EXPERT OPINION

Ulipristal acetate as an emergency contraceptive agent

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Introduction: Emergency contraceptive agents play a crucial role in preventing unplanned pregnancy. These agents and devices have been studied since the 1960s and have had varied results in terms of side effects and efficacy. A new oral tablet for emergency contraception (EC), ulipristal acetate (UPA), is a selective progesterone receptor modulator and can be used up to 120 h following unprotected intercourse, without an increase in adverse effects or a decrease in efficacy.

Areas covered: This article reviews studies that evaluate the pharmacodynamics, pharmacokinetics, clinical efficacy, and safety profile of UPA as an emergency contraceptive agent.

Expert opinion: UPA, a selective progesterone receptor modulator, is administered as a single 30 mg dose for EC. This agent provides a comparable, if not better, efficacy and side effect profile than seen with levonorgestrel or mifepristone. Because it has both agonistic and antagonistic effects on the progesterone receptor, ongoing clinical trials are documenting UPA's use for patients with endometriosis and as an extended use contraceptive.

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

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1. Introduction

Emergency contraception (EC) is used to prevent an unintended pregnancy. The most common indications for its use are related to failure of a contraceptive to work properly (condom breakage or slippage, missed oral contraceptive pills, intrauterine device [IUD] expulsion) or not using a contraceptive agent. The probability of an unintended pregnancy after a contraceptive failure or non-use may be as high as 30% [1,2]. Though the use of high doses of estrogen as an EC option was first described in the 1960s [3,4], Yuzpe first described the use of combined oral contraceptives (ethinyl estradiol/levonorgestrel [LNG]) for this purpose in 1974 [5]. Since that time, the use of progestins, copper IUDs, and antiprogestins have also been used as emergency contraceptive agents.

Antiprogestins or selective progesterone receptor modulators (SPRM) are an effective form of EC that can be used up to 120 hours after intercourse [6,7]. Mifepristone, though not US Food and Drug Administration (FDA) approved for EC use, is thought to have 2 potential methods of actions. It has been found to delay ovulation and prevent implantation [8,9]. Ulipristal acetate (UPA) (**Box 1**), which is also known as CDB-2914 or VA 2914, is a second-generation SPRM that directly blocks progesterone action in target tissues and has little glucocorticoid receptor activity compared to what has been documented with mifepristone [10-12].

2. Overview of the market

The FDA first approved the combination oral contraceptive pills for EC in 1998. LNG is a progestin-only method for EC in the United States was approved in

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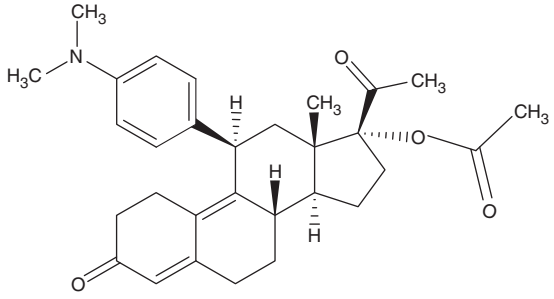
Box 1. Drug summary.

Drug name	Ulipristal acetate
Phase	Launched
Indication	Female contraception
Pharmacology description/mechanism of action	Progesterone receptor agonist Progesterone receptor antagonist Glucocorticoid antagonist Hormone receptor agonist Inhibition of ovulation Inhibitor of endometrial proliferation Decreased implantation potential
Route of administration	Oral
Chemical structure	
Pivotal trials	[20,7,19]

1999, and can be obtained over the counter for women 17 years and older [13]. It is given as a 0.75 mg dose 12 h apart or as a one-time dose of 1.5 mg. Both the approved combination pill and the progestin-only formulations have to be given within 72 h following intercourse. In 2010, UPA was approved as a single 30 mg tablet for EC in the United States, but not as an ongoing contraceptive (**Box 1**). UPA can be administered within 120 h of intercourse, but currently is available via prescription only.

