Original Article

Brief Overview About Prostaglandins & Misoprostol For Cervical Ripening

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Abstract

Background: Prostaglandins (PG) are a whole family of compounds with a wide spectrum of biologic effect. The first PG effect was discovered in 1930. During artificial insemination to treat sterility in women, it was observed in a number of cases, semen that was injected into the uterine cavity was promptly expelled. However when Ringer's solution was injected , it was retained. In some cases it was noted that semen also caused contraction of human uterine muscle in vitro. Prostaglandin E2 (PGE2): PGE2 has been shown to regulate the synthesis of hydrophilic glycosaminoglycans and increases the activity of elastin, both of which induce cervical ripening by separating and dispersing collagen bundles. The application of PGE2 to the human cervix has been reported to increase collagenase activity in cervical biopsies. In addition, PGE2 modulates the inflammatory response that characterizes cervical ripening and remodeling. commonly used for mid-trimester induction of abortion. Two PGE2 analogues are commercially available and have been investigated for mid-trimester abortion: Dinoprostone (Prostin) and Meteneprost. Only Prostin is FDA approved in the United States as an abortifacient up to 28 weeks' gestation

Keywords: PROSTAGLANDINS, Misoprostol, Cervical Ripening

INTRODUCTION

Prostaglandins (PG) are a whole family of compounds with a wide spectrum of biologic effect. The first PG effect was discovered in 1930. During artificial insemination to treat sterility in women, it was observed in a number of cases, semen that was injected into the uterine cavity was promptly expelled. However, when Ringer's solution was injected, it was retained. In some cases it was noted that semen also caused contraction of human uterine muscle in vitro **(1)**.

Human seminal plasma was discovered to contain a substance that is a powerful vasodilator and can stimulate muscle activity. This acid, lipid-soluble, smooth muscle-stimulating and blood pressure-lowering principle was named prostaglandins, and was shown to consist of highly active, lipid soluble, unsaturated hydroxy acids **(2)**.

Sultan Karim was the first to use PGs for successful induction of labor and abortions, and this clinical application was responsible for a great surge of interest both clinically and in the laboratory. The prostaglandin EP receptor family consists of 4 subtypes: EP1, EP2, EP3, and EP4, each of which has been shown to have a variety of effects. These receptors are G protein-coupled receptors (GPCRs) that mediate smooth muscle cell contractility and relaxation **(3).**

Metabolism

PG metabolism is initiated by 15-hydroxyprostaglandin dehydrogenase (PGDH). PGDH activity is reduced by antiprogestins and cytokines such as IL-1β **(2)**.and in presence of infection **(4)**.

Primary PGs are very rapidly metabolized locally and only appear in the circulation in insignificant amounts. Because of the rapidly half-lives, studies are often performed by measuring the inactive end products, for example, 6-keto-PGF1α, the metabolite of prostacyclin **(5)**.

The inflammatory role of PGs in cervical remodeling

This inflammatory response is characterized by the differentiation of fibroblast cells into activated myofibroblasts, an influx of inflammatory cells into the cervix, increased expression of inflammatory cytokines, and increased production of MMPs. Key inflammatory mediators include IL-8, IL-1, TNF-α, and PGHS-2 (leading to increased prostaglandin synthesis). Other cytokines involved in cervical remodeling include IL-6, platelet-activating factor (PAF), and monocyte chemoattractant protein-1 (MCP-

1) **(6).**
IL-8, a critical mediator of cervical remodeling, is produced by numerous types of cervical cells, including endocervical epithelial cells, cervical stromal fibroblasts, leukocytes, and macrophages. IL-8 production is believed to begin in cervical stromal cells and is augmented through the recruitment of numerous immune cells that produce IL-8 and its receptors after activation by IL-8. IL-8 has two key functions: to induce neutrophil activation and migration, and to cause degranulation, releasing collagenase. **(7).**
Studies have shown that TNF-α and IL-1β act on prostanoid biosynthesis at multiple points in a coordinated fashion. These cytokines have been shown to increase the expression of PGHS-2 and subsequently increase the production of prostaglandins at various tissue sites during pregnancy. High doses of IL-6 have also been shown in amnion and decidua tissue to stimulate the production of prostaglandins. **(7).**
Evidence suggests that there is a positive feedback mechanism between prostaglandins and the inflammatory cytokines released by infiltrating leukocytes during cervical remodeling. For example, outside the uterus, a synergy may exist between PGE2 and IL-8 to facilitate the recruitment of neutrophils. Moreover, PGE2 can upregulate IL-8 release in a dose-dependent manner. **(8).**
PGE2 may also stimulate vasodilation and increase vascular permeability for IL-8-directed recruitment of neutrophils. In addition, myometrial cell cultures indicate that proinflammatory cytokines may upregulate prostaglandin receptors, such as EP4. The proinflammatory cytokine IL-1β has also been shown to facilitate cervical ripening by inducing progesterone metabolism in cervical fibroblasts, leading to functional progesterone withdrawal **(8).**
In a study of post-term women who received dinoprostone for cervical priming post-term, the influx of leukocytes as assessed by leukocyte common antigen (CD45) was strongest in women who responded to therapy and significantly lower in women who did not respond. Cervical leukocyte influx was intermediate in women who achieved labor spontaneously. **(9).**

