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Mifepristone and misoprostol for early medical abortion: 18 months experience in the United States

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Abstract

In the first 18 months since mifepristone was approved by the Food and Drug Administration (FDA) for use with misoprostol for early medical abortion, approximately 80,000 women have been treated. One-hundred thirty-nine adverse events were reported to Danco Laboratories LLC and subsequently reported to the FDA. Thirteen patients required blood transfusions, 10 patients were treated with antibiotics for infection and 6 had a generalized allergic reaction. Fifty patients had an ongoing pregnancy, with 48 having suction curettage, leaving 2 ongoing pregnancies. Thirty-nine patients had a suction curettage for heavy or prolonged vaginal bleeding. The overall national experience has been highly favorable.

Keywords: Mifepristone; Mifeprex; Abortion complications; Medical abortion

1. Introduction

Adverse events associated with mifepristone and misoprostol abortions in early pregnancy are uncommon [1,2]. Both Food and Drug Administration (FDA)-approved [3] and alternative regimens [4] have been reported to have high efficacy and few complications. However, most reports to date stem from formal research studies and not from general use, as has occurred in France and the United Kingdom [5,6]. Thus, morbidity rates in the literature may not reflect the experience in general use. This brief report describes the complications reported during the first year of clinical use of mifepristone and misoprostol in the United States.

2. Methods

In September 2000, mifepristone followed by misoprostol was approved by the FDA for medical abortions up to 49 days gestation. Distribution began in November of that year. Each physician ordering mifepristone must sign an agreement that requires them to report adverse events to Danco Laboratories, LLC (Danco), which, in turn, relays these to the FDA. The method of reporting complications has included letter, facsimile, phone call and e-mail from rural and urban clinics as well as private physicians' offices. Mifepristone was used in 46 states as well as Guam and the District of Columbia. In this first 18 months, clinics provided about 90% of the Mifeprex used and physicians in private practice provided the remainder.

Denominators for complication rates were estimated from sales figures. Although the FDA-approved regimen specified a single oral dose of mifepristone 600 mg, many physicians are using a lower dose (200 mg), which has been reported in several randomized controlled trials to have comparable efficacy [5–11]. A report of nationwide clinical use [12] indicated that 83% (estimated range, 83–93%) of providers used 200 mg mifepristone. The estimated range was based upon Planned Parenthood practices and National Abortion Federation (NAF) polling of their membership practices. Adjusting for utilization patterns of providers around the country, we estimated that approximately 80,000 women received mifepristone for early medical abortion from November 2000 to May 31, 2002. In this time period, a total of 139 adverse events (0.17%) associated with the use of the marketed product were filed with the FDA. Of these, 14 concerned events that, while falling under FDA reporting regulations, were of little medical significance.

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Five patients were seen in emergency rooms with complaints of bleeding. They had negative ultrasound examinations and were sent home without any treatment. Another two patients bled following mifepristone and went to an emergency room. They were found to have a gestational sac by ultrasound examination and told to use the misoprostol. After doing so, they had a completed medical abortion. Six patients were seen in emergency rooms for faintness and received no therapy. Another patient felt dizzy and had a headache; she received acetaminophen and reassurance. This report is concerned with the remaining 125 adverse events reported to the FDA. Several patients fit into more than one category such as hospitalization, transfusion and heavy bleeding.

Planned Parenthood Federation of America (PPFA) monitored the use of mifepristone and misoprostol in 63 of its affiliates that offered medical abortion. This report includes the experience of 21,703 women treated at PPFA in the same time period. All of the women received the regimen of mifepristone 200 mg by mouth followed by misoprostol 800 mcg per vagina. These data are included in the aggregate figures presented below for the entire nation. Using the estimated denominator of 80,000, the proportions of women experiencing reported complications were calculated. Because of the rarity of these complications, we calculated 95% confidence intervals (CI) using the Poisson distribution.

3. Results

The denominator of 80,000 patients (74k–89,000) chosen for this time period is based upon actual sales figures and known patterns of mifepristone utilization throughout the country.

Five ectopic pregnancies occurred (0.006%, 95% CI 0.002–0.15%), one resulting in death of the patient. This patient died from intraperitoneal hemorrhage from a ruptured tube. She reportedly refused hospitalization and treatment at least 36 h before her death, despite the urging of her physician. A second patient had a ruptured cornual pregnancy that had initially been diagnosed as intrauterine. The third patient had a pregnancy in the midportion of her tube; it ruptured 5 days after she received misoprostol 800 mcg vaginally. The remaining two patients had successful surgical treatment after misoprostol.

