Safety of triptans for migraine headaches during pregnancy and breastfeeding

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ABSTRACT

QUESTION A patient who just found out that she is pregnant and suffers from migraine headaches informs me that she has been taking naratriptan. She indicates that she is planning on breastfeeding her baby and might need to continue treatment. How safe are the medications from this class of drugs during pregnancy and breastfeeding?

ANSWER Accumulated data suggest that exposure to sumatriptan during pregnancy does not increase the risk of birth defects above the baseline rate. There are currently insufficient data to confirm the safety of other triptans; however, evidence to date is reassuring. Information regarding safety of triptans while breastfeeding is limited but also reassuring, as the minimal amounts excreted into the milk are insufficient to cause any adverse effects on the breastfeeding infant.

RÉSUMÉ

QUESTION Une patiente qui vient d'apprendre qu'elle est enceinte et souffre de migraine m'a dit qu'elle prenait du naratriptan. Elle m'a aussi informé qu'elle avait l'intention d'allaiter son bébé et qu'elle aurait peut-être besoin de continuer son traitement. Dans quelle mesure les médicaments de cette classe sont-ils sécuritaires durant la grossesse et l'allaitement?

RÉPONSE Selon les données recueillies, l'exposition au sumatriptan durant la grossesse n'augmente pas le risque d'anomalies congénitales au-delà de la normale. Les données sont actuellement insuffisantes pour confirmer l'innocuité des autres triptans; par ailleurs, les données publiées scientifiques jusqu'à maintenant sont rassurantes. Les renseignements concernant la sécurité des triptans durant l'allaitement sont limités, mais eux aussi rassurants, étant donné que les quantités minimes excrétées dans le lait sont insuffisantes pour causer des effets indésirables sur le nourrisson allaité.

Migraine headache is a common neurologic condition that affects many women of childbearing age. In Canada, approximately 15% of women between 25 and 54 years of age suffer from migraines.[1] Observational studies have indicated that, as levels of estrogen increase, 55% to 90% of mothers experience decreases in both the frequency and severity of migraines during their second and third trimesters.[1-4] However, 25% of women with a history of migraines experience minimal changes in frequency or might even experience an increase in attacks.[1,5] To date, there are no reports that indicate the occurrence of migraines increases the risk of spontaneous abortion, other pregnancy-related complications, or major malformations.[4-6] However, inadequate treatment of migraines might have a serious effect on maternal well-being (eg, sleep deprivation, poor nutrition, dehydration, increased stress, and depression).[4]

Treatment of migraines

Nonpharmacologic measures are usually tried first because of their proven efficacy and innocuity. Strategies include relaxation techniques, appropriate duration of sleep, stress management, massages, application of ice packs, and biofeedback. To prevent recurrence of migraines, pregnant women should also avoid triggers such as lack of sleep, emotional stress, strong odours, and skipping meals.[2,4,5] Among therapeutic options, analgesics are most often the initial drug of choice to manage migraine attacks. Acetaminophen remains the drug of choice during pregnancy because of its lack of teratogenic effects.[7] However, for many women, especially with severe migraines, it might not be effective. Consequently, a substantial number of women have been treated with triptans before becoming pregnant and might need to continue treatment during pregnancy and breastfeeding.[8]

Triptans: pharmacologic properties and mechanism of action

The 5-hydroxytryptamine (5-HT) agonists (triptans) are effective for the acute management of migraines, but they do not prevent future attacks. In contrast to analgesics, the efficacy of triptans is due to the specifically targeted pathogenesis of migraine headaches. Migraine is considered a neurovascular disorder: the sensitization and activation of the trigeminal ganglia promote inflammation of the nerves supplying the meningeal blood vessels and in turn cause dilation of

the blood vessel walls.[4] Triptans alleviate migraines by binding to serotonin 5-$HT_{1B/1D}$ receptors, thereby leading to vasoconstriction and inhibition of neuronal inflammation.[3,9] There are currently 6 triptans available in Canada: almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. Although the first triptan (ie, sumatriptan) has been on the market for more than 2 decades, there is a paucity of published evidence regarding the safety of triptans as a group in human pregnancy.

