Ulpristal Acetate in Emergency Contraception

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ABSTRACT

Despite the widespread availability of highly effective methods of contraception, unintended pregnancy is common. Unplanned pregnancies have been linked to a range of health, social and economic consequences. Emergency contraception reduces risk of pregnancy after unprotected intercourse, and represents an opportunity to decrease number of unplanned pregnancies and abortions. Emergency contraception pills (ECP) prevent pregnancy by delaying or inhibiting ovulation, without interfering with post fertilization events. If pregnancy has already occurred, ECPs will not be effective, therefore ECPs are not abortificants. Ulipristal acetate (17α-acetooxy-11β-[4N-N,N-dymethilaminophenyl]-19-norpregn-4,9-diene-3,20-dione) is the first drug that was specifically developed and licensed for use as an emergency contraceptive. It is an orally active, synthetic, selective progesterone modulator that acts by binding with high affinity to the human progesterone receptor where it has both antagonist and partial agonist effects. It is a new molecular entity and the first compound in a new pharmacological class defined by the pristal stem. Up on the superior clinical efficacy evidence, UPA has been quickly recognized as the most effective emergency contraceptive pill, and recently recommended as the first prescription choice for all women regardless of the age and timing after intercourse. This article provides literature review of UPA and its role in emergency contraception.

Key words: emergency contraception, ulipristal acetate

Introduction

Despite the widespread availability of highly effective methods of contraception, unintended pregnancy is common. In both US and EU it is estimated that about half of all pregnancies are unplanned1,2. Situation in Croatia is estimated to be similarly unsatisfactory3. More than half of unwanted pregnancies – an estimated 45.5. million worldwide – are resolved by induced abortion each year4. Unplanned pregnancies have been linked to a range of health, social and economic consequences1.

Emergency contraception (EC) is defined as the use of any drug or device used after an unprotected sexual intercourse or contraceptive method failure to prevent an unwanted pregnancy5. It is an occasional contraception method and should not replace regular contraception. EC significantly reduces the risk of unintended pregnancy after the sexual intercourse6–8. It has been estimated that millions of unintended pregnancies could be avoided if effective EC were widely accessible9. While interventions to make EC available have clearly failed in reducing abortion rates10, it has been well recognized that EC is underused worldwide. In order to benefit from lessons learned and to secure positive population impacts from introducing dedicated ECPs in Croatia, EC methods and policies have been recently evaluated and four actionable points were recognized11.

Methods used postcoitally included estrogen only regimen, combination of estrogen and levonorgestrel (LNG), LNG only , mifepristone and insertion of a copper intrauterine device (IUD)6. Recently, a new class of progesterone receptor modulator ulipristal acetate has been introduced6. Up on the superior clinical efficacy evidence, UPA has been quickly recognized as the most effective emergency contraceptive pill, and recently recommended as the first choice ECP12 for all women regardless of the age and timing after intercourse. UPA is considered to be a pluripotent molecule, already confirmed to be effective in preoperative treatment of uterine fibroids13,14 and intensively investigated in various different indications15.

Objective of this paper is to provide overview on UPA and its role in EC.

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Following unprotected sexual intercourse, pregnancy is likely to result only during the fertile period that extends from 5 days before ovulation to the day of ovulation. Once released, oocyte deteriorates rapidly to a point where fertilization is unlikely. During this fertile period probability of conception varies. In estimating the need for emergency contraception after the unprotected intercourse, it is important to consider variability of the ovulation, and major discrepancy observed between women’s self-report of stage of a menstrual cycle and the dating calculation based on endocrine data. As it is difficult to accurately predict the exact stage of the menstrual cycle at which unprotected intercourse occurred, emergency contraception is generally indicated at any time of the cycle.

Yuzpe method was introduced in late 1970s, and consisted of 200 mcg ethinyl estradiol and 1000 mcg levonorgestrel divided in two doses, and given within 72 h after the intercourse. It has remained the standard hormonal EC method until the introduction of LNG only and mifepristone regimens. LNG only regimen is monal EC method until the introduction of LNG only by delaying or inhibiting ovulation. Emergency contraception pills (ECP) prevent pregnancy if pregnancy has already occurred, ECPs will not be effective, therefore ECPs are not abortificants. When IUD is used as a regular or emergency method of contraception, it acts primarily to prevent fertilization. EC insertion of a copper IUD is significantly more effective than use of ECPs, reducing the risk of pregnancy by more than 99.9%. Such a high level of effectiveness implies that emergency insertion of a copper IUD might prevent some pregnancies after fertilization.

