REVIEW ARTICLE

UPDATE ON THE USE OF MISOPROSTOL IN CURRENT OBSTETRIC PRACTICE.

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SUMMARY:

Misoprostol is one of the most important drugs in obstetric practice today. However, because of its uterotonic effects and consequent adverse effects on the pregnant uterus and foetus, the use of this drug requires extreme caution and very close monitoring particularly in developing countries. The aim of this update is to review the pharmacokinetics and the physiology of misoprostol and to familiarise fellow practitioners with information and evidence concerning this medication as it is currently available for use in obstetric practice.

KEY WORDS: Misoprostol update - Current obstetric practice.

MISE A JOUR SUR L'UTILISATION DE MISOPROSTOL EN OBSTETRIQUE.

RESUME:

Misoprostol est l'un des médicaments le plus important dans la pratique courante en obstétrique. Mais à cause de ses effets utérotoniques et ses conséquences néfastes sur l'utérus gravide et le fétus, l'utilisation de ce médicament demande des précautions extrêmes et des monitorings attentifs surtout dans les pays en voie de développement. Cette mise à jour a pour but de rappeler la pharmacocinétique et la physiologie de misoprostol et de fournir aux confrères médecins les informations et les évidences concernant l'utilisation de ce produit en obstétrique.

MOTS CLES: Mise à jour sur misoprostol - Pratique courante en obstétrique.

I- INTRODUCTION

Misoprostol (Cytotec®) is a synthetic prostaglandin E_1 analogue that is used in the treatment of active gastric and duodenal ulcers and in the prevention and treatment of gastric ulcers associated with the use of anti-inflammatory non- steroidal agents [1]. However, because of its uterotonic and cervical ripening actions, misoprostol has become a very useful drug in obstetrics and gynaecology. Misoprostol is currently in wide use in Cameroon although there is yet no licence by the Ministry of Public health for its use. The aim of this update is to familiarise fellow practitioners with information and evidence concerning misoprostol as it is currently recommended for use in obstetric practice.

Misoprostol is used in obstetrics and gynaecology for elective medical abortions, evacuation of the uterus in cases of missed abortions or intra-uterine deaths, induction of labour and in the prevention and treatment of postpartum haemorrhage.

II- PHARMOKINETICS

Misoprostol is available for oral, vaginal and rectal use in the form of 100ì g unscored and 200ì g scored tablets in the United States. However, in Cameroon only the 200ì g form is available and it is manufactured by Monsato France SA (Division Searle). After oral administration, misoprostol is rapidly absorbed and converted to its pharmacologically active metabolite, misoprostol acid. The plasma concentration of misoprostol reaches its peak within 30 minutes but rapidly declines thereafter [2]. Concomitant ingestion of foods or antacids decrease the bioavailability of misoprostol after oral ingestion. It is primarily metabolised in the liver but less than 1% of misoprostol acid is excreted in urine [3]. Misoprostol has no known drug interactions and does not induce the hepatic cytochrome P-450 enzyme system. Therefore whilst patients with liver disease should be given a reduced dose of the drug when necessary, patients with renal impairment who are not on dialysis do not require dose adjustments [3].

The side effects of misoprostol are dose dependent and they include nausea, vomiting, diarrhoea,

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abdominal pains, chills, shivering and fever. Unlike other prostaglandins (E_2 and $E_{2á}$), misoprostol does not cause myocardial infarction [4]. There is not much known about the toxicity of misoprostol. The evidence so far seems to suggest that misoprostol can only be toxic at extremely high doses. For instance, cumulative doses of up to 2200ì g administered over a period of 12 hours have been tolerated by pregnant women without any serious adverse effects [5]. However, it has been shown that 6000ì g of misoprostol, taken orally to induce an abortion (in conjunction with trifluoperazine), could result in abortion, hyperthermia, rhabdomyolysis, hypoxaemia, and a complex acid-base disorder [6].

