

MOTHERISK UPDATE

Can we use metronidazole during pregnancy and breastfeeding?

Putting an end to the controversy

A. Einarson, RN E. Ho G. Koren, MD, FRCPC

ABSTRACT

QUESTION Two of my patients have been diagnosed with giardiasis, and I would like to treat them with the drug of choice for this infection, metronidazole (Flagyl®). One of them is 6 weeks pregnant and the other is breastfeeding a 2-month-old infant, and I have received conflicting information about the safety of this drug during pregnancy and breastfeeding. What should I do?

ANSWER Although metronidazole has been on the market for almost 40 years, its use remains controversial during pregnancy and breastfeeding. Recent evidence has shown, however, that this drug is not associated with adverse effects during either pregnancy or breastfeeding.

RÉSUMÉ

QUESTION On a diagnostiqué une lambliaose chez deux de mes patientes et j'aimerais leur prescrire le médicament indiqué pour cette infection, du metronidazole (Flagyl®). L'une d'entre elles est enceinte de six semaines et l'autre allaite son enfant de deux mois. Les renseignements que j'ai reçus sont contradictoires quant à l'innocuité de ce médicament durant la grossesse et l'allaitement. Que devrais-je faire?

RÉPONSE Même si le metronidazole est sur le marché depuis près de 40 ans, son usage demeure controversé durant la grossesse et l'allaitement. Par ailleurs, de récentes données probantes font valoir que ce médicament n'est pas associé à des effets indésirables durant la grossesse ou l'allaitement.

Metronidazole is bactericidal against anaerobic bacteria. It exerts trichomonocidal activity and is also active against *Giardia lamblia* and *Entamoeba histolytica*. Its exact mechanism of action is unknown. A chemically reactive reduced form of metronidazole appears to be responsible for the drug's activity.¹

Pregnancy

Use of metronidazole during pregnancy has been controversial. The drug is mutagenic in bacteria and carcinogenic in rodents, but has never, in almost 40 years of use, been shown to be associated with human cancer.^{2,3} These concerns, together with some old case reports describing three cases of midline facial

defects, are probably the main reason this drug has not been recommended for use during pregnancy.⁴

Adding to the fear and uncertainty is a passage in the product monograph describing use of metronidazole during pregnancy: "metronidazole crosses the placental barrier; it should be withheld during the first trimester. In addition, it is advisable that administration be avoided during the second and third trimesters; however, if treatment is

considered necessary, its use requires that the potential benefits outweigh the possible risks."¹ After reading that, it is quite understandable that physicians would hesitate to prescribe this drug to pregnant women, even when indicated.

The latest studies, which examined the cases of thousands of women exposed to metronidazole during pregnancy, including a Medicaid cohort study, a large case-control study, and two meta-analyses, have concluded that there is no evidence that using metronidazole during pregnancy increases the rate of major birth defects above the baseline rate of 1% to 3% or that there are any detectable adverse effects on fetuses.⁵⁻⁸

Do you have questions about the safety of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them by fax to (416) 813-7562; they will be addressed in future Motherisk Updates. Published Motherisk Updates are available on the College of Family Physicians of Canada website (www.cfpc.ca). Some articles are published in *The Motherisk Newsletter* and Motherisk website (www.motherisk.org) also.

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto. Ms Einarson, Ms Ho, and Dr Koren are members of the Motherisk Team.

Breastfeeding

Most drugs are excreted into breast milk in small amounts (ie, less than 5% of the mother's dose corrected for the infant's body weight) and are generally considered safe to use because it is thought that full-term infants can handle that amount of drug. Use of metronidazole during breastfeeding has been controversial, however, probably because it is excreted into breast milk in relatively large amounts, up to 20%. Despite this, there have been no reports of adverse effects on breastfed infants of mothers who took metronidazole.⁹ Furthermore, in a group of 12 mothers who received 400 mg of metronidazole three times daily and breastfed their babies, no adverse reactions were seen in any of the babies.¹⁰ ♦

References

1. Rhône-Poulenc Rorer. Product monograph (Flagyl®). Ville St-Laurent, Que: Rhône-Poulenc Rorer; 1999.
 2. Finegold SM. Metronidazole. *Ann Intern Med* 1980;93:585-7.
 3. Beard CM, Noller KL, O'Fallon WM, Kurland LT, Dockerty MB. Lack of evidence for cancer due to use of metronidazole. *N Engl J Med* 1979;301:519-22.

4. Cantu JM, Garcia-Cruz D. Midline facial defect as a teratogenic effect of metronidazole. *Birth Defects* 1982;18:85-8.
 5. Piper JM, Mitchel EF, Ray WA. Prenatal use of metronidazole and birth defects: no association. *Obstet Gynecol* 1993;82(3):348-52.
 6. Czeizel AE, Rockenbauer M. A population based case-control teratologic study of oral metronidazole. *Br J Obstet Gynaecol* 1998;105(3):322-7.
 7. Burtin P, Taddio A, Ariburnu O, Einarson TR, Koren G. Safety of metronidazole in pregnancy: a meta-analysis. *Am J Obstet Gynecol* 1995;172(2 Pt 1):525-9.
 8. Caro-Paton T, Carvajal A, Martin de Diego I, Alvarez Requejo A, Martin Amas LH, Rodriguez Pinilla E, et al. Is metronidazole teratogenic? A meta-analysis. *Br J Clin Pharmacol* 1997;44(2):179-82.
 9. Thomas Hale. *Medications and mother's milk*. Amarillo, Tex: Pharmasoft Medical Publishing; 1998. p. 455.
 10. Passmore CM, McElnay JC, Rainey EA, D'Arcy PF. Metronidazole excretion in human milk and its effect on suckling neonates. *Br J Clin Pharmacol* 1988;26(1):45-51.

...

Reprint Service

Are you still receiving requests for reprints or do you need copies of an article for distribution at a seminar?

Whether you require 50 or 2500 press quality (about \$1.30 per copy) or photocopy quality copies (about \$0.33 per copy) we can provide them.

We can even handle special orders involving laminated covers, binding, or larger quantities. For details, contact Peter Thomlison (Production Manager) at (905) 629-0900 ext 317 or fill out the form below.

Name _____

 Mailing address _____

 Phone number _____
 Fax number _____
 Title of article _____

 Volume/month/year/no. of pages of article _____

 No. of copies _____

Return to:
 Canadian Family Physician
 2630 Skymark Avenue
 Mississauga, Ontario L4W 5A4
 fax (905) 629-0893
 e-mail pat@ctpc.ca
 c/o Peter Thomlison
 Production Manager