The EC should be taken as early as possible but no later than 120 hours for IUD and UPA, and no later than 72 hours for LNG. Inserting IUD for emergency contraception has the advantage of providing further contraception, while all ECP users need to use additional barrier methods till end of the cycle during which they took ECP.

UPA – Structure

The development of molecules with specific steroid antagonist properties holds great promise for a variety of therapeutic applications. Ulipristal acetate (17α-acetoxy-11β-(4N,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione) was first synthesized by Research Triangle Institute under a contract with the National Institute of Child Health and Human Development (NICHD) for the development of new compounds that exhibit selective inhibition of the progesterone receptor with minimal effect on other steroid receptors. It is therefore a new molecular entity and the first compound in a new pharmacological class defined by the pristal stem. Its hormonal and antihormonal activity, selectivity and potency of its proximal metabolites were thoroughly evaluated.

UPA – Pharmacodynamics

UPA is an orally active, synthetic, selective progesterone modulator that acts by binding with high affinity to the human progesterone receptor, where it has both antagonist and partial agonist effects. The drug has minimal affinity for the androgen receptor and no affinity for the human estrogen or mineralocorticoid receptors. Although UPA has demonstrated some affinity for glucocorticoid receptor in animals, no antiglucocorticoid effects have been observed in humans. Moreover, its glucocorticoid receptor antagonist activity is much reduced compared to that of mifepristone indicating that ulipristal acetate belongs to a new class of progesterone receptor modulators with dissociated glucocorticoid activity.

The key UPA mechanism of action in emergency contraception is to inhibit or to delay ovulation, although it is not fully clear by which mechanism this occurs. A series of clinical pharmacodynamics studies found that when administered at a point in the menstrual cycle prior to the onset of the LH surge, or before the peak in LH level had been reached, UPA significantly delays the LH peak by at least five days. When administered prior to the LH peak, UPA significantly delayed follicular rupture. In a placebo controlled study in women with normal menstrual cycles, single doses of UPA 10, 50, 100 mg administered at the mid follicular stage with the follicle diameter of 14–16 mm significantly suppressed lead follicle growth, which lead to a dose dependent delay in folliculogenesis and plasma estradiol levels suppression. Double blind crossover randomized placebo controlled study demonstrated that a single UPA dose of 30 mg given immediately prior ovulation significantly delayed follicular rupture even in women in whom LH surge has already commenced. This indicates that UPA is effective during a longer period compared to LNG, which needs to be administered before the onset of LH surge in order to effectively prevent pregnancy. However it is important to recognize that if UPA is administered after the LH peak being reached, follicular rupture
is not delayed\textsuperscript{25}. Animal studies indicate that UPA may have a direct inhibitory effect on follicular rupture\textsuperscript{30}.

Endometrial effects of UPA were shown to be dose dependent. Following a single UPA dose of 10, 50 and 100 mg given in the early luteal phase and within 2 days of LH surge, endometrial thickness was reduced in a dose dependent manner with statistic difference, for all doses combined with statistic difference, for all doses combined and \textit{mann}, alpha-1-acid-glycoprotein and high density lipoprotein\textsuperscript{28,29}. Following ingestion, UPA is intensively metabolized in the liver to mono-demethylated metabolites of ulipristal acetate of 176 ng/mL and 69 ng/mL respectively at 0.9 and 1.0 hours\textsuperscript{28,29}. Corresponding values for the area under the plasma concentration-time curve from time zero to infinity AUC were 556 and 246 ng h/mL.

A high fat meal reduces mean Cmax by –45%, and delays tmax from a median of 0.75 hours to 3 hours, and mean AUC is increased by 24% compared with the administration in the fasting state\textsuperscript{28,29}. Similar was observed with the main metabolite. In despite of this finding, phase III trials have not demonstrated any effects of concomitant food intake and UPA efficacy\textsuperscript{25}.

