EDITORIALS

Which Drug for the Pregnant Woman with Epilepsy?

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Approximately 25,000 children are born in the United States each year to mothers with epilepsy.[1] Most of these women need to continue taking medication during pregnancy, since uncontrolled seizures may be harmful to the women as well as to the fetuses.[2] The challenge to physicians is to prescribe a treatment that is effective in controlling seizures but has minimal associated risks.

More than 40 years have passed since the first report on increased rates of birth defects in the offspring of women with epilepsy.[3] Subsequent research has clarified that this is related to the antiepileptic drugs rather than the underlying epileptic disorder.[4] More recent research has focused on differential risks associated with particular drugs.[5-8] The results consistently indicate that the risk of major congenital malformations is two to four times as high with the use of valproate as with the use of other antiepileptic drugs such as carbamazepine and lamotrigine[5-8]; absolute rates of congenital malformations among offspring exposed to valproate in utero have ranged from 6 to 11%.

Although research on the teratogenicity of antiepileptic drugs has focused on anatomical birth defects, less attention has been paid to the possibility of adverse effects on the child's cognitive development. A Cochrane report from 2004 concluded that the majority of studies on the developmental effects of antiepileptic drugs were of limited quality and that there was little evidence to inform whether the risks differed with the use of different agents.[9] Since the publication of that report, some studies have indicated that valproate might be associated with a particular risk of adverse developmental effects.[2,10-12] A retrospective study revealed that children exposed to valproate had lower verbal IQs than unexposed children and children exposed to carbamazepine or phenytoin.[2] Although results remained significant after controlling for confounding factors such as maternal IQ and major seizures during pregnancy, these observations should be interpreted with caution, given the small number of subjects and the retrospective design. Two small population-based prospective studies also showed that children exposed to valproate had lower verbal IQs than did those exposed to carbamazepine, but associations between valproate and reduced IQs were not significant after adjusting for maternal education and IQ.[10,11]

In this issue of the *Journal,* Meador and colleagues[13] report interim results of the largest prospective study to date of long-term cognitive development in children exposed in utero to antiepileptic-drug monotherapy. Women taking valproate, carbamazepine, lamotrigine, or phenytoin were enrolled in early pregnancy, and the cognitive development of their children was assessed at 3 years of age. Children exposed to valproate in utero had significantly lower IQs (92; 95% confidence interval, 88 to 97) than did children exposed to one of the other antiepileptic drugs (carbamazepine, 98; lamotrigine, 101; and phenytoin, 99), whereas IQ scores did not differ significantly among children exposed to the other three antiepileptic drugs. There was a significant correlation between the dose of valproate during pregnancy and the child's IQ.

The study has certain limitations. It is an observational (nonrandomized) study involving a selected population; it is possible that selection of the antiepileptic drug might be associated with factors that independently predict poor cognitive development. However, a randomized trial to answer this question would pose ethical and prac-

tical difficulties, and the authors performed analyses to control for important potential confounding factors (including maternal IQ, maternal age at delivery, antiepileptic-drug dose, and gestational age at birth). Moreover, the study does not include a control group of children who were not exposed to antiepileptic drugs, but it would be difficult to identify an appropriate control group. Finally, although the study by Meador and colleagues is the largest study of this question to date, the numbers of children exposed to individual antiepileptic drugs are still small, and additional studies are needed to confirm the results and refine risk assessments.

How should these results affect clinical practice? Women with epilepsy should be taught the importance of planning their pregnancies, and potential adverse fetal effects should be considered in antiepileptic-drug selection for all women with epilepsy who are of childbearing potential. Discussion of the current findings should be included in prepregnancy counseling. Most major congenital malformations can be detected with the use of prenatal screening, and many can be successfully treated surgically after birth, but cognitive impairment cannot. In addition, antiepileptic drugs confer a risk of anatomical birth defects only during the first 2 to 3 months of gestation, whereas cognitive development of a child may be affected by exposure throughout pregnancy.

