Title: Pharmacokinetics of repeated doses of misoprostol

Running title: Pharmacokinetics of misoprostol

Authors and their roles:

Oi Shan Tang[1]: Design of study, data analysis and interpretation, clinical management of subjects, drafting of manuscript and final approval of paper.

Horst Schweer[2]: Design of study, assay of misoprostol acid, data interpretation, revising the paper and final approval of paper.

Sharon WH Lee[1]:Clinical management of subjects, data analysis, revising the paper and final approval of paper.

Pak Chung Ho[1,3]: Design of study, data analysis and interpretation, drafting of manuscript and final approval of paper.

Address:

[1] Department of Obstetrics and Gynaecology, The University of Hong Kong, 6/F., Professorial Block, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong SAR, China

[2] Department of Pediatrics, Philipps University Marburg, Baldingerstrasse 35043 Marburg, Germany.

[3] To whom correspondence should be addressed, email address: *pcho@hkusua.hku.hk*

Abstract

Background: The pharmacokinetic parameters after the vaginal or sublingual administration of repeated doses of 400 μg of misoprostol were studied.

Methods: Women undergoing termination of pregnancy by suction evacuation were randomized to receive 400 μg of sublingual or vaginal misoprostol every 3 hours for 5 doses. Venous blood samplings were taken at 180, 200, 240, 360, 380, 420, 540, 560, 600, 720, 740, 780 and 900 minutes after the first dose of misoprostol. Misoprostol acid (MPA) was determined in plasma samples using gas chromatography/tandem mass spectrometry.

Results: The peak plasma levels of MPA decreased with successive doses of vaginal misoprostol, whereas the peak plasma levels were similar with successive doses of sublingual misoprostol. The peak plasma levels of MPA after sublingual misoprostol were significantly higher than those after vaginal administration after the third dose. As a result, the area under the MPA concentration-time curve after sublingual administration became significantly higher than that after vaginal misoprostol after the final dose ($p<0.031$). However, subgroup analysis in the vaginal administration group showed that the progressive decline in the peak plasma levels of MPA occurred only in women with significant vaginal bleeding.

Conclusion: The peak plasma level of MPA after each dose of misoprostol is higher and the bioavailability is also greater after sublingual administration of repeated doses of misoprostol when compared to those after vaginal administration. The difference was probably due to the reduction in absorption of vaginal misoprostol in the presence of significant vaginal bleeding.

Key words: misoprostol / pharmacokinetics / sublingual / vaginal

Introduction:

Misoprostol is widely used in obstetrics and gynaecology for medical abortion, cervical priming and induction of labour (El-Refaey et al, 1995; Ho et al, 1997; WHO, 1993; Ashok et al, 1998; Ngai et al, 1995; Ngai et al, 1996; El-Refaey et al, 1994). Although misoprostol is originally developed for oral administration for the management of peptic ulcer, it was commonly used vaginally for medical abortion, cervical priming and labour management in obstetrics and gynaecology. Recently, it was found that misoprostol can be used sublingually as well. A pharmacokinetic study has compared the absorption kinetics of misoprostol after vaginal or sublingual administration of a single dose of misoprostol. It was shown that after sublingual administration of misoprostol, the time for misoprostol acid (MPA), the active metabolite of misoprostol, to reach peak concentration was significantly shorter, while the peak plasma concentration and the bioavailability (as measured by the area under the time-concentration curve of MPA) of MPA were significantly higher than those after vaginal administration. However, the plasma level of MPA was sustained for a longer time after vaginal administration. The plasma level of MPA dropped to a negligible level 4 hours after sublingual administration, but the plasma level was still maintained at the end of 6 hours after vaginal administration (Tang et al, 2002). A number of clinical studies have demonstrated the effectiveness of sublingual administration of misoprostol (Tang et al, 2003; Tang et al, 2004). However, in certain applications like second trimester medical abortion, the efficacy of the vaginal route is superior to that of the sublingual route despite the more favourable pharmacokinetic profile (Tang et al, 2004). This may be due to the fact that in second trimester medical abortion, repeated doses are often required and the pharmacokinetic profile of repeated administration may be different from that after a single dose. Knowing the pharmacokinetic properties of the drug after repeated doses is important for designing an effective and safe regimen for different clinical indications. Therefore, in this study, we

compared the pharmacokinetics of misoprostol after vaginal or sublingual administration of repeated doses of misoprostol.

