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# Pharmacokinetics of different routes of administration of misoprostol

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**BACKGROUND: The pharmacokinetic parameters of four different routes of administration of a single dose of 400 μg of misoprostol were studied. METHODS: A total of 40 women undergoing termination of pregnancy by suction evacuation was randomized by computer model to receive 400 μg of misoprostol by one of four routes: (i) sublingual (ii) oral (iii) vaginal and (iv) vaginal with addition of water. Venous blood samples were taken at 0, 1, 2, 5, 10, 20, 30, 45, 60, 120, 240 and 360 min after the administration of misoprostol. Misoprostol acid (MPA) was determined in serum samples using gas chromatography/tandem mass spectrometry. RESULTS: Sublingual misoprostol achieved the highest serum peak concentration ($C_{max}$) (574.8 ± 250.7 pg/ml) of MPA and this was significantly higher than those in the other groups [Oral: 287.6 ± 144.3 pg/ml ($P < 0.01$), vaginal: 125.2 ± 53.8 pg/ml ($P < 0.001$) and vaginal with water: 162.8 ± 57.1 pg/ml ($P < 0.001$)]. The time to peak concentration ($T_{max}$) was similar in both the sublingual (26.0 ± 11.5 min) and oral groups (27.5 ± 14.8 min) and was significantly shorter than those in both vaginal groups. The area under the MPA concentration versus time curve up to 360 min in the sublingual group (743.7 ± 291.2 pg·h/ml) was significantly greater than those in oral (402.8 ± 151.6 pg·h/ml, $P < 0.05$) and vaginal (433.7 ± 182.6 pg·h/ml, $P < 0.05$) groups, but no significant difference was found between sublingual and vaginal administration if water (649.3 ± 333.8 pg·h/ml) was added. CONCLUSION: The new sublingual route of administration of misoprostol demonstrated a great potential to be developed into a method of medical abortion.**

*Key words:* misoprostol/oral/pharmacokinetics/sublingual/vaginal

## Introduction

Misoprostol is widely used in obstetrics and gynaecology for medical abortion, cervical priming and induction of labour (World Health Organization, 1993; El-Refaey *et al.*, 1994, 1995; Ngai *et al.*, 1995b, 1996; Ho *et al.*, 1997; Ashok *et al.*, 1998). It is a prostaglandin $E_1$ analogue originally developed for the treatment of peptic ulcers. It is licensed for oral use. However, vaginal administration is becoming a common practice in both medical abortion and cervical priming. Many clinical studies have found that vaginal administration is more effective than oral administration (El-Refaey *et al.*, 1995; Ho *et al.*, 1997). This was supported by a pharmacokinetic study showing that the systemic bioavailability, as demonstrated by the area under the curve, after vaginal misoprostol was three times higher than that after oral misoprostol (Ziemen *et al.*, 1997). There has been suggestive evidence showing that absorption through the vaginal route is inconsistent and absorption could be improved by adding water to the misoprostol tablets (Carbonell *et al.*, 1997, 1999). It was not uncommon to find that the majority of the misoprostol tablet was still not completely dissolved several hours after vaginal administration (Ziemen *et al.*, 1997; Singh *et al.*, 1999). In addition, women preferred to take the misoprostol tablets by mouth in order to avoid the uncomfortable vaginal examination and provide more privacy during medical abortion (Ho *et al.*, 1997). Therefore, the oral and the vaginal routes of administration may not be the optimal way of administering misoprostol for medical abortion and cervical priming. Recently, we developed a new route of giving misoprostol by sublingual administration. The misoprostol tablet, being very soluble in water, was put under the tongue. It was observed that it would dissolve within 10–15 min. Preliminary data showed that this is a promising method for medical abortion. The objective of this study was to determine the pharmacokinetics of various routes of administration of misoprostol.

## Materials and methods

Forty pregnant women requesting termination of pregnancy at a gestation of <12 weeks were recruited into the study. These 40 women were recruited from women requesting surgical termination

of pregnancy. The study was approved by the Ethics Committee of the Faculty of Medicine, University of Hong Kong. Inclusion criteria were healthy women who were pregnant for <12 weeks. Women with a history of allergy to misoprostol and major medical problems were excluded.

