

A randomized comparison of pharmacokinetics of a single vaginal dose of dry misoprostol or misoprostol moistened with normal saline or with acetic acid

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BACKGROUND: The pharmacokinetics of vaginal misoprostol as a dry tablet or as a tablet moistened with normal saline or with acetic acid were studied.

METHODS: For this study, 42 women requesting termination of pregnancy at gestational age of <12 weeks were recruited and received 400 µg vaginal misoprostol tablets. They were randomized into three groups: (i) dry tablets, (ii) tablets moistened with 3 ml of normal saline and (iii) tablets moistened with 3 ml of 5% acetic acid. Venous blood samples were taken at 0, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330 and 360 min after misoprostol administration. Misoprostol acid (MPA) was determined in serum samples using gas chromatography/tandem mass spectrometry.

RESULTS: The serum peak MPA concentration (C_{\max}) was significantly higher and the time-to-peak concentration (T_{\max}) was significantly shorter in the normal saline and acetic acid groups, when compared with the dry tablet group. Both areas under the curve at 240 and 360 min (AUC_{240} and AUC_{360}) of the normal saline and acetic acid groups were also significantly greater than that of the dry tablet group. The coefficients of variation in C_{\max} and T_{\max} were highest in the normal saline group, while that of AUC_{240} and AUC_{360} were highest in the dry tablet group. The C_{\max} was significantly higher in subjects in the dry tablet group with vaginal pH < 5 than in those with pH 5. There were no significant differences in other pharmacokinetic parameters between subjects with vaginal pH < 5 and those with vaginal pH 5 in all three groups.

CONCLUSIONS: Vaginal misoprostol tablets moistened with normal saline or 5% acetic acid achieved better absorption than the dry tablet. The use of vaginal misoprostol tablets moistened with normal saline or 5% acetic acid would potentially improve the clinical efficacy of misoprostol.

HKClinicalTrials.com registration: HKCTR-821.

Key words: acetic acid / normal saline / pharmacokinetics / vaginal misoprostol

Introduction

Misoprostol, a synthetic analogue of naturally occurring prostaglandin E_1 , was originally manufactured for oral use in the treatment of gastric ulcers (www.pfizer.co.uk). This drug is now commonly used for

termination of pregnancy (Tang *et al.*, 2003, 2004, 2005), cervical ripening (Singh *et al.*, 1999), induction of labour (Sanchez-Ramos *et al.*, 2002) and treating post-partum haemorrhage (Hofmeyr *et al.*, 2009). It is considered to be the drug of choice in both first and second trimester termination of pregnancy (von Hertzen *et al.*, 2007; Lee *et al.*, 2010).

Misoprostol can be given through various routes, namely oral, sublingual, buccal, vaginal or rectal. When it is used for termination of pregnancy in the first trimester, the complete abortion rate with the vaginal route is higher than that with the oral route (El-Refaey et al., 1995), but comparable to those with the sublingual (Tang et al., 2003) or buccal routes (Middleton et al., 2005). In termination of pregnancy in the second trimester, the vaginal route is more effective than the oral or sublingual route (Tang et al., 2004; von Hertzen et al., 2007). Some investigators have suggested that the use of normal saline or acetic acid to moisten the vaginal tablets may improve the absorption of misoprostol and further increase the success of pregnancy termination. However, the results of these clinical studies are not consistent (Creinin et al., 1999; Singh et al., 1999; Sanchez-Ramos et al., 2002; Gilles et al., 2004; Kelekci et al., 2004; Yilmaz et al., 2005, 2007; Pongsatha and Tongsong, 2008, 2011). A study on the pharmacokinetics of vaginal misoprostol moistened with normal saline or with acetic acid may shed light on the rationale of such approach.

