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COMPREHENSIVE REVIEW ON THE PHARMACOLOGICAL USE, SAFETY, AND CLINICAL EFFICACY OF MIFEPRISTONE AND MISOPROSTOL IN MEDICAL ABORTION

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ABSTRACT

Medical abortion is commonly performed at different stages of pregnancy using the antiprogestin mifepristone in conjunction with the prostaglandin analogue misoprostol. This routine is widely acknowledged and quite successful, particularly in the early stages of pregnancy. The usual procedure is to administer 800 mcg of misoprostol, usually sublingually or vaginally, after 200 mg of mifepristone. With a low frequency of major problems, the safety profile is still robust despite minor side effects including nausea and bleeding. This study focuses on the drug interactions, clinical results, complication rates, animal and human safety data, optimal regimens, and mechanism of action. Risk reduction requires appropriate supervision and emergency care access, particularly in isolated locations.

KEYWORDS: Mifepristone, misoprostol, early pregnancy termination, progesterone antagonist, prostaglandin analog, pharmacological activities.

INTRODUCTION

Mifepristone is a synthetic steroid that is taken orally and has antiprogesterone and antiglucocorticoid properties. Many nations have licensed it for four primary indications: cervical dilatation before surgical TOP, early termination of pregnancy (TOP), second trimester preparation for prostaglandin-induced TOP, and third trimester expulsion of a dead fetus. Millions of women throughout the world have safely taken mifepristone for early-stage TOP when administered in a sequential regimen with prostaglandins, as long as the cautions and contraindications are followed. Retained tissue, infection, and bleeding are possible complications. Mifepristone-based medical abortion has spread throughout the world and is currently legal in many nations since it was first used in France and China more than 20 years ago. Approximately one-fifth of outpatient abortions in the US are carried out under medical supervision; in other European nations, this percentage is much higher. 200 mg is now the accepted dosage in practice, even though the majority of regulatory bodies authorized a 600 mg dosage. Although its dosage, method, and time vary, misoprostol is given after mifepristone to increase efficacy. Oral, sublingual, buccal, or vaginal administration are common methods, especially up to 49 days of pregnancy.[7] In both clinical and scientific contexts, variations in dosage, timing, and technique have been investigated. In addition to summarizing information on the 200 mg mifepristone-misoprostol regimen's safety and efficacy, this review will investigate potential effects of study design, treatment procedures, and population variations.

DRUGS USED IN MEDICAL ABORTION

Medical abortion has been shown to be safe and effective when performed between weeks 13 and 24 of pregnancy. It involves the use of mifepristone and a prostaglandin (PG) analog. Together, misoprostol and mifepristone encourage pregnancy termination. Misoprostol administered 24–48 hours following mifepristone is the most commonly used combination. Mifepristone is the only antiprogestin approved for the induction of abortion. It is a 19-norsteroid that binds to the progesterone receptor with great affinity, hence blocking the actions of progesterone. Progesterone is a crucial hormone for maintaining pregnancy because it keeps the uterus inactive. It inhibits uterine contractions, prevents the cervix from softening and dilatation, and decreases the decidua's PG output. Thus, vascular damage, decidual necrosis, and bleeding result from mifepristone's blocking of progesterone receptors. This softens the cervical region, increases uterine sensitivity to PG, and turns the quiet pregnant uterus into an organ of spontaneous activity, with the greatest effect taking place 36–48 hours later. Strong uterine contractions and cervical ripening are caused by

misoprostol, a synthetic PGE-1 analogue that ultimately leads to the evacuation of a pregnancy. Prostaglandins are essential for regulating uterine contractility during pregnancy. PGs and their equivalents can successfully terminate a pregnancy since the receptors are still active during pregnancy. Misoprostol has been shown to have several advantages over other prostaglandins, such as being long-lasting, stable at room temperature, and reasonably priced. When compared to the PG analogue gemeprost, misoprostol is just as effective, if not more so.[8]

