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Review Article

Clinical Use of Misoprostol Prior to Transcervical Procedures in Non-pregnant Women

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Abstract

Misoprostol, a synthetic prostaglandin E1 analogue, is commonly used for medical abortion, cervical priming and the management of miscarriage, induction of labor and the management of postpartum hemorrhage. It can be given orally, sublingually, vaginally and rectally. It has been widely used in non-pregnant women because of its cervical ripening and uterotonic effects. A large number of studies have demonstrated its effectiveness in enhancing ease of cervical dilatation. This review article describes the pharmacokinetics and clinical use of the drug misoprostol in non-pregnant women including cervical priming before hysteroscopy, before insertion of an intrauterine device, in endometrial biopsy and before intrauterine insemination to improve pregnancy rates.

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE1) is a synthetic prostaglandin E1 analogue. It was developed for the prevention and treatment of peptic ulcers because of its gastric acid anti-secretory properties and its various mucosal protective properties.[1] It was first approved in 1988 by the US Food and Drug Administration for prevention and treatment of gastric ulcers induced by nonsteroidal anti-inflammatory drugs.[2] It has become an important drug in obstetrics and gynaecological practice because of its utero-tonic and cervical priming action. It is inexpensive, stable at room temperature, and available in more than 80 countries, making it particularly useful in resource-poor settings. It is a drug that can replace other mechanical cervical priming methods that can lead to cervical injury during dilatation, creation of false passages and uterine perforations. Given its low cost and ease of administration it has the potential to improve women's health world-wide.[3]

A website, http.//www.misoprostol.org/, is devoted to obstetrics and gynecologic uses of misoprostol with an extensive bibliography. There are many studies which demonstrated its effectiveness in first and second trimester termination of pregnancy.[4,5] It is also used for induction of labor and for treatment of postpartum hemorrhage.[6,7]

WHO recognizes the crucial role of misoprostol in reproductive health and has incorporated recommendations for its use into four reproductive health guidelines. These guidelines focus on induction of labor, prevention and treatment of postpartum hemorrhage and management of spontaneous and induced abortion.[8] Its clinical applications include medical abortion, medical evacuation for miscarriages cervical priming before surgical procedure, induction of labor and management of postpartum hemorrhage.

A retrospective study was conducted in 5359 non-obstetric D&Cs performed in 2542 premenopausal and 2817 postmenopausal patient. Intraoperative procedure-associated complication rate and identification of risk factors for the occurrence of complications were the main outcome measures. A total of 103 (1.9%) intraoperative complications were noted. Uterine perforation occurred in 50 cases (0.9%) (perforation site: fundus, n=47; cervix, n=3). Forty-two (0.8%) cases of false passage, seven cases (0.1%) with severe hemorrhage, three cases of vaginal laceration, and one case of cervical laceration were noted. In a multivariable analysis, retroversion of the uterus (P=.008), postmenopausal status (P=.003), and nulliparity (P=.03) were significantly associated with occurrence of intraoperative complication, the study concluded that the overall complication rate of D&C is low. A retroverted uterus, postmenopausal status and nulliparity are independent risk factors for intraoperative complications.[9]

Misoprostol has been used in non-pregnant women as well and many authors have shown its use prior to hysteroscopy for cervical priming[20-28,31,32], before intrauterine insemination to improve pregnancy rate [29, 33-35], before insertion of intrauterine contraceptive device[36-40], at endometrial sampling.[41, 42]

For this review, electronic searches were undertaken in PubMed using the key words misoprostol, pharmacokinetics, cervical priming, uterine contractility, non-pregnant women, hysteroscopy, intrauterine insemination (IUI), intrauterine contraceptive device (IUCD) insertion, endometrial sampling.

Structure and chemistry of misoprostol

The naturally occurring prostaglandin E series was discovered to inhibit gastric acid secretion in 1967 by Robert et al.[10] Naturally occurring prostaglandin have three drawbacks that have hindered clinical application: (1) rapid metabolism manifested as a lack of oral activity and short

duration of action when given parenterally, (2) incidence of numerous side effects and (3) chemical instability leading to short shelf life.[11]

Misoprostol (C22 H38 05, M: W 382.5; [11 α, 13 E, 16-dihydroxy-16 methyl-9 oxyprost-13-en-1-oic acid methyl ester], is a synthetic PGE 1 analogue developed in 1973 by Searle for the treatment and prevention of gastric ulcers. Fig. 1 shows the naturally occurring prostaglandin E1 and misoprostol.