The subjects were asked to keep fasted overnight and were admitted to the hospital on the morning of the operation. They were randomized into four groups to receive 400 μg of misoprostol either sublingually, orally or vaginally with or without the addition of 3 drops of water. The randomization schedule was generated by computer and the allocations were put in opaque sealed envelopes. An 18-gauge i.v. catheter suitable for repeated blood sampling was inserted into the antecubital vein at the beginning of the study. Sublingual misoprostol was given by putting two tablets of misoprotol under the tongue and allowing them to dissolve spontaneously. Oral misoprostol was given by asking the subject to take the tablets with water. For vaginal misoprostol, two tablets of the drug were inserted into the posterior fornix of the vagina by one of the investigators. The tablets were dampened by 3 drops of water immediately prior to insertion in the group using vaginal misoprostol with water.

Venous blood samples (10 ml) were drawn over the next 6 hours at 0, 1, 2, 5, 10, 20, 30, 45, 60, 120, 240 and 360 min after the administration of misoprostol. Surgical termination of pregnancy was performed for the 40 subjects upon completion of the study. The blood samples were centrifuged and frozen in liquid nitrogen immediately. The samples were then stored below –20°C and sent to the Department of Pediatrics, Philipps University Marburg for analysis. Misoprostol acid (MPA) was determined in serum samples using gas chromatography/tandem mass spectrometry (GC/MS/MS). After addition of 15(S)-15-methyl prostaglandin estradiol (15-methyl-$PGE_2$) as internal standard, MPA was extracted from both matrices using a reversed phase cartridge. The prostanoids were derivatized with *O*-2,3,4,5,6-pentafluorobenzylhydroxylamine hydrochloride (PFBHA) and 2,3,4,5,6-pentafluorobenzylbromide (PFBB) to the pentafluorobenzyl oxime (PFBO)-pentafluorobenzyl ester (PFB) derivatives. The sample was applied to thin-layer chromatography with ethylacetate/hexane 1:1 (v/v) as the developing solvent. The corresponding zone was extracted. After derivatization to the trimethylsilylether, MPA was determined by GC/MS/MS using the $[M\text{-pentafluorobenzyl}]^-$ ions as precursor in the negative ion chemical ionization mode. The product ions used for quantification were $[P–2TMSOH–C_6F_5CH_2OH]^-$ (MPA) and $[P–2TMSOH–C_6F_5CH_2OH–CO_2]^-$ (15-methyl-$PGE_2$) respectively. The detection limit of the assay is 1 pg/sample.

The primary outcome measures of the study were the area under the curve of serum concentrations of MPA against time up to 240 ($AUC_{240}$) and 360 ($AUC_{360}$) min, peak concentration of misoprostol level ($C_{max}$) and the time to attain the peak concentration ($T_{max}$). The area under the curve was calculated by the trapezoidal method. The area under the curve 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 calculation of trapezium area: $0.5\ [C_x + C_{x-1}]$ [time interval], x = 1 to 12. The $AUC_{240}$ and $AUC_{360}$ were calculated by summating the first 10 and 11 trapezium segments respectively. The difference in the $AUC_{240}$ was used for calculation of the sample size.

Previous studies showed that the $AUC_{240}$ was 500 ± 296 pg·h/ml for vaginal misoprostol (Zieman *et al.*, 1997). Therefore, 10 subjects in each group gave 80% power in detecting a difference of 400 pg·h/ml in $AUC_{240}$ at 5% level of significance. Statistics Package for Social Sciences 7.5 for Windows was used for data analysis. Continuous variables were compared by one-way analysis of variance (ANOVA) and post-hoc (Tukey) test for multiple comparison if the data were normally distributed. Kruskal–Wallis or Mann–Whitney tests were used if the data were skewed. Kolmogorov–Smirnov's test was used to test for the distribution of samples. A *P*-value (two-tailed) of $< 0.05$ was taken as statistically significant.