MIFEPRISTONE–MISOPROSTOL REGIMEN

Mifepristone 200 mg orally, 800 micrograms of misoprostol vaginally 36–48 hours later, and then 400 micrograms of misoprostol orally every 3 hours, up to a maximum of 4 oral doses. The median induction-to-abortion period is as short as 6.0 hours, and the combined regimen of misoprostol and mifepristone has an abortion rate as high as 97%. The way misoprostol is administered affects its effectiveness.[6]

Some women may find vaginal misoprostol less acceptable, despite the fact that it is more effective and has fewer adverse effects. Therefore, research has been done on the sublingual route, which has been found to be acceptable and convenient despite being marginally less effective. 32–34 Misoprostol and mifepristone interval: The myometrium has its maximum priming effect 36–48 hours following mifepristone pretreatment. A somewhat longer induction-to-abortion interval, a larger total dose of misoprostol, and a higher rate of uterine curettage were the outcomes of a shorter 24-hour period (pb0.001).35 The induction-to-abortion delay was also longer (9.8 hours vs. 7.5 hours) when the interval was shortened to 24 hours, according to retrospective data comparing 24 and 48-hour intervals (pb0.01). If feasible for services, the 36–48 hour administration interval could be better because both of

these trials show noticeably longer induction periods. With mifepristone alone, 0.2-0.4% of women terminate their pregnancies.

SAFETY IN ANIMALS

In the middle of the 1980s, Roussel Uclaf carried out an extensive toxicology program that proved the molecule's safety and authorized the use of mifepristone in people. The majority of the effort was devoted to developing indications for the compound's single-dose delivery. As a result, toxicological investigations were carried out with animal exposure times no more than six months. When administered acutely to many species, the chemical demonstrated no mutagenic potential and no toxic effect up to 1000 mg/kg. Daily doses up to 200 or 125 mg/kg, respectively, showed no toxicity in subchronic toxicity trials in rodents for 30 days and 26 weeks, but they did cause symptoms linked to the compound's antihormonal properties. Rats' menstruation was suppressed, monkeys' blood progesterone levels dropped, rats experienced frequent estrus, and mammary development and uterine weight decreased as a result of the antiprogesterone effects. Serum levels of cortisol and adrenocorticotropic hormone (ACTH) increased along with kidney and adrenal weights in rats and monkeys, indicating antiglucocorticoid actions. Prostate and seminal vesical weights decreased in male rats, indicating an antiandrogenic action. Monkeys were more susceptible to the molecule's antiglucocorticoid action. Dosages of 15 or 20 mg/kg caused increases in serum cortisol and ACTH levels, whereas dosages as low as 4 mg/kg had no impact. In conclusion, mifepristone's antiglucocorticoid, antiprogesterone, and antiandrogenic properties did not cause any real damage in rats or monkeys treated for one or six months. Since the medication was created for a single-dose usage for the indications that have been approved thus far, no long-term toxicity and carcinogenicity studies were conducted. Studies on the embryotoxicity of subabortive dosages in rodents revealed no abnormalities in the surviving fetuses of rats and mice. Although isolated abnormalities were noted in rabbits, they were not dose-dependent and, as a result, could not be linked to the medication. In another study, pregnant female rabbits given with a low dose of mifepristone (0.08–0.33 mg kg_1 day_1) showed rare encephalon abnormalities. The authors did not attribute these defects to a direct effect of the product on the embryo, but rather to a uterine retraction effect associated with the antiprogesterone activity of mifepristone prior to or during the formation of the chondrocranium. In fact, the abortifacient action of mifepristone was completely inhibited by additional progesterone treatment (100 mg/kg), and no abnormalities were seen in these conditions. In rats used in a neonatal exposure research, giving males and females a

subcutaneous dose of mifepristone up to 100 mg/kg on the first day after birth had no negative effects on their future ability to reproduce. Female rats treated to mifepristone as neonates showed a somewhat earlier start of puberty.[2]

