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Pharmacokinetic profiles up to 12 h after administration of vaginal, sublingual and slow-release oral misoprostol

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BACKGROUND: It has been shown that the route of administration of misoprostol has a strong impact on the pharmacokinetic profile and result in different clinical efficacy. No study has so far evaluated the pharmacokinetics beyond 6 hours. Furthermore a new slow-release misoprostol formulation was included in the study. METHODS: Pharmacokinetics of a novel slow-release (SR) oral misoprostol was compared during 12 h after administration to conventional misoprostol administered vaginally or sublingually. Thirty-three women requesting surgical abortion up to 12 weeks were randomly allocated to groups receiving a single dose of 400 μg conventional misoprostol administered vaginally or sublingually or 800 μg SR oral misoprostol. Blood samples were taken before (0 h) and 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h after misoprostol administration. Misoprostol acid (MPA) was determined in serum samples using liquid chromatography/tandem mass spectrometry. RESULTS: Three women did not complete the study. Serum concentrations reached their highest level following sublingual misoprostol ($P < 0.0001$) and the time to peak concentration was shortest for this group ($P = 0.0094$). The area under the curve (AUC) up to 12 h was greater following sublingual treatment than for the other alternatives ($P < 0.0001$) and lowest for SR misoprostol. Cumulative serum levels of MPA did not increase beyond 6 h following sublingual and vaginal administration, while they continued to increase up to 12 h following SR misoprostol. CONCLUSIONS: The new SR form of misoprostol demonstrated lower peak levels and a lower AUC but longer lasting elevation in serum levels when compared to conventional misoprostol administered sublingually or vaginally. SR misoprostol may offer an alternative to repeated administration of conventional misoprostol.

Keywords: induced abortion; misoprostol; pharmacokinetics; slow release

Introduction

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE1) is a synthetic prostaglandin (PG) E1 analogue, developed because of its gastric acid anti-secretory properties and its various mucosal protective properties for the prevention and treatment of the ulcerogenic effects of non-steroidal anti-inflammatory drugs (Watkinson *et al.*, 1988). Misoprostol has the advantages of being cheap, widely available and stable at room temperature when compared to other PG analogues (Scheepers *et al.*, 1999). It has become a very important drug in obstetric and gynaecological practice because of its uterotonic and cervical priming action.

Misoprostol has been extensively studied in reproductive health (Goldberg *et al.*, 2001; Blanchard *et al.*, 2002) and is widely recommended for indications such as induced abortion, treatment of incomplete miscarriage and dilatation of the cervix prior to surgical abortion. It also shows considerable promise in terms of the prevention and treatment of postpartum hemorrhage, as well as for labour induction. Misoprostol is available in tablets containing 200 μg misoprostol (Cytotec®, Pfizer, USA), produced and approved for oral use. The dose used therapeutically for ulcer treatment is 400–800 μg daily. The same doses are also used when combined with mifepristone for termination of early pregnancy and dilatation of the cervix prior to vacuum aspiration.

For termination of early pregnancy, oral administration of misoprostol in combination with mifepristone (Mifegyne, Exelgyn, Paris, France) is effective if the duration of

amenorrhea is less than 50 days (Medical methods for termination of pregnancy, WHO technical report series 871, 1997, Geneva, World Health Organization). Beyond this gestational age, clinical data indicate that oral misoprostol is less effective (Mc Kinley *et al.*, 1993). In contrast, vaginal application is highly effective even after 49 days of amenorrhoea (El Refaey *et al.*, 1995). Other routes of administration besides the oral one have therefore been studied, especially the vaginal and sublingual, as well as the buccal and rectal routes. The vaginal route has been use extensively in obstetric and gynaecological applications. Differences in efficacy depending on the administration route can probably be explained by pharmacological data and by studies of uterine contractility (Gemzell-Danielsson *et al.*, 1999; Tang *et al.*, 2002; Aronsson *et al.*, 2004).

There are only a few studies of the pharmacokinetic profiles of misoprostol depending on the administration route. After a single oral dose, 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 misoprostol acid (MPA), the principal active metabolite of the drug. Following 400 μg oral misoprostol administration, the Serum misoprostol level increases rapidly and peaks at about 30 min. However, the Serum level declines rapidly by 120 min after intake and remains low thereafter (Robert *et al.*, 1967; Zieman *et al.*, 1997; Tang *et al.*, 2002; Khan *et al.*, 2004).

