Oral, Rectal, and Vaginal Pharmacokinetics of Misoprostol

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OBJECTIVE: To compare the pharmacokinetic profiles of orally, rectally, and vaginally administered misoprostol tablets in pregnant women.

METHODS: Women between 7 and 14 completed weeks of gestation were recruited and randomly assigned to be given 400 μg misoprostol orally, rectally, or vaginally 3 hours before surgical termination of pregnancy. Blood samples were obtained at 0, 7.5, 15, 30, 45, 60, 90, 120, and 240 minutes and later analyzed for plasma concentrations of misoprostol free acid (the principle metabolite).

RESULTS: Vaginal misoprostol was present in the circulation longer than oral misoprostol and had a greater area under curve at 240 minutes ($P < .001$). Rectal misoprostol had a similar pattern but a much lower area under curve at 240 minutes. Oral misoprostol had a significantly greater peak plasma concentration and a shorter duration to maximum concentration than either rectal or vaginal misoprostol (both $P < .001$).

CONCLUSION: Oral misoprostol tablet is also absorbed by the rectal and vaginal routes. Misoprostol administered in early pregnancy has route-dependent pharmacokinetics and is absorbed best when administered vaginally. (Obstet Gynecol 2004;103:866–70. © 2004 by The American College of Obstetricians and Gynecologists.)

LEVEL OF EVIDENCE: I

More than 30 different dosage regimens have been described for the use of misoprostol in obstetrics and gynecology. These varying regimens include at least 3 different routes of administration in a large number of observational and randomized studies. Certain dosages and modes of delivery have been investigated more extensively than others. Misoprostol 600 μg administered orally was examined in a large third-stage study involving 10,000 women.[1] The safety profile of this dosage regimen was established, although overall conclusions regarding the efficacy of misoprostol were debated (Shannon C, Winikoff B. Use of misoprostol in third stage of labour [letter]. Lancet 2002;359:709). The vaginal administration of misoprostol up to a dose of 800 μg for medical induction of abortion and cervical priming before surgical abortion is now recommended in the published guidelines.[2] The rectal administration of misoprostol at doses up to 1,000 μg has not been as extensively examined but seems to be proliferating widely around the world as evidenced in the literature.[3–7] Recent proposals include vaginal administration of misoprostol for prevention of postpartum hemorrhage as well as the use of the sublingual route for early pregnancy indications.[8,9]

Because the drug was developed for oral use, only orally formulated misoprostol tablets are available. However, these tablets are used orally, rectally, vaginally, and, more recently, sublingually. This might be considered an advantage because alterations of available formulation might interfere with its thermostability. Misoprostol's absorption profiles when administered by different routes should be compared because such comparisons may reveal weaknesses inherent in some of the proposed regimens. The results may also be used to fine-tune some regimens or suggest new regimens.

The purpose of this study is to elucidate and compare the pharmacokinetics of misoprostol 400 μg when given by the oral, rectal, or vaginal route. We examined misoprostol absorption in women before surgical termination of pregnancy.

METHODS

The study was performed at Chelsea and Westminster Hospital, London. The Riverside Research Ethics Committee of Chelsea and Westminster Hospital approved the study. Women were enrolled via the Chelsea and Westminster Hospital Termination Services clinic over a 7-month period. Eligible women were between 7 and 14 completed weeks of gestation. They were aged more than 18 years and had singleton pregnancies. Exclusion criteria were contraindications to prostaglandin therapy (eg, history of severe bronchial asthma, preexisting car-

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diac disease, and renal failure), renal disorders, and any other circumstances in which the clinician in charge felt that there were serious contraindications to involvement in the study. Women with a body mass index more than 25 kg/m^2 or less than 20 kg/m^2 were also excluded. Women were informed of the study and signed a consent form in the preoperative assessment clinic.

We chose the sample size of 10 women per group to have an 80% power to detect a 35% difference in the primary response measure (area under curve [AUC]), assuming a coefficient of variation of 25% using a 2-sided 5% significance level. This would correspond to an estimated increase in the mean of the primary outcome (AUC) from approximately 250 pg/h/mL in the oral arm to 340 pg/h/mL in the vaginal arm, with an estimated standard deviation of approximately 75 pg/h/mL. These estimates are based on the sample size calculation and results shown in previous misoprostol pharmacokinetic studies in gynecology.[10]

Sequentially numbered sealed opaque envelopes were prepared, each containing a folded slip of paper with the treatment route written on it: oral, rectal, or vaginal. The written treatment followed a randomized allocation that was prepared by an independent statistician using computer-generated random numbers with block randomization and varying block size. Thus, the investigator and patient could not predict the treatment.