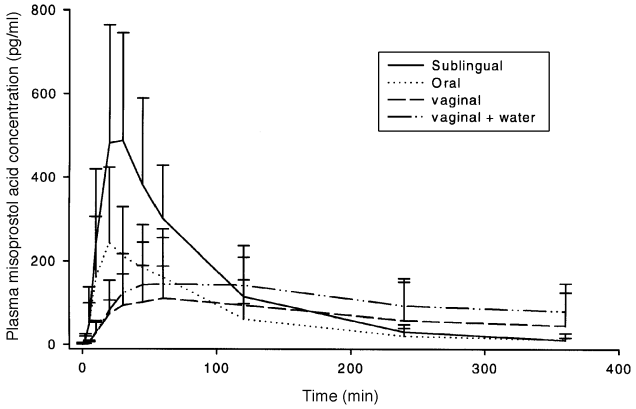


**Figure 1.** Mean plasma concentrations of misoprostol acid over time (arrowbars = 1 SD).

## Results

The age, gestational age and body surface area of the four groups are listed in Table I. There were no statistically significant difference between the four groups in the above demographic characteristics. The mean serum concentrations of MPA after administration of 400 μg misoprostol by sublingual, oral and vaginal routes with or without the addition of water are shown in Figure 1. Four pharmacokinetic parameters were studied, namely the peak concentration, time to the peak concentration, $AUC_{240}$ and $AUC_{360}$ (Table II). Sublingual misoprostol was able to achieve the highest serum peak concentration and this was statistically significantly higher than each of the other groups. The oral route of administration gave a significantly higher serum peak concentration compared with the vaginal route, but there was no difference if water was added to the tablets. The time to peak concentration was significantly shorter in the sublingual and oral groups than in either of the two vaginal routes of administration. The $AUC_{240}$ and $AUC_{360}$ in the sublingual group were significantly greater than those in the oral and vaginal groups, but no significant difference was found between sublingual and vaginal administration if water was added to the misoprostol tablets before administration. The individual variability of these pharmacokinetic parameters was denoted by the coefficient of variation (CV). Oral misoprostol had the greatest CV for $C_{max}$ (50.0%) and $T_{max}$ (53.7%), whereas vaginal misoprostol with water had the greatest CV for $AUC_{240}$ and $AUC_{360}$.

## Discussion

Although misoprostol has been extensively used for medical abortion, cervical priming and induction of labour, the regimens varied in different studies. The doses and dosing intervals were usually derived empirically from clinical trials. Misoprostol is licensed for the oral treatment of peptic ulcers. The tablet was designed for oral absorption and there were only two studies which reported the absorption kinetics after vaginal misoprostol

**Table I.** Demographic characteristics of the 40 subjects (± SD)

| | Sublingual ($n$ = 10) | Oral ($n$ = 10) | Vaginal ($n$ = 10) | Vaginal + water ($n$ = 10) | $P$-value |
|---|---|---|---|---|---|
| Mean age (years) | 25.9 ± 6.3 | 27.5 ± 8.5 | 29.1 ± 8.4 | 28 ± 8.5 | NS[a] |
| Mean gestational age (days) | 72.4 ± 9.4 | 76.0 ± 7.2 | 76.4 ± 5.3 | 71.7 ± 13.4 | NS[b] |
| Mean weight (kg) | 48.5 ± 5.2 | 52.6 ± 5.9 | 52.1 ± 7.5 | 57.5 ± 12.7 | NS[a] |
| Mean height (cm) | 157.3 ± 3.3 | 158.4 ± 9.8 | 157.0 ± 6.8 | 158.8 ± 4.2 | NS[a] |
| Body surface area ($m^2$) | 1.45 ± 0.09 | 1.52 ± 0.12 | 1.50 ± 0.12 | 1.59 ± 0.17 | NS[a] |

[a]ANOVA; [b]Kruskal–Wallis test.
NS = not significant.