In contrast to the oral route, vaginal administration results in Serum concentrations that increase gradually, reaching a maximum level after 70–80 min and slowly declining, with detectable levels of MPA remaining 6 h after administration (Zieman *et al.*, 1997). The peak concentration (Cmax) achieved is lower than following oral administration but bioavailability, measured as the area under the curve (AUC) of Serum MPA, is significantly greater after vaginal administration. The greater bioavailability of vaginal misoprostol may help to explain why vaginal administration is more effective in inducing uterine contractions (Gemzell-Danielsson *et al.*, 1999).

An increasingly common alternative is to administer misoprostol sublingually. Pharmacokinetic studies (Tang *et al.*, 2002) show a rapid rise to peak Serum level and a sustained elevation in MPA, resulting in a bioavailability that is higher than for the vaginal route. This results in the development of uterine contractility similar to that seen with vaginal treatment (Aronsson *et al.*, 2004). However, although vaginal absorption has been shown to be slower and the Cmax achieved by the vaginal route is lower than that of the other routes of administration, the serum level of misoprostol is sustained for as long as, or possibly for longer than, with sublingual misoprostol. Furthermore, the effect on uterine contractility following sublingual administration seems to last for a shorter time than with vaginal administration (Tang *et al.*, 2002; Aronsson *et al.*, 2004). The effect of misoprostol may linger for >6 h after a single dose administered vaginally.

Recently, a new formulation of slow-release (SR) misoprostol was described (Chen *et al.*, 2000). SR misoprostol resulted in lower Serum levels of MPA, but also in longer duration of elevated levels compared to conventional oral misoprostol (Fiala *et al.*, 2005a). The effect on uterine contractility was shown to be more pronounced following SR misoprostol compared to conventional oral administration, with a development of uterine contractions similar to that observed for vaginal or sublingual administration (Fiala *et al.*, 2005b).

So far, the pharmacokinetic profiles of conventional and SR misoprostol resulting from different administration routes have not been studied beyond 6 h. Since, the effects of vaginal and sublingual misoprostol are similar and more pronounced than for oral misoprostol, it seems that it is the sustained plasma levels, rather than the high peak plasma concentration, that are crucial to efficacy.

The aim of the present study is to evaluate Serum levels of MPA up to 12 h after administration of conventional misoprostol, given either vaginally and sublingually, and oral SR misoprostol. The doses studied were the reference doses of 400 μg conventional misoprostol and 800 μg SR misoprostol used in previous studies.

Materials and Methods

Study group

The study was performed at the Department of Woman and Child Health, Division for Obstetrics and Gynaecology, Karolinska University Hospital, Stockholm, Sweden during the period from March to August 2006. Healthy women $\geq$18 years with a viable intrauterine pregnancy of up to 12 weeks (47–83 days) of gestation who had requested termination of pregnancy by vacuum aspiration were asked to participate. All eligible women gave written informed consent before entering the study. The study was approved by the Karolinska University Hospital Ethics Committee.

Exclusion criteria were asthma or any other contraindication to PG therapy (e.g. a history of allergic reaction to PG), breastfeeding or inability to understand the information provided. The patient's medical history was taken and gestational length according to last menstruation period was confirmed with the help of gynaecological examination and vaginal ultrasound. Screening for genital infection was performed on all patients according to clinical routines.

Experimental protocol

After giving their informed consent, eligible women were allocated randomly to the three treatment groups using computer generated random tables and numbered, sealed, opaque envelopes opened consecutively. The participants were allocated to receive a single dose of either two tablets misoprostol (Cytotec® 200 μg) administered sublingually or vaginally, or two tablets SR misoprostol (400 μg/tablet) administered orally.

The women were admitted to hospital in the morning after fasting overnight. Following the insertion of an i.v. 18-gauge catheter suitable for repeated blood sampling, preferably into the antecubital vein, a baseline blood sample was obtained and the envelope with the treatment dosage and administration route was opened.

