

1 **Title:** Pharmacokinetics of repeated doses of misoprostol

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3 **Running title:** Pharmacokinetics of misoprostol

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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

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2 Introduction:

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

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

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4 **Materials and methods**

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6 Twenty pregnant women requesting termination of pregnancy at a gestation of less than 12 weeks
7 were recruited into the study. These 20 women were recruited from women requesting surgical
8 termination of pregnancy. The study was approved by the Institutional Review Board of the
9 University of Hong Kong / Hospital Authority Hong Kong West Cluster. Inclusion criteria were
10 healthy women who were pregnant for less than 12 weeks. Women with a history of allergy to
11 misoprostol and major medical problems were excluded. The subjects were asked to keep fasted
12 overnight and were admitted to the hospital on the morning one day before the operation. They
13 were randomized into 2 groups to receive 400 µg of misoprostol every 3 hours for 5 doses either
14 sublingually or vaginally. The randomization schedule was generated by computer and the
15 allocations were put in opaque sealed envelopes. Sublingual misoprostol was given by putting 2
16 tablets of misoprostol under the tongue and allowing them to dissolve spontaneously. For vaginal
17 misoprostol, two tablets of the drug were inserted into the posterior fornix of the vagina by one of
18 the investigators. Venous blood samples (10 ml) were drawn over the next 15 hours at 180, 200,
19 240, 360, 380, 420, 540, 560, 600, 720, 740, 780 and 900 minutes after the administration of
20 misoprostol. The time intervals were chosen according to our previous pharmacokinetic study
21 which showed that the peak concentration was reached after a median of 20 and 60 minutes for
22 sublingual and vaginal administration respectively (Tang et al 2002). We did not collect blood
23 samples in the first 180 minutes because the data were already available in our previous study
24 (Tang et al 2002). Surgical termination of pregnancy with vacuum aspiration was performed for
25 these subjects if there was an on-going pregnancy or incomplete abortion upon completion of the 5
26 doses of misoprostol. The blood samples were centrifuged to obtain the plasma and frozen in

1 liquid nitrogen immediately. The samples were then stored at below -20°C and were sent to
2 Department of Pediatrics, Philipps University Marburg for analysis. MPA was determined in the
3 plasma samples using gas chromatography/tandem mass spectrometry (GC/MS/MS). After addition
4 of 15(S)-15-methyl prostaglandin E_2 (15-methyl-PGE $_2$) as internal standard, MPA was extracted
5 from both matrices using a reversed phase cartridge. The prostanoids were derivatized with *O*-
6 2,3,4,5,6-pentafluorobenzylhydroxylamine hydrochloride (PFBHA) and 2,3,4,5,6-
7 pentafluorobenzylbromide (PFBB) to the pentafluorobenzyl oxime (PFBO)-pentafluorobenzyl ester
8 (PFB) derivatives. The sample was applied to TLC with ethylacetate/hexane 1:1 (v/v) as the
9 developing solvent. The corresponding zone was extracted. After derivatization to the
10 trimethylsilylether, MPA was determined by GC/MS/MS using the [M-pentafluorobenzyl] $^-$ -ions as
11 precursor in the negative ion chemical ionization mode. The product ions used for quantification
12 were [P - 2TMSOH - C $_6$ F $_5$ CH $_2$ OH] $^-$ (MPA) and [P - 2TMSOH - C $_6$ F $_5$ CH $_2$ OH - CO $_2$] $^-$ (15-methyl-
13 PGE $_2$), respectively. The detection limit of the assay is 1 pg/sample.

14 The primary outcome measures of the study were the area under the curve of plasma
15 concentrations of MPA against time from 180 to 900 minutes (AUC $_{180-900}$). The area under the
16 time-concentration curve was calculated by the trapezoidal method. The area under the time-
17 concentration curve was divided into trapezium segments according to the time intervals of blood
18 sampling. The area of each segment was computed according to the following formula for
19 calculation of trapezium area: $0.5 [C_x + C_{x-1}] [\text{time interval}]$, $x = 1$ to 12 (x is the order of the blood
20 samplings). The AUC $_{180-900}$ was calculated by summing the 12 trapezium segments. No similar
21 study was found in the literature on the pharmacokinetics of repeated doses of sublingual or vaginal
22 misoprostol. According to a previous pharmacokinetic study on a single dose of misoprostol, 10
23 subjects in each arm will have 80% power in detecting a 50% difference in bioavailability at 5%
24 significance level.

