Solo Lamotrigine Not Linked to Birth Defects

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

WASHINGTON — There is no evidence that lamotrigine monotherapy increases the risk of major congenital malformations in infants exposed prenatally to the drug, according to updated data from the International Lamotrigine Pregnancy Registry.

However, when the drug was used as adjunctive therapy along with valproate, the rate of major congenital malformations was significantly higher than the rate for the background population, reported Dr. John A. Messenheimer of GlaxoSmithKline, Research Triangle Park, N.C.

The malformation rate among the women on lamotrigine monotherapy was 2.8%; among those on polytherapy with valproate it was 11.8%.

Since its inception in 1992, the lamotrigine registry has recorded 2,000 pregnancies exposed to the drug during the first trimester. The interim report contains data up to September 2005 and was presented as a poster at the joint annual meeting of the American Epilepsy Society and the American Clinical Neurophysiology Society.

The updated report contained the following outcome data. Most of the women (707) were taking lamotrigine (Lamictal) as monotherapy, 256 were on polytherapy with lamotrigine but without valproate, and 119 were on polytherapy with lamotrigine and valproate.

There were 20 major congenital malformations reported. Of those, two were club feet, two were cases of anencephaly, and three were ventricular septal defects. The remaining malformations included midline defects, urogenital defects, cortical dysplasia, hypoplastic left heart syndrome, hypoplasia of the left ventricle, and diaphragmatic hernia with abdominal organ displacement.

The malformation rate among women on lamotrigine monotherapy was 2.8%; among those on polytherapy without valproate it was 2.7%. The rate among women on polytherapy with valproate was 11.8%—significantly higher than the background population rate of 2%-3%.

There was no significant relationship between lamotrigine dosage and the incidence of malformation, Dr. Messenheimer said. The rate of malformations among women taking more than 400 mg/day was slightly elevated at 4%. But only 100 women were taking such a high dose, and the confidence intervals in the analysis were wide.

Published reports have identified a significantly increased risk of major congenital malformations among women taking valproate as monotherapy (10.7%). These studies prompted the American Epilepsy Society's pregnancy outcomes forum panel to recommend last year that valproate be avoided as a first-line therapy for any indication in women of childbearing age.

However, the lamotrigine registry could not determine whether valproate exposure alone could explain the higher frequency of defects in the lamotrigine/valproate group, said Dr. Messenheimer. The registry determined that because the numbers of antiepileptic drugs used may be inextricably tied to the frequency and severity of seizures, it would be difficult to assess the contribution of each of these factors to the risk of major malformations.

In adults, lamotrigine is approved as adjunctive therapy for the generalized seizures of Lennox-Gastaut syndrome and for conversion to monotherapy in adults with partial seizures who are receiving treatment. It is also approved for maintenance treatment of bipolar disorder, and it is a pregnancy category C drug.

Physicians are asked to report exposed pregnancies to the international registry by calling 800-336-2176 as soon as the pregnancy is identified. ■

Defect Rate Drops With Reduced Use of Valproate in Australia

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

WASHINGTON — Decreased use of valproate to manage epilepsy during pregnancy in Australia has produced a corresponding drop in fetal malformations associated with the drug, Dr. Frank Vajda said at the joint annual meeting of the American Epilepsy Society and the American Clinical Neurophysiology Society.

Dr. Vajda, a neurologist at the Victorian Epilepsy Centre in Victoria, Australia, presented the most recent data from the Australian Pregnancy Registry for Women on Antiepileptic Medication. The registry, established in 1999, has enrolled 810 women—77% of all Australian women who had taken antiepilepsy drugs (AEDs) for any reason. The 64-month data contained outcome information on 715 births.

Of the women in the registry, most who were currently taking AEDs (692) were taking the drugs for epilepsy. Other indications were bipolar disorder (11), pain (4), sleep (1), and unspecified (14). The majority of the women (504) were on AED monotherapy.

Most of the births (640) were of live infants without congenital malformations. There were 44 births with fetal malformations: 27 live births with defects, 9 live births with defects that emerged by 1 year, and 8 induced abortions of malformed fetuses. The malformations included spina bifida, anencephaly, holoprosencephaly, Dandy-Walker syndrome, and a variety of cardiac defects.

There were also 23 spontaneous abortions, one induced abortion for maternal indications, and seven stillbirths; no malformations were noted in these fetuses.