The SR misoprostol tablets were swallowed with a small amount of water. Women allocated to vaginal misoprostol treatment inserted the tablets intravaginally themselves. All treatment was handed out to the participants in accordance with randomization routines by a research nurse who had been thoroughly informed about the study in advance. All other staff and investigators were unaware of the type of treatment given to the women. The women were not blinded to the route of administration.

Venous blood samples (10 ml) were taken before treatment (0 or baseline test) and up to 12 h after treatment at 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h after administration of misoprostol. The blood samples were immediately cooled in a refrigerator at +6°C for 30–60 min and thereafter centrifuged in a cooled centrifuge for 10 min at 1430*g*. The Serum was then drawn from the blood samples and stored at below −20°C until further analyses. Vacuum aspiration was performed according to clinical routine 3 h after misoprostol treatment. The women then remained at the research clinic until 12 h after initial misoprostol treatment. Pulse, blood pressure and temperature were measured repeatedly and side-effects such as nausea, abdominal pain, skin rash or diarrhoea were recorded, as well as any analgesics given.

Sample analysis

The samples were sent for analysis to the Department of Pediatrics, Philipps University Marburg. Based on a former published gas chromatography/tandem mass spectrometry (GC-MS/MS) method, MPA was measured in Serum samples using a modified liquid chromatography (LC)-MS/MS isotope dilution assay (Watzer *et al.*, 2002). After addition of 15(S)-15-methyl PGE2 (15-methyl-PGE2) as internal standard, MPA was extracted using a monolithic reversed phase cartridge. After consecutive clean-ups, the prostanoids were eluted with diisopropyl ether. The dried and reconstituted sample was determined by LC-MS/MS using the molecular ions [M]− as precursor in the negative ion electrospray ionization mode. The product ions used for quantification were [M-2H2O-C6H10-H] for MPA and [M-2H2O-CO2-C7H12-H] for 15-methyl-PGE2. The extraction recovery for MPA was about 95%. The limit of detection was 1 pg/ml MPA in serum samples. The correlation coefficients of the linear calibration graphs for MPA were $r > 0.998$ in the 10–1000 pg/ml range for the tested matrix. For the spiked quality control standards of MPA, the inter-day precision ranged from 4.3 to 9.7%, with an inter-day accuracy (relative error) between −8.7 and 7.2%. The intra-day precision and relative error of MPA ranged from 4.2–6.2% and between −7.3 and 6.9%, respectively.

The primary objectives of the study were to determine MPA Serum concentration and AUC up to 720 min after administration of misoprostol, Cmax of MPA and time to peak concentration (Tmax). The area under the MPA concentration curve was calculated according to the trapezoidal method. The AUC was divided into trapezium segments according to the time intervals of blood sampling. The area of each segment was computed according to the following formula for the calculation of trapezium area: 0.5 [Cx + Cx − 1] [time interval], x = 1 − 10. The AUC_{720} was calculated by summation of the trapezium segments.

The difference in the AUC was used to calculate the sample size (Tang *et al.*, 2002). In previous studies, Serum levels of MPA have been followed for a maximum of 6 h following intake (Tang *et al.*, 2002; Fiala *et al.*, 2005b). One previous study has shown that the AUC_{360} was 433 ± 183 pg h/ml for vaginal misoprostol (Tang *et al.*, 2002). Ten subjects in each group would thus result in 80% power to detect a difference of 243 pg h/ml in AUC_{360} at a 5% level of significance. To compensate for any potential dropping out, 11 women were recruited to each group.

Statistical analysis

Kruskal–Wallis tests were used to test the overall difference between the three groups. If the overall difference was significant, Wilcoxon two-sample tests were used to test pair-wise differences. $P < 0.05$ (two-tailed) was considered statistically significant. *P*-values were not corrected for multiple comparisons. However, all stated differences remained significant ($P < 0.05$) after applying Bonferroni–Holm correction (Holm, 1979). Statistical analyses were performed by PROC NPAR1WAY (exact tests) in SAS software (SAS Institute Inc., 1997).

