First-Trimester Lamotrigine Use Tied to Oral Clefts

BY ROBERT FINN
San Francisco Bureau

MONTEREY, CALIF. — Women who take the anticonvulsant lamotrigine during their first trimester of pregnancy have a 10-fold greater risk of having a baby with nonsyndromal cleft lip, cleft palate, or both, according to a peer-reviewed study.

Among 684 women enrolled in the North American Anti-Epileptic Drug (AED) Pregnancy Registry who reported taking lamotrigine monotherapy during their first trimester, there were 16 infants born with major malformations, Dr. Lewis B. Holmes said at the annual meeting of the Teratology Society. This translates to a rate of 2.3%, compared with a baseline rate of 1.6% in unexposed newborn infants (Neurology 2008;70:2152-8).

Although this difference in combined major malformation rates was not statistically significant, the investigators observed a significantly increased risk when they restricted the analysis to oral clefts.

Three of the infants had an isolated cleft palate, one had an isolated cleft lip, and one had bilateral cleft lip and palate, for an overall prevalence rate of 7.3/1,000 infants. In comparison, the rate was 0.7/1,000 for unexposed controls, yielding a significant relative risk of 10.4.

"That's a whopping increase," said Dr. Holmes of Massachusetts General Hospital for Children, Boston. "You wonder if it's a sample size [effect], but it's certainly a point to be pursued in comparison to other databases."

"A larger sample size is needed to see whether the rate of clefts is a 10-fold increase or as low as 4-fold, or somewhere in between," Dr. Holmes said.

Dr. Holmes disclosed that he received a salary support from funds provided since 1997 by the six sponsors of the North American AED Registry: Abbott Laboratories, Eisai Co., GlaxoSmithKline Inc., Novartis, Ortho-McNeil Inc., and Pfizer Inc. ■

Congenital Malformation Risk Rose With Use of Topiramate

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, 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 about medication changes, said Dr. Martha Morrell, director of the Columbia Comprehensive Epilepsy Center, New York.

The analysis was drawn from the U.K. Epilepsy and Pregnancy Register. 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.

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

The combination of valproate with topiramate 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.

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

DRUGS, PREGNANCY, AND LACTATION

When Human Data Are Lacking

In 2007, the Food and Drug Administration approved 16 new molecular entities and several new biologics. None of these agents have human pregnancy experience, but some will be prescribed to women of reproductive age and exposure in early gestation is inevitable.

There also are situations when a woman's condition requires drug therapy, regardless of pregnancy. New antineoplastics are indicated when other therapies have failed to fit into this category, such as ixabepilone (Ixempra) and lapatinib (Tykerb), for breast cancer; nilotinib (Tasigna), for leukemia; and temsirolimus (Torisel), for advanced renal cancer.

BY GERALD G. BRIGGS, B.PHARM.

Regardless of the circumstances, clinicians caring for women of reproductive age will be faced with the dilemma of how to counsel patients when there are few or no human pregnancy data. One method, using some of the drugs approved in 2007 as examples, is described here. When an exposure has already occurred, or when the maternal benefit for starting therapy clearly exceeds the fetal risk and there are no other alternatives, the estimation of fetal risk can be based on four questions:

- ► Is there human pregnancy experience for the drug?
- ► Is there human pregnancy experience with other drugs in the same class or with similar mechanisms of action?
- ► Does the drug cross the human placenta?
- ► Does the drug cause developmental toxicity in animals at doses less than or equal to 10 times the human dose?

Timing of the exposure is critical, and must be included in any estimation. Although organogenesis (5-10 weeks) is usually the most vulnerable period and exposure at that time should be avoided if possible, drugs can cause developmental toxicity throughout gestation.

For the new drugs described, the answer to the first question is no.

There are several examples that fit the second question. Aliskiren (Tekturna) is an antihypertensive that acts as a renin inhibitor. Two other classes of drugs acting on the renin-angiotensin system, angiotensin-converting–enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), are known to cause marked fetal toxicity in the second and third trimesters; a similar effect might occur with aliskiren. Nebivolol (Bystolic) is a β-blocker used for hypertension. It has no intrinsic sympathomimetic activity (ISA), so, as with other β-blockers without ISA, its effects may include restricted placental and fetal weights when used during the second half of gestation.

Levocetirizine (Xyzal), the L-isomer of cetirizine (Zyrtec), is an antihistamine. There is no evidence of fetal harm from antihistamines, so the risk from exposure to levocetirizine is probably low. On the other hand, lisdexamfetamine (Vyvanse), which is indicated for attention-deficit/hyperactivity disorder, is a prodrug of dextroamphetamine, a drug known to cause human developmental toxicity.

Package inserts typically provide at least four important factors that help answer the third question: maternal concentration, elimination half-life, plasma protein binding, and molecular weight. For example, a small percentage of nonpregnant adults had measurable plasma concentrations of retapamulin (Altabax), a topical antibiotic, but the levels were very low (less than 1 ng/mL). The elimination half-life is unknown, but the medium molecular weight (518) suggests that the drug will cross the placenta. However, the amounts available for transfer appear to be clinically insignificant.

Although there are no definite methods to interpret animal studies, nearly all drugs known to cause human developmental toxicity also cause such toxicity in at least one animal species

The dose that causes toxicity in animals is critical, as is its relationship to the maximum recommend human dose (MRHD). Guidelines released by the Environmental Protection Agency in 1991 stated that if a drug did not cause developmental toxicity at doses less than or equal to 10 times the human dose based on body surface area (BSA) or systemic exposure (AUC), then the drug could be considered low risk for human fetal toxicity. Conversely, if a drug did cause toxicity at doses less than or equal to 10 times the human dose (in the absence of maternal toxicity), then it could be classified as having risk, but the risk magnitude would be unknown. These conclusions were similar to those reached by a panel convened in 2004 (Birth Defects Res. 2004;70[Part A]:7-12).

The strength of any risk estimation increases if two or more of the responses concur. For example, animal studies with retapamulin found no fetal toxicity after high systemic doses. These results, combined with the low systemic levels, reinforce the estimation that this is a low-risk drug. Conversely, animal studies with aliskiren observed fetal growth restriction. Thus, the estimation that this drug may cause fetal growth restriction is strengthened.

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