**Table II.** Pharmacokinetic parameters of the four routes of administration of misoprostol

| ($n$ = 10) | Sublingual ($n$ = 10) | Oral ($n$ = 10) | Vaginal ($n$ = 10) | Vaginal + water (overall) | $P$-value |
|---|---|---|---|---|---|
| Peak concentration of misoprostol acid ($C_{max}$) (pg/ml) | | | | | |
| Mean ± SD | 574.8 ± 250.7[c] | 287.6 ± 144.3[d] | 125.2 ± 53.8 | 162.8 ± 57.1 | < 0.001[a] |
| Median | 611.6 | 311.8 | 132.7 | 150.6 | |
| CV | 43.6 | 50 | 43.0 | 35.1 | |
| Time to attain peak concentration ($T_{max}$) (min) | | | | | |
| Mean ± SD | 26.0 ± 11.5[e] | 27.5 ± 14.8[f] | 72.0 ± 34.5 | 75.0 ± 31.6 | < 0.001[a] |
| Median | 20.0 | 20.0 | 60.0 | 60.0 | |
| CV | 44.2 | 53.7 | 47.9 | 42.2 | |
| Area under the curve to 240 min ($AUC_{240}$) (pg·h/ml) | | | | | |
| Mean ± SD | 702.1 ± 274.8[g] | 369.3 ± 155.2 | 329.7 ± 139.0 | 476.5 ± 206.3 | 0.001[b] |
| Median | 736.9 | 322.7 | 358.7 | 378.6 | |
| CV | 39.2 | 42.0 | 42.2 | 43.3 | |
| Area under the curve to 360 min ($AUC_{360}$) (pg·h/ml) | | | | | |
| Mean ± SD | 743.7 ± 291.2[h] | 402.8 ± 151.6 | 433.7 ± 182.6 | 649.3 ± 333.8 | 0.01[b] |
| Median | 785.1 | 373.4 | 423.8 | 498.0 | |
| CV | 39.2 | 37.6 | 42.0 | 51.4 | |

[a]Kruskal–Wallis test.
[b]ANOVA.
[c,d]$C_{max}$ for sublingual group was significantly higher than oral ($P$ = 0.009), vaginal ($P$ < 0.001) and vaginal + water groups ($P$ < 0.001); $C_{max}$ for the oral group was significantly higher than vaginal group ($P$ = 0.01) by Mann–Whitney $U$-test.
[e, f]$T_{max}$ for sublingual group was significantly shorter than vaginal ($P$ < 0.001) and vaginal + water groups ($P$ < 0.001); $T_{max}$ for the oral group was significantly shorter than vaginal ($P$ = 0.001) and vaginal + water groups ($P$ < 0.001) by Mann–Whitney $U$-test.
[g]$AUC_{240}$ was significantly greater than oral ($P$ = 0.004) and vaginal ($P$ = 0.001) groups by multiple comparison using post-hoc test (Tukey).
[h]AUC360 was significantly greater than oral ($P$ = 0.022) and vaginal ($P$ = 0.043) groups by multiple comparison using post-hoc test (Tukey).
CV = coefficient of variation (%).

(Zieman *et al.*, 1997; Gemzell Danielsson *et al.*, 1999). Recently, we explored a new route of administration of misoprostol by giving it sublingually. Preliminary data showed that it is a promising method of administration. This study gives insight to the optimal dose and dosing interval of sublingual misoprostol.

The data in this study show that sublingual and oral administration have the quickest onset of action when compared with vaginal administration with or without water. Sublingual administration can achieve the highest plasma concentration when compared with all other routes of administration. The systemic bioavailability, as measured by the AUC, is also highest after sublingual administration of misoprostol. The $AUC_{360}$ after oral administration was only 54% of that after sublingual administration. This may be explained by the absence of a first-pass effect by the liver after sublingual administration. The good blood supply under the tongue and the relatively neutral pH in the buccal cavity may also be contributing factors.

In the two previous pharmacokinetic studies comparing the pharmacokinetics of vaginal and oral administration of misoprostol (Zieman *et al.*, 1997; Gemzell Danielsson *et al.*, 1999), the peak plasma concentration of MPA was higher and achieved earlier after oral administration, but the detectable plasma concentrations lasted longer after vaginal administration. This study has shown similar results. The peak plasma concentrations and the time to reach maximum concentrations in our study were also comparable with those of the two previous studies. In one of the previous studies (Zieman *et al.*, 1997), the systemic bioavailability of vaginally administered

misoprostol ($AUC_{360}$) was three times higher than that of orally administered misoprostol. In this case, our results are different. The $AUC_{360}$ after oral and vaginal administration were similar and they were only 54 and 58% of that after sublingual administration. The $AUC_{360}$ in the vaginal-with-water group was higher than that of the vaginal group, but the difference was not statistically significant. It should be noted that there was a wide individual variability in the absorption of vaginal misoprostol with the addition of water. The coefficients of variation of $AUC_{360}$ for sublingual, oral, vaginal and vaginal-with-water groups were 39.2, 37.6, 42 and 51.4% respectively. The wide variation in absorption of vaginal misoprostol may explain the difference between this and a previous similar study (Zieman *et al.*, 1997).