Results

A total of 38 women requested surgical termination of pregnancy during the study period and met the inclusion criteria (Fig. 1). Of these, five women did not wish to participate in the study. Their reasons for declining were either that they were "not interested in participating in any research studies" or "not able to stay for 12 h after misoprostol administration". Thirty-three women agreed to participate in the study and were randomly allocated to receive treatment. Three women did not complete the study. Two of them did not want to continue with the study after 0.5 and 8 h, and one dropped out after 3 h

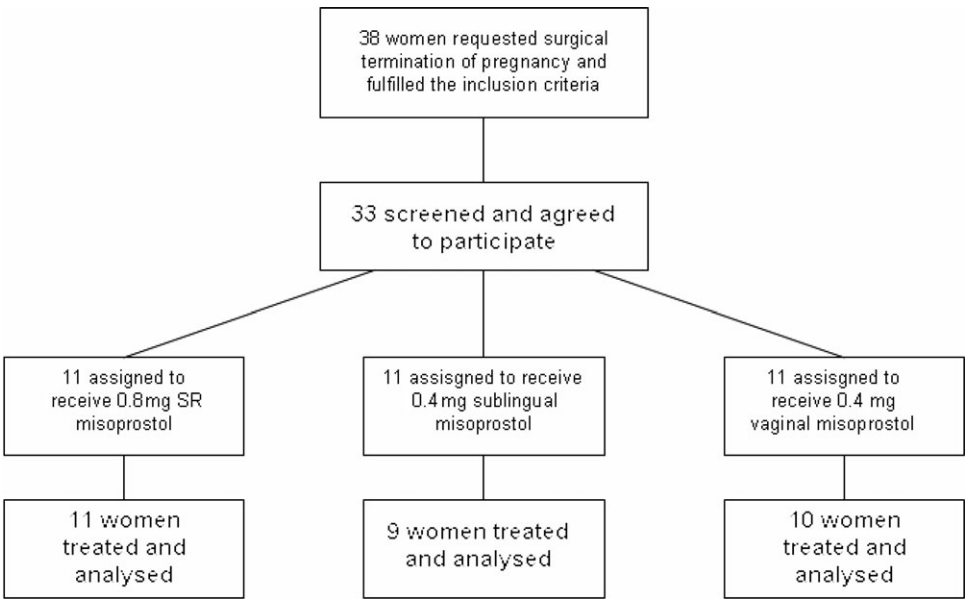

Figure 1: Study flow chart

Table 1: Patient characteristics

Misoprostol dose and route	800 μg SR oral	400 μg sublingual	400 μg vaginal	*P*-value
Age (years)	22 (20–43)	24 (20–42)	32 (21–40)	0.30
Parity	0 (0–5)	2 (0–3)	0.5 (0–4)	0.42
Gestational length (days of amenorrhoea)	65 (48–83)	69 (46–77)	71.5 (53–78)	0.52
BMI	21.3 (17.5–31.8)	22.6 (20.3–27.1)	22.2 (19.7–27.9)	0.74
Body surface area	1.68 (1.56–2.03)	1.68 (1.57–1.87)	1.72 (1.57–1.94)	0.84

Values are median (range); *P*-values by Kruskal–Wallis test; SR, slow release.

because of problems with the i.v. catheter. The remaining 30 women completed the 12 h blood sampling: 11 of these were in the SR oral misoprostol group, 9 in the sublingual misoprostol group and 10 in the vaginal misoprostol group.

The clinical characteristics of the patients are shown in Table 1. Women in the three groups did not differ significantly in terms of age, number of pregnancies, parity, gestational age, height, weight or body mass index (BMI). Gestational length for all women was 46–83 days and the median number of pregnancies was 3 (range 1–8), while parity was 0 (range 0–5).

The mean serum concentrations of MPA after administration of 400 μg sublingual or vaginal misoprostol or 800 μg SR oral misoprostol are shown in Fig. 2. A number of pharmacokinetic parameters were studied, namely the Cmax, Tmax and AUC_{720} (Table 2). The individual variability of these pharmacokinetic parameters was denoted by the coefficient of variation.

The Cmax and Tmax differed significantly between the three groups. Treatment with sublingually administered misoprostol resulted in the earliest serum Cmax of MPA (Fig. 2; Table 2). Sublingual administration also resulted in the highest Cmax, which was significantly higher than the peak levels following SR misoprostol or vaginal administration of misoprostol ($P < 0.0001$).