A pharmacokinetic study demonstrated that misoprostol given in the sublingual route achieved a significantly higher serum peak concentration of misoprostol acid (MPA) than those of the oral and vaginal routes, while the area under the MPA concentration versus time curve (AUC) was significantly higher in the sublingual route when compared with the oral or vaginal route, but comparable to the vaginal route moistened with water (Tang et al., 2002). Abd-El-Maeboud et al. (2008) studied the effect of vaginal pH on the efficacy of vaginal misoprostol tablets moistened with 3 ml of 5% acetic acid for medical evacuation of second trimester miscarriages and found a significantly shorter induction-to-abortion interval, significantly higher abortion rate, significantly lower dose of misoprostol and significantly lower incidence of side effects in women with upper vaginal pH of <5, when compared with those whose pH was 5.

The pharmacokinetics of misoprostol when used as dry tablets or as tablets moistened with normal saline or with acetic acid has not yet been studied. The aims of this randomized study were to compare the pharmacokinetics of vaginal misoprostol as dry tablets or tablets moistened with normal saline or with 5% acetic acid and the effect of the acidity of upper vagina on the pharmacokinetic parameters.

Materials and Methods

Study population

Women attending Department of Obstetrics and Gynecology, the University of Hong Kong, for legal termination of pregnancy by suction evacuation at gestational age of ≤ 12 weeks were recruited. Women with major medical problems or a known history of allergy to misoprostol were excluded.

Subjects who fulfilled the selection criteria and were willing to participate gave their informed written consent. The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. The study was registered on HKClinicalTrials.com with the trial number HKCTR-821.

Randomization

The subjects were randomized into three groups by a research nurse, who was not involved in the clinical management of patients, according to a computer-generated list with the results placed in opaque envelopes. The insertion of vaginal misoprostol in all subjects was performed by a

designated research nurse. The patients' attending clinicians and laboratory technicians performing the assays were all blinded to the allocation of treatment arms.

Study design and treatment regimen

Menstrual history was recorded and general and vaginal examinations were performed on eligible women to confirm the uterine size corresponding to the gestational age. If there was any doubt, an ultrasound scan was performed to assess the gestational age. As prophylactic antibiotics were given to all patients undergoing surgical termination of pregnancy according to our department protocol, no routine screening for genital tract infection was performed. If there was any sign of infection, namely purulent and foul smelling vaginal discharge, vaginal swabs would be taken. The subjects were asked to fast overnight and admitted into hospital on the morning of the operation. At the beginning of the study, an 18-gauge intravenous catheter was inserted for repeated blood sampling and the upper vaginal wall was tested for the pH before vaginal administration of the misoprostol tablet. A speculum examination was performed and the pH indicator paper (Acilit[®] pH 0.5–5.0 produced by Merck in Germany) was held with an artery forceps against the upper part of the vaginal wall until it became wet.

Subjects were then randomized into three groups: (i) receiving 400 μ g dry misoprostol tablets in the posterior vaginal fornix (dry tablet group), (ii) receiving 400 μ g misoprostol tablets moistened with 3 ml of normal saline before insertion into the posterior vaginal fornix (normal saline group) and (iii) receiving 400 μ g misoprostol tablets moistened with 3 ml of 5% acetic acid before insertion into the posterior vaginal fornix (acetic acid group). For the normal saline group and the acetic acid group, the two tablets of misoprostol were held by fingers which were placed just at the introitus. Then, 3 ml of acetic acid or normal saline were drawn into a syringe and squirted onto the tablets. The tablets were then quickly inserted into the posterior fornix of the vagina. None of our patients received mifepristone.

According to our previous study (Tang et al., 2002), the peak serum level of MPA was achieved after a median time of 60 min following vaginal administration of misoprostol. Venous blood sampling was started before vaginal misoprostol administration, at 15, 30, 45 and 60 min and then every 30 min up to 360 min after vaginal misoprostol administration. When the venous blood samples were taken from the indwelling catheter, the research nurse withdrew 4 ml first and discarded it before taking the blood sample for the assay of MPA. This was to ensure that the assays were not done on the blood which had remained in the catheter after the previous blood sampling. Blood pressure, pulse and side effects were regularly monitored during this period.

