

Misoprostol Use as Potent Induction Agent Grows

The drug's pharmacokinetics vary with the route of administration; sublingual onset of action is fastest.

BY ALICIA AULT

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ASHEVILLE, N.C. — Six years after its manufacturer, G.D. Searle, warned against using the drug in pregnancy due to litigation and political concerns, misoprostol is finding off-label use throughout pregnancy, Dr. Wendy Hansen said at the Southern Obstetric and Gynecologic Seminar.

Dr. Hansen, of the University of Kentucky, Lexington, said misoprostol is being used as an abortifacient in first- and second-trimester pregnancy failures, as an induction agent in the third trimester, and to manage postpartum hemorrhage.

The drug's pharmacokinetics are dependent on its route of administration. Orally, it is rapidly absorbed with a peak concentration in 12 minutes and a half-life of 21 minutes. The drug has the shortest onset of action and greatest bioavailability when given sublingually. There is also great bioavailability when misoprostol is given vaginally or rectally, but the absorption is not as consistent, said Dr. Hansen. Peak concentration with vaginal administration is 1 hour, with a slow decline over the 4 hours post administration.

However, vaginal dosing has been shown to be superior to oral regimens in hastening delivery time and reducing the

need for oxytocin (Obstet. Gynecol. 1997;89:392-7; Am. J. Obstet. Gynecol. 1999;180:1155-60). That route also decreases side effects, which include nausea, vomiting, diarrhea, abdominal pain, chills, shivering, and fever.

Misoprostol is usually given in 25-mcg doses vaginally, though it comes in a 100-mcg tablet. Dr. Hansen says she has her pharmacy cut the 100-mcg tablets into quarters and then weigh each to be sure of providing the right dose. Doses should be reduced for women with hepatic disease.

The drug fell out of favor in the late 1990s after Searle issued its warning, but the American College of Obstetricians and Gynecologists countered with a letter to members stating that the evidence backed use of misoprostol in pregnancy. Use picked up, but it was tempered with caution after there were many sporadic reports of uterine rupture in the presence of a uterine scar, said Dr. Hansen. A retrospective study of 20,000 women with a prior cesarean delivery found that prostaglandins such as misoprostol did increase the rupture risk (N. Engl. J. Med. 2001;345:3-8).

Dr. Hansen recommends considering a repeat cesarean if induction is necessary in a woman with a uterine scar.

A relatively new use of misoprostol is in

the first trimester for women who have missed a therapeutic abortion or have a pregnancy failure. Expectant management has been the customary approach, but the interval to spontaneous expulsion is unpredictable, which leads to sadness and uncertainty, noted Dr. Hansen. Misoprostol gives more control over timing and provides prompter evacuation, she said. A large randomized, controlled trial found that success rates for misoprostol ranged from 71% at day 3 to 85% at day 15, compared with nearly 100% success for surgical management (N. Engl. J. Med. 2005; 353:761-9).

Patients who had an incomplete or inevitable abortion were administered 800 mcg of misoprostol vaginally on day 1 and again on day 3 if expulsion was incomplete (491 patients) or given electric or manual vacuum aspiration (161 patients). The pain was worse in the group given misoprostol, as was nausea, vomiting, and diarrhea. But the acceptability was the same, and 78% of women said they'd try misoprostol again, compared with 75% of the surgical group.

Women considering misoprostol for first-trimester failure should be told that success diminishes with parity, and that success can't be predicted by the biometry of the sac or the gestational age of the fetal pole, said Dr. Hansen. And, misoprostol does not seem to affect long-term fertility (Hum. Reprod. 2005;20:3355-9).

Misoprostol has become a standard

treatment for second-trimester terminations or induction for intrauterine fetal demise, Dr. Hansen said. Two regimens are used, but it is not clear which is better: 400 mcg vaginally every 4 hours up to a maximum of five doses, or 800 mcg every 6, 8, or 12 hours for 24 hours. Oral routes are sometimes used also: 400 mcg every 2 hours for 24 hours or 200 mcg every hour for 8 hours. Several studies have now shown that it is safe to use in the second trimester, even in women who have had previous cesareans or uterine ruptures, said Dr. Hansen.

The drug has a history of being used successfully to manage postpartum hemorrhage, she said, adding that the rectal route is best for this purpose. Patients are given 600-800 mcg rectally, 200 mcg orally, or 400 mcg sublingually.

Dr. Hansen was asked if there had been any reports of infections with *Clostridium sordellii*. There have been at least five deaths attributable to that pathogen in women who took misoprostol in combination with mifepristone. But Dr. Hansen said she had not heard any such reports with misoprostol alone or outside the setting of elective medical abortion.