The Tmax of MPA was significantly shorter following sublingual administration compared to SR administration ($P = 0.0379$) and vaginal administration ($P = 0.0027$). Treatment with vaginal and SR misoprostol resulted in plasma peaks of MPA 1.6–1.7 h after administration.

Although MPA Serum levels remained elevated for a shorter time following sublingual administration than the two other administration routes, the AUC_{720} in the sublingual misoprostol group was significantly larger than in the vaginal and SR oral misoprostol groups ($P < 0.0001$) (Fig. 2). A significant difference was also found between the two latter groups, with higher levels for the AUC in the vaginal misoprostol group ($P = 0.043$).

Serum MPA levels following SR misoprostol administration remained elevated for up to 12 h. Starting 5–6 h after administration of misoprostol, Serum levels of MPA in the SR group exceeded those in the other groups. The cumulative AUC for the sublingual and vaginal groups did not continue to rise after 6 h (Fig. 3).

No clinically significant changes occurred in blood pressure or body temperature. The only side-effects reported were abdominal pain, nausea and vomiting. Four women reported pain, three in the SR oral misoprostol group and one in the vaginal misoprostol group. These women received pain treatment with paracetamol and ibuprofen. The pain was regarded as mild or moderate. Only one woman reported nausea (after 3 h) and one woman vomited 2 h after administration. These women were both in the SR misoprostol group. They were not excluded from the analysis.

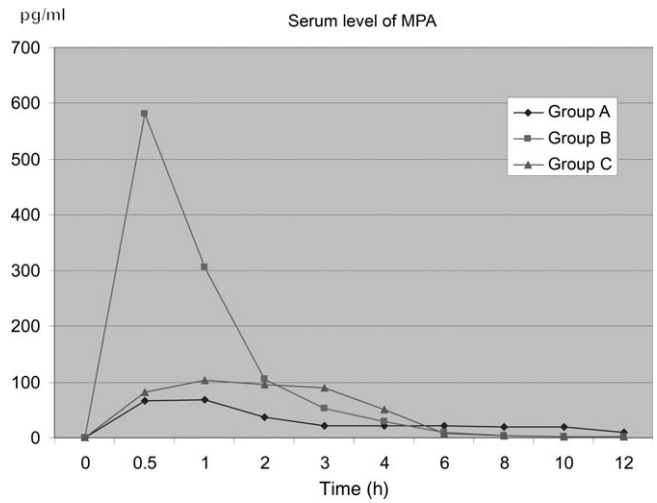

Figure 2: Mean Serum concentrations of MPA over time. A, slow release; B, sublingual; C, vaginal

Discussion

To the best of our knowledge, no previous studies have measured Serum levels beyond 6 h after a single dose of misoprostol. In this study, we evaluated certain pharmacokinetic parameters (plasma concentration, Tmax and bioavailability measured as the AUC) of 800 μg SR misoprostol given orally and 400 μg conventional misoprostol given sublingually or vaginally. The study covered a period of 12 h following administration.

As found in a previous study, sublingual administration of misoprostol achieved the highest Serum levels, reaching its peak level faster than vaginal administration (Tang *et al.*, 2002). In the present study, Serum levels following sublingual misoprostol were lower compared to vaginal administration 2 h after treatment. A tendency towards shorter duration of elevated Serum levels was also observed in the previous study (Tang *et al.*, 2002). This corresponds well with our observations on uterine contractility (Aronsson *et al.*, 2004).

Table 2: Pharmacokinetic parameters of the three routes of misoprostol administration

Misoprostol dose and route	800 μg SR, $n = 11$	400 μg sublingual, $n = 9$	400 μg vaginal, $n = 10$	P-value[a]
Cmax of MPA (pg/ml)				
Mean ± SD	78.8 ± 51.1	580 ± 178.1	117.7 ± 42.1	<0.0001[b]
CV	64.8	30.7	35.8	
Tmax (hours)				
Mean ± SD	1.6 ± 2.8	0.5 ± 0	1.7 ± 1.2	0.0094[c]
CV	175	0	70.6	
AUC_{720} (pg h/ml)				
Mean ± SD	301.5 ± 105.8	757.8 ± 200.5	414.6 ± 128.2	<0.0001[d]
CV	35.8	26.5	30.9	

