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Review Article

The state-of-the-art of emergency contraception with the cutting edge drug

Stand der Wissenschaft und Technik bei der Notfall-Kontrazeption mit innovativen Arzneimitteln

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Abstract

The objective of this study is to evaluate and elucidated the potential of selective progesterone receptor modulators (SPRMs) to be an effective emergency contraception (EC). The data are extracted from the literature through the MEDLINE database service from 2000–2010.

The SPRMs are in fact progesterone receptor ligands that could bind to progesterone receptor (PR) and exert antagonistic, agonistic or mixed agonist-antagonistic effects. These SPRMs are mifepristone, onapristone, asoprisnil, ulipristal, proellex among other compounds.

Currently developed SPRMs may exert contraceptive effects by inhibiting ovulation and retarding endometrial synchronization. Low-doses of progesterone antagonists retard endometrial maturation without affecting ovulation. Mifepristone being a SPRM is effective for prevention of pregnancy but with prostaglandin acts as an excellent abortifacient; yet could not compete with levonorgestrel as EC. However, a single dose of 30 mg ulipristal acetate, another SPRM with similar effectiveness and side effect profiles as 1.5 mg levonorgestrel EC, has shown wider 'window of effect' by inhibition of the LH peak even if administered at the advanced pre-ovulatory phase, a time when use of levonorgestrel EC is no longer effective. Thus, ulipristal acetate goes one-step ahead of levonorgestrel in the field of emergency contraception treatment.

Further studies are needed to explore the potential of other SPRMs to be cutting edge emergency contraceptive drugs.

Keywords: receptor modulator, steroid ligands, ulipristal acetate, EC, agonists, antagonists

Zusammenfassung

Das Ziel der Studie ist es, das Potential der selektiven Modulatoren des Progesteronrezeptors (SPRM) zur wirksamen Notfall-Kontrazeption zu evaluieren und darzustellen. Die Daten der Literatur sind mit Hilfe der MEDLINE-Datenbank von 2000–2010 gesammelt worden.

Die Modulatoren des Progesteronrezeptors sind Liganden, die an den Progesteronrezeptor binden und antagonistische, agonistische oder gemischte agonistisch-antagonistische Effekte bewirken. SPRMs sind u. a. Mifepristone, Onapristone, Asoprisnil, Ulipristal, Proellex.

Die derzeit entwickelten SPRMs entfalten ihre Wirkung durch Hemmung der Ovulation und Verzögerung der endometrialen Synchronisation. Niedrige Dosen von Progesteronantagonisten verzögern die endometriale Reifung, ohne die Ovulation zu beeinträchtigen. Mifepristone als SPRM ist bei der Schwangerschaftsverhütung wirksam, aber mit Prostaglandin zusammen wirkt es als exzellentes Abortivum; es ist allerdings zur notfallmäßigen Empfängnisverhütung weniger wirksam als Levonorgestrel. Eine Einzelgabe vom 30 mg Ulipristalacetat, einem anderen SPRM mit ähnlicher Wirksamkeit und Nebenwirkungen wie 1,5 mg Levonorgestrel, hat ein breiteres Wirkungsspektrum durch Hemmung der LH-Sekretion, selbst wenn es in der vorausgegangenen präovulatori-

schen Phase verabreicht wurde, ein Zeitabschnitt, bei dem Levonorgestrel als Antikonzeptionsmittel keine Wirkung mehr hat. Ulipristalacetat wird bevorzugt vor Levonorgestrel als Mittel bei Notfall-Kontrazeption eingesetzt.
Weitere Studien werden benötigt, um das Potential anderer hochwirksamer SPRMs als Kontrazeptionsmittel im Notfall zu untersuchen.

Schlüsselwörter: Rezeptormodulator, Steroide, Ulipristalacetat, Agonisten, Antagonisten, Notfall-Kontrazeption

