Introduction

Misoprostol, a prostaglandin E1, is effective in treating non-steroidal anti-inflammatory drug-induced gastric ulcers. It is orally administered, cheap, stable at room temperature, and does not need to be stored in refrigerators. Misoprostol concentration in blood reaches its peak 12 minutes after oral administration, with a half-life of 21 minutes [1]. It has two effects on the uterus. First, it is effective in cervical priming. Second, it induces uterine muscles to contract, which causes the cervix to dilate. The US Food and Drug Administration (FDA) approved the auxiliary role of mifepristone (RU486) in early pregnancy termination, and its exclusive use in termination of full term pregnancy. After 25 years of development, mifepristone is widely used to induce abortion, treating postpartum hemorrhage, and priming the cervix before surgery.

In addition to oral administration, misoprostol can be administered via the vagina. As research has shown, its absorption via the vagina is slow, taking 80 minutes to reach a maximum level, but then its serum level drops slowly; hence, its efficacy lasts relatively longer. On the whole, serum misoprostol acid bioavailability (concentration x time) is increased by three times when vaginal administration is compared to oral administration [2]. However, the results of vaginal absorption vary greatly. Total absorption does not occur in some patients despite hours of vaginal administration. Some believe that absorption can be enhanced if a little water
is applied to the vagina while vaginal administration is underway. There is a need to find a method that enables fast absorption and long-term efficacy.

Recent research shows that the mucous membrane of the oral cavity has a very rich blood supply and is therefore a potential drug delivery path. Misoprostol sublingually administered for approximately 10–20 minutes can be fully absorbed without leaving any odor, indicating that misoprostol sublingually administered reaches a maximum level in serum in 26 minutes [1]. In another study, grass polygraphy of the uterus was used to measure the uterine pressure of women whose early pregnancy was to be terminated. About 11.5 minutes after sublingual administration of misoprostol 400 μg, the uterus began to contract, and uterine contraction came to a climax in 52 minutes [3]. Comparison of oral and vaginal administrations of the same dose show that sublingual administration is as fast as oral administration in terms of efficacy, and sublingual administration also lasts as long as vaginal administration. When sublingually administered, misoprostol can directly act on the uterus and has high bioavailability. In contrast, its efficacy is not brought into full play when orally administered and thereby metabolized by the liver. Hence, in the near future, sublingual administration of misoprostol may become the most effective way to induce abortion. We studied the effects of sublingual administration of misoprostol on termination of early pregnancy.

Materials and Methods

Between January 2002 and December 2005, a total of 356 women with early pregnancy requested medical abortion. The program had the approval of the ethics committee of Kuo General Hospital, Tainan, Taiwan.

Patients were eligible to receive medical abortion if they met the following criteria: (1) patient requests medical abortion; (2) gestational age ≤ 49 days, as confirmed by vaginal ultrasonography; (3) patient signs an agreement of consent and is informed of the advantages and risks of medical abortion and the necessity of receiving surgical abortion in case of medical abortion failure; and (4) patient promises to attend follow-up appointments.

No medical abortion was performed on pregnant women who met any of the following exclusion criteria: (1) drug allergy to prostaglandins; (2) symptoms of threatened abortion; (3) medical history of diseases related to the heart, respiratory system, kidneys, liver, or adrenal gland; (4) medical history of thromboembolism, hypertension, coagulopathy, or diabetes mellitus; (5) medical history of ultrasonographic or uterine pathology; and (6) active pelvic infection.

Four clinic visits were scheduled. At visit 1 (day 1), patients received oral mifepristone 200 mg, and stayed in the hospital for 1 hour of observation before being discharged. Patients were told that they should visit the hospital again promptly if they experienced marked symptoms or excessive hemorrhage.

At visit 2 (day 3), 48 hours after oral administration of mifepristone, patients visited the hospital again to receive sublingual administration of misoprostol 600 μg by taking three 200 μg capsules. The misoprostol capsules were put under the tongue, and all the capsules were completely dissolved and absorbed 10–15 minutes later. After that, they stayed in the hospital for 1 hour of observation before being discharged with three tablets of acetaminophen 500 mg, to be taken every 6 hours should they have lower abdominal pain.

At visit 3 (day 6), patients visited the hospital again for vaginal ultrasound. Patients were instructed to be alert for the expulsion of the conceptus and to note the amount of bleeding, as well as to record all symptoms such as abdominal pain, shivering, vomiting, nausea, headache, and diarrhea. If the patient had menses as usual or complained of menorrhagia, and the gestational sac was no longer visible on ultrasound, then the patient was scheduled to visit the hospital 8 days later. If the gestational sac was intact on ultrasound, surgical abortion was recommended, and the patient received gynecologic examination.

At visit 4 (day 14), the physician asked the patient whether she had had bleeding, and performed transvaginal ultrasonography. Normal ultrasonographic findings indicated the end of therapy, although a follow-up appointment 1 week later was made when necessary. The definition of a successfully induced complete medical abortion was that the abortion occurred without surgery or evacuating the uterus.

At the end of therapy, patients completed a questionnaire to evaluate whether the medical abortion had been performed to their satisfaction. The questionnaire consisted of multiple choice questions with the following choices: strongly disagree; disagree; neutral; agree; strongly agree.