Safety studies in pregnancy

Available data are currently derived from manufacturer-sponsored pregnancy registries, as well as retrospective and prospective observational studies. Evidence-based information regarding sumatriptan is the most abundant, most likely because it was the prototype of the drug class and has been available for many years. Pregnancy registry data are available for 3 triptans: sumatriptan, naratriptan, and rizatriptan. To date, the risk of major malformations has been reported to be similar to the baseline risk in the general population (1% to 3%). The rates of major malformations were 4.5% for sumatriptan in 494 pregnancies; 2.2% for exposure to naratriptan during the first trimester in 52 pregnancies; and 3.1% for rizatriptan in 51 pregnancies.[10,11] Because pregnancy cases are gathered on a voluntary basis, the accumulated data from company registries are limited by the lack of comparison groups and recall bias. Furthermore, these data need to be interpreted with caution in light of the small sample sizes and insufficient power to reliably detect an increased risk of major malformations.

To date, 3 published prospective comparative studies confirmed no increased risk of major malformations reported with exposure to sumatriptan during pregnancy.[12-14] Two subsequent systematic reviews also found no association between teratogenicity and use of sumatriptan during pregnancy.[15,16] Most recently, as part of the Norwegian Mother and Child Cohort Study, a large observational, prospective cohort study evaluated fetal outcomes following exposure to triptans during pregnancy. The authors identified 1535 pregnant women who received triptans during their pregnancies; 90% of the women used triptans in the first trimester and 65% used them during the second or third trimesters. These women were compared with 373 migraine controls (ie, women treated with triptans 6 months before pregnancy) and 68 021 nonmigraine controls (ie, no reported use of triptans). In the first trimester, 47% (n = 653) of triptan users were treated with sumatriptan; 23.6% (n = 328) with rizatriptan; 17.5% (n = 243) with zolmitriptan; 12.9% (n = 179) with eletriptan; 2.2% (n = 31) with naratriptan; and 2.1% (n = 29) with almotriptan. There was no association between triptan use during the first trimester and an increased risk of major malformations (odds ratio [OR] 1.0, 95% confidence interval [CI] 0.7 to 1.2). Triptan therapy during the second or third trimesters was associated with a small increase in the risk of atonic uterus (OR 1.4, 95% CI 1.1 to 1.8) and blood loss (>500 mL) during labour (OR 1.3, 95% CI 1.1 to 1.5), but not with a risk of adverse fetal outcomes.[17]

Triptans and breastfeeding

Regarding the use of triptans during breastfeeding, human data remain scarce. In a study with 5 nursing women who had received subcutaneous sumatriptan, it was estimated that the infants received, at the most, 3.5% of the maternal dose through breast milk.[18] As a rule, a medication with a relative infant dose of less than 10% of the administered maternal dose is considered compatible with breastfeeding.[19] In addition, given the low oral bioavailability of sumatriptan of 14% when compared with the subcutaneous route of 96%, it is expected that the amounts ingested by suckling infants would be small and would most likely not cause adverse effects. The American Academy of Pediatrics also considers sumatriptan as usually compatible with breastfeeding.[20] Furthermore, a small study indicates that a single 80-mg oral dose of eletriptan results in a relative infant dose of 0.02% of the maternal dose; however, the concentration of the active metabolite (with a longer plasma half-life) was not measured in the breast milk.[21]

Conclusion

The accumulated evidence from sumatriptan's pregnancy registry and other studies suggest that this drug is a safe therapeutic option for the treatment of migraine attacks in pregnant women. More studies are needed to confirm the safety of the other triptans in pregnancy; however, evidence to date is reassuring. In addition, sumatriptan is considered compatible with breastfeeding, as minimal amounts are excreted into milk.

Women who suffer from these migraine headaches, which often render them unable to carry out tasks of daily living, can use triptans during pregnancy and breastfeeding without fear of harming their unborn children or infants.

Competing interests
None declared

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MOTHERISK

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