[a]Kruskal–Wallis test. Overall comparison between the three groups; [b]Cmax was significantly higher in the 400 μg sublingual group than in the 800 μg SR and the 400 μg vaginal group ($P < 0.0001$). In the vaginal group, it was significantly higher than in the SR group ($P = 0.0242$); [c]Tmax was significantly shorter for the 400 μg sublingual group compared to the 800 μg SR group ($P = 0.0379$) and for the 400 μg vaginal group ($P = 0.0027$). There was no significant difference between the SR and vaginal groups; [d]The AUC_{720} was significantly greater for the 400 μg sublingual group compared to the 800 μg SR and 400 μg vaginal groups ($P < 0.0001$). The AUC_{720} was significantly greater in the vaginal group than in the SR group ($P = 0.043$); [b–d]Wilcoxon two-sample test; CV, coefficient of variation (%).

Compared with vaginal administration, sublingual misoprostol resulted in a faster onset of contractions. However, the effect was shorter lasting and uterine contractility tended to decrease at 2.5 h after 400 μg given sublingually. A shorter lasting effect for the sublingual route is in agreement with clinical data (Tang *et al.*, 2004). When misoprostol was used alone to induce second-trimester abortion, the effect seemed to be more pronounced following vaginal administration as compared with sublingual administration.

Bioavailability, measured as the AUC_{720}, was greater in the sublingual group compared to the other groups, and lowest following oral SR misoprostol. Oral SR misoprostol intake resulted in lower Serum levels and a later plasma peak of MPA. Interestingly, however, it was noted that starting 5–6 h after misoprostol administration, Serum levels of MPA in the SR group exceeded those in the other groups and the cumulative AUC for the sublingual and vaginal groups did not continue to rise after 6 h.

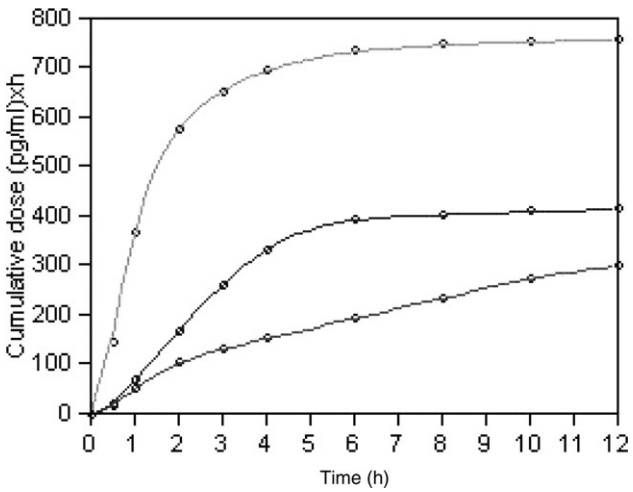

Figure 3: Cumulative dose of misoprostol (pg/ml) by time Curves showing the result of sublingual administration (green), vaginal administration (purple) and slow-release misoprostol (red)

The SR form of misoprostol was recently formulated and described (Chen *et al.*, 2000). In an earlier study, we showed a dose-dependent effect of orally administered SR misoprostol on uterine contractility (Fiala *et al.*, 2005a). While 400 μg conventional misoprostol was used as the reference dose in previous studies of pharmacokinetics and uterine contractility, *in vitro* data indicate that a higher dose of SR misoprostol is needed to reach adequate Serum levels (Chen *et al.*, 2000). Indeed, our previous *in vivo* data show that 800 μg SR misoprostol gave rise to a significantly higher bioavailability of MPA compared to 400 μg misoprostol. It also had a pronounced effect on uterine contractility, while the lower dose was almost without effect (Fiala *et al.*, 2005 a, b). We therefore decided to make a further investigation of the effect of 800 μg SR misoprostol, which resulted in the present study. Conventional orally administered misoprostol was not included for comparison, since earlier pharmacokinetic studies have shown that plasma levels of MPA drop to 2% of the peak value within 6 hours following oral administration (Zieman *et al.*, 1997; Gemzell-Danielsson *et al.*, 1999; Tang *et al.*, 2002; Khan *et al.*, 2004).

