Topiramate Tied to Risk Of Major Birth Defects

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

Topiramate is associated with a significantly increased risk of major congenital malformations, whether given as monotherapy or as part of a polytherapy antiepileptic regimen, Dr. Stephen Hunt and his colleagues have reported.

Although the associations were strong—an 11-fold increase in the risk of oral clefts and a 14-fold increase in the risk of hypospadias, compared with background rates in the United Kingdom—the confidence intervals surrounding them were wide, noted Dr. Hunt of the Royal Group of Hospitals, Belfast, Northern Ireland. Therefore, the data "should be interpreted with caution," he and his colleagues wrote (Neurology 2008;71:272-6).

The U.K. registry is one of three national registries that track pregnancy outcomes in women taking antiepileptic drugs. Neither of the others—a North American and an Australian registry—has reported an association between topiramate and birth defects, said Dr. Kimford Meador, the Melvin Greer Professor of Neurology at the University of Florida, Gainesville.

"The U.K. data are the first data on topiramate risks during pregnancy," Dr. Meador said in an interview. "The data suggest an association of increased malformations with topiramate exposure during pregnancy. However, the sample is small and the confidence intervals are large, so no definitive conclusion can be drawn."

Because the results are preliminary, clinicians and their patients should be cautious when they consider medication changes, said Dr. Martha Morrell , director of the Columbia Comprehensive Epilepsy Center, New York.

"The first objective of treatment is to control seizures," she said in an interview. "Seizures during pregnancy place the mother at risk for injury and may also pose risk for the fetus. These results will be compared to data coming from other pregnancy registries as they become available. In the meantime, women taking topiramate should not make any adjustment in medications without consulting a physician."

The analysis was drawn from the U.K. Epilepsy and Pregnancy Register, a prospective observational registry and follow-up study that tracks pregnancy outcomes among women in the United Kingdom who are taking antiepileptic medications. The present study included outcomes for 203 pregnancies with exposure to topiramate during the first trimester. Most of the women (133) were taking the drug as part of a polytherapy regimen (mean topiramate dose, 299 mg/day); the rest were on topiramate monotherapy (mean dose 245 mg/day). Of all these pregnancies, 178 (88%) resulted in a live birth; there were a total of 31 congenital anomalies among these infants (16 major and 15 minor).

Among women on monotherapy, there were eight infants born with anomalies, three of which were considered major. Two infants had a cleft lip/palate, and one had hypospadias. The average daily dose of topiramate for the mothers of these infants was 400 mg/day, compared with the average 238-mg dose among women on monotherapy who had normal pregnancy outcomes. Dosage had no significant effect on gestational age or birth weight.

The five minor anomalies in the monotherapy group were sacral dimple, "clicky" hips, plagiocephaly, webbed toes, and immature hip joints.

In the polytherapy group, there were 23 malformations, 13 of which were considered major. The major anomalies included pyloric stenosis, anal atresia, hypospadias, cleft palate, talipes, and dislocated hips. The average daily dosage for mothers of infants with a major anomaly was 342 mg, which was not significantly higher than the average dose of 294 mg/day for mothers on polytherapy who had normal infants. As in the monotherapy group, there were no significant dosage associations with gestational age or birth weight.

The combination of valproate with topiramate as duotherapy was associated with the highest rate of major congenital malformations (36%; 12 cases), followed by a regimen of three or more antiepileptic drugs (24%; 23 cases). Conversely, only 8% of polytherapy regimens that did not include valproate resulted in a major anomaly.

"It is not clear if this is a consequence of an interaction between the drugs, a reflection of unidentified patient characteristics, or due to valproate, which has increasingly been shown to be associated with a high risk of major congenital malformations," Dr. Hunt and his colleagues wrote.

The results are particularly compelling in light of the rapid expansion of indications for topiramate, which in 2004 was approved for prophylaxis of migraine—a condition that is much more common than epilepsy among women of childbearing years, the authors noted.

Janssen-Cilag, U.K. manufacturer of topiramate (Topamax), and other pharmaceutical firms provided unrestricted educational grants to help support the study. Several of the study authors have received honoraria from Janssen-Cilag and other pharmaceutical firms. ■

Drugs, Pregnancy, And Lactation

Antirejection Drugs

Stopping a medication during pregnancy because of potential risks to the fetus is not an option for women who have had an organ transplant, because they risk losing the transplanted organ. Despite considerable concerns in the past about the reproductive safety of cyclosporine, by far the most commonly used antirejection drug for several decades, the data have been quite reassuring.

