Panel to MDs: Avoid Valproate in Fertile Women

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NEW ORLEANS — Valproate should not be prescribed as first-line therapy for any indication in women of childbearing age because it significantly increases the risk of major malformations in exposed infants, the American Epilepsy Society's pregnancy outcomes forum panel recommended.

Converging data from six studies presented at the annual meeting of the American Epilepsy Society and two recently published studies prompted the recommendation, said Kimford Meador, M.D., director of the epilepsy program at the University of Florida, Gainesville, and a member of the panel.

"This isn't class I evidence—we're never going to have that—but what is the chance that these different studies in different populations would all come to this same conclusion?" Dr. Meador asked. "In my opinion, this drug should not be used as first-line therapy for this population."

The studies presented linked valproate with up to a sevenfold increased relative risk of major malformation, compared with the general population; the rate of malformations was 10% for these infants and 1.6% in the general population.

Cardiac, neural tube, and multiple anomalies were among the malformations noted. None of the registries had high enough power to determine the risks for any particular malformation, however, said Lewis Holmes, M.D., chief of the genetics and teratology unit at Massachusetts General Hospital, Boston, and the director of the North American Antiepileptic Drug Pregnancy Registry, which is managed by the hospital.

The registry was established in 1977; as of July 2004, it included 3,708 women. Sixteen infants with major malformations have been born to 149 valproate-exposed women (10.7% and a relative risk of 7.3).

In light of these findings, the panel agreed, physicians should offer safer medications for epilepsy, migraine, and mood disorders to fertile women. "There are lots of other equally effective medications for many of these women," said panelist Martha Morrell, M.D., of Stanford (Calif.) University.

For women with epilepsy, one such alternative is lamotrigine. "Several studies have indicated that the rate of major malformations associated with this drug is about 3%—similar to what we see in the general population," Dr. Morrell said.

The panel acknowledged that for some women, valproate's benefits outweigh the risks. "There may be patients for whom this is the only effective drug," said panelist Gregory Barkley, M.D., chair of the Epilepsy Foundation's professional advisory board. "These women should be counseled to avoid pregnancy," said Dr. Barkley, professor of neurology at Wayne State University, Detroit.

Valproate is the most frequently prescribed antiepileptic drug, with 12 million prescriptions written annually to women of childbearing years. Only about 20% of those prescriptions are for epilepsy—the rest are for migraine and mood disorders.

But many primary care providers and psychiatrists appear unaware of valproate's significant teratogenicity. Treatment guidelines for mood disorders, which recommend the use of valproate, don't include warnings of its effect on developing fetuses, Dr. Morrell said.

Even neurologists may not fully appreciate the problem, Dr. Holmes said. A patient referred to him said her neurologist told her that folic acid supplements would counteract valproate's increased risk of neural tube defects.

"There are no published data supporting that," he said. Anecdotal evidence indicates that the normal 1-mg dose of folate does not change the increased risk.

The recommendation to decrease valproate exposure makes "intuitive sense," said Lee Cohen, M.D., director of the perinatal and reproductive psychiatry clinic at Massachusetts General Hospital.

"It's an ugly drug for reproductive-aged women," he said. Numerous published and ongoing studies have documented behavioral abnormalities and developmental delay in children prenatally exposed to the drug; it also increases the risk of polycystic ovary disease in women who take it.

Panel members want to encourage U.S. and Canadian physicians to have pregnant patients who are taking any antiepileptic drug join the Antiepileptic Drug Pregnancy Registry. More information is available by calling 888-233-2334 or by going to www.aedpregnancyregistry.org. ■

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