Route of misoprostol administration: Examining efficacy, side effects and acceptability

Gynuity
HEALTH PROJECTS

Route of misoprostol administration: Examining efficacy, side effects and acceptability

Summary and Outcomes of a Meeting September 2003

Editor

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Summary and Outcomes of a Meeting

To date, the large body of high-quality scientific work on misoprostol for women's health has not systematically addressed the importance of route of administration. Often, the use of misoprostol for women's health indications follows untested practices with different routes of administration. Clinical research comparing different routes of administrations for some indications is relatively scarce. Consequently, assertions about the "best" route of administration for a particular indication are often not grounded in scientific evidence. Moreover, many comparisons do not take into account either the population or provider effect on the efficacy or acceptability of a given route. As a result, experts at a previous meeting entitled "Misoprostol: An emerging technology for women's health" held at the Population Council, in New York in May 2001 identified the need for consensus on the clinical importance of route and an examination of the implications of route for future research and drug development (Shannon and Winikoff, in press).

On September 8 and 9, 2003, a small group of experts met to review current understanding of the various routes of misoprostol administration, including pharmacokinetics, relevant clinical correlates, and implications for research and pharmaceutical development. Participants examined in detail the issue of route with regard to each of the women's health indications for which misoprostol is commonly administered, including early pregnancy termination (both with and without mifepristone), cervical priming, labor induction, prevention and treatment of postpartum hemorrhage, and treatment of incomplete and missed abortion. To date, there is an enormous body of research exploring the effect of route on efficacy, acceptability and side effects for these various indications. The goal of the meeting was to establish consensus on the clinical importance of route, as grounded in scientific evidence, and the implications of route for registration of new products and for future directions in research.

Understanding the Problem

Beverly Winikoff, of Gynuity Health Projects, opened the meeting with a summary of why the route of misoprostol administration is important for patients, services and drug development. Route of administration may affect efficacy, side effects, acceptability, and feasibility of use in services. In turn, different indications, the investigator, population characteristics and culture may affect patient and provider preferences for a particular route of administration. These issues present challenges when designing clinical studies: Blinding may obscure acceptability; or non-blinded studies may allow investigator bias in efficacy assessment. At the same time, because of this diversity, there may be several "good" regimens rather than one "best" regimen. Finally, bringing these regimens to women and providers may entail multiple strategies – including clinical research, targeted product development and advocacy.

Navigating the Routes: Current Knowledge

In the first session "Navigating the routes: Current knowledge", panelists reviewed current understanding of misoprostol's mechanism of action and provided comparisons of the pharmacokinetics and clinical correlates of vaginal, oral, rectal, buccal and sublingual administration. Jane Norman, Royal Infirmary, Glasgow, UK, described the effects of misoprostol on uterine contractions, uterine tone, uterine blood flow and both the pregnant and non-pregnant cervix.

Misoprostol's effects on the uterus may be exploited clinically for cervical ripening, induced abortion and the treatment of postpartum hemorrhage.

Miriam Zieman, Emory University, summarized the pharmacokinetics of vaginal, oral and sublingual administration. Studies suggest that sublingual administration yields the highest bioavailability followed, in decreasing order, by moistened tablets administered vaginally, vaginal administration and oral administration. Given the high variability with coefficients of variation in each of these studies, Zieman stressed the need for an increased sample size when comparing routes of administration. Future studies should also explore how other factors may influence vaginal administration including the use of different moistening agents (water or acetic acid), the breaking of tablets and the pH of the vagina.

P.C. Ho, University of Hong Kong, next examined the clinical correlates of different routes of administration. Previous studies have shown that vaginal misoprostol is more effective than oral misoprostol for a variety of clinical indications; however, many women prefer oral, rather than vaginal, administration. Based on pharmacokinetic data, a research group at the University of Hong Kong conducted a series of trials to assess the clinical efficacy of sublingual misoprostol for a number of gynecological indications. The results suggest that clinical efficacy of sublingual misoprostol is similar to that of vaginal misoprostol in many clinical indications but the incidence of side effects including nausea, diarrhea and fever was higher. The sublingual route may be considered in women who do not like the vaginal administration of drugs.

