Neurodevelopmental outcomes of children born to mothers with epilepsy

KIMFORD J. MEADOR, MD, AND MARY L. ZUPANC, MD

ABSTRACT

Most children born to women with epilepsy are normal, but there is an increased risk of abnormal functional neurodevelopment in these children. Although there are many contributing factors, antiepileptic drugs (AEDs) may play a role. Most women with epilepsy must take AEDs during pregnancy because the potential for injury from seizures to both mother and fetus is a greater risk. AEDs are also used to treat other disorders, including depression and pain. Thus, an understanding of the effects of AEDs on the unborn child is relevant to physicians who treat nonepileptic mothers as well. This review discusses animal and human studies of the neurodevelopmental effects of AEDs and briefly reviews the possible mechanisms underlying these effects. Flaws in the methodology of some studies of these effects require that the results be interpreted cautiously and highlight the need for well-designed studies to explore this issue further.

The majority of children born to mothers with epilepsy are anatomically and functionally normal, but the risk for adverse outcomes is increased in these children. Both somatic malformations and abnormal functional neurodevelopment occur with increased frequency in these children.[1,2] A variety of factors contribute to the cognitive disabilities in children of mothers with epilepsy, and antiepileptic drugs (AEDs) may be an important factor.[1,2] For example, the risk of neurodevelopmental defects is increased in the children of women with epilepsy but not the children of fathers with epilepsy. However, the large majority of women with epilepsy cannot choose to avoid AEDs because of the risks that seizures pose to the mother and her unborn child. Trauma is the leading cause of nonobstetric deaths in pregnant women with epilepsy, and the risks of maternal seizures to the fetus include intracranial hemorrhage, suppression of fetal heart rate, premature delivery, and miscarriage.

From the Department of Neurology, Georgetown University Hospital, Washington, D.C. (K.J.M.), and the Department of Neurology, Medical College of Wisconsin, Milwaukee (M.L.Z.).

Address: Kimford J. Meador, MD, Department of Neurology, Georgetown University Hospital, 1st Floor Bles, 3800 Reservoir Rd., NW, Washington, DC 20007; e-mail: kjm32@georgetown.edu.

IN UTERO EXPOSURE TO AEDs IS WIDESPREAD

Epilepsy affects 0.6% to 1.0% of the population.[3] If the lower estimate of epilepsy prevalence is used, about 24,000 children are born to women with epilepsy each year in the United States alone. Because about 95% of women with epilepsy take AEDs, approximately 22,800 children each year are exposed in utero to AEDs taken by mothers with epilepsy. Given that AEDs are also used to treat other disorders, including depression and pain, and that fewer than half of all prescriptions for AEDs are for epilepsy or seizures, the total number of US children exposed in utero to AEDs each year is probably at least 45,000. This is why understanding the effects of AEDs on the unborn child is important. Nevertheless, consensus guidelines have not been able to determine which of the AEDs is the most teratogenic.[4,5]

BEHAVIORAL TERATOGENICITY: THE EVIDENCE BASE

Animal studies

In utero AED exposure can produce behavioral deficits in animals, and this occurs at blood levels similar to therapeutic levels in humans.[6,7] Phenobarbital can cause neuronal deficits, reduced brain weight, and impairment of behavioral development.[8–10] Phenytoin can affect genetic expression

and delay neurodevelopment.[11–13] Prenatal phenytoin has been associated with hyperexcitability in monkeys, producing a syndrome similar to attention-deficit/hyperactivity disorder.[14] Behavioral impairments have been seen as a result of in utero exposure to primidone, trimethadione, or valproate.[12,15] Animal studies suggest that in utero exposure to AEDs can produce neurobehavioral deficits at dosages lower than those required to produce anatomic malformations, but direct extrapolation of these results to humans may be misleading.

