

## GUEST EDITORIAL

## Anticonvulsants in Pregnancy

Although it has been known for years that some first-generation antiepileptic drugs (AEDs) cause birth defects, intrauterine growth retardation (IUGR), and, possibly, developmental delay, these toxicities were not thought to apply to the second-generation AEDs. New information has challenged that belief.

The first-generation AEDs known to cause birth defects and other developmental toxicities include the hydantoin (ethotoin [Peganone], fosphenytoin [Cerebyx], mephenytoin [Mesantoin], and phenytoin [Dilantin]), phenobarbital, primidone (Mysoline), carbamazepine (Tegretol), and valproic acid derivatives (Depakene, Depakote). In a 2001 study, the incidence of embryopathy (major and minor anomalies, microcephaly, and IUGR) after first-trimester monotherapy was 21% (phenytoin), 27% (phenobarbital), 14% (carbamazepine), 21% (any monotherapy), and 28% (polytherapy) (N. Engl. J. Med. 2001;344:1132-8).

Phenytoin also causes a pattern of defects collectively called the fetal hydantoin syndrome (FHS), characterized by variable degrees of hypoplasia and ossification of the distal phalanges and cranio-

facial abnormalities. Other defects, such as those involving the heart and growth, are commonly observed. A syndrome with carbamazepine consisting of minor craniofacial defects, fingernail hypoplasia, and developmental delay has been observed; this drug may also cause neural tube defects (NTDs).

The defects observed with primidone are similar to those in FHS. Phenobarbital has been associated with an increase in congenital defects when used for epilepsy, but not when used for other indications. The use of valproic acid derivatives between the 17th and 30th day after fertilization is associated with a 1%-2% risk of NTDs. Other defects are those of the head and face, digits, urogenital tract, and mental and physical growth. Carbamazepine, phenytoin, primidone, and phenobarbital affect folate metabolism or absorption, and this may increase the risk of birth defects, including NTDs. Women taking these agents should take folic acid 4-5 mg/day, preferably starting before conception. The hydantoin and barbiturates, are related to hemorrhagic disease of the newborn, so adequate doses of vitamin K should be administered to newborns exposed to AEDs in utero.



BY GERALD G. BRIGGS, B.PHARM.

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In contrast, first-generation AEDs that do not appear to be associated with a significant risk of birth defects include the benzodiazepines (clonazepam [Klonopin], clorazepate [Tranxene], diazepam [Valium], and lorazepam [Ativan]) and succinimides (ethosuximide [Zarontin] and methsuximide [Celontin]). However, some of these drugs have very little human data, and the benzodiazepines are known to cause toxicity in the newborn, most notably, floppy infant syndrome and withdrawal syndrome. In addition, the risk for birth defects from seizures alone is at least two to three times greater than the background risk of 2%-3%.

Until recently, the second-generation AEDs had not been associated with congenital defects. However, new data from the North American AED Pregnancy Registry and five other pregnancy registries have shown a very significant risk of isolated, nonsyndromic oral clefts after first-trimester exposure to lamotrigine (Lamictal) monotherapy (Birth Defects Res. A Clin. Mol. Teratol. 2006;76:313-428).

The prevalence of oral clefts in the North American registry was 8.9/1,000, even though all of the mothers had been supplemented with folic acid before conception. This was significantly higher than the prevalence of 0.37/1,000 in a comparison group.

The human pregnancy experience is too limited to assess the embryo/fetal risk

for the other second-generation agents: felbamate (Felbatol), gabapentin (Neurontin), pregabalin (Lyrica), levetiracetam (Keppra), tiagabine (Gabitril), and topiramate (Topamax).

Although the data also are limited for zonisamide (Zonegran), the drug is teratogenic in three animal species and embryo lethal in a fourth and therefore is best avoided in the first trimester. Oxcarbazepine (Trileptal), a drug closely related to carbamazepine, has been associated with minor facial defects, but the data are too limited to assess the risk in humans.