Blood samples were centrifuged immediately and the serum samples were stored below -20°C . The samples were sent for analysis to the Department of Pediatrics, Philipps University Marburg. Based on a formerly published gas chromatography/tandem mass spectrometry (MS/MS) method (Tang et al., 2002), MPA was measured using a liquid chromatography (LC)-MS/MS isotope dilution assay. After addition of 15(S)-15-methyl PGE₂ (15-methyl-PGE₂) as the internal standard, MPA was extracted using a monolithic reversed-phase cartridge. After consecutive clean-ups, the prostanooids were eluted with diisopropyl ether. The dried and reconstituted sample was determined by LC-MS/MS using the molecular ions $[\text{M-H}]^{-}$ ($[\text{P}]^{-}$) as precursors in the negative ion electrospray ionization mode. The product ions used for quantification were $[\text{P-2H}_2\text{O-C}_6\text{H}_{10}]^{-}$ for MPA and $[\text{P-2H}_2\text{O-CO}_2\text{-C}_7\text{H}_{12}]^{-}$ for 15-methyl-PGE₂. The extraction recovery for MPA was $\sim 95\%$. The limit of detection was 1 pg/ml MPA in serum samples. The correlation coefficients of the linear calibration graphs for MPA were >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 to 6.2% and from -7.3 to 6.9%, respectively.

Outcome measures

The outcome measures included the peak concentration of MPA (C_{\max}), the time-to-peak concentration (T_{\max}) and the AUC at 240 min (AUC_{240}) and 360 min (AUC_{360}). The primary outcome measure used to calculate the sample size was AUC_{360} .

Statistical analysis

Based on our previous pharmacokinetics study on a single dose of misoprostol (Tang *et al.*, 2002), the AUC_{360} of vaginal misoprostol was 433.7 ± 182.6 pg h/ml. Therefore, 14 subjects in each arm would have 80% power in detecting a 50% difference in bioavailability at a 5% significance level.

The AUC was calculated according to the trapezoidal method: $0.5 [C_x + C_{x-1}] [time\ interval]$, where $x = 1, 2, \dots, 12$. The AUC_{240} and the AUC_{360} were calculated by summing the trapezium segments from time 0 to 240 and 360 min, respectively. The coefficient of variation (CV) was the ratio of the standard deviation over the mean. The higher the number, the higher is the variance.

The Kolmogorov-Smirnov test was used to test the normal distribution of continuous variables. Results of continuous variables were given as the mean \pm SD if normally distributed, and as median (range) if not normally distributed. Statistical comparison was carried out by the Student's *t*-test, Mann-Whitney *U*-test, Wilcoxon signed-rank test and Kruskal-Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, where appropriate. Statistical analysis was performed using the Statistical Program for Social Sciences (SPSS Inc., Version 17.0, Chicago, USA). The two-tailed value of $P < 0.05$ was considered as statistically significant.

Results

Study population

During the study period between 1 April and 31 December 2010, 83 women requesting legal termination of pregnancy were approached and 41 patients were excluded or declined to participate in the study. Thus, 42 subjects were recruited with 14 subjects in each group (Fig. 1).

The demographic and clinical data are shown in Table I. There were no significant differences in age, body height and weight, body surface area, gestational age and upper vaginal pH among the three groups. None of our patients experienced any vaginal bleeding prior to misoprostol administration.

Outcomes

The serum MPA concentrations of the three groups at various time points are shown in Fig. 2. Both the normal saline group and the acetic acid group attained a significantly higher C_{\max} than the dry tablet group (Table II). There was no difference in C_{\max} between the normal saline and acetic acid groups. T_{\max} was significantly shorter in the normal saline [median (range): 45 (15–180) min] and acetic acid groups [37.5 (15–150) min] than in the dry tablet group [90 (45–360) min] ($P = 0.008$). The AUC_{240} and the AUC_{360} are shown in Fig. 3. Both the AUC_{240} and the AUC_{360} of normal saline

and acetic acid groups were significantly higher than those of the dry tablet group (Table II). The CVs of C_{\max} (140.8%) and T_{\max} (80.4%) were highest in the normal saline group, while the CVs of AUC_{240} (61.7%) and AUC_{360} (50.3%) were highest in the dry tablet group.