Results

During the study period, medical abortion was performed in 356 women. Their mean age was 24.8 years (range, 18–40 years), and mean gestational age was 45.2 days (range, 36–49 days). Of the 356 women,
206 (57.9%) were nulliparous, 56 (15.7%) were primiparous, and 94 (26.4%) were multiparous.

The vast majority of patients (350, 98.3%) had complete medical abortion. However, medical abortion was unsuccessful in five (1.7%) women (3 cases of incomplete abortion, 2 of gestational sac remaining), who eventually had to undergo dilation and curettage to evacuate the uterus. The mean induction to abortion interval was 3.5 hours (range, 1.5–6 hours). The mean bleeding duration was 12.5 days (range, 7–36 days).

Reported side effects were abdominal pain (84.8%), nausea (21.9%), fever (16.8%), shivering (14.9%), diarrhea (7.8%), headache (5.3%), and vomiting (3.9%), although all were mild and did not require any medication except analgesics. No patient had infection, severe hemorrhage or any need for blood transfusion.

The rates for how much patients agreed that the procedure had been performed to their satisfaction were: strongly agree 4.3%; agree 25%; neutral 5.8%; disagree 4.3%; resulting in a satisfaction rate of 89.9% (325 patients).

**Discussion**

This study shows that sublingual administration of misoprostol is an effective and safe treatment option for the termination of a short pregnancy < 7 gestational weeks. The most widely used method of early abortion involves oral administration of mifepristone 600 μg followed by oral administration of misoprostol 400 μg 48 hours later, which results in a complete abortion rate of 87–96.9% [4–7], a somewhat variable therapeutic result. However, mifepristone pharmacokinetic studies show equivalent serum levels for doses ≥ 100 mg [8]. A dose of 200 mg has been shown to have similar effectiveness for medical abortion as a 600 mg dose [9]. Thus, we selected a dose of 200 mg misoprostol for this study. Some research shows that the therapeutic effect is even better when oral administration of mifepristone is followed by vaginal administration of misoprostol; however, some young women are reluctant to receive vaginal administration for privacy reasons.

In their 2001 pilot study, Tang and Ho gave 25 patients (mean gestational age, 10.6 weeks) sublingual misoprostol 600 μg only, and the sublingual administration of misoprostol could be repeated every 3 hours for a maximum of three times [10]. Twenty-three (92%) patients had complete abortion, with side effects like diarrhea (60%) and fever (38°C; 60%). In conclusion, the sole sublingual administration of misoprostol is a very effective way to induce late abortion.

In addition, Tang et al compared the pharmacokinetics of different routes of misoprostol administration, namely sublingual, oral, per vagina, and vaginal with the addition of water, by measuring misoprostol acid in venous blood samples using gas chromatography/tandem mass spectrometry [1]. Sublingual misoprostol achieved the highest peak serum concentration of misoprostol acid, and the area under the curve with sublingual misoprostol was also significantly higher than those in the other groups, suggesting that it may be the most potent way of administration.

In 2003, Cheung et al reported giving sublingual misoprostol 400 µg every 3 hours, for three times, to 50 women with pregnancies < 7 weeks' gestation. Complete abortion was achieved in 86% of women; 4% had incomplete abortion and 10% proceeded with their pregnancy [11]. The abortion took a mean of 14 hours to finish, and bleeding took 20 days on average to stop; there were few side effects. Sublingual administration of misoprostol is a very effective way to induce abortion in women with pregnancies < 7 gestational weeks. Although the therapeutic effect would be even better if mifepristone is used or the dosage of misoprostol is increased, the sole sublingual administration of misoprostol is an effective way to induce abortion in countries where mifepristone is prohibited.

In 2003, Tang et al reported giving oral mifepristone 200 mg followed by sublingual misoprostol 800 μg 48 hours later to 29 women (< 7 gestational weeks) [12]. All patients (100%) had complete abortion. The side effects mainly involved the stomach and intestines, and included fever and shivering, but were mostly tolerable and did not require treatment. Similarly, also in 2003, Hamoda et al gave oral mifepristone 200 mg followed by sublingual misoprostol 600 μg 36–48 hours later to 96 women with pregnancies < 63 days' gestation; 98.9% of patients had complete abortion, with very mild side effects [13].

In conclusion, to terminate early pregnancy by medical abortion, sublingual administration of misoprostol following oral administration of mifepristone as well as sole sublingual administration of misoprostol are effective therapeutic methods. In this study, oral administration of mifepristone 200 mg followed by sublingual administration of misoprostol 600 μg 48 hours later resulted in a complete abortion rate of 98.5% of pregnancies ≤ 49 days' gestation, with tolerable side effects and a high satisfaction rate of 89.9%. However, further study is required to determine the optimal dosage and times of sublingual misoprostol administration. Since sublingual administration of misoprostol bypasses metabolism by the gastroenterologic system, its efficacy is theoretically better than that of oral
misoprostol. Hence, in the near future, we will conduct a comparative study on the therapeutic effects of sublingual versus oral administration of misoprostol of the same dosage, following oral mifepristone, on abortion.

References