Materials and methods

Twenty pregnant women requesting termination of pregnancy at a gestation of less than 12 weeks were recruited into the study. These 20 women were recruited from women requesting surgical termination of pregnancy. The study was approved by the Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster. Inclusion criteria were healthy women who were pregnant for less than 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 one day before the operation. They were randomized into 2 groups to receive 400 μg of misoprostol every 3 hours for 5 doses either sublingually or vaginally. The randomization schedule was generated by computer and the allocations were put in opaque sealed envelops. Sublingual misoprostol was given by putting 2 tablets of misoprotol under the tongue and allowing them to dissolve spontaneously. For vaginal misoprostol, two tablets of the drug were inserted into the posterior fornix of the vagina by one of the investigators. Venous blood samples (10 ml) were drawn over the next 15 hours at 180, 200, 240, 360, 380, 420, 540, 560, 600, 720, 740, 780 and 900 minutes after the administration of misoprostol. The time intervals were chosen according to our previous pharmacokinetic study which showed that the peak concentration was reached after a median of 20 and 60 minutes for sublingual and vaginal administration respectively (Tang et al 2002). We did not collect blood samples in the first 180 minutes because the data were already available in our previous study (Tang et al 2002). Surgical termination of pregnancy with vacuum aspiration was performed for these subjects if there was an on-going pregnancy or incomplete abortion upon completion of the 5 doses of misoprostol. The blood samples were centrifuged to obtain the plasma and frozen in

liquid nitrogen immediately. The samples were then stored at below –20ºC and were sent to Department of Pediatrics, Philipps University Marburg for analysis. MPA was determined in the plasma samples using gas chromatography/tandem mass spectrometry (GC/MS/MS). After addition of 15(S)-15-methyl prostaglandin E_2 (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 TLC 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-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 plasma concentrations of MPA against time from 180 to 900 minutes ($AUC_{180-900}$). The area under the time-concentration curve was calculated by the trapezoidal method. The area under the time-concentration 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 (x is the order of the blood samplings). The $AUC_{180-900}$ was calculated by summating the 12 trapezium segments. No similar study was found in the literature on the pharmacokinetics of repeated doses of sublingual or vaginal misoprostol. According to a previous pharmacokinetic study on a single dose of misoprostol, 10 subjects in each arm will have 80% power in detecting a 50% difference in bioavailability at 5% significance level.

SPSS 11 for window statistical package was used for data analysis. Continuous variables were compared by Student t test if the data were normally distributed. Kruskal-Wallis test or Mann-

Whitney test was used if the data were skewed. P value (two-tailed) of <0.05 was taken as statistically significant.

Results

The age, gestational age and body surface area of the 2 groups are listed in Table 1. There was no statistically significant difference between the 2 groups in these demographic characteristics. The mean plasma concentrations of MPA after administration of 400 μg misoprostol every 3 hours for 5 doses by sublingual and vaginal routes are shown in Figure 1. The peak plasma levels of MPA decreased with successive doses of vaginal misoprostol, whereas the peak plasma levels were similar with successive doses of sublingual misoprostol. The peak plasma levels after sublingual misoprostol were significantly higher than those after vaginal administration after the third dose. As a result, the area under the curve after sublingual administration became significantly higher than that after vaginal administration after the final dose ($p<0.031$) (Table 2 and Fig. 2).