Introduction

The idea of mimicking the effect of progesterone in blocking ovulation and thus inhibiting fertility was first coined out by Gregory Pincus in 1950s. However, over the years, the original method of hormonal contraception developed into a variety of modalities that today utilize number of new routes of administration [1]. Curiosity besides necessity is also a very potent factor that may lead to discovery. Curious researches do not stop being satisfied with the current state of emergency contraception (EC) with levonorgestrel (LNG) only compound though oral administration of a single dose of 1.5 mg LNG is very effective and safe for use as EC and is being used in many countries for a long time. The search for the new EC regimen with LNG is still going on to find out more effective system for better use-effectiveness with no adverse effect as a step to develop emergency contraceptive drug delivery system that could also prevent sexually transmitted infections as well. Thus, a vaginal gel levonorgestrel delivery system has recently been developed to use as EC in reproductive health care for potential 'dual protection' from unintended pregnancy as well as sexually transmitted infections (STIs)/AIDS [2]. However, levonorgestrel is a synthetic steroid and an agonist to progesterone. At present, scientific idea is pushing ahead to develop EC with selective progesterone receptor modulators (SPRMs) – the cutting edge drugs in the field of reproductive medicine. In this review article, an endeavour has been made to evaluate and elucidate the potential of the existing SPRMs to be used as an emergency contraceptive drug.

Data extraction

Data were extracted from the literature through MEDLINE data base service using key words 'emergency contraception' and 'progesterone receptor modulators' from 2000–2010. Search outcome, the articles, surveys, review, and clinical investigations relevant to the theme of the article were included to build up this perspective review.

Emergency contraception

What does it mean by emergency contraception?

Emergency contraception (EC) may be defined as the treatment received by or given to women for prevention of pregnancy within 72 or 120 hours after unprotected sexual intercourse. Levonorgestrel alone or in combination with ethinylestradiol, the Yuzpe regimen, and intrauterine device (IUD)/copper IUD are the commonly used EC available to women. Mifepristone is also used as EC in China, Cuba and Thailand [3], [4], [5]. The FDA in the USA in August 2010 has approved ulipristal acetate as a prescription drug for EC under the brand name, 'ella' for prevention of pregnancy within 5 days after unprotected sexual intercourse or contraceptive failure. It is not intended to use as routine contraceptive. However, ulipristal acetate as a prescription product for EC has been available in European countries under the brand name, 'ellaOne' since 2009. Emergency contraception is available in more than 140 countries and this is also available over-the-counter without clinician's prescription in about 50 countries [6].

Drug, doses and devices

A single dose of 1.5 mg LNG pill in various local brand names is presently available over-the-counter (OTC) in many countries, e.g. Plan B/Plan B One step in the USA, Levonelle/Levonelle One step in the UK and i-pill in India. The 0.75 mg LNG two pills regimen known as E-pills is also available to Indian women free of cost from the state health service outlets. The single dose EC pill is to be taken by women within 72 or 120 hours after unprotected sexual intercourse. Two 0.75 mg LNG pills may be taken together as a single dose or either 12 or 24 hours apart within 72 or 120 hours after unprotected intercourse because of similar effect [7], [8] .
In an attempt to incorporate LNG emergency contraceptive drug to a delivery system that could also discharge an active compound (a potent microbicide) against microorganisms, the Carraguard vaginal gel (4 ml) containing 0.75 mg or 1.5 mg LNG has been developed for dual protection against conception and STI/AIDS [2].
Among the selective progesterone receptor modulators, mifepristone and ulipristal acetate are being used as EC.

A single dose of 10 mg mifepristone and 30 mg ulipristal acetate is used as EC within 72 or 120 hours after unprotected sexual intercourse to prevent unintended pregnancy.

The IUDs/copper IUDs can be inserted as EC within 120 hours after unprotected intercourse and are very effective to prevent pregnancy. Women are offered IUD as in usual clinical practice if they presented >72 hours after unprotected sexual intercourse. However, an IUD would provide a regular method of contraception.

Selective progesterone receptor modulators

What are selective progesterone receptor modulators?

The selective progesterone receptor modulators (SPRMs) are progesterone receptor ligands that could bind with progesterone receptors and exert antagonistic, agonistic or mixed agonistic-antagonistic effects depending on the cellular context of the target tissues [9], [10]. Among several hundred, nearly a dozen of SPRMs have been evaluated to any significant extent. The best known SPRMs are mifepristone, asoprisnil, onapristone, ulipristal, and proellex [11].

Currently developed SPRMs are derivatives of steroid compounds with mild or potent anti-progestogen activity. SPRMs may exert a contraceptive activity by different mechanisms such as inhibition of ovulation and disruption of endometrial synchronization. Their potential clinical applications are manifold and very promising in major public health areas, including emergency contraception, long term estrogen-free contraception administered alone or in association with a progestogen-only pill to improve bleeding patterns. In future clinical application, SPRMs may be administered through the oral, intra-uterine or vaginal route [12].