Human studies

Children of mothers with epilepsy have an increased risk of developmental delay and cognitive impairments.[1,2] AEDs appear to play a role, although the exact mechanisms remain uncertain. Like anatomic defects, cognitive impairments are increased in children of mothers with epilepsy, but not in children of fathers with epilepsy.[16] In addition, children of women with epilepsy who do not take an AED during pregnancy have no behavioral deficits compared with children of matched controls.[17]

Because children exposed in utero to AEDs in mothers without epilepsy appear to have the same risks for somatic malformations as children exposed in utero to AEDs in mothers with epilepsy,[18] they are probably at similar risk for behavioral deficits, but no data are available in these children. Differential behavioral effects of in utero AED exposure are uncertain, and methodologic disparities across studies have led to inconsistent results.[1,2,19] Several studies are described below because they either raise concerns of potential risks or highlight research design flaws.

In two studies from Denmark, men exposed in utero to phenobarbital had lower verbal IQ scores than predicted (by approximately 7 IQ points, or half a standard deviation in IQ score).[20] The deficit rose to 20 IQ points if these men also were born as the result of an unwanted pregnancy and were of lower socioeconomic status. Although retrospective and not definitive, these results suggest that prenatal phenobarbital exposure in humans can produce cognitive deficits lasting into adulthood. Further, the increased deficit seen in those men with multiple risk factors is consistent with other research on mental retardation.

In a study attempting to reduce the risk of intracranial hemorrhage in their children, pregnant mothers at risk for premature delivery were randomized to receive placebo plus vitamin K or phenobarbital plus vitamin K.[21] Behavioral outcomes were assessed at 2 years in 121 of the original 353 children. Children exposed to phenobarbital had a lower Bayley Mental Developmental Index score (104 ± 21 SD) compared with the placebo group (113 ± 22 SD). Although the results are consistent with the Danish studies' findings, their validity remains in doubt because only 32% of the total group of randomized children were tested at the 2-year follow-up.

In another study, 20 children exposed in utero to phenytoin had lower IQ scores (109 ± 11 SD) at 4 to 8 years of age compared with 98 controls (118 ± 12 SD).[22] However, failure to control for parental IQ limits its confidence in the interpretation of these results.

The adverse effects of phenobarbital are further supported by the preliminary report of a comparative study.[23] Children 6 to 16 years of age exposed in utero to carbamazepine, phenobarbital, or phenytoin were evaluated along with matched controls. Phenobarbital- and carbamazepine-exposed children had lower Full Scale IQ scores compared with matched controls, but the phenytoin group did not differ from its controls. Further details and replication are needed.

A prospective study comparing carbamazepine and phenytoin reported greater adverse effects with phenytoin.[24] However, the results are inconclusive because a greater proportion of the pregnant women taking carbamazepine were nonepileptic, the relative AED dose was lower for carbamazepine, and maternal IQ scores were not used in the analyses even though they were available. Comparison of child-mother IQ differences suggests that the carbamazepine-exposed and phenytoin-exposed children did not differ.[25]

A recent retrospective study assessed the relative risk of additional educational needs in 594 school-age children exposed in utero to AEDs.[26] Special education needs across groups were as follows:

- No drug, 11%
- Monotherapy with valproate, 30%
- Monotherapy with carbamazepine, 3%
- Other AED monotherapy, 6%
- Polytherapy with valproate, 24%
- Polytherapy without valproate, 16%.

The results suggest that the risk of special educational needs may be elevated with valproate use, but replication is needed to rule out selection bias. A preliminary report from the same research group, based on a retrospective study of 251 children, noted that the mean IQ score for children exposed to valproate was 82 compared with 95 for children exposed to carbamazepine and 92 for children not

exposed to AEDs.[27]

Preliminary results from a prospective study support the observation of poorer outcomes with valproate.[28] The investigators tested 60% of 299 children of mothers with epilepsy and 50% of 277 children of healthy control mothers who had been followed since birth. The mean IQ score following in utero exposure to valproate was 83 compared with 95 for the rest of the epilepsy group. This difference was significant even after controlling for age, education, and polytherapy. However, a weakness of the study is that the valproate monotherapy group consisted of only 11 children. Thus, additional studies are needed to confirm this finding.

