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Medical abortion in lactating women – low levels of mifepristone in breast milk

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Abstract

Objective. Medical abortion using mifepristone followed by misoprostol is increasingly used for termination of an unwanted pregnancy. Consequently, an increasing number of women undergo medical abortion while still breastfeeding from a previous pregnancy. But there are no data on mifepristone use during lactation. We studied the levels of mifepristone in breast milk collected from women undergoing medical abortion. *Design and samples.* Samples of milk were collected from 12 women during the first 7 days after intake of either 200 mg ($n = 2$) or 600 mg ($n = 10$) of mifepristone. In addition, serum samples were collected on day 3 ($n = 4$). *Main outcome measures.* The levels of mifepristone, quantified using radioimmunoassay. *Results.* The milk concentrations of mifepristone were highest in the first samples collected during the first 12 hours following drug intake, and ranged from undetectable (< 0.013 μmol/l) to 0.913 μmol/l. Thereafter, declining concentrations of mifepristone were detected up to 7 days. The lowest levels of mifepristone in milk were measured following ingestion of the 200 mg dose. The milk:serum ratio of mifepristone ranged from < 0.013:1 to 0.042:1 on day 3 ($n = 4$). The calculated relative infant dose (RID) was 1.5% at its highest. *Conclusions.* The levels of mifepristone in milk are low, especially when using the 200 mg dose. Breastfeeding can be safely continued in an uninterrupted manner during medical abortion of this kind.

Key words: *Lactation, medical abortion, mifepristone, safety, toxicology*

Introduction

The introduction of medical abortion has changed abortion practices dramatically in several countries. For example, in 2007, 69% of all abortions were performed using the medical method in Finland, and the corresponding figure for Sweden was 83% for abortions carried out at up to 9 weeks of gestation (1,2). Today, mifepristone is available in more than 30 countries. Given the choice, most women choose medical rather than surgical abortion (3–5).

Contraception often fails during lactation and the postpartum period. For example, in Finland, approximately 10% of women seeking abortion will have delivered during the previous year (1). However, little is known about medical abortion during lactation. Because of the lack of evidence, there are no guidelines concerning breastfeeding women undergoing medical abortion. Thus, women may hesitate to choose medical abortion because of the fear of passing the drugs used to the suckling infant.

The transfer of drugs to breast milk depends mainly on molecular size, hydrophilic versus lipophilic nature and the degree of protein binding in serum and maternal serum concentrations (6,7). Accordingly, contraceptive steroids are passed to breast milk, although the effects on the newborn are presumed to be minor (8–10). Mifepristone is a lipophilic steroid with high circulating concentrations, and therefore likely to be passed to breast milk if used during

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lactation. The molecular mass of 429.6 Da favors transfer of mifepristone to breast milk, although the high degree of plasma protein binding of 95% does not.

When administered orally, absorption of mifepristone is rapid and peak plasma concentrations are reached within one–two hours, irrespective of dose. Following oral administration of doses exceeding 100 mg, steady-state plasma concentrations of approximately 2.5 μmol/l are seen four hours after ingestion (11–13). Thereafter, the concentrations decrease slowly, with an elimination half-life of 25–30 hours (11). The long half-life of mifepristone could potentially mean that the drug is secreted into breast milk over a long time period.

The objective of the present study was to investigate the levels of mifepristone in serum and milk in lactating women undergoing medical abortion. Knowledge of the kinetics of mifepristone in breast milk will help in clarifying whether breastfeeding can or cannot safely continue during medical abortion. This information not only gives women the opportunity to choose the abortion method they prefer, but could also prevent women from undergoing a more hazardous surgical procedure where abortion care is poor or non-existent.

Material and methods

The study protocol, subject information and informed consent forms were approved by the Ethics Committee at Karolinska Institutet. All women gave their oral and written informed consent before participating in the study.

The clinical study was conducted at the Department of Obstetrics and Gynaecology of the Karolinska University Hospital, Stockholm, Sweden, and at the GynMed Ambulatorium Clinic in Vienna and Salzburg, Austria, between June 2003 and August 2006. Mifepristone assays were performed at the Biomedicum Institute, Helsinki, Finland, during fall 2008.

A total of 12 lactating women (6 in Stockholm and 6 in Austria) were recruited among women requesting medical termination of pregnancy. Healthy, lactating women over 18 years of age requesting medical termination of pregnancy were considered as being eligible for the study.