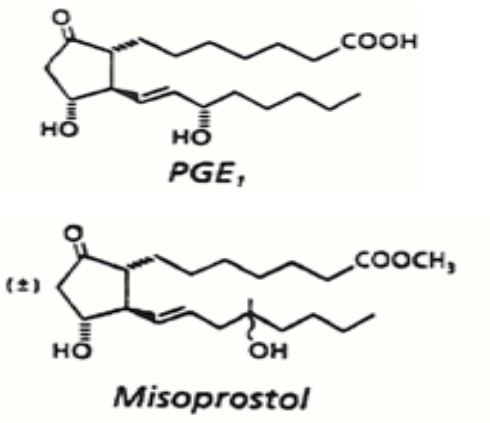


Figure 1: Chemical structure of prostaglandin E1 (PGE 1) and misoprostol.

Misoprostol differs structurally from PGE 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. It appears that the methyl ester at C-1 increases the antisecretory potency and duration of action of misoprostol, while the movement of the hydroxyl group from C-15 to C-16 and the addition of methyl group at C-16 improve oral activity, increases duration of action and improve safety profile of the drug compared with PGE.[11] However the chemical was still unstable at room temperature. This problem was solved by dispersion of misoprostol in hydroxypropylmethylcellulose.[12]

Pharmacokinetics of misoprostol

Misoprostol is extensively absorbed, and undergoes rapid de esterification to its free acid, which is responsible for its clinical activity and, unlike the parent compound, is detectable in plasma. The alpha side chain undergoes beta oxidation and the beta side chain undergoes omega oxidation followed by reduction of the ketone to give prostaglandin F analogs. In normal volunteers, Cytotec (misoprostol) is rapidly absorbed after oral administration with a Tmax of misoprostol acid of 12 ± 3 minutes and a terminal half-life of 20–40 minutes. There is high variability of plasma levels of misoprostol acid between and within studies but mean values after single doses show a linear relationship with dose over the range of 200–400 mcg. No accumulation of misoprostol acid was noted in multiple dose studies; plasma steady state was achieved within two days. The pharmacokinetic profile is no different between pregnant and non-pregnant women.[13]

Pharmacokinetic data on misoprostol are available following oral, vaginal and sublingual administration. Following oral treatment, plasma levels peaked at about 30 minutes, while after vaginal administration of the tablets the levels increased gradually and reached maximum levels after 70-80 minutes, but remained detectable for a significantly longer time. After sublingual administration the peak concentration was the same as for oral treatment but declined significantly more slowly.[14]

Effect of prostaglandin E1 on cervical priming

It has been shown that various prostaglandin analogues can decrease the hydroxyproline content of the pregnant cervix.[15] The histochemical changes in the pregnant cervix after misoprostol administration were studied using electron microscopy and proline uptake assay. The mean proline incorporation per microgram protein and collagen density, estimated by light intensity, was significantly less than in the control group. The diameter of the collagen fibres was also smaller in the misoprostol group, although the difference was not statistically significant. This indicated that the action of misoprostol appeared to focus mainly on the connective tissue stroma, with evidence of disintegration and dissolution of collagen.[16] There are also many clinical studies that have demonstrated the cervical priming effect of misoprostol in the pregnant state. Misoprostol has been used extensively for its cervical softening effect before induction of labour and surgical evacuation of the uterus. Studies have demonstrated that less force was required for mechanical dilation of the cervix if misoprostol was applied before the procedure.[16,17] While this softening effect on the cervix may be secondary to the uterine contractions induced by misoprostol, it is more likely to be due to a direct effect of misoprostol on the cervix. Dilatation of the softened cervix may thereafter increase following induction of uterine contractions.