There were no differences in all the side effects, namely nausea, fever, chills and rigors, abdominal pain and vaginal bleeding, among the three groups (all P -values > 0.05). None of our subjects had clinical evidence of infections.

The association between the pH of the upper vagina before misoprostol insertion and the pharmacokinetic parameters is shown in Table III. In the dry tablet group, the C_{\max} in the subgroup with vaginal pH < 5 was significantly higher than that in the subgroup with pH 5, but there was no significant difference regarding pH in the other pharmacokinetic parameters. In the normal saline and acetic acid groups, there were no significant differences between the two subgroups with different vaginal pH in any of the pharmacokinetic parameters.

Discussion

The use of misoprostol in gynaecological practice is now well established and it is listed as essential medicine by the World Health Organization (WHO; Blum *et al.*, 2010). It was first manufactured as an oral medication to treat gastric ulcer. Although the vaginal absorption of misoprostol varies widely (Zieman *et al.*, 1997; Tang *et al.*, 2002), the vaginal route is one of the most effective routes in inducing abortion in both the first and the second trimesters (El-Refaey *et al.*, 1995; Ho *et al.*, 1997).

After vaginal administration, remnants of misoprostol tablets have often been found in the vagina at the time of repeated dose administration or prior to surgical evacuation (Zieman *et al.*, 1997; Kelekci *et al.*, 2004). The most common strategy in a hope to improve its absorption is to moisten the tablets with normal saline (Singh *et al.*, 1999; Gilles *et al.*, 2004; Yilmaz *et al.*, 2007) or acetic acid (Sanchez-Ramos *et al.*, 2002; Kelekci *et al.*, 2004; Yilmaz *et al.*, 2005; Abd-El-Maeboud *et al.*, 2008; Pongsatha and Tongsong, 2011). However, the results in clinical outcomes have been inconsistent. The majority of the studies have shown non-significant findings. Three studies compared dry misoprostol tablets and tablets moistened with normal saline or water in women for first trimester termination (Creinin *et al.*, 1999) or miscarriage (Gilles *et al.*, 2004) or second trimester abortion (Yilmaz *et al.*, 2007). All clinical outcomes were non-significant. Another two studies reported no difference in treatment outcomes between the dry tablets and tablets moistened with acetic acid in induction of labour (Sanchez-Ramos *et al.*, 2002) or second trimester abortion (Pongsatha and Tongsong, 2011). Two studies comparing misoprostol tablets moistened by acetic acid versus normal saline showed that moistening with acetic acid was associated with significantly greater cervical dilatation before surgical termination of first trimester pregnancy (Kelekci *et al.*, 2004) or shorter induction-to-abortion interval in second trimester abortion (Yilmaz *et al.*, 2005). There was only one study using normal saline or acetic acid to dissolve the misoprostol tablets for cervical priming before surgical termination of pregnancy in the first trimester; it demonstrated no significantly different results in the clinical outcomes in the two groups, including mean cervical dilatation, and pre- and

