Monitor Newer Antiepileptics Closely

BY SHERRY BOSCHERT

FROM A MEETING ON ANTEPARTUM AND INTRAPARTUM MANAGEMENT

SAN FRANCISCO – Third-generation antiepileptic drugs such as lamotrigine and oxcarbazepine are less likely than earlier treatments to cause congenital malformations, but serum levels of the newer drugs must be monitored more closely during pregnancy to avoid other problems.

"The good news is that the third-generation drugs seem to have a spectrum of safety that we did not see with earlier generations," said Dr. Yasser Y. El-Sayed. "It took awhile for this to be evaluated, as many of these third-generation drugs were part of polytherapy. They were add-on treatments. It seems that with these newer drugs, the incidence of congenital malformation is within the expected range for the general population."

The risk of birth defects with older antiepileptics has been reported to be 4%-9%, double to triple the 2%-3% rate of birth defects in the general population. Therapy with four or more antiepileptic drugs boosts the risk for malformations to as high as 25%, said Dr. El-Sayed, professor of maternal-fetal medicine and obstetrics at Stanford (Calif.) University. High peak serum levels of the drugs also increase risk, he said.

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Valproic acid, in particular, stands out among older antiepileptics for elevating risk of congenital malformations. A 2009 report by the quality standards subcommittee of the American Academy of Neurology and the American Epilepsy Society recommended that physicians avoid valproic acid and polytherapy for women in their first trimesters of pregnancy, if possible, to reduce overall risk of congenital malformations.

The report also said to avoid phenytoin, carbamazepine, and phenobarbital during the first trimester to reduce risks of specific anomalies, Dr. El-Sayed said at the meeting, which was sponsored by the University of California, San Francisco.

"Having said that, the majority of women on these drugs will not have malformations, so if that's the drug you need to use to control the seizure, then so be it," he added. Many women hear about the teratogenic potential of antiepileptics and decide to stop epilepsy treatment entirely. "The problem is that seizure activity is hugely problematic" in pregnancy, with potentially grave consequences for both mother and baby.

The most practical approach to treating pregnant women with epilepsy is to pick the single most effective drug and use it at the lowest possible dose, Dr. El-Sayed suggested.

Unlike the older drugs, third-generation antiepileptics have not shown their risks for anomalies to be dose dependent, he added. It's important with the older antiepileptics to keep the whole clinical picture in mind and not respond only to changes in serum levels.

The story is very different with the newer agents. "Their management in pregnancy is much more problematic. The drop in serum levels can be dramatic, and unlike with the older drugs, we tend to see an increase in seizures," he said. "They require much more stringent monitoring in pregnancy and a much more reactionary approach to lower serum levels."

Assessing a patient's therapeutic serum level for a drug before conception helps guide treatment during pregnancy. At a minimum, check serum levels at the beginning of each trimester, or monthly for lamotrigine or oxcarbazepine, Dr. El-Sayed advised. Check levels again in the last month of pregnancy and through postpartum week 8, with close attention to third-generation agents because "there tends to be a reactive toxicity post partum. If you've increased the dose during pregnancy, post partum you may run into some toxicity." Get free fraction levels, if available, and not just total fraction measurements, he said.

Besides sticking to monotherapy and more closely monitoring newer antiepileptic drug levels, good management involves partnering between obstetricians and neurologists in the care of these patients, Dr. El-Sayed added.

Most women with epilepsy give birth safely and successfully, but 1%-2% will develop tonic-clonic seizure during labor, and another 1%-2% will do so during the 24 hours after delivery.

"This can be from stress or lack of sleep, but also from failure to continue adequate administration of antiepileptic drugs during labor," Dr. El-Sayed said.

Don't forget to give medicine in labor, and consider intravenous or intramuscular administration if needed, he noted. ■

Disclosures: *Dr. El-Sayed said he has no relevant conflicts of interest.*

DRUGS, PREGNANCY, AND LACTATION

Topiramate

BY GIDEON KOREN, M.D.

The use of topiramate – approved in the United States for epilepsy in 1996 and migraine prophylaxis in 2002 – continues to increase.

Because the drug is used in women of reproductive age, several registries are collecting data on pregnancy exposures to address the question of the reproductive safety of topiramate in humans, which has not yet been fully characterized.

In different animal species, the drug appears to be generally safe. Yet not much data exist on human pregnancy exposures to topiramate, considering its widespread use.

There are reports of major malformations among babies who are exposed to topiramate in utero, but the numbers of cases are small and none of these associations is statistically significant.

At Motherisk, we conducted an analysis of data from four registries published between 2007 and 2010 – the North American AED (Antiepileptic Drug) Pregnancy Registry, the Australian Pregnancy Register, the U.K. Epilepsy and Pregnancy Register, and the Israeli Teratogen Information Service – that included cases that were exposed to topiramate in the first trimester.

We compared women who took topiramate monotherapy during pregnancy vs. a control group of 710 pregnancies in women who were enrolled in 12 published registries of untreated women with epilepsy.

We chose women with epilepsy as the "disease control" group to more accurately compare with the women with epilepsy who were treated with topiramate, rather than use healthy women as the control group.

Most cases had been exposed to the recommended topiramate dosage of 200-400 mg/day.

Among the 406 pregnancies that were exposed to topiramate monotherapy in the four registries, the mean rate of major malformations was 3.7%, compared with the mean rate of 3.4% among the pregnancies in the untreated women with epilepsy.

The relative risk of 1.09 for topiramate-exposed pregnancies was not statistically significant.

Based on these findings, topiramate did not appear to be associated with a malformation rate that exceeded the baseline rate.

In the North American AED Pregnancy Registry, the rate of cleft lip among topiramate-exposed pregnancies was 0.69%, which the authors suggest may exceed the 0.07% background incidence of this malformation.

But this difference is not statistically significant, and a higher-than-background rate of cleft lip in pregnancies exposed to topiramate in other registries has not been reported.

At present, the North American registry has not yet collected sufficient live-birth cases to have adequate power to confirm an association between topiramate exposure and any malformation.

Of the 64 cases of malformations in topiramate-exposed pregnancies reported to the Food and Drug Administration's Adverse Event Reporting System (AERS), almost 33% (21 cases) were craniofacial abnormalities, which included 11 reports of cleft lip and/or palate reports, 6 reports of facial dysmorphism, 4 reports of micrognathia, 3 cases of skull deformation and ossification abnormalities, and 1 case of macroglossia.

Almost 30% (19 cases) were skeletal malformations, and 23% (15) were cardiovascular malformations.

Most exposures were in the first trimester, and in half the cases, exposure was only in the first trimester. (The FDA presented these data in July 2010 at an advisory panel meeting on a weight loss drug that combines topiramate with phentermine.)

It must be remembered that this database is based on spontaneous reports, and it is impossible to calculate malformation rates from such data because of an unknown denominator.

However, no specific malformation was overrepresented among these cases.

To date, the drug does not appear to elicit a risk for malformations that we have been able to confirm, which may be reassuring to reproductive-age women who use the drug.

Although continuous collection of data is warranted, it is not likely that a major teratogenic risk will emerge.

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 at the department of medicine, University of Western Ontario, London. E-mail him at obnews@elsevier.com. Dr. Koren served as a consultant to the company that has a weight loss drug that contains topiramate that is under review by the FDA for approval, and he presented a review on pregnancy safety data on the drug at an FDA advisory panel in July 2010.