Another meeting attendee said that her clinic provides patients with a consent form stating that misoprostol for induction is an off-label use. But Dr. Hansen said she does not feel that it's necessary to discuss the off-label aspect because ACOG endorses its use throughout pregnancy. ■

Simultaneous Abortion Medications Match 24-Hour Dosing

BY BRUCE K. DIXON

Chicago Bureau

LA JOLLA, CALIF. — Women choosing medical abortion through 63 days' gestation can achieve effective results with simultaneous administration of mifepristone and misoprostol, according to a study presented at the annual meeting of the Association of Reproductive Health Professionals.

"Our study shows that using simultaneous administration of 200 mg mifepristone and 800 mcg vaginal misoprostol is as effective and as acceptable to patients as a 24-hour dosing interval," reported Dr. Mitchell Creinin, professor and director of family planning at the University of Pittsburgh.

Success, defined as complete abortion that did not require suction aspiration for any reason, did not achieve equivalency in the simultaneous group, though this assessment was limited by undersampling for this secondary outcome, he said.

The standard regimen for medical abortion, approved by the Food and Drug Administration, consists of taking 600 mg of oral mifepristone on day 1 and 400 mcg oral misoprostol 36-40 hours later. This regimen typically is used up to 49 days gestation, Dr. Creinin said.

Previous research by Dr. Eric Schaff, medical director of Planned Parenthood of Delaware, had shown that, with the newer vaginal regimen, women favor a short-

er dosing interval, Dr. Creinin explained. "And we do know that during the 36-48 hour interval in the standard regimen that up to half of women will begin to bleed, which may have something to do with its acceptability as well as the desire to get things over with more quickly."

A 2004 study compared the 23- to 25-hour interval with a 6- to 8-hour interval and showed the two to be equivalent in effectiveness. This led to the idea of simultaneous administration, Dr. Creinin said. "In our pilot studies of medical abortion regimens, we tend to look at our expulsion rate with the idea that we don't want to doom women to a surgical abortion if they really don't want it, and we can rescue them with a standard vaginal dose at 24 hours should the new method not work," he explained. The expulsion rates in those pilot studies was around 90%, which meant the researchers could forge ahead with a trial.

The four-center study enrolled more than 1,100 women between June 2004 and April 2006, with follow-up at 7 and 14 days and phone follow-up 5 weeks post treatment "to check to see if the women had a D&C or problems that caused them to go somewhere else for care," said Dr. Creinin. If documented expulsion had not

occurred by the first follow-up visit, women were given a repeat dose of misoprostol. Of the total sample, two women withdrew prior to randomization and 2% of the women were lost to follow-up, so that the final number of women taking the drugs was 1,126.

All study centers held teleconferences with site monitoring at regular intervals and data queries came from the coordinating center, based on irregularities in the data. "We performed two interim analyses when one-third and two-thirds of the women had completed follow-up, and these analyses were structured to both look at overall efficacy and to address efficacy by gestational age to see if there were problems with continuing on with the study,"

Dr. Creinin said, adding that 40% of the women had had a prior abortion, one-fourth of which were medical. Treatment was considered a failure if suction aspiration was performed for any indication.

Overall efficacy between the groups was comparable, with the standard treatment group achieving a success rate of 96.7%—just short of the expected 97% success rate—and the simultaneous administration group achieving a success rate of 95%. Also, almost every gestational age group

came close to reaching statistically significant noninferiority, Dr. Creinin said.

Failures, such as continued pregnancy and persistent sac at 2 and 5 weeks were evenly distributed between the cohorts. On day 4, two women in the simultaneous group requested a D&C. The larger incidence of side effects was in the simultaneous group; though it reached statistical significance, it was deemed clinically irrelevant. These side effects included nausea, diarrhea, warmth, and chills. There was no difference in pain and acceptability scores, he said.

"We had relatively few adverse events, though interestingly, there were four transfusions in the standard treatment group. There was one heterotopic pregnancy in the simultaneous group, and five women in each group developed infections and were treated as outpatients without hospitalization," Dr. Creinin said.

On Nov. 4, 2005, the FDA issued a Public Health Advisory "to inform the public that it is aware of four women in California who died from sepsis following medical abortion with mifepristone and misoprostol."

In two of the cases, the culprit bacteria were identified as *Clostridium sordellii*, anaerobic bacteria that in rare cases are fatal. The deaths followed the off-label use of oral mifepristone and vaginal misoprostol given as 200 mg mifepristone orally followed the next day by 800 mcg misoprostol inserted vaginally. ■

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