Drugs, Pregnancy, and Lactation

Valproic Acid

For more than 20 years, the risk of neural tube defects (NTDs) associated with first-trimester exposure to valproic acid has been well known: The estimated risk is 2%, about 10- to 20-fold higher than the baseline risk. With more widespread use of valproic acid, partly due to increasing use of the drug for psychiatric conditions, more data and larger controlled studies on its teratogenic effects have accumulated over the past 3-4 years, revealing an association with major malformations that previously had been reported anecdotally. The main anomalies that have been identified are cardiac and limb malformations.

BY GIDEON KOREN, M.D.

The results of these studies reflect what we found in a metaanalysis of data from 13 cohort studies in the medical literature, published between 1982 and 2005. The studies in the metaanalysis, published in April in a Canadian journal, compared rates of major malformations among women who reported taking valproic acid during the first trimester with rates among pregnant women who were taking other antiepileptic drugs (AEDs) and among women who were not taking any such drugs.

Nearly 1,000 pregnant women were exposed to valproic acid in the 13 studies. The risk of major malformations, including NTDs, associated with exposure to valproic acid was twofold greater than the risk with exposure to other AEDs. The risk was 4.4-fold greater than in the healthy controls, representing a highly significant increase in risk among valproic acid–exposed pregnancies.

We could not include three studies comparing the neurobehavioral risks of in utero exposure to valproic acid and other AEDs in the metaanalysis, because of their different designs and the variety of cognitive tests used. Still, all three reported an association between valproic acid and developmental delays and cognitive deficits. The most prominent effect was on verbal IQ. More studies on the neurodevelopmental effects of in utero exposure that control for maternal education and other confounding factors need to be conducted to further examine these associations.

On the positive side, in 3 of the 13 studies that also looked at the dose-dependent effects of valproic acid, the threshold dose to cause malformations was about 1,000 mg/day, which has been reported over the past few years. This is true for all malformations associated with valproic acid, including NTDs. In one study, first-trimester valproic acid plasma levels in women were higher among those who had a child with a malformation; in another, a daily dose of 1,000 mg was associated with a significantly increased risk for major malformations, especially NTDs; and in the third, mothers who had a child with spina bifida were on a mean dose of 1,640 mg/day vs. a mean of 941 mg/day among those whose children had no malformations. The same studies indicated that at less than 600 mg/day, there was no increased risk.

These relatively new findings of major malformations other than NTDs and the potentially increased risk of cognitive effects of valproic acid are important for women and physicians to consider when women are planning a pregnancy. Sometimes, women who have been on a drug for epilepsy for many years may no longer need it. If a switch to another drug is not possible, patients need to be monitored closely for malformations, as has been the practice for NTDs, although there is no way to monitor for potential cognitive effects.

Another approach for women who are dependent on valproic acid is to make every effort to keep the daily dose at 600 mg or below or, if that is not feasible, under 1,000 mg/day. Patients should be monitored with ultrasound, fetal echocardiography, and maternal and amniotic α-fetoprotein testing.

Evidence that reducing the dose can effectively reduce malformations came in a report last year from the Australian pregnancy registry for women on AEDs, which found the risk of fetal malformations was 13 times higher among women taking more than 1,100 mg of valproic acid per day as monotherapy, compared with women not taking an antiepileptic drug. Although the fetal malformation rate among those on lower doses was greater than the 2%-3% risk in the general population, the difference was not significant.

If possible, a different medication for controlling seizures should be considered. Carbamazepine (Tegretol) is considered by many neurologists and obstetricians to be the AED of choice in pregnancy, because the cumulative data to date do not reveal any risks of major malformations, except for spina bifida at about 1%, which is half the rate associated with valproic acid.

However, there are far fewer data on the reproductive risks of newer antiepileptics such as lamotrigine and gabapentin. Of the newer drugs, lamotrigine seems to be the most promising in terms of adverse fetal outcomes, but the number of pregnancies with data is much smaller than is available with valproic acid and carbamazepine.

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Lamotrigine + Valproate 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.

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

Most of the women (707) were taking lamotrigine as monotherapy, 256 were on polytherapy with lamotrigine but without valproate, and 119 were on polytherapy with lamotrigine and valproate.

Of the 20 major congenital malformations reported, 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 in women on lamotrigine monotherapy was 2.8%; the rate in those on polytherapy without valproate was 2.7%. The rate in 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 in 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 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.

The lamotrigine registry could not determine whether valproate exposure alone could explain the higher rate of defects in the lamotrigine/valproate group. The numbers of antiepileptic drugs used may be inextricably tied to the frequency and severity of seizures, making it difficult to assess the contribution of each factor, he said.

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. The complete interim report of the registry is available by calling the same number. ■

Two Deaths After Mifepristone Medical Abortion Prompt FDA to Issue Advisory

Two additional deaths after medical abortion with mifepristone (Mifeprex) have prompted the Food and Drug Administration to issue a public health advisory alerting health care providers and advising review of prescribing information.

The drug's manufacturer, Danco Laboratories, notified the agency of the deaths, which took place in the United States.

One of the deaths has since been determined to not be related to either an abortion or to the use of mifepristone and misoprostol. The FDA is investigating the other death, which involved symptoms of infection.

The agency advises physicians to discuss with their patients the risk of sepsis as well as early signs and symptoms that may warrant immediate medical evaluation. In addition, the FDA advises physicians and emergency department personnel to investigate the possibility of sepsis in patients who are undergoing medical abortion and present with all of the following:

► Nausea, vomiting, or diarrhea.

► Weakness with or without abdominal pain.

► No fever or other signs of infection more than 24 hours after taking misoprostol.

Strong consideration should be given to obtaining a complete blood count to identify those patients with hidden infection.

The FDA recommends that if physicians suspect infection in patients with this presentation, they should consider immediately initiating treatment with antibiotics that include coverage of anaerobic bacteria, such as *Clostridium sordellii*. However, the agency does not recommend the use of prophylactic antibiotics at this time.

Four previous deaths from sepsis have been confirmed in U.S. women following medical abortion with mifepristone and misoprostol from September 2003 to June 2005. All four cases of fatal infection tested positive for *C. sordellii*.

For more information, go to: www.fda.gov/cder/drug/infopage/mifepristone.

—Kerri Wachter