As the majority of women developed vaginal bleeding after administration of misoprostol, this might adversely affect the absorption of misoprostol given vaginally. We suspected that this might account for the progressive decline of the plasma levels of MPA after vaginal administration. In the vaginal administration group in this study, eight women developed vaginal bleeding and subsequently aborted while two women had no vaginal bleeding. Therefore, we compared the pharmacokinetics of misoprostol in these two subgroups of women in the vaginal administration group. The plasma concentrations of MPA in these two subgroups of women are shown in Figure 3 while the areas under the MPA time-concentration curves are shown in Figure 4. It can be seen in the subgroup with vaginal bleeding, there was a progressive decline in the peak plasma concentrations of MPA with repeated doses of vaginal misoprostol while in the subgroup with no vaginal bleeding, there was no progressive decline in the peak plasma concentrations of MPA with repeated doses. The plasma concentrations of MPA in the subgroup with significant amount of

vaginal bleeding and abortion were significantly lower than the subgroup without vaginal bleeding at 540 minutes ($p<0.05$), 560 minutes ($p<0.05$), 600 minutes ($p<0.05$), 720 minutes ($p<0.05$), 740 minutes ($p<0.05$) and 740 minutes ($p<0.05$). Because of the progressive decline in the peak plasma concentrations of MPA after vaginal administration of repeated doses of misoprostol in the vaginal bleeding group, the areas under the time-concentration curve of MPA in this subgroup were significantly lower than those in the subgroup with no vaginal bleeding at 720 minutes ($p<0.05$) and 740 minutes ($p<0.05$). In the group of women given misoprostol sublingually, the plasma concentrations of MPA were comparable in the two subgroups of women with or without vaginal bleeding (data not shown). The plasma concentrations of MPA in the two subgroups of women given misoprosstol vaginally were also compared with those in the sublingual group. The plasma concentrations of MPA in the subgroup of women with vaginal bleeding after vaginal administration of misoprostol were significantly lower than those after sublingual administration (whole group) at 420 minutes ($p<0.01$), 560 minutes ($p<0.001$), 600 minutes ($p<0.001$), 720 minutes ($p<0.001$), 740 minutes ($p<0.001$), 780 minutes ($p<0.001$) and 900 minutes ($p<0.001$). The areas under the time-concentrations curves of MPA in this subgroup were also significantly lower than those in the sublingual group at 720 minutes ($p<0.05$), 740 minutes ($p<0.05$), 780 minutes ($p<0.05$) and 900 minutes ($p<0.01$). On the other hand, the plasma concentrations of MPA in the subgroup of women without vaginal bleeding after vaginal administration of misoprostol were significantly higher than those in the sublingual group (whole group with and without vaginal bleeding) at 360 minutes ($p<0.05$), 540 minutes ($p<0.05$) and 90 minutes ($p<0.05$). Although the areas under the time-concentration curves of MPA in this subgroup without vaginal bleeding after vaginal administration of misoprostol were all higher than those in the sublingual group, the differences were not statistically significant, probably because of the small sample size in this subgroup.

Discussion

This is the first study on the pharmacokinetics of MPA after vaginal or sublingual administration of repeated doses of misoprostol. According to the previous studies, the peak plasma concentration and bioavailability after a single dose of misoprostol are higher after sublingual administration than those after vaginal administration (Tang et al, 2002, Aronsson et al, 2007). However, the plasma level of MPA after a single dose of vaginal misoprostol is sustained for a longer time than that after sublingual misoprostol. Despite a rapid rise of plasma level of MPA after sublingual administration, the plasma level of MPA dropped more rapidly than that after vaginal administration so that after 3 hours the plasma level is lower than that after vaginal administration. This may be attributed to the continuous absorption of misoprostol from the vaginal mucosa over the few hours after its administration. There is still a measurable amount of MPA in the blood at 6 hours after vaginal administration (Aronsson et al, 2007). Therefore, it is expected that with repeated vaginal administration at an interval of less than 6 hours, the MPA may accumulate in the plasma and reach a level consistently higher than that after sublingual administration of misoprostol so that the total area under the time-concentration curve, an indication of the bioavailability, will also be higher. However, the results of this study do not appear to be consistent with this hypothesis. The peak plasma level after successive doses of vaginal misoprostol actually becomes lower and lower. As a result the total bioavailability of the drug at the end of the study at 900 minutes is actually higher for sublingual misoprostol. It seems that there is no accumulation of MPA after repeated vaginal administration of misoprostol. The present pharmacokinetic study has shown that the absorption of vaginal misoprostol actually became less efficient with time. We postulate that this may be due to the presence of vaginal bleeding with the onset of the abortion process. The vaginal bleeding may interfere with the absorption of misoprostol. It may also wash away some misoprostol tablets inserted vaginally.

