

## VALPROATE POSES RISK TO UNBORN CHILD

### The Longer Term Outcome of Children Born to Mothers with Epilepsy

Adab N, Kini U, Vinten J, Ayres J, Baker G, Clayton-Smith J, Coyle H, Fryer A, Gorry J, Gregg J, Mawer G, Nicolaidis P, Pickering L, Tunncliffe L, Chadwick DW

J Neurol Neurosurg Psychiatry 2004;75:1575–1583

**OBJECTIVES:** To determine the prevalence of cognitive delay and possible associated dysmorphic features in children exposed to antiepileptic drugs (AEDs) in utero.

**METHODS:** In a retrospective study of children born to mothers with epilepsy, in regional epilepsy clinics in Liverpool and Manchester, U.K., the children were aged between 6 months and 16 years and born to mothers with epilepsy. Structured interviews, hospital records, clinical examination, and psychometric tests (Wechsler) were used to assess exposure and intelligence quotient (IQ). Blinded assessment of photographs was used to score children with characteristic dysmorphic features.

**RESULTS:** In total, 249 children aged 6 and older were studied: 41 were exposed to sodium valproate (VPA), 52 to carbamazepine, 21 to phenytoin, 49 to polytherapy, and 80

were unexposed. Mean verbal IQ was significantly lower in the VPA group compared with that in unexposed and other monotherapy groups. Multiple regression analysis showed that both VPA exposure and frequent tonic-clonic seizures in pregnancy were significantly associated with a lower verbal IQ, despite adjusting for other confounding factors. A significant negative correlation was found between dysmorphic features and verbal IQ in children exposed to VPA. **CONCLUSIONS:** This study identifies VPA as a drug carrying potential risks for developmental delay and cognitive impairment and is the first to suggest that frequent tonic-clonic seizures have a similar effect. Our results must be interpreted with caution, given their retrospective nature. Women with epilepsy need careful counseling about individual risk benefit of AED treatment before pregnancy.

### COMMENTARY

Antiepileptic drugs (AEDs) are commonly used for women of childbearing potential. Although AEDs can produce both anatomic and behavioral teratogenesis, the magnitude and differential effects of AEDs are uncertain, as reviewed in the last issue of *Epilepsy Currents* (1). Adab et al. conducted a large retrospective study of cognitive outcomes in children born to women with epilepsy. Multivariate analyses revealed that the verbal IQ (VIQ) of the children was significantly affected by maternal IQ and seizure frequency during pregnancy, as well as an independent effect of in utero AED exposure. Children exposed to monotherapy valproate (VPA) had a mean VIQ that was significantly lower (−7.9 VIQ points) than those in unexposed children, those with carbamazepine (CBZ) monotherapy (−10.5), and those with phenytoin (PHT) monotherapy (−14.9). Further, the effect of VPA was found to be dose dependent. The percentage of children with mental retardation in the general population is 2.5%. In the Adab et al. study, the percentage of children with mental retardation (i.e., VIQ <70) was 7% in the unexposed children, 8% in the CBZ monotherapy group, and 22% in the VPA monotherapy group. The analyses of IQ were performed in children aged 6 to 16 years. Adab et al. also

examined cognitive outcomes by using an age-appropriate developmental scale, in a second cohort of children who were younger than 6 years. A greater proportion of children exposed to VPA in this younger cohort exhibited developmental delay. Thus, VPA produced worse outcomes in both cohorts studied by Adab et al.

The study by Adab et al. was well conducted with appropriate control of many confounding factors, but it has limitations that are due to its retrospective design. However, the relatively greater risk associated with VPA administration is supported by several other studies. A prospective Finnish study also reported poorer outcomes with VPA: mean VIQ score after in utero monotherapy exposure to VPA was 84, compared with 96 for CBZ and 95 for healthy controls (2). The effect of VPA on VIQ was found to be greater at higher dosages. Three pregnancy registries also all found a greater risk for VPA. The North American Pregnancy Registry, which has prospectively enrolled more than 3,000 women, reported a 6.5% risk of congenital malformations with phenobarbital monotherapy (3) and a 10.7% risk with VPA monotherapy (4). These rates are statistically greater than the rates for the general population, but confidence intervals are inadequate to differentiate AEDs. The Australian Pregnancy Registry, which has assessed more than