3. Introduction to the compound

UPA is available as an off-white, round, curved single tablet of 30 mg in a blister card. It can be taken at anytime during the menstrual cycle with or without food. If vomiting occurs within 3 h of UPA's intake, repeating the dose should be considered to increase efficacy. When taken immediately before ovulation, UPA is thought to postpone follicular rupture [14]. The method of action as an agent for EC is thought to be the inhibition or delay of ovulation [15,16]. Also, UPA may alter the endometrium to affect implantation [17].

UPA has a favorable side effect profile. The most common complaints include headache, nausea, abdominal pain, dysmenorrhea, fatigue, and vertigo [18,19]. Because it is not indicated for use during pregnancy (Pregnancy category X), an ongoing gestation should be excluded before UPA is prescribed. The observed pregnancy rates based on a Phase-II and two Phase-III trials ranged between 0.7 – 2.1% [7,10,19,20]. Following discontinuation of UPA, a rapid return to fertility was noted, therefore routine contraception should be continued or initiated after its use.

4. Chemistry

The chemical formula is as follows: Ulipristal acetate 17 alpha-acetoxy-11beta-[4-N, N-dimethylaminophenyl]-19-norpregna-4,9-diene-3,20-dione. It is a synthetic progesterone agonist/antagonist and has a molecular weight of 475.6 g/mol. The structural formula is presented in **Box 1**. The inactive ingredients are lactose monohydrate, povidone K-30, croscarmellose sodium and magnesium stearate.

5. Pharmacodynamics

UPA is a SPRM with mixed effects at the level of the progesterone receptor. It can exhibit both antagonistic and a partial agonistic effect. When it binds to the progesterone receptor, it prevents endogenous progesterone from occupying its receptor, inhibiting progesterone receptor-mediated DNA transcription [21]. SPRMs have been demonstrated to inhibit ovulation, decrease proliferation of the endometrium (with possible alteration of implantation potential), and result in amenorrhea [15,17,22]. UPA can exhibit different effects depending on when is it administered in the menstrual cycle. During the mid-follicular phase, UPA inhibits folliculogenesis and reduces estradiol concentrations [15,16]. At the time of the luteinizing hormone (LH) peak, it delays follicular rupture by 5 – 9 days. When taken during the early luteal phase of the cycle, UPA does not have a significant effect on the maturation of the endometrium, but it decreases endometrial thickness by 0.6 ± 2.2 mm [23].

When comparing LNG to UPA, LNG acts primarily by blocking or delaying the LH surge. Its efficacy is limited to

the time frame preceding the onset of this surge, with no subsequent effects on follicular dynamics once LH levels increase [24,25]. In contrast, UPA has the potential to prevent pregnancy even in the presence of increased LH levels in the advanced follicular phase [15]. A single dose of 30 mg of UPA administered immediately prior to ovulation (dominant follicle > 18 mm) was effective in delaying subsequent follicular rupture for 5 days in 60% of subjects, primarily through postponement of the LH peak [6].

Although the mechanism of ovulation prevention is not clearly defined, it is thought that UPA may delay peak LH levels, and have direct effects on the dominant follicle through inhibition of progesterone regulated pathways, as demonstrated in a mouse model [26]. There is also evidence for possible disruption of implantation potential regarding Mifepristone. It has been demonstrated that endometrial receptivity markers in a human endometrial cell culture model showed altered expression profiles, and inhibition of human blastocyst attachment for Mifepristone, but not LNG, showing that SPRMs may have an inhibitory role in the implantation process itself [27,28].

6. Pharmacokinetics

When a 30 mg dose of UPA was administered to 20 fasting women, the active maximum plasma concentration (Cmax) of its active metabolite, monodemethyl-ulipristal acetate, was 176 ng/ml at 0.9 h and 69 ng/ml at 1 h [29]. When UPA was taken with a high-fat breakfast, the Cmax was 40 – 45% lower than that seen in the fasting state. In this same group, the Tmax was delayed from a median of 0.75 to 3 h. Despite these differences in Cmax and Tmax, no change in efficacy or safety would be predicted if UPA is taken with or without food. UPA is also highly bound to plasma proteins (> 94%). The proteins to which UPA is bound include HDL, alpha-1-acid glycoprotein, and albumin.

