

Antiepileptic drugs and neurocognitive development

Pavel Klein, MB, BChir
Gregory C. Mathews,
MD, PhD

Correspondence to
Dr. Klein:
kleinp@epilepsydc.com

Neurology® 2014;82:194–195

In a prospective observational study published in the current issue of *Neurology*®, Shallcross et al.¹ compared cognitive and language skills of children born to women with epilepsy (WWE) exposed in utero to levetiracetam (LEV, n = 53) or sodium valproate (VPA, n = 44), and control children born to mothers without epilepsy or medication exposure during pregnancy (n = 133). WWE were recruited from the UK Epilepsy Pregnancy Registry. Children were evaluated at the age of 36–54 months, building on previous findings at 24 months of age. The authors found no difference between LEV-exposed and control children. VPA-exposed children had lower scores on tests of gross motor skills, comprehension, and expressive language abilities than LEV-exposed children. The authors conclude that in utero exposure to VPA, but not LEV, is associated with neurodevelopmental deficits of motor and language abilities.

The present study adds information regarding potential effects of antiepileptic drugs (AEDs) used by WWE during pregnancy on the child's cognitive development. In the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study,² children born to WWE using VPA monotherapy during pregnancy had lower IQs (7–10 points) and verbal and memory abilities at 6 years of age than children born to WWE treated with lamotrigine, carbamazepine, and phenytoin. Both studies show an adverse effect of VPA exposure on cognitive development, carrying important implications for clinical practice. The present study also suggests that LEV, like lamotrigine, carbamazepine, and phenytoin, may not adversely affect cognitive development.

One of the strengths of the study is inclusion of a control group, absent in the NEAD study. However, the study has several shortcomings that may limit generalization of its findings. The number of exposed subjects was relatively small. The LEV and VPA groups differed markedly in their response rate to the invitation to participate in the study (82% of LEV-contacted mothers responded vs 33% VPA-contacted mothers), raising the possibility of a bias, and in socioeconomic status (SES; more professional, fewer manual/unemployed mothers in the LEV vs VPA groups, more smokers in the VPA group). The difference in SES could indicate

a difference in maternal biology and nurturing environment between the groups in favor of LEV that could affect cognitive development of the offspring independently of AED treatment. There is a paucity of information regarding seizure frequency, type, and severity. Seizures during pregnancy were associated with poorer developmental outcome. However, it is not known whether seizure type, severity, or frequency was important in determining that association, and whether these variables differed between the VPA and LEV groups. For example, occurrence of generalized tonic-clonic (GTC) seizures during pregnancy is associated with shorter gestational age and reduced birthweight, which could affect subsequent development.³ In clinical practice, refractory primary GTC seizures are preferentially treated with VPA, so it would have been helpful to know whether the VPA group had more GTC seizures. There is no information about AED doses and levels, nor about use of folate, which has recently been shown to positively affect IQ development.² Although the authors state that “no dose effect was detected,” they do not provide supporting data; in the NEAD study, dose effects were present.²

Accumulating reports of VPA's teratogenicity, and now its potential to impair neurodevelopmental outcome, have resulted in a growing reluctance by neurologists to prescribe VPA to women of reproductive age. American Academy of Neurology and American Epilepsy Society guidelines⁴ suggest that if seizures can be controlled without substantial side effects by one of the AEDs for which pregnancy outcome and neurodevelopmental data appear superior to VPA, i.e., lamotrigine, carbamazepine, and levetiracetam, those AEDs should be used in preference to VPA. The decision is more difficult for those women whose seizures fail to respond to these other AEDs and may respond to VPA.⁵ In this relatively small but important group of women with refractory primary generalized epilepsy or symptomatic epilepsy with primary generalized seizures, the practitioner is challenged with the common dilemma of whether the potential benefit of treatment outweighs the potential harm of the medication. For refractory generalized seizures, the data are lacking to make an informed, rational choice. Adding to the choice

See page 213

From the Mid-Atlantic Epilepsy and Sleep Center, Bethesda, MD.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

dilemma, the EURAP study showed that lamotrigine, the most common alternative to VPA in WWE, is associated with exacerbation of seizures during pregnancy. Lamotrigine-treated WWE experienced more GTC seizures during pregnancy than women treated with VPA, carbamazepine, or phenobarbital.⁶ Data regarding neurodevelopmental outcome of offspring born to these women are not available.

Studies in animals may provide answers to some of these questions. Disruption of developmental programs at critical stages permanently alters structural and functional properties of the postnatal brain. Exposure to VPA, as well as phenytoin and phenobarbital, induces apoptosis, or programmed cell death, throughout the brains of developing rats,⁷ but LEV does not.⁸ Such models may help address whether VPA can be safely used at any time during pregnancy, what doses may be safe, and whether its harmful effects can be prevented (e.g., with folate).

Shallcross et al. have provided important new information regarding potential risks of VPA use during pregnancy. Further prospective studies are needed to separate the potential contribution of seizures/epilepsy severity and AED treatment in the subgroup of women with refractory seizures, including intractable primary generalized seizures responsive to VPA but not other AEDs, and to relate those outcomes to VPA dose and concentration. When those data are available, the rational choice between potential benefit and harm of AED use during pregnancy can be extended from responsive to pharmacoresistant epilepsy and for VPA use in other conditions such as migraine and bipolar affective disorder for which there are few data^{9,10} and in which lower doses may be used.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

P. Klein serves on the speakers' bureaus for UCB and GlaxoSmithKline; has served on Advisory Boards of Accordia, Inc. and Eisai; and has participated in clinical trials sponsored by UCB, Eisai, GlaxoSmithKline, Sunovion, Lundbeck, and SK Life Sciences. G. Mathews has participated

in clinical trials sponsored by UCB, Eisai, GlaxoSmithKline, Lundbeck, and SK Life Sciences. Go to Neurology.org for full disclosures.

REFERENCES

1. Shallcross R, Bromley RL, Cheyne CP, et al. In utero exposure to levetiracetam vs valproate: development and language at 3 years of age. *Neurology* 2014;82:213–221.
2. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 2013;12:244–252.
3. Rauchenzauner M, Ehrensberger M, Prieschl M, et al. Generalized tonic-clonic seizures and antiepileptic drugs during pregnancy: a matter of importance for the baby? *J Neurol* 2013;260:484–488.
4. Harden CL, Meador KJ, Pennell PB, et al; American Epilepsy Society. Practice parameter update: management issues for women with epilepsy: focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology* 2009;73:133–141.
5. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007;369:1016–1026.
6. Battino D, Tomson T, Bonizzoni E, et al; EURAP Study Group. Seizure control and treatment changes in pregnancy: observations from the EURAP epilepsy pregnancy registry. *Epilepsia* 2013;54:1621–1627.
7. Bittigau P, Sifringer M, Genz K, et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. *PNAS* 2002;99:15089–15094.
8. Manthey D, Asimiadou S, Stefovskaja V, et al. Sulthiame but not levetiracetam exerts neurotoxic effect in the developing rat brain. *Exp Neurol* 2005;193:497–503.
9. Bodén R, Maria Lundgren M, Lena Brandt L, et al. Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population based cohort study. *BMJ* 2012;345:e7085.
10. National Institute for Health and Clinical Excellence (2006). The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. In: National Collaborating Centre for Mental Health (UK), eds. *Bipolar Disorder*. Leicester, UK: British Psychological Society; 2006.