SAFETY IN HUMANS

Antiglucocorticoid effects

In a variety of models, mifepristone completely blocked the effects of dexamethasone, including its thymolytic activity, diuretic effects, and reduction of ACTH secretion. It also possesses antiglucocorticoid characteristics. Mifepristone also has antiglucocorticoid effects in humans. Both the central actions of cortisol (inhibition of feedback control of cortisol over its own production, as demonstrated by an increase in ACTH and LPH) and the peripheral effects (suppression of cutaneous vasoconstriction or decrease in circulating eosinophils induced by glucocorticoids) are affected by mifepristone's antiglucocorticoid effect.[2]

DRUG INTERACTIONS

The metabolism of mifepristone by CYP 3A4 suggests that ketoconazole, itraconazole, erythromycin, and grapefruit juice may block this metabolism and raise serum levels of mifepristone, even though specific drug or food interactions with this medication have not been investigated. Additionally, mifepristone metabolism may be induced and serum levels of mifepristone may be decreased by rifampicin, dexamethasone, and several anticonvulsants (phenytoin, phenobarbital, and carbamazepine). Coadministration of mifepristone may raise serum levels of medications that are CYP 3A4 substrates, according to data on in vitro inhibition. Such an interaction may be seen for a long time following the delivery of mifepristone because of its sluggish removal. As a result, care should be used while taking mifepristone with medications that have a limited therapeutic range and are CYP 3A4 substrates, such as several medications used in general anesthesia.[6]

CLINICAL TRAILS

Mifepristone followed with prostaglandins

The safety concerns assessed in 5743 patients exposed to mifepristone and prostaglandins for first-trimester pregnancy termination in four pivotal trials carried out in France and the UK, as well as one sizable study carried out in the US, served as the basis for the approval of the medical method of TOP. The safety database has grown with additional information from postmarketing experience in the US and Europe. It is normal to have painful uterine contractions, menstrual cramps, or labor-like symptoms, as well as uterine bleeding. Implications of the use of prostaglandins and mifepristone during the abortion procedure. Some studies accurately verified safety following mifepristone administration and before prostaglandin administration. The most common symptoms, as noted by a checklist, were breast pain (28%) and nausea (54%), fatigue (50%), and abdominal pain or discomfort (56%). Before using mifepristone, many women experienced these symptoms, which are frequently linked to pregnancy. The pharmacologic effect of the antiprogesterone chemical then made these symptoms worse. Henderson more recently examined three years of clinical experience in the United States with mifepristone plus misoprostol, and he provided data from a database of 95,163 women who had received treatment. The authors found that the safety of mifepristone plus misoprostol + misoprostol is high with few significant medical complications occurring in normal clinical use. They reported an incidence of 2.2/1000 serious sequelae (95% CI, 1.9–2.5), with heavy bleeding being the most common.[3,5]

Bleeding

According to preliminary research done before the medication was approved, 30–40% of participants bled somewhat before prostaglandin was administered, and most women who weren't bleeding started bleeding two hours after prostaglandin was administered. Light spotting before to prostaglandin tended to give way to light to moderate spotting four hours after prostaglandin. 10% of patients on average reported experiencing heavy bleeding. The V49-day group experienced an average bleeding duration of 9 days in the French trials, 13 days in the US study, and 15 days in the other two groups (50–56 and 57–63 days). 1.45% of women in the V49-day group and 0.33–2.6% of all women needed hemostatic curettage due to heavy bleeding. In 14 women, a transfusion was required (0.25%). In three trials, hemoglobin changes revealed a slight but substantial drop of 0.5–0.8 g/dL. N3 g/dL decreased in 2.1% of patients, according to the Urquart study. Henderson reported a

postmarketing experience in the US where 1.3 out of 1000 patients experienced significant bleeding, and 0.5 out of 1000 patients needed a transfusion.

