Comparison of misoprostol plasma concentrations following buccal and sublingual administration

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Abstract

Background: New indications for misoprostol include medical abortion, cervical softening, induction of labor and treatment of postpartum hemorrhage. Various routes of misoprostol administration under study include oral, vaginal, buccal, sublingual and rectal.

Materials and Methods: This was an open-label, randomized, cross-over study of the pharmacokinetic differences of buccal vs. sublingual misoprostol 800 μg in 10 healthy women.

Results: Of the 10 women enrolled, 2 withdrew after experiencing excessive cramping from the sublingual route of misoprostol. The mean misoprostol plasma concentration–time curves at 4 h [area under the curve (AUC)0–4] and the maximum concentration (Cmax) showed that levels were significantly higher for sublingual administration than the buccal route. Buccal misoprostol administration resulted in fewer symptoms and was found to be more acceptable.

Conclusions: Sublingual administration of misoprostol had a higher AUC and Cmax compared with buccal administration. The pharmacokinetics may help to determine the best application of misoprostol depending on the indication.

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1. Introduction

Misoprostol is an inexpensive, orally active synthetic prostaglandin PGE1 that is used for the prevention of nonsteroidal, anti-inflammatory, drug-induced gastric ulcers at a dose of 100–200 μg qid. It does not need refrigeration and has few gastrointestinal side effects. Misoprostol has been used for medical abortion, cervical softening, induction of labor and treatment of postpartum hemorrhage. Various routes of misoprostol administration are currently under study and include oral, vaginal, buccal, sublingual and rectal. The indications, side effects and acceptability of misoprostol appear to be related to its pharmacokinetics, that is, its maximum plasma concentration (Cmax), the time to Cmax (Tmax), the amount available (bioavailability) over time or the area under the curve (AUC) and its half-life (T1/2). These parameters are affected by the route of misoprostol administration and the dose used. The differences in route may be related to absorption, local effects and whether there is increased metabolism from a first pass through the enterohepatic circulation.

Misoprostol use in medical abortion with mifepristone was first studied in France. High success rates were noted in women up to 49 days of pregnancy when 400 μg oral misoprostol was administered 48 h after 600 mg mifepristone [1–3]. The route of administration of misoprostol was noted to be a significant factor when multiple studies indicated that vaginal misoprostol was more effective than oral misoprostol for abortion from 50 to 63 days of pregnancy [4,5]. El-Rafeay et al. [6] randomized women obtaining a medical abortion to either oral or vaginal misoprostol 800 μg at 48 h after mifepristone 600 mg and found that vaginal misoprostol was significantly more effective in inducing abortion and had fewer side effects.

In a pharmacokinetic study of 20 women by Zieman and colleagues [7] of oral vs. vaginal misoprostol 400 μg, the oral misoprostol Cmax mean was 34 min and decreased quickly by 2 h compared with a Cmax mean of 80 min for vaginal misoprostol. Vaginal misoprostol also had bioavailability...
(AUC) three times higher than the oral route at 360 min [7]. Similar results of sustained uterine contractility with vaginal misoprostol compared with oral misoprostol was noted by Danielsson and colleagues [8]. In a study by Tang and colleagues [9] of the pharmacokinetics of oral, sublingual, vaginal and vaginal moistened tablets of misoprostol 400 µg in 40 women undergoing a first-trimester abortion, they found that sublingual misoprostol achieved a significantly higher C_max compared with the other groups. The T_max was similar in both the sublingual and oral groups (20–27 min) and was significantly shorter than in those using vaginal misoprostol. They also found that the AUC at 360 min in the sublingual group was significantly greater than those in the oral and vaginal groups. There were no significant differences in the dry and moistened vaginal tablets. They concluded that the sublingual route of administration of misoprostol demonstrated great potential. In a study of rectal vs. oral misoprostol, the rectal route had similar pharmacokinetics as noted in previous studies of the vaginal route [10].