The vaginal route of misoprostol administration has previously been demonstrated to result in higher efficacy than the oral route in medical abortion (El-Refaey *et al.*, 1995. Following vaginal administration, the time to peak Serum levels of MPA occurs later and the peak is lower compared to both oral and sublingual administration. The maximum Serum concentration is lower but bioavailability, measured as the AUC, is higher following vaginal administration than following oral misoprostol. This could explain the differences in efficacy. However, the sublingual misoprostol route has been shown to have the highest AUC. In spite of this, however, sublingual misoprostol does not seem to be more effective than vaginal misoprostol (Tang *et al.*, 2004).

A direct vagina-to-uterus transport was recently described for progesterone absorption (Cicinelli *et al.*, 2000a, b). A similar mechanism may exist for misoprostol absorption and could also explain the more favourable clinical effects using vaginal

administration, as compared with sublingual administration. However, a recent study comparing the buccal and vaginal routes indicates that this may not be the only explanation (Meckstroth *et al.*, 2006). Interestingly, while the effects on uterine contractility were similar, the AUC for buccal misoprostol was only 50% of the AUC for vaginal misoprostol. So far, the clinical data on buccal misoprostol remain too limited for any conclusions to be drawn concerning its efficacy compared to vaginal and sublingual administration.

Based on the results of our previous study, it seems that a certain, and so far unknown, threshold must be reached before uterine contractions can be initiated (Fiala *et al.*, 2005b). In a previous study of 400 μg SR misoprostol, MPA reached very low Serum levels and had only a minor effect on uterine contractility in contrast to a higher dose of 800 μg (Fiala *et al.*, a, b). Furthermore, the same doses of buccal and vaginal misoprostol result in different maximum serum levels and AUC but yield a similar effect on uterine contractility (Meckstroth *et al.*, 2006). The duration of Serum levels above this possible unknown threshold seems to be more important than the absolute level of MPA or the AUC. Oral treatment with misoprostol leads to a high but short-lived peak of MPA, which does not generate uterine contractions. On the other hand, regular uterine contractions are seen after treatment with SR misoprostol despite lower serum levels of MPA and a lower AUC compared to vaginal misoprostol. The elevation of MPA also lasts longer with SR misoprostol.

On the other hand, the incidence of side-effects seems to be associated with high Serum levels of MPA. Conventional oral misoprostol results in a rapid and short-lived Serum peak after intake. This is even more pronounced for the sublingual route (Tang *et al.*, 2002; Hamoda et al., 2004). Oral, and particularly sublingual, misoprostol also lead to the highest reported incidence of side-effects (El-Refaey *et al.*, 1995; Hamoda *et al.*, 2004). The present study was too small to allow proper comparison of side-effects, which appeared to be similar in the three groups. Furthermore, women were not blinded to the route of administration which could have introduced bias regarding the experienced side-effects.

Whether removing the vaginal tablet remnants affects absorption and at which time point absorption can be considered to be finished is not know. In the present study, the time between inserting the tablets and vacuum aspiration was kept constant at about 3 h. No vaginal cleansing was performed prior to the vacuum aspiration according to the clinical routine and remaining tablets were not actively removed. However, a theoretical effect of the vaginal intervention on absorption after 3 h cannot be excluded.

Taken together, the available data indicate that while the peak MPA Serum levels seems to correlate with the incidence of side-effects, the duration of elevated Serum levels seems to correlate with the effect on uterine contractility. A certain threshold level of MPA is needed, but once reached, the duration of elevated MPA over this critical threshold seems to be the most important parameter. Prolonged stimulation of the uterus seems to be needed to overcome the progesterone block, which normally prevents uterine contractions (Csapo, 1956).

In conclusion, SR oral misoprostol showed a lower AUC and lower peak Serum level but exceeded those of the other routes more than 6 h after intake. Our results so far indicate that SR oral misoprostol could be an effective alternative to other routes, providing elevated Serum levels up to at least 12 h after administration. Whether the pharmacokinetic data and effects on uterine contractility correspond to high clinical efficacy remains to be shown. The optimal dose of the SR formula needs further assessment and should be followed by assessment of its feasibility, efficacy and acceptability in clinical studies compared to that of the standard misoprostol formula.