Types of prostaglandins involved in cervical ripening

§ Prostaglandin E2 (PGE2): PGE2 has been shown to regulate the synthesis of hydrophilic glycosaminoglycans and increases the activity of elastin, both of which induce cervical ripening by separating and dispersing collagen bundles. The application of PGE2 to the human cervix has been reported to increase collagenase activity in cervical biopsies. In addition, PGE2 modulates the inflammatory response that characterizes cervical ripening and remodeling. commonly used for mid-trimester induction of abortion. Two PGE2 analogues are commercially available and have been investigated for mid-trimester abortion: Dinoprostone (Prostin) and Meteneprost. Only Prostin is FDA approved in the United States as an abortifacient up to 28 weeks' gestation. Dinoprostone is a synthetic preparation chemically identical to PGE2 that is delivered by cervical gel or vaginal insert and provides sufficient quantities of PGE2 to local tissues to induce cervical ripening. **(7).**
Common side effects from PGE2 include nausea, emesis, fever, diarrhea, and headache. Also hypotension can occur, but it is uncommon. The addition of an antipyretics (acetaminophen) as aprophylactic treatment regimen is useful **(10)**.

§ Prostaglandin F2α (PGFα): Naturally occurring PGF2α was initially approved in the United States in 1973, then it had been withdrawn by the manufacturer from the market. In the US the native PGF2α has been replaced by a long-acting methylated form (carboprost). It is the only other commercially available PG that is FDA-approved in the US as abortifacient agent at 13-20 weeks of gestation **(11)**.
Common side effects associated with it include vomiting, diarrhea, fever, flushing, and hypotension. Also bronchoconstriction can occur in susceptible patients **(11)**.

§ Prostaglandin E1 (PGE1) series (Alprostadil): They are potent uterotonic agent with tolerable side effects. Two PGE1 analogues are commercially available and have been evaluated for mid-trimester induction of abortion: misoprostol (Cytotec®) and gameprost. **(12)**.

Misoprostol

Definition

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE1) is a synthetic prostaglandin E1 analogue. It was developed in 1973 by Searle for the treatment and prevention of gastric ulcers because of its gastric acid anti-secretory properties and its various mucosal protective properties. It has become an important drug in obstetric and gynecological practice because of its uterotonic and cervical priming action. Its clinical applications include medical abortion, medical evacuation for miscarriages, cervical priming before surgical procedure and induction of labor and management of postpartum hemorrhage **(13).**

Forms

Misoprostol is approved in most countries under the brand name Cytotec® (Pfizer, NY, USA). The tablets are produced for oral use and contain either 100 or 200 µg of misoprostol. More recently 25 µg tablets for vaginal use have been approved in Brazil and Egypt for labor induction (Vagiprost®) **(2)**.

Arthrotec (Pfizer, NY, USA) is further development of Cytotec and in addition to misoprostol, it also contains diclofenac. In some places Arthrotec is now replacing cytotec as the source of misoprostol. The included doses of diclofenac vary and must be considered in order not to exceed recommended maximal intake **(2)**.

Structure and chemistry

Fig. 1 shows the structures of misoprostol and the naturally occurring prostaglandin E1. The naturally occurring prostaglandin E series was discovered to inhibit gastric acid secretion. However, naturally occurring prostaglandins have three drawbacks that hindered their clinical application. These problems were:

- Rapid metabolism resulting in a lack of oral activity and a short duration of action when given parenterally,
- Numerous side effects, and
- Chemical instability leading to a short shelf life.

(7).

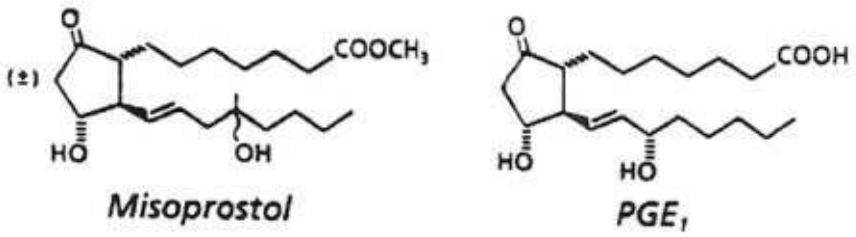

Fig. 1:The structure of misoprostol and naturally occurring prostaglandin (PGE1) **(7).**

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 at 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 C-16 and the addition of a methyl group at C-16 improves oral activity, increases the duration of action, and improves the safety profile of the drug**.** However, the compound was still chemically unstable at room temperature. This problem was solved by the dispersion of misoprostol in hydroxyl-propyl-methyl-cellulosa **(14)**.

