THE NORTHERN HOSPITAL

MIFEPRISTONE

"Red on Maroon", oil on canvas, 1959, Mark Rothko, Tate Gallery, London

"A picture lives by companionship, expanding and quickening in the eyes of the sensitive observer. It dies by the same token. It is therefore a risky and unfeeling act to send it out into the world..."

Mark Rothko, 1957.

Mark Rothko always had a deep connection with his paintings, as if they were his own living children. He regarded this relationship as critical. He felt that the paintings themselves, once created took on a life of their own. In turn they would thrive, "quicken", and continue to evolve in the companionship of their creator - or their owner. Without the owner's care, love and attention, the painting was nothing -in a cold and uncaring world it would soon die! This explains Rothko's often extreme reluctance to part with his works, unless he was absolutely sure that they were going to a good owner. When he did make a sale, he suffered the pangs of parent, when their child finally leaves home. He grew anxious and concerned for their well being. Sometimes he would even visit the new owner's home, making a "welfare" check on his child, ensuring that it has been hung correctly, in just the right space, just the right lighting. He insisted that people view his works in the correct manner. When asked, he replied, "Oh right back. About eighteen inches". At the height of his powers and fame, he refused the biggest commission he was ever offered, the Seagram's Murals in the "Four Seasons Restaurant" of New York City - a commission in today's terms that was worth millions!

The magisterial Simon Schama explains..... "Early in 1959, like some omnipotent sorcerer, Rothko painted Red on Maroon, one of the most dramatic of the murals destined for the Four Seasons. With the vision of Michelangelo's blind windows burnt on his retina, he turned his paintings on their side. Instead of uprights, they were now expansive horizontals. What had been shutter-like bars of darkness and light became something akin to load-bearing columns. And the load they were bearing was human history. That autumn, months after the glamorous opening, he and his wife, Mel, went to eat at the Four Seasons. Rothko was someone who thought it was immoral to spend more than five bucks on a meal, and was often perfectly happy with a Chinese takeaway, the cheaper the better. But as he sat among the millionaires with Mel, his heart and his confidence sank like a stone. "Anybody who will eat that kind of food for that kind of money will never look at a painting of mine", he said. The next morning, he looked at the 30 or so paintings, some of the most beautiful and moving things not only Rothko but any modern artist had ever created, and saw only the ruin of a great project. His paintings would never hang in the Four Seasons. Manhattan had beaten Mark. Or had art triumphed over money? After all, how many artists do you know who would say no to two and a half million (1959) dollars?"

When the medical abortant mifepristone is prescribed, doctors need heed the philosophy of the tortured Mark Rothko. They must never send their patients out into the cold and uncaring world, without the most carefully planned ongoing emotional support and backup emergency plans. The RANZCOG policy on the prescribing of mifepristone states, "The woman must be advised to have an accompanying support person present at least until the conceptus is passed, who should be able to assist in contacting and accessing support and/or emergency care if needed".

MIFEPRISTONE

Introduction

Mifepristone (RU 486) is a synthetic anti-progesterone agent.

It has two principle actions:

- Progesterone receptor antagonist.
- Glucocorticoid receptor antagonist.

A *combination* of **mifepristone** followed by **misoprostol** (a prostaglandin E_1 derivative), is the most effective and safe **medical** method for inducing abortion in the **first** and **second trimester** of pregnancy.

For around 95% of women up to 9 weeks gestation, mifepristone with a suitable misoprostol regimen results in complete expulsion of the products of conception within a few hours of the administration of the misoprostol, but up to around 5% of women will need surgical evacuation of the uterus for heavy or prolonged bleeding or for continuing pregnancy.

Complication rates are comparable to surgical termination of pregnancy.

There is also good evidence for effective regimens for medical termination of pregnancy beyond 9 weeks and in the second trimester of pregnancy.

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.

Mifepristone remains a controversial drugs, with many religious and pro-life groups remaining opposed to its use.

Mifepristone can only be prescribed by doctors who have had specific training and who are registered to administer it. Similarly mifepristone can only be dispensed by accredited pharmacists.