III- PHYSIOLOGY

Taken orally, misoprostol increases the activities of the reproductive tract. However when administered vaginally, these adverse effects are greatly reduced [7-8]. When misoprostol tablets are placed in the posterior fornix of the vagina, plasma concentrations of misoprostol acid peak in one to two hours and thereafter decline slowly over 3 to 4 hours [2]. It has been shown that whereas uterine contractility initiated after an oral dose plateaus after one hour, uterine contractility increases continuously for 4 hours after vaginal administration. In fact, maximal uterine contractility has been shown to be significantly higher after vaginal than after oral administration [7].

IV- TERATOGENICITY

Mobius' syndrome (congenital facial paralysis) and limb defects have been reported in the infants of some women, who took misoprostol during the first trimester in an unsuccessful attempt to induce abortion [9,10]. However, the absolute risk of Mobius' syndrome is probably low among all women exposed to misoprostol in the first trimester [10]. Other possible teratogenic effects of misoprostol include transverse limb defects, ring-shaped constrictions of the extremities, arthrogryposis, hydrocephalus, holoprosenphaly and extrophy of the bladder [11].

It is worth mentioning that other drugs used in combination with misoprostol for induction of abortion in the first trimester may also be teratogenic. Such teratogenic effects have been found to be more commonly associated with methotrexate than with mifepristone or misoprostol [12] and include craniofacial and digital anomalies [13,14].

V- INDICATIONS

1- Use of misoprostol in the first trimester of pregnancy

- Misoprostol in the management of first trimester abortions

Misoprostol is used extensively in the first trimester of pregnancy in combination with either mifepristone or methotrexate for medical abortions. The role of mifepristone or methotrexate in first trimester pregnancy terminations is to 'destabilise' the ongoing pregnancy whilst that of misoprostol is to expel the products of conception. Various oral combination regimens of mifepristone given at variable intervals followed by misoprostol have been described [15-19]. In general, misoprostol is more effective in inducing abortions in the first trimester when administered vaginally than orally [20]. In fact, some of these regimens have been self-administered at home with equal efficacy [21]. When methotrexate is used instead of mifepristone, the rate of complete abortion is often lower and there is often a need for repeated doses [22-23]. The majority of studies on medical abortions in the first trimester with either mifepristone or methotrexate and misoprostol have been carried out on women who were no more than 63 days pregnant. The younger the pregnancy, the higher the rate of complete abortion [17,19,23,24]. Misoprostol alone is much less effective in inducing first trimester abortions [25,26]. The effectiveness of vaginal misoprostol regimens in achieving complete abortion in the first trimester is not affected by whether the tablets are moistened or dry [27]. Given the inconsistency of complete abortion rates when vaginal misoprostol is used alone, as well as the existence of safe alternative regimens, it is not recommended for medical abortions in the first trimester [28].

- Misoprostol in the management of failed pregnancies and missed abortions

Failed pregnancies are mainly cases of blighted ova. In such cases and in cases of missed abortions, the pregnancy is already destabilised and the physiological changes that eventually lead to a spontaneous expulsion are under way (such as placental degeneration and decidual sloughing). If spontaneous abortion is delayed, drug therapy may be indicated to evacuate the uterus in order to avoid surgery or prolonged wait for expulsion. Misoprostol alone is sufficient and effective in evacuating the uterus in such cases [29-31].

It has been shown that 400ì g of misoprostol given orally or 800ì g administered vaginally in 2 doses with 24 to 48 hours interval between the two doses is sufficient to completely evacuate the uterus in most cases of failed pregnancies without excessive bleeding [29]. Misoprostol has also been shown to be useful for the treatment of incomplete abortions [32]. However, medical evacuation of the uterus in cases of incomplete abortions is associated with considerable blood loss when compared with surgical evacuations [32]. For this reason misoprostol is not recommended for the treatment of inevitable or incomplete abortion [28].

- The role of misoprostol in the ripening the cervix prior to surgical abortions

Ripening the cervix prior to surgical abortions in the first trimester significantly reduces the risk of cervical lacerations and perforation of the uterus at the time of abortion [33, 34]. Four hundred micrograms of misoprostol inserted vaginally has been shown to be more effective than oral misoprostol in ripening the cervix before abortions [35]. Doses higher than 400ì g have been shown to be associated with more side effects such as fever, vaginal bleeding and products of conception clogging the cervical os [35]. The best regimen for cervical ripening in the first trimester is 400ì g inserted vaginally 3 to 4 hours before suction evacuation [28].