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

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

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4 **Results**

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

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

1 vaginal bleeding and abortion were significantly lower than the subgroup without vaginal bleeding
2 at 540 minutes ($p<0.05$), 560 minutes ($p<0.05$), 600 minutes ($p<0.05$), 720 minutes ($p<0.05$), 740
3 minutes ($p<0.05$) and 740 minutes ($p<0.05$). Because of the progressive decline in the peak plasma
4 concentrations of MPA after vaginal administration of repeated doses of misoprostol in the vaginal
5 bleeding group, the areas under the time-concentration curve of MPA in this subgroup were
6 significantly lower than those in the subgroup with no vaginal bleeding at 720 minutes ($p<0.05$)
7 and 740 minutes ($p<0.05$). In the group of women given misoprostol sublingually, the plasma
8 concentrations of MPA were comparable in the two subgroups of women with or without vaginal
9 bleeding (data not shown). The plasma concentrations of MPA in the two subgroups of women
10 given misoprostol vaginally were also compared with those in the sublingual group. The plasma
11 concentrations of MPA in the subgroup of women with vaginal bleeding after vaginal
12 administration of misoprostol were significantly lower than those after sublingual administration
13 (whole group) at 420 minutes ($p<0.01$), 560 minutes ($p<0.001$), 600 minutes ($p<0.001$), 720
14 minutes ($p<0.001$), 740 minutes ($p<0.001$), 780 minutes ($p<0.001$) and 900 minutes ($p<0.001$). The
15 areas under the time-concentrations curves of MPA in this subgroup were also significantly lower
16 than those in the sublingual group at 720 minutes ($p<0.05$), 740 minutes ($p<0.05$), 780 minutes
17 ($p<0.05$) and 900 minutes ($p<0.01$). On the other hand, the plasma concentrations of MPA in the
18 subgroup of women without vaginal bleeding after vaginal administration of misoprostol were
19 significantly higher than those in the sublingual group (whole group with and without vaginal
20 bleeding) at 360 minutes ($p<0.05$), 540 minutes ($p<0.05$) and 90 minutes ($p<0.05$). Although the
21 areas under the time-concentration curves of MPA in this subgroup without vaginal bleeding after
22 vaginal administration of misoprostol were all higher than those in the sublingual group, the
23 differences were not statistically significant, probably because of the small sample size in this
24 subgroup.

25

26 **Discussion**

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

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

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

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

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

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

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

17

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5

1 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

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1 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) Median	123.1 ± 119.5 (86.8)	202.2 ± 143.2 (171.5)	0.096
Area under the curve to 180 minutes (AUC ₁₈₀)/ pg · hr/mL* Mean(SD) Median	184.7 ± 179.3 (130.2)	303.4 ± 214.9 (257.3)	0.096
Plasma level at 200 minutes/ pg/mL Mean(SD) Median	380.0 ± 239.2 (257.0)	438.2 ± 293.3 (394.5)	0.597
Area under the curve to 200 minutes (AUC ₂₀₀)/ pg · hr/mL Mean(SD) Median	268.6 ± 233.3 (229.8)	410.1 ± 272.2 (349.5)	0.131
Plasma level at 240 minutes/ pg/mL Mean(SD) Median	489.5 ± 213.6 (423.5)	395.1 ± 247.6 (429.0)	0.406
Area under the curve to 240 minutes (AUC ₂₄₀)/ pg · hr/mL Mean(SD) Median	558.4 ± 360.8 (486.5)	687.9 ± 426.6 (641.6)	0.326
Plasma level at 360 minutes/ pg/mL Mean(SD) Median	100.5 ± 68.8 (74.1)	209.9 ± 174.3 (215.0)	0.226
Area under the curve to 360 minutes (AUC ₃₆₀)/ pg · hr/mL Mean(SD) Median	1148.4 ± 611.6 (938.0)	1292.8 ± 821.1 (1274.6)	0.545
Plasma level at 380 minutes/ pg/mL Mean(SD) Median	331.4 ± 281.3 (251.0)	369.2 ± 288.1 (382.0)	0.597
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) Median	483.1 ± 234.4 (436.0)	188.5 ± 141.5 (150.0)	0.002
Area under the curve to 740 minutes (AUC ₇₄₀)/ pg · hr/mL	Mean(SD) Median	3430.3 ± 1600.8 (3115.6)	2544.7 ± 1799.9 (2057.6)	0.226
Plasma level at 780 minutes/ pg/mL	Mean(SD) Median	323.8 ± 154.0 (276.0)	157.9 ± 173.8 (85.0)	0.007
Area under the curve to 780 minutes (AUC ₇₈₀)/ pg · hr/mL	Mean(SD) Median	3699.2 ± 1674.3 (3353.1)	2433.7 ± 1829.4 (2013.3)	0.072
Plasma level at 900 minutes/ pg/mL	Mean(SD) Median	98.9 ± 71.3 (81.0)	101.2 ± 154.5 (27.6)	0.060
Area under the curve to 900 minutes (AUC ₉₀₀)/ pg · hr/mL	Mean(SD) Median	4342.6 ± 1723.3 (4032.0)	2655.9 ± 2056.4 (2107.0)	0.031

