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Misoprostol – Drug That Changed the Practice of Gynecology and Obstetrics with Its Off-Label Indications

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Abstract

Misoprostol is a synthetic analogue of prostaglandin E_1. The drug was developed by G. D. Searle & Company in 1973 for prevention of stomach ulcers. Since 1986, it is being used for its 'off label' indications in obstetrics and gynecology. [1] The common indications are medical termination of pregnancy (MTP), medical management of incomplete abortion, induction of labor, cervical ripening before surgical procedures and prevention and treatment of postpartum hemorrhage [2]. Since it is inexpensive, heat stable, no drug interactions and wide range of applications in reproductive health, 'WHO' in 2011 has added it in the model list of essential medicines. In this article we have reviewed misoprostol its uses and recommendations in modern obstetrics and gynecology.

Keywords: *Misoprostol, PGE $_{1,}$ Mifepristone, Induction of Labor, MTP, PPH*

INTRODUCTION

Misoprostol is a synthetic analogue of prostaglandin E_1. The drug was developed by G.D. Searle & Company in 1973. It was initially approved by the Food and Drug Administration (FDA) to prevent stomach ulcers in patients taking NSAIDS in 1986 [3]. However now it is used more widely for its 'off-label' indications in obstetrics and gynecology. Its common uses include Medical termination of pregnancy (MTP), induction of labor, cervical ripening before surgical procedures and treatment of postpartum hemorrhage (PPH). Despite of being a very commonly used drug for above mentioned indications, misoprostol is not yet approved by the US Food and Drug Administration (FDA) for use in pregnancy. However in 2002, the label of 'pregnancy as an absolute contraindication for misoprostol use' was removed from the drug pack [4]. The drug is a boon to a developing country like India. Unlike other prostaglandin preparations, misoprostol does not require refrigeration or parenteral administration. It is also inexpensive, has long shelf life and available worldwide.

Historical Aspect

It all started in 1930 when Kurzok R and Lieb C described that the freshly emitted human semen, when instilled in the uterus or uterine fibers caused strong contractions. For the next 20 years no further progress was made until the invention of chromatography and mass spectrometry. Since then 20 different prostaglandins have being isolated till date [5]. However, only few are of medicinal value.

Pharmacokinetics

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE1) is a synthetic analogue of prostaglandin E1 with chemical formula – $C_{22}H_{38}O_5$ and molar mass- 382.534 g/mol. It is extensively absorbed, 80-90% protein bound, metabolized in liver, excreted in urine (80%) with elimination half-life of 20-40 minutes [6]. The naturally occurring prostaglandin E series was discovered to inhibit gastric acid secretion in 1967 by Robert et al. however; naturally occurring prostaglandins have three drawbacks that hindered their clinical

application [7]. These problems were: a) rapid metabolism resulting in a lack of oral activity and a short duration of action when given parenterally, b) numerous side effects, and c) chemical instability leading to a short shelf life. Misoprostol differs structurally from prostaglandin E1 by the presence of a methyl ester at C-1, a methyl group at C-16 and a hydroxyl group at C-16 rather than C-15. The methyl ester at C-1 increases the anti-secretory potency and duration of action of misoprostol, while the movement of the hydroxyl group from C-15 to -16 and the addition of a methyl group at C-16 improves oral activity, increases the duration of action, and improves the safety of the drug.

Routes of Misoprostol administration

The tablet form of misoprostol may be used through oral, vaginal, sublingual, buccal, or rectal routes. There have been a number of studies in the past few decades on the pharmacokinetic profile of different routes of administration of misoprostol [8].

Oral Route

With oral route, the drug undergoes extensive and rapid first pass metabolism but is rapidly and almost completely absorbed from gastrointestinal tract. After a single 400mcg dose of misoprostol, the misoprostol plasma level increases rapidly and Peaks at 30 minutes, declines rapidly by 120 minutes and remains low after that.