Mifepristone and misoprostol are both on the World Health Organization's List of Essential Medicines, a list of the most important medications needed in a basic health system.

Advantages and Disadvantages:

The decision to choose medical rather than surgical termination will often be a matter of personal patient preference.

Procedure	Advantages	Disadvantages
Medical	Avoidance of a GA Avoidance of surgery A more private treatment. At least 95 per cent of women up to nine weeks gestation, will have a complete abortion within a few hours. Less stressful for some women than having an operation. Cheaper than surgery. Most of the treatment can take place at home. Easier for women in rural and remote regions, as well as women in some ethnic groups whose access to surgical abortion is limited.	Excessive bleeding (uncommon). Rarely may take days to work. Small risk of failure, (in which case surgery will be required). Infection due to retained products of conception (uncommon). Recovery time is similar in both methods, and most women are able to return to their normal daily activities within 2-3 days of either a medical or a surgical termination. However, this doesn't include the 36-48 hours between taking the first and second medicine in the case of medical termination, thus making a medical termination a longer process *overall*.
Surgical	Preference of woman to be "asleep".	Risks of a GA Risks of a surgical procedure - cervical or uterine trauma or post surgical sepsis. Surgical termination can be used up to 24 weeks depending on local State laws; (compared to 9 weeks for mifepristone).

History

The anti-estrogens, clomiphene citrate and tamoxifen have been used for years for infertility and breast cancer respectively.

It was not until 1980 that a drug with anti-progestogenic activity was developed. Mifepristone was the first drug to compete with progesterone at its receptor.

Its initial experimental designation was RU-38486, the 38,486th compound synthesized by Roussel-Uclaf from 1949 to 1980 - shortened to **RU - 486.**

The World Health Organization (WHO) estimated in 1994 that approximately 150, 000 unwanted pregnancies were aborted each day. At least 500 women died daily from abortion attempts, especially in low income countries. This led the WHO to assess the combination of mifepristone and various prostaglandin analogues for medical abortion.

Roussel-Uclaf received approval for use in medical abortion in France on September 23, 1988.

Mifepristone was approved for abortion in the United States by the FDA in September 2000.

The Australian Therapeutic Goods Administration (TGA) included mifepristone on the Australian Register of Therapeutic Goods (ARTG) on 29 August 2012.

Physiology

Progesterone is of critical importance for human conception and the ongoing support of pregnancy

Legal

Termination of pregnancy *by any method* should be conducted in accordance with the legal and regulatory requirements of the jurisdiction within which it occurs.

Clinicians should be familiar with local requirements, which in some jurisdictions determine where the relevant drugs may be administered and by whom, and may preclude home administration of misoprostol.

Preparations

Tablets:

Combination packs of:

- **Mifepristone 200 mg, 1 tablet.**

And

- **Misoprostol 200 mcg, 4 tablets.**

Mechanism of Action

Mifepristone competitively binds to the progesterone receptor five times more avidly than progesterone.

It 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

It has essentially **no** binding to the:

- Mineralocorticoid receptor
- Oestradiol receptors.

Mifepristone acts by inhibiting the action of progesterone in the maintenance of early pregnancy, causing degeneration of the decidua, and thus the separation of the developing embryo and placenta from the uterine wall; it also causes cervical softening and the release of endogenous prostaglandins.

Misoprostol (a prostaglandin E_1 derivative), softens and dilates the cervix and helps the uterus contract and expel the pregnancy

Pharmacodynamics

Mifepristone has been used for:

1. **Medical abortion in the first and second trimester of pregnancy**
2. Emergency contraception
3. The management of fetal death *in utero* in the third trimester of pregnancy.

Based on its mechanism of action, further possible indications for mifepristone may include: [1]

1. Potential use is the control of bleeding associated with uterine fibroids.

    - 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.

      As expected from its antiprogestogenic action, endometrial hyperplasia has been observed after three months continued use of mifepristone.

2. Cushing's syndrome:

- As mifepristone is a glucocorticoid receptor antagonist, it has been studied in Cushing's syndrome.

