Defects Seen With Other AEDs

Valproate *from page 1*

were on AED monotherapy. Most of the births (640) were of live infants without congenital malformations. There were 44 births with fetal malformations: 27 live births with defects, 9 live births with defects that emerged by 1 year, and 8 induced abortions of malformed fetuses. The malformations included spina bifida, anencephaly, holoprosencephaly, Dandy-Walker syndrome, and a variety of cardiac defects.

There were also 23 spontaneous abortions, one induced abortion for maternal indications, and seven stillbirths; no malformations were noted in these fetuses. The only significant drug/defect associations occurred in women taking high doses of valproate, either as monotherapy or polytherapy. Women taking more than 1,100 mg/day of valproate as monotherapy had a 13-fold increased risk of fetal malformations, compared with women not taking any AEDs. Women taking similar doses of the drug as polytherapy had a sixfold increased risk of fetal malformations.

The rate of malformation among women taking less than 1,100 mg/day was higher than the 2%-3% that occurs in the general population, but the difference was not statistically significant.

Australian physicians appear to be heeding the data linking valproate to birth defects, Dr. Vajda said. The rate of valproate prescribing and dosages prescribed has decreased over the length of the registry, as have the rates of fetal malformation. In 1999, 26% of women in the registry were on the drug. The rate increased to 33% by 2001 and has since dropped to 21%. The average daily dose has decreased from 1,780 mg in 1999 to 936 mg in 2004.

The rate of malformation associated with valproate monotherapy was 16% before 2004, compared with 7% in 2004; the rate associated with polytherapy was 10% before 2004 and 0% in 2004.

The rates of malformation among women on carbamazepine or lamotrigine monotherapy have increased. For carbamazepine, the pre-2004 rate was 4.8%; it rose to 6.5% in 2004. The rate associated with lamotrigine monotherapy was 4.5% before 2004 and rose to 8.6% in 2004. The average dosages of these drugs increased from 1999-2004 as well, he noted.

Valproate is the most frequently prescribed AED in the U.S., with 12 million prescriptions written annually for women of childbearing age. About 20% of prescriptions are for epilepsy, and the rest are for migraine and mood disorders. ■

Refractory Seizures Linked to Cardiac Arrhythmias, Ischemia

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WASHINGTON — Patients with refractory epilepsy may be at increased risk for cardiac arrhythmias and resultant cardiac ischemia during seizures, as well as interictal sinus rhythm pauses, Dr. Maromi Nei reported in a poster at the joint annual meeting of the American Epilepsy Society and the American Clinical Neurophysiology Society.

In some cases, such arrhythmias may be a contributing factor to sudden unexpected death in epilepsy (SUDEP), said Dr. Nei of the Jefferson Comprehensive Epilepsy Center, Philadelphia, although more study is necessary to confirm this association.

SUDEP accounts for 8%-17% of deaths among people with epilepsy and is most common in those with refractory disease. SUDEP is defined as sudden, unexpected, nontraumatic, nondrowning death in an individual with epilepsy, witnessed or unwitnessed, in which postmortem examination does not reveal an anatomic or toxicologic cause for the death.

Using an implantable cardiac monitoring device, Dr. Nei recorded heart rhythm in 14 patients (mean age 40 years) with refractory epilepsy for a mean of 10 months. Epilepsy was idiopathic generalized in two, symptomatic generalized in three, and partial in nine. They had failed a mean of seven antiepileptic drugs, and eight had failed epilepsy surgery. None of the patients had a history of heart disease.

A subcutaneous cardiac loop recording device was implanted in all patients. The cardiac monitor was programmed to record when the heart rate fell below 30 beats per minute (BPM) or when it exceeded 180 BPM. Patients were asked to activate the device at the time of any seizures, episodic loss of consciousness, presyncope, or palpitations. They also kept diaries documenting these events.

At the conclusion of monitoring, patients had experienced a mean of 37 seizures each (range 2-236). Their mean ictal heart rate was 110 BPM (range 76-198).

Two patients had T wave inversions during their seizures. One patient had ST segment elevation during seizures, and one patient had frequent atrial premature contractions in the postictal period. Sinus arrest of up to 4.8 seconds occurred in one patient during sleep that was not associated with seizure. All other patients had sinus rhythm pauses or sinus tachycardia associated with their seizures. The significance of these rhythm disturbances is unknown, Dr. Nei said in an interview.