Many clinical studies showed that vaginal misoprostol performed better than similar doses of oral misoprostol in both first and second trimesters. This is true for a single dose as well as multiple doses of administration (El-Refaey *et al.*, 1995; Ho *et al.*, 1997). Similar doses of vaginal misoprostol also gave long-lasting and continuously increasing uterine contractility when compared with oral administration (Gemzell-Danielsson *et al.*, 1999). The present study only measured the serum level of MPA up to 6 h. At the end of 6 h, the serum levels of MPA in both of the vaginal groups were higher than those of the sublingual and oral routes. Therefore, the effect of misoprostol may linger on for >6 h after a single dose. Although the clinical effect of the low serum level is difficult to ascertain, the serum level can accumulate if vaginal misoprostol is repeated at an interval shorter than 6 h. Recently, a direct vagina-to-uterus transport was described for progesterone absorption (Cicinelli *et al.*, 2000a,b). A similar mechanism may exist for misoprostol absorption and can explain the more favourable clinical effects with vaginal administration when compared with oral administration, despite similar bioavailability.

The misoprostol tablet was not manufactured and developed for use by routes other than oral administration. It is not uncommon to identify remnants of the tablets hours after vaginal administration, indicating that absorption is variable and incomplete. However, it is cheap and stable at room temperature and has been shown to be effective by vaginal route. Therefore, it is widely used off-label by vaginal administration. The potential of developing another misoprostol preparation that can give a more consistent pharmacokinetic profile with such a cheap price is low. Numerous attempts were made to improve the absorption of vaginal misoprostol. Acetic acid was used to dissolve the tablets but did not improve the clinical outcome (Singh *et al.*, 1999). The addition of water to the misoprostol tablet was a common practice. It has been shown to give a complete abortion rate in 90% of the women requesting medical abortion at <9 weeks gestation by repeated doses of misoprostol (Carbonell *et al.*, 1999). However, this finding could not be repeated by a randomized trial (Ngai *et al.*, 2000). In the present study, the bioavailability of vaginal misoprostol as shown by the $AUC_{360}$ was not improved by adding water into the tablets. The water-added group also showed the greatest individual variation in the AUC. This may explain the inconsistent clinical effects of adding water to the tablet.

The new sublingual route of administration of misoprostol demonstrated a great potential to be developed into a method of medical abortion and cervical priming. The $T_{max}$ of sublingual misoprostol was similar to that of oral administration. Oral misoprostol has been shown in a recent randomized trial to be an effective cervical priming agent when given 3 h prior to vacuum aspiration in the first trimester (Ngai *et al.*, 1999). This was in contrast with the previous belief that oral misoprostol needed to be given the night before the operation because it is less effective than vaginal misoprostol (Ngai *et al.*, 1995a; Lawrie *et al.*, 1996). Sublingual misoprostol, having a similar $T_{max}$ and a higher $C_{max}$ when compared with oral misoprostol, may have a better cervical priming effect. It also has the advantage of avoiding fluid intake before the operation and this is especially important if the vacuum aspiration is done under general anaesthesia. The highest bioavailability of sublingual misoprostol, as shown by the $AUC_{360}$, indicates that it is probably the most potent route of administration of misoprostol if its effect on the uterus is proportional to its serum level. Randomized clinical trials are required to compare its efficacy and side effects profile with vaginal administration.

This study only measured the serum levels of MPA after the administration of a single dose of misoprostol. The effect of multiple dosing is unknown. This is especially difficult to predict in vaginal administration given its slow and less predictable absorption and elimination. The study only involved women in the first trimester of pregnancy and caution is needed when the results are extrapolated to a more advanced gestation. This is especially true when the use of sublingual misoprostol is extended to the third trimester for labour induction and cervical priming. Although oral or vaginal routes of administration have been shown to be effective for labour induction and cervical priming in the third trimester, the data on optimal regimens and safety are lacking. A lower dose of vaginal or oral misprostol (50–100 μg) is used in most studies on labour induction when compared with first or second trimester medical abortion (Afirevic, 2001; Hofmeyr and Gulmezoglu, 2001). Given the current data on the pharmacokinetics of oral, vaginal and sublingual misoprostol, the dose of sublingual misoprostol may need to be further reduced. More data on the safety of this route of administration should be available before its clinical application.

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