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Review Article

Role of Mifepristone in Obstetrics and Gynecology and Endocrinology

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ABSTRACT

Mifepristone, a synthetic steroid with potent antiprogestational and antiglucocorticoid activity, has established itself as a versatile pharmacological agent with significant clinical implications. Initially approved for medical termination of early pregnancy, mifepristone functions by competitively inhibiting progesterone receptors, disrupting endometrial support and promoting uterine contractility when used alongside prostaglandins. Its clinical utility, however, extends well beyond reproductive health. It is employed in cervical ripening, second-trimester abortion, and labor induction.

Furthermore, mifepristone has demonstrated therapeutic potential in the management of uterine fibroids, endometriosis, and as a targeted treatment in Cushing's syndrome by modulating glucocorticoid receptors. Emerging research also explores its role in treating hormone-sensitive malignancies, including breast and ovarian cancers. As evidence continues to grow, mifepristone represents a promising tool in both gynecological and endocrine therapy, warranting further exploration and integration into broader clinical practice.

KEYWORDS

• Mifepristone • Medical abortion • Emergency contraception • Fibroid

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INTRODUCTION

Mifepristone, commonly known as RU-486, is a synthetic steroid with diverse medical applications, primarily in reproductive and endocrine health. It is FDA-approved for two key indications: as part of a combination regimen with misoprostol for medical abortion up to 10 weeks of gestation and for managing hyperglycemia in individuals with Cushing syndrome. Its mechanism of action involves competitively binding to intracellular progesterone receptors at low doses, inhibiting pregnancy maintenance, while at higher doses, it blocks cortisol activity at glucocorticoid receptors, helping regulate blood sugar levels.[1]

Beyond its approved uses, mifepristone has shown promise in off-label applications, including emergency contraception, cervical ripening, and adjunct therapy for uterine fibroids. As research continues to expand its therapeutic potential, mifepristone remains a vital medication in both gynecological and endocrine treatments, offering non-surgical alternatives and improving patient outcomes across various conditions.

PHARMACOLOGICAL AND THERAPEUTIC EFFECTS

Mifepristone acts as a competitive antagonist of progesterone, glucocorticoid, and estrogen receptors, making it effective in various hormone-dependent conditions, including gynecological disorders and certain cancers. Its anticancer po tential is attributed to its ability to inhibit progesterone receptors in tumors such as endometrial adenocarcinoma, uterine fibroids, and breast cancer. Recent studies further showed that mifepristone also inhibited the growth of different cancer cell lines regardless of the expression of hormone responsiveness.[2,3] Studies suggest that in PR-positive endometrial adenocarcinoma or sarcoma, a daily dose of 200 mg results in a 25% stable disease rate, while in ER-positive premenopausal women, 50 mg on alternate days for three months reduces Ki-67, a marker of cell proliferation.[4,5]

Additionally, mifepristone influences key signaling pathways involved in cancer metastasis, such as the FAK/Src/Paxillin complex, offering a potential strategy for metastasis prevention.

MECHANISM OF ACTION

Mifepristone exerts its effects through competitive antagonism of progesterone and glucocorticoid receptors: At low doses, it acts as a selective progesterone receptor antagonist, preventing progesterone from sustaining pregnancy, leading to decidual breakdown and embryo detachment.

At high doses, mifepristone blocks glucocorticoid receptors, disrupting cortisol activity. This affects the hypothalamic-pituitary-adrenal (HPA) axis, resulting in elevated circulating cortisol levels, which helps regulate hyperglycemia in Cushing's syndrome. Mifepristone exhibits a higher affinity for the glucocorticoid type II receptor than the type I receptor, influencing metabolic and endocrine pathways. By carefully selecting appropriate patients, monitoring treatment response, and maintaining effective communication, healthcare providers can optimize mifepristone therapy and ensure safe and effective patient outcomes.

Role of Mifepristone in Medical Abortion

Mifepristone plays a crucial role in medical abortion by blocking progesterone receptors, a hormone essential for maintaining pregnancy. This inhibits endometrial support, leading to endometrial breakdown, increased prostaglandin release, and uterine contractions, which facilitate pregnancy termination.[6]

ADMINISTRATION AND DOSAGE

Mifepristone is available in 200 mg and 300 mg oral tablets and is used within the first 10 weeks (70 days) of gestation. The standard medical abortion regimen involves:

1. Mifepristone (200 mg) orally, followed by
2. Misoprostol (800 µg) buccally, vaginally, or sublingually, administered 24-48 hours later.
3. For pregnancies ≤7 weeks (49 days), a 400 µg oral dose of misoprostol may be used.

The timing of misoprostol is crucial, as its effectiveness decreases if taken too early (<24 hours) or too late (>48 hours) after mifepristone.