When the patient was admitted to the surgical unit, the investigator opened the treatment envelope and informed the patient which treatment she would be receiving. The investigator administered misoprostol 400 μg to the subject by the route determined in the randomization envelope. Women receiving the misoprostol orally were observed swallowing the tablets with water. Women in the rectal misoprostol group had the tablets inserted digitally by an attendant. Those in the vaginal group had the tablets inserted digitally into the posterior fornix.

After administration of the randomized treatment, each patient was observed by the investigator for the presence of side effects. Three hours after tablet administration, surgical termination of the pregnancy was performed under general anesthesia.

Before administration of misoprostol, the investigator inserted an intravenous canula to allow removal of blood samples. Blood samples were obtained at 0, 7.5, 15, 30, 45, 60, 90, 120, and 240 minutes after drug administration. These samples were centrifuged for 30 minutes at 3,000*g*, and the plasma was then aliquoted into 1-mL lots and frozen at −20°C within 6 hours of being taken. Plasma was subsequently analyzed by using competitive enzyme linked immunosorbent assay (ELISA). The concentration of misoprostol free acid in each plasma sample was quantified.

Table 1. Demographic Characteristics of Study Subjects

	Oral (n = 9)	Rectal (n = 9)	Vaginal (n = 9)
Age (y)	25.7 (5.2)	23.6 (5.7)	24.5 (6.1)
Weight (kg)	62.2 (7.3)	61.0 (4.7)	64.2 (7.5)
Height (cm)	162.3 (11.2)	160.7 (8.9)	166.2 (13.0)

Values are expressed as mean (standard deviation).

Areas under the plasma misoprostol acid concentration time curve were calculated according to the trapezoidal method: AUC(T_n) = Sum^2, where AUC is the area under the curve, T = time, n = number of plasma measurements, and AUC(T_n) = area under the curve until the time of measurement n. We calculated the AUC through 240 minutes (AUC[240]) for all patients. Continuous variables are summarized as mean, standard deviation (SD), and range. We used one-way analysis of variance and corresponding *F* test to compare the mean maximum plasma concentration of misoprostol acid (C_{max}), time to C_{max} (T_{max}), and AUC(240) between the 3 trial arms. Mean difference and corresponding 95% confidence interval (CI) for difference in means were also calculated for comparison between any 2 specific groups. Two-sided tests were performed with a significance level set at 5%.

RESULTS

The 30 patients recruited were well matched for age, gestation, and other demographic characteristics (Table 1). Twenty-seven patients completed the study, 9 in each group (Figure 1). One patient decided to continue her pregnancy and declined the medication after her envelope had been opened. Two other patients declined further blood tests after the control sample had been taken.

Figure 2 shows the mean plasma concentration of misoprostol free acid after oral, rectal, and vaginal administration. In women receiving oral misoprostol, plasma concentration rose quickly, peaked between 7.5 and 30 minutes (mean = 14 minutes) after administration, fell steeply by 60 minutes, and remained low for the remainder of the study period. In contrast, plasma concentration of misoprostol free acid in women receiving the vaginal doses rose gradually, reached a maximum level between 45 and 120 minutes (mean = 65 minutes), and declined slowly. By 240 minutes after administration, the concentration reached an average of 88.5 pg/mL in the vaginal group, constituting 42% of the maximum level. The absorption pattern of rectal misoprostol demonstrates some qualitative similarity to the vaginal pattern. Plasma concentration of misoprostol free acid rose gradually and peaked at between 45 and 120 minutes (mean = 71.7 minutes), and then gradually fell. By 240