Medical termination was performed according to clinical routine. In brief, on day one of treatment the women received 600 mg (10 subjects) or 200 mg of mifepristone (2 subjects) orally. This was followed by 0.4 or 0.8 mg of misoprostol 36–48 hours later (treatment day 3), orally or vaginally depending on the length of gestation.

According to our clinical routine, lactating women were advised to discard breast milk for the first three days following mifepristone administration. The women who participated in the study were asked to pump and save 10–20 ml of milk from each pumping or breastfeeding session during the first 7 days after abortion. Samples of milk were thus collected at various intervals during the first 7 days. The samples were frozen following collection at home, and stored at -20°C until analyzed. In addition, serum samples were collected from four of the women on day 3.

The levels of mifepristone in serum and breast milk were quantified by radioimmunoassay (RIA) as described previously (14). In brief, mifepristone was separated from its cross-reacting metabolites using Chromosorb®(Sigma Chemical Co, St Louis, MO, USA) column chromatography, after which the samples were analyzed by RIA. For analysis of mifepristone in breast milk, the samples were diluted with phosphate-buffered saline (to reduce the influence of fat) in the ratios of 1:10, 1:20 and 1:50. The practical detection limit of the mifepristone assay when using milk was 0.013 μmol/l. The intra- and interassay co-efficients of variation in these assays were 11.8 and 19.6%, respectively.

Results

Declining concentrations of mifepristone were detected for up to 7 days following intake in those women who received the higher dose (600 mg) (Figure 1). The women had been asked to collect daily milk samples from days 1 to 7 after mifepristone intake, but two (subjects 6 and 2) of them did not manage to express any milk until day 3 and day 4, respectively. One of these women then decided to give up breastfeeding. In samples from the other woman the concentration on day 3 was already below the detection limit of the assay (0.013 μmol/l). In milk samples from two women (subjects 1 and 2) mifepristone levels were below the detection limit in all samples collected during the 7 days. Both subjects with concentrations below the detection limit had received the lower dose (200 mg) of mifepristone.

Six of the women collected the first milk sample as early as during the first 6 hours after intake. These samples were found to have the highest concentrations of mifepristone, ranging from 0.063 to 0.913 μmol/l. Among the other women, who collected the first milk samples between 9 and 15 hours after mifepristone administration, concentrations ranging from under the detection limit of the assay up to 0.190 μmol/l were found. Only very low levels were detected in a few women after day 3.

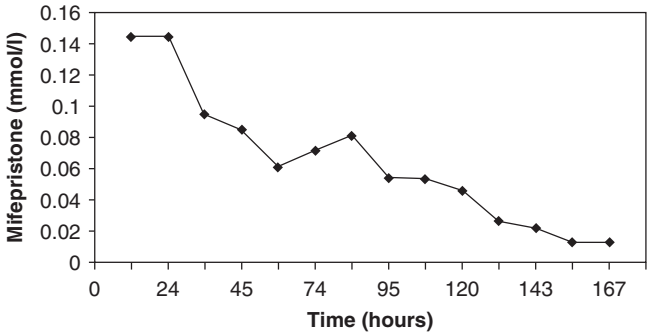

Figure 1. Levels of mifepristone in samples of breast milk collected from a lactating woman undergoing medical abortion on days 1–7 following intake of 600 mg of mifepristone (subject 3 in Table 1). On day 3 (i.e., at ~74 hours), the corresponding serum level of mifepristone was 2.118 μmol/l (data not shown).

The milk:serum ratio of mifepristone concentrations ranged from < 0.013:1 to 0.042:1 when calculated from the concentrations of mifepristone measured in milk and serum samples collected on the morning of day 3. The breast milk samples were collected 4 hours before the serum samples.

Discussion

In the present study we found that the concentrations of mifepristone in breast milk were low, and there was considerable interindividual variation. The highest concentrations occurred during the first 12 hours after drug intake, and were followed by a rapid decrease, which was similar in all women studied. These results, with peak levels within the first 6 hours of drug intake, indicate that the highest drug concentrations occur during the distribution phase. On day 3 the milk:serum ratio was found to vary from < 0.013:1 to 0.042:1, which means that breastfed infants would be exposed to significantly lower levels of mifepristone than their mothers.

The present study is the first in which the passage and levels of mifepristone in breast milk have been investigated. Although the small number of subjects, with milk samples collected at various time points following ingestion of mifepristone, is a limitation, we believe that these results will have an important clinical impact.