The only significant drug/defect associations occurred in women taking high doses of valproate, either as monotherapy or polytherapy.

Women who were taking more than 1,100 mg/day of valproate as monotherapy had a 13-fold increased risk of fetal malformations, compared with women not taking any AEDs. Women taking similar doses of the drug as polytherapy had a sixfold increased risk of fetal malformations.

The rate of malformation among women taking less than 1,100 mg/day was higher than the 2%-3% that occurs in the general population, but the difference was not statistically significant.

Australian physicians appear to be heeding the data linking valproate to birth defects, Dr. Vajda said. The rate of valproate prescribing and dosages prescribed has decreased over the length of the registry, as have the rates of fetal malformation. In 1999, 26% of women on the registry were on the drug. The rate increased to 33% by 2001 and has since dropped to 21%. The average daily dose has decreased from 1,780 mg in 1999 to 936 mg in 2004.

The rate of malformation associated with valproate monotherapy was 16% before 2004, compared with 7% in 2004; the rate associated with polytherapy was 10% before 2004 and 0% in 2004.

However, he noted, the rates of malformation among women on carbamazepine or lamotrigine monotherapy have increased.

For carbamazepine, the pre-2004 rate was 4.8%; it rose to 6.5% in 2004. The rate associated with lamotrigine monotherapy was 4.5% before 2004 and rose to 8.6% in 2004. The average dosages of these drugs increased from 1999-2004 as well.

"These are not regarded as significant as the numbers are," Dr. Vajda said in an interview. "It's possible that the increases in dosing may play a part, but there is no significant data available as yet."

The registry does not address the possibility of cognitive problems in children exposed to AEDs in utero, he added.

Valproate is the most frequently prescribed antiepileptic drug in the United States, with 12 million prescriptions written annually for women of childbearing age. About 20% of those prescriptions are for epilepsy, and the rest are for migraine and mood disorders. ■

Eszopiclone Improves Sleep Disruptions Caused by Hot Flashes

BY DOUG BRUNK
San Diego Bureau

SAN DIEGO — Perimenopausal women who took eszopiclone for 1 month experienced significant improvements in sleep problems brought on by hot flashes, results from a randomized trial have found.

The drug had no apparent effect on the number or severity of daytime and nighttime hot flashes, however, Rob Mariani, Ph.D., reported during a poster session at the American Psychiatric Association's Institute on Psychiatric Services.

"I think this is another example of how you can improve the quality of your life in great part by improving how well you can sleep at night, especially in perimenopausal women who complain of sleep difficulties," said Dr. Mariani, senior medical liaison for Sepracor Inc., which markets eszopiclone under the brand name Lunesta. The nonbenzodiazepine drug was approved by the Food and Drug Administration in 2004 for the treatment of insomnia.

Dr. Mariani went on to note that most of the published studies in the area of menopause and sleep "indicate that there are really not any significant sleep architecture changes in patients at menopause or perimenopausal age. Yet at the same time, women who are perimenopausal and postmenopausal complain about a significant number of sleep problems, especially those who have vasomotor symptoms."

In a study funded by Sepracor Inc., Dr. Mariani and his associates enrolled 410 perimenopausal women aged 40-60 years who met the Stages of Reproductive Aging Workshop criteria for early menopausal transition, late menopausal transition, and early postmenopause, and who reported sleep latency of 30 minutes or more and total sleep time of 6 hours or less per night at least three times a week for 1 month.

Investigators randomized 201 women to receive 3 mg eszopiclone and 209 to receive placebo nightly for 4 weeks. Study end points included sleep latency, wake time after sleep onset, total sleep time, awakenings due to hot flashes, daytime hot flashes, and physician global evaluations.

Compared with the women in the placebo group, those who took eszopiclone had significant changes in median sleep latency (reduction from baseline of 18.6 minutes vs. 8.1 minutes) and in median wake time after sleep onset (reduction of 30.6 minutes vs. 16 minutes). The increase in median total sleep time was greater among women who took eszopiclone (48.9 minutes per day vs. 29.7 minutes).

Eszopiclone did not affect the frequency or duration of daytime hot flashes, but it did yield significant benefits in the Montgomery Asberg Depression Rating scale score and in the vasomotor and physical domains of the Menopause Quality of Life scale. ■