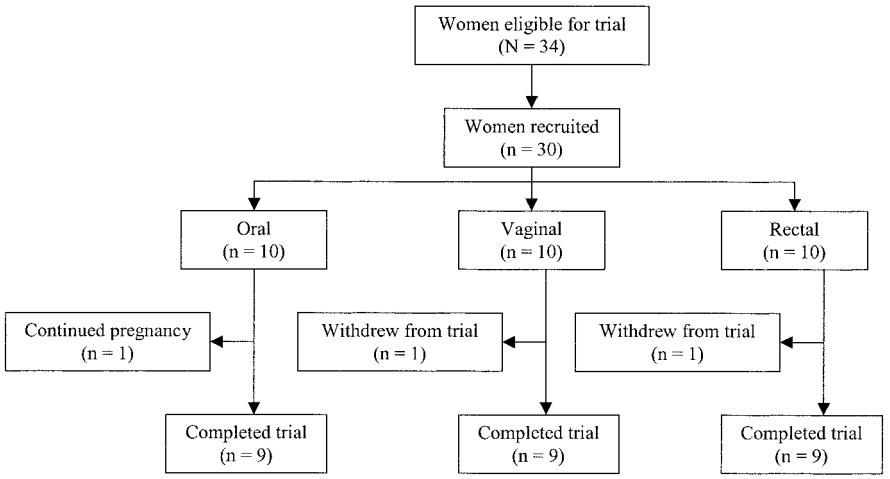

Figure 1. Patient flow chart.
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minutes, the average concentration in the rectal group was 32.8 pg/mL or 46% of the maximum. However, the graph clearly shows that rectal misoprostol levels are much lower than vaginal misoprostol levels, and thus AUC(240) is much greater in the vaginal group.

Table 2 summarizes the main outcome measures by randomized groups. The time interval taken to reach peak concentration levels, the maximum peak concentration, and the AUC(240) were significantly different among the 3 groups. However, specific comparison of the mean between any 3 groups showed that the oral arm had a significantly lower time interval to reach peak concentration levels than either vaginal or rectal arms, with a mean difference of 57.5 minutes between oral and rectal arms (95% CI 39.3, 75.7 minutes), and 50.8 minutes between oral and vaginal arms (95% CI 32.6, 69.0 minutes). We found no significant difference between rectal and vaginal arms in time interval to peak concentration. Rectal misoprostol had a significantly lower maximum peak concentration than either oral or vaginal misoprostol (mean differences 171.9 pg/mL with 95% CI 107, 236 between oral and rectal groups, and 124.0 pg/mL with 95% CI 60, 188 between vaginal and rectal groups). There was no significant difference between the oral and vaginal peak plasma concentration. Vaginal misoprostol had a significantly higher AUC(240) than either oral or rectal misoprostol, with the mean value in the vaginal arm more than double that in any other arm. Oral and rectal misoprostol AUC(240) were not significantly different from one another.

DISCUSSION

This study identifies 4 main findings. Oral misoprostol tablet is absorbed by both rectal and vaginal routes in early pregnancy. Misoprostol demonstrates a route-de-

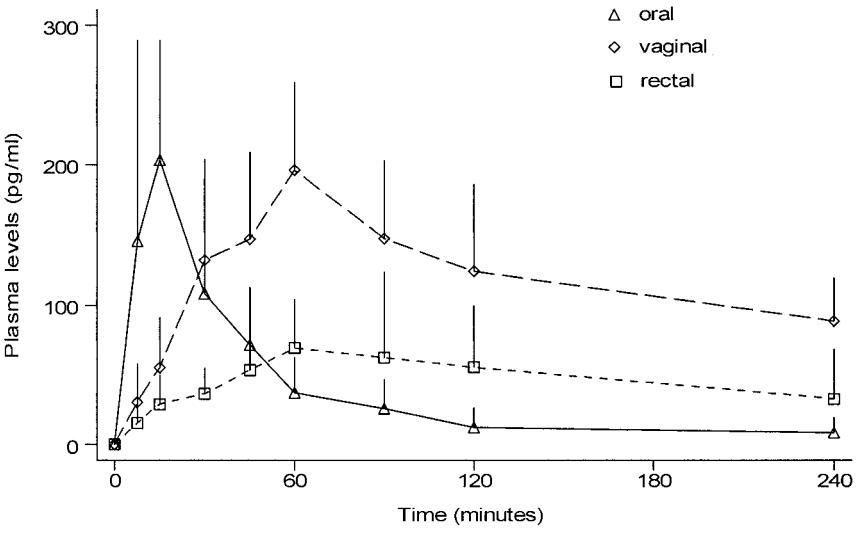

Figure 2. Mean plasma concentrations of misoprostol acid over time with oral, rectal, and vaginal administration. (Error bars represent 1 standard deviation.)
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Table 2. Pharmacokinetic Parameters of Oral, Rectal, and Vaginal Misoprostol