The effects of exposure to mifepristone on an infant are poorly known. When used for second trimester abortion, effects on fetal steroid levels have been reported (15). Also, some indications of fetal distress have also been documented when mifepristone has been used for induction of labor (16,17). Nevertheless, no harmful effects on the newborns have been documented (17).

The majority of breastfed infants in the present study were between 6 and 12 months of age. As exclusive breastfeeding often diminishes at this time, there is also an increased risk of an unplanned pregnancy. An infant of this age is estimated to drink between 500 and 1000 ml of milk per day (18), and according to Swedish weight curves should weigh 7.5–9.5 kg. If exclusive breastfeeding were to continue with no pause at the time of abortion, with feeds of 500–1000 ml of breast milk containing the highest measured concentration of mifepristone (0.913 μmol/l), the infant would ingest 0.18–0.36 mg of the drug, corresponding to a dose of 0.05 mg/kg in an 8 kg infant. In contrast, the adult dose per kilogram is much higher, for example, 3.3 mg/kg following administration of 200 mg of mifepristone and 9.9 mg/kg following administration of 600 mg to a woman weighing 60 kg. This would result in a relative infant dose (RID) of 1.5% or 0.5%, respectively. As RID values < 10% are generally considered safe (6,7), breastfeeding could be continued uninterrupted despite medical abortion. After only 6 hours, the infant would be exposed to even lower doses of mifepristone ranging from 0.029 to 0.058 mg during day 1, or 0.0036–0.0072 mg/kg.

It is noteworthy that the levels of mifepristone in milk were lower, or non-detectable, in the samples collected following intake of 200 mg of mifepristone. However, only two subjects had used the 200 mg dose. Nevertheless, the dose of 200 mg of mifepristone might be safer to use also during lactation.

On the basis of these data, we propose that instead of the current practice of discarding breast milk for 3 days after mifepristone intake, lactating mothers undergoing medical abortion could continue breastfeeding without interruption, especially if the dose of 200 mg of mifepristone is used.

Table 1. Concentrations of mifepristone (μmol/l) in breast milk (day 1–3) and in serum (day 3) following ingestion of 200 or 600 mg mifepristone on day 1.

Patient ID	1	2	3	4	5	6	7	8	9	10	11	12
Dose (mg)	200	200	600	600	600	600	600	600	600	600	600	600
Milk, day 1	<0.013	ND	0.144	0.190	0.058	ND	0.869	0.913	0.217	0.063	0.506	0.641
Milk, day 2	<0.013	ND	0.144	0.105	0.061	ND	0.167	0.088	0.072	0.046	0.304	0.394
Milk, day 3	<0.013	ND	0.085	0.104	0.056	0.073	0.142	0.072	0.049	0.029	0.047	0.053
Milk, day 4	<0.013	<0.013	0.071	ND	0.057	ND	ND	0.076	ND	0.017	ND	ND
Milk, day 5	<0.013	<0.013	0.054	ND	0.057	ND	ND	0.062	ND	ND	ND	ND
Serum, day 3	0.676	ND	2.118	3.807	1.372	ND	ND	ND	ND	ND	ND	ND
Milk/serum ratio on day 3	<0.013:1		0.040:1	0.027:1	0.042:1							

Note: ND, no sample available.

Levels of misoprostol, a prostaglandin commonly combined with mifepristone in medical abortion, have previously been studied in breast milk. Following oral intake, levels of misoprostol in milk have been reported to be one-third of those in plasma (19,20). There is no data on the pharmacokinetics of misoprostol in milk following non-oral administration routes. However, on the basis of its pharmacokinetics in plasma, it may be speculated that the concentration of misoprostol in milk would be lower but could be more prolonged following vaginal administration (21,22). In addition, since the elimination half-life of misoprostol is only 20–40 minutes after oral intake (23,24), excretion to breast milk occurs only during a very limited time. Also, the side effects of misoprostol are few and dose-dependent, with gastrointestinal symptoms being the most common.

We conclude that the levels of mifepristone in milk are lower than those in serum. Thus, the infant would be exposed to significantly lower levels of mifepristone than the mother. Thus, continuation of breastfeeding can be recommended despite the medical abortion.