POSSIBLE MECHANISMS OF AED EFFECTS ON NEURODEVELOPMENT

The mechanisms underlying the teratogenicity of AEDs are uncertain, and it is unclear whether functional and anatomic defects involve the same factors. Mechanisms hypothesized to underlie the teratogenic effects of AEDs include neuronal suppression, folate-related mechanisms, *N*-methyl-D-aspartate/γ-aminobutyric acid (NMDA/GABA)-related mechanisms, ischemia/hypoxia, and reactive intermediates (eg, epoxides and free radicals).

Neuronal suppression

AEDs suppress neuronal irritability, and thus may impair neuronal excitation, in turn altering synaptic growth and connectivity. There is no experimental proof of this hypothesis, but these effects could potentially lead to long-term deficits in cognition and behavior, especially in the rapidly developing brain of a fetus, infant, or child.

Folate-related mechanisms

Folate is important for DNA and RNA synthesis. Phenobarbital, phenytoin, primidone, and valproate can interfere with folate metabolism,[21] and folate requirements are increased during pregnancy. Blood folate concentrations are reported to be lower in women with epilepsy who have abnormal pregnancy outcomes,[29] but no controlled trial has been conducted. The effects of folate on malformation rates in mice exposed to phenytoin in utero are controversial.[30,31]

NMDA/GABA-related mechanisms

An animal model of fetal alcohol syndrome has shown that cognitive deficits from in utero ethanol exposure are due to the combined effects of NMDA glutamate receptor blockade and $GABA_A$ receptor activation.[32] The effect of alcohol is greatest in the third trimester, resulting in widespread apoptotic neurodegeneration, reduced brain mass, and neurobehavioral deficits. A recent study in neonatal rats demonstrated that several AEDs can produce neuronal apoptosis.[33]

Ischemia/hypoxia

AEDs may affect cardiac function. Phenytoin-induced congenital defects in animals resemble the effects of ischemia, and hyperbaric oxygen can reduce phenytoin malformations.[34] The similarity of the effects of ischemia and phenytoin may be due to free radical formation. No studies have been conducted in humans to confirm or refute this hypothesis.

Reactive intermediates

AED teratogenicity may not be mediated by the parent compound but may be the result of toxic intermediary metabolites, which can bind protein, lipids, and nucleic acid, causing cellular damage.

Epoxides. Some AEDs are metabolized to highly reactive arene oxide intermediates called epoxides. Arene oxides can be detoxified by epoxide hydrolase, and inhibition of this enzyme leads to an increase in malformations in animals.[35] Further, children exposed to phenytoin are more likely to have dysmorphic features if they have low epoxide hydrolase activity in their amniocytes.[36] However, it is unclear whether this is a viable hypothesis because the P450 enzymes that convert an AED to an epoxide are not expressed in embryonic tissues.[37] It seems unlikely that an epoxide formed by maternal enzymes would reach the fetus before binding to maternal tissues.

Free radicals. Prostaglandin H synthetase and lipoxygenases are active in the fetus and can bioactivate AEDs to free radical–reactive intermediates.[38] These reactive oxygen species can bind to DNA, protein, or lipids, leading to teratogenesis in the fetus. Consistent with this hypothesis, prostaglandin H synthetase inhibitors, free radical–trapping agents, antioxidants (eg, vitamin E), and antioxidative enzymes (eg, superoxide dismutase) can reduce phenytoin-induced teratogenic defects in animals.[39,40] Studies in humans are needed to confirm this hypothesis.

CONCLUSIONS

Children born to women with epilepsy are at increased risk for somatic malformations and behavioral impairments. AEDs probably contribute to this risk, but the potential for injury from seizures to both the mother and the unborn child is a greater risk. Thus, most women with epilepsy must take AEDs

during pregnancy. The above risks should be balanced with the knowledge that the majority of children born to women with epilepsy are normal. Design flaws in human studies preclude firm conclusions as to the incidence and magnitude of AED effects in humans. Most important, it is unknown whether there are different effects among the AEDs. Further, the mechanisms underlying these effects need to be delineated. Ultimately, a well-controlled prospective study will be required to resolve this important issue. The results of such a study would directly affect the management of women with epilepsy.

