Pharmacokinetics of repeated doses of misoprostol

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Introduction

Misoprostol is widely used in obstetrics and gynaecology for medical abortion, cervical priming and induction of labour. Although misoprostol was 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; whereas 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 h after sublingual administration, but the plasma level was still maintained at the end of 6 h 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 such as 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

Background:
Misoprostol is widely used in obstetrics and gynaecology for medical abortion, cervical priming and induction of labour. To aid the design of effective and safe regimens, we have investigated the pharmacokinetic parameters after the vaginal or sublingual administration of repeated doses of 400 μg of misoprostol.

Methods:
Women undergoing termination of pregnancy by suction evacuation were randomized to receive 400 μg of sublingual or vaginal misoprostol every 3 h for five doses. Venous blood was taken at 180, 200, 240, 360, 380, 420, 540, 560, 600, 720, 740, 780 and 900 min after the first dose of misoprostol for determination of the plasma level of misoprostol acid (MPA).

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. After the third dose, the peak plasma levels of MPA after sublingual misoprostol were significantly higher than those after vaginal administration. After the final dose, the area under the MPA concentration–time curve after sublingual administration was significantly higher than that after vaginal misoprostol (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.

Conclusions:
The peak plasma level of MPA after each dose of misoprostol is higher and the bioavailability is also greater after sublingual administration, compared with that after vaginal administration, of repeated doses of misoprostol. 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
pharmacokinetics of misoprostol after vaginal or sublingual administra-
tion of repeated doses of misoprostol.

Materials and Methods

There were 20 pregnant women, requesting termination of pregnancy at a
gestation of <12 weeks, 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 cri-
teria 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 1 day before the operation.
They were randomized into two groups to receive 400 μg of misoprostol
every 3 h for five doses either sublingually or vaginally. Although a previous
study showed that the plasma concentration of MPA was maintained at the
end of 6 h after vaginal administration, we chose the 3-hourly interval
because a previous study showed that the regimen of 3-hourly vaginal
administration of misoprostol was more effective than the regimen of
6-hourly vaginal administration of misoprostol (Wong et al., 2000). The
randomization schedule was generated by computer and the allocations
were put in opaque, sealed envelops. Sublingual misoprostol was given
by putting two tablets of misoprostol 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 by repeated
venepunctures over the next 15 h at 180, 200, 240, 360, 380, 420, 540,
560, 600, 720, 740, 780 and 900 min after the administration of misopros-
tol. The time intervals were chosen according to our previous pharmaco-
kinec study which showed that the peak concentration was reached after
a median of 20 and 60 min for sublingual and vaginal administration,
respectively (Tang et al., 2002). We did not collect blood samples in the
first 180 min because the data were already available from our pre-
vious study (Tang et al., 2002). Surgical termination of pregnancy with
vacuum aspiration was performed for these subjects if there was an
ongoing pregnancy or incomplete abortion upon completion of the five
doses of misoprostol. The blood samples were centrifuged to obtain
the plasma, then frozen in liquid nitrogen immediately. The samples
were then stored at below –20°C and were sent to Department of Pedi-
atrics, Philippus University Marburg, for analysis. MPA was determined in
the plasma samples using gas chromatography/tandem mass spectrometry
(GC/MS/MS). After addition of 15(–15-methyl prostaglandin E2
(15-methyl-PGE2) as the internal standard, MPA was extracted from
the plasma, then frozen in liquid nitrogen immediately. The samples
were then stored at below –20°C and were sent to Department of Pedi-
atrics, Philippus 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 E2
(15-methyl-PGE2) as the internal standard, MPA was extracted from
both matrices using a reversed-phase cartridge. The prostanoids were
derivatized with 0–2,3,4,5,6-pentafluorobenzylhydroxylamine hydrochlor-
ide and 2,3,4,5,6-pentafluorobenzylidene (PFB) to the pentafluoro-
benzyl oxime–pentafluorobenzyl ester 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 trimethylsilyl ether, 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–2TMSO–C6F5CH2OH]– (MPA) and [P–2TMSO–C6F5CH2OH–
CO3]– (15-methyl-PGE2), respectively. The detection limit of the assay
is 1 pg/sample.

The primary outcome measure of the study was the area under the
curve of plasma concentrations of MPA against time from 180 to
900 min (AUC180–900). The area under the time–concentration 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), \(x = 1–12\) (x is the order of the blood sampling). The
AUC_{180–900} was calculated by the sum of 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 pre-
vious pharmacokinetic study on a single dose of misoprostol, 10 subjects
in each arm will have 80% power in detecting a 50% difference in bioavail-
ability at 5% significance level.

