Data Tie Valproate to Risk of Birth Defects

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

BOSTON — Two new data sets reinforce the recommendation to avoid valproate as a first-line therapy for any indication in women of childbearing age. The findings, presented at the annual meeting of the American Academy of Neurology, strengthen evidence of a link between valproate use and an increased risk of major congenital malformations as well as impaired cognitive development of children exposed in utero.

"Nine other studies on valproate’s anatomical and behavioral effects have shown similar signals of poor outcome," Dr. Kimford J. Meador said. "[T]he above should not be a first-line therapy for any indication in women of childbearing age. Women need to be aware of these risks if they are going to take this drug. We must remember that half of U.S. pregnancies are unplanned.

Dr. Meador, the Melvin Greer Professor of Neurology and director of the epilepsy program at the University of Florida, Gainesville, presented interim data from the ongoing Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study for which investigators enrolled 183 children whose mothers took carbamazepine (48), lamotrigine (66), phenytoin (42), or valproate (29) for epilepsy during pregnancy.

Dr. Meador presented data on the children’s mental development at 2 years, the prospective study will follow the cohort to age 6. Mean IQ scores based on the Mental Development Index (MDI) from the Bayley Scale were lowest for children in the valproate group (81). A score below 85 is considered below normal limits. Mean scores in the other groups were 94 for lamotrigine, 95 for phenytoin, and 96 for carbamazepine. The percentage of children in the valproate group with an MDI of less than 70 (corresponding with mental retardation) was 24%, about double that seen in any of the other groups (carbamazepine, 13%; lamotrigine, 11%; and phenytoin, 12%).

The study also found an inverse relationship when maternal valproate blood levels during pregnancy and MDI scores in the children. All of the valproate relationships remained constant even after maternal IQ, maternal epilepsy type, and past medical history were controlled for.

The mechanism of brain injury in the valproate group is probably third-trimester neuronal apoptosis, Dr. Meador said in an interview. NEAD includes only the children of women with epilepsy, the group that accounts for the smallest proportion of valproate prescriptions. Most of the prescriptions are written for other things, including psychotropic and pain indications," he said.

In the second study, the lamotrigine pregnancy registry—run by the drug’s maker, GlaxoSmithKline—valproate with lamotrigine significantly raised the risk of a major birth defect. The registry, in its 14th year, has prospectively enrolled 2,400 pregnancies in 32 countries. There were 38 lamotrigine polytherapy data on 1,539 pregnancies, said Marianne Cun- nington, Ph.D., of GlaxoSmithKline.

A risk of the major birth defect in the 908 first-trimester exposures to lamotrigine only was 2.9%, similar to the background population risk of 2%-3%. The risk associated with nonvalproate polytherapy was 2.6%. But when lamotrigine polytherapy included valproate, the risk of a ma- jor congenital malformation was more than 11%. "We have a signal for an increased risk for polytherapy including valproate [but] it’s unclear if valproate is responsible for this increased risk," Dr. Cunnington said.

Dr. Meador noted that six other studies have shown that valproate significantly increases the risk of birth defects. "Each has different cohort, but [rates were] similar. The evidence is compelling."

Mental Retardation in Children Whose Mothers Took Antiepileptics During Pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent of Children with MDI Score &lt; 70</th>
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<tr>
<td>Valproate</td>
<td>24%</td>
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Valproate (n = 29) Carbamazepine (n = 48) Phenytoin (n = 42) Lamotrigine (n = 66)

Notes: Mental retardation is defined as a Mental Development Index score of less than 70. Based on data from the NEAD study.
Source: Dr. Meador

Hypnotic Sleep Aids

Drugs, Pregnancy, and Lactation

The physical discomfort of pregnancy induced by the surge of progesterone and the expanding uterus can result in sleep deprivation in pregnancy. An increased need to urinate, nausea and vomiting, heartburn, difficulty in finding a comfortable sleeping position, and the physical discomfort of pregnancy, the kicking and movement of the fetus, all conspire against a good night’s sleep.

Prescribing sleeping medications in preg- nancy may not be the best solution because long-term use can lead to habituation in the woman and her fetus. But patients often seek drug ther- apy to help them sleep, so it is essential to know what is relatively safe and what is not. Hypnotics fall into five subclasses:

- Oral barbiturates. Included in this group are aprop- barital (pregnancy risk factor C) (Alurate); pentobarbital (D) (Nembutal); and secob- barbital (D) (Seconal). Developmental toxicity has not been proven, but more stud- ies are needed regarding the potential for behavioral toxicity after long-term in utero exposure.

Their long elimination half-lives (24, 22- 28, and 28 days, respectively) can cause prolonged sedation, or hangover. They are controlled substances with potential for abuse, which makes them more difficult to prescribe.

Although they are excreted into milk in low amounts, they can be classified as compat- ible with breast-feeding.

- Benzodiazepines. Estazolam (ProSom), flurazepam (Dalmane), quazepam (Doral), and temazepam (Restoril) are in this catego- ry. Data on using these agents in pregnancy are limited. Although there has been no proven association between any of these agents and birth defects, they probably have effects on the embryo or fetus similar to dia- azepames (Valium), including neonatal motor depression (foppy infant syndrome) and/or withdrawal if used in the trimester.

Moreover, all four agents are categorized as contraindicated during breast-feeding, the lack of toxicity reports suggests these anti- depressants probably are low risk for full-term nursing infants.

- Natural products. About 50 natural prod- ucts are or have been advocated for sleep, but few have enough data to recommend their use in pregnancy or lactation. Moreover, the content and purity of natural products are often unregulated.

Natural agents that seem to be low risk are ginseng (not Siberian), honey, nutmeg, oats, and St. John’s wort. But note that ginseng can cause hypertension and hypoglycemia.

Agents to be avoided include American belledere, butternut or other pataeas, kava, mariuana, melatonin (available only as an orphan drug in the United States), mugwort, passion flower, quassa, rauwolfia, Siberian ginseng, taumelloolch, tulip tree, and valerian.

A nonpharmacologic approach is the best and safest course for pregnant patients with insomnia. If medications are required, oc- casional, short-term use is recommended; one of the OTC antihistamines is probably best.

A nonbenzodiazepine agent, such as zolpi- dine, would be my second choice. For more information, visit www.babycenter.com, a Web site frequently visited by women to ob- tain information about their pregnancies, in- cluding tips on sleeping well.

MR. BRIGGS is pharmacist clinical specialist, Women’s Pavilion, Miller Children’s Hospital, Long Beach, Calif.; clinical professor of pharmacy, University of Southern California, San Francisco; and adjunct professor of pharmacy, University of Southern California, Los Angeles. He is also a fellow of the American College of Clinical Pharmacy and author of a reference book “Drugs in Pregnancy and Lactation.”

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