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Review Article

Misoprostol: history and clinical aspects

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ABSTRACT

Misoprostol, a synthetic prostaglandin E1 analog, was originally developed for NSAID-induced gastric ulcers and is now widely used in obstetric and gynaecologic procedures. It acts as a prodrug, rapidly converted in the liver to misoprostol acid, which binds EP-3 receptors to induce uterine contractions. Misoprostol is effective for medical abortion, postpartum hemorrhage prevention, labour induction, cervical preparation and reducing blood loss during gynaecologic surgeries. Administration routes include oral, sublingual, buccal, rectal and vaginal, with dosing tailored to indication and gestational age. Adverse effects are generally mild but may include diarrhoea, nausea, fever and rarely, uterine rupture or teratogenic effects. Contraindications include prostaglandin hypersensitivity and advanced pregnancy with prior uterine scars. Overall, misoprostol is a versatile, generally safe drug with significant clinical applications in reproductive health.

Keywords: Misoprostol, Prostaglandins, Abortion, Medical termination of pregnancy, Postpartum haemorrhage

INTRODUCTION

Misoprostol, a prostaglandin E1 (PGE1) derivative originally discovered in 1973 at Searle, was first approved in 1988 by the US Food and Drug Administration for the prevention and treatment of gastric ulcers induced by nonsteroidal anti-inflammatory drugs.[1] Misoprostol is widely used off-label for obstetric and gynecologic procedures. Misoprostol is a synthetic 15-deoxy-16-hydroxy-16-methyl analog of PGE1. Prostaglandins are fatty acids made up of 20 carbon atoms, produced by almost all cells in the body and act as local hormones.

Unlike some other substances, they are not typically stored in tissues; instead, they are synthesized from essential fatty acids when needed. Their production begins with the action of the enzyme phospholipase on cell membrane phospholipids, which releases arachidonic acid. This acid is then transformed into prostaglandins through a series of reactions involving an enzyme system commonly known as prostaglandin synthetase.[2] The study of prostaglandins began in the 1930s when researchers Kurzrok and Lieb observed that human semen could induce uterine contractions. Around the same time, Von Euler introduced the term "prostaglandin" to describe the biologically active components found in semen extracts. Research in this field remained largely inactive until after World War II, when Bergström and other scientists at the Karolinska Institute in Sweden resumed investigations.

Later, Samuelsson and his colleagues at Karolinska successfully identified the chemical structures of prostaglandins and mapped out their biosynthetic pathways. By the mid-1960s, significant research efforts were underway in both academic and industrial labs to synthesize these complex compounds and explore their various biological effects. These investigations revealed that prostaglandins had a wide range of physiological actions, indicating their potential for numerous medical applications. These included inducing labour, treating asthma, arthritis, peptic ulcers, high blood pressure, platelet disorders and even gum disease. At one time, their importance was so highly regarded that prostaglandins were referred to as the "steroids" of the 1970s.[3]

PHARMACOKINETICS

Misoprostol acts as a prodrug; it has no direct pharmacological effect until it is rapidly converted in the liver through de-esterification into its active form, misoprostol acid (MPA). Due to this rapid transformation, the original form of misoprostol is undetectable in the bloodstream as early as 5 minutes after oral administration. After administration, MPA reaches its highest concentration in the plasma approximately 30 minutes later, then declines sharply over the next 2 hours, remaining at low levels for up to 5 hours.

Misoprostol acid binds to serum proteins at a rate of less than 90% and this binding is not influenced by the concentration within the therapeutic range.[4] Misoprostol tablets can be administered orally, sublingually, rectally or vaginally. Misorpostol is primarily excreted in urine as an inactive metabolite.[5]

MECHANISM

Misoprostol acid binds to the E prostanoid receptor 3 (EP-3). When the EP-3 receptor on myometrial cells is activated, it stimulates intracellular phosphoinositol turnover and promotes calcium release within the cells. This leads to an increase in free intracellular calcium, which activates actin-myosin interactions, resulting in muscle contractions. The rise in calcium levels is transmitted between myometrial cells via gap junctions, allowing for the coordination of the uterine.[6]

Although prostaglandins (PGs) are very effective, their effectiveness depends on the number of PG receptors in the uterus, which changes with gestational age. In early pregnancy, there are fewer receptors, so higher and repeated doses of misoprostol may be required to achieve the desired effect. The uterus's response to misoprostol can be enhanced by administering mifepristone.[7]

INDICATIONS

For NSAID-induced ulcers, oral misoprostol should be taken with meals and at bedtime to help reduce gastrointestinal discomfort. The usual regimen is 200 mcg four times daily (total 800 mcg/day). A dose of 800 mcg/day is more effective than 400 mcg/day in preventing gastric ulcers, but it is linked to a higher rate of side effects.[8]

Postpartum haemorrhage

The World Health Organization (WHO) recommends that in situations where skilled birth attendants are absent and oxytocin is not accessible, community health workers and lay health workers can administer misoprostol (600 µg orally) to prevent postpartum hemorrhage (PPH) and for the treatment of Postpartum haemorrhage, sublingual misoprostol (800 µg).[9]

Medical abortion up to 70 days of gestation

Combination regimen

For pregnancy termination, ACOG recommends a regimen of a single oral dose of 200 mg mifepristone followed by 800 mcg of misoprostol administered via the buccal route. On the first day, one 200 mg mifepristone tablet is taken orally. Then, on the second or third day, four 200 mcg misoprostol tablets (totalling 800 mcg) are placed between the cheek and gums (buccal pouch) and left in place for at least 30 minutes. Misoprostol should be taken within 24 to 48 hours after mifepristone. Complete abortion rates are reported at 96–97% in women up to 49 days of pregnancy and 89–93% in those between 50 and 63 days of gestation.[10]