Karen Meckstroth, University of California, San Francisco, provided a more detailed discussion of the difference between buccal and sublingual misoprostol administration. While the evidence is unclear or conflicting, buccal and sublingual administration are promising, as they may offer decreased gastro-intestinal side effects when compared to oral and even vaginal routes. Buccal or sublingual routes may also offer improved efficacy, better patient acceptance because of the absence of a vaginal exam and less variability in serum levels and uterine response. However, pharmacokinetic evidence for buccal and sublingual administration is limited, misoprostol tablets are formulated for oral (swallowed) absorption and optimal patient instructions are unknown. In a comparison to oral, vaginal and vaginal moistened misoprostol, Tang et al found the area under the curve from sublingual administration to be equal to vaginal moistened, and greater than oral or vaginal dry. Sublingual produced the highest peak serum levels, with a time to peak equivalent to oral administration (Tang et al, 2002). In contrast, buccal administration is characterized by slower absorption over a longer time and a larger surface area leading to a sustained serum level but lower peak levels. The pharmacokinetic data suggest that sublingual administration leads to serum levels similar in time to peak and rate of clearance to oral administration, but with higher peak levels. Effects of sublingual administration, however, may differ from oral since the first pass hepatic metabolism is mostly avoided. The buccal route produces serum levels that appear similar to vaginal administration. In addition, the relationship between clinical effects and serum levels is unclear. Only comparative clinical studies, however, can determine if there is a difference between the sublingual and buccal routes and other routes for obstetric and gynecological indications.

Participants also discussed the relationship between research and clinical practice. While the desire to find a "best" regimen may compel researchers to explore different routes and dosages, more practical demands related to product labeling, regulation and distribution may demand different types of studies. It may be appealing to use misoprostol rectally, but registration of a product approved for rectal use will require costly safety tests on the rectal mucosa that from the perspective

of a pharmaceutical company may not be economically reasonable. If formulated as a suppository, the product may not stand up well to heat, rendering it impractical for many low resource settings. At the same time, the tradition of off-label use may negate the need for either costly studies associated with relabelling or a new formulation. Instead, references from professional bodies, rather than a new label, may be sufficient for providers to gain confidence in a given regimen.

Examining the Indications: Does Route Matter?

In the second session "Examining the Indications: Does Route Matter?" panelists presented recent findings for each of the women's health indications for which misoprostol is currently used. Sylvia Leung, Prince of Wales Hospital, Hong Kong, reviewed current findings on the implications of route for the treatment of incomplete and missed abortion. Evidence to date is inadequate to reach a firm conclusion on the best route of misoprostol administration in managing spontaneous miscarriage. Comparisons between studies are difficult because there are different protocols and different ways of determining 'success.' Most randomized clinical trials (RCT) are not powered enough to examine complications. In the future, a RCT with 3 arm comparison of sublingual, oral and vaginal route with approximately 300 subjects in each arm could be useful to study the difference in treatment efficacy and complication profiles.

Hazem El-Refaey, Chelsea and Westminster Hospital, London, reviewed the current research on the use of misoprostol in the third stage of labor. Several studies have explored whether it is beneficial to replace the practice of administering oxytocic agents in the third stage of labor by orally administered misoprostol. A multi-centered study conducted by WHO confirmed the safety of misoprostol for the management of the third stage of labor (Gulmezoglu AM et al., 2001). Rectal administration may be particularly useful in cases of severe bleeding when the oral and vaginal routes are not practical. Rectal administration may also be associated with a lower incidence of side effects, particularly shivering. Finally, rectal administration may require minimal skill compared to intramyometrial inflection (injection?) of carboprost that is sometimes practiced in extreme situations.

Luis Sanchez-Ramos, University of Florida, summarized the literature on labor induction with misoprostol. Studies suggest that misoprostol appears to be effective irrespective of the formulation employed. Higher doses are associated with rapid labor but with more hyperstimulation. Twenty-five and 50 microgram doses both appear safe and effective. Further studies are needed to assess the safety and efficacy of sublingual administration. That said, studies frequently focus on outcomes that may be simply "noise." Particularly for labor induction, the most important outcome for the patient may be labor, i.e. the slope of the active phase of labor, or the c-section rate.

In the second part of the panel "Examining the Indications: Does Route Matter," panelists reviewed the various uses of misoprostol for abortion. Allan Templeton, University of Aberdeen, presented findings on the use of misoprostol in combination with mifepristone for the induction of abortion in the first trimester. The highest success rates (defined as no need for surgical intervention) are associated with the vaginal administration of misoprostol (800 micrograms). The oral route does not provide acceptable levels of efficacy in the late first trimester. However, analgesia use is higher when misoprostol is administered vaginally. Sublingual administration of misoprostol is associated with similar efficacy to the vaginal route, but with more gastro-intestinal side effects.

