Ulipristal acetate. A new emergency contraceptive. Ethical aspects of its use

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Introduction

Current presentations of the morning-after pill can be used effectively for up to 72 hours after unprotected sexual intercourse. However in some cases, this period can be short. For that reason, a pill, ulipristal acetate (Ellaone), which is licensed for post-coital emergency contraception up to 120 hours (5 days) following unprotected sexual intercourse or contraceptive failure,1[1] has now been marketed for the first time.

The use of the new drug, developed and marketed by HRA Pharma, UK Limited, Kensal Green, London, was authorised in May 2009. Ulipristal acetate is a synthetic selective progesterone receptor modulator that has antagonistic and partial agonistic effects at the progesterone receptor.[2]

Mechanism of action

An important aspect to consider in the ethical assessment of any drug used in emergency contraception is its mechanism of action, as this assessment will be very different if the drug acts by inhibition or delaying the ovulation or by preventing the implantation of the blastocyst in the maternal uterus, since in the latter case it would exert its action by terminating the life of an already living embryo, i.e. by an abortive mechanism.

In general, the mechanism of action of a new drug can be evaluated using three types of sources: *a.* information provided by the manufacturing company itself, *b.* reports by the official health bodies that have authorised its use and *c.* that provided by various scientific bodies or qualified experts.

Following this criterion, in the first place, according to the company HRA Pharma, the primary mechanism of action of ulipristal acetate is the "inhibition or delay of ovulation, but alterations to the endometrium may also contribute to the efficacy of the medicinalproduct".[3]

Secondly, among the reports by official bodies is that issued by the European Medicines Agency.4 It appears to conclude that its mechanism of action will depend on the time at which the drug is taken. In fact, administration in the mid-luteal period resulted in early endometrial bleeding, indicating a direct action on the endometrium.

At mid-follicular phase it caused a suppression of the growth of the lead follicle and subsequent delay in ovulation, and inhibited luteal phase endometrial maturation. At early-luteal phase it did not affect the length of the follicular, luteal or overall cycle

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[1] COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP). *Summary of Positive Opinion for EllaOne*. (accessed on 04.08.2009, to: http://www.emea.europa.eu/pdfs/human/opinion/Ellaone 16775009en.pdf on 4/08/09).

[2] ID. *Assesment Report for EllaOne. European Medicines Ulipristal acetate*. Doc ref: EMEA/261787/2009 (accessed on 04.08.2009, to: http://www.emea.europa.eu).

[3] *EllaOne 30 mg. HRA Pharma UK daunted. Summary of Product Characteristics last update on the emc: 18-IX-2009* (accessed on 04.08.2009, to: http://www.hra-pharma.com).

length, but caused a significant delay in endometrial maturation.
In conclusion, “the primary mechanism of action is thought to be inhibition or delay of ovulation, but alterations to the endometrium may also contribute to the efficacy of the product”.
With reference to the third group of reports, those produced by scientific societies, the report by the United Kingdom Royal College of Obstetricians and Gynaecologists [4] appears particularly interesting; it states that ulipristal’s primary mechanism of action is thought to be inhibition or delay of ovulation. A single mid-follicular dose has been shown to suppress growth of lead follicles.[5] Administration just before, or in some cases just after, the luteinising hormone surge can inhibit follicular rupture.[6]
Endometrial changes may also play a role. Early luteal administration of ulipristal results in delayed endometrial maturation and alterations in progesterone-dependent markers of implantation.[7] A mid-luteal dose has been shown to induce early endometrial bleeding in a dose-dependent manner,[8] and “it has been postulated that alterations to the endometrium may inhibit implantation by rendering the uterus less receptive to the trophoblast”.
Among the studies conducted by qualified experts, a paper published by Stratton et al[9] seems especially interesting; they showed that ulipristal acetate causes “alteration in endometrial thickness and Pdependent markers of implantation”. This clearly suggests that one of the Ellaone mechanisms of action may be to make it difficult for the embryo to implant in an altered endometrium.
Therefore, after evaluation of the previous studies, in our opinion, it can be reasonably concluded that ulipristal acetate (Ellaone) may inhibit or delay ovulation, while altering the endometrium, actions which explain its contraceptive effect; undoubtedly however, how the drug acts in each specific case will essentially depend on the day of the female cycle on which it is taken.
So how does this translate in practical reality?
To evaluate this pill in the first place, it is necessary to refer to its efficacy in comparison with that of levonorgestrel in roder to prevent unwanted pregnancies. In this respect, some documents state that ulipristal is at least as

