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# Pharmacokinetic Analysis of Hourly Oral Misoprostol Administration – A Pilot Study

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## Abstract

**Objective:** To conduct a pilot study of optimal misoprostol dosing to induce moderate labor among woman and to understand the pharmacokinetic parameters of moderate labor induction or augmentation.

**Methods:** We administered high doses of oral misoprostol (200 μg) hourly to nine mid-trimester pregnant women who had requested termination of gestation to determine whether misoprostol metabolites (misoprostol acid, MPA) accumulated in the blood plasma. We then chose five pregnant women at term to receive individual hourly oral misoprostol administration program and measured plasma concentrations of MPA at various stages of labor including the beginning of misoprostol solution administration, the initial response of regular uterine contractions, and full cervical dilation.

**Results:** The concentration of MPA, which is responsible for misoprostol's clinical activity and toxicity, had no obvious accumulation after high-dose hourly oral misoprostol administration. Furthermore, the five moderate dosing programs of hourly oral misoprostol administration ripened the cervix with very low concentrations of MPA detected in the plasma.

**Conclusions:** The preliminary results show that the five defined programs in labor induction or augmentation are promising dosing regimens that avoid uterine hyperstimulation, shorten the labor course, and prevent the risk of potential toxicity from excess MPA.

**Keywords:** Misoprostol acid; Labor induction; Labor augmentation; Uterine hyperstimulation; Cervical ripening; Toxicity

## Introduction

Clinical history shows that more than 15% of all gravid women require labor induction to achieve cervical ripening, which often results in a long labor course [1-3]. The most fundamental reason for a long labor course is an unripe cervix; it is the greatest barrier to spontaneous birth and leads to unnecessary cesarean deliveries. Thus, it is necessary to consider the cause of this problem and overcome the issues associated with an unripe cervix.

Misoprostol, a synthetic prostaglandin E1 analogue, was initially developed to treat peptic ulcers. It is commonly used off-label in the practice of obstetrics and gynecology to induce labor and cervical ripening [4,5]. Misoprostol has powerful uterotropic and uterotonic effects as evidenced in many studies since 1992 [6,7].

Obstetricians are greatly concerned about safety issues regarding labor induction as uterine tachysystole or hypersystole causes fetal hypoxia. Early studies indicated that the risk of inducing fetal hypoxia occurs with fixed-dosage of misoprostol such as 100 μg orally or 25 μg vaginally every 4 hours (recommended dose) until adequate labor commences [8-10]. In one pilot study, small, frequent (every 2 hours), titrated doses of oral misoprostol minimized the risk of uterine hyperstimulation and prevented fetal hypoxia [11,12]. Investigators developed an advanced approach with hourly oral misoprostol administration relative to uterine response for labor induction or augmentation at term or for terminating mid-trimester pregnancies [4,13-17]; they achieved a high rate of success within 24 hours. According to the results of titration studies, misoprostol is an ideal candidate for labor induction and augmentation due to its convenience of administration and cervical ripening characteristics.

Misoprostol acid (MPA) is responsible for the clinical activity and toxicity of misoprostol; however, there is little, if any, research detailing the pharmacokinetics of hourly oral misoprostol administration. Pharmacokinetic data on the minimal plasma MPA concentrations by dosage and over the course of labor are lacking. In this study, we first analyzed the pharmacokinetic profile of high-dosage oral misoprostol administration (200 μg/hour) over 8 hours. We then investigated its pharmacokinetic profile using different administration regimens with individual dosages; we determined the minimal plasma MPA concentrations during induction or augmentation of smooth labor courses.

## Materials and Methods

### Study participants

This pilot study was approval by the Institutional Review Board

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of China Medical University Hospital and Beigang Hospital, and was granted from Dec 08, 2010 to Dec 07, 2011 at the Departments of Obstetrics and Gynecology. All of participants had signed the informed consent before participating in this pilot study. Inclusion criteria were as follows: 20–40 year-old healthy woman requesting termination of mid-trimester pregnancies or women requiring medically indicated labor induction or augmentation. Exclusion criteria: Adult women with diseases of the heart, liver, or kidneys, and those allergic to misoprostol. Nine women with living fetuses underwent oral misoprostol treatment at 12–25 weeks of gestation. Additionally, five women underwent labor induction or augmentation with different individual hourly oral misoprostol regimens. Thus, we acquired five regimens to determine whether misoprostol metabolites accumulated in the plasma. Under medical indication, these patients randomly selected after consent signed with autonomic right.