John Jain of the University of Southern California reviewed the implications of route for the use of misoprostol alone for medical abortion. A study conducted at the University of Southern California (USC) compared the efficacy and side effects of misoprostol alone and misoprostol and mifepristone. A regimen of mifepristone and misoprostol was significantly more effective for early pregnancy termination. However, the 88% efficacy obtained with vaginal misoprostol alone may be clinically acceptable when mifepristone is not available. A lower incidence of vomiting and diarrhea and higher incidence of fever and chills were found in the misoprostol group compared to the mifepristone-misoprostol group (Jain et al., 2002). Another study (Jain et al., 2001) examined the efficacy of vaginal misoprostol for early pregnancy termination and whether the incidence of side effects is lower with prophylactic loperamide and acetominophen. The study found vaginal misoprostol effective for early pregnancy termination and the incidence of diarrhea and opiate analgesia significantly reduced with prophylactic loperamide and acetaminophen.

Gillian Penney, University of Aberdeen, examined the implications of route for cervical priming prior to surgical abortion and other gynecological procedures. Two recent studies compared sublingual and vaginal administration (Hamoda et al., in press) and sublingual and oral misoprostol (Aronsson, et al., in press) for cervical priming before surgical abortion. The studies suggest the efficacy of sublingual administration may be comparable to vaginal administration. Vaginal administration may have fewer side effects than either sublingual or oral administration. For patients, all three methods may be equally acceptable; providers, however, may prefer sublingual administration to vaginal because of the ease of administration. Current evidence for cervical preparation in non-pregnant women suggests that oral and vaginal misoprostol increase baseline dilatation and reduce cumulative force in premenopausal women during transcervical procedures. On balance, studies suggest that misoprostol orally or vaginally is ineffective for this indication in postmenopausal women.

Appreciating Acceptability: Does Route Matter?

The next panel "Appreciating Acceptability: Does Route Matter?" explored the impact of route on acceptability research and study design. Batya Elul, Population Council, New York, discussed how route of administration may influence drug acceptability for national, local and regional governments; service delivery organizations, providers and patients. The discomfort, time and person responsible for administration (whether the woman or provider) may influence the acceptability of the method for each of these actors. In addition, the experience of administration – whether side effects, time to outcome or the actual outcome – may shape whether a particular route is more or less acceptable. Researchers have employed various approaches to measuring acceptability among patients and providers including comparative, experiential and future acceptability. Acceptability research presents particular methodological challenges: For example, randomization may be impossible if both choices already exist in services; and self-section may render all methods equally acceptable as women may be choosing what they want.

Bryna Harwood, University of Pittsburgh, reviewed findings on the effect of route on acceptability for women. A few studies compared the acceptability of oral vs. vaginal administration for early medical abortion and found either no difference in acceptability (Schaff, 2001) or the oral route more acceptable (Schaff 2002). Tang examined the acceptability of the sublingual route for medical abortion and found 80 percent of women (n=43) preferred the sublingual route (Tang, 2002). Several other studies examined the acceptability of different routes of administration for different

indications such as labor induction (Shetty et al. 2002) or management of early pregnancy failure (Tang 2003) and found no difference in acceptability by route of administration.

That said, current studies rarely test for acceptability of route of administration. Moreover, little is known about how differences in outcome make a difference to women. Future studies need to test for specific aspects of the misoprostol regimen – including routes – and the cut off points for differences in acceptability. Finally, qualitative methods may provide more insight into the acceptability of different routes for both providers and women.

Route of Misoprostol Administration: Research and Development

The last panel "Route of Misoprostol Administration: Research and Development" explored the implications of route for study design and the development, approval and marketability of different formulations. Alisa Goldberg, Planned Parenthood League of Massachusetts, discussed key approaches to designing appropriate trials for studying route of administration. Whereas the oral and vaginal routes of administration have been extensively compared, only a handful of trials have compared buccal, sublingual or rectal administration to other routes of administration for any indication. In designing clinical trials to study new routes of administration, clinically important outcome measures should be clearly defined and then standardized instruments should be created and validated, if not already in use for a given indication. New pharmacokinetic data should guide the choice of route of administration. For newer routes of administration, dose finding studies will be necessary. For more extensively studied indications, new routes of administration can be compared to misoprostol regimens previously proven effective. For less-studied indications, more established routes of administration (oral or vaginal) should be investigated first, and then alternative routes of administration can be explored. In addition to dose finding and efficacy studies, comparisons of side effect profiles and acceptability for different routes of administration are of critical importance.