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References

Aronsson A, Bygdeman M, Gemzell-Danielsson K. Effects of Misoprostol on uterine contractility following different routes of administration. *Hum Reprod* 2004;**19**:81–84.

Blanchard K, Clark S, Coyaji K *et al.* Misoprostol for wome's health: a review. *Obstet Gynecol* 2002;**99**:316–332.

Chen D, Tsay R-J, Lin H-I *et al.* Stabilization and sustained-release effect of misoprostol with metharylate copolymer. *Int J Pharm* 2000;**203**:141–148.

Cicinelli C, De Ziegler D, Bulletti C *et al.* Direct transport of progesterone from vagina to uterus. *Obstet Gynecol* 2000b;**95**:403–406.

Cicinelli C, Schonauer LM, Galantino P *et al.* Mechanisms of uterine specifity of vaginal progesterone. *Hum Reprod* 2000a;**15**:159–165.

Csapo A. Progesterone block. *Am J Anat* 1956;**98**:273–291.

El-Refaey H, Rajasekar D, Abdalla M *et al.* Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol. *N Eng J Med* 1995;**332**:983–987.

Fiala C, Aronsson A, Granath F *et al.* Pharmacokinetics of a novel oral slow-release form of misoprostol. *Hum Reprod* 2005b;**20**:3414–3418.

Fiala C, Aronsson A, Stephansson O *et al.* Effects of slow release misoprostol on uterine contractility in early pregnancy. *Hum Reprod* 2005a;**20**:2648–2652.

Gemzell-Danielsson K, Marions L, Rodriguez A *et al.* Comparison between oral and vaginal administration of misoprostol on uterine contractility. *Obstet Gynaecol* 1999;**93**:275–280.

Goldberg AB, Greenberg MB, Darney PD. Misoprostol and pregnancy. *N Engl J Med* 2001;**344**:38–47.

Hamoda H, Ashok PW, Flett GM *et al.* A randomized controlled comparison of sublingual and vaginal administration of misoprostol for cervical priming before first-trimester surgical abortion. *Am J Obstet Gynecol* 2004;**190**:55–59.

Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat* 1979;**6**:65–70.

Khan R, El-Refaey H, Sharma S *et al.* Oral, rectal and vaginal pharmacokinetics of misoprostol. *Obstet Gynaecol* 2004;**103**:866–870.

Mc Kinley C, Thong KJ, Baird DT. The effect of dose of mifepristone and gestation on the efficacy of medical abortion with mifepristone and misoprostol. *Hum Reprod* 1993;**8**:1502–1505.

Meckstroth KR, Whitaker AK, Bertisch S *et al.* Misoprostol administered by epithelial routes. *Obstet Gynaecol* 2006;**108**:582–590.

Robert A, Nezamis JE, Phillips JP. Inhibition of gastric secretion by prostaglandins. *Am J Dig Dis* 1967;**12**:1073–1076.

SAS Institute Inc. SAS/STATTM Software: SAS Institute Inc., Cary, NC, 1997.

Scheepers HC, van Erp EJ, van den Bergh AS. Use of misoprostol in first and second trimester abortion: a review. Obstet Gynecol Surv 1999;**54**:592–600.

Tang OS, Lau WNT, Chan CCW *et al.* A prospective randomized comparison of sublingual and vaginal misoprostol in second trimester termination of pregnancy. *BJOG* 2004;**111**:1001–1005.

Tang OS, Schweer H, Seyberth HW *et al.* Pharmacokinetics of different routes of administration of misoprostol. *Hum Reprod* 2002;**17**:332–336.

Watkinson G, Hopkins A, Akbar FA. The therapeutic efficacy of misoprostol in peptic ulcer disease. *Postgrad Med J* 1988;**64**:60–77.

Watzer B, Seyberth HW, Schweer H. Determination of misoprostol free acid in human breast milk and serum by gas chromotography/negative ion chemical ionization tandem mass spectrometry. *J Mass Spectrom* 2002;**37**:927–933.

World Health Organization. Medical methods for termination of pregnancy, WHO technical report series 871, 1997.

Zieman M, Fong SK, Benowitz NL *et al.* Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol* 1997;**90**:88–92.

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