There are some theoretical advantages of buccal and sublingual administration including similarly high absorption and possible greater patient acceptance compared with vaginal use. The disadvantage includes the sometimes irritating, chalky taste. There are few clinical studies on buccal use of misoprostol including one for second-trimester abortion [11] and one for term labor induction [12]. There are several clinical studies on sublingual misoprostol for surgical abortion [13,14], missed abortion [15], term labor induction [16] and medical abortion [17].

The purpose of the present study was to determine whether there were significant differences in the pharmacokinetics of sublingual vs. buccal routes of misoprostol.

2. Materials and methods

This open-label, randomized cross-over trial was approved by the University of Rochester institutional review board. After informed consent, 10 healthy, nonpregnant women were randomized by computer-generated numbers to use misoprostol 800 µg by either the buccal or sublingual route for 30 min and then removing the remaining pills. Healthy women were chosen in this initial pharmacokinetic study because of the unpredictable but likely miscarriage in pregnant women. After a minimum of 4 days washout period, the women used misoprostol by the other route. For the buccal route, women placed two pills in each cheek for 30 min.

The 4-day washout period was chosen because of the known misoprostol terminal half-life of 40–60 min after the oral route and the desire to wait at least five half-lives for almost complete elimination of drug.

Women were their own control. An indwelling line was established to obtain misoprostol plasma levels at 0, 0.25, 0.5, 0.75, 1, 2 and 4 h. After the 4 h, women completed a questionnaire regarding symptoms and acceptability using a 5-point Likert scale for each experience.

Plasma was frozen and shipped on dry ice to Protech Pharmaservices Corporation in Taipei, Taiwan (www.ppccro.com) for measurement of misoprostol levels. Assays were performed by liquid chromatography and mass spectrometry.

A noncompartmental pharmacokinetic analysis was performed using WinNonlin Professional Version 3.2 (Pharsight, Palo Alto, CA). AUC_{0–∞} is the area under the concentration–time curve from time zero to infinity, whereas AUC_{0–4} is the area under the concentration–time curve during the sampling interval from zero to 4 h after the dose. C_min is the minimum concentration during the 4-h sampling period, T_max is the time to the maximum concentration during the sampling period, and C_max is the maximum concentration during the sampling period.

Pharmacokinetic parameters (half-life) or their log transformations (AUC, C_min and C_max) were compared using both the paired and unpaired Student’s t test in SAS® System v8 (SAS Institute, Cary, NC).

3. Results

Ten nonpregnant women with a mean age of 22.3 (SD ± 4.3) and average weight of 150 lb (SD ± 28) were recruited. Two of the 10 women withdrew prior to using buccal misoprostol after experiencing excessive cramping from the 800-µg sublingual misoprostol dose. Of the 8 women using buccal misoprostol, 1 person described mild nausea and cramping, 1 had moderate cramping, 1 had headache and 2 women described mild buccal irritation. Of the 10 women who used sublingual misoprostol, 4 had mild nausea, 2 had diarrhea, 8 experienced chills, 5 experienced abdominal cramps and 7 experienced mild to moderate mouth irritation. Buccal misoprostol use was found to be acceptable to all 8 users, whereas sublingual use was acceptable in 4 of 10 users.

Table 1 shows the pharmacokinetic parameters for both sublingual and buccal misoprostol administration. Misoprostol plasma concentrations were higher for the sublingual vs. the buccal route (Fig. 1). The misoprostol AUC_{0–∞} (p <.04) and AUC_{0–4} (p <.03) were lower when given by the buccal route. Sublingual misoprostol administration achieved a higher C_max compared to buccal (p <.03). No difference

<table>
<thead>
<tr>
<th>Route</th>
<th>AUC_{0–∞} (pg/ml)*</th>
<th>AUC_{0–4} (pg/ml)*</th>
<th>C_min (pg/ml)</th>
<th>T_max (h)</th>
<th>C_max (pg/ml)*</th>
<th>T_{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublingual (n = 10)</td>
<td>1910 (1117–2680)</td>
<td>1600 (1100–2370)</td>
<td>90.4 (25–199)</td>
<td>0.5 (0.5–0.5)</td>
<td>1140 (817–2060)</td>
<td>1.49 (0.928–2.42)</td>
</tr>
<tr>
<td>Buccal (n = 8)</td>
<td>484 (350–2030)</td>
<td>380 (223–1470)</td>
<td>56.2 (25–156)</td>
<td>0.5 (0.375–0.75)</td>
<td>229 (140–1160)</td>
<td>2.28 (1.70–2.49)</td>
</tr>
</tbody>
</table>

* p-value <.05.
was found when comparing sublingual and buccal $C_{\text{min}}$ ($p = .53$) or half-life ($p = .24$).