7. Metabolism

UPA is metabolized to mono-demethylated and di-demethylated metabolites. The pharmacologically active form is the mono-demethylated metabolite. The metabolism for this substance appears to be by the cytochrome P450 pathway, including CYP3A4 and to a lesser extent CYP1A2 by in vivo data. The half life (t ½) for a single 30 mg dose is 32.4 ± 6.3 h [30].

8. Clinical efficacy

UPA has been shown to serve as an effective emergency contraceptive agent, with evidence supporting a treatment effect up to 120 h after intercourse. Glasier, *et al*. [19] directly compared the effectiveness of a single 30 mg dose of UPA to 1.5 mg of LNG in a randomized, multicenter, single-blinded, non-inferiority trial, involving 1,696 women. With the primary outcome being pregnancy rate in women who received EC within 72 hours of unprotected intercourse, 15 pregnancies occurred in the UPA group (1.8%, 95% CI 1.0 – 3.0), compared to 22 in the LNG group (2.6%, 95% CI 1.7 – 3.9) (odds ratio 0.68) [19]. No significant difference in pregnancy rates (p = 0.091) between the UPA and LNG group was observed. Secondary outcome was pregnancy rate from 72 to 120 h of intercourse, and in this subgroup of 203 women, a total of 3 pregnancies were observed, all from the LNG group. A significant number of pregnancies were prevented in the UPA group compared to the LNG group (p = 0.037). When the authors analyzed the pregnancy rates between the groups over the entire 120 h period, there was no statistical significance (p = 0.091). Therefore, a metanalysis was performed using a Creinin *et al.* [20] study involving an additional 1,546 women, demonstrating a lower pregnancy rate at the timepoints of 24 (p = 0.035), 72 (p = 0.046), and 120 h (p = 0.025) [19,20]. Unlike LNG, UPA can be used over a 5 day period, and it does not exhibit the same magnitude of decreased efficacy the longer one administers it after intercourse.

In addition to it's use as an emergency contraceptive agent, UPA is being investigated as a potential agent for estrogen-free long-term contraception, uterine leiomyomas, and in the treatment of endometriosis. The capacity of UPA to inhibit or prevent ovulation for contraception has been investigated. In a prospective, randomized, placebo-controlled trial of 46 women, 5 or 10 mg of daily UPA was shown to effectively prevent ovulation over a 3-month period (81.8% and 80%, respectively) [31]. Further studies will be needed to assess these treatment applications, but the current results suggest that there may be a role for SPRMs in the future.

9. Safety and tolerability

Overall, it appears that UPA is an effective agent for emergency contraceptive purposes in the reproductive age woman with a minimal side effect profile. Although UPA has demonstrable effects on suppressing ovulation, estrogen levels are essentially unchanged, and therefore any bone density changes seen secondary to a hypoestrogenic environment are not observed. Commonly experienced symptoms observed include headache, nausea, and abdominal pain. In the two Phase-III studies, the rates were 18%, 12%, and 12%, respectively [7,19]. Other symptoms include dysmenorrhea, fatigue, and dizziness, as well as a delay in menses that ranged between 2.1 and 2.8 days [18].

UPA has been shown to transiently elevate liver enzymes, with no liver toxicity being reported to date. Unlike, previous SPRMs such as telapristone acetate that resulted in a dangerously elevated transaminase profile, the effect is only mild in nature and has produced no clinical morbidity to date.

In 2009, the new drug review application for UPA by the FDA discussed the possibility of drug – drug interactions, including agents which induce or inhibit CYP3A4 enzymes.

