



Mifepristone: an overview for Australian practice

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Summary

Mifepristone was the first antiprogestogen to be developed for clinical use. It is not only a progesterone receptor antagonist, but also acts as a glucocorticoid receptor antagonist. The fundamental importance of progesterone for human conception and throughout pregnancy has meant that mifepristone has been used in other countries for emergency contraception and medical abortion in the first and second trimester of pregnancy. It has also been used to manage fetal death *in utero* in the third trimester of pregnancy. There are other potential uses based on its mechanism of action, such as reducing the bleeding associated with uterine fibroids.

Key words: Cushing's syndrome, meningioma, pregnancy, progesterone, progestogen, RU486, therapeutic abortion.

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Introduction

Most health professionals will be familiar with the antioestrogens, clomiphene citrate and tamoxifen. These drugs have been used for years for conditions as diverse as infertility and breast cancer respectively. It was not until 1983 that a drug with antiprogestogenic activity was developed.¹ Mifepristone was the first drug to compete with progesterone at its receptor.

Pharmacology

The progesterone receptor is one of several proteins synthesised by the action of oestradiol on the endometrium. This receptor is a dimer of two distinct proteins and binds progesterone which is a planar steroid. By contrast, mifepristone is a non-planar molecule. This bent, rigid, molecular structure seems important for antisteroid compounds.

Mifepristone binds to the progesterone receptor five times more avidly than progesterone. It also binds with the glucocorticoid receptor three times more strongly than dexamethasone. By contrast, mifepristone binds to the androgen receptor with only one quarter of the affinity of testosterone and has essentially no binding to the mineralocorticoid receptor or oestradiol receptors. Approximately 85% of mifepristone is absorbed after oral administration. It has a long elimination half-life.

Medical abortion

The World Health Organization (WHO) estimated in 1994 that approximately 150 000 unwanted pregnancies were aborted each

day, with at least 500 women dying daily from abortion attempts, especially in low income countries.² This led the WHO to assess the combination of mifepristone and various prostaglandin analogues for medical abortion.

Several double-blind randomised controlled trials showed that mifepristone 200 mg, when combined with misoprostol, a prostaglandin E₁ derivative, was as effective as surgical abortion. Misoprostol is only about 1% of the cost of other prostaglandins, is stable at room temperature and is associated with much less pain than gemeprost, so it has become widely used.³

Mifepristone can be used as early as five weeks of pregnancy. By contrast, surgical abortion is generally delayed until seven weeks or later. About 1% of women will abort following mifepristone but before the administration of misoprostol. The adverse effects of mifepristone are minimal, but misoprostol can cause nausea, vomiting, diarrhoea and headache.

Following approval from the Therapeutic Goods Administration in March 1994, the WHO selected Monash University and Family Planning Victoria to participate in an international multicentre, double-blind randomised controlled trial of mifepristone and misoprostol for termination of early pregnancy. This trial showed that the efficacy of the mifepristone–misoprostol regimen was the same with 200 mg of mifepristone as with 600 mg of mifepristone.⁴

Regimens

The WHO and the Royal College of Obstetricians and Gynaecologists have shown that a combination of mifepristone followed by misoprostol is the most effective and safe medical method for inducing abortion in the first and second trimester of pregnancy.⁴ A typical regimen for medical abortion was 600 mg oral mifepristone followed by 400 microgram of misoprostol administered vaginally 48 hours later. As first shown by the WHO Taskforce on Postovulatory Methods of Fertility Regulation⁴, the dose of mifepristone used currently in Australia is 200 mg. This is consistent with the recommendations of the Royal College of Obstetricians and Gynaecologists and with practice in New Zealand. A dose of misoprostol 800 microgram is administered intravaginally 48 hours after administration of mifepristone and most women will abort within the next six hours.⁵ For women having medical abortion at up to nine weeks of pregnancy, effective and complete abortion typically occurs in up to 97.5% of women given the 200 mg mifepristone/800 microgram misoprostol regimen.⁵

When mifepristone is not available, as is the situation in many low income countries, abortion can be induced with misoprostol

alone or with intramuscular methotrexate alone. However, complete abortion is less likely and repeated administration is often necessary.

Medical and surgical abortion compared

In most studies of women undergoing first trimester abortion, approximately 25% choose medical abortion, a further 25% prefer surgery and the remainder have no strong preference for either technique.^{6,7} The requirements for a medical abortion differ in many respects from those of a surgical abortion. Some patients strongly prefer that friends or family can be present during medical abortion, and patients are not required to fast. Patients in the WHO studies commented on a more friendly approach with medical abortion, which they considered psychologically beneficial at a time when anxiety levels were increased.⁸

Randomised comparisons of medical abortion and surgical abortion at 10–13 weeks gestation have been undertaken.⁹ The clinical outcomes were equivalent. The Royal College of Obstetricians and Gynaecologists recommends that abortion services must provide a choice of methods for abortion.¹⁰ Women considering the option of medical abortion or surgical abortion should be told that they may require (further) surgery if the abortion is incomplete. All women undergoing medical or surgical abortion should attend for the recommended medical care after the procedure. Completeness of abortion is typically judged on clinical grounds at this follow-up.