How does progesterone receptor work?

Progesterone receptor (PR) contains well defined functional domains: the N-terminal transcription domain, the central DNA binding domain, the hinge region and the C-terminal hormone binding domain. The binding of progesterone or antagonist such as mifepristone produces conformational changes in the form of PR that permits it to bind to DNA of the target cells. Human PR has two isoforms, PR-A and PR-B that form homo and/or hetero dimmers in the transcription activation process. The activated receptor dimmers (AA, BB, or AB) bind to progesterone response elements in the promoter region of progesterone gene [13].

In the case of progesterone, this binding increases the transcription of these genes producing progesterone effects. In contrast, a receptor dimer complex that has been activated by mifepristone also binds to progesterone response elements, but an inhibitory function in the C-terminal region of hormone binding domain renders this DNA bound receptor transcription inactive. This is the basis of the progesterone antagonistic action of mifepristone or other SPRMs underlying their abortifacient and contraceptive actions [13].

How do SPRMs work?

In the field of contraception, SPRMs have shown contraceptive potential by suppressing follicular development, delaying surge of luteinizing hormone (LH), retarding endometrial maturation and promoting endometrial bleeding. Mifepristone, a best known SPRM, showed a strong intercepting action. Studies suggested that the endometrium was more susceptible to mifepristone than were the hypothalamus and pituitary regions [14], [15]. Shortly after LH surge, treatment with mifepristone affected the secretary apparatus and polarity of the endometrial cells in women. Administration of mifepristone in early luteal phase disrupted the secretory activity of endometrial glandular cells. This finding suggested a cellular mechanism of progesterone receptor (PR) blockage by mifepristone in the peri-implantation period [16]. Mifepristone at a low dose resulted in abnormal endometrial morphology in women. The endometrial glands exhibited irregularities in shape and size and were lined by mixed epithelial cells some of which were secretory. The concentration of estrogen receptor (ER) was greater in the stroma with no difference in PR compared with the control, whereas no change in ER or PR concentration was observed in endometrial glands. Thus, low dose of mifepristone seems to antagonize progesterone induced secretory changes that are necessary for the implantation [17], [18].

Mifepristone, in daily doses of 2–10 mg blocks the LH surge and ovulation. There is evidence that daily doses of 2 or 5 mg mifepristone have contraceptive potential. Because of anovulation, there may be an unopposed effect of estrogen on the endometrium, although this risk may be mitigated by the noncompetitive anti-estrogenic activity exhibited by SPRMs. Low doses of SPRMs retard endometrial maturation, without affecting ovulation, thereby indicating that the endometrium is exquisitely sensitive to these compounds. Here is the prospect for the development of endometrial contraception. This means that contraception could be achieved with these compounds by prevention of endometrial maturation without disturbing ovulation or producing alteration in bleeding patters [19].

Though 200 mg mifepristone as an effective contraceptive drug administered 48 hours after LH surge does not affect ovulation or bleeding pattern, yet it is not a popularly acceptable approach for contraception. Mifepristone administered at late luteal phase either alone or together with prostaglandins produces menstrual bleeding and is not very effective for prevention of pregnancy. However, treatment with mifepristone-prostaglandin combination is very effective for occasional menstrual regulation, induction of vaginal bleeding in 98% of pregnant women,

and menstrual delay of 11 days or less. Mifepristone could also be used as an effective emergency contraceptive agent [13]; but because of delay in onset of next menstrual cycle that is significantly dose related, mifepristone could not compete with levonorgestrel compound for EC [20]. Mifepristone is widely used to terminate pregnancy and as such is commercially available in many countries. The negative abortion-related image of mifepristone has clearly limited the involvement of major pharmaceutical companies in the development of mifepristone as well as other SPRMs as contraceptive drugs [21].

Many SPRMs displayed direct anti-proliferative effects on the endometrium, although with variable actions which seemed to be product- and dose-dependent. Progesterone antagonists suppressed late follicular development, blocked the LH surge and retarded endometrial maturation, which rendered them potential estrogen-free contraceptive drugs. However, a SPRM such as asoprisnil was not so effective as to block the LH surge but appeared to target the endometrium directly and produced amenorrhoea. Treatment with these compounds was not associated with hypo-estrogenism and bone loss. The potential clinical application of these compounds covered a broad field and was very promising in major public health areas such as emergency contraception, long-term estrogen-free contraception, myoma and endometriosis [20]. However, the data from mid- to long-term continuous administration studies have raised the issue of endometrial safety. In consequence, long-term applications of SPRMs are currently postponed [9].

