First-Trimester Lamotrigine Use May Cause Oral Clefts

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After several years of little indication that lamotrigine was linked to specific birth defects, a major pregnancy registry has found a significant increase in the risk of oral clefts associated with first-trimester use of the drug.

Data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry revealed "an elevated prevalence" of isolated, nonsyndromic oral clefts in infants exposed to lamotrigine monotherapy during the first trimester, when they were compared with a reference population, according to a "Dear Health Care Professional" letter issued by the drug's manufacturer, GlaxoSmithKline (GSK).

The letter reports that there were five cases of oral clefts (three cleft palates and two cleft lips) among 564 pregnancies exposed to lamotrigine monotherapy in the first trimester, for a rate of 8.9/1,000. Based on these numbers, the prevalence of oral cleft is 24 times higher among lamotrigine-exposed neonates than the prevalence of 0.37/1,000 in the general population at the Brigham and Women's Hospital surveillance program, the letter said.

The letter noted that the prevalence of oral clefts in the 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, including 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 Massachusetts General 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. 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. "So this is something that women have to be told about," he said.

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.

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DR. HOLMES

Gerald G. Briggs, B.Pharm., a pharmacist clinical specialist at the Women's Pavilion, Miller Children's Hospital, Long Beach, Calif., 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 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.

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 that 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 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.

GSK's letter said that the company would discuss the new data with the Food and Drug Administration and regulatory officials in other countries. GSK encouraged physicians to register pregnant women exposed to lamotrigine before the fetal outcome is known. ■

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

DRUGS, PREGNANCY, AND LACTATION

New Data on Antiepileptic Drugs

It has been known for years that some first-generation antiepileptic drugs (AEDs) cause birth defects, intrauterine growth retardation (IUGR), and, possibly, developmental delay, but these toxicities were not thought to apply to the second-generation AEDs. New information has challenged that belief.

The first-generation AEDs known to cause birth defects and other developmental toxicities include the hydantoins (ethotoin [Peganone], fosphenytoin [Cerebyx], mephenytoin [Mesantoin], and phenytoin [Dilantin]), phenobarbital, primidone (Mysoline), carbamazepine (Tegretol), and valproic acid derivatives (Depakene, Depakote). In a 2001 study, the incidence of embryopathy (major and minor anomalies, microcephaly, and IUGR) after first-trimester monotherapy was 21% (phenytoin), 27% (phenobarbital), 14% (carbamazepine), 21% any monotherapy, and 28% (polytherapy) (N. Engl. J. Med. 2001;344:1132-8).

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Phenytoin causes a pattern of defects called fetal hydantoin syndrome (FHS) as well as other defects, such as those involving the heart and growth. Carbamazepine can cause a syndrome of minor craniofacial defects, fingernail hypoplasia, and developmental delay as well as neural-tube defects (NTDs).

The defects observed with primidone are similar to those in FHS. Phenobarbital has been associated with an increase in congenital defects when used for epilepsy, but not when used for other indications. Use of valproic acid derivatives between the 17th and 30th day after fertilization is associated with a 1%-2% risk of NTDs. Other defects are those of the head and face, digits, urogenital tract, and mental and physical growth.

Carbamazepine, phenytoin, primidone, and phenobarbital affect folate metabolism or absorption, and this may increase the risk of birth defects, including NTDs. Women taking these agents should take folic acid 4-5 mg/day, preferably starting before conception. Anticonvulsants, particularly the hydantoins and barbiturates, are related to hemorrhagic disease of the newborn, so adequate doses of vitamin K should be administered to newborns exposed to AEDs in utero.

In contrast, first-generation AEDs that do not appear to be associated with a significant risk of birth defects include the benzodiazepines (clonazepam [Klonopin], clorazepate [Tranxene], diazepam [Valium], and lorazepam [Ativan]) and succinimides (ethosuximide [Zarontin] and methsuximide [Celontin]). However, some of these drugs have very little human data, and the benzodiazepines are known to cause toxicity in the newborn, most notably, floppy infant syndrome and withdrawal syndrome.

Until recently, second-generation AEDs had not been linked to congenital defects. But new data from the North American AED Pregnancy Registry and five other pregnancy registries have shown a very significant risk of isolated, nonsyndromic oral clefts after first-trimester exposure to lamotrigine (Lamictal) monotherapy (Birth Defects Res. A Clin. Mol. Teratol. 2006;76:313-428).

The human pregnancy experience is too limited to assess the embryo/fetal risk for the other second-generation agents: felbamate (Felbatol), gabapentin (Neurontin), pregabalin (Lyrica), levetiracetam (Keppra), tiagabine (Gabitril), and topiramate (Topamax). Although the data also are limited for zonisamide (Zonegran), the drug is teratogenic in three animal species and embryo lethal in a fourth and therefore is best avoided in the first trimester. Oxcarbazepine (Trileptal), a drug closely related to carbamazepine, has been associated with minor facial defects, but the data are too limited to assess the risk in humans.

In summary, women with epilepsy should not be denied treatment with the most effective agents for their condition because of pregnancy or nursing. They should be treated with the lowest dose and the fewest drugs possible to control their seizures. They should take folic acid (4-5 mg/day), and vitamin K should be given to the newborns.

AEDs that appear to have the lowest risk for major birth defects are the benzodiazepines, the succinimides, and the second-generation agents. However, the human pregnancy data are very limited for many of these agents.

Carbamazepine and phenytoin are considered compatible with breast-feeding, and gabapentin, levetiracetam, oxcarbazepine, and tiagabine are probably compatible. Two AEDs (primidone and phenobarbital) are known to cause toxicity in the nursing infant and should not be given during breast-feeding. There are no data for the remaining AEDs, but they have the potential to cause toxicity and, if used during breast-feeding, the infants should be closely monitored.

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