2- Use of misoprostol in the second trimester of pregnancy

A pregnancy in the second trimester may be terminated for maternal medical reasons, severe foetal abnormalities, foetal deaths and electively. The uterus can be emptied early in the second trimester by suction evacuation. However, in late second trimester, the uterus can only be emptied by cervical dilatation and extraction of the foetus or by induction of labour. Misoprostol can ripen the cervix and can also induce labour during the second trimester of pregnancy [36,37]. In general, the uterus becomes more sensitive to uterotonic agents as the gestational age increases. For instance, a dose of misoprostol may be sufficient to induce labour in the second but not in the first half of the second trimester. It has been noticed that inductions tend to proceed more rapidly when the foetus is dead than when labour is induced for other reasons [38,39].

During the first trimester, up to 800ì g of vaginal misoprostol is required to successfully induce an abortion. In the third trimester, doses in the range of 25 to 50ì g induce labour. However in the second trimester, the dose of misoprostol required to induce labour probably lies somewhere between 50 and 800µg. Within this range, higher doses may be needed to cause abortions early in the second trimester, whereas lower doses may be sufficient later in the second trimester.

Using the usual regimen for induction of labour in the second trimester of 200ì g of misoprostol given vaginally every 12 hours, the rate of successful abortion is more than 71% [38-40]. Increasing the frequency of misoprostol administration does not increase the efficacy. However, when doses of 400ì g of misoprostol is administered vaginally every 3 hours (up to a maximum of 5 doses within 24 hours) yields a better result of over 91% complete abortion within 48 hours [41]. Increasing the vaginal dose of misoprostol to 600µg with the aim of improving the rate of complete abortion is associated with higher rates of adverse effects such as fever, nausea, vomiting and diarrhoea [40].

The risk of uterine rupture associated with induction of labour with misoprostol in the second trimester is not known because most trials of misoprostol for induction of labour in the second trimester have excluded women with uterine scars. However, uterine rupture can occur whether the uterus has been previously scarred or not. For instance, uterine rupture during induction of labour with misoprostol has been reported in a primigravida with no previous uterine scar [42]. Although the optimal regimen has not been determined, it appears that 200 to 600ì g of misoprostol given vaginally every 12 hours or 400ì g given vaginally every 3 hours successfully induces labour in the second trimester [28]. Such inductions are more successful if mifepristone is given 36 to 48 hours before misoprostol [5,43,44]. The evidence in support of the use of misoprostol to induce labour in the second trimester in the presence of a previous scar is insufficient to recommend its routine use [28].

3- The role of misoprostol in the third trimester of pregnancy

- Misoprostol and induction of labour when the foetus is viable

Studies have shown that misoprostol given vaginally for induction of labour at term is superior to placebo in ripening the uterine cervix [45,46]. Similarly, misoprostol alone is effective for inducing labour at term but its major limiting factor is uterine hyper stimulation with associated foetal heart rate changes often resulting in caesarean section with (or without) adverse foetal and/or maternal outcomes [47,48]. The truth is that adverse outcomes associated with misoprostol use at term are so few that that the relative risk of adverse outcomes with the use of misoprostol for induction of labour remains unknown [28].

Concerning a safe (in terms of rate of uterine hyper stimulation with foetal heart rate changes, caesarean delivery rate, Apgar scores, admissions into neonatal intensive care unit and passage of

meconium) and effective (induction-delivery interval) dose and regimen of misoprostol for induction of labour at term when the foetus is viable seems to be 25ì g administered vaginally every four to six hours [28,49].

- Misoprostol and induction of labour in cases of intra-uterine deaths

Misoprostol is particularly suitable for inducing labour in cases of intra-uterine deaths because there is no concern about the adverse effects of uterine hyper stimulation on the foetus. It has been shown that a dose of 100ìg administered vaginally every 12 hours is very adequate [50,51]. However, a slightly higher dose (200ìg) may be necessary early in the third trimester. In fact, for intra-uterine deaths at term, a dose as low as 50ìg administered intra-vaginally every 12 hours may be quite sufficient.