  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.

3. 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.

     Patients with unresectable meningioma have been treated with oral mifepristone and tumour shrinkage has been demonstrated on CT and MRI.

Pharmacokinetics

Absorption:

- **Mifepristone** can be administered orally or by the buccal route, (i.e holding the tablets between the gum and cheek for 30 minutes and allowing them to dissolve).

- **Misoprostol** can be given intravaginally or orally or by the buccal route.

Oral and buccal routes have the advantage of rapid onset of action, while the sublingual and vaginal routes have the advantage of prolonged activity and greatest bioavailability.

Distribution

- Mifepristone is 98% bound to plasma proteins.

Metabolism and excretion:

- CYP3A4 appears as the isoenzyme primarily responsible for mifepristone metabolism.

- Mifepristone has a long elimination half-life.

Indications

In Australia the current indication for mifepristone (and misoprostol) is:

- Medical abortion of intrauterine pregnancy up to **9 weeks** of gestation.

  Taken in conjunction with misoprostol.

Contra-indications/precautions

These include:

1. Smokers
2. Aged 35 years or older
3. Coagulopathies:
   - Medical termination may not be appropriate; seek specialist advice.
4. Adrenal insufficiency (contraindicated).
5. Drug interactions:

   Patients on long-term steroids:

   - Corticosteroids mifepristone may reduce the activity of inhaled and systemic corticosteroids for 3 - 4 days after its use due to its anti-glucocorticoid effects.

     In patients with significant asthma avoid using mifepristone or consider temporarily increasing the corticosteroid dose and monitoring carefully.

   Patients on anticoagulants

   - Risk of excessive bleeding.
6. Ectopic pregnancy
7. More than nine weeks pregnant
8. Have had allergic reactions to mifepristone
9. Are fitted with an intrauterine device (the device needs to be removed before taking mifepristone).
10. Medical termination should not be performed in an isolated or an inaccessible setting which lacks ready access to suitable emergency care (in a service accepting this responsibility) from administration of mifepristone until termination of pregnancy is complete.

Adverse Effects

The adverse effects of mifepristone are minimal, but may include:

1. GIT upset:
    - Nausea/ vomiting/ diarrhoea
2. Headache.
3. Allergic reactions.
4. Excessive bleeding:
    - Note that ongoing bleeding, (with or without signs of an infection), may suggest an unsuccessful termination

Note that continuing with a pregnancy in the event that the medical termination has failed is strongly advised against because of the risk of teratogenic effects.

Dosing

Mifepristone can only be prescribed by doctors who have had specific training and who are registered to administer it. Similarly mifepristone can only be dispensed by accredited pharmacists.

In early pregnancy, ultrasound confirmation that the pregnancy is intrauterine is essential.

Local protocols can vary but in Australia the regimen, in general, is:

Written consent,

Followed by:

- **Mifepristone 200 mg orally**

  The administration of mifepristone must take place under the direct vision of the medical practitioner (or a health professional under their supervision).

  This ensures that it is the woman who has requested the abortion who is taking the drug and at the gestation expected.

Then 48 hours later:

- **Misoprostol 800 microgram is administered intravaginally or orally**

It may be taken by the woman at home, but the patient should have access to a telephone and transport to a hospital in case complications arise.

The woman must be advised to have an accompanying support person present at least until the conceptus is passed, who should be able to assist in contacting and accessing support and/or emergency care if needed.

Later terminations of pregnancy (i.e > 9 weeks) must take place in a **hospital** with access to all necessary clinical and psychological support.

The range of time for abortion is around 4 - 24 hours.

Most women however will abort within the next six hours.

Products of conception should be treated in accordance with local and legislative protocols.

PV bleeding and/ or abdominal cramps may continue for up to12 hours after treatment.

Most women up to nine weeks of pregnancy, will have complete abortion in up to 97.5% of cases, using this regimen.

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.

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, generally at 14 -21 days.

Appropriate counselling/ emotional support must be provided in all cases.

Patient resources

National Prescribing Service:

- http://www.nps.org.au/

References

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