Safety of antiviral medication for the treatment of herpes during pregnancy

So-Hee Kang RPh Angela Chua-Gocheco MD Pina Bozzo Adrienne Einarson RN

Abstract

Question One of my patients is a pregnant woman in her first trimester with a history of recurrent genital herpes. She is concerned about whether use of her antiviral medication will adversely affect her baby. What should I tell her?

Answer Studies have shown that the use of acyclovir or valacyclovir is not associated with an increase in birth defects. Limited data exist for famciclovir and therefore it would not be considered a first-line choice for treatment of herpes during pregnancy.

Résumé

Question L'une de mes patientes enceintes en est à son premier trimestre de grossesse et elle a des antécédents d'herpès génital récurrent. Elle se demande si l'utilisation de ses médicaments antiviraux pourrait nuire à son bébé. Que devrais-je lui répondre?

Réponse Des études ont démontré que l'utilisation de l'acyclovir ou du valacyclovir n'est pas associée à une augmentation des anomalies congénitales. Les données concernant le famciclovir sont limitées et ce médicament ne devrait donc pas être considéré comme choix de traitement de première intention pour l'herpès durant la grossesse.

Herpes simplex virus (HSV) infections are common viral infections, with almost 40% of infected patients encountering frequent recurrence within the first year of disease onset.[1] In Ontario the seroprevalence for HSV type 1 (HSV-1) and type 2 was 51.1% and 9.1%, respectively.[2] A Canadian study revealed HSV type 2 seropositivity in pregnant women to be 17.3%, which raises the concern of potential viral transmission from mother to infant.[3] It is also important to note that genital herpes due to HSV-1 infections has increased in frequency and is responsible for up to 30% to 50% of new genital HSV infections.[3,4] Recent findings indicate that pregnant women who acquire HSV as a primary infection in the latter half of their pregnancies are at greatest risk of transmission to neonates.[5]

Neonatal HSV infections are considered more serious compared with adult infections, having consequences that include the following: skin, eye, and mouth infections; central nervous system diseases; disseminated infections; and death. The Canadian neonatal HSV surveillance data indicate that there are 5.9 cases per 100 000 live births, stressing the importance of antiviral treatment during pregnancy to reduce such complications.[6] Treatment with antivirals in adults has established their efficacy and safety, but evidence of the safety of acyclovir, famciclovir, and valacyclovir during pregnancy is relatively lacking. It is important to discuss the use of topical antiviral preparations owing to the need to prevent potential orolabial to genital transmission of HSV-1.

General properties and mechanism of action

Valacyclovir is well absorbed after oral administration; absorption of a single dose of 1000 mg is 54% higher than that achieved after single 200- or 800-mg doses of oral acyclovir.[7] Valacyclovir is rapidly metabolized to acyclovir, the triphosphorylated form of which selectively inhibits human HSV DNA polymerase, reducing viral DNA replication. Similarly, famciclovir is the oral prodrug of its active form penciclovir; it is more stable than acyclovir triphosphate, as evidenced by longer half-lives intracellularly, which might account for the prolonged in vitro antiviral activity.[8] Acyclovir 5% and penciclovir 1% creams are used to treat orolabial herpes (HSV-1). Penciclovir was not detected in the plasma or urine of healthy volunteers after single or repeated application of the 1% cream.[9] Systemic absorption of acyclovir following topical application is minimal or undetectable in adults.[10]

Safety of antivirals during pregnancy

Although controlled studies evaluating the effectiveness of oral antivirals for recurrent HSV outbreaks in the mother and neonatal HSV infections at delivery do exist, they are limited by small sample sizes, the lack of fetal safety outcomes, and variation in timing of exposure.[11] However, data on the safety of antiviral drugs during pregnancy have been collected in pregnancy registries, usually established by the manufacturers. The oldest registry (ie, Acyclovir Pregnancy Registry) was

open from 1984 to 1998, evaluating the use of oral or intravenous acyclovir in pregnant women. In total, 1234 pregnancies were noted with 1246 outcomes from 24 countries; 756 exposed pregnancies were studied in the first trimester. The risk of birth defects was 3.2% (95% confidence interval 2.0% to 5.0%), which is similar to the baseline risk of birth defects in the general population. No unusual defects or patterns of defects were seen, but the limitation of the results was the high loss to follow-up (27% of registrants).[12] During the years 1995 to 1999, the manufacturer of valacyclovir maintained its pregnancy registry, and 110 exposures were reported with 111 known outcomes. Within the first trimester, 1 birth defect was reported out of 28 exposures; 2 of 31 and 1 of 51 exposures resulted in defects in the second and third trimesters, respectively. Prenatal exposures were too limited to provide pregnancy outcomes. According to personal written correspondence from GlaxoSmithKline to Motherisk (January 2010), this registry was limited by the number of registrants and the length of monitoring.