Investigation and clinical trials

The SPRMs are a class of drugs with progesterone antagonist activity that may confer therapeutic benefit for reproductive disorders in postmenopausal women. The endometrial structure of those women is likely to be perturbed by SPRMs through their progesterone antagonist properties. The histological findings after treatment for endometriosis with proellex showed generally inactive or atrophic endometrium and less frequently, proliferative or secretary, and superimposed upon changes including formation of cystically dilated glands. The secretory changes coexisted with mitoses and apoptotic bodies, with increasing treatment, dose and duration. None of the proellex treated patients developed endometrial carcinoma or hyperplasia while on therapy [22]. Pharmacologically, ulipristal acetate is a synthetic steroid that has demonstrated potent progesterone antagonist activity in vitro and in vivo. As compared to mifepristone, this compound has reduced anti-glucocorticoid activity, inhibited ovulation in rats in a dose dependent manner and exhibited anti-fertility activity during continuous administration. Because of unique pharmacological profile, ulipristal acetate seemed to be a promising candidate for use as contraceptive drug [23]. Therefore further studies are required to explore the use-effective functions of these cutting edge compounds in the field of reproductive health care.

Use as emergency contraception

Mifepristone

Mifepristone is well recognized as an abortifacient but in a low dose, it is still used as EC in a few countries. In Cuba, effectiveness of 10 mg mifepristone for EC up to 5 days after unprotected intercourse in 635 women was evaluated. The pregnancy was prevented in 88% cases and the rate was 1.1%. Fatigue (10.7%), dizziness (6.1%), nausea (4.9%), and vomiting (0.6%) were common adverse effects reported by women. Menstruation was delayed more than 7 days in 6% women [4]. Thai women also used 10 mg mifepristone for EC within 120 hours after unprotected sexual intercourse. No pregnancy occurred among them. The interval and duration of the treatment cycles were significantly longer than untreated controlled cycles [5]. A comparative clinical trial in China showed that the treatment with 10 mg mifepristone in 499 women up to 72 hours after unprotected sexual intercourse resulted in 1.8% pregnancy rate as compare to 2.4% with 10 mg gestrinone for EC. Majority of women menstruated in the first day of the expected menses. Two treated groups did not differ significantly regarding the adverse effects of the treatment. The effectiveness of 10 mg gestrinone was not significantly different from those of 10 mg mifepristone as an emergency contraceptive drug [3].

Mifepristone at 25–50 mg was superior to other hormonal regimens; but at low dose, it could be more effective than LNG, 0.75 mg two doses. A single dose of 1.5 mg LNG seemed to have similar effectiveness as the standard 0.75 mg two doses at 12 hours apart. LNG was more effective than Yuzpe regimen. There was more pregnancies with LNG as compared to 25–50 mg or <25 mg mifepristone. Ulipristal acetate seemed to be as effective as LNG but the confidence interval was wide and the result compatible with higher or lower effectiveness [24]. The pregnancies rates were 1.5% in women given 10 mg mifepristone, 1.5% in those assigned a single 1.5 mg dose of LNG, and 1.8% in women assigned 0.75 mg two doses of LNG. These rates were not statistically significant. The relative risk of pregnancy for 1.5 mg LNG compared with two doses LNG was 0.83 and that for 0.75 mg two doses LNG compared with 10 mg mifepristone was 1.05. The adverse effects were mild and did not differ greatly between groups. The most women menstruated within two days of the expected date; women who took LNG had earlier menstruation than did those who took mifepristone. These regimens of EC were very effective to prevent high proportion of pregnancies if taken within five days of unprotected sexual intercourse. Mifepristone and LNG did not differ in efficacy. A single dose of 1.5 mg LNG could substitute two doses of 0.75 mg taken at 12 hours apart [25].

Ulipristal acetate

In a comparative clinical trial with 50 mg ulipristal acetate versus two doses of 0.75 mg LNG, the pregnancy rate was 0.9% and 1.7%, respectively. About 85% and 69% of anticipated pregnancy were averted, respectively based on the estimated cycle day of unprotected sexual intercourse. Nausea was experienced by more women (29%) of ulipristal group than women (24%) of LNG group. Thus, ulipristal acetate was as effective as LNG in preventing pregnancy after unprotected sexual intercourse and both drugs had similar side effect profiles [26].