### Mid-trimester pregnancy interruption

Nine patients were admitted to the delivery unit for interruption of mid-trimester pregnancies and were evaluated without uterine surgery. The patients received misoprostol 200 μg tablets orally every hour until fetus was expelled. During hourly oral misoprostol administration, venous blood samples were drawn over the next 8 hours at various time points as follows: initial 1st dose administration ($T_{0\ min}$), 0.25 hour post 1st dose administration ($T_{15\ min}$), 0.5 hour post 1st dose administration ($T_{30\ min}$), 1 hour post 1st dose administration ($T_{60\ min}$), 1 hour post 2nd dose administration ($T_{120\ min}$), 1 hour post 3rd dose administration ($T_{240\ min}$), 1 hour post 5th dose administration ($T_{360\ min}$), and 1 hour post 7th dose administration ($T_{480\ min}$). The blood samples were centrifuged and frozen in liquid nitrogen immediately. The samples were then stored at -20°C or less and were sent to the department of Chemistry at National Chung Hsing University for analysis. The concentration of MPA was determined by liquid chromatography-tandem mass spectrometry (LC/MS/MS).

### Labor induction or augmentation

Five women were admitted to the delivery unit for labor induction or augmentation. Each of them received individual route of hourly oral misoprostol solution titration regimens for labor induction or augmentation; therefore, there were five regimens as the followings:

1) 20 μg→20 μg→20 μg,

2) 20 μg→20 μg→20 μg→20 μg→20 μg,

3)20 μg→20 μg→20 μg→20 μg→40 μg→40 μg→20 μg,

4) 20 μg→20 μg→20 μg→20 μg→40 μg→40 μg→40 μg,

5) 20 μg→20 μg→20 μg→20 μg→40 μg→40 μg→40 μg→40 μg→60 μg→40 μg→40 μg.

During these courses, venous blood samples were drawn at the beginning of misoprostol administration, at the initial time of regular uterine response, and at full cervical dilatation. The blood samples were also sent to the chemistry department at National Chung Hsing University for analysis.

### LC/MS/MS

HPLC analyses were performed on an Accela LC system with an autosampler (Thermo Scientific, San Jose, CA, USA). The gradient separation was achieved using a Cogent Bidentate C18 column (100 mm × 2.1 mm i.d., 4 μm) with a Bidentate C18 guard column (20 mm × 2 mm i.d.). The mobile phases were water and acetonitrile. The separation conditions began at 60% water held for 1 min and reached 5% water within 0.5 min, where it was held for 2 min. Afterward, the conditions returned to 60% water and were held for 2 min for column equilibration. The flow rate was 0.4 mL/min, and the column temperature was maintained at 30°C.

A TSQ Qauntum Ultra EMR triple-stage quadrupole tandem mass spectrometer (Thermo Scientific, San Jose, CA, USA) equipped with heated electrospray ionization (H-ESI) interface was used. The MS analysis was performed in the negative ionization mode with H-ESI ionization and was quantified using the H-SRM mode. The tuning parameters were optimized for MPA by infusing a solution containing 10 μg $mL^{-1}$MPA via syringe pump into the HPLC flow using a post-column T infusion method. The sheath and auxiliary gases were set at 20 and 10 arbitrary units, respectively. The vaporizer temperature was 300°C, and the spray voltage was 4.5 kV. For collision-induced dissociation (CID), argon was used as the collision gas at 1.5 mTorr. The transitions were quantified (m/z 367 →249 for MPA and m/z 372→249 for MPA-d5) using highly selective reaction monitoring (H-SRM). The first quadrupole (Q1) was set at 0.4 full width at half maximum (FWHM) for H-SRM. The optimized collision energy was 20 eV forMPA and MPA-d5. The data were collected before being processed using Xcalibur 2.0.7 software (Thermo Scientific, San Jose, CA, USA). The detection limit of MPA in plasma was 1.2 fg/μL.

## Results

For mid-trimester pregnancy interruption, the clinical dosage of misoprostol was an initial dose of 200 μg/h repeated hourly until the fetus was expelled. We first tested the pharmacokinetic profile of hourly oral misoprostol administration with a dose of 200 μg/h for 8 hours to determine whether metabolites accumulated in the plasma. The concentrations of MPA were determined at $T_{0\ min}$, $T_{15\ min}$, $T_{30\ min}$, $T_{60\ min}$, $T_{120\ min}$, $T_{240\ min}$, $T_{360\ min}$, and $T_{480\ min}$; the results indicated that the detectable metabolites did not accumulate (Table 1). The MPA concentrations ranged from 4.2 fg/μL to 61.2 fg/μL, and there was no relative time correlation (Figure 1).