UPA is highly bound to plasma proteins (>94%) albumin, alpha-1-acid-glycoprotein and high density lipoprotein\textsuperscript{25,28}. Following ingestion, UPA is intensively metabolized in the liver to mono-demethylated metabolites of which only the mono-demethylated metabolite is pharmacologically active. In vitro studies show that metabolism is predominantly mediated by cytochrome P450 (CYP)3A4 enzymes, and to a lesser extent by CYP1A2 and CYP2D6\textsuperscript{28,29}.

Excretion of UPA is primarily via the feces. After a single dose of 30 mg micronized UPA, 32 hours is the estimated terminal elimination plasma half-life for UPA, and 27 for mono-demethylated-ulipristal acetate\textsuperscript{28,29}.

No differences have been observed between women of different ethnic groups in clinical studies\textsuperscript{25,26}. Pharmacokinetic studies in women with renal impairment or in women aged <16 years have not been performed. Repeated UPA doses in animal studies resulted in some embryo-fetal loss, but at doses low enough to maintain gestation, no indication of any teratogenic potential has been detected\textsuperscript{25,29}. As for any new molecular entity, the sum of information on the impact of exposure to UPA in early pregnancy remains limited, however currently raising no concern. An online registry has been established in order to facilitate the collection of information on pregnancies that were exposed to UPA in the early stages of pregnancy.

Drug interaction studies have not been performed with UPA. Having in mind major CYP3A4 metabolism pathway, interactions are possible when co-administered with agents that induce or inhibit CYP3A4\textsuperscript{25,29}. Therefore, co-administration of CYP3A4 inducers (rifampicin, phenytoin, phenobarbital, long tem use of ritonavir, ECP containing levonorgestrel) or agents that increase gastric pH is not recommended as plasma concentrations of UPA may be decreased leading to a loss of efficacy.

Having in mind UPA’s affinity for progesterone receptor, it could interfere with progesterone actions. Although the use of UPA is not contraindicated to the continued use of regular hormonal contraception, it is possible that the contraceptive action of combined hormonal contraceptives (CHC) and progesterone only contraceptives (POC) may be reduced\textsuperscript{29}.

### UPA – Pharmacokinetics

In a study of 20 women under fasting conditions following the administration of a single 30 mg oral dose, UPA was demonstrated to be rapidly absorbed. It reached mean peak plasma concentrations (Cmax) of the drug and its major active metabolite mono-demethylated ulipristal acetate of 176 ng/mL and 69 ng/mL respectively at 0.9 and 1.0 hours\textsuperscript{28,29}. Corresponding values for the area under the plasma concentration-time curve from time zero to infinity AUC were 556 and 246 ng h/mL.

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Having in mind UPA’s affinity for progesterone receptor, it could interfere with progesterone actions. Although the use of UPA is not contraindicated to the continued use of regular hormonal contraception, it is possible that the contraceptive action of combined hormonal contraceptives (CHC) and progesterone only contraceptives (POC) may be reduced\textsuperscript{29}.
while in UPA treatment group (N=1617) there were 22 pregnancies. Even more important, within 24 hours after the intercourse, during the day of the best LNG efficacy, UPA was found to have 65% lower pregnancy rate than LNG: in LNG treatment group (N=600) there were 15 pregnancies, while in UPA group (N=584) there were 5 pregnancies. In the open label trial, the pregnancy rate in patients receiving UPA within 48–120 hours from unprotected sexual intercourse was significantly lower than that of expected pregnancy rate in the absence of emergency contraception. This study delivered another important learning, that unlike LNG, UPA demonstrates sustained efficacy when administered at any time between 48–120 hours from unprotected intercourse.

Rational behind significantly lower pregnancy rates on UPA when compared to LNG seems to be higher UPA efficacy in postponing imminent ovulation as LNG is no more effective than placebo in preventing ovulation after the onset of the LH surge, and after the follicular diameter has reached 15–17 mm. On the contrary, UPA can effectively delay ovulation even after the onset of the LH surge (till it reaches its peak concentration), and follicular diameter reached 18–20 mm. Additional efficacy related advantage of UPA is sustained efficacy through 120 hours from unprotected sexual intercourse.

