Valproate In Utero May Affect Child's Language

BY MICHELE G. SULLIVAN

BAN, THAILAND — Expressive and receptive language abilities are significantly lower in 3-year-olds who were exposed to sodium valproate in utero than they are in children who were exposed to other individual antiepileptic drugs during gestation, according to a subanalysis of the Neurodevelopmental Effects of Antiepileptic Drugs study.

Valproate exposure was associated with a 10-point difference on both language measures compared with exposure to phenytoin, carbamazepine, or lamotrigine—a difference that is not only statistically significant, but clinically important as well, Gus A. Baker, Ph.D., said at the World Congress of Neurology.

The differences apparent in these 3-year-old subjects will likely expand as the groups grow older, said Dr. Baker, director of the division of neurosciences at the Walton Centre for Neurology and Neurosurgery in Liverpool, England and professor of clinical neuropsychology at the University of Liverpool.

"We can expect the difference in the magnitude to get greater and not smaller with age," he said. Already, Dr. Baker noted, valproate-exposed 3-year-olds in the U.K. portion of the study are lagging behind a group of matched controls. "Well over a third of those exposed to valproate have been referred for speech therapy, so we see that this 10-point difference has real meaning in terms of day-to-day practice."

The prospective, observational Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study included 303 pregnant women who were taking sodium valproate, carbamazepine, lamotrigine, or phenytoin as monotherapy. Enrollment occurred during 1999-2004 in 25 epilepsy centers in the United States and the United Kingdom. Separate investigations in the two countries were later combined. The primary outcome is cognitive performance of the children at 6 years of age.

Dr. Baker presented the results of the drugs' effect on expressive and receptive language development among 234 children who were 3 years old at the time of assessment.

The children all underwent testing of verbal and nonverbal communication, including expressive and receptive language, visual motor construction, and nonverbal intellectual ability. The children's abilities in these areas were determined by calculating subscores on screening tests called the Differential Ability Scales (Second Edition) and the Preschool Language Scale (Fourth Edition). The scores were adjusted for factors known to affect child intellect, including maternal IQ, maternal age, gestational age, antiepileptic drug (AED) dose, and prenatal exposure to folate.

"We saw that maternal IQ, AED dose, maternal age, gestational age, and preconceptional exposure to folate were significant factors predicting the scores, as we would expect," Dr. Baker said. "But we also showed that overall, the scores for valproate-exposed children were significantly lower than all other drugs and the magnitude of the effect was greater for verbal than nonverbal language."

Testing showed that the children exposed to valproate scored significantly lower on measures of expressive language (mean score of 91 vs. 102 for carbamazepine, 104 for lamotrigine, and 101 for phenytoin); and receptive language (mean score of 89 vs. 97 for carbamazepine, 101 for lamotrigine, and 101 for phenytoin). On visual motor construction and nonverbal intellectual ability, children exposed to valproate scored lower, but not significantly lower, than children exposed to the other drugs.

In terms of developmental milestones, this finding could bode ill for the valproate-exposed children, said Dr. Baker.

Unlike the physical results of in utero valproate exposure, which can be surgically corrected to at least some degree, the cognitive effects cannot be erased, he pointed out.

The study confirms earlier NEAD findings, which strongly suggest that women of childbearing age who need AED therapy should avoid valproate if possible.

"For women for whom sodium valproate is the first choice because of the nature of their seizures, we should be thinking about reducing the dose to the least possible effective level," Dr. Baker said.

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DRUGS, PREGNANCY, AND LACTATION

Toxicity of Diabetes Mellitus in Pregnancy

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

Diabetes is the most common medical complication of pregnancy, occurring in up to 7%-8% of all pregnancies. Gestational diabetes mellitus (GDM), in which the onset or recognition of glucose intolerance occurs in pregnancy, accounts for approximately 90% of diabetes cases. Although most represent true GDM (type 3), a significant number of cases are newly diagnosed type 2 diabetes. Distinguishing the two types is important because uncontrolled pregestational diabetes can cause all aspects of developmental toxicity (growth alteration, structural anomalies, functional/neurobehavioral deficits, and death), whereas true GDM does not cause structural anomalies because its onset is usually after organogenesis. However, both types have the potential to cause major toxicity in the mother and her offspring.

