GSK Letter Reports Five Cases

Lamotrigine *from page 1*

Massachusetts General Hospital–run NAAED registry is also greater than the background prevalence of nonsyndromic oral clefts ranging from 0.50 to 2.16 per 1,000 reported in the literature, which includes studies from the United States, Australia, and Europe.

Lamotrigine, marketed as Lamictal by GSK, is approved as a treatment for seizures and for maintenance therapy in bipolar I disorder. It is classified as a pregnancy category C drug, and its label reads that while no evidence of teratogenicity has been found in animals, the drug has been found to reduce folate concentrations in rats, an effect "known to be associated with teratogenesis in animals and humans." Because there are no adequate and well-controlled studies in pregnant women, lamotrigine "should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus," according to the label.

The five cases described in the GSK letter were reported by Dr. Lewis B. Holmes, chief of the genetics and teratology unit at MassGeneral Hospital for Children, Boston, and director of the North American AED pregnancy registry, at the Teratology Society meeting in June.

"This was the first study big enough to be able to look at the frequency of specific major malformations," Dr. Holmes said in an interview. He pointed out that earlier studies from the company registry and the United Kingdom registry with smaller sample sizes looked at all malformations and showed a modest increase in the rate of major malformations but did not have enough patients to pick up increases in specific malformations. At the meeting, he reported that a greater risk of oral clefts was also detected in five other registries, suggesting the same association. In those registries, there were four oral clefts reported among 1,623 lamotrigine-exposed infants, for a frequency of 2.5/1,000, compared with 0.37/1,000 in the comparison group, Dr. Holmes said.

"So this is something that women have to be told about," and physicians "need to know this is a serious issue that's been raised and it is not a trivial sample size," facts that should be brought up with their patients.

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DR. HOLMES

This information has to be put into a practical perspective, and physicians should discuss the absolute risk with patients, Dr. Holmes said. Based on the data he presented, the absolute risk of having an infant with an oral cleft is close to 1%—and is much less than 1% based on the other data—so "it's still a very small risk and it is a very treatable problem," he pointed out. The abstract notes that the findings in a pregnancy registry "are the first step in developing the hypothesis of possible teratogenicity" (Birth Defects Res. A. Clin. Mol. Teratol. 2006;76:318).

Gerald G. Briggs, B. Pharm., a pharmacist clinical specialist at the Women's Pavilion, Miller Children's Hospital, Long Beach, Calif., who was at the meeting, said that this information "is significant because this is the first report of teratogenicity in a second-generation anticonvulsant." All of the first-generation anticonvulsants—phenytoin, phenobarbital, carbamazepine, and valproic acid—are known to have teratogenic effects.

Furthermore, none of the women whose infants had oral clefts was a smoker, which has been associated with isolated oral clefts in some studies, and all were taking folic acid supplements at conception, so folic acid did not appear to be protective, he pointed out. He added, however, that the folic acid dose was not specified, leaving open the possibility that women might not have been compliant.

Although he considers the findings significant, at this point, they "can only raise a hypothesis," said Mr. Briggs, a professor of pharmacy at the University of California, San Francisco. "Consequently, women taking lamotrigine should be advised that exposure in the first trimester might increase the risk for isolated oral clefts [lip or palate], but the absolute risk [is] still low," he said in an interview.

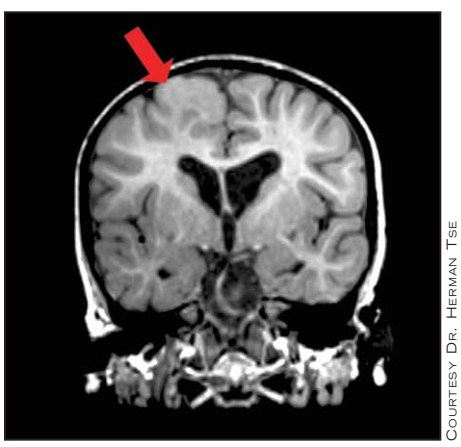
Mr. Briggs said he would counsel women who are on lamotrigine monotherapy and who may become pregnant that seizures can also have adverse effects on them and on the embryo and fetus, and he would recommend that they take 4-5 mg of folic acid with multivitamins and to abstain from smoking or drinking. "Changing to another second-generation anticonvulsant before conception is an option but no guarantee, because the other agents have not been adequately studied," he said, noting that the same recommendations apply to a woman with bipolar disorder, if there is no other drug that can control her symptoms.