To test our hypothesis, we compared the pharmacokinetics of MPA after vaginal administration of misoprostol in the eight women with significant vaginal bleeding with those in

the two women with no vaginal bleeding. The results in the two subgroups of women in the vaginal administration group show that the progressive decline in the peak plasma concentrations of MPA occurred only in the subgroup with significant vaginal bleeding. In the vaginal subgroup without vaginal bleeding, the plasma concentrations of MPA were significantly higher than those in the sublingual group at several time points, usually about 180 minutes after the misoprostol administration. The areas under the time-concentration curves in this subgroup were also higher than those in the sublingual group though the differences were not statistically significant. In the sublingual administration group, the presence of significant vaginal bleeding did not affect the pharmacokinetics of misoprostol. These data support our hypothesis that the vaginal bleeding can adversely affect the absorption of misoprostol in the vagina. They also support our original hypothesis that in the absence of vaginal bleeding, vaginal administration of repeated doses of misoprostol will lead to accumulation of MPA in the plasma leading to higher plasma concentrations and possibly also higher areas under the time-concentration curves of MPA.

The results in this study appear to be inconsistent with the findings of a clinical trial (Tang et al 2004) comparing vaginal misoprostol with sublingual misoprostol in termination of second trimester pregnancies. In this clinical trial, the regimens were similar to those in this pharmacokinetic study with 400μg of misoprostol given every 3 hours for 5 doses in both the vaginal and the sublingual administration groups. It was found that the success rate for second trimester abortion for vaginal misoprostol was 85% which was higher than that of sublingual misoprostol (64%). However, the outcome of treatment in those with vaginal administration of misoprostol in the presence of heavy vaginal bleeding may not be affected by the reduced absorption of misoprostol as those patients with the heaviest vaginal bleeding are usually aborting and they may not require high plasma levels of MPA. Moreover, although it is logical to presume that a higher plasma level is associated with a more potent clinical effect, the plasma thresholds for various clinical actions have never been established. A very low and sustained plasma level may already be adequate for many of the clinical actions. Regular uterine contractions have been

demonstrated for vaginal misoprostol up to 4 hours despite a low plasma level of MPA (Aronsson et al 2004). In addition, the local cervical priming effect of vaginal misoprostol should not be overlooked. A direct vagina-to-uterus transport described for progesterone absorption may also exist for misoprostol absorption and can explain the more favourable clinical effects with vaginal administration when compared with sublingual administration despite a more favourable bioavailability of the latter (Cicinelli et al, 2000; Cicinelli et al, 2000).

On the other hand, vaginal administration of misoprostol may not be appropriate in the prophylaxis or management of postpartum haemorrhage. In this situation, a rapid rise in the plasma concentration of MPA may be needed for its clinical action. Moreover the presence of bleeding after delivery may affect the absorption of vaginal misoprostol.

In conclusion, the peak plasma level of MPA after each dose of misoprostol is higher and the bioavailability is also greater after sublingual administration of misoprostol than those after vaginal administration. This difference is likely to be due to the adverse effect of heavy vaginal bleeding on the absorption of misoprostol given vaginally. However, a better bioavailability does not necessarily mean a better clinical effect in medical abortion because other factors may affect the efficacy of the drug.

Acknowledgements: We are grateful to the staff of the Division of Reproductive Medicine in the Department of Obstetrics and Gynaecology, University for Hong Kong for their assistance in handling the blood specimens. The work described in this paper was fully supported by Research Group of Post-ovulatory Methods for Fertility Regulation of the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human reproduction.