A recent Danish population-based retrospective cohort study used data from its nationwide registry to examine live-born infants born between 1996 and 2008 who were exposed to antivirals during pregnancy and the rate of major birth defects within the first year of life. Of the 837 795 enrolled infants, 1804 pregnancies were exposed to acyclovir, valacyclovir, or famciclovir in the first trimester; prevalence odds ratios were considered no different between exposed and unexposed cohorts. Similar results were found when evaluating second and third trimester data. There was also no significant difference in the prevalence of malformations between exposed and unexposed groups when examining exposure during the first trimester to individual antivirals. The rate of malformations was 2.0% for acyclovir (32 of 1561 infants) and 3.1% for valacyclovir (7 of 229 infants). For famciclovir, exposure was uncommon with 1 infant of 26 exposed having a birth defect. As a supplementary analysis, the association between the use of dermatologic acyclovir and penciclovir creams and major birth defects was evaluated. The rate of malformations in those exposed to acyclovir cream and penciclovir cream in the first trimester (2.3%, 65 of 2850 infants, and 4.2%, 5 of 118 infants, respectively) was not different from the unexposed cohort; similar results were found in the second and third trimesters of pregnancy.[13]

Conclusion

The accumulated evidence for the safety of oral acyclovir and valacyclovir, established from the manufacturer's pregnancy registries and as a result of the Danish cohort study, does not demonstrate an increase in the rate of major birth defects when compared with the general population or an unexposed group. Data on the safety of famciclovir's use during pregnancy is quite limited, and although it might not be expected to increase the risk of major malformations, it should not be the first choice of medication for treatment of HSV during pregnancy. In addition, topical antiviral preparations of acyclovir and penciclovir resulted in no increased rate of major birth defects during pregnancy. Limitations of the safety data on antivirals include a high lost-to-follow-up rate in the registries and the lack of prospective controlled studies. However, these data are reassuring, allowing physicians to offer pregnant patients either acyclovir or valacyclovir for treatment of primary or recurrent HSV infection, which not only treats the mother's condition, but also reduces the likelihood of transmission to the neonate, without unduly compromising fetal safety.

Competing interests
None declared

References

1. Benedetti J, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first-episode infection. *Ann Intern Med* 1994;121(11):847-54.
2. Howard M, Sellors JW, Jang D, Robinson NJ, Fearon M, Kaczorowski J, et al. Regional distribution of antibodies to herpes simplex virus type 1 (HSV-1) and HSV-2 in men and women in Ontario, Canada. *J Clin Microbiol* 2003;41(1):84-9.
3. Patrick DM, Dawar M, Cook DA, Krajden M, Ng HC, Rekart ML. Antenatal seroprevalence of herpes simplex virus type 2 (HSV-2) in Canadian women: HSV-2 prevalence increases throughout the reproductive years. *Sex Transm Dis* 2001;28(7):424-8.
4. Xu F, Sternberg MR, Kottiri BJ, McQuillan GM, Lee FK, Nahmias AJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. *JAMA* 2006;296(8):964-73.
5. Anzivino E, Fioriti D, Mischitelli M, Bellizzi A, Barucca V, Chiarini F, et al. Herpes simplex virus infection in pregnancy and in neonate: status of art of epidemiology, diagnosis, therapy and prevention. *Virol J* 2009;6:40.
6. Kropp RY, Wong T, Cormier L, Ringrose A, Burton S, Embree JE, et al. Neonatal herpes simplex virus infections in Canada: results of a 3-year national prospective study. *Pediatrics* 2006;117(6):1955-62.
7. Ormrod D, Scott LJ, Perry CM. Valaciclovir: a review of its long term utility in the management of genital herpes simplex virus and cytomegalovirus infections. *Drugs* 2000;59(4):839-63.
8. Simpson D, Lyseng-Williamson KA. Famciclovir: a review of its use in herpes zoster and genital and orolabial herpes. *Drugs* 2006;66(18):2397-416.
9. Denavir cream 1% [package insert]. Parsippany, NJ: Novartis Consumer Health, Inc; 2002.
10. Zovirax cream 5% [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2002.
11. Hollier LM, Wendel GD. Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex virus (HSV) recurrences and neonatal infection. *Cochrane Database Syst Rev* 2008;(1):CD004946.
12. GlaxoSmithKline. *Acyclovir pregnancy registry and valacyclovir pregnancy registry* [interim report]. Research Triangle Park, NC: Glaxo Wellcome; 1997.
13. Pasternak B, Hviid A. Use of acyclovir, valacyclovir, and famciclovir in the first trimester of pregnancy and the risk of birth defects. *JAMA* 2010;304(8):859-66.

MOTHERISK Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. **Ms Kang** is a doctoral candidate in the Faculty of Pharmacy at the University of Toronto. **Dr Chua-Gocheco** is a member of the Motherisk Program. At the time this paper was written, **Ms Bozzo** was a member and **Ms Einarson** was Assistant Director of the Motherisk Program. **Ms Bozzo** is now Assistant Director and **Ms Einarson** has retired but continues to be a member of the Motherisk Program.

Do you have questions about the effects of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at 416 813-7562; they will be addressed in future **Motherisk Updates**.

Published **Motherisk Updates** are available on the *Canadian Family Physician* website (**www.cfp.ca**) and also on the Motherisk website (**www.motherisk.org**).