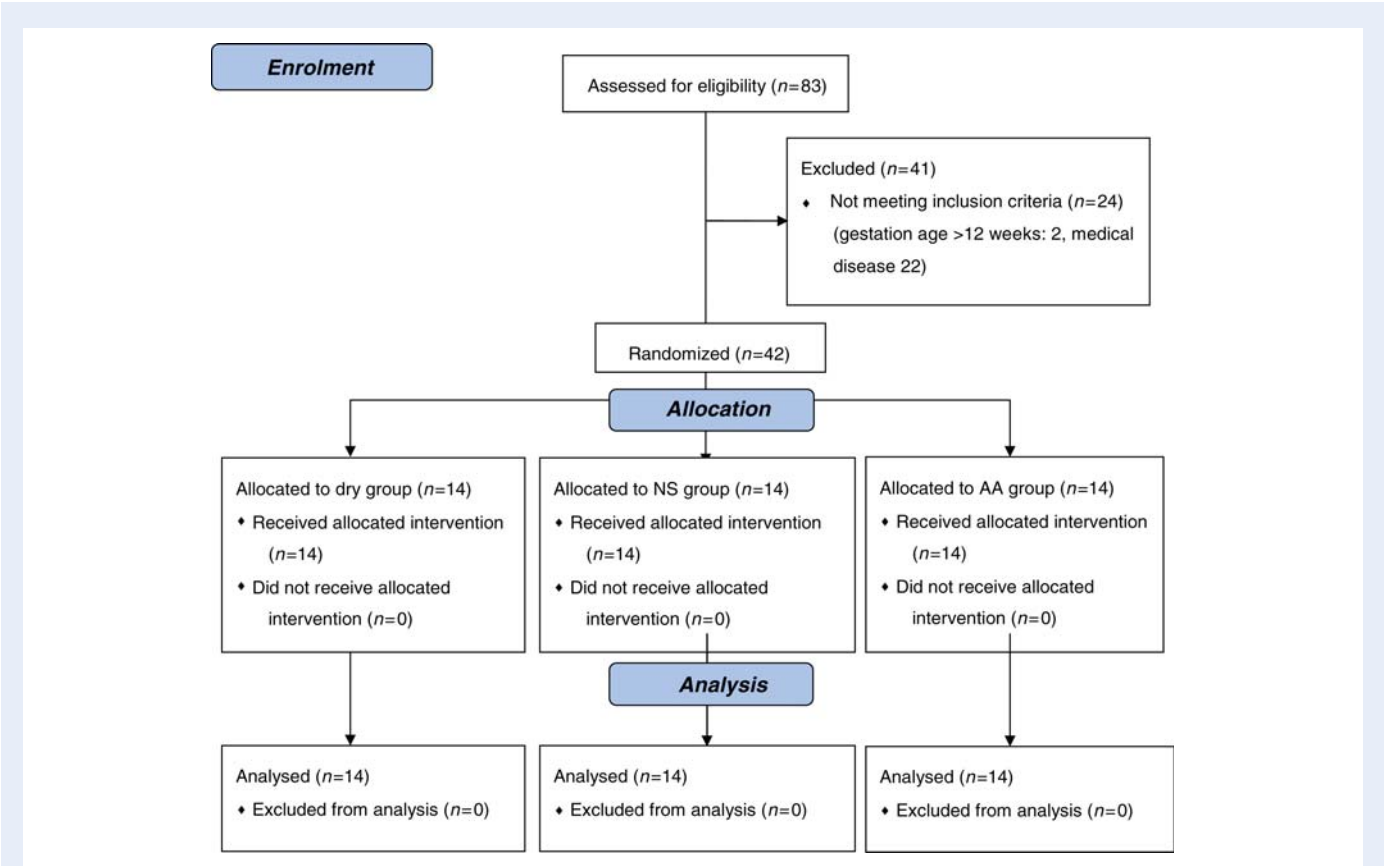


Figure 1 CONSORT flow diagram. Dry group, dry misoprostol group; NS group, misoprostol moistened with 3 ml of normal saline; AA group, misoprostol moistened with 3 ml of 5% acetic acid.

Table 1 Demographic and clinical data.			
	Dry tablet group (n = 14)	Normal saline group (n = 14)	Acetic acid group (n = 14)
Age of women (years)	30.1 ± 5.9	32.1 ± 8.2	30.6 ± 7.8
Height (cm)	158 ± 4.8	159 ± 4.2	158 ± 5.6
Weight (kg)	53.4 ± 6.0	54.8 ± 6.7	55.4 ± 9.3
Body surface area (m ²)	1.53 ± 0.09	1.55 ± 0.10	1.55 ± 0.14
Gestational age (days)	78 ± 8	72 ± 6	74 ± 7
pH of upper vaginal wall ^a	5.0 (4.0–5.0)	5.0 (4.0–5.0)	5.0 (4.0–5.0)

Data are presented as the mean ± SD. All comparisons were non-significant.
^aData presented as median (range).