Surgical Abortion: Dilatation & Evacuation (D&E) for Pregnancies >12 Weeks D&E is the preferred surgical method for pregnancies beyond 12–14 weeks. Cervical preparation is necessary and may involve:

Mifepristone (200 mg) orally (24–48 hours before)

Role of Mifepristone as Emergency Contraception[7]

Mifepristone can be used as an emergency contraceptive to prevent pregnancy when taken within 72 hours of unprotected intercourse. At a 600 mg oral dose, mifepristone works by delaying ovulation, preventing implantation, and altering the endometrial lining, making it less receptive to fertilization. Its ability to block progesterone receptors disrupts the hormonal environment necessary for pregnancy establishment.

Role of Mifepristone in second trimester abortion

Mifepristone is increasingly used in second-trimester pregnancy terminations for both medical and surgical approaches. It enhances the effectiveness of misoprostol, increasing expulsion rates from ~70% to over 90% and reducing induction time by up to 50%. Global health authorities, including WHO and FIGO, recommend mifepristone misoprostol regimens over outdated instillation methods due to better outcomes and fewer side effects. The combined regimen also reduces the need for repeated misoprostol doses, improving patient experience.[8]

Role of Mifepristone in intrauterine fetal demise

The mifepristone–misoprostol combination is highly effective for labor induction after second- and third-trimester fetal demise, reducing expulsion time by nearly four hours compared to misoprostol alone. Timely evacuation helps prevent complications like infection and hemorrhage, and eases emotional distress. Despite limited large trials, RCOG recommends this regimen as first-line treatment for late intrauterine death and stillbirth.[9,10]

Premature Luteinizing Hormone Surges Undergoing Controlled Ovarian Hyperstimulation in In Vitro Fertilization

A single dose of mifepristone in the preovulatory phase can delay the LH surge and ovulation. In controlled ovarian hyperstimulation (COH) cycles, low doses may correct early luteal progesterone rise and improve endometrial receptivity. However, optimal dosing and timing require further research and standardization.Various dosages and timing schedules (depending upon the COH protocol used, continuous administration from day two with follicle-stimulating hormone or after follicle aspiration and on the following day) for its efficacy needs to be studied ahead.[11,12]

Breakthrough Bleeding in Levonorgestrel and Depot Medroxyprogesterone

Mifepristone shows promise in reducing breakthrough bleeding (BTB) in DMPA and LNG-IUS users. A 50 mg dose every two weeks reduced BTB in new DMPA users, likely by modulating endometrial receptors. In LNG-IUS users, 100 mg monthly for three months or 25 mg daily significantly reduced bleeding and spotting. Further research is needed to determine the optimal dose, schedule, and duration.[13]

Role of Mifepristone in management of leiomyomas[1]

Beyond emergency contraception, mifepristone is also utilized in the management of uterine leiomyomas (fibroids). When administered at 25 to 50 mg daily, it can effectively reduce fibroid size, offering a non-surgical option for women experiencing fibroid-related symptoms.

ENDOMETRIOSIS

Mifepristone, through its antiprogesterone action, upregulates androgen receptors and inhibits estradiol-driven endometrial growth, offering symptom relief in endometriosis. Low doses (5 mg for 3 months) reduce pelvic pain without affecting lesion size, while higher doses (50 mg for 6 months) significantly reduce both symptoms and lesion size.[14]

ADENOMYOSIS

Mifepristone inhibits adenomyosis by causing cell cycle arrest (via CDK1/2 suppression), inducing apoptosis (through mitochondrial pathways and caspase 3), and reducing CXCR4 expression to limit cell invasion and migration. It decreases uterine volume, CA-125 levels, and improves hemoglobin in patients. A study using 5 mg/day showed significant relief from dysmenorrhea, reduced IL-6 and TNF-α, mast cell activity, and nerve fiber density, suggesting strong therapeutic potential.[15]

Role of Mifepristone as Male contraception (2)

Progesterone increases calcium uptake by human sperm and favors the acrosome reaction. Recently, a negative effect on calcium uptake by RU486, as opposed to the positive effect of progesterone, has been described with human sperm. It was suggested that this effect takes place at the membrane level. Whether RU486 may be useful as a novel approach to male contraception remains an open question.

Mifepristone as a Glucocorticoid Receptor Antagonist in Cushing's Syndrome

Mifepristone is a potent glucocorticoid receptor (GR) antagonist that blocks cortisol's effects both centrally and peripherally. It also binds to progesterone and androgen receptors but does not affect estrogen or mineralocorticoid receptors. Due to the widespread role of GRs, their inhibition has significant physiological impacts. Mifepristone acts rapidly, making it valuable in emergencies like severe hypercortisolism and Cushing's syndrome psychosis.[16]

A study by Fleseriu *et al.* assessed mifepristone in Cushing's syndrome patients resistant to standard treatments. Starting at 300 mg/day and increasing up to 1200 mg, the mean dose by week 24 was 732 mg. The drug significantly improved glucose control in diabetics and lowered diastolic blood pressure in hypertensive patients.

Dosing is challenging as cortisol levels remain elevated, making biochemical monitoring unreliable. Guidelines recommend starting at 300 mg and adjusting based on clinical response. Close monitoring is needed to detect adverse effects such as adrenal insufficiency, mineralocorticoid excess, and progesterone antagonism.