When estimating the AUC$_{0-\infty}$ using data collected 4 h after the dose, the median percent of the AUC$_{0-\infty}$ that was estimated by extrapolation for sublingual and buccal administration was 13.8% (4.45–25.0) and 27.9% (19.7–30.6), respectively.

4. Discussion

The preferred route of administration of misoprostol continues to be widely discussed depending on the indication. In this study, bioavailability was higher when misoprostol was administered by the sublingual route compared with the buccal route. Misoprostol sublingual administration also resulted in higher peak misoprostol plasma concentrations ($C_{\text{max}}$) compared with buccal. Increased misoprostol plasma concentrations over the dosing interval (AUC) or peak plasma concentrations ($C_{\text{max}}$) may explain the higher frequency of reported adverse events and lower level of acceptability for sublingual administration. While 10 women are a small sample, the mean misoprostol plasma concentration–time curves at 4 h (AUC$_{0-4}$) and the maximum concentration ($C_{\text{max}}$) showed that levels were significantly higher for sublingual administration than the buccal route. Therefore, since there was a difference, the study did not suffer a Type II error from inadequate sample size for the two most important pharmacokinetic parameters for determining bioequivalence.

Of note, two women using the sublingual route experienced significant side effects of cramping causing them to withdraw and not use the buccal route of misoprostol. One possible explanation of the higher bioavailability of sublingual misoprostol is the increased and more complete absorption of misoprostol due to increased blood circulation sublingually. A propensity to swallow misoprostol from the buccal route once dissolved in the mouth is another potential reason for decreased misoprostol bioavailability. Unlike sublingual and buccal administration, portions of the dose that are swallowed are metabolized by the liver before reaching the systemic circulation (first-pass metabolism).

When comparing the results in Table 1 with two other published studies, the misoprostol plasma concentrations for buccal administration for AUC$_{0-4}$ of a mean 380 pg/mL is similar to those reported previously for the oral route of 273 pg/mL by Zieman et al. [7] and 402 pg/mL by Tang et al. [9] and for the vaginal routes of 503 pg/mL by Zieman et al. and 433 pg/mL by Tang et al. However, sublingual misoprostol results in our study revealed higher plasma concentrations for AUC$_{0-4}$ of a mean of 1600 pg/mL (also noted by Tang et al. with an AUC$_{0-4}$ of 703 pg/mL) compared with buccal, oral and vaginal administration as noted above. The maximum misoprostol plasma concentration also appears to be higher for sublingual use (114 pg/mL) compared with buccal administration or results previously reported by other investigators for oral administration. Our estimated time to maximum plasma concentration of 30 min was similar to results previously reported for oral administration, that is, 34 min by Zieman et al. and 27 min by Tang et al. The half-life from our results is slightly longer than the previously reported half-life in the FDA labeling, which may be due to differences in blood sampling strategies.

Higher plasma concentrations, peak plasma concentrations, and a higher incidence of adverse events indicate the need to evaluate the use of lower misoprostol doses for sublingual administration. Indications that require a rapid uterotonic response from misoprostol, such as when treating acute postpartum hemorrhage, may prefer the sublingual route of administration but possibly at a lower dose. In general, buccal misoprostol had fewer symptoms and was more acceptable. A lower dose of sublingual misoprostol may be more acceptable.
5. Conclusion

In this study, sublingual misoprostol resulted in higher bioavailability compared with buccal misoprostol. Sublingual administration in an 800-μg dose was also associated with more symptoms and less acceptability compared with buccal misoprostol. Further study is necessary to confirm these findings and to determine if the pharmacokinetic difference translates into clinical differences and the need to administer sublingual misoprostol at lower doses.

Acknowledgments

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References