The GSK letter says that the company is currently discussing the new data with the Food and Drug Administration and regulatory officials in other countries, and when those discussions are concluded, GSK will update the label, pregnancy category, and other information. For now, GSK is encouraging physicians to register pregnant women exposed to lamotrigine before the fetal outcome is known. ■

The Lamotrigine Pregnancy Registry (the company's registry) can be contacted for more information at 800-336-2176. Women can enroll themselves in the NAAED registry by calling 888-233-2334.

Serial MRIs in Epileptic Infants May ID Cortical Dysplasia

San Francisco — Infants with intractable seizures and normal imaging results may have focal cortical dysplasia that can be detected by serial high-resolution MRI, Dr. Herman Tse said in a poster presentation at the annual meeting of the American Association of Neurological Surgeons.



Courtesy Dr. Herman Tse

Coronal view of a repeat MRI identifying focal cortical dysplasia at 30 months.

Identifying and resecting focal cortical dysplasia can significantly decrease seizures in patients who do not respond to other therapies, said Dr. Tse, of Oregon Health and Science University, Portland, and his associates.

He described the case of a 12-month-old boy with multiple episodes of partial seizures whose EEG results showed the seizure onset to be focused in the brain's right hemisphere but whose CT and MRI results were normal. Treatment with multiple anticonvulsant medications failed to improve the patient's seizures.

Repeat MRI studies at 13, 23, and 30 months of age revealed progression of a right posterior frontal lesion with increased signals on T2-weighted images and fluid-attenuated inversion recovery (FLAIR) MRI. These findings and disruption of the gray-white junction were consistent with focal cortical dysplasia, said Dr. Tse.

At age 30 months, the infant underwent staged cortical mapping and resection of the lesion with the aid of subdural grid placement and stereotactic navigation, he said. Pathology showed large, bizarrely shaped dyslaminated neurons with nodules of cortical dysplasia. The surgical resection caused no complications and reduced the frequency of seizures by more than 90%.

Focal cortical dysplasia, a type of cortical development malformation first described in 1971, is a common cause of pediatric intractable epilepsy. During infancy, as the cerebral cortex undergoes significant development, MRI may be normal initially in infants with intractable partial epilepsy, especially if the focus of seizures is located in areas of late myelination.

Therefore, serial imaging, especially with high-resolution MRI, may be helpful, particularly in infants under 18 months of age with intractable seizures, said Dr. Tse.

—Sherry Boschert

Dire Prognosis Unjustified in Retarded Kids

BY AMY ROTHMAN SCHONFELD

Contributing Writer

Montreal — Children with epilepsy who are also mentally retarded can become seizure free, and more than half can eventually discontinue seizure medication, although repeated efforts may be required to reach those goals, reported Dr. Carol Camfield at the 10th International Child Neurology Congress.

Because children with epilepsy and mental retardation have a poor prognosis for seizure control, physicians and parents may be reluctant to discontinue antiepileptic drugs (AEDs), noted Dr. Camfield, of Dalhousie University and the IWK Health Center, Halifax, Nova Scotia. The result is that these patients may unnecessarily remain on AEDs.

Dr. Camfield—working in collaboration with her husband Dr. Peter Camfield, of the same affiliation—for more than 20 years followed 692 children in Nova Scotia aged 1 month to 16 years who were diagnosed with epilepsy between 1977 and 1985. Children with a mental handicap (IQ less than 70) were studied to establish whether they could become seizure free long enough to discontinue AEDs, and were then followed to see how long they could remain seizure free without AEDs.

Twenty-one percent of the children with epilepsy had an IQ of less than 70 at the time of diagnosis. Of these patients, 117 children with epilepsy and mental retardation were still alive at the end of the follow-up period, Dr. Camfield reported.

Of this group, 45% were deemed to be severely mentally disabled, 26% moderately disabled, and 28% mildly disabled. Epilepsy started earlier in children with a low IQ, compared with children of normal intelligence (3.3 years vs. 7.0 years), with 40% having a seizure within the first year of life.

Sixty-nine (59%) of the epilepsy/low IQ subgroup became seizure free and attempted to end AED therapy. Of these, 35 (51%) were able to discontinue AEDs on the first attempt without seizure recurrence. Eleven others achieved the goal after two tries, and four were able to discontinue AEDs after three tries. Overall, 61% of the children with epilepsy and low IQ were able to discontinue the medications successfully, compared with 73% of children with epilepsy of normal intelligence. However, it took an average of more than 5 years to make the initial try.

Those children with more severe mental retardation, status epilepticus, neurologic deficits, and poor mobility were less likely to discontinue AEDs. Those with symptomatic partial epilepsies were more likely to attempt discontinuation than were those with secondary generalized epilepsies.

"The practice had been to keep any child on AEDs for 2-4 years once they became seizure free—these children were clearly kept on longer," commented Dr. Camfield. ■