Pharmacokinetics

Misoprostol is extensively absorbed and undergoes rapid de-esterification by the liver to form the free acid (Misoprostol acid, MPA), which is responsible for its clinical activity. Unlike the parent compound, it is detectable in plasma. Misoprostol tablets were developed to be used orally. Other routes of administration, however, including vaginal, sublingual, buccal and rectal, have also been used extensively in obstetric and gynecological applications. Over the past decade there have been a number of studies looking at the pharmacokinetic profile of various routes of administration of misoprostol. Three pharmacokinetic properties, the peak concentration, time to peak concentration and the area under the serum concentration versus time curve were studied. The time to peak concentration (Tmax) represents how rapidly the drug can be absorbed; the peak concentration (Cmax) reflects how well the drug is being absorbed while the area under the serum concentration versus time curve (AUC, equivalent to bioavailability) denotes the total exposure to the drug **(15).**

Different routes of administration of misoprostol

Oral route:

Earlier studies focused exclusively on the pharmacokinetic properties of misoprostol after oral administration. Most of these studies reported the pharmacokinetic profile after a single dose of misoprostol. After oral administration, misoprostol is rapidly and almost completely absorbed from the gastrointestinal tract. However, the drug undergoes extensive and rapid first-pass metabolism (de-esterification) to form MPA, the principal and active metabolite of the drug **(2)**.

Following a single dose of 400 µg oral misoprostol, the plasma misoprostol level increases rapidly and peak at about 30 minutes. However, the plasma level declines rapidly by 120 minutes and remains low thereafter **(16)**.

Vaginal route:

It was discovered and proven by clinical studies that vaginal administration was more effective than oral administration in medical abortion. It was performed the first pharmacokinetic study comparing oral and vaginal routes of administration. In contrast to the oral route, the plasma concentration after vaginal administration increases gradually, reaching maximum level after 70-80 minutes. It then slowly declines, with detectable drug levels present up to 6 hours after administration. The peak concentration reached following oral administration is higher than that following vaginal administration **(17).**

Although the peak concentration after oral administration is higher than for vaginal administration, the 'area under the curve' is higher when given vaginally. The greater bioavailability of vaginal misoprostol may help to explain why it is more effective in medical abortion. Due to its clinical efficacy, vaginal misoprostol is widely used off label. However, the misoprostol tablet was not manufactured and developed for use by routes other than the oral one. The uterine contractions after 400 µg vaginally administered misoprostol varies between different studies **(18)**.

The mean peak serum levels in a recent study were 2.7 times higher than mean peak levels in earlier studies. This means that the absorption of misoprostol when using the vaginal route is less consistent than that of the oral route **(18)**.

In clinical practice, remnants of tablets are commonly identified hours after vaginal administration, indicating that the absorption is variable and incomplete. This may be due to variations in the amount and pH value of the vaginal discharge in different women. Variations in the amount of bleeding during medical abortion may also affect the absorption of misoprostol through the vaginal mucosa **(18).**
Numerous attempts have been made to improve the absorption of vaginal misoprostol. The addition of water to the misoprostol tablets is a common practice. However, the bioavailability of vaginal misoprostol was not improved significantly by this practice, indicating that adding water to the tablets may not in fact improve absorption **(18)**.
Drawbacks of vaginal administration include the fact that tablets may, as mentioned above, be found in the vagina during an examination. Studies have also shown that a majority of women prefer the oral route of administration as being more private and convenient. Alternative routes of administration have therefore been sought **(2)**.

Sublingual route:
Recently, sublingual administration of misoprostol has been studied for medical abortion and cervical priming. The misoprostol tablet is very soluble and can be dissolved in 20 minutes when it is put under the tongue **(7).**
the clinical effect of sublingual administration of misoprostol (the tablet is held under the tongue to dissolve) was investigated in two pilot studies with promising results. Following pre-treatment with 200 mg mifepristone, 800 µg misoprostol were administered sublingually, Complete abortion occurred in 94% of treated women. In the second pilot study, sublingual misoprostol was used for termination of pregnancy up to 12 weeks and showed an 86% abortion rate and 97.7% acceptability **(2)**.
A pharmacokinetic study showed that sublingual and oral administration produce the quickest increase in MPA when compared with vaginal administration. The systemic bioavailability as measured by the AUC and the peak concentration were also highest following sublingual misoprostol when compared to other routes **(7).**

Buccal route:
At about the same time as the studies on sublingual misoprostol were initiated, the buccal route was described. The drug is placed between the teeth and the cheek and allowed to be absorbed through the buccal mucosa. Clinical studies are limited compared to other routes. However they have shown that the buccal route is also effective for early medical abortion, cervical priming and labour induction **(19)**.