Vital signs

Vital indicators include heart rate and blood pressure. In the early trials, the participants were closely observed at the clinic for four hours after ingesting a prostaglandin, such as gemeprost injected into the vagina or misoprostol taken orally. During the 4-hour monitoring period, the majority of the adverse events recorded following prostaglandin injection were mild. After taking gemeprost (pb.0001), the systolic blood pressure decreased slightly but significantly, going from 124.4F13.8 mmHg prior to prostaglandin to 117.3F16.2 mmHg three hours later. This was also true for heart rate (from 80.2F8.9 to 77.1F6.8 beats/min; pb.0001) and diastolic blood pressure (from 74.4F10.8 to 70.4F11.5 mmHg; pb.0001). Peyron documented four occurrences of lowered blood pressure with clinical symptoms following the use of misoprostol. In 2% of cases, the systolic blood pressure dropped by 30 mmHg, and in 7% of cases, the diastolic blood pressure dropped by 15 mmHg.[5]

Mifepristone used alone without prostaglandins

The two medications, mifepristone and prostaglandin, are administered in succession because, when taken early in pregnancy, mifepristone inhibits the effect of progesterone on the endometrium and causes uterine contractions, which can be significantly accelerated by a small dose of prostaglandin. The uterus is dormant in the early stages of pregnancy, most likely as a result of progesterone's inhibitory action. The substance makes the myometrium more sensitive to prostaglandins' ability to induce contractions during pregnancy. The onset of uterine contractions occurs 24–36 hours after taking mifepristone. Concurrently, heightened contractility causes a roughly five-fold increase in prostaglandin sensitivity. The uterus became more sensitive to prostaglandin 24 hours after the mifepristone treatment began, reaching its peak at 36 and 48 hours. These studies provide the rationale for combining mifepristone and a low dose of prostaglandin for termination of early pregnancy. The side effects of mifepristone used in single dosages of 200–600 mg to pregnant women were documented in placebo-controlled trials in research aimed to inducing cervical dilatation prior to surgical TOP. This makes it possible to evaluate the antiprogestin's actual impact in comparison to a placebo. The incidence of headache and dizziness did not differ between the mifepristone and placebo groups; however, the mifepristone group reported somewhat more fatigue and nausea. Only in the mifepristone group was bleeding seen.

SIDE EFFECTS AND COMPLICATIONS

The stimulatory impact of PG on the gastrointestinal tract results in side effects, such as nausea, vomiting, and diarrhea, which are typical of PG therapy. Women taking gemeprost are more likely to experience diarrhea, whereas those taking misoprostol are more likely to experience fever.45 Serious side effects are uncommon and include cervical tears, large hemorrhages, and uterine rupture.40,59 Both gemeprost and misoprostol have been known to cause uterine rupture, either with or without mifepristone priming.60–62 Using mifepristone and gemeprost, the incidence of uterine rupture in women who have never had a scar is predicted to be 0.1-0.2% during the second trimester of pregnancy.15,63 Prolonged placenta retention is typically linked to significant hemorrhage. Less than 1% of women have been observed to experience severe bleeding that necessitates a transfusion.40, 54, and 59 Any induced abortion has the potential to become infected. In a large series of more than 1,000 women who had a second trimester abortion, around 3% of women needed antibiotic treatment due to suspected infections.

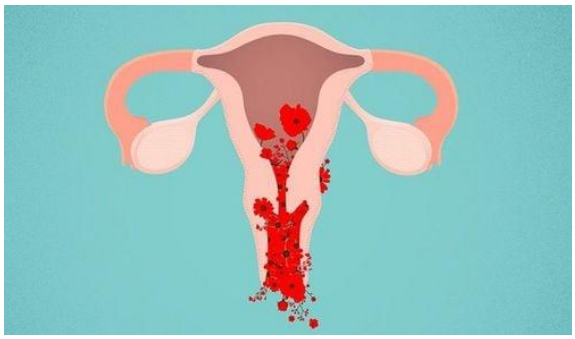
Complication Rates of the Management of Early Pregnancy Loss and Medication Abortion[1]

