity of up to 120 h after sexual intercourse should also be highlighted.

Keywords: emergency contraception, selective progesterone receptor modulator, ulipristal acetate, unintended pregnancy

Unintended pregnancy is a worldwide reproductive health issue with social and economic expansions. Emergency contraception (EC) provides women with secure means of preventing unintended pregnancy after sexual intercourse and protects from unintended pregnancy in cases of sexual violence [1,2]. Several hormonal agents have been used since the 1960s, the combination of 0.1 mg ethinyl estradiol and 0.5 mg Levonorgestrel (LNG), given within 72 h of the intercourse and repeated after 12 h, was used commonly until the late 1990s when it was gradually replaced by LNG [3]. LNG, at a total dose of 1.5 mg has been used for hormonal EC and is approved for use up to 72 h after unprotected intercourse [2]. In 2009, a new agent called Ulipristal acetate (UPA), a selective progesterone receptor modulator (SPRM), was introduced [4].

In this issue of Expert Opinion on Pharmacotherapy, the pharmacological properties, clinical efficacy, and safety profile of UPA as an EC agent are reviewed [5]. The current comment is related to the aforementioned review; furthermore the most basic points on the importance of UPA in EC are discussed.

UPA, also referred to as CDB-2914 or VA2914, a SPRM which has been developed and used as an oral agent of EC, demonstrates both antagonistic and partial agonistic effect, thus inhibiting ovulation and delaying endometrial maturation [4]. UPA demonstrates activity after luteinizing hormone (LH) surge; the activity related with increased efficacy [4].

The drug was approved by European Medicines Agency (EMEA) in May 2009 and by the Food and Drug Administration (FDA) in the USA in June 2010 [6].

The approved treatment consists of 1 tablet of 30 mg UPA to be administered orally as soon as possible and no later than 120 h (5 days) after unprotected intercourse [6]. UPA is offered only with prescription in contrast to LNG which is distributed without prescription in about 62 out of 140 countries that have a dedicated LNG EC product on the market [6].

Active maximum plasma concentration (C_max) of its active metabolite, monodemethyl-UPA is achieved between 0.9 h and 1h and 18 min; C_max is decreased...
in vivo appears to be by CYP3A4 and to a lesser extent CYP1A2 by demethylated metabolite. The metabolism for this substance metabolized to mono-demethylated and di-dimethylated or after food intake. The predominant route of UPA is would not be affected if the agent was administered before P. Peitsidis LNG for EC. In the meta-analysis (0 meta-analysis, comparing the efficacy and safety of UPA with 18 2.1 and 2.8 days[9].

In 2010 Glasier et al. [7] performed Phase-III trials and a meta-analysis, comparing the efficacy and safety of UPA with LNG for EC. In the meta-analysis (0 - 72 h) after sexual intercourse, there were 22 (1.4%) pregnancies in 1617 women in the UPA group and 35 (2.2%) in 1625 women in the LNG group (OR 0.58, 0.33 – 0.99; p = 0.046) [5]. The authors stated a lower pregnancy rate at the timepoints of 24 (P = 0.035), 72 (P = 0.046), and 120 h (P = 0.025) [5]. This study exhibited clearly the advantage of UPA vs. LNG in EC and completed the previous two important pivotal trials performed by Creinin et al. [8] in 2006 and Fine et al. [9] in 2010, respectively.

We need to know what the adverse effects for the women are. The adverse effects are related to progesterone actions and are common. They may occur in the range of 12 – 18 % of cases, where the effects may be nausea, headache, and abdominal pain [8,9]. Women should be aware that other adverse reaction may include dysmenorrhea, fatigue, and dizziness, as well and a delay in menstruation which might range from 2.1 and 2.8 days [9].

UPA has demonstrated that it suppresses ovulation; however, the levels of estrogen are not altered therefore no bone changes related to hypoestrogenism are observed. This evidence may stimulate its use by fertile women who have decreased bone density due to various metabolic or endocrinologic disbalances.