SPSS 11 for Windows statistical package was used for data analysis.
Continuous variables were compared by Student’s t-test if the data were
normally distributed. Kruskal–Wallis test or Mann–Whitney test
was used if the data were skewed. P-values (two-tailed) of <0.05 were
taken as statistically significant.

Results

The age, gestational age and body surface area of the two groups are
listed in Table I. There was no statistically significant difference
between the two groups in these demographic characteristics.
The mean plasma concentrations of MPA after administration of 400 μg
misoprostol every 3 h for five doses by sublingual and vaginal routes
are shown in Fig. 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 II and Fig. 2). The peak plasma con-
centrations in the vaginal group were achieved at 20 min after each
dose of misoprostol except for the fourth dose when the peak
plasma concentration was achieved at 60 min. In the sublingual
group, the highest plasma concentration was achieved between 20 and
60 min after each dose of misoprostol.

As the majority of women developed vaginal bleeding after adminis-
tration 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, whereas
two women had no vaginal bleeding. In the sublingual
group, six women developed vaginal bleeding and aborted, whereas

<table>
<thead>
<tr>
<th>Table I</th>
<th>Demographic characteristics of the 20 subjects (SD)</th>
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<tbody>
<tr>
<td>Sublingual</td>
<td>Vaginal</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>Mean gestational age (days)</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>Mean height (cm)</td>
</tr>
<tr>
<td>Mean body surface area (m²)</td>
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</tr>
<tr>
<td>(n = 10)</td>
<td>(n = 10)</td>
</tr>
<tr>
<td>31.7 (8.3)</td>
<td>29.8 (7.7)</td>
</tr>
<tr>
<td>59.9 (14.2)</td>
<td>54.8 (14.2)</td>
</tr>
<tr>
<td>52.1 (9.9)</td>
<td>51.2 (4.0)</td>
</tr>
<tr>
<td>158.1 (6.5)</td>
<td>159.3 (4.1)</td>
</tr>
<tr>
<td>1.51 (0.16)</td>
<td>1.50 (0.06)</td>
</tr>
</tbody>
</table>
four women did not develop any significant vaginal bleeding. The plasma concentrations of MPA in these four subgroups were analysed separately: (i) vaginal subgroup with vaginal bleeding, (ii) vaginal subgroup without vaginal bleeding, (iii) sublingual subgroup with vaginal bleeding and (iv) sublingual subgroup without vaginal bleeding. The results are shown in Figs 3 and 4. In the vaginal subgroup with vaginal bleeding, the peak plasma concentrations of MPA after each dose showed a progressive decline but this was not observed in the vaginal subgroup without vaginal bleeding. The plasma concentrations of the two sublingual subgroups with or without vaginal bleeding were similar. The plasma MPA concentrations in the vaginal subgroup with vaginal bleeding were significantly lower than those in the sublingual subgroup with vaginal bleeding at 420 min ($P < 0.03$), 560 min ($P < 0.001$), 720 min ($P < 0.001$), 740 min ($P < 0.001$) and 800 min ($P < 0.01$) so that the area under the MPA concentration–time curve became significantly lower in the former subgroup after 780 min ($P < 0.05$). Although the plasma MPA concentrations in the vaginal subgroup without vaginal bleeding were higher than those in the sublingual subgroup without vaginal bleeding except for the plasma concentrations at 420 and 740 min, the differences were not statistically significant. The area under the MPA concentration–time curve was higher in the vaginal subgroup without vaginal bleeding than the sublingual subgroup without vaginal bleeding, but the difference was not statistically significant. When we compared the pharmacokinetics of misoprostol in the two subgroups of women in the vaginal administration group, the plasma concentrations of MPA in the subgroup with significant amount of vaginal bleeding and abortion were significantly lower than in the subgroup with vaginal bleeding at 540 min ($P < 0.05$), 560 min ($P < 0.05$), 600 min ($P < 0.05$), 720 min ($P < 0.05$) and 740 min ($P < 0.05$). 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 area under the time–concentration curves of MPA in this subgroup were significantly lower than those in the subgroup with no vaginal bleeding at 720 min ($P < 0.05$) and 740 min ($P < 0.05$). 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.