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[4] *Mipristal acetate (EllaOne®). Faculty of sexual and Reproductive Healthcare Clinical Effectiveness Unit, New Product Review (October 2009).* (access on 04.08.2009, to: http://www.Ceu.members@gge.scot.nhs.uk).

[5] STRATTON P, HARTOG B, HAJZADEH N ET AL. *A single mid-follicular dose of CDB-2914, a new antiprogestin, a new antiprogestin, inhibits folliculogenesis and endometrial differentiation in normally cycling women*. Hum Reprod. 2000; 15: 1092-1099.

[6] CROXATTO HB, BRACHE V, COCHON L ET AL. *The effects of immediate pre-ovulatory administration of 30 mg ulipristal acetate on follicular rupture*. Abstract presented at the 8th Congress of the European Society of Gynecology, Rome, Italy, 10-13 September 2009.

[7] STRATTON P, LEVENS ED, HARTAG B ET AL. *Endometrial effects of a single early luteal dose of the selective progesterone receptor modulator CDB-2914*. Fertil Steril. 2009 (Epub ahead of print).

[8] PASSARO MD, PIQUION J, MULLEN N ET AL. *Luteal phase dose-response relationship of the antiprogestin CDB-2914 in normally cycling women*. Hum Reprod. 2003; 18: 1820-1827.

[9] STRATTON, LEVENS, HARTAG ET AL. *Endometrial effects of…*

effective as levonorgestrel.[10] However, other authors11[11] indicate that the efficacy of levonorgestrel taken in the first 72 hours after the sexual act is higher than that of ulipristal acetate, since according to the pharmaceutical company that markets it, the efficacy of levonorgestrel varies around 85%, while that of ulipristal acetate is around 73%.[12] When the drug was used between 48 and 120 hours after unprotected intercourse, the observed pregnancy rate was 2.1%, and the prevented fraction was 61%. Another study[13] specified that when the drug was administered between 48 and 72 hours after sexual intercourse, the efficacy was 61.9%; it was 57.9% when administered between 73 and 96 hours and 75% when taken between 97 and 120 hours after unprotected sexual intercourse.

Agreeing therefore, that the efficacy of levonorgestrel in preventing an unwanted pregnancy is approximately 85% while that of Ellaone varies between about 60% and 75%, it seems logical to accept that in those cases in which levonorgestrel can be taken within 72 hours of sexual intercourse, this is the pill that will be used. Therefore, the ulipristal acetate pill (Ellaone) will probably be used only when more than 72 hours have passed since sexual intercourse.

On the other hand it is also known that sperm can remain active in the female genital tract for about five days and the egg, once released, only two.[14] Consequently, the window of fertilisation will be approximately seven days, five before ovulation and two afterwards.

Therefore, (fig. 1) when Ellaone is taken five days before ovulation its action will be basically anticonceptive, and the same if it is taken four days beforehand. When it is taken three days before ovulation, it may be anticonceptive or by prenventing implantation, but from then on, the mechanism by which Ellaone may prevent unwanted pregnancies will be by an anti-implantation mechanism, in other words, abortive. In summary, between 50% and 70% of the time, Ellaone will act by an abortive mechanism.

It seems to us that this is the objective reality about the mechanism of action of ulipristal acetate (Ellaone), and therefore its anti-implantation effect will have to be taken into consideration when issuing an ethical judgement on its use.

Medicina e Morale 1; 15-21, 2010.

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[10] *Ulipristal acetate (EllaOne®)*. London New Drugs Group. APC/DTC briefing document. September 2009.

