Valproate Linked to Poor Fetal Outcomes

BY MIRIAM E. TUCKER
Senior Writer

Valproate poses by far the greatest teratogenic risk of all the commonly prescribed antiepileptic drugs, according to Dr. Kimford J. Meador of the University of Florida, Gainesville, and his associates in the Neurodevelopmental Effects of Antiepileptic Drugs Study Group.

"We advise that [valproate] not be used as the AED of first choice for women of childbearing potential, and, when used, its dose should be limited, if possible," the group wrote (Neurology 2006;67:407-12).

Current guidelines from the American Academy of Neurology advise a variety of ways to minimize the risk of teratogenicity with AEDs, including use of monotherapy if possible, use of the lowest effective dose, supplementation with folate, and treatment of the infant with vitamin K at birth (Neurology 1998;51:944-8). However, no current recommendation addresses the differential teratogenetic risk associated with individual AEDs, Dr. Meador and his associates noted.

The data come from an ongoing prospective observational study of mother/child pairs across 25 epilepsy centers in the United States and United Kingdom. A total of 323 mothers and 333 children were available for analysis. Mean gestational ages at the time of enrollment were 17 weeks for the 69 infants exposed to valproate, 18 weeks for the 98 lamotrigine-exposed infants, and 19 weeks for both the 110 whose mothers who used carbamazepine and for the 56 infants exposed to phenytoin. Mean age of the children at the time of analysis ranged from 2.7 years with lamotrigine to 3.5 years for valproate and carbamazepine.

Major congenital malformation or fetal death occurred in 20.3% with valproate, 10.7% with phenytoin, 8.2% carbamazepine, and 1.02% with lamotrigine. Not only was the valproate risk approximately twice that of the other AEDs, but valproate was the only one to show a dose-response relationship: The mean valproate dose for the pregnancies with serious adverse fetal outcomes was 1,268 mg/day compared with just 844 mg/day for those without serious adverse outcomes.

The differences in risk between the AEDs were accounted for by congenital malformation rather than death. Indeed, death rates were actually slightly higher for both carbamazepine and phenytoin (3.6%) than for valproate (2.9%). There were no deaths with lamotrigine. Congenital malformations, on the other hand, occurred in 17.4% with valproate compared with 7.1% with phenytoin, 4.5% carbamazepine, and 1.0% lamotrigine.

Clinicians are urged to encourage their pregnant patients on AEDs to join one of the pregnancy registries around the world that are seeking additional information on AED risk for anatomic teratogenesis. The North American Pregnancy Registry has a toll-free number, 888-AED-AED4. The EURAP registry, which covers Europe and elsewhere, is online at www.eurapinternational.org. ■

Cardiovascular Risk Data Added To Label of Contraceptive Patch

ROCKVILLE, MD. — The Food and Drug Administration has added a warning to the Ortho Evra brand contraceptive patch label to include data indicating a possible increased risk of deep vein thrombosis, MI, and other cardiovascular events in women using the patch.

Dr. David Shames, acting deputy director of FDA's Office of Drug Evaluation III, discussed the studies and the new labeling in a conference call with news media.

The data are from two studies using data obtained from large databases of medical insurance claims, he said. One of the studies, conducted by researchers at Boston University—and funded by Ortho Evra's manufacturer, Johnson & Johnson—concluded that women taking the drug had no more risk of thrombotic events (odds ratio 0.9) than women taking 35 mcg oral estradiol (Contraception 2006;73:223-8).

The other study, by i3 Research, an Ingenix company, showed more than twice the risk (OR 2.4) for serious nonfatal blood clot as women on 35 mcg of estrogen and norgestimate; this study has yet to be published. Dr. Shames said participants in this study will be followed for another 18 months or 2 years.

Ortho-Evra is marketed by Merck & Co. and contains norelgestromin and ethinyl estradiol (EE).

Dr. Shames said FDA has asked Merck to conduct studies with longer follow-up regarding serious blood clots and other adverse events, such as MI and stroke.

—John R. Bell

DRUGS, PREGNANCY, AND LACTATION

Lamotrigine and Oral Clefts

BY LEE COHEN, M.D.

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.

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 cleft.

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 about 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?

Although 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.

Although 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.

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