**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 in plasma level of MPA after sublingual administration, the plasma level of MPA dropped more rapidly than that after vaginal administration so that after 3 h 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 h after vaginal administration (Aronsson et al., 2007). Therefore, it is expected that with repeated vaginal administration at an interval of <6 h, 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. The results in this study showed that at 180 min, the plasma MPA concentration in the vaginal group was higher than that in the sublingual group. This is consistent with the results of our
<table>
<thead>
<tr>
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<th>Sublingual (n = 10)</th>
<th>Vaginal (n = 10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma level at 180 min/pg/ml</td>
<td>123.1 ± 119.5 (86.8)</td>
<td>202.2 ± 143.2 (171.5)</td>
<td>0.096</td>
</tr>
<tr>
<td>Area under the curve to 180 min (AUC180)/pg h/ml</td>
<td>184.7 ± 179.3 (130.2)</td>
<td>304.4 ± 214.9 (257.3)</td>
<td>0.096</td>
</tr>
<tr>
<td>Plasma level at 200 min/pg/ml</td>
<td>380.0 ± 239.2 (257.0)</td>
<td>438.2 ± 293.3 (394.5)</td>
<td>0.597</td>
</tr>
<tr>
<td>Area under the curve to 200 min (AUC200)/pg h/ml</td>
<td>268.6 ± 233.3 (229.8)</td>
<td>410.1 ± 272.2 (349.5)</td>
<td>0.131</td>
</tr>
<tr>
<td>Plasma level at 240 min/pg/ml</td>
<td>489.5 ± 213.6 (423.5)</td>
<td>395.1 ± 247.6 (429.0)</td>
<td>0.406</td>
</tr>
<tr>
<td>Area under the curve to 240 min (AUC240)/pg h/ml</td>
<td>558.4 ± 360.8 (486.5)</td>
<td>687.9 ± 426.6 (641.6)</td>
<td>0.326</td>
</tr>
<tr>
<td>Plasma level at 360 min/pg/ml</td>
<td>100.5 ± 68.8 (74.1)</td>
<td>209.9 ± 174.3 (215.0)</td>
<td>0.226</td>
</tr>
<tr>
<td>Area under the curve to 360 min (AUC360)/pg h/ml</td>
<td>1148.4 ± 611.6 (938.0)</td>
<td>1292.8 ± 821.1 (1274.6)</td>
<td>0.545</td>
</tr>
<tr>
<td>Plasma level at 380 min/pg/ml</td>
<td>331.4 ± 281.3 (251.0)</td>
<td>369.2 ± 288.1 (382.0)</td>
<td>0.597</td>
</tr>
<tr>
<td>Area under the curve to 380 min (AUC380)/pg h/ml</td>
<td>1220.4 ± 665.5 (977.7)</td>
<td>1389.4 ± 883.0 (1376.5)</td>
<td>0.496</td>
</tr>
<tr>
<td>Plasma level at 420 min/pg/ml</td>
<td>610.5 ± 402.0 (481.0)</td>
<td>255.3 ± 212.7 (239.0)</td>
<td>0.041</td>
</tr>
<tr>
<td>Area under the curve to 420 min (AUC420)/pg h/ml</td>
<td>1534.3 ± 840.0 (1188.9)</td>
<td>1597.5 ± 1009.0 (1570.6)</td>
<td>0.65</td>
</tr>
<tr>
<td>Plasma level at 540 min/pg/ml</td>
<td>91.5 ± 37.2 (93.3)</td>
<td>127.3 ± 150.8 (54.2)</td>
<td>0.406</td>
</tr>
<tr>
<td>Area under the curve to 540 min (AUC540)/pg h/ml</td>
<td>2236.3 ± 1170.9 (1792.2)</td>
<td>1980.2 ± 1289.4 (1808.3)</td>
<td>0.821</td>
</tr>
<tr>
<td>Plasma level at 560 min/pg/ml</td>
<td>429.6 ± 164.1 (514.5)</td>
<td>212.4 ± 209.7 (145.0)</td>
<td>0.028</td>
</tr>
<tr>
<td>Area under the curve to 560 min (AUC560)/pg h/ml</td>
<td>2323.1 ± 1186.1 (1882.0)</td>
<td>2036.8 ± 1333.9 (1838.4)</td>
<td>0.762</td>
</tr>
<tr>
<td>Plasma level at 600 min/pg/ml</td>
<td>568.3 ± 307.6 (590.0)</td>
<td>215.2 ± 257.7 (121.0)</td>
<td>0.007</td>
</tr>
<tr>
<td>Area under the curve to 600 min (AUC600)/pg h/ml</td>
<td>2655.8 ± 1292.9 (2179.7)</td>
<td>2179.3 ± 1444.2 (1910.7)</td>
<td>0.45</td>
</tr>
<tr>
<td>Plasma level at 720 min/pg/ml</td>
<td>107.7 ± 39.3 (120.0)</td>
<td>101.9 ± 163.0 (25.1)</td>
<td>0.023</td>
</tr>
<tr>
<td>Area under the curve to 720 min (AUC720)/pg h/ml</td>
<td>3331.8 ± 1570.1 (3037.3)</td>
<td>2496.4 ± 1762.8 (2034.0)</td>
<td>0.226</td>
</tr>
<tr>
<td>Plasma level at 740 min/pg/ml</td>
<td>483.1 ± 234.4 (436.0)</td>
<td>188.5 ± 141.5 (150.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Area under the curve to 740 min (AUC740)/pg h/ml</td>
<td>3430.3 ± 1600.8 (3115.6)</td>
<td>2544.7 ± 1799.9 (2057.6)</td>
<td>0.226</td>
</tr>
<tr>
<td>Plasma level at 780 min/pg/ml</td>
<td>323.8 ± 154.0 (276.0)</td>
<td>157.9 ± 173.8 (85.0)</td>
<td>0.007</td>
</tr>
</tbody>
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Continued
previous study. The rapid rise in the plasma MPA concentrations after the subsequent doses of misoprostol given probably reflected the summation of the absorption of the misoprostol left from previous doses and the absorption from the newly administered dose. However, the results in this study do not appear to be entirely consistent with the hypothesis of accumulation of misoprostol after vaginal administration. The peak plasma level after successive doses of vaginal misoprostol actually became lower and lower. As a result, the total bioavailability of the drug at the end of the study at 900 min is higher for sublingual misoprostol. It seems that there is no accumulation of MPA after repeated vaginal administration of misoprostol in the whole vaginal group (which includes all women with or without vaginal bleeding). 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 of four subgroups of women: (i) vaginal subgroup with vaginal bleeding, (ii) vaginal subgroup without vaginal bleeding, (iii) sublingual subgroup with vaginal bleeding and (iv) sublingual subgroup without vaginal bleeding. The results showed that the progressive decline in the peak plasma concentrations of MPA occurred only in the vaginal subgroup with significant vaginal bleeding. In the vaginal subgroup without vaginal bleeding, the plasma concentrations of MPA did not decline with repeated doses and were higher than those in the sublingual group without vaginal bleeding at most of the time points, although 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. The finding that the plasma levels of MPA in the vaginal group without vaginal bleeding were at most of the time points higher than those in the sublingual group without vaginal bleeding suggests that some accumulation may