Several years ago, we published a meta-analysis of 15 studies looking at pregnancy outcomes in women after cyclosporine therapy that suggested in utero exposure probably does not increase the risk for major malformations: The prevalence rate of major malformations was not substantially different from the rate usually reported in studies in the general population (Transplantation 2001;71:1051-5).

BY GIDEON KOREN, M.D.

The neurotoxic side effects of cyclosporine in adult and pediatric patients have raised concerns about the potential effects on brain development in children exposed to the drug during pregnancy. At Motherisk, we recently completed a prospective study evaluating IQ, language, and development in about 40 children of transplant recipients who took cyclosporine during pregnancy, and controls, correcting for the maternal socioeconomic education level and IQ. Follow-up of the children to ages 3 years through 8 years found similar achievement in the children exposed to cyclosporine and those in the control group. (This study has been presented at meetings and is not yet published.)

The use of cyclosporine has decreased, largely because of its nephrotoxic side effects and the availability of other, newer, highly effective immunosuppressive drugs. However, there are far fewer reproductive safety data available on these newer drugs, which need to be studied further; for one, mycophenolate mofetil (Cellcept), the available data are worrisome. To date, the data do not suggest tacrolimus (Prograf) is associated with an increased rate of major malformations, but there are still no data available on the drug's effect on the neurobehavioral development of children exposed in utero. Because cyclosporine, tacrolimus, and sirolimus are associated with some serious adverse effects, particularly chronic kidney damage, new immunosuppressive drugs are being used—particularly mycophenolate mofetil—which have similar effects on preventing rejection, with far fewer nephrotoxic effects.

But evidence that mycophenolate mofetil (MMF) is associated with an increased rate of major malformations has recently begun to emerge. The drug's label states that treatment should not be started until the patient has a negative pregnancy test, and women of childbearing potential should use two forms of contraception.

Over the past several years, reports of malformations in babies exposed to MMF during the first trimester include microtia, cleft lip and palate, hypoplastic fingers and toenails, diaphragmatic hernia, congenital heart defects, and micrognathia. Although these reports come from small case series and case reports and do not prove causation, they have raised serious concerns about the drug's reproductive safety because of the clustering of similar defects, instead of the distribution of malformations seen in the general population. However, cases need to be collected prospectively to determine a better estimate of risk.

In a National Transplantation Pregnancy Registry (NTPR) study of outcomes of pregnancies exposed to MMF or sirolimus, there were 26 pregnancies, including 11 that ended in spontaneous abortions, among 18 kidney recipients treated with MMF. Of the 15 live births, 4 (26.7%) had a structural malformation, including hypoplastic nails and shortened fifth fingers, microtia with and without cleft lip and palate, and a death in a neonate with microtia and other malformations.

Among the seven transplant recipients who received sirolimus (Rapamune) while pregnant, there were three spontaneous abortions. Of the four live births, three had no malformations and one baby whose mother had been treated with MMF during pregnancy but had changed to sirolimus late in pregnancy had microtia and a cleft lip and palate (Transplantation 2006;82:1698-702).

In response to a question from a doctor about a patient who became pregnant 2 years after a kidney transplant, while taking MMF, we recently published a precautionary note about this drug in women. In it we advised that, because of the malformation reports, a woman who has had a transplant and is on MMF and is considering a pregnancy should consider the option of switching to cyclosporine for a short period of time (Canadian Family Physician 2008;54:1112-3).

It is important to note that many women who are transplant recipients are also taking corticosteroids, which are known to increase the risk for oral clefts by about threefold.

Many women are also on azathioprine (Imuran), which has been studied by several groups. Among those studies was a prospective, controlled multicenter trial that compared pregnancy outcomes of 189 women in Europe, Asia, and North America (including patients from Motherisk) who took azathioprine during pregnancy with a group of 230 women who took nonteratogenic drugs during pregnancy. The study found no evidence of an increased rate of malformations, with a similar rate of major malformations in each group (3.5% among those on azathioprine and 3% among the controls, although azathioprine was associated with lower birth weight, gestational age, and prematurity (Birth Defects Res. A Clin. Mol. Teratol. 2007;696:701).

Dr. Koren *is a professor of pediatrics, pharmacology, pharmacy, medicine, and medical genetics at the University of Toronto. He heads the Research Leadership in Better Pharmacotherapy During Pregnancy and Lactation at the Hospital for Sick Children, Toronto, where he is director of the Motherisk Program. He also holds the Ivey Chair in Molecular Toxicology, department of medicine, University of Western Ontario, London.*

Pages 8a—8b◊