Agents which may induce this enzyme include carbamazepine, phenytoin, barbiturates, griseofulvin, felbamate, topiramate, rifampin, oxcarbazepine, bosentan, and St. John's Wort. Inhibitors of this enzyme such as ketoconazole and itraconazole could possibly increase blood levels of this agent, as UPA is primarily degraded by the cytochrome P450 system [10].

UPA is categorized as a pregnancy-X drug, and is therefore contraindicated for use during pregnancy. In addition, the potential of drug secretion into breast milk is yet unknown, so breastfeeding is not recommended. There is animal evidence that exposure of UPA during organogenesis resulted in fetal loss, however in the fetuses that survived no malformations were seen in the offspring [10]. Unlike mifepristone, it is not approved for use in termination of pregnancy.

With previous SPRMs, there has been concern over medium to long-term use of these agents and the possibility of permanent endometrial changes. Specifically, progesterone receptor modulator-associated endometrial changes (PAECs) with mifepristone were evaluated by pathologists and the conclusion was that there are no safety concerns associated with the observed endometrial changes [12]. Although further long-term administration of these agents is necessary, the short-term studies on UPA and other SPRMs have shown no evidence of endometrial hyperplasia in these patients [32].

10. Regulatory affairs

UPA was approved by the FDA for use as an emergency contraceptive agent in the United States in August 2010. Currently, it is available in over 29 countries throughout the world. Taken as a one-time 30 mg oral micronized dose, the recommended window of administration extends up to 120 h following unprotected sexual intercourse, making this agent a valuable entity for EC.

11. Conclusion

Selective progesterone receptor modulators have the capability to affect both ovulation and implantation, as evidenced by their effects on progesterone and the role of this hormone in the female reproductive process. Therefore, SPRMs have been investigated for their potential role in contraception, with mifepristone and UPA currently being evaluated for this purpose. Mifepristone has been approved for the termination of pregnancy, but not for EC.

UPA is the first SPRM approved for EC in the United States. It is also currently undergoing Phase-III trials as treatment for uterine leiomyomas, and Phase-II trials as a long-term contraceptive agent. Given as a single 30 mg oral dose, it has been shown to exhibit an equal or better efficacy (up to 72 h period) when directly compared to the current EC standard, LNG. The advantages of this prescription medication is that it can be given up to 120 h (5days) following sexual intercourse, and that the efficacy does not decrease to the extent of LNG the longer a patient waits to be treated following unprotected intercourse.

Common mild side effects include nausea, headache, and abdominal pain, which can be seen in up to 18% of patients. There are, to date, no studies providing evidence of a more severe side effect profile, including liver function abnormalities, permanent hormonal changes, or long-term endometrial changes.

Advantages observed with SPRM agents, such as UPA, are that there are no clinically significant changes in ovarian estrogen levels, and subsequently no negative effects on bone mineral density. It offers patients the opportunity to decrease their chances of pregnancy following unprotected intercourse, and allows physicians to effectively provide EC for up to 5 days. As a reminder, this agent is currently available only as a prescription drug, which may limit access to those patients who may not otherwise visit a practitioner (although availability through online prescription services do exist). It is important that physicians educate their reproductive age women about the availability and effective window of this medication, which makes it uniquely different from other forms of EC. Patients should also be counseled to proceed with barrier contraceptive methods for the remainder of the cycle following use of UPA, and that this drug does not protect against sexually transmitted infections and HIV.

12. Expert opinion

Since 2010, UPA has been marketed as an alternative EC option over the more commonly prescribed LNG. Both Phase-II and Phase-III clinical trials provide evidence that UPA is an effective EC agent, with a minimal side effect profile. The advantage being that this agent can be given for a longer duration from intercourse (120 h) without loss of effectiveness. Studies clearly demonstrate that UPA does not exhibit the observed decreased efficacy that is seen with the use of LNG over time. The caveat is that patients must visit their health care provider for a prescription, which makes access to care a major difference between the use of UPA and LNG. Health care providers should benefit from educating their patients that UPA is an alternative EC agent available, and that effective contraception can be expected up to a 5-day period following intercourse.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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