REFERENCES

1. **Dansky LV, Finnell RH.** Parental epilepsy, anticonvulsant drugs, and reproductive outcome: epidemiologic and experimental findings spanning three decades; 2: human studies. Reprod Toxicol 1991; 5:301–335.
2. **Meador KJ.** Cognitive effects of epilepsy and of antiepileptic medications. In: Wyllie E, ed. The Treatment of Epilepsy: Principles and Practice. 3rd ed. Philadelphia: Williams & Wilkins; 2001:1215–1225.
3. **Hauser WA, Hesdorffer DC.** Epilepsy: frequency, causes, and consequences. New York: Demos; 1990.
4. Practice parameter: management issues for women with epilepsy (summary statement). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 1998; 51:944–948.
5. Seizure disorders in pregnancy. Am Coll Obstet Gynecol Physicians Educational Bulletin 1996; 231:1–13.
6. **Adams J, Vorhees CV, Middaugh LD.** Developmental neurotoxicity of anticonvulsants: human and animal evidence on phenytoin. Neurotoxicol Teratol 1990; 12:203–214.
7. **Finnell RH, Dansky LV.** Parental epilepsy, anticonvulsant drugs, and reproductive outcome: epidemiologic and experimental findings spanning three decades; 1: animal studies. Reprod Toxicol 1991; 5:281–299.
8. **Middaugh LD, Santos CA, Zemp JW.** Phenobarbital during pregnancy alters operant behavior of offspring in C57 BL/6J mice. Pharmacol Biochem Behav 1975; 3:1137–1139.
9. **Middaugh LD, Thomas TN, Simpson LW, Zemp JW.** Effects of prenatal maternal injections of phenobarbital on brain neurotransmitter and behavior of young C57 mice. Neurobehav Toxicol Teratol 1981; 3:271–275.
10. **Fishman RHB, Gaathon A, Yanai J.** Early barbiturate treatment eliminates peak serum thyroxide levels in neonatal mice and produces ultrastructural damage in brain of adults. Dev Brain Res 1982; 5:202–205.
11. **Bennett GD, Lau F, Calvin JA, Finnell RH.** Phenytoin-induced teratogenesis: a molecular basis for the observed developmental delay during neurulation. Epilepsia 1997; 38:415–423.
12. **Vorhees CV, Minck DR, Berry HK.** Anticonvulsants and brain development. Prog Brain Res 1988; 73:229–244.
13. **Vorhees CV, Rindler JM, Minck DR.** Effects of exposure period and nutrition on the developmental neurotoxicity of anticonvulsants in rats: short and long-term effects. Neurotoxicology 1990; 11:273–284.
14. **Phillips NK, Lockard JS.** Infant monkey hyperexcitability after prenatal exposure to antiepileptic compounds. Epilepsia 1996; 37:991–999.
15. **Pizzi WJ, Alexander TD, Loftus JT.** Developmental and behavioral effects of prenatal primidone exposure in the rat. Pharmacol Biochem Behav 1996; 55:481–487.
16. **Majewski F, Steger M, Richter B, Gill J, Rabe F.** The teratogenicity of hydantoins and barbiturates in humans, with considerations on the etiology of malformations and cerebral disturbances in the children of epileptic parents. Int J Biol Res Pregnancy 1981; 2:37–45.
17. **Holmes LB, Rosenberger PB, Harvey EA, Khoshbin S, Ryan L.** Intelligence and physical features of children of women with epilepsy. Teratology 2000; 61:196–202.
18. **Holmes LB, Harvey EA, Coull BA, et al.** The teratogenicity of anticonvulsant drugs. N Engl J Med 2001; 344:1132–1138.
19. **Gaily EK, Granström M-L, Hiilesmaa VK, Bardy AH.** Head circumference in children of epileptic mothers: contributions of drug exposure and genetic background. Epilepsy Res 1990; 5:217–222.
20. **Reinisch JM, Sanders SA, Mortensen EL, Rubin DB.** In utero exposure to phenobarbital and intelligence deficits in adult men. JAMA 1995; 274:1518–1525.