For labor induction or augmentation, five women were enrolled in their individual regimen relative to uterine response and their maternal demographics and plasma concentrations of MPA at the specified time points are given in Table 2. All of women were successfully underwent labor induction or augmentation after treatment within 4–12 hours. The concentration of MPA was measured at three time points: 1) At the beginning of misoprostol administration, 2) At the initial response of regular uterine contractions, and 3) At full cervical dilatation. The intervals from intake of last misoprostol dose to cervix at full dilatation were all within one hour. The pharmacokinetic results indicated that only regimen 4 and 5 had detectable MPA concentrations at the start of regular uterine contractions and regimen 4 has detectable MPA concentration at the full cervical dilatation while the other regimens showed no detectable MPA at any time point.

## Discussion

Upon oral administration of misoprostol, it undergoes rapid and extensive hydrolysis to form an active metabolite known as MPA [18]. Because MPA is responsible for its clinical activity with a peak serum concentration after oral misoprostol administration of 34 minutes and a half-life of 20-40 minutes [14], only plasma concentration of misoprostol acid need to be detected. A pharmacokinetic analysis of misoprostol was previously performed for a single dose of 400 μg via five different routes: 1) Sublingual, 2) Oral, 3) Vaginal, and 4) Vaginal

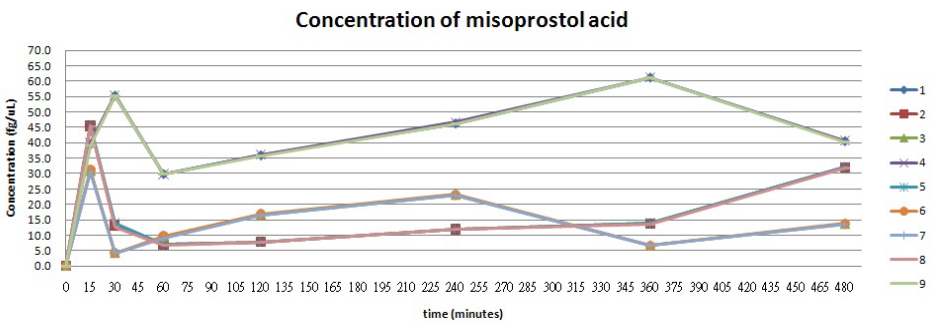


**Figure 1:** Concentration of misoprostol acid during hourly oral misoprostol (200 μg/h) dosing for pregnancy interruption

| Concentation of misoprostol acid (fg/μL) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Case No** | **T0 min** | **T15 min** | **T30 min** | **T60 min** | **T120 min** | **T240 min** | **T360 min** | **T480 min** |
| 1 | N.D. | 39.5 | 55.3 | 29.8 | 35.9 | 46.3 | 61.2 | 40.5 |
| 2 | N.D. | 45.5 | 13.2 | 6.9 | 7.8 | 11.9 | 13.8 | 32.0 |
| 3 | N.D. | 30.8 | 4.2 | 9.4 | 16.6 | 23.1 | 6.6 | 13.6 |
| 4 | N.D. | 39.9 | 55.4 | 29.8 | 36.1 | 46.6 | 61.2 | 40.7 |
| 5 | N.D. | 45.7 | 13.9 | 7.1 | 7.8 | 11.9 | 13.9 | 32.1 |
| 6 | N.D. | 31.3 | 4.2 | 9.7 | 16.8 | 23.2 | 6.6 | 13.8 |
| 7 | N.D. | 30.5 | 4.2 | 9.1 | 16.4 | 23.0 | 6.6 | 13.4 |
| 8 | N.D. | 45.3 | 12.5 | 6.7 | 7.8 | 11.9 | 13.7 | 31.9 |
| 9 | N.D. | 39.1 | 55.2 | 29.8 | 35.7 | 46.0 | 61.2 | 40.3 |
| N.D. : Non-Detectable | | | | | | | | |