The premature atrial contractions are probably not clinically significant, but are consistent with an increase in autonomic stimulation occurring with the seizure, she added.

The case of sinus arrest suggests that there could be an increase in vagal tone that might result in an increased risk for sinus arrest, particularly during sleep. "This is important because SUDEP often occurs during sleep, and this finding suggests that one possible mechanism for SUDEP is sinus arrest," she said. ■

Catecholamines Released During Status Epilepticus Injure Heart

WASHINGTON — The flood of catecholamines released during status epilepticus appears to damage myocardium, and may be the root cause of death during status, Dr. Edward Manno reported in a poster presented at the joint annual meeting of the American Epilepsy Society and the American Clinical Neurophysiology Society.

When he examined cardiac pathology slides obtained at autopsy, Dr. Manno found a high occurrence of cardiac contraction band necrosis among patients who died during status. These necrotic areas form when myocardium dies in a hypercontracted state. "These findings provide presumptive evidence that excessive catecholamine released during status epilepticus is the mechanism for cardiac decompensation and death during status," wrote Dr. Manno of the Mayo Clinic, Rochester, Minn.

He reviewed the cardiac pathology of 11 patients who had died during status and 22 control patients who died of known causes other than status. Eight of those who died directly as a result of status had identifiable contraction band necrosis (72%), compared with five of the controls (23%). The difference between these two groups achieved statistical significance. Dr. Manno said the mechanism for cardiac deterioration during status is speculative at this point. A 1998 study of death during status identified two mechanisms: a gradual decline in blood pressure and cardiac function in older patients, and sudden cardiac death in younger patients. "These two mechanisms may represent an imbalance between parasympathetic and sympathetic autonomic activity during status epilepticus," Dr. Manno wrote.

Three of those in his study had seizures originating in brain areas associated with cardiorespiratory activity. "We speculate that in these patients, increased sympathetic activity may have led to the development of cardiac arrhythmia and contraction band necrosis."

The site of the contraction bands hints at their relationship to catecholamines, he said. "These features are located in the myocardium adjacent to the insertion of the sympathetic end plates, suggesting that massive catecholamine release is the mechanism of contraction band necrosis."

"In selected patients with refractory status epilepticus, a short-acting β-blocker could provide some cardiac protection and prevent cardiac decompensation," he said. ■

Pediatric Epilepsy Surgery Doesn't Improve Adult Cognition

WASHINGTON — Childhood epilepsy surgery isn't associated with a long-term improvement in cognitive functioning, Janet Olds, Ph.D., and her colleagues reported in a poster at the joint annual meeting of the American Epilepsy Society and the American Clinical Neurophysiology Society.

While findings from previous studies have shown that the surgery has no short-term effect on childhood cognition, little was known until now about its long-term effect on adult cognition, noted Dr. Olds, a psychologist at the Children's Hospital of Eastern Ontario. She assessed cognitive function in 50 adults (mean age 22 years) with a history of childhood epilepsy; 34 had undergone epilepsy surgery at least 2 years prior to assessment. Of these, 21 were seizure-free and 13 continued to have seizures. The other 16 subjects, who served as controls, had never had surgery for their epilepsy as children and continued to have seizures as adults.

Seizure-free surgical subjects were taking a mean of one antiepileptic drug. Both the surgical group with continued seizures and the nonsurgical group were taking a mean of two antiepileptic drugs.

All of the subjects completed a neuropsychological assessment consisting of measures of intelligence, memory, and executive functioning (Wechsler Adult Intelligence Scale, vocabulary and block design; Wechsler Memory Scale, logical memory and memory for faces; Wisconsin Card Sort Test). Scores were compared with the subjects' pre- and postsurgical scores on the same tests.

There were no group differences in problem solving as reflected in the Wisconsin Card Sort Test. Surgery subjects who continued to have seizures scored lower on vocabulary and verbal memory tests, compared with both the seizure-free surgery group and the no-surgery group. When the scores in two surgical groups were compared, the seizure-free group did better on vocabulary and block design, compared with the group still having seizures. However, there were no differences in scores across the three test periods, indicating no significant change in functioning over time.

It's important to include a discussion of cognitive function when counseling parents about the potential impact of epilepsy surgery, said Mary Lou Smith, Ph.D., of the University of Toronto, the study's principal investigator.

The majority of research suggests that cognitive skills won't change—a fact that can be construed in a positive, as well as potentially negative, light. ■