Data Tie Valproate to Risk of Birth Defects

BY MICHELE G. SULLIVAN
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BOSTON — Two new data sets reinforce the recommendation to avoid valproate as a first-line therapy for any indication in women of childbearing years.

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. "[It] 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 185 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 (correlating 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 between 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.

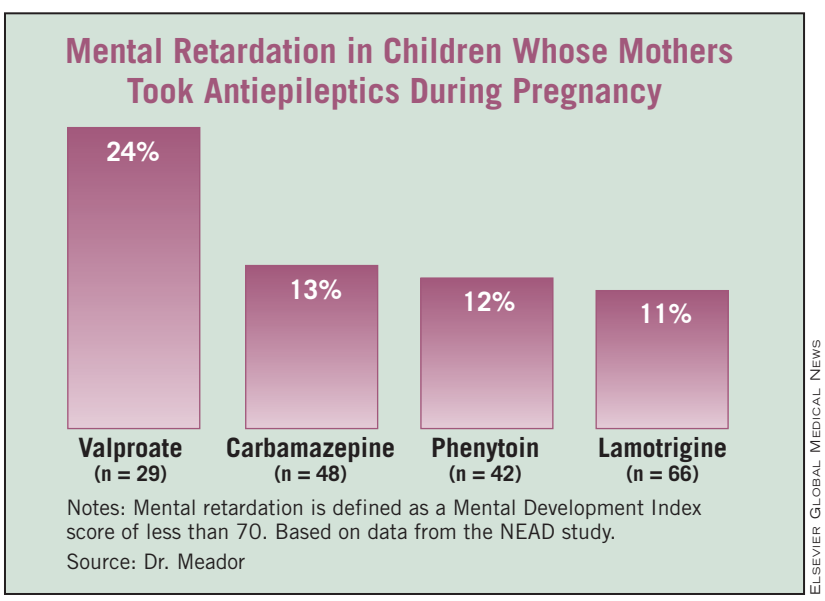
The mechanism of brain injury in the valproate group is probably third-trimester neuronal apoptosis, Dr. Meador said in an interview.

NEAD includes only the children of women with epilepsy, the group that accounts for the smallest proportion of valproate scrips. "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 are known outcome data on 1,539 pregnancies, said Marianne Cunnington, Ph.D., of GlaxoSmithKline.

The risk of a 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 major 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.

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



ELSEVIER GLOBAL MEDICAL NEWS

DRUGS, PREGNANCY, AND LACTATION

Hypnotic Sleep Aids

BY GERALD G. BRIGGS, B.PHARM., FCCP

The physical discomforts 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, as the pregnancy progresses, the kicking and movement of the fetus, all conspire against a good night's sleep.

Prescribing sleeping medications in pregnancy 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 therapy 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 aprobarbital (pregnancy risk factor C) (Alurate); pentobarbital (D) (Nembutal); and secobarbital (D) (Seconal). Developmental toxicity has not been proven, but more studies are needed regarding the potential for behavioral toxicity after long-term in utero exposure.

Their long elimination half-lives (24, 22-50, and 28 hours, 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 compatible with breast-feeding.

▶ **Benzodiazepines.** Estazolam (ProSom), flurazepam (Dalmane), quazepam (Doral), and temazepam (Restoril) are in this category. 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 diazepam (Valium), including neonatal motor depression (floppy infant syndrome) and/or withdrawal if used in the third trimester.

Moreover, all four agents are categorized as contraindicated (risk factor X) by their manufacturers, so they should not be prescribed. Small amounts of quazepam and temazepam are excreted into milk, and the other two agents are most likely in milk as well. Occasional dosing during breast-feeding is probably safe, but the long-term effects on a nursing infant are unknown.

▶ **Nonbenzodiazepines.** There are five drugs in this category: chloral hydrate (for example, Somnote), ramelteon (Rozerem), zaleplon (Sonata), and low-dose (25-75 mg) trazodone (Desyrel), all risk factor C, and zolpidem (Ambien), risk factor B.

The use for sleep of the antidepressant trazodone is off label, but the drug is sometimes combined with other antidepressants for this purpose.

As with the benzodiazepines, the human pregnancy data are limited or nonexistent. There are no animal data for chloral hydrate, an old product that is now rarely used, but animal data on the other nonbenzodiazepines suggest low risk in pregnancy. But, as with most drugs, the best course is to avoid them in the first trimester.

Occasional use in the second and third trimesters probably is low risk, but long-term use (more than 4 weeks) should be avoided. Small amounts of these drugs are excreted into milk, but occasional, short-term use probably is compatible with breast-feeding.

▶ **OTC antihistamines.** There are two in this category, diphenhydramine (such as Benadryl), and doxylamine (Unisom Nighttime Sleep Aid). Diphenhydramine (risk factor B) is safe throughout gestation, as is doxylamine (risk factor A). A major advantage of these antihistamines is that both have antiemetic properties that can reduce pregnancy-induced nausea and vomiting. If pyridoxine (vitamin B_6) is taken with doxylamine, the combination is the antiemetic most frequently studied in pregnancy.

There is little or no experience with these agents during lactation. Although some manufacturers consider them contraindicated during breast-feeding, the lack of toxicity reports suggests these antihistamines probably are low risk for full-term nursing infants.

▶ **Natural products.** About 50 natural products 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 hellebore, butterbur or other petasites, kava, marijuana, melatonin (available only as an orphan drug in the United States), mugwort, passion flower, quassia, 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, occasional, short-term use is recommended; one of the OTC antihistamines is probably best.

A nonbenzodiazepine agent, such as zolpidem, would be my second choice. For more information, visit www.babycenter.com, a Web site frequently visited by women to obtain information about their pregnancies, including tips on sleeping well.

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