Complication	Rate
Early pregnancy loss using mifepristone (Mifeprex) and misoprostol (Cytotec)	-
Need for unplanned uterine aspiration	8.8%
Hemorrhage requiring transfusion	2.0%
Pelvic infection	1.3%
Early pregnancy loss using misoprostol alone	-
Need for unplanned uterine aspiration	23.5%
Hemorrhage requiring transfusion	0.7%
Pelvic infection	0.6% to 1.3%
Medication abortion using mifepristone and misoprostol	-
Need for unplanned uterine aspiration for reason other than ongoing pregnancy	1.8% to 4.2%
Ongoing pregnancy	0.8%
Hemorrhage requiring transfusion	0.03% to 0.6%
Undiagnosed ectopic pregnancy	0.02%
Pelvic infection	0.01% to 0.5%

Discussion of the key issues

Even though the results of extensive research show that mifepristone is well tolerated, certain problems have been found that need particular attention.[2]

Bleeding



The treatment process has resulted in some bleeding for every woman included in the TOP clinical trials. Light spotting before prostaglandin tended to give way to light-moderate bleeding four hours after prostaglandin. On average, 10% of women reported experiencing heavy bleeding. In 0.3% to 1.4% of women, hemostatic curettage was necessary due to severe bleeding. 0.25% of all cases required a transfusion; 0.1% required one when misoprostol was used, and 0.1% required one when the treatment was administered during the first 49 days of amenorrhea. Less than 1% of individuals in the clinical trials mentioned above experienced hypotension accompanied by clinical symptoms. Just 0.5 out of 1000 patients in the extensive US postapproval experience needed a transfusion. Variations in hemoglobin revealed a little but noteworthy drop of 0.5–0.8 g/dL. As a result, it is essential to warn the ladies about the possibility of severe bleeding and to provide them with emergency protocols. TOP's medical protocol shouldn't involve women who live in places without access to healthcare unless referrals are available and there is potential for emergency transportation.

INFECTIONS

While infectious problems have been infrequently seen in medical TOP, they are a common complication of surgical abortion. However, recent reports of five deaths in North America due to severe bacterial infections and septic shock have brought this issue to the attention of more people.[3]

Endometritis and pelvic infections

Three endometritis instances—which are regarded as major adverse events—were reported among 1195 women in the previous studies, and Spitz documented 19 endometritis cases. According to Urquhart, 87 out of 964 women (54 with symptoms or a proven vaginal and uterine infection) received antibiotic prescriptions. Rather than reflecting actual variations in occurrence, these discrepancies most likely reflect local therapy standards and policies. After

three years of experience, a database of therapies in the US revealed 16 cases of endometritis and two cases of sepsis. Results cannot be directly compared to those of the approved oral regimen of misoprostol because the majority of treatments in the United States involve a single oral dose of 200 mg of mifepristone followed by 800 Ag of misoprostol self-applied in the vagina. However, when mifepristone was used with either vaginal or oral prostaglandin, additional isolated occurrences of pelvic infection have been documented in the literature.[3,4]

DISCUSSION

Mifepristone and misoprostol together provide a very successful, non-invasive method of medically ending a pregnancy. The most important factors are the interval between dosages (preferably 36–48 hours), the method of administration (sublingual and vaginal are the most effective), and the patient's education of potential adverse effects. Despite the rarity of adverse events like bleeding and infections, patients must be made fully aware of them. Uterine rupture, hemorrhage, and hypotension are rare events that usually happen in the second trimester or in cases when there has been prior uterine scarring. Despite the low risk of infection, unsupervised settings now require caution. Improving safety still mostly depends on accessible emergency care, local guideline adaption, and routine monitoring.

CONCLUSION

When used according to the right procedures and under close supervision, mifepristone and misoprostol make form a safe and efficient medical regimen for ending a pregnancy. Their usage during the early to mid-trimester stages of pregnancy is supported by a wealth of clinical data, and the risks of serious consequences are low. The availability of post-treatment care, route selection, and adherence to dosing scheduling are critical to the effectiveness of this strategy. To improve results and guarantee patient safety, especially in settings with limited resources, ongoing assessment and international education initiatives are required.

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