What is the current evidence about the use of UPA during pregnancy and lactation? The agent has been categorized as X drug, which means that its usage is contraindicated in pregnancy therefore a pregnancy has to be excluded prior to its usage; in the literature are reported studies that have exhibited embryotoxicity only in animals. With regard to the lactation, it is not clear if the drug is excreted to the milk, therefore breastfeeding is not recommended in the 36 h following UPA intake [10,11].

Always should be taken under consideration the endometrial changes in patients receiving selective progesterone modulator treatment. Ioffe et al. [12] examined endometrial histology in 58 premenopausal women treated with the progesterone receptor modulator CDB-4124 for endometriosis or uterine leiomyomata in two clinical trials. No endometrial hyperplasia or carcinoma were observed in these patients. Similarly Mifepristone a well known SPRM has not shown any endometrial pathology however this agent is not approved for EC purposes but only for pregnancy termination. It should be underlined and endometrial changes are not related with dosage used for EC purposes with UPA. However further investigational studies are required to establish conclusions about the role of SPRMs in endometrial pathology.

Apart from its EC role, UPA has exhibited its pharmacetical role in menorrhagia. Recently in two randomized, double-blind, multinational Phase-III trials in women aged 18 – 50 years with uterine fibroids, a once-daily regimen of oral UPA 5mg/day controlled excessive uterine bleeding in ≥ 90% of patients. UPA 5mg/day was more effective than placebo and was shown to be non-inferior to intramuscular leuprolide acetate 3.75 mg once monthly in controlling uterine bleeding [13,14].

We agree with the authors which report that UPA shows obvious advantage to LNG due to the fact that it can be administered up to 120 h postcoitally. In addition it should be emphasized the activity of UPA after LH surge a cardinal sign which is absent in LNG contraceptive efficacy.

What will be the future of progesterone receptor modulators in order to achieve maximum protection against unintended pregnancy? Will the UPA and the SPRMs be used for long-term estrogen-free contraception and also as conservative treatments of endometriosis? Is it going to replace agents like Gonadotropin-releasing hormone (GnRH) agonists in the management of menorrhagia due to fibroids? Despite the lack of number of studies the role of the SPRMs seems to be challenging and promising in the future.

**Expert opinion**

Studies have demonstrated that UPA is more potent in inhibiting ovulation than LNG. UPA exhibits an obvious advantage: it can be administered 120 h after the intercourse without losing its efficacy and safety. The fact that UPA requires prescription may limit its distribution in contrast to LNG.

The use of UPA for the prevention unintended pregnancy is prudent, not only for the simplicity in the dosage administration, but mostly for its excellent tolerability status.

It is not completely clear however when a woman has to start the usual hormonal contraception after usage of UPA, the current evidence should be relied on larger clinical studies with more precise results. In addition women should have clear knowledge that UPA is not replacing the standard combined hormonal contraceptive regimen.

Women should be advised that UPA is a method of EC however its administration is not offering protection against sexual transmitted diseases (STDs); special educational programs handled by health provides should emphasize this important end-point.

Health care practitioners should inform women of all reproductive ages that UPA is an alternative agent of EC in patients who are dissatisfied to other means of EC, its efficacy even 120 h after sexual intercourse should be highlighted.

**Declaration of interest**

The author states no conflict of interest and has received no payment in preparation of this manuscript.
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Papers of special note have been highlighted as either of interest (●) or of considerable interest (★★) to readers.


11. In depth systematic analytic review of Ulipristal acetate in emergency contraception.


15. Large good non-inferiority trial to compare ulipristal acetate with leuprolide acetate in management of uterine fibroids.


Affiliation

Panagiotis Peitsidis MD PhD
Department of Obstetrics and Gynecology
“Helena Venizelou” Hospital, Proussis 22 P.C 17123, Athens, Greece
Tel: +00306972221553;
E-mail: panagiotis_pp@yahoo.com