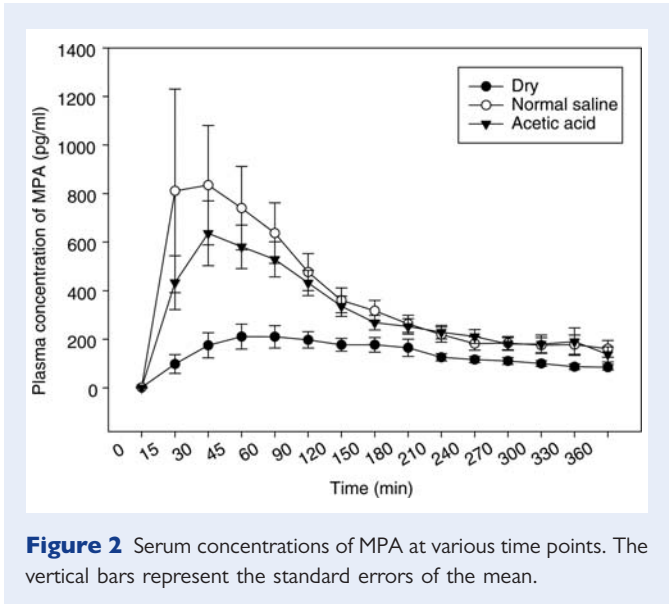


Figure 2 Serum concentrations of MPA at various time points. The vertical bars represent the standard errors of the mean.

intra-operative blood loss (Singh et al., 1999). One group of investigators compared misoprostol gel with dry tablets in second trimester abortion. There was no difference in the abortion rate, induction-to-abortion interval and total dosage of misoprostol, except significantly more chills and diarrhoea in the group using the gel form (Pongsatha and Tongsong, 2008). It should be noted that there has been wide variation in the technique of moistening the tablets. The volume of the fluid used to moisten the tablets varied from 1 ml (Pongsatha and Tongsong, 2011) and 2 ml (Gilles et al., 2004) to 3 ml (Yilmaz et al., 2005). In some studies, the misoprostol

Table II The peak serum concentration (C_{max}), time-to-peak concentration (T_{max}), AUC_{240} and AUC_{360} among the three groups.

	Dry tablet group (n = 14)	Normal saline group (n = 14)	Acetic acid group (n = 14)	P-value
C_{\max} (pg/ml)				
Mean \pm SD	262.6 \pm 201.1	1092.4 \pm 1538.3	703.4 \pm 464.6	<0.001
Median (95% CI)	202 (147–379)	586 (204–1981) ^a	544 (435–972) ^a	
CV (%)	76.6	140.8	66.1	
T_{\max} (min)				
Mean \pm SD	120 \pm 90	56.8 \pm 45.6	52.5 \pm 37.16	0.008
Median (95% CI)	90 (68–172)	45 (31–83) ^b	37.5 (31–74) ^b	
CV (%)	75	80.4	70.7	
AUC_{240} (pg h/ml)				
Mean \pm SD	650.6 \pm 401.6	1699.9 \pm 967	1423.4 \pm 679.8	<0.001
Median (95% CI)	586 (419–883)	1409 (1142–2258) ^c	1162 (1031–1816) ^c	
CV (%)	61.7	56.9	47.8	
AUC_{360} (pg h/ml)				
Mean \pm SD	849.7 \pm 427.0	2054.6 \pm 957.4	1846.8 \pm 844.6	<0.001
Median (95% CI)	764 (603–1096)	1769 (1502–2607) ^d	1590 (1359–2335) ^d	
CV (%)	50.3	46.6	45.7	

CI, confidence interval.

^a C_{max} of normal saline and acetic acid groups were significantly higher than that of the dry tablet group ($P < 0.001$ and $P = 0.001$, respectively).

^b T_{max} of normal saline and acetic acid groups were significantly shorter than that of the dry tablet group ($P = 0.009$ and $P = 0.006$, respectively).

^c AUC_{240} of normal saline and acetic acid groups were significantly higher than that of the dry tablet group ($P < 0.001$ and $P = 0.001$, respectively).

^d AUC_{360} of normal saline and acetic acid groups were significantly higher than that of the dry tablet group ($P < 0.001$ and $P < 0.001$, respectively).