Misoprostol-only regimen (off-label use)

As an alternative, ACOG supports a misoprostol-only protocol using 800 mcg per dose, repeated every three hours for up to three doses. This can be administered vaginally, sublingually or buccally. According to FIGO guidelines, misoprostol alone can be used to terminate pregnancies up to 13 weeks. FIGO suggests 800 mcg sublingually every three hours. Alternatively, 800 mcg can be given vaginally or buccally every 3 to 12 hours for 2 to 3 doses. However, intravaginal use should be avoided if there are signs of bleeding or infection.11Using a combination of mifepristone and misoprostol achieves complete abortion in 94–95% of women between 9 and 13 weeks of gestation; however, the likelihood of heavy vaginal bleeding is greater compared to those at earlier stages of pregnancy.[12]

The FIGO 2023 provides updated guidance on using misoprostol alone when mifepristone is unavailable. It outlines dosing regimens for induced abortion, missed abortion, incomplete abortion and fetal demise across different gestational ages, as well as for induction of labor, cervical preparation before procedures and prevention or treatment of postpartum hemorrhage (PPH). Misoprostol can be given buccally, sublingually, vaginally or orally, with SL/PO routes causing more side effects and PV avoided if there is vaginal bleeding. It is considered safe for use below 28 weeks even in women with prior cesarean delivery, though not recommended at ≥28 weeks with a scarred uterus. There is no maximum dose limit—doses can be repeated until expulsion occurs.[13]

Induction of labour

According to ACOG, vaginal misoprostol is the preferred method for inducing labor before 28 weeks of gestation. For cervical ripening and labour induction, a 25mcg dose may be given either intravaginally or orally. The dosing interval should be at least every 3–6 hours for the vaginal route and every 2 hours for the oral route, while sublingual and buccal administration are not recommended.[14]

Role in hysteroscopy

Using misoprostol before hysteroscopy can help with cervical dilation and reduce the risk of complications such as cervical laceration and false passage. Reported side effects are generally mild and not clinically significant. Some authors recommend a dose of 200–400 µg of vaginal misoprostol appears to be the most effective option, particularly before operative hysteroscopy.[15]

Role in myomectomy

Misoprostol may help in decreasing blood loss during myomectomy and decrease the likelihood of requiring a blood transfusion or hysterectomy. Some authors recommend a single rectal dose of 800 mcg misoprostol administered 30 minutes before open myomectomy has been shown to reduce intraoperative blood loss by at least 20% which is significant and associated with less postoperative morbidity in myomectomy.[16]

ADVERSE EFFECTS

Teratogenicity

Misoprostol has been linked to Möbius sequence, a rare condition marked by congenital paralysis of the sixth and seventh cranial nerves, sometimes involving additional cranial nerves and often accompanied by limb abnormalities and craniofacial malformations.[17] The absolute risk of congenital malformations following misoprostol exposure is relatively low, estimated at around 1% of exposed fetuses.[18] Other defects, like terminal transverse-limb defects, hydrocephalus and arthrogryposis, have also been found in some studies.[19]

Diarrhea is the most frequently reported side effect of misoprostol, though it is generally mild and self-limiting. Nausea and vomiting may also occur but usually resolve within 2–6 hours. When taken sublingually or buccally, some women experience an unpleasant taste and sublingual use has also been linked to temporary numbness in the mouth and throat.[20]

Fever and chills are additional side effects, particularly after high doses used to prevent or treat postpartum hemorrhage. Studies on PPH prevention have shown chills in 32%–57% of women receiving misoprostol. Cases of hyperpyrexia (> 40 °C)have been reported with a 600 µg dose, while 800 µg orally has been associated with hyperpyrexia accompanied by delirium and, in rare cases, ICU admission.[21]

Another potential and serious risk is uterine rupture, especially in women with a history of uterine scarring. While rupture is very uncommon in first-trimester medical abortion, the risk increases with advancing gestation. Most documented cases occur during labor induction in the third trimester, typically in women with prior uterine scars and other contributing risk factors.[22]

CONTRAINDICATIONS

Misoprostol should not be used in patients with a known allergy or hypersensitivity to prostaglandins. Pregnant patients at risk of NSAID-induced gastric ulcers should not use misoprostol, as it can lead to serious adverse effects during pregnancy.[5] Misoprostol is listed as a pregnancy category X drug. It should be used with caution in pregnant patients for the termination of pregnancy, in patients with a history of a previous uterine scar.[22] Misoprostol is not recommended for breastfeeding mothers due to the risk of causing diarrhea in the infant.[23]

Misoprostol toxicity

A rare case of a 29 years old woman developed fever, chills and confusion after self-administering 8 mg of misoprostol (oral and intravaginal) to induce abortion. Other reports of first-trimester misoprostol overdose include mild GI symptoms after 8.4 mg and fatal multiorgan failure after 12 mg ingestion. Acute misoprostol toxicity in pregnancy, though rare, can be life-threatening.[24]

CONCLUSION

Misoprostol has been a major focus of research in obstetrics and gynecology over the past 2 decades. It plays a critical role in pregnancy termination across gestational ages, induction of labour and prevention and treatment of postpartum hemorrhage (PPH). Its wide availability, low cost and ease of administration through multiple routes (oral, sublingual, buccal, rectal and vaginal) make it especially valuable in both high-resource and low-resource settings. Broader knowledge and access to misoprostol can significantly improve maternal health outcomes by reducing morbidity and mortality from unsafe abortion, postpartum hemorrhage and complications of pregnancy.

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