Other uses

As mifepristone has antiprogestogenic activity, it has been studied in situations where its action on receptors may alter the course of the conditions.

Intrauterine fetal death

Progesterone is critical for establishing and maintaining pregnancy. The first WHO study in Australia used mifepristone to manage fetal death in late pregnancy. In these cases, the baby has died, but the placenta has not and it continues to synthesise progesterone for some weeks. This prevents labour and continues the pregnancy in very difficult emotional circumstances for the woman carrying a dead baby. For women with an unexplained fetal death *in utero*, and who have an unripe cervix, mifepristone typically induces delivery within 72 hours.

Contraception

Mifepristone has been used as an emergency contraceptive. In randomised controlled studies, it appears as effective as other regimens, such as those using levonorgestrel. In WHO studies of emergency contraception within seven days of unprotected intercourse, mifepristone was effective at doses of 600 mg, 50 mg and even 10 mg.¹¹ This is important in low income countries with limited pharmaceutical resources.

Uterine fibroids

Uterine fibroids, or leiomyomata, are the most common tumours in women. The fibroids and their nourishing blood vessels are rich in progesterone receptors. Several trials have shown that mifepristone can reduce the size of uterine fibroids and effectively reduce menstrual blood loss. A recent randomised double-blind clinical trial of 10 mg mifepristone or placebo found that mifepristone reduced uterine and fibroid size and reduced menstrual blood loss. It also increased haemoglobin concentration. As expected from its antiprogestogenic action, endometrial hyperplasia has been observed after three months continued use of mifepristone.¹²

Cushing's syndrome

As mifepristone is a glucocorticoid receptor antagonist, it has been studied in Cushing's syndrome. The first patient to be treated received mifepristone doses of up to 1500 mg daily for nine weeks. No adverse effects were observed. Some patients with Cushing's syndrome have been treated with mifepristone for up to 10 years.¹³ Endometrial hyperplasia has been reported in long-term treatment with mifepristone. It appears to be the result of unopposed oestradiol action on the endometrium due to progesterone receptor blockade. Regular vaginal ultrasound every four months to monitor for endometrial hyperplasia is recommended in women receiving long-term treatment with mifepristone.

Meningioma

Meningioma is a generally benign tumour of the central nervous system. Surprisingly, many of these tumours contain progesterone receptors. Unlike breast cancer, meningiomas are commonly strongly progesterone receptor positive yet only rarely oestrogen receptor positive. Mifepristone inhibits growth of meningioma cells in culture and reduces the size of human meningioma implanted into nude mice.

Patients with unresectable meningioma have been treated with oral mifepristone 200 mg daily for a median duration of therapy of 35 months (range 2–157 months). In one series there were 19 women and 9 men with persistent or recurrent unresectable meningioma. Eight patients responded to therapy, as shown by reduced tumour size on computerised tomography or magnetic resonance imaging and improvement in visual field examination.¹⁴ Endometrial hyperplasia did occur in three premenopausal women, but did not prove dose limiting.

Breast cancer

Progesterone receptors are found in normal breast tissue and in specimens from breast carcinoma. It was therefore hoped that mifepristone would be of value in treating breast cancer, especially in view of its long-term safety in patients with Cushing's syndrome. Unfortunately, the results of clinical trials have been disappointing in advanced breast carcinoma.¹⁵

Future directions

Recently, selective progesterone receptor modulators have been developed. These are the 'successors' to mifepristone. They show partial agonist and partial antagonist effects on various progesterone target tissues. For example, asoprisnil has antiproliferative effects on the endometrium and can decrease the size and growth of uterine fibroids by reducing uterine artery blood flow.¹⁶

Conclusion

In the 25 years since its use was first reported, mifepristone has been registered and widely used for medical abortion in many countries with regulatory standards comparable to Australia. These include the United Kingdom (since 1991), Sweden (1992), USA (2000) and New Zealand (2001). The WHO estimates that at least 1.5 million medical abortions have been undertaken in Europe, with at least 500 000 medical abortions in China and 500 000 in the USA.¹⁷

Introduction of mifepristone for medical abortion produced a furore which continues to this day. Mifepristone has not yet been sponsored by a pharmaceutical company for use in Australia. There has recently been a change in legislation in Australia.¹⁸ A sponsor may emerge for mifepristone in the near future.

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Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 171)

1. Mifepristone is a glucocorticoid receptor antagonist.
2. In the first nine weeks of pregnancy, mifepristone and misoprostol induce complete abortion in only 50% of patients.