Thirteen patients had serious bleeding serious enough to require blood transfusions (0.016%, 95% CI 0.009–0.028). Two of these patients had ectopic pregnancies described above. Among the 11 women with intrauterine pregnancies, only 1 required a transfusion within 5 days of taking misoprostol. The other 10 patients received blood transfusions 7–20 days after administration of misoprostol; all reported heavy bleeding during that time either continuously or in multiple episodes.

Ten patients (0.013%, 95% CI 0.006–0.023%) were treated with antibiotics for presumed infection and one of these was serious. A 15-year-old woman became febrile 3 days after successful completion of the medical abortion. She rapidly developed adult respiratory distress syndrome and was treated with antibiotics and other supportive measures. All bacteriological cultures upon admission were negative. Among the other nine patients, six were hospitalized, and four were treated as outpatients.

Six women developed generalized urticarial reactions following ingestion of mifepristone (0.008%, 95% CI 0.003–0.016%). In each case, the reactions promptly resolved after administration of oral diphenhydramine hydrochloride. Each woman then successfully completed the mifepristone and misoprostol regimen.

Three additional patients had serious adverse events. A 21-year-old woman with a strong family history of heart disease suffered a coronary artery occlusion 5 days after receiving misoprostol 800 mcg vaginally. She was found to have a thrombotic occlusion of a single vessel, the ramus intermedius. A balloon angioplasty with stent placement was performed and she made a full recovery.

A 29-year-old woman developed a concurrent breast abscess due to *Staphylococcus aureus*, which caused a toxic shock syndrome. The abscess arose from an insect bite. She had an uncomplicated medical abortion.

A 19-year-old woman developed hepato-renal failure and disseminated intravascular coagulopathy 3 days after using 800 mcg misoprostol vaginally. Her illness was thought to be the result of abuse of alcohol and acetaminophen. She had a successful medical abortion.

A total of 117 patients had a suction curettage, with 50 performed for heavy bleeding. Most of these procedures were performed 10 days or more after misoprostol and a few were performed more than 30 days later. Almost all of these were performed on a nonemergent basis. An additional 19 patients had a suction procedure for a persistent and apparently nonviable gestational sac.

Ongoing pregnancy after mifepristone and misoprostol was uncommon. A total of 50 women had this occur, as documented by either a growing gestational sac or fetal cardiac activity (0.063%, 95% CI 0.46–0.082). One of these patients took mifepristone only. Forty-eight of these women chose to have a suction curettage and two chose to continue the pregnancy despite warnings about the potential adverse effect of this regimen on fetal development [13]. Both pregnancies are ongoing at this time.

4. Discussion

Initial United States experience with mifepristone and misoprostol for early medical abortion confirmed the safety and efficacy of this approach. Success rates have been reported to Danco that varied from 94–97%. The one fatality from a ruptured ectopic pregnancy was not related to the medical abortion. However, had surgical abortion been cho-

sen, the lack of fetal tissue in the aspirate should have provided immediate evidence of an extrauterine gestation. The rates of hemorrhage requiring transfusion, infection, and allergic reactions reported are similar to those reported in both pivotal research studies [2,3,8] and broader nationwide use [9]. Moreover, these estimates compare favorably with complication rates reported with early surgical abortion in the United States [10]. Which approach to early abortion, medical or surgical, is safer remains unknown but it does appear that medical abortion is as safe as early surgical abortion. There are no recent data on failed surgical abortions but the failure rate of mifepristone/misoprostol medical abortions is higher than that reported decades ago for suction curettage [14].

This initial report has both strengths and weaknesses. First among strengths, the postmarketing surveillance conducted by Danco provides a nationwide mechanism for reporting of complications. Second, this provides the first national assessment of the safety of use of mifepristone and misoprostol for abortion. Because of the small numbers of complications, we have provided 95% confidence intervals to indicate the statistical imprecision of these estimates. The data supplied by Planned Parenthood affiliates offers confirmable data on a known number of patients (21,703) and a comparison of these data to those reported for the remaining approximately 58,297 patients are quite comparable. Weaknesses include the inexactitude of the denominator calculation; determining how many women received a single dose of 600 mg vs. 200 mg of mifepristone is impossible, so the denominator reported here must be considered a conservative estimate. The obligatory reporting of adverse events is limited to transfusions, hospitalizations, ongoing pregnancies or "other serious adverse events," which allows considerable subjective judgment on the part of the providers. In addition, the reporting of other common adverse events may not be reported at all. The degree of underreporting is not known and interpretation of the occurrence rate for the various adverse events must take into account the inexactitude of both the denominator and numerators. Nevertheless, this is the only such information available and does reflect the usage of the mifepristone regimen throughout the country. Experience overseas has shown that rates of both complications and failed attempted medical abortion decline with increasing clinical experience. Thus, the complication rates estimated here are possibly higher than will be reported in the future.

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