**UPA – Tolerability and Safety**

In all trials UPA was generally well tolerated, with majority of side effects being mild to moderate in severity and resolving spontaneously in 89–94%. Tolerability of UPA seems to be comparable to LNG. The most frequently reported UPA treatment related adverse effects were headache, nausea, dysmenorrhea and abdominal pain, a profile similar to that reported in LNG comparative groups.

In an open label phase II study the most frequently reported treatment related adverse events (AE) of UPA were headache (9.3%), nausea (9.2%) and abdominal pain (6.8%). Other AE reported in this study were dysmenorrhea (4.15%), dizziness (3.5%) and fatigue (3.4%). In another phase III study UPA was demonstrated to be as well tolerated as LNG. The most common adverse events in UPA and LNG treatment groups were headache (19% vs. 18.5%), nausea (13% vs. 11.5%), dysmenorrhea (13% vs. 14.5%), fatigue (5.5% vs. 4%) and abdominal pain (5% vs. 6.5%).

UPA was generally associated with delayed onset of menses. Mean menstrual cycle length increased by 2.18, 2.63 and 2.89 days in UPA groups, while the onset of menses was a mean of 3.26 and 2.134 days earlier in LNG groups.

UPA has not affected the duration of bleeding.

Intermenstrual bleedings with UPA in most cases were described as spotting and were reported by 8.7% of women compared of 3.3% before enrolment.

There were no changes of clinical significance in complete blood count, hepatic and renal function, lipids and random glucose analysis in 100 women monitored before and after UPA treatment.

There are no medical contraindications to the use of combined or progestin only ECPs with the exception of pregnancy. UPA is a novel chemical entity and is contraindicated in existing or suspected pregnancy. As for any new molecular entity, the sum of information on the impact of exposure to UPA in early pregnancy remains limited and currently raising no concern. Although no teratogenic potential was observed, animal data are insufficient with regard to reproduction toxicity. Therefore, a pregnancy registry has been established in order to facilitate the collection of information on pregnancies in EU that were exposed to UPA in early stages of pregnancy, allowing further investigation. The key reason ECP should not be used in pregnancy is not because they are harmful but because they are ineffective.

UPA is lipophilic compound and therefore excreted in the human milk. Risk to the breast-fed child cannot be excluded. After the intake of UPA, breastfeeding should be discontinued for a week. During this time it is recommended to express and discard the milk in order to stimulate lactation.

A rapid return of fertility is likely following UPA treatment, therefore continuing or initiating regular contraception is recommended as soon as possible.

**Conclusion**

UPA is the first of a new class selective progesterone receptor modulators that acts by binding with high affinity to the human progesterone receptor where it has both antagonist and partial agonist effects. It is the first entity specifically developed for EC, but it is also intensively investigated in other indications. UPA provides effective, sustained and well tolerated emergency contraception when taken within 120 hours after unprotected intercourse or contraceptive failure. Before prescribing UPA and all other ECPs pregnancy must be excluded, usually by reviewing dates and the nature of the last period. Unlike LNG, UPA is able to prevent follicular rupture and to potentially prevent pregnancy even when given in advanced follicular stage of the menstrual cycle and thus provides a longer treatment window than LNG. Because of superior efficacy within 24 hours, 72 hours and 120 hours from unprotected intercourse when compared to LNG, UPA is recognized as the most effective ECP and recently recommended as the first prescription choice for all women regardless of the age and timing after intercourse.
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ULIPRISTAT ACETAT U HITNOJ KONTRACEPCIJI

SAŽETAK

Unatoč dostupnosti vrlo učinkovitih metoda kontracepcije, učestalost neželjenih trudnoća vrlo je visoka. Neplanirane trudnoće dovode do niza zdravstvenih rizika, te nose socijalne i ekonomske posljedice. Hitna kontracepcija umanjuje rizik od trudnoće nakon nezaštićenog spolnog odnosa, i predstavlja mogućnost za smanjenje broja neplaniranih trudnoća i pobačaja. Pilule za hitnu kontracepciju (eng. emergency contraceptive pill, ECP) sprječavaju trudnoću odgađajući ili inhibirajući ovulaciju, bez interferencije sa postfertilizacijskim procesom. Ukoliko je do trudnoće već došlo, ECP neće biti učinkovita. Stoga se ECP ne smatraju abortivnim sredstvima. Ulipristal acetat (UPA) (17α-acekgli-