[11] HORSLEY N. *Ulipristal (ellaOne®) for post-coital contraception*. Nort East Treatment Advisory Group. September 2009.

[12] *EllaOne 30 mg. HRA Pharma UK daunted. Summary of Product Characteristics last update on the emc: 18-IX-2009.* (accessed on 04.08.2009, to: http://www.hra-pharma.com).

[13] *Ulipristal acetate (EllaOne®)…*

[14] WILCOX AJ, WEINBERG CR, BAIRD DD. *Post ovulatory agein of the human oocyte and embryo failure*. Human Reproduction 1998; 13: 394-397.

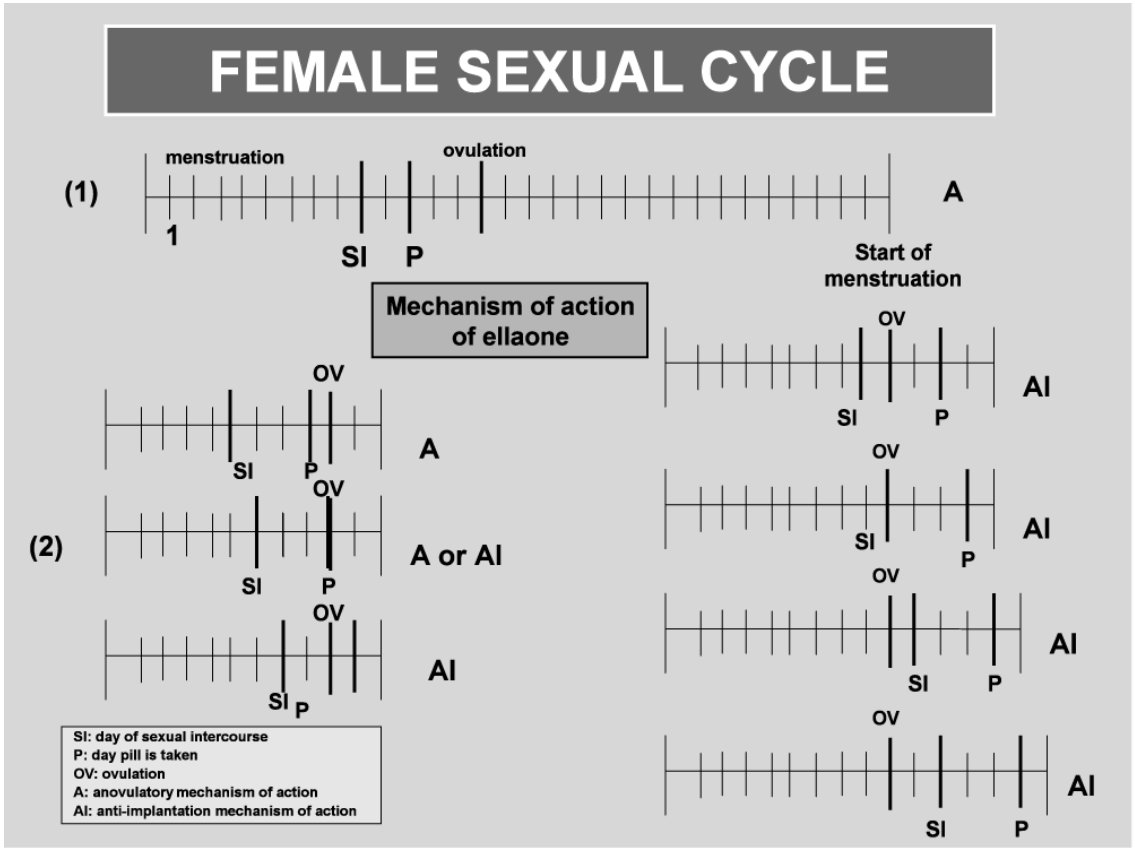

Fig. 1 Mecanism of action of ellaone according to to the day on which the pill is taken

Figure 1

(1) Diagram of the female sexual cycle showing the day of sexual intercourse and the day on which the pill is taken

(2) Abbreviated scheme of the female sexual cycle, showing only the 7 days on which fertilisation is possible