Vaginal Route

Zieman et al. performed the first pharmacokinetic study comparing and vaginal routes of administration and found that vaginal administration was more effective than oral administration in medical abortion. The plasma concentration increases gradually after vaginal administration reaching to a maximum level after 70-80 minutes and slowly declines with detectable drug levels present even after 6 hours. The area under curve AUC (area under drug concentration) is higher with vaginal misoprostol and therefore its greater bioavailability. This should explain why vaginal route is more effective in medical abortion. There is, however, a wide variation in the absorption of misoprostol through the vaginal epithelium among different women may be because of variation in amount and pH of vaginal discharge.

Sublingual Route

The sublingual route of administration has an AUC similar to vaginal administration, but more rapid absorption and higher peak levels than either vaginal or oral administration. A pharmacokinetic study found that sublingual misoprostol has the shortest time to peak concentration, the highest peak concentration and the greatest bioavailability when compared to other routes.

Buccal Route

Buccal route is another way of administering misoprostol, in which drug is placed between the teeth and the cheek and allowed to absorb through buccal mucosa. The buccal route of administration shows a lower AUC, a lower peak concentration than sublingual administration, also the AUC of buccal administration is just half that of vaginal administration.

Rectal Route

The rectal route of administration shows a similar pattern to vaginal Administration, but has a lower AUC, almost 1/3rd, including a significantly lower maximum peak concentration.

It is important to understand the pharmacokinetics of different routes of administration of misoprostol to formulate the best regimens for various clinical applications. Evidence shows that the sublingual route may be the most promising and should be considered for treatment of postpartum hemorrhage as it demands a fast onset of clinical action. In cases of medical abortion where longer

time of clinical manifestation of misoprostol is needed, vaginal route is useful because of its high bioavailability and sustained serum level. The administration of NSAIDs for pain relief does not alter the efficacy of misoprostol. There are no known drug interactions with misoprostol.

Adverse Effects

The common side effects are - Nausea, vomiting, diarrhea, abdominal cramps, dehydration. Relatively uncommon side effects are itching, rash, swelling, dizziness, trouble breathing [9].

Teratogenicity and Secretion in Breast Milk

Misoprostol belongs to pregnancy category X drugs and is considered a teratogen. Congenital defects following prenatal exposure in early pregnancy to misoprostol include skull defects, bladder exstrophy, arthrogryposis, cranial nerve palsies, facial malformations, terminal transverse limb defects, and Moebius sequence [1, 10, 11]. It is thought to be due to vascular disruption secondary to uterine contractions caused by misoprostol. The absolute risk of congenital malformations after prenatal exposure to misoprostol is estimated to be approximately 1% [12]. Misoprostol is excreted into the breastmilk but the levels fall quickly. Levels become undetectable within 5 hours of maternal ingestion [13]. However, lactating women should be informed about possibility of infant diarrhea with misoprostol use [14].

Uses of Misoprostol in Obstetrics and Gynecology

Termination of Pregnancy

Medical Abortion (1st trimester up to 63 days)

The FDA IN 2000 approved for medical abortion using 600 mg of oral mifepristone, aprogesterone antagonist, with 400 µg of oral misoprostol 48 hours later for pregnancies up to49 days of gestation [9]. However, the evidence of efficacy up to 63 days of gestation using the regimens of 200 mg of mifepristone orally followed by administration of either800 µg of buccal misoprostol in 24 to 36 hours or 800 µg of vaginal misoprostol in 6 to 48hours is excellent [15, 16]. A woman comes back from 4 to 14 days later for a clinical evaluation to document complete abortion. Mifepristone medication abortion is safe with an estimated complication rate of 2.2 per 1000 women [17]. Where mifepristone is not available, medication abortion can be accomplished with methotrexate and misoprostol or misoprostol alone [18].