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.

Aronsson A, Fiala C, Stephansson O, Granath F, Watzer B, Schweer H, Gemzell-Danielsson K. Pharmacokinetic profiles up to 12 h after administration of vaginal, sublingual and slow-release oral misoprostol. *Hum Reprod* 2007;**22:**1912-1918.

Ashok PW, Penney GC, Flett GMM, Templeton A. An effective regimen for early medical abortion: a report of 2000 consecutive cases. *Hum Reprod* 1998;**13**:2962-2965.

Cicinelli E, Schonauer LM, Galantino P, Matteo MG, Cassetta R, Pinto V. Mechanisms of uterine specificity of vaginal progesterone. *Hum Reprod* 2000;**15** Suppl 1:159-165.

Cicinelli E, de Ziegler D, Bulletti C, Matteo MG, Schonauer LM, Galantino P. Direct transport of progesterone from vagina to uterus. *Obstet Gynecol* 2000;**95**:403-406.

El-Refaey H, Rajasekar D, Abdalia M, Calder L, Templeton A. Induction of abortion with mifepristone and oral or vaginal misoprostol. *N Eng J Med* 1995;**332**:983-987.

El-Refaey, Calder L, Wheatley DN, Templeton. Cervical priming with prostaglandin E1 analgues, misoprostol and gemeprost. *Lancet* 1994;**343**:1207-1209.

Ho PC, Ngai SW, Liu KL, Wong GCY, Lee SWH. Vaginal misoprostol compared with oral misoprostol in termination of second trimester pregnancy. *Obstet Gynaecol* 1997;**90**:735-738.

Ngai SW, Tang OS, Lao T, Ho PC, Ma HK. Oral misoprostol versus placebo for cervical dilatation before vacuum aspiration in first trimester pregnancy. *Hum Reprod* 1995;**10**:1220-1222.

Ngai SW, Au Yeung KC, Lao T, Ho PC. Oral misoprostol versus mifepristone for cervical dilatation before vacuum aspiration in first trimester nulliparous pregnancy: a double blind prospective randomized study. *Br J Obstet Gynaecol* 1996;**103**:1120-1123.

Tang OS, Schweer H, Seyberth HW, Lee SWH, Ho PC. Pharmacokinetics of different routes of administration of misoprostol. *Hum Reprod* 2002;**17**:332-336.

Tang OS, Chan CCW, Ng EHY, Lee SWH, Ho PC. A prospective, randomized, placebo-controlled trial on the use of mifepristone with sublingual or vaginal misoprostol for medical abortions of less than 9 weeks gestation. *Hum Reprod* 2003;**18**:2315-2318.

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

World Health Organization. Termination of pregnancy with reduced doses of mifepristone. *BMJ* 1993;**307**:532-537.

Table 1 Demographic characteristics of the 20 subjects (SD)

	Sublingual (n=10)	Vaginal (n=10)	P value
Mean age/ years	31.7 (8.3)	29.8 (7.7)	0.704
Mean gestational age/days	59.9 (14.2)	54.8 (14.2)	0.283
Mean weight/kg	52.1 (9.9)	51.2 (4.0)	0.544
Mean height/cm	158.1 (6.5)	159.3 (4.1)	0.849
Mean Body surface area/m^2	1.51 (0.16)	1.50 (0.06)	0.326

[a]

[b]