In a study in Texas, USA, the efficacy and safety of ulipristal acetate for EC was evaluated. Women were treated with 30 mg ulipristal acetate within 48 to120 hours after unprotected intercourse. The pregnancy rates were 2.3%, 2.1%, and 1.3% for treatment intervals of 48 to 72 hours, >72 to 96 hours and >96 to 120 hours, respectively. Adverse effects were mild or moderate, mostly being headache, nausea and abdominal pain. Duration of menstrual bleeding did not change but cycle length increased by 2.8 days. Ulipristal acetate EC was effective and well tolerated by women [27].

The multicentre study in Europe and the USA compared the efficacy and safety of 30 mg ulipristal acetate with that of 1.5 mg levonorgestrel for EC in 1,696 women, on administering within 72 hours after unprotected intercourse. The pregnancy rate was 1.8% and 2.6% with ulipristal acetate and LNG, respectively. However, 103 women who received EC between 72 to 120 hours had three pregnancies all in LNG group. The headache was the most frequent adverse effect among users of ulipristal acetate (19.3%) and LNG (18.9%). Ulipristal acetate could be used for EC up to 5 days after unprotected sexual intercourse [6].

The current methods of hormonal EC are ineffective to prevent rupture of follicle when taken at the advanced preovulatory phase. However, follicular rupture failed to occur during the 5 day period in 44%, 50%, and 36% of the cycles in women treated with 1.5 mg, 0.75 mg LNG and placebo, respectively. Ovulatory dysfunction characterized by follicular rupture associated with absent, blunted or mistimed gonadotrophin surge occurred in 35%, 36%, and 5% of 1.5 mg, 0.75 mg LNG or placebo cycles, respectively. Thus, LNG could disrupt the ovulatory process in 93% of cycles treated when the diameter of the dominant follicle was between 12 and 17 mm. Most probably, this mode of action accounts for the contraceptive effectiveness and failure rate of levonorgestrel as EC [28].

Does ulipristal acetate block follicular rupture when administered at the preovulatory phase with a follicle ≥18 mm diameter? The study showed that follicular rupture failed to occur over 5 days following ulipristal acetate intake in 59% of women. When this drug was taken by women before onset of the LH surge, or after onset of the LH surge but before the LH peak, the ovarian follicles failed to rupture for at least 5 days in 100% or 78.6% of cycles, respectively. When ulipristal acetate was administered after LH peak, failure of follicular rupture was noticed only in 8.3% cycles. Thus, ulipristal acetate could delay follicular rupture if taken immediately before ovulation. This SPRM as EC could perhaps prevent pregnancy when given in advanced follicular phase at the onset of LH surge, a time when LNG EC is no longer effective in inhibiting ovulation [29].

The main mechanism of action of both LNG EC and ulipristal acetate EC is delay in, or inhibition of ovulation. The 'window of effect' for LNG EC appears to be rather narrow – it begins after the selection of dominating follicle and ends at the beginning of the rise of LH surge – whereas, ulipristal acetate seems to cause suppression of the preovulatory LH peak, as envisaged by Brache et al. [29], that boosts its effectiveness further even when administered shortly before ovulation, the time when use of LNG EC is no longer effective. Thus, ulipristal acetate seems to have higher efficacy for EC as compared to LNG EC and being a new type of second generation progesterone receptor modulator, represents a new evolutionary step in EC treatment [30].

Conclusions

With great potential of selective progesterone receptor modulators to be a drug of choice in the various fields of reproductive health care, it is not impossible to have state-of-the-art of emergency contraception with cutting edge SPRMs in near future. Though 1.5 mg single dose or 0.75 mg double doses of LNG at 12 hours apart is currently gold standard regimen for EC, the 30 mg ulipristal acetate with its functional and safety profiles similar to that of LNG EC goes one-step ahead of LNG because of its increased window of effect by inhibition of the LH peak even when administered shortly before ovulation, a time when LNG is no longer effective. This advantage seems to stamp out ulipristal acetate as superior to LNG for EC; further studies may confirm this view in near future.

Notes

Competing interests

The authors declare that they have no competing interests.

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