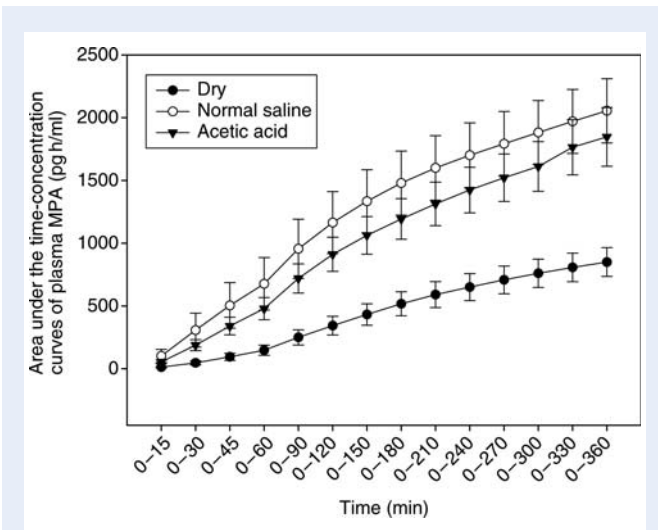


Figure 3 Areas under the time-concentration curves of plasma MPA after misoprostol (dry, moistened with 3 ml of normal saline or 3 ml of 5% acetic acid) administration. The vertical bars represent the standard errors of the mean.

tablets were inserted with the speculum followed by injection of the saline (Gilles *et al.*, 2004), while in some studies, the tablets were moistened with the acetic acid or saline before insertion (Yilmaz *et al.*, 2005). Moreover, the regimen of misoprostol has also varied and the study populations have been heterogeneous.

To the best of our knowledge, this is the first pharmacokinetic study of misoprostol comparing dry tablets and tablets moistened with normal saline or with acetic acid. Serum MPA concentration was significantly higher when the tablets were moistened with normal saline or acetic acid before insertion, when compared with that of the dry tablet group. AUC_{240} and AUC_{360} of both the normal saline and the acetic acid groups were also significantly higher than those of the dry tablet group. These results clearly showed that the absorption of moistened misoprostol is significantly better than that of dry misoprostol tablets.

The comparison of the pharmacokinetic parameters between the normal saline and the acetic acid groups was non-significant. The idea of using acetic acid is based on the fact that misoprostol tablets liquefy better in acidic medium (Karim *et al.*, 1989; Abd-El-Maeboud *et al.*, 2008). However, as shown in our results, the absorption of misoprostol was not improved with the use of acetic acid compared with normal saline. Previous studies comparing the use of normal saline and acetic acid with misoprostol under various clinical conditions showed insignificant findings in some studies (Singh *et al.*, 1999; Pongsatha and Tongsong, 2011), but better results with acetic acid in others (Kelekci *et al.*, 2004; Yilmaz *et al.*, 2005). The CVs of C_{max} and T_{max} in the normal saline group were highest, consistent with a previous study (Tang *et al.*, 2002), indicating that there is wide individual variations in the absorption of misoprostol when the tablets are moistened with normal saline. In addition, there have been significant differences in the techniques of moistening the tablets in different studies, and differences in the study populations and possibly other factors as well, which may explain the differences in results of the various clinical trials.

Table III Correlation between pH of upper vagina and the pharmacokinetic parameters.

	Dry tablet (n = 14)	Normal saline (n = 14)	Acetic acid (n = 14)
C_{\max} (pg/ml)			
pH < 5.0	n = 5, 239 (63–756)*	n = 5, 650 (361–978)	n = 3, 535 (176–744)
pH 5.0	n = 9, 151 (122–240)*	n = 9, 484 (80–2574)	n = 11, 552 (389–1151)
T_{\max} (min)			
pH < 5.0	90 (38–160)	45 (26–64)	45 (1–149)
pH 5.0	120 (49–214)	45 (20–106)	30 (26–67)
AUC ₃₆₀ (pg h/ml)			
pH < 5.0	1091.8 (545.2–1735.6)	1994.1 (1175.8–2976.0)	1410.5 (305.1–2335.1)
pH 5.0	584.5 (446.0–930.4)	1698.9 (1191.6–2894.0)	1636.8 (1367.5–2642.1)

Data presented as median (95% confidence interval). C_{\max} , peak concentration of MPA; T_{\max} , the time-to-peak concentration; total AUC, total area under the curve. *P = 0.039.