Even before publication of the report by Meador et al., valproate was not a first-choice agent for women with epilepsy who are of childbearing potential, because of the risks of birth defects. Alternatives are available for patients with focal epilepsy. Carbamazepine, for example, appears comparatively safe with respect to malformations as well as neurodevelopmental outcome.[1,2,5-7,10,13]

Alternatives are less clear for patients with generalized epilepsies, for whom valproate has appeared to be more effective than lamotrigine or topiramate.[14] A trial of lamotrigine could be considered, since malformation rates associated with its use are similar to those associated with the use of carbamazepine. However, lamotrigine is difficult to use in pregnancy because of pharmacokinetic alterations and the risk of breakthrough seizures.[15] The safety of topiramate and levetiracetam, other newer-generation antiepileptic drugs with efficacy in generalized epilepsies, has not been sufficiently assessed for use during pregnancy. A low dose of valproate remains an option if seizures cannot be controlled by other drugs. Doses below 800 mg per day may not be associated with fetal risks that are any greater than the risks associated with the use of other antiepileptic drugs.[2,5,7,13]

Because of the risks associated with a loss of seizure control during pregnancy, changes from valproate to another antiepileptic drug should be made and evaluated before conception. By the time a woman realizes that she is pregnant, switching drugs is unlikely to reduce the risk of birth defects. Because safe practice involves changing antiepileptic drugs only over a prolonged period (i.e., typically over a period of months, with the use of polytherapy during the transition period), a switch from valproate once pregnancy has been established is also unlikely to eliminate the risk of cognitive impairment in the child. For women taking high doses of valproate, dose reduction may be reasonable, but only after careful risk–benefit assessment by the physician.

The results of the study by Meador et al. should help inform the counseling of women who require antiepileptic drugs during pregnancy. However, to avoid potentially harmful abrupt withdrawals of the antiepileptic drug or changes in treatment during pregnancy, discussion of the risks of valproate should be balanced with consideration of the risks of uncontrolled seizures.

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Angiotensin-Receptor Blockers for Prevention of Atrial Fibrillation — A Matter of Timing or Target?

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Atrial fibrillation is the most common sustained arrhythmia and is associated with substantial morbidity and mortality.[1] Antiarrhythmic drug therapy is often ineffective and may cause serious adverse effects, including ventricular proarrhythmia. In the past decade, we have learned much about the electrical, mechanical, and structural remodeling that occurs as a result of atrial fibrillation and that leads to more atrial fibrillation.[1-4] These adaptations include ionic and genomic alterations over the short term and cellular changes over the medium term; fortunately, these effects may be reversible.[2-4] Apoptosis and interstitial fibrosis develop over the longer term and are usually irreversible.[2-4]

There is strong evidence that the renin–angiotensin–aldosterone system is involved in the genesis of atrial fibrillation.[2-4] Data suggest that angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) prevent the atrial electrical and structural remodeling that is associated with atrial fibrillation.[2-4] Previous clinical studies have suggested that ACE inhibitors and ARBs may prevent atrial fibrillation.[2-9] The potential mechanisms include hemodynamic, antiproliferative, antiinflammatory, and antioxidant effects that may prevent the development of left atrial stretch and enlargement, interstitial fibrosis, and adverse atrial electrical remodeling, which is manifested by a shortening of the duration of the action potential, abnormalities of intracellular calcium handling, and disruption of cell-to-cell conduction.[2-4]

In this issue of the *Journal*, the investigators of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Atrial Fibrillation (GISSI-AF) trial report the results of the first large, prospective, randomized trial to test the hypothesis that blockade of the renin–angiotensin–aldosterone system in addition to established therapies could prevent the recurrence of atrial fibrillation.[10] The GISSI-AF investigators randomly assigned 1442 patients with symptomatic atrial fibrillation who also had cardiovascular disease, diabetes mellitus, or left atrial enlargement to either valsartan or placebo. The primary outcomes were the time to the first recurrence of atrial fibrillation and the proportion of patients who had more than one episode of atrial fibrillation during a brief 1-year follow-up. Atrial fibrillation recurred in 51.4% of the patients in the valsartan group and in 52.1% of the patients in the placebo group. More than one episode of atrial fibrillation occurred in 26.9% of the patients in the valsartan group and in 27.9% of the patients in the placebo group. These results appear to provide strong evidence that valsartan and possibly other ARBs do not prevent the recurrence of atrial fibrillation in this patient population.

How widely can these results be extrapolated to the larger population of patients with atrial fibrillation? There are some important caveats with respect to the study population and concomitant therapies that may limit the conclusions of this study. The majority of the study population (85%) had reasonably well-controlled hypertension, 57% were already taking ACE inhibitors, and more than 70% were receiving class I or III antiarrhythmic drugs for the prevention of atrial fibrillation. The majority (88%) had undergone electrical or phar-