The shape of the absorption curve is very similar to that of the vaginal route, although the serum drug levels attained are lower throughout the 6-hour study period **(16)**.

The T_{max} is reached 75 minutes after buccal administration, which is similar to that after vaginal administration. The AUC for buccal administration is however only half that seen after vaginal administration **(2)**.

Rectal route:
Rectal administration has been studied for the management of postpartum hemorrhage. This route of administration is less commonly used for other applications, such as medical abortion, cervical priming or labor induction. The shape of the absorption curve after rectal administration is similar to that seen after vaginal administration, although the AUC for vaginal administration is 3 times that seen after rectal administration (**2)**.

Effects of misoprostol on the uterus and the cervix

The uterotonic and cervical softening effects of misoprostol in the female genital tract were originally regarded as side-effects rather than therapeutic effects when misoprostol was first introduced. However, it is precisely these effects that nowadays make misoprostol so widely applicable and used in daily obstetric and gynecological practice **(2)**.

Uterus:

The typical effect of a single dose of oral misoprostol is an increase in uterine tonus. 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 labor **(2)**.

The effect of vaginal administration of a single dose of misoprostol on uterine contractility is initially similar to that of oral administration in the increase in uterine tonus. However, after 1-2 hours, regular uterine contractions appear and they last at least up to 4 hours after administration. The development of regular contractions after vaginal administration may explain the better clinical efficacy of vaginal administration when compared to oral administration **(20)**.

Uses of Misoprostol in Obstetrics and Gynaecology

In cervical ripening

Misoprostol was found to be safe and effective agent for cervical ripening as a part of labor induction. It is effective when used intravaginally, or orally for cervical ripening and induction of labor, although there is a high rate of uterine tachysystole. When misoprostol is used prior to surgical abortion, cervical priming has been shown to result in a shorter operation time, reduced blood loss and easier mechanical dilation. Cervical priming may also reduce the incidence of complications during the procedure and is therefore recommended in a number of guidelines. A variety of procedures and agents have been studied with the aim of developing a simple, safe and less traumatic method of preparing the cervix prior to dilation and vacuum aspiration. Misoprostol has several advantages over other priming agents, such as osmotic dilators, other prostaglandins and mifepristone **(21)**

Misoprostol was evaluated in perimenopausal woman for effectiveness and safety prior to hysteroscopy in achieving cervical dilatation and reducing complications including cervical laceration. It appeared to be promising as a cervical ripening agent prior to hysteroscopy. In postmenopausal women, it was different with misoprostol. As its efficacy is limited probably due to estrogen deficit, misoprostol treatment alone is not effective to get cervical priming in postmenopausal women and pretreatment with local estrogen overcome the failure **(22)**.

In labor Induction

Misoprostol tablets, administered orally and vaginally, are used for the induction of labour or cervical ripening, but are not currently approved by Health Canada for this indication The usual dose is 50 mcg orally or 25 mcg vaginally, which may be repeated every 4 hours if contractions are absent or not painful **(23)**.

In medically induced abortion (Medication Abortion)

Misoprostol alone has also been studied for medical abortion in terms of effectiveness and safety. The effectiveness of misoprostol alone is lower, the time to complete abortion is prolonged, and the abortion process is more painful , require higher doses of misoprostol and associated with higher rates of gastrointestinal side-effects than when misoprostol is combined with mifepristone**.** the combination is highly effective, resulting in complete abortion in more than 95% of women through 63 days of gestation and 93% between 64 and 70 days (**19)**. A recent randomized study showed that pre-treatment with mifepristone prior to misoprostol administration leads to better outcome and reduces the need for subsequent uterine evacuation for retained products of conception **(24).** However, mifepristone is costly and is unavailable in many settings

In post-partum hemorrhage

Misoprostol has been used both as prevention and treatment of postpartum hemorrhage secondary to its uterotonic properties. Several randomized controlled trials and a large prospective observational study have examined the use of misoprostol as an agent for the prevention of postpartum hemorrhage. There are insufficient data to support the use of misoprostol as a primary preventive measure for postpartum hemorrhage when conventional injectable uterotonics (such as oxytocin and/or methylergotomine) are available as part of the management of the third stage of labor **(25)**

Misoprostol has also not yet been found to be better than oxytocin or ergotamine in well-controlled, randomized trials for the treatment of postpartum hemorrhage**.** However, it remains an important option for treating postpartum hemorrhage when other agents are not available or fail **(25)**

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