21. **Thorp JA, O'Conner M, Jones AMH, Hoffman EL, Belden B.** Does perinatal phenobarbital exposure affect development outcome at age 2? Am J Perinatol 1999; 16:51–60.
22. **Vanoverloop D, Schnell RR, Harvey EA, Holmes LB.** The effects of prenatal exposure to phenytoin and other anticonvulsants on intellectual function at 4 to 8 years of age. Neurotoxicol Teratol 1992; 14:329–335.
23. **Adams J, Harvey EA, Holmes LB.** Cognitive deficits following gestational monotherapy with phenobarbital and carbamazepine. Neurotoxicol Teratol 2000; 22:466. Abstract.
24. **Scolnik D, Nulman I, Rovet J, et al.** Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. JAMA 1994; 271:767–770.
25. **Loring DW, Meador KJ, Thompson WO.** Neurodevelopment effects of phenytoin and carbamazepine. JAMA 1994; 272:850–851.
26. **Adab N, Jacoby A, Smith D, Chadwick D.** Additional educational needs in children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2001; 70:15–21.
27. **Vinten J, Gorry J, Baker GA.** The long-term neuropsychological development of children exposed to antiepileptic drugs in utero (the Liverpool and Manchester Neurodevelopmental Study Group). Epilepsia 2001; 42(suppl 2):36. Abstract.
28. **Gailey E, Kantola-Sorsa E, Hiilesmaa V, et al.** Intelligence in children of mothers with epilepsy. Epilepsia 2002; 43(suppl 8):56. Abstract.
29. **Danksy LV, Andermann E, Rosenblatt D, Sherwin AL, Andermann F.** Anticonvulsants, folate levels and pregnancy outcome: a prospective study. Ann Neurol 1987; 21:176–182.
30. **Zhu M, Zhou S.** Reduction of the teratogenic effects of phenytoin by folic acid and a mixture of folic acid, vitamins, and amino acids: a preliminary trial. Epilepsia 1989; 30:246–251.
31. **Juchau MR.** Chemical teratogenesis in humans: biochemical and molecular mechanisms. Prog Drug Res 1997: 49:25–92.
32. **Ikonomidou C, Bittigau P, Ishimaru MJ, et al.** Ethanol-induced apoptotic neurodegeneration in fetal alcohol syndrome. Science 2000; 287:1056–1060.
33. **Bittigau P, Sifringer M, Ikonomidou C.** Antiepileptic drugs and apoptosis in the developing brain. Ann N Y Acad Sci 2003; 993:103–114.
34. **Danielsson B, Skold AC, Azarbayjani F, Ohman I, Webster W.** Pharmacokinetic data support pharmacologically induced embryonic dysrhythmia as explanation to Fetal Hydantoin Syndrome in rats. Toxicol Appl Pharmacol 2000; 163:164–175.
35. **Martz F, Failinger C, Blake D.** Phenytoin teratogenesis: correlation between embryopathic effect and covalent binding of putative arene oxide metabolite in gestational tissue. J Pharmacol Exp Ther 1977; 203:231–239.
36. **Buehler BA, Delimont D, Waes MV, Finnell R.** Prenatal prediction of risk of the fetal hydantoin syndrome. N Engl J Med 1990; 322:1567–1572.
37. **Juchau MR.** Chemical teratogenesis. In: Jucker E, ed. Progress in Drug Research. Basel, Switzerland: Birkhauser Verlag; 1993:9–50.
38. **Wells PG, Kim PM, Laposa RR, et al.** Oxidative damage in chemical teratogenesis. Mutat Res 1997; 396:65–78.
39. **Wells PG, Zubovits JT, Wong ST, Molinari LM, Ali S.** Modulation of phenytoin teratogenicity and embryonic covalent binding by acetylsalicylic acid, caffeic acid, and alpha-phenyl-N-t-butylnitrone: implications for bioactivation by prostaglandin synthetase. Toxicol Appl Pharmacol 1989; 97:192–202.
40. **Wong M, Wells PG.** Modulation of embryonic glutathione reductase and phenytoin teratogenicity by 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). J Pharmacol Exp Ther 1989; 250:336–342.