Jose G. Cecatti, Universidad Estadual de Campinas, Sao Paulo, Brazil, discussed the benefits of a vaginal formulation of misoprostol. In 2001, a vaginal formulation of misoprostol was approved by the Ministry of Health and then made commercially available under the name Prostokos for use for labor induction. It is available only in hospitals. Two studies compared the use of Prostokos to standard clinical practices for cervical ripening and labor induction. The first study compared two formulations of misoprostol, Prostokos 25 microgram vaginal tablet and 1/8 of a Cytotec 200 microgram oral tablet administered vaginally for cervical ripening and labor induction. The results showed that the Prostokos vaginal tablets had the same effectiveness and safety as the dose-equivalent fraction of Cytotec tablets. Another study compared intravaginal misoprostol versus Foley catheter followed by intravenous oxytocin for induction of labor in term and post term pregnancy. Intravaginal misoprostol was more effective than and as safe as Foley catheter and oxytocin. A vaginal formulation of misoprostol has proven to be easy to use, less expensive and allows for better dosage control and less waste than a 200 microgram tablet. Based on the Brazilian experience, similar formulations could also be considered for other developing countries where there are very few alternatives for labor induction and cervical ripening.

Andre Ulmann, Laboratoire HRA Pharma, Paris, France, reviewed the pharmaceutical development and regulatory issues for misoprostol. From a medical standpoint, the availability of a dedicated ob/gyn formulation of misoprostol is highly desirable: It would provide precise guidelines for medical staff on indications, routes of administration and dosages and provide women with precise

recommendations for treatment thus improving efficacy and safety. Given the unwillingness of the current owner of Cytotec to develop a dedicated product, it is necessary to use a generic formulation of misoprostol and seek market authorization based on the published literature. However, the current published data are inadequate for these purposes. Instead, new adequately designed clinical trials for each indication may be the only option. Given the costs associated with these studies as well as manufacturing and promotional activities, making a dedicated product available will require innovative approaches and partnerships between pharmaceutical companies, research and non profit organizations.

Kirsten Moore, Reproductive Health Technologies Project, Washington, D.C., discussed innovative strategies to bridge the gap between research and policy. The nature of the scientific method and the types of research encouraged by the academy may not produce data or results that are easily accessible to policy makers or the general public. By formulating "testable hypotheses," publishing in media accessible to a general reader and engaging with professionals outside the usual research community, researchers may ensure that 'good science' informs public policy and, in turn, health care provision. Advocates must be alert to the multiple strategies for translating research into policy. While the development of a registered product may be ideal, the development of training guidelines, standards of care and consumer information may also help to ensure that research informs clinical practice.

Outcomes

Research

- Pharmacokinetic evidence for buccal or sublingual administration is limited; misoprostol tablets are formulated for oral (swallowed) absorption and optimal patient instructions are unknown. More comparative clinical studies are necessary to determine if there is a difference between the sublingual and buccal routes for obstetric and gynecological indications.
- Future studies should explore how other factors may influence vaginal administration including the use of different moistening agents (water or acetic acid), the breaking of tablets and the pH of the vagina.
- Research should balance the demand for a "best" regimen for different indications with the more practical requirements related to product labeling, regulation and distribution. Ultimately, the choice of route may be both determined by the particular use and pharmacokinetic data.

Practice

- Where there are small differences in the acceptability of different routes of administration, the choice of route should ultimately be left to the woman.
- The tradition of "off-label" use may negate the need for costly studies associated with relabelling or a new formulation. Instead, references from professional bodies, rather than a new label, may be sufficient for providers to gain confidence in a given regimen.
- Advocates should be aware of the multiple strategies for translating research into policy and programs. Particularly where the development of a registered product may not be feasible, the development of training guidelines, standards of care and consumer information may also help to ensure that research informs clinical practice, policy and programs.