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References

1. Available online at: www.stakes.fi/FI/tilastot/aiheittain/Lisaantyminen/raskaudenkeskeytykset/raskaudenkeskeytykset_ennakko.htm. (accessed on June 28, 2009)
2. Available online at: www.socialstyrelsen.se/NR/rdonlyres/93831CA6-90A3-4755-8BCE-CD6EABCD6209/13853/200912510_rev3.pdf. (accessed on June 28, 2009)
3. Henshaw RC, Naji SA, Russell IT, Templeton AA. Comparison of medical abortion with surgical vacuum aspiration: women's preferences and acceptability of treatment. BMJ. 1993;89:714–17.
4. Winikoff B. Acceptability of medical abortion in early pregnancy. Fam Plann Perspect. 1995;185:142–48.
5. Fiala C and Gemzell-Danielsson K. Review on medical abortion using mifepristone in combination with a prostaglandin analogue. Contraception. 2006;74:66–8.
6. Berlin C, Briggs G. Drugs and chemicals in human milk. Semin Fetal Neonal Med. 2005;10:149–59.
7. Anderson GD. Using pharmacokinetics to predict the effects of pregnancy and maternal-infant transfer of drugs during lactation. Expert Opin Drug Metab Toxicol. 2006;2:947–60.
8. Nilsson S, Nygren KG, Johansson ED. Megestrol acetate concentrations in plasma and milk during administration of an oral contraceptive containing 4 mg megestrol acetate to nursing women. Contraception. 1977a;16:615–24.
9. Nilsson S, Nygren KG, Johansson ED. d-Norgestrel concentrations in maternal plasma, milk and child plasma during administration of oral contraceptives to nursing women. Am J Obstet Gynecol. 1977b;15:178–84.
10. Truitt ST, Frazer AB, Grimes DA, Gallo MF, Schulz KF. Hormonal contraception during lactation: systematic review of randomized controlled trials. Contraception. 2003;68:233–38.
11. Lähteenmäki P, Heikinheimo O, Croxatto H, Spitz I, Shoupe D, Birgerson L and Luukkainen T. Pharmacokinetics and metabolism of RU 486. J Steroid Biochem. 1987;27:859–63.
12. Heikinheimo O, Ylikorkala O, Turpeinen U, Lahteenmaki P. Pharmacokinetics of the antiprogesterone RU486: no

correlation to clinical performance of RU486. Acta Endocrinol. 1990;123:298–304.
13. Available online at: emc.medicines.org.uk/document.aspx?documentId=617#furtherInfo. (accessed on June 28, 2009)
14. Heikinheimo O, Tevilin M, Shoupe D, Croxatto H, Lähteenmäki P. Quantitation of RU486 in human plasma by HPLC and RIA after column chromatography. Contraception. 1986;34:613–24.
15. Hill NC, Selinger M, Ferguson J, MacKenzie IZ. Transplacental passage of mifepristone and its influence on maternal and fetal steroid concentrations in the second trimester of pregnancy. Hum Reprod. 1991;6:458–62.
16. Elliott CL, Brennand JE, Calder AA. The effects of mifepristone on cervical ripening and labor induction in primigravidae. Obstet Gynecol. 1998;92:804–09.
17. Wing DA, Fassett MJ, Mishell DR.Mifepristone for preinduction cervical ripening beyond 41 weeks' gestation: a randomized controlled trial. Obstet Gynecol. 2000;96:543–48.
18. Wallgren A. Breastmilk consumption of healthy full-term infants. Acta Paediatr Scand. 1944;32:778.
19. Abdel-Aleem H, Villar J, Gulmezoglu AM, Mostafa SA, Youssef AA, Shokry M, Watzer B. The pharmacokinetics of the prostaglandin E1 analogue misoprostol in plasma and colostrum after postpartum oral administration. Eur J Obstet Gynecol Reprod Biol. 2003;108:25–8.
20. Vogel D, Burkhardt T, Rentsch K, Schwee H, Watzer B, Zimmermann R, Von Mandach U. Misoprostol versus methylergometrine: pharmacokinetics in human milk. Am J Obstet Gynecol. 2004;191:2168–173.
21. Aronsson A, Fiala C, Stephansson O, Granath F, Watzer B, Gemzell-Danielsson K. Pharmacokinetic profiles up to 12 hours after administration of vaginal, sublingual and slow release oral misoprostol. Hum Reprod. 2007;22:1912–18.
22. Tang OS, Gemzell-Danielsson K, Ho PC. Misoprostol Pharmacokinetic profiles, effects on the uterus and side-effects. Int J Gynaecol Obstet. 2007;99(Suppl 2):160–67.
23. Foote EF, Lee DR, Karim A, Keane WF, Halstenson CE. Disposition of misoprostol and its active metabolite in patients with normal and impaired renal function. J Clin Pharmacol. 1995;35:384–89.
24. Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. Obstet Gynecol. 1997;90:88–92.