Medical Abortion (1st trimester 63 days to 12 weeks)

WHO recommendations for first trimester induced abortions: - misoprostol 800µg can be Used per-vaginally every 12 hourly for maximum of 3 doses. The success rate is approximately85% as long as at least 7 to 14 days is allowed for completion of expulsion and a second dose of misoprostol is considered for initial failures. According to FIGO 800µg misoprostol can be used sublingually every 3 hourly or per vaginally every 3-12hours for maximum of 2-3 doses [19].

Missed Abortions

WHO recommends 800 mcg vaginal misoprostol or 600 mcg sublingual misoprostol can be used 3 hourly for maximum of 2 doses [19]. FIGO recommends800mcg misoprostol can be used per vaginally every 3 hourly or sublingually 600mcgevery 3 hourly for maximum of 2 doses [20].

Incomplete Abortion

WHO recommends 600 mcg as single oral dose. Depending on the study, success rates range from 66% to 100% using these doses. FIGO recommends 600µg per orally or 400µg sublingually or 400-800µg per vaginally as single dose [19].

Medical Abortion (2nd trimester)

WHO recommended 400µg vaginal misoprostol 3 hourly for maximum of 5 doses in second trimester induced abortion [21]. Vaginal misoprostol was found to be more effective than oral misoprostol in second and third trimester.

FIGO Recommendations

a) 13-24 weeks: 400 µg Per-Vaginal/Sublingual/Buccal every 3hrs.
b) 25-26 weeks: 200µg Per Vaginal/Sublingual /Buccal every 4 hourly.
c) 27-28 weeks: 200µg Per-Vaginal/Sublingual/Buccal every 4 hourly.
d) > 28 weeks: 100µgPer-Vaginal/Sublingual/Buccal every 6 hourly.

Intra Uterine Fetal Death

WHO recommendations

1. IUFD 13-17 weeks 200 mcg misoprostol
2. IUFD 18-26 weeks 100µg misoprostol 6 hourly with maximum of 4 doses [22].

FIGO recommendations

1. 13-26 weeks 200µg Per-Vaginal/Sublingual/Buccalevery 4-6 hourly.
2. 27-28 weeks 100µg Per-Vaginal/Sublingual/Buccal every4 hourly
3. > 28 weeks 25µg Per-Vaginal every 6 hourly or 25µg orally every 2 hourly [19].

Use in Patients with Scarred Uterus

It should be used with caution in women with uterine scars. In a study of 80 women [23] undergoing termination of pregnancy, between 13 and 26 weeks of gestation, for a variety of reasons, with one or more caesarean section scars, misoprostol 400 µg, was administered to women up to 20 weeks of gestation and 200 µg for women greater than 20 weeks of gestation, vaginally or sublingually, every 6 hours up to 24 hours. The mean induction to abortion interval was 16.4 hours and was not statistically different between women with and without a prior caesarean delivery scar [1]. There was no case of uterine rupture or scar dehiscence. No statistically significant differences were found in rates of incomplete abortion, blood loss, or sepsis.

Caution, Complications and Contraindications

The candidates for medical abortion must adhere to the treatment regimen and have easy access to a medical facility in case of emergency. Medical abortion involves pain abdomen and heavy bleeding when the pregnancy is expelled. Other side effects of misoprostol include nausea and vomiting, diarrhea, fever and chills. Women with persistent nonviable pregnancies may opt for expectant management, a repeat dose of misoprostol, or suction curettage [24]. The contraindications for its use are hemorrhagic disorder; concurrent anticoagulant therapy; inherited porphyrias; concurrent long-term systemic corticosteroid use; confirmed or suspected ectopic or molar pregnancy; allergy to mifepristone, misoprostol, or other prostaglandin; and unwillingness to undergo a vacuum aspiration if needed. If the woman has an intrauterine device in place, it must be removed before treatment. Women with serious systemic illnesses (e.g. severe cardiac, renal, or liver disease or severe anemia) should be evaluated individually to determine which method of abortion is safest. Rhesus (Rh)-negative women typically receive Rh immune globulin on the day of mifepristone administration [25].