**Table 1:** Pharmacokinetic analysis of high dosage, hourly oral misoprostol (200 μg/h) for pregnancy interruption.

| **Case No** | **Age** | **Body Height (cm)** | **Body Weight (Kg)** | **Para** | **Bishop Score*** | **Concentation of misoprostol acid (fg/μL)** | | | **Dosing Regimen** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Time 0 | Time 1 | Time 2 | |
| 1 | 24.0 | 159 | 74.0 | 3 | 5 | N.D. | N.D. | N.D. | 20 μg→20 μg→20 μg |
| 2 | 25.9 | 158 | 78.0 | 1 | 3 | N.D. | N.D. | N.D. | 20 μg→20 μg→20 μg→20 μg→20 μg |
| 3 | 30.7 | 158 | 60.0 | 2 | 4 | N.D. | N.D. | N.D. | 20 μg→20 μg→20 μg→20 μg→40 μg→40 μg→20 μg |
| 4 | 32.5 | 18 | 70.0 | 4 | 8 | N.D. | 7.7 | 8.8 | 20 μg→20 μg→20 μg→20 μg→40 μg→40 μg→40 μg |
| 5 | 24.8 | 165 | 67.0 | 3 | 4 | N.D. | 4.7 | N.D. | 20 μg→20 μg→20 μg→20 μg→40 μg→40 μg→40 μg |
| | | | | | | | | | →40 μg→60 μg→40 μg→40 μg |
| *: Bishop score on admission before labor induction or augmentation | | | | | | | | | |
| N.D.: Non-Detectable | | | | | | | | | |
| Time 0: Immediately after initial misoprostol administration. | | | | | | | | | |
| Time 1: At the start of regular uterine contractions. | | | | | | | | | |
| Time 2: At full cervical dilatation. | | | | | | | | | |

**Table 2:** Pharmacokinetic analysis of five regimens of hourly oral misoprostol administration.

with addition of water [19]. The results indicated that the highest serum peak MPA concentration ($C_{max}$) was 287.6 ± 144.3 fg/μL and the time to peak concentration ($T_{max}$) was 27.5 ± 14.8 min for oral administration. Additionally, a randomized comparison of pharmacokinetics of a single vaginal dose (400 μg) of dry misoprostol or misoprostol moistened with normal saline or with acetic acid was performed [19]. All of these pharmacokinetic studies analyzed MPA serum concentrations at various time points after administration of a single, high dose of misoprostol to determine which routes were most efficient. We found no relevant studies of low-dose pharmacokinetic analyses of hourly oral misoprostol administration. Thus, we conducted a pilot study for ensuring the optimal misoprostol delivery dosing method for laboring woman; we sought to understand the pharmacokinetic parameters of misoprostol for labor induction or augmentation.

At the beginning of our study, we first investigated high doses of hourly oral misoprostol (200 μg) administration to mid-trimester pregnant woman requesting termination of their pregnancies to determine whether MPA accumulated in the plasma. The results indicated that no metabolite accumulated over the course of therapy, and the concentration of MPA ranged from 4.2 fg/μL to 61.2 fg/μL. The

concentration of plasma MPA in our study was relatively lower than in previous studies in which a single dose of misoprostol 400 μg was used [20].

We next investigated low-dosage hourly oral misoprostol regimen for labor induction or augmentation to determine the concentration of MPA in the plasma. It was well known that the $T_{max}$ of MPA was 12 ± 3 min, and its terminal half-life was 20 to 40 min [18]. Although the detection limit of MPA in the plasma was 1.2 fg/μL in our method, the results showed almost no detectable MPA at any of the three measurement times. It meant that they were almost below the concentration of 1.2 fg/μL.

The detection limit of MPA is dependent on the method of chromatography-tandem mass spectrometry that was developed by what technique and how much the dosage of misoprostol was. Although the high dosage in our study was 200 μg/h that was lower than that dosage in other studies [18-20], the method we developed was liquid chromatography-tandem mass spectrometry that was reliable and sensitive. Therefore we can detect plasma concentration of MPA as low as 1.2 fg/μL. If the event of MPA accumulation occurred during labor induction or augmentation with hourly oral misoprostol administration, the concentration level of MPA accumulated at the initial time of regular uterine contraction and full cervical dilatation would appear on regimen 4 and 5, where the total accumulated dosages of intake were equal to or greater than 200 μg. Fortunately, these data showed no accumulation effect. Although the case number we collected in this study was not great enough, our previous studies of titrated oral misoprostol with enough case number in labor induction or augmentation showed little risk in clinical practice [4,16].

The pharmacokinetic pilot study of hourly oral misoprostol administration showed that no metabolite of misoprostol accumulated in the plasma via hourly oral administration. Therefore, there will be little risk of maternal tachysystole or fetal hypoxia arising from titrated oral misoprostol. The small, frequent of titrated oral misoprostol administration [4,13,15-17] in labor induction or augmentation was safe in clinical practice according to these findings.

The hourly, titrated oral misoprostol solution is a promising regimen with little risk for labor induction or augmentation. Future studies with larger numbers of patients are required to verify the pharmacokinetic characteristics of misoprostol and to determine optimal dosing.

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### Disclosure

No conflicts of interest to declare. The study was approved by the Institutional Review Board of China Medical University Hospital (IRB# DMR99-IRB-242, approved 09 December 2010), and written informed consent was obtained from all participants. Clinical trial registration number: NCT01271257

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