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

	Sublingual (n=10)	Vaginal (n=10)	P value
Plasma level at 180 minutes/ pg/mL			
Mean(SD)	123.1 ± 119.5	202.2 ± 143.2	0.096
Median	(86.8)	(171.5)	
Area under the curve to 180 minutes (AUC_{180})/ pg · hr/mL*			
Mean(SD)	184.7 ± 179.3	303.4 ± 214.9	0.096
Median	(130.2)	(257.3)	
Plasma level at 200 minutes/ pg/mL			
Mean(SD)	380.0 ± 239.2	438.2 ± 293.3	0.597
Median	(257.0)	(394.5)	
Area under the curve to 200 minutes (AUC_{200})/ pg · hr/mL			
Mean(SD)	268.6 ± 233.3	410.1 ± 272.2	0.131
Median	(229.8)	(349.5)	
Plasma level at 240 minutes/ pg/mL			
Mean(SD)	489.5 ± 213.6	395.1 ± 247.6	0.406
Median	(423.5)	(429.0)	
Area under the curve to 240 minutes (AUC_{240})/ pg · hr/mL			
Mean(SD)	558.4 ± 360.8	687.9 ± 426.6	0.326
Median	(486.5)	(641.6)	
Plasma level at 360 minutes/ pg/mL			
Mean(SD)	100.5 ± 68.8	209.9 ± 174.3	0.226
Median	(74.1)	(215.0)	
Area under the curve to 360 minutes (AUC_{360})/ pg · hr/mL			
Mean(SD)	1148.4 ± 611.6	1292.8 ± 821.1	0.545
Median	(938.0)	(1274.6)	
Plasma level at 380 minutes/ pg/mL			
Mean(SD)	331.4 ± 281.3	369.2 ± 288.1	0.597
Median	(251.0)	(382.0)	
Area under the curve to 380			

minutes (AUC_{380})/ pg · hr/mL Mean(SD) Median	1220.4 ± 665.5 (977.7)	1389.4 ± 883.0 (1376.5)	0.496
Plasma level at 420 minutes/ pg/mL Mean(SD) Median	610.5 ± 402.0 (481.0)	255.3 ± 212.7 (239.0)	0.041
Area under the curve to 420 minutes (AUC_{420})/ pg · hr/mL Mean(SD) Median	1534.3 ± 840.0 (1188.9)	1597.5 ± 1009.0 (1570.6)	0.650
Plasma level at 540 minutes/ pg/mL Mean(SD) Median	91.5 ± 37.2 (93.3)	127.3 ± 150.8 (54.2)	0.406
Area under the curve to 540 minutes (AUC_{540})/ pg · hr/mL Mean(SD) Median	2236.3 ± 1170.9 (1792.2)	1980.2 ± 1289.4 (1808.3)	0.821
Plasma level at 560 minutes/ pg/mL Mean(SD) Median	429.6 ± 164.1 (514.5)	212.4 ± 209.7 (145.0)	0.028
Area under the curve to 560 minutes (AUC_{560})/ pg · hr/mL Mean(SD) Median	2323.1 ± 1186.1 (1882.0)	2036.8± 1333.9 (1838.4)	0.762
Plasma level at 600 minutes/ pg/mL Mean(SD) Median	568.3 ± 307.6 (590.0)	215.2 ± 257.7 (121.0)	0.007
Area under the curve to 600 minutes (AUC_{600})/ pg · hr/mL Mean(SD) Median	2655.8 ± 1292.9 (2179.7)	2179.3 ± 1444.2 (1910.7)	0.450
Plasma level at 720 minutes/ pg/mL Mean(SD) Median	107.7 ± 39.3 (120.0)	101.9 ± 163.0 (25.1)	0.023
Area under the curve to 720 minutes (AUC_{720})/ pg · hr/mL Mean(SD)	3331.8 ± 1570.1	2496.4 ± 1762.8	0.226

Median	(3037.3)	(2034.0)	
Plasma level at 740 minutes/ pg/mL			
Mean(SD)	483.1 ± 234.4	188.5 ± 141.5	0.002
Median	(436.0)	(150.0)	
Area under the curve to 740 minutes (AUC_{740})/ pg · hr/mL			
Mean(SD)	3430.3 ± 1600.8	2544.7± 1799.9	0.226
Median	(3115.6)	(2057.6)	
Plasma level at 780 minutes/ pg/mL			
Mean(SD)	323.8 ± 154.0	157.9 ± 173.8	0.007
Median	(276.0)	(85.0)	
Area under the curve to 780 minutes (AUC_{780})/ pg · hr/mL			
Mean(SD)	3699.2 ± 1674.3	2433.7 ± 1829.4	0.072
Median	(3353.1)	(2013.3)	
Plasma level at 900 minutes/ pg/mL			
Mean(SD)	98.9 ± 71.3	101.2 ± 154.5	0.060
Median	(81.0)	(27.6)	
Area under the curve to 900 minutes (AUC_{900})/ pg · hr/mL			
Mean(SD)	4342.6 ± 1723.3	2655.9± 2056.4	0.031
Median	(4032.0)	(2107.0)	