- Misoprostol and induction of labour in women with previous caesarean delivery

There have been several reports of uterine rupture associated with the administration of misoprostol for induction of labour in women attempting vaginal delivery after previous caesarean section [52-55]. In fact, one randomised trial to induce labour in women with one previous caesarean scar using 25µg of misoprostol inserted vaginally had to be discontinued because uterine rupture occurred in two women in the misoprostol group [53]. A similar disastrous result was noted in a case control study in which 5.6 % of symptomatic uterine rupture was noted in the control as against 0.2% in the study group which was undergoing a trial of labour without the administration of misoprostol ($p<0.001$) [56]. Notably in that study, there was no uterine rupture in any of the women who had undergone caesarean delivery after labour had begun spontaneously.

It is still not clear why the uterus ruptures in the presence of a previous scar when misoprostol is used. Does the use of misoprostol per se in such circumstances increase the frequency of uterine rupture or would uterine rupture occur when any other drug is used to induce labour when the cervix is unfavourable? In fact, until the answers to such questions as these are found and misoprostol is proved safe, misoprostol should not be used to induce labour in the presence of previous uterine scars [28].

- Misoprostol and the control of postpartum haemorrhage

Because of its uterotonic effects, there have been attempts to use misoprostol to prevent and treat postpartum haemorrhage. In a prospective observational study involving 237 women, 600ì g of misoprostol given orally just after clamping the umbilical cord was associated with an estimated blood loss of 500 ml or more in 6% of women; none of the women had blood loss of 1000 ml or more [57]. Subsequently, three randomised trials involving a total of 1115 women examined the efficacy of misoprostol in the prevention of postpartum haemorrhage [58-60]. These trials evaluated a dose of 400ì g of misoprostol given rectally or a dose of 400 to 600ì g given orally. The frequency of postpartum haemorrhage (defined as blood loss >1000 ml) was not lower in the misoprostol group than in the control group in any of the trials. However, in all three trials (two of which were blinded), oxytocin was given to more women in the control groups [58-60]. Thus there is currently insufficient evidence to support the routine use of misoprostol to prevent postpartum haemorrhage when oxytocin and methergin are available, but misoprostol may lower the incidence of postpartum haemorrhage if these drugs are not readily available [28].

VI- CONCLUSION

Misoprostol is one of the most important drugs in obstetric practice today. However, because of its uterotonic effects and consequent adverse effects on the pregnant uterus and foetus, the use of this drug requires caution and very close monitoring particularly in developing countries [61,62].

VII- RECOMMENDATIONS

Misoprostol is currently in use in Cameroon without license from the Ministry of Public Health. However, data from clinical trials provide strong and consistent support for its use in obstetric practice. On the basis of available evidence, misoprostol should be used as follows:

- In the first trimester of pregnancy, vaginal misoprostol alone should not be used for medical abortions unless it is associated with either mifepristone or methotrexate.
- Vaginal misoprostol alone is sufficient and effective in evacuating the uterus in cases of failed pregnancies (blighted ovum) during the first trimester. However, it is not recommended for evacuating the uterus in cases of inevitable or incomplete abortions.
- Misoprostol administered vaginally is suitable for ripening the cervix prior to surgical evacuation of the uterus in the first trimester.
- Misoprostol alone administered vaginally is sufficient and effective in evacuating the uterus in cases of missed abortions in the second trimester. However, the evidence in support of its use to induce labour in the second trimester in the presence of a previous scar is insufficient at the moment to recommend its routine use for this purpose.

- Misoprostol is recommended for induction of labour at term when the foetus is viable. The safe and effective dose recommended is 25ìg inserted vaginally every 4 to 6 hours until labour is well established; up to a maximum of 6 doses.
- Misoprostol is particularly suitable for inducing labour in cases of intra-uterine deaths at term. A dose as low as 50ìg administered vaginally every 12 hours has been found to be quite adequate.
- Since it is not clear why the uterus tends to rupture when misoprostol is used to induce labour in the presence of a previous uterine scar, it should not be used to induce labour in the presence of previous uterine scars.
- There is currently insufficient evidence to support the routine use of misoprostol to prevent postpartum haemorrhage when oxytocin and methergin are available, but misoprostol may lower the incidence of postpartum haemorrhage if these drugs are not readily available■

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