Effect of prostaglandin E1 on uterine contractility

The typical effect of a single dose of oral misoprostol is an increase in uterine tonus.[18,19] It is only following repeated treatment that regular uterine contractions appear. Thus it seems that a sustained plasma level of misoprostol is required for the development of regular contractions. Regular contractions are essential for many of the clinical effects of misoprostol in medical abortion and induction of labour. The effect of vaginal administration of a single dose of misoprostol on uterine contractility is initially similar to that of oral administration i.e. an increase in uterine tonus. After 1-2 hours, however, regular uterine contractions appear and they last at least up to 4 hours after administration.[19] The development of regular contractions after vaginal administration may explain the better

clinical efficacy of vaginal administration when compared to oral administration.[16]

Clinical uses of misoprostol in non-pregnant women

Misoprostol use for Preoperative cervical ripening before hysteroscopy

In premenopausal women:

Effect of misoprostol for cervical ripening in non-pregnant women to prevent cervical injury during dilatation has been evaluated to reduce cervical injury during dilatation, creation of false passages. Misoprostol can be administered by many routes such as orally, vaginally and rectally. A trial has shown misoprostol to be effective among premenopausal women achieving 88% of cervical dilatation of ≥5mm as compared to 65% in the placebo group.[20,21] Another study showed misoprostol to be promising but further research is required to identify ideal dose, route, and timing of administration of misoprostol. The mean cervical dilatation of ≥5mm will be considered satisfactory.[21-23] A review by Crane and Haley concludes that in premenopausal women, misoprostol appears to be promising as a cervical ripening agent prior to hysteroscopy, although further research is needed to identify the ideal dose, route and timing.[22] The dosages used in studies have varied from 200 and 1000 micrograms of misoprostol given between 2 and 24 hours before hysteroscopy via oral, sublingual and vaginal routes.[23-26] Aronsson et al studied the effect of vaginally and orally administered misoprostol on the local cervical inflammatory response.[27] Khan Ru et al showed that vaginal misoprostol is present in the circulation longer than oral misoprostol.[28]

In postmenopausal women

Most studies that have examined the use of misoprostol in postmenopausal women before hysteroscopy have failed to demonstrate any benefits.[21,25,30-32] Administration of 400 mg of vaginal misoprostol in perimenopausal and postmenopausal women 12 hours before hysteroscopy produced a greater cervical diameter and less need for further dilation than in the placebo group.[20] In contrast, 3 randomized control trials did not show any benefits with 200 or 800 mg of vaginal misoprostol at approximately 8 hours or 1000 mg of vaginal misoprostol at 12 hours before hysteroscopy.[21,31,32] The hypoestrogenic status may be related to poor cervical response to misoprostol in postmenopausal women because estrogen receptors are present in the human cervix.[21,25] It seems that there is still not enough evidence to support a positive effect for misoprostol on cervical dilation in postmenopausal women.

Misoprostol use in intrauterine insemination (IUI)

Human in-vitro research has shown that PGE induces relaxation response on the non-pregnant human uterine and fallopian tube smooth muscle, whereas PGF has shown in vitro to create a contractile response. Moreover it has shown that PGE is more potent than PGF on myometrial response and that both prostaglandins inhibit tubal motility, thus suggesting that the relaxation of the tubal isthmus is a prerequisite for sperm penetration into fallopian tube.[29] Additional effect such as immunosuppression afforded by seminal PG has been shown both in vivo and in vitro, suggesting an attenuated female immunological response to spermatozoa.[33] Due to these favorable effects of prostaglandins in regard to potentiation of fertilization, utility of augmenting IUI with vaginally placed PGE1 analogue was investigated with regards to pregnancy success and complications. A significant increase was found in pregnancy rates of women undergoing ovarian stimulation with clomiphene citrate and there was a trend in increasing pregnancy rates both in natural cycles and in woman where gonadotrophins were used for stimulation, when vaginal misoprostol was placed at the time of insemination.[34]

The study by brown et al examined whether the prostaglandin E analogue misoprostol (400 µg), when placed vaginally at the time of intrauterine insemination (IUI), improves pregnancy rates. A prospective, placebo-controlled, randomized and double-blind study involving 274 women in 494 IUI cycles resulted in a total of 64 pregnancies (13% per cycle). Misoprostol cycles total 253, with 43 pregnancies (17% per cycle), whereas placebo cycles total 241, with 21 pregnancies (9% per cycle). The cumulative pregnancy rate with misoprostol treatment was significantly greater than with placebo (P 0.004, Cox proportional hazards regression). The benefit of misoprostol was seen in clomiphene cycles (14 versus 4%, P 0.006), and was indicated in FSH cycles (33 versus 15%, borderline significance) and natural cycles (15.6 versus 7.7%, not significant), but was not seen in clomiphene/FSH cycles (18.2 versus 23.5%, not significant). Misoprostol treatment did not increase pain score on the day of IUI (1.1 versus 1.4) and at 1 day post IUI (0.6 versus 0.8). Complications were rare in both groups 6 (2%) subject cycles in the misoprostol cycles compared with 2 (1%) in the placebo group. It concluded that the use of vaginal misoprostol may improve the chance for pregnancy in women having IUI in a wide variety of cycle types.[34]