MENINGIOMA

Owing to the antiprogestational activity of mifepristone, it is used as monotherapy for PR-positive benign central nervous system tumors, such as meningioma, at a dose of 200 mg/day. Usually, the long-term treatments are well tolerated; however, endometrial hyperplasia in some patients is noted and requires histological evaluation. Biochemical hypothyroidism is commonly associated with long-term mifepristone therapy in meningioma and requires periodic thyroid function screening[17]

Mifepristone Use in Specific Patient Populations

Mifepristone's safety and efficacy vary across patient groups, requiring careful consideration of dosage adjustments, contraindications, and potential risks based on individual health conditions.

Hepatic Impairment

For patients with hyperglycemia due to Cushing's syndrome, the maximum recommended dose is 600 mg daily for those with mild to moderate hepatic impairment. However, its use in severe hepatic impairment is not advised due to insufficient safety data. In pregnancy termination, no specific studies assess mifepristone's effects in liver dysfunction, so caution is necessary.

Renal Impairment

Similarly, in Cushing's syndrome-related hyperglycemia, the maximum dose remains 600 mg daily. However, dedicated studies on mifepristone use in renal impairment for abortion are lacking, requiring careful clinical judgment when prescribing the drug in such cases.

Pregnancy Considerations

Mifepristone is contraindicated in pregnancy when treating hypercortisolism due to its abortifacient properties. As a key component in medical abortion, potential teratogenic effects (e.g., limb malformations, Moebius syndrome) should be considered in cases of unintended fetal exposure. Animal studies show dose-dependent teratogenic effects in rabbits, but evidence in humans remains inconclusive. Incomplete abortion risks should be discussed, and continued pregnancy requires close follow-up.[18]

Breastfeeding Considerations

Mifepristone is excreted in breast milk, though in small amounts. A single dose for abortion does not typically require breastfeeding cessation, but prolonged use (e.g., for Cushing's syndrome) is not recommended. Studies show milk concentrations peak within 12 hours after a 600 mg dose, with an estimated 1.5% infant exposure. Women may be advised to pump and discard milk for 3 days after taking the medication.[7,19]

Pediatric and Geriatric Populations

Adolescents: Mifepristone is a safe and effective option for pregnancy termination in younger patients when medically indicated.

Older Adults: Limited clinical data exist on mifepristone's use in older adults, particularly for endogenous Cushing's syndrome. Prescribing should be based on individual health status and potential risks.

Fetal Risk and Ectopic Pregnancy

Mifepristone blocks progesterone receptors and has antiglucocorticoid effects, but it does not terminate ectopic pregnancies. Animal studies suggest potential growth restrictions and cranial defects, but human data are limited. Some pregnancies exposed to mifepristone resulted in fetal malformations, while others had normal births, leaving risks uncertain.

By understanding population-specific considerations, healthcare providers can ensure safe and effective mifepristone use, minimizing risks while optimizing treatment outcomes.

ADVERSE EFFECTS AND SAFETY CONSIDERATIONS

Common side effects of mifepristone include fatigue, nausea, headache, hypokalemia, arthralgia, vomiting, edema, hypertension, dizziness, decreased appetite, and endometrial thickening. Due to GR antagonism, ACTH and cortisol levels often rise, leading to mineralocorticoid excess. This occurs because of 11β-hydroxysteroid dehydrogenase type 2 saturation in the kidneys, allowing cortisol to activate mineralocorticoid receptors, which contributes to hypokalemia, hypertension, and fluid retention.

Severe: Anaphylaxis, toxic epidermal necrolysis, angioedema, fetal death, teratogenic effects.

Moderate: Hypokalemia, hypertension, vaginal bleeding, uterine contractions, adrenal insufficiency, endometrial hyperplasia.

Mild: Nausea, headache, abdominal pain, fatigue, dizziness, fever, menstrual irregularities.

Despite these challenges, mifepristone remains a valuable treatment option for Cushing's syndrome, particularly in cases unresponsive to conventional therapies. Careful dose adjustments, regular clinical assessments, and symptom-based monitoring are essential for optimizing patient outcomes while minimizing adverse effects.

CONCLUSION

Navigating Promise and Paradox in the Future of Mifepristone and Misoprostol.

The evolving narrative of mifepristone stands at a critical intersection of medical innovation, regulatory transformation, and sociopolitical contention. While their inclusion on the WHO's Essential Medicines List and expanding clinical applications signal a new era of recognition, access remains uneven and deeply entangled in legal and cultural complexities. The WHO's dual emphasis on evidence-based access and stringent drug quality further reflects the broader tension between progressive health policy and practical implementation.

At the same time, mifepristone's potential beyond reproductive care ranging from hormone-sensitive tumors to fibroid management invites both excitement and caution. Despite growing scientific interest, fragmented regulations and inconsistent clinical practices blur its role in mainstream medicine.

Ultimately, the future of mifepristone is marked by both opportunity and ambiguity. Realizing its full potential will require not only continued scientific inquiry, but also a global commitment to depoliticized, patient-centered regulation. Until then, mifepristone will remain at once essential and elusive symbols of both medical progress and the persistent struggle for equitable healthcare access.

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