The recruitment rate is about 50%, and 41% of these subjects refused to join the study due to multiple blood takings. We are uncertain whether this may have led to a selection bias. This study involved women in the first trimester of pregnancy with a single vaginal dose of misoprostol only. The pharmacokinetics of repeated doses of misoprostol may be quite different from those of a single dose, as illustrated in our previous study on the comparison of the pharmacokinetics of a single dose and repeated doses of sublingual and vaginal misoprostol (Tang et al., 2009). As repeated doses are used in the second trimester abortion, moistening with normal saline or acetic acid may exert different effects on absorption. Therefore, our results may not be applicable to other situations such as later gestations or non-pregnant or menopausal women, as the physiological changes in pregnancy would alter the drug distribution and the renal excretion of the drug. Further pharmacokinetic studies on repeated dosage of misoprostol, in non-pregnant women and women during the second trimester are needed to address these.

Another possible confounder is the acidity of the vagina. As shown by a previous study, the more acidic vaginal environment (i.e. pH < 5) was associated with a significantly shorter induction-to-abortion interval and a significantly higher abortion rate within 24 h (100 versus 63.8%) in mid-trimester miscarriage and significantly lower incidence of side effects, namely fever and abdominal pain, although in all women in the study acetic acid was used to moisten the misoprostol tablets (Abd-El-Maeboud et al., 2008). Our data also showed that in the dry tablet group, C_{\max} was significantly higher in the subgroup with a lower vaginal pH (i.e. <5). As shown in the normal saline and acetic acid groups, the absorption was improved with the use of either normal saline or acetic acid in women no matter whether the acidity of their vagina. However, the sample size in each group was small and the post-test sample size calculation revealed that 66 subjects are needed in each group in order to have the power of 80%. Therefore, the results should be interpreted with caution. Overall, the evidence suggests that acidity in the vagina may affect the absorption of vaginal misoprostol. As the acidity in the vagina may be affected by physiological or pathological conditions (such as vaginal infections), the absorption may vary in different populations.

It can be argued that a better absorption of the drug may not be associated with better clinical outcomes in termination of pregnancy as there is the possibility that the tissue concentration in the uterus

may be different from that in the serum of peripheral blood. A slower absorption may also be associated with a lower but more sustained concentration for a longer period, thereby leading to a longer duration of uterine contractions. This may be especially true when the uterus has been sensitized with mifepristone. Therefore, whether moistening of misoprostol with normal saline or acetic acid can improve the clinical outcome will require confirmation with a clinical trial of an adequate sample size using a technique of moistening that has been shown to be effective in improving absorption.

All this evidence suggests that there are many other factors affecting the absorption as well as the clinical effects of vaginal misoprostol, which may explain the differences in the results of the previous clinical trials. As the misoprostol tablets were designed for oral ingestion, there is an urgent need for the development of an approved vaginal form of misoprostol.

In summary, vaginal misoprostol tablets moistened with normal saline and 5% acetic acid achieved better absorption than the dry tablet. The use of vaginal misoprostol tablets moistened with normal saline or 5% acetic acid would potentially improve the clinical efficacy of misoprostol. However, this needs to be confirmed with properly conducted randomized controlled trials on the clinical outcomes with the use of misoprostol moistened with normal saline or acetic acid.

Authors' roles

E.H.Y.N. and P.C.H. contributed to the conception and design of the study. V.C.Y.L. and R.H.W.L. recruited patients and arranged blood draws. V.C.Y.L. and S.S.F.Y. interpreted the data. B.W. and H.S. performed the laboratory analysis. V.C.Y.L. drafted the manuscript, which was reviewed, revised and approved by all authors.

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