Table II

<table>
<thead>
<tr>
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<th>Sublingual (n = 10)</th>
<th>Vaginal (n = 10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area under the curve to 780 min (AUC780)/pg h/ml</td>
<td>Mean ± SD (median)</td>
<td>3699.2 ± 1674.3 (3353.1)</td>
<td>2433.7 ± 1829.4 (2013.3)</td>
</tr>
<tr>
<td>Plasma level at 900 min/pg/ml</td>
<td>Mean ± SD (median)</td>
<td>98.9 ± 71.3 (81.0)</td>
<td>101.2 ± 154.5 (27.6)</td>
</tr>
<tr>
<td>Area under the curve to 900 min (AUC900)/pg h/ml</td>
<td>Mean ± SD (median)</td>
<td>4342.6 ± 1723.3 (4032.0)</td>
<td>2655.9 ± 2056.4 (2107.0)</td>
</tr>
</tbody>
</table>

Figure 2

Areas under the time–concentration curves of plasma MPA in the vaginal and sublingual groups (the vertical bars represent standard errors of the mean).
Figure 3 Plasma concentrations of MPA in the sublingual subgroup with vaginal bleeding and the vaginal subgroup with vaginal bleeding (the vertical bars represent standard errors of the mean).

Figure 4 Plasma concentrations of MPA in the sublingual subgroup without vaginal bleeding and the vaginal subgroup without vaginal bleeding (the vertical bars represent standard errors of the mean).
be possible after vaginal administration of repeated doses of misoprostol. However, as the sample sizes are small, the results of subgroup analysis should be interpreted with caution. Further studies with larger sample sizes will be needed for a definitive conclusion. Moreover, the accumulation may only occur with a 3-hourly interval of vaginal administration but not with a 6-hourly vaginal administration.

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 400 mg of misoprostol given every 3 h for five doses in both the vaginal and 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 h, despite a low plasma level of MPA (Aronsson et al., 2004). It is also possible that higher plasma levels of MPA may lead to an increased but ineffective tonus rather than regular effective contractions (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 could 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., 2000a, b).

On the other hand, vaginal administration of misoprostol may not be appropriate in the prophylaxis or management of post-partum 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, when administering repeated doses, 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 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.

**Author’s role**

O.S.T.: design of study, data analysis and interpretation, clinical management of subjects, drafting of manuscript and final approval of paper. H.S.: design of study, assay of misoprostol acid, data interpretation, revising the paper and final approval of paper. S.W.H.L.: clinical management of subjects, data analysis, revising the paper and final approval of paper. P.C.H.: design of study, data analysis and interpretation, drafting of manuscript and final approval of paper.

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