Lamotrigine Exposure Linked to 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 lamotrigine monotherapy.

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

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 says.

The letter notes 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. 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. "So this is something that women have to be told about," Dr. Holmes 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.

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 Teratology Society 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 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.

GSK's letter says the company is discussing the new data with the Food and Drug Administration and regulatory officials in other countries. GSK is encouraging 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

A Clinician's Approach to Anticonvulsants

Historically, lithium has been a mainstay of treatment for bipolar disorder. However, over the last decade, anticonvulsant drugs such as sodium valproate and lamotrigine (Lamictal) have become more widely used to treat this disorder.

The use of lithium in the first trimester is associated with a 0.05%-0.1% risk for Ebstein's anomaly, a well-described and frequently serious cardiac malformation. But data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry and other international registries indicate that first-trimester exposure to sodium valproate is associated with an 8%-10% risk of major congenital malformations, notably neural tube defects and cardiac malformations.

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As a result, many clinicians have been relieved to have the option of lamotrigine, which is an effective treatment for bipolar disorder and for which there had been extremely reassuring reproductive safety data over the last 5-7 years.

And until recently, several global teratovigilance programs had not found any indication that first-trimester use of this medication was associated with an increased risk for major congenital malformations.

In what is an important development, recent data from the NAAED registry note a prevalence rate of 2.7% for overall major malformations; however, five infants (8.9/1,000) had oral clefts. (See accompanying article.)

The baseline incidence of oral clefts in the general population has been calculated to be between 0.5 and 2.16 per 1,000 births; thus the data from the NAAED registry suggest at least a fourfold increase in the risk of cleft lip and palate or an absolute risk of approximately 0.9%. Interestingly, in five other registries surveyed, the frequency of oral clefts was 2.5 per 1,000 births, far less than reported by the NAAED Registry.

So how is the clinician to understand these new data, which suggest a signal of teratogenic risk, and how do the data inform the clinical care of patients who rely on the medication for control of chronic relapsing illnesses such as epilepsy or bipolar illness?

While stopping medication for the first trimester may appear to be an option for patients with bipolar disorder, unfortunately, a significant proportion of bipolar patients who do so will relapse.

Pregnancy does not appear to protect women with bipolar disorder against relapse if the mood stabilizer they are using is discontinued: In both a retrospective and prospective study, approximately 50% of patients relapsed during the first 6 months of pregnancy following discontinuation of mood stabilizer. It is also noteworthy that women with bipolar disorder are already at a fivefold increased risk for postpartum depression, compared with the general population, a risk that increases further if they relapse during pregnancy.

Therefore, many women with bipolar disorder who want to conceive are caught between a rock and a hard place, because many compounds used to treat bipolar disorder are either known teratogens, or are agents for which the available reproductive safety data are extremely sparse, such as the atypical antipsychotics, i.e., olanzapine (Zyprexa), risperidone (Ripserdal), quetiapine (Seroquel), and aripiprazole (Abilify).

Clinicians need to work collaboratively with patients to make treatment decisions, making every effort to minimize risk of relapse and fetal risk, realizing that some patients may have to assume some risk if they are to sustain affective well-being during pregnancy. For women who are on lamotrigine and are planning to conceive, the patients and prescribing clinician should now discuss the increased risk for oral clefts.

Patients who require treatment with a mood stabilizer, particularly those with recurrent disease, may consider a trial of lithium, which, while a teratogen, is associated with an extremely small risk for a cardiovascular malformation.

Certainly, the risk associated with lamotrigine is dramatically more modest than the risk associated with first-trimester exposure to sodium valproate, and many patients may elect to continue lamotrigine.

While it may seem intuitive to consider one of the atypical antipsychotics as an alternative to lamotrigine or lithium, given their efficacy in bipolar illness, the total absence of systematically derived data regarding the reproductive safety of atypicals makes them a less attractive alternative, and frankly the last resort, as compared with medications with known reproductive safety data.

When drug choice during pregnancy is considered, proceeding with a drug with known small risks as opposed to one with totally unknown risks is advantageous, particularly if the known risk is a modest one, which is the case with lamotrigine and lithium.

Ultimately, the clinician is left having to make decisions on a case-by-case basis, in collaboration with the patient, realizing that no decision is absolutely risk-free. But decisions can be made that minimize morbidity associated with recurrence of bipolar illness, as well as prenatal exposure to any potentially harmful compound.

When presented with the options, women may make very different decisions. Some women in fact may decide to assume a small risk of oral cleft over a 0.05% risk for a heart malformation because they feel that oral clefts can be repaired more easily, while the morbidity and mortality of Ebstein's anomaly is high, even though the risk is exceedingly small. That is why these decisions have to be made individually, because such decisions will be made not based on relative risk or even absolute risk but rather on each patient's perception of risk.

Dr. Cohen *directs the perinatal psychiatry program at Massachusetts General Hospital, Boston, which provides information about pregnancy and mental health at www.womensmentalhealth.org. He is a consultant to manufacturers of anticonvulsants.*