Motherisk Update

Use of proton pump inhibitors during pregnancy and breastfeeding

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ABSTRACT

QUESTION A 36-year-old pregnant patient has symptoms of peptic disease. Treatment with diet and lifestyle modifications and also antacids has given her little relief. If she were not pregnant, I would prescribe a proton pump inhibitor (PPI) for her. She is now 4 weeks pregnant, and I need to determine whether PPIs are safe during pregnancy.

ANSWER Data currently available suggest that omeprazole is not teratogenic in humans. While information on other PPIs is limited, a systematic review of the evidence suggests that they are also not teratogenic.

RÉSUMÉ

QUESTION Une patiente enceinte âgée de 36 ans présente des symptômes de maladie peptique. Le traitement par des changements dans l'alimentation et le mode de vie ainsi que l'administration d'antiacides l'ont très peu soulagée. Si elle n'était pas enceinte, je lui prescrirais l'inhibiteur de pompe à protons (IPP). Elle en est à quatre semaines de gestation et je dois déterminer si les IPP sont sans danger durant la grossesse.

RÉPONSE Les données actuellement accessibles indiquent que l'oméprazole n'est pas tératogène chez l'humain. Même si les renseignements sur d'autres IPP sont limités, une synthèse critique des données scientifiques fait valoir qu'ils ne sont pas tératogènes non plus.

Proton pump inhibitors (PPIs) remain central to management of acid-suppression disorders and are considered safe in the general population.[1] About two thirds of pregnant patients develop heartburn.[2] The origin is multifactorial, but the predominant factor is a decrease in lower esophageal sphincter pressure caused by female sex hormones, especially progesterone.

Although serious reflux complications during pregnancy are rare, symptomatic gastroesophageal reflux disorders should be managed during pregnancy. Treatment is based on a step-up algorithm (which moves in a single direction whereas a standard algorithm might have several directions) beginning with lifestyle modifications and dietary changes followed by antacids or sucralfate as first-line medication. Treatment might eventually include PPIs. Information about their safety during pregnancy mostly relates to omeprazole, the oldest PPI in this group. There is, however, some new information on pantoprazole and lansoprazole in pregnant women that should be noted also.

Omeprazole

A multicentre prospective cohort study conducted by Motherisk looked at the outcomes among 113 mothers exposed to omeprazole during pregnancy, including 101 mothers exposed during organogenesis.[3] Two control groups were used: a disease-paired control group using histamine H_2-blockers and a control group of healthy women exposed to nonteratogenic medications. The rate of major malformations in the omeprazole group (5%) did not differ significantly from rates in the nonteratogenic drug control group (3%) and in the disease-paired control group (3%). Rates of spontaneous abortions, preterm deliveries, cesarean sections, and neonatal health problems; birth weight; and gestational age at delivery were also comparable in the 3 groups.

The Motherisk Program also conducted a meta-analysis on use of PPIs during pregnancy.[4] All exposures to PPIs (593 cases) had a relative risk of 1.18 (95% confidence interval [CI] 0.72 to 1.94) and exposures to omeprazole only (534 cases) had a relative risk of 1.05 (95% CI 0.59 to 1.85), indicating no increase in risk of malformations.

A large cohort study from the Swedish Medical Birth Registry reported on 955 infants whose mothers used omeprazole during pregnancy.[5] In this report, 863 of the infants were exposed at least during the first trimester, and 92 were exposed only after the first trimester. Birth weights, rates of congenital malformations and perinatal death, and low Apgar scores in the exposed group were comparable to rates observed in the general Swedish population.

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A recent multicentre, prospective controlled cohort study followed 295 pregnancies where mothers were exposed to omeprazole (233 exposed during the first trimester), 62 pregnancies where mothers were exposed to lansoprazole, and 53 pregnancies where mothers were exposed to pantoprazole. The pregnancy outcomes of these mothers were compared with those of 868 control subjects.[6] In the omeprazole group, 3.6% (9/249) of babies were born with malformations, a rate similar to the 3.8% (30/792) observed in the control group. There was no pattern of anomalies among the babies born with birth defects.

Administration of oral omeprazole to a 41-year-old woman during the third trimester of pregnancy, after ranitidine and cisapride failed to control her refractory gastroesophageal reflux disorder, was reported.[7] No adverse fetal effects were apparent, and the patient elected to continue omeprazole therapy (20 mg/d) while breastfeeding. Peak omeprazole concentrations in breast milk of 58 nM at 3 hours after ingestion of the drug were lower than 7% of the peak maternal serum concentration (950 nM at 4 h), indicating limited excretion into milk.

Pantoprazole

The recent multicentre, prospective controlled cohort study mentioned above followed 295 pregnancies exposed to PPIs, including 53 exposed to pantoprazole, and compared pregnancy outcomes with those of 868 control subjects.[6] Rate of major congenital malformations in the pantoprazole group was 2.1% (1/48) compared with 3.8% in the control group (30/792). There was no pattern of anomalies.

A 42-year-old woman was studied over a 24-hour period after oral administration of 40 mg of pantoprazole.[8] A milk-to-plasma ratio of 0.022 was observed 2 hours after drug administration. The relative dose to the infant was estimated to be 7.3 µg of pantoprazole, which is equivalent to 0.14% of the weight-normalized dose received by the mother. The mother reported no adverse events in the infant. Because pantoprazole is unstable in acidic pH, the systemic dose received by the infant could have been lower.

Esomeprazole

There is no information regarding exposure to esomeprazole during pregnancy. Because esomeprazole is the S-isomer of omeprazole, however, some of the information related to omeprazole might inform our use of this drug.

Lansoprazole

Previous reports on lansoprazole exposure during pregnancy have described 7 cases with no malformations,[9] and the Motherisk Program is aware of an additional 6 cases with no malformations. Also, the study mentioned above followed 62 pregnant patients exposed to lansoprazole and compared the outcomes of their pregnancies with those of 868 control subjects.[6] Rate of major congenital malformations in the lansoprazole group was 3.9% (2/51) and was not statistically different from the 3.8% observed in the control group (30/792). There was no pattern of anomalies in the babies born with malformations.

Conclusion

Overall, a rule of thumb during pregnancy is to choose an older agent in a pharmacologic class for which there are more fetal safety data that indicate the medication is effective. Applying this rule to PPIs makes omeprazole the drug of choice for now.

References

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MOTHERISK

Motherisk questions are prepared by the **Motherisk Team** at the Hospital for Sick Children in Toronto, Ont. **Dr Nava-Ocampo** and **Ms Velázquez-Armenta** are fellows and **Dr Koren** is Director of the Motherisk Program. **Dr Han** is Director of the Motherisk Program at Samsung Cheil Hospital, Sungkyunkwan University School of Medicine, in Seoul, Korea. **Dr Koren** is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation and, in part, by a grant from the Canadian Institutes of Health Research. He holds the Ivey Chair in Molecular Toxicology at the University of Western Ontario in London.

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.

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