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1 Legend to Figure 1
2
3 Figure 1 Plasma concentrations of misoprostol acid after vaginal and sublingual administration of
4 repeated doses of misoprostol
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6 Figure 2 Areas under the time-concentration curves of plasma misoprostol acid in the vaginal and
7 sublingual groups
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9 Figure 3 Plasma concentrations of misoprostol acid in the sublingual group and the two subgroups
10 of women in the vaginal group: (a) with vaginal bleeding and (b) without vaginal bleeding
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12 Figure 4 Areas under the time-concentration curves of plasma misoprostol acid in the two
13 subgroups of women in the vaginal group: (a) with vaginal bleeding and (b) without vaginal
14 bleeding.
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1 Figure 1

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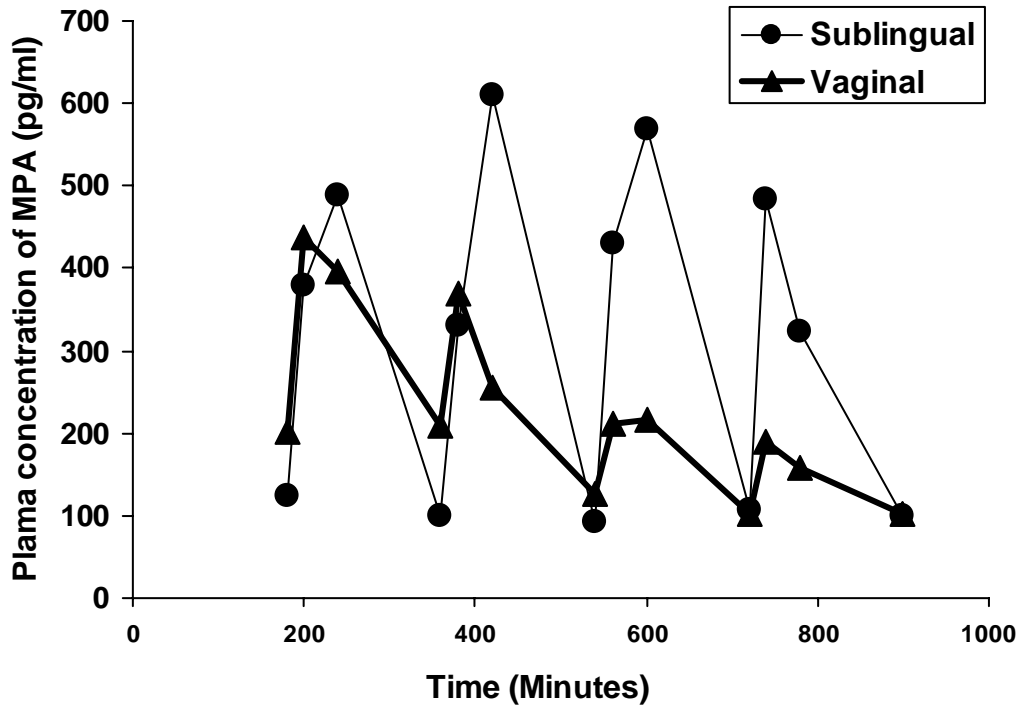
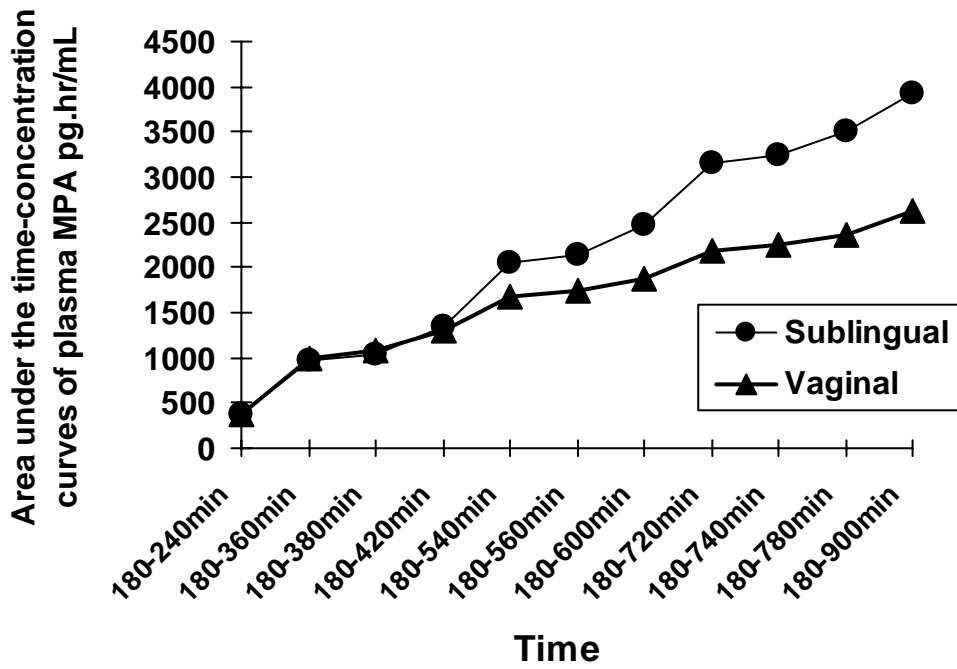
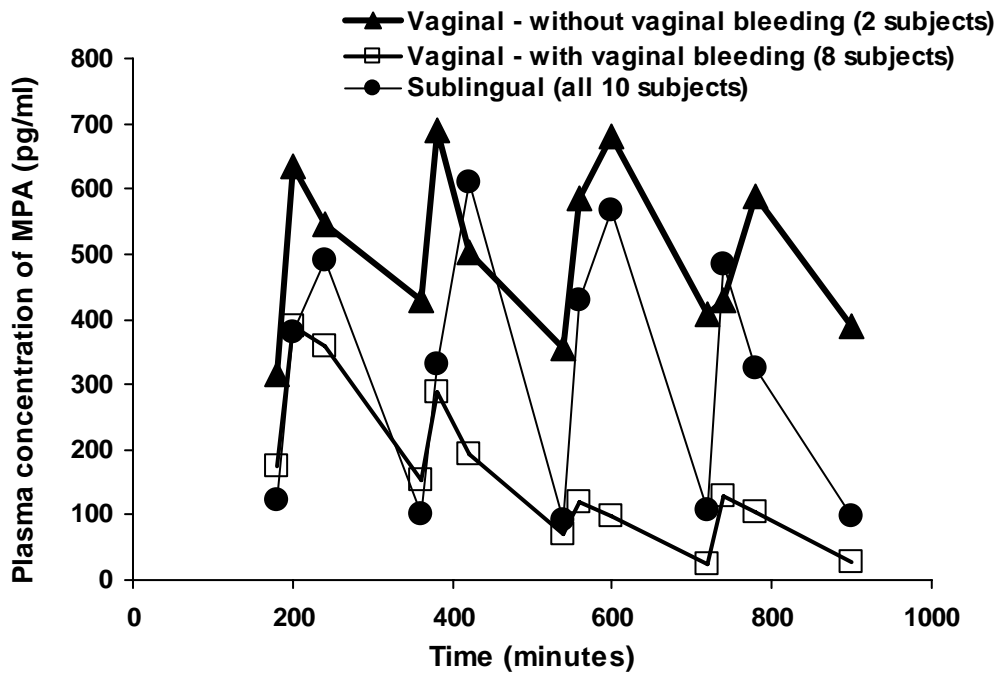


Figure 2



1 Figure 3



26 Figure 4

