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Author

Hemmerling, A

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TITLE: **The Safety of Misoprostol**

AUTHOR: Anke Hemmerling, MD, MPH
Bixby Fellow of Population and International Health
University of California, Berkeley
School of Public Health
513 Warren Hall
Berkeley, CA 94720-6390
Email: anke@berkeley.edu

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Misoprostol is currently on the WHO Essential Drug List for treatment of gastric ulcers, for induced abortion in combination with mifepristone, and more recently for induction of labor. The WHO will review its role as an essential drug for control of post partum hemorrhage (PPH) in early 2007. Relevant data on the safety of misoprostol has been accumulated since the introduction of the drug in the late 1980s. Since then, millions of individuals worldwide have used up to four tablets (800 mcg) daily for treatment and prevention of gastric ulcer.

Multi-center trials following thousands of users [1, 2], as well as a review of the worldwide safety data [3] and a Cochrane Review in 2002 [4] failed to report any misoprostol related deaths or side effects severe enough to demand the cessation of treatment. Common side effects for long term misoprostol users with gastric ulcers were the same as seen in some women treated for PPH – and include chills, fever, diarrhea and nausea.

Four cases of acute toxicity after accidental or intentional overdose with misoprostol are described in the peer-reviewed literature, two of them in women beyond 30 weeks of pregnancy. [5-8] After ingesting a large number of misoprostol tablets, sometimes mixed with other medication, tachycardia, nausea and abdominal pain and, in some cases, hyperthermia was reported, although the authors of these reports emphasize the complete resolution with supportive care within 12 hours. Bentov [7] concludes that his case of overdose with 42 tablets (8.4 mg) over three days “illustrates the relative safety of the drug”.

The literature also reports one case of severe hyperthermia post partum reaching 41.9 C following a normal dose of 800 mcg of oral misoprostol and requiring intensive supportive care. [9] Although no other extreme cases of severe hyperpyrexia are reported, several studies on PPH using oral misoprostol of 400-600 mcg describe transient pyrexia of 38 degrees Celsius

(100.4 degrees Fahrenheit) or higher. [10-14] In these trials a limited number of parturients (5 – 28%) were affected and very few sustained a fever of 39-40 degrees C. The temperature elevations generally last 1-2 hours and then rapidly cease with minor or no intervention. Oral and sublingual routes of administration seem to trigger pyrexia more frequently than the rectal application.

Interestingly, pyrexia after misoprostol administration also seems to occur in women employing the drug late in gestation and at delivery but rarely in ulcer patients or women in early pregnancy. The author is not aware of a conclusive explanation for this phenomenon at this time. Including careful monitoring of body temperature into the design of future misoprostol studies would be helpful and users should be taught simple techniques of diagnosing and treating transient fevers associated with misoprostol use.

Among more than two dozen studies of the use of misoprostol for PPH death was not reported to have occurred during these trials. In four other studies, deaths were reported, and for six of the total of eight cases detailed information was presented. One woman died of a malaria-related disseminated intravascular coagulation after average blood loss. A high risk multiparous woman with a low prenatal hemoglobin level died of severe PPH before she reached the hospital.[14] One woman died secondary to a coagulopathy after hysterectomy and consequent re-laparotomy 48 hours after delivery. Another woman with a previous C-section died of PPH and did not receive an autopsy to evaluate the possibility of a ruptured scar. A third woman in the same trial died of severe blood loss caused by a torn cervix after labor induction and post partum application of several uterotonics.[12] In another trial, a woman died suddenly after severe blood loss 90 minutes after delivery of an inconclusive cause of death.[15] In a fourth trial with two cases no reason for death was specified by the authors.[11] None of the cases with fatal complications were associated with misoprostol side effects such as severe hyperthermia or tachycardia reported.

In conclusion, there have been no serious side effects among millions of ulcer patients using misoprostol. The few reported cases of extreme overdose experienced a rapid recovery. None of the fatal cases among misoprostol recipients in PPH trials is definitively linked to a misoprostol side effect. The occurrence of transient pyrexia of 38-40 Celsius among a minority of women receiving misoprostol for PPH should be monitored in the future and clearly addressed during the training of community health workers. The data from several dozen trials completed at this time - combining the experience of more than 17,000 women who have used misoprostol to control PPH – shows that the drug has a remarkably benign safety profile and

would appear safe to use outside of hospital settings. This stable, low cost and easy-to-use medication has the potential to improve significantly the control of post partum hemorrhage at the community level.

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