Another study by moslemizadeh et al used 200 µg vaginal misoprostol prior to IUI procedure but it did not improve clinical pregnancy rates instead increased the uterine cramping and side effects.[35]

At present there is limited evidence that misoprostol is effective prior to IUI procedures.

Misoprostol use in intrauterine contraceptive device (IUD) insertion

Intrauterine contraceptive device (IUD) insertion is used for long acting contraception. In certain cases IUD insertion may be difficult due to severe cervical stenosis or constricted cervix in nulliparous women. Currently, the mechanical means to overcome anatomical cervical stenosis are by direct cervical traction with tenaculum and additional use of probe or dilators. These techniques are usually associated with increased pain, tissue injuries, anxiety and even failure. It is even more difficult with levonorgestral

intrauterine system because of larger frame. A study was conducted in 2005 by Y.T Li who selected 8 women with cervical stenosis. They were treated 24 hours prior to IUD insertion with 400 µg vaginal misoprostol. IUD insertion was successful in these women.[36]

Aronson et al conducted a randomized control trial in nulliparous women who were treated with sublingual misoprostol for cervical priming one hour prior to IUD insertion. Sublingual misoprostol was effective in IUD insertion.[37]

Another study by Kirsten showed no benefit of use of vaginal misoprostol prior to IUD insertion and patient developed side effects. Therefore the author would not recommend standard pre-treatment with misoprostol.[38]

Carolyn Swenson, MD, from the Department of Obstetrics and Gynecology, University of Utah, Salt Lake City, and colleagues published the results of their randomized study in the August issue of Obstetrics and Gynecology. The results of the study do not support the routine use of misoprostol before IUD insertion in nulliparous women.[39]

Latest FDA approved drug information systems July 24 2012 cited that misoprostol is not helpful for IUD Insertion. It does not ease intrauterine device (IUD) insertion or reduce patient-perceived pain in nulliparous women, according to a new randomized controlled trial. Alternative methods to decrease pain and ease insertion in this patient population should be explored.[40]

Misoprostol prior to endometrial sampling

A study has shown that oral misoprostol 400 µg caused more uterine cramping and pain in non-pregnant women undergoing office endometrial biopsy when given 3 hours before biopsy attempt. No other cervical effects were noted.[41]

Another study determined if the use of oral misoprostol in women undergoing endometrial biopsy reduces procedural discomfort. The use of 400 µg oral misoprostol 12 hours prior to endometrial biopsy did not reduce procedural discomfort and was associated with more side effects than use of placebo. This finding was noted in all women as well as among subgroups of premenopausal and postmenopausal women.[42]

Adverse effects

Many reports have found that the severity of adverse symptoms (Table 2) after using misoprostol vary considerablyand are often not correlated with dosage, interval of use, or route of administration.[4,16,20,25,29,30] Abnormal vaginal bleeding, lower abdominal pain or uterine cramping, and fever or shivering are the major adverse effects of misoprostol, with nausea, diarrhea, and dizziness the more common minor adverse effects. Various reports indicate that the vaginal route of administration leads to more uterine cramping and abnormal vaginal bleeding com-more uterine cramping and abnormal vaginal bleeding com-bioavailability of misoprostol acid 6 hours after vaginal administration was greater than with oral administration; however, the difference was not significant.[28,44] In conclusion, appropriate use of misoprostol in each patient should be considered individually.

Conclusion

The clinical use of misoprostol for cervical priming in premenopausal women before hysteroscopy is effective in cervical dilatation. Misoprostol does not ease intrauterine device (IUD) insertion or reduce patient-perceived pain in nulliparous women. Although it is a drug that can be replaced to other mechanical cervical dilatation methods which can lead cervical injury during dilatation, creation of false passages and uterine perforations. Given its low cost and ease of administration it has the potential to improve women's health world-wide.

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