Suboptimal treatment of diabetes is indicated by the biomarker, HbA_{1c}, a measure of the mean blood glucose concentration over the preceding 6-8 weeks. HbA_{1c} results when glucose and hemoglobin A react (glycosylation) to form an irreversible compound. Values above normal (greater than 6%, mean blood glucose level greater than 126 mg/dL) are associated with significant maternal, embryonic, fetal, neonatal, and adolescent morbidity and mortality.

Other than serial blood glucose levels, an elevated HbA_{1c} level is the most useful biomarker for predicting diabetes-induced developmental toxicity. Normal levels of HbA_{1c} in nondiabetic patients indicate that even euglycemia and/or brief periods of hyperglycemia cause glycosylation of hemoglobin A and result in accumulation over time. In pregnancy, fetal risks increase directly with increasing HbA_{1c} levels, but it has been thought that the risk does not exceed the risk in nondiabetic pregnancies until HbA_{1c} concentrations exceed 7% (mean blood glucose level greater than 154 mg/dL).

Recent data challenge this belief. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study examined the effects of hyperglycemia less severe than that in diabetes in 23,316 women. Inclusion requirements were a fasting plasma glucose level of 105 mg/dL or less; after a standard 75-g oral glucose test given between 24 and 32 weeks, a 2-hour plasma glucose level of 200 mg/dL or less; and glucose levels below the predefined threshold at 34-37 weeks (N. Engl. J. Med. 2008;358:1991-2002). The primary outcomes were a birth weight above the 90th percentile, a primary cesarean section, neonatal hypoglycemia, and fetal hyperinsulinemia; secondary outcomes were preterm birth, shoulder dystocia or a birth injury, the need for intensive neonatal care, hyperbilirubinemia, and preeclampsia.

For most primary outcomes, there was a clear dose-response relationship between increasing glucose levels and increasing frequency of the outcomes. This relationship was apparent even among groups with plasma glucose levels below those commonly set as goals for adequate therapy of diabetes. The strongest associations were increased birth weight and increased fetal hyperinsulinemia. There also were associations with secondary outcomes, especially preeclampsia.

In a 2009 study, the records of 14,693 women, who had been screened and treated for GDM between 1988 and 2001 using only the National Diabetes Data Group (NDDG) criteria, were evaluated on the basis of Carpenter-Coustan (CC) criteria. For both criteria, two of the four threshold values following a 100-g, 3-hour glucose tolerance test need to be exceeded for a diagnosis of GDM. The thresholds for the CC and NDDG, respectively, were a fasting blood glucose of 95 mg/dL and 105 mg/dL, a 1-hour blood glucose of 180 mg/dL and 190 mg/dL, a 2-hour level of 155 mg/dL and 165 mg/dL, and a 3-hour level of 140 mg/dL and 145 mg/dL. The CC and NDDG criteria would have diagnosed GDM in 5.1% and 3.3% of the women.

Compared with controls (women without GDM by either criterion), the 273 women with GDM based on CC, but not NDDG criteria, had significantly higher odds of cesarean delivery, operative vaginal delivery, macrosomia (above 4,500 g), and shoulder dystocia. The authors recommended using the CC method because of its increased sensitivity (Obstet. Gynecol. 2009;114:326-32).

Maternal morbidity associated with poorly controlled pregestational diabetes can worsen underlying metabolic disturbances. Retinopathy and nephropathy may worsen during pregnancy. Ketoacidosis, preeclampsia, infection, and preterm birth also are more common when glucose control is suboptimal. The severity of these complications may be increased if there is underlying vascular disease. Moreover, maternal vascular disease can result in fetal growth restriction. For patients with GDM, poor third-trimester glucose control is associated with increased risks for preeclampsia, traumatic birth, and cesarean section.

A significant risk of major structural anomalies is a concern with uncontrolled types 1 and 2 diabetes early in gestation. An HbA_{1c} of 8.1% has been reported as the threshold at which the rate of birth defects begins to exceed the background incidence. An HbA_{1c} level near 10% is associated with a birth defect rate of 20%-25%, according to an ACOG Practice Bulletin published in 2005 (Obstet. Gynecol. 2005;105:675-85). This is evidence that the dose-response relationship required to establish a causal association exists between plasma glucose and structural anomalies. Hyperglycemia in the latter portion of pregnancy is associated with major neonatal toxicity. Exposure to hyperglycemia during pregnancy also is associated with significantly increased risks of diseases in the adolescent, including morbid obesity, chronic hypertension, and diabetes mellitus.

Taken in sum, poorly controlled diabetes in pregnancy extracts a heavy toll on the mother and her offspring.

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