Cervical Ripening and Induction of Labor

Misoprostol causes cervical ripening before induction with oxytocin. It can be administered orally, sublingually, or vaginally. A commonly used dose for induction of labor in third trimester

'as per WHO recommendation is 25 µg administered vaginally every 4 hours, with a maximum 6 doses'. FIGO recommends 25 µg per- vaginal very 6 hourly or 25 µg orally every 2 hourly [19] Doses are withheld if there is tachysystole or compromised fetal heart rate. The Cochrane Pregnancy and Childbirth Group reviewed randomized trials comparing vaginal misoprostol with placebo, oxytocin, or prostaglandin E_2 for cervical ripening or induction of a viable fetus in the third trimester [3, 26].

Postpartum Haemorrhage (PPH)

Misoprostol has been used both as prevention and treatment of postpartum hemorrhagedue to its uterotonic properties. There are insufficient data to support the use of misoprostol as a primary preventive measure for PPH when injectable uterotonics (such as oxytocin and/or methyl ergotomine) are available as part of them anagement of the third stage of labor. It is also not found to be better than other injectable uterotonicsin well-controlled, randomized trials for the treatment of PPH. However, it remains an important option for treating PPH when other agents are not available or fail. It is recommended as part of many international guidelines for PPH management (WHO, FIGO, RCOG) and also included in WHO Model list of Essential Medicines in 2011 for the prevention of PPH and in 2015 for the treatment of PPH. The recommended dosages are 600 mcg orally or sublingually where injectable uterotonics are not available for treatment, evidence shows that oral route of administration has fast uptake, but shortest duration of action. Rectal route has slow uptake but with prolonged duration of action. Buccal and sublingual routes have rapid uptake, prolonged duration of action and greatest total bioavailability.

ATRAUMATIC CERVICAL DILATATION BEFORE SURGERY

There are many studies on misoprostol about its use in cervical ripening prior to surgical procedures such as surgical abortion, hysteroscopy, intrauterine device insertion with the aim to prevent complications of mechanical dilation such as cervical laceration, uterine perforation, and the creation of a false passage. One meta-analysis of 10 studies concluded that misoprostol leads to greater preoperative dilation, decreased need for additional dilation, and reduced rates of cervical laceration in premenopausal women. However there may be potential concerns regarding loss of distension from excessive cervical dilatation by misoprostol, higher rates of transient vaginal bleeding, cramping and fever preoperatively. The optimal dosing regimen for cervical ripening before surgical procedures is unclear but WHO recommends 400µg vaginalor sublingual misoprostol 3 hours prior to procedure. Based on a single, small study, IUD insertion in nulliparous women may be facilitated by misoprostol use. A Swedish trial randomized 80 women to 400 µg of sublingual misoprostol plus 100 mg of diclofenac or 100 mg of diclofenac alone 1 hour before Nova-T IUD insertion was found the combination of misoprostol and diclofenac highly effective.

Our experience at MGM Hospital Navi Mumbai

The medical records of the patients who were treated with misoprostol for any Obstetric or gynecological indication were collected for the period from 01 January 2015 to December 2018. Records show that more than 2000 procedures was carried out under misoprostol with very good success rate. The gynecological procedures done under misoprostol were hysteroscopy and D&C to make the cervix softer and pliable for dilation. The MTPs up to 20 weeks, induction of labor from 21-42 weeks (on non-scarred uterus) were also performed with misoprostol with very high degree of success.

CONCLUSION

Misoprostol is a miracle drug. Though the use of misoprostol in pregnant patient is off-label, it's legal and has been highly recommended by several authorities. It has many applications in obstetrics and gynecology. Its low cost, easy to use has a worldwide potential to improve women's health. Its use in medical termination of pregnancy (MTP), induction of labor, cervical ripening before surgical procedures and prevention and treatment of postpartum hemorrhage has been life saving for many patients around the world.

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