500 AED-exposure fetal outcomes, found a malformation rate of 16.5% for VPA monotherapy, which was significantly greater than that with no AED (5). The United Kingdom Pregnancy Registry, which includes more than 3,000 women, reported a rate of 6.1% for VPA, a finding significantly greater than that for CBZ (6). The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study (7), a prospective, multicenter study in the United Kingdom and United States, has enrolled more than 300 mothers with epilepsy during their pregnancies to determine the long-term neurobehavioral developmental effects of in utero AED monotherapy exposure to the four commonly used AEDs [i.e., CBZ, lamotrigine (LTG), PHT, and VPA]. A preliminary analysis of serious adverse fetal outcomes (i.e., fetal death, major congenital malformation, or developmental delay) revealed significant differences across AEDs. Serious adverse outcomes occurred in 8% of CBZ, 1% of LTG, 10% of PHT, and 25% of VPA children.

Thus, seven different investigations of children exposed in utero to VPA have found worse outcomes for VPA, although the investigations evaluated different cohorts from around the world, used different methods, and even had different outcome measures. The pregnancy registries and the NEAD study are ongoing, and statistical differentiation of the AEDs for the pregnancy registries is not complete. However, the likelihood of all seven studies consistently finding a worse outcome for VPA by chance is statistically unlikely. Taken together, these studies raise serious concerns over the use of VPA as a first-line AED in women of childbearing potential. Should VPA never be used in women of childbearing potential? No, VPA is an excellent AED and may be the only AED that can control the patient's epilepsy; however, VPA should not be used in women of childbearing potential without consideration of the risk to future children and the discussion of these risks with the patient.

Treatment choice for women with epilepsy is difficult because of conflicting risks. AEDs pose a risk of teratogenesis, but the seizures also can pose grave risks to both the mother and child. In the Adab et al. study, the children of women who experienced more than five convulsions had impaired cognitive

outcomes. Further, Adab et al. point out that the risk of maternal death during pregnancy for women with epilepsy is 10 times higher than that in the general population, and this risk appears to be due to the occurrence of seizures, which were often associated with stopping AEDs or poor compliance. A subset of women with epilepsy can stop AEDs before pregnancy because they have very mild epilepsy, but the large majority of women with epilepsy cannot stop AEDs because of the greater risk posed by seizures. The present evidence supports a differential risk across AEDs, with the greatest risk to the child's outcome posed by VPA. Additional research is imperative to understand better the differential risks among AEDs and to improve treatment choices.

by *Kimford Meador, M.D.*

## References

1. Pennell PB. Using current evidence in selecting antiepileptic drugs for use during pregnancy. *Epilepsy Curr* 2004;5:45–51.
2. Gaily E, Kantola-Sorsa E, Hiilesmaa V, Isoaho M, Matila R, Kotila M, Nylund T, Bardy A, Kaaja E, Granstrom ML. Normal intelligence in children with prenatal exposure to carbamazepine. *Neurology* 2004;62:28–32.
3. Holmes LB, Wyszynski DF, Lieberman E. The AED (Antiepileptic Drug) pregnancy registry: A 6 year experience. *Arch Neurol* 2004;61:673–678.
4. Holmes LB, Wyszynski DF. The AED (antiepileptic drug) pregnancy registry: A seven-year experience. *Epilepsia* 2004;45(suppl 7):187.
5. Vajda FJ, O'Brien TJ, Hitchcock RN, Graham J, Lander C. The Australian Registry of Anti-epileptic Drugs in Pregnancy: experience after 30 months. *J Clin Neurosci* 2003;10:543–549.
6. Craig JJ, Russell A, Parsons L, Guthrie E, Robertson I, Morrison P, Waddell R, Morrow J, Irwin B. The UK Epilepsy and Pregnancy Register: update of results 1996-2003. *Epilepsia* 2004;45(suppl 7):229.
7. Meador K, Baker G, Clayton Smith J, Liporace J, Kalayian L, Kini U, and the NEAD Study Group. Preliminary results from the NEAD (Neurodevelopmental Effects of Antiepileptic Drugs) study group. First Annual AES Pregnancy Outcomes Forum; American Epilepsy Society 58th Annual Meeting; December 5, 2004.