	Oral (n = 9)	Rectal (n = 9)	Vaginal (n = 9)	*P*
Maximum plasma concentration (pg/mL)	258.7 (83.8) [145–372]	86.8 (44.7) [59.0–200]	210.8 (63.0) [95–283]	< .001
Duration to maximum concentration (min)	14.2 (7.0) [7.5–30]	71.7 (23.5) [45–120]	65.0 (21.2) [45–120]	< .001
Area under the curve to 240 minutes (pg/h/mL)	151.8 (61.1) [56.8–222.4]	188.9 (126.1) [46.1–442.6]	446.0 (172.1) [129.0–647.4]	< .001

Values are expressed as mean (standard deviation) [range].

pendent pharmacokinetic profile, with best absorption following vaginal administration. Rectal misoprostol is associated with a qualitatively similar absorption curve to that of the vaginal route but with a lower bioavailability. Oral misoprostol reached a very high peak concentration very quickly before a rapid fall in plasma levels.

These findings will help fine-tune existing regimens and identify ideal routes of administration for different clinical indications. For example, prompt induction of myometrial contractility by misoprostol is desired in postpartum hemorrhage. This study confirms that oral misoprostol has the shortest interval to peak concentration compared with all other routes. This reproducible finding is relevant when formulating postpartum hemorrhage regimens and interventions. However, when misoprostol is administered by the vaginal or the rectal route, it remains in the circulation for a longer time. The threshold level of plasma misoprostol needed to produce a clinical response and its maintenance remains unknown. Tiny drug doses (25–50 μg), administered vaginally, were capable of inducing uterine contractility slowly and maintaining it for substantial time interval for induction of labor.

Shivering and hyperpyrexia were reported as side effects associated with orally administered misoprostol at dosages of 600 μg and 800 μg.[3,11] These side effects are reported with a much lower incidence with other routes of administration. These 2 specific side effects might be related to the very high peak levels reached with oral administration and are obstacles to administering misoprostol by higher dosages orally and probably sublingually.

The rectal and vaginal absorption of misoprostol could be pharmacologically manipulated to enhance bioavailability by changing the dosage or formulation. For example, rectal misoprostol may have a higher bioavailability in the third stage of labor than in the first trimester, probably because in the former the rectal mucosa is moister and thus enhances absorption. We have recently reported that, when misoprostol 600 μg is administered in the third stage of labor, peak levels higher than those noted in this study are achieved by both the oral and rectal route.[11] Thus, bioavailability may be dose-dependent, at least within the range of doses examined in these 2 studies.

Sublingual administration of misoprostol has been proposed as a potential method of medical abortion. A pharmacokinetics study suggested that sublingual misoprostol has a similarly shaped absorption profile to that of oral misoprostol and that the sublingual route gives higher peak concentrations and higher bioavailability than the oral route.[9] A subsequent clinical study showed that sublingual and oral misoprostol had similar efficacy in the management of silent miscarriage.[12] However, dose-dependent side effects, such as fever, shivering, and vomiting, are higher with the sublingual route.[13] It has been suggested that this increase in side effects is possibly due to very high peak drug levels achieved (Chong YS, Chua S, Arulkumaran S. Sublingual misoprostol for first trimester termination of pregnancy: safety concerns [letter]. Hum Reprod 2002;17:2777). We believe that the sublingual route does not offer an advantage over the oral route. The above pharmacokinetic study also demonstrated that tablet moistening in the nonoral route can increase bioavailability.[9] We did not moisten tablets in this study because there is no consensus on the role of moistening, but it may have resulted in higher bioavailability in the vaginal and rectal groups.

It is of interest that vaginal administration has also been proposed for clinical use in the third stage of labor.[8] Vaginal absorption of misoprostol is reliable, with minimal side effects, and has been established for use in abortion. The combined vaginal and oral route has been used widely and successfully to induce abortion in the second trimester.[2] This study has shown distinct pharmacokinetic characteristics for the 3 routes of administration investigated. There might be advantages in considering combination dosage regimens that use the speed of oral administration and the higher bioavailability and the longer persistence of either the rectal or vaginal route in other indications and in particular the third stage of labor and postpartum hemorrhage.

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