To summarize, women with epilepsy should not be denied treatment with the most effective agents for their condition because of pregnancy or nursing. They should be treated with the lowest dose and the fewest drugs possible to control their seizures. Periodic serum levels are needed throughout pregnancy to ensure that therapeutic levels are maintained. They should take folic acid (4-5 mg/day), and vitamin K should be given to the newborns. ■

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## Valproate Associated With Worse Fetal Outcome Than Other AEDs

BY MIRIAM E. TUCKER  
Senior Writer

Valproate poses by far the greatest teratogenic risk of all the commonly prescribed antiepileptic drugs, according to Dr. Kimford J. Meador of the University of Florida, Gainesville, and his associates in the Neurodevelopmental Effects of Antiepileptic Drugs Study Group.

"We advise that [valproate] not be used as the AED of first choice for women of childbearing potential, and, when used, its dose should be limited, if possible," the group wrote (Neurology 2006;67:407-12).

Current guidelines from the American Academy of Neurology advise a variety of ways to minimize the risk of teratogenicity with AEDs, including use of monotherapy if possible, use of the lowest effective dose, supplementation with folate, and treatment of the infant with vitamin K at birth (Neurology 1998;51:944-8). However, no current recommendation addresses the differential teratogenic risk associated with individual AEDs, Dr. Meador and his associates noted.

The data come from an ongoing prospective observational study of mother/child pairs across 25 epilepsy centers in the United States and United Kingdom. A total of 323 mothers and 333 children were available for analysis. Mean gestational ages at the time of enrollment were 17 weeks for the 69 infants exposed to valproate, 18 weeks for the 98 lamotrigine-exposed infants, and 19 weeks for

both the 110 whose mothers who used carbamazepine and for the 56 infants exposed to phenytoin. Mean age of the children at the time of analysis ranged from 2.7 years with lamotrigine to 3.5 years for valproate and carbamazepine.

Major congenital malformation or fetal death occurred in 20.3% with valproate, 10.7% with phenytoin, 8.2% carbamazepine, and 1.02% with lamotrigine. Not only was the valproate risk approximately twice that of the other AEDs, but valproate was the only one to show a dose-response relationship: The mean valproate dose for the pregnancies with serious adverse fetal outcomes was 1,268 mg/day compared with just 844 mg/day for those without serious adverse outcomes.

The differences in risk between the AEDs were accounted for by congenital malformation rather than death. Indeed, death rates were actually slightly higher for both carbamazepine and phenytoin (3.6%) than for valproate (2.9%). There were no deaths with lamotrigine. Congenital malformations, on the other hand, occurred in 17.4% with valproate compared with 7.1% with phenytoin, 4.5% carbamazepine, and 1.0% lamotrigine.

Clinicians are urged to encourage their pregnant patients on AEDs to join one of the pregnancy registries around the world that are seeking additional information on AED risk for anatomic teratogenesis. The North American Pregnancy Registry has a toll-free number, 1-888-AED-AED4. The EURAP registry, covering Europe and elsewhere, is online at [www.eurapinternational.org](http://www.eurapinternational.org). ■

## Use of AEDs May Undermine Effect of Contraceptive Implant

Implanon, the first long-term implantable contraceptive to win FDA approval and become available in the United States since 2000 when Wyeth stopped marketing Norplant, may not be effective in women taking antiepileptic drugs, said Dr. Andrew M. Kaunitz.

A single-rod contraceptive implant that is about the size of a

cacy is associated with low serum progestin levels, "contraceptive implants and progestin-only OCs do not represent optimal contraceptives for women who take (or will soon initiate) anticonvulsants or other concomitant medications, which induce hepatic enzymes." Dr. Kaunitz's department has conducted clinical trials for Organon.

**Implants and progestin-only OCs could induce hepatic enzymes in those taking anticonvulsants.**

DR. KAUNITZ



matchstick, Implanon is highly effective for up to 3 years in women who do not take anti-seizure medication.

In an interview, Dr. Kaunitz, professor and assistant chairman of the department of obstetrics and gynecology at the University of Florida Health Science Center, Jacksonville, said that because their contraceptive effi-

The label includes a warning and precautions about Implanon and antiepileptic interactions and other drugs that are potent inducers of hepatic enzymes, because coadministration may substantially lower etonogestrel levels and reduce the effectiveness of the contraceptive. The drugs include phenytoin, carbamazepine, felbamate, topiramate, and oxcarbazepine.

In trials, bleeding irregularities were frequent and were the most common reason for choosing to discontinue the contraceptive.

—Elizabeth Mechtat