Legend to Figure 1

Figure 1 Plasma concentrations of misoprostol acid after vaginal and sublingual administration of repeated doses of misoprostol

Figure 2 Areas under the time-concentration curves of plasma misoprostol acid in the vaginal and sublingual groups

Figure 3 Plasma concentrations of misoprostol acid in the sublingual group and the two subgroups of women in the vaginal group: (a) with vaginal bleeding and (b) without vaginal bleeding

Figure 4 Areas under the time-concentration curves of plasma misoprostol acid in the two subgroups of women in the vaginal group: (a) with vaginal bleeding and (b) without vaginal bleeding.

Figure 1

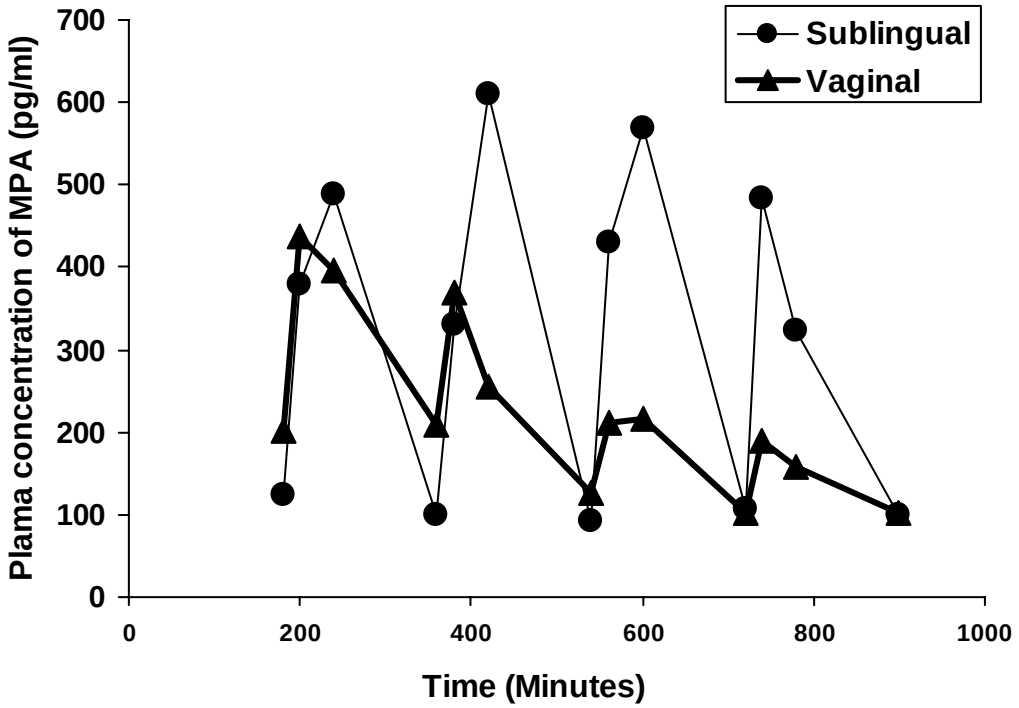

Figure 2

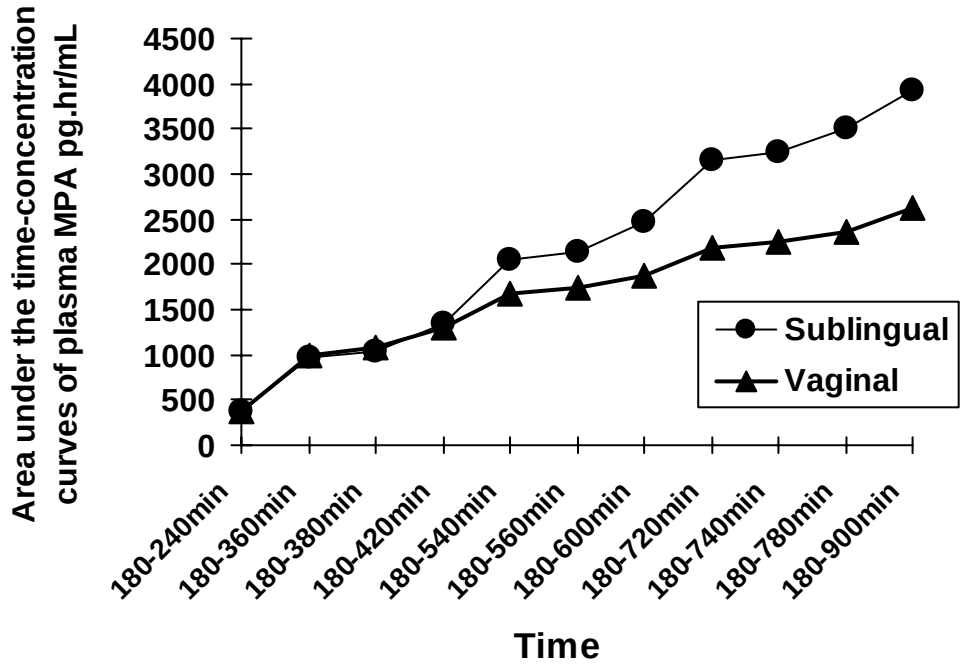

Figure 3

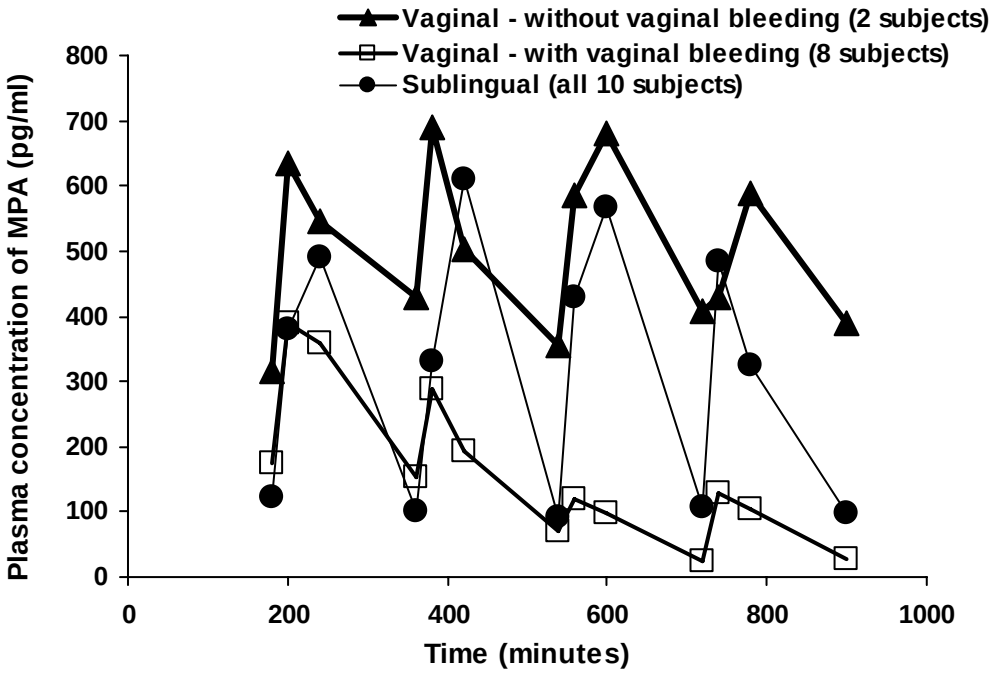

Figure 4