ROUTE OF MISOPROSTOL ADMINISTRATION: EXAMINING EFFICACY, SIDE EFFECTS, AND ACCEPTABILITY

A Technical Seminar
September 8 and 9, 2003

I. UNDERSTANDING THE PROBLEM

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III. EXAMINING THE INDICATIONS: DOES ROUTE MATTER?

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IV. APPRECIATING ACCEPTABILITY: DOES ROUTE MATTER?

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ROUTE OF MISOPROSTOL ADMINISTRATION:
EXAMINING EFFICACY, SIDE EFFECTS, AND ACCEPTABILITY
A Technical Seminar

AGENDA

Monday, September 8, 2003
9:00 am – 4:30 pm

9:00 – 9:30	**BREAKFAST**
9:30 – 9:40	**INTRODUCTIONS**
9:40 – 10:00	**UNDERSTANDING THE PROBLEM**
	• Why are we here? Why all the fuss about route of administration? *Beverly Winikoff, Gynuity Health Projects, New York City, USA*
10:00 – 1:00	**NAVIGATING THE ROUTES: CURRENT KNOWLEDGE** **Moderator: Beverly Winikoff**
COFFEE BREAK 11:20 - 11:40	• Misoprostol's action on the uterus. *Jane Norman, Royal Infirmary, Glasgow, UK* • Comparing the routes (Part 1): Pharmacokinetics of vaginal, oral, rectal, buccal and sublingual administration. *Miriam Zieman, Emory University, Atlanta, USA* • Comparing the routes (Part 2): Clinical correlates of vaginal, oral, rectal, buccal and sublingual administration. *P.C. Ho, University of Hong Kong, China* • Buccal and sublingual administration: What's the difference? *Karen Meckstroth, University of California, San Francisco, USA*
1:00 – 2:00	**LUNCH**
2:00 – 4:30	**EXAMINING THE INDICATIONS: DOES ROUTE MATTER? (PART 1)** **Moderator: Charlotte Ellertson**
	• Treatment of incomplete and missed abortion. *Sylvia Leung, Prince of Wales Hospital, Hong Kong, China* • Misoprostol for the treatment and prevention of PPH. *Hazem El-Refaey, Chelsea and Westminster Hospital, London, UK* • Labor induction with misoprostol. *Luis Sanchez-Ramos, University of Florida, Jacksonville, USA*
4:30 – 6:00	**WINE AND CHEESE RECEPTION**

ROUTE OF MISOPROSTOL ADMINISTRATION: EXAMINING EFFICACY, SIDE EFFECTS, AND ACCEPTABILITY

A Technical Seminar

Tuesday, September 9, 2003
8:30 am – 4:30 pm

8:30 – 9:00	**BREAKFAST**
9:00 – 11:00	**EXAMINING THE INDICATIONS: DOES ROUTE MATTER? (PART 2)** **Moderator: Felicia Stewart**
	• Medical abortion with misoprostol in combination with mifepristone. *Allan Templeton, University of Aberdeen, Aberdeen, UK* • Medical abortion with misoprostol alone. *John Jain, University of Southern California, Los Angeles, USA* • Cervical priming prior to surgical abortion and other gynecologic procedures. *Gillian Penney, University of Aberdeen, Aberdeen, UK*
11:00 – 11:15	**COFFEE BREAK**
11:15 – 12:15	**APPRECIATING ACCEPTABILITY: DOES ROUTE MATTER?** **Moderator: Felicia Stewart**
	• Approaches to acceptability research. *Batya Elul, Population Council, New York City, USA* • What do women prefer?: The effect of route on acceptability. *Bryna Harwood, University of Pittsburgh, Pittsburgh, USA*
12:15 – 1:15	**LUNCH**
1:15 – 4:15	**ROUTE OF MISOPROSTOL ADMINISTRATION: RESEARCH & DEVELOPMENT** **Moderator: Daniel Grossman**
	• Designing appropriate trials for studying route of administration: Key questions and approaches. *Alisa Goldberg, Planned Parenthood League of Massachusetts, Boston, USA* • A vaginal formulation of misoprostol: What is the benefit? *José Guilherme Cecatti, Universidad Estadual de Campinas, São Paulo, Brasil* • Pharmaceutical development and regulatory issues for misoprostol. *André Ulmann, Laboratoire HRA Pharma, Paris, France* • Bridging the gap between research and policy. *Kirsten Moore, Reproductive Health Technologies Project, Washington, DC, USA*
4:15 – 4:30	**CLOSING**

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