

ANTIEPILEPTIC DRUGS IN PREGNANCY: GREAT PROMISE FROM PREGNANCY REGISTRIES

The Australian Registry of Anti-epileptic Drugs in Pregnancy: Experience after 30 Months

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J Clin Neurosci 2003;10:543-549

BACKGROUND: Most women with epilepsy need to take antiepileptic drugs (AEDs) in pregnancy to prevent the potentially harmful effects of seizures. Retrospective studies have demonstrated an increased chance of having a child with a birth defect (BD) in women with epilepsy taking AEDs. It is uncertain how much of this risk is directly caused by the AEDs and whether certain drugs or combinations are associated with a greater risk. **PURPOSE:** To establish a register to evaluate prospectively the incidence of adverse pregnancy outcomes in women exposed to specific AEDs; to determine whether certain AEDs or combinations were associated with a greater risk; and to determine whether other factors influenced the risk.

METHODS: An Australia-wide, prospective, voluntary, telephone interview-based, observational register. Three groups of pregnant women were enrolled: those with epilepsy taking AEDs, those with epilepsy not taking AEDs, and those taking AEDs for a nonepilepsy indication. The pregnancy outcomes were evaluated by follow-up interviews and by reference to hospital and treating doctors' records.

RESULTS: Over the first 30 months of the study (till December 2001), 334 eligible women were enrolled, with all states and territories being represented. Two hundred ninety-two pregnancies had been completed, of which 256 (88%) resulted in a healthy live birth; 19 (6.5%), a live birth with a birth defect; 4, an induced abortion because of a detected malformation on ultrasound; 1, premature labor with a stillbirth; and 12 (4%), spontaneous abortions. Of the completed pregnancies, 269 were exposed to at least one AED during the first trimester. The incidence of birth defects in relation to specific AEDs was as follows: valproate (16.7%), phenytoin (10.5%), lamotrigine (7.7%), and carbamazepine (3.3%), none of

which was significantly different from that in women with epilepsy not taking an AED (4.3%, NS). The dose of valproate taken was higher in pregnancies with BD compared with those without (mean, 2,081 mg vs. 1,149 mg; $P < 0.0001$). The incidence of folate supplementation being taken before conception did not differ for pregnancy outcomes with or without BD (70% vs. 66%, NS). **CONCLUSIONS:** The model for the Australian Pregnancy Register appears to be successful, with strong enrollment from all regions over the first 30-month period. The study is prospective and includes reference to all new AEDs approved in Australia over the past decade. Analysis of the pregnancy outcomes to date may reveal early trends, but numbers are still too small for any definitive conclusions to be made regarding the relative risk in pregnancy of individual AEDs.

COMMENTARY

Much evidence exists for the association between the old antiepileptic drugs (AEDs) and an increased risk of major malformations after intrauterine exposure. However, aside from an association between spina bifida and valproate (VPA) exposure, there is no clear evidence that the classic AEDs differ from one another in their potential teratogenicity. It also is not totally clear if epilepsy, itself, or certain epileptic syndromes contribute to the risk of birth defects. Folate supplementation to prevent birth defects has become a standard recommendation for women of child bearing potential receiving AEDs, based predominantly on evidence that folate may reduce the incidence of spina bifida in the general population and in women who previously have had a child with spina bifida (1,2). However, there is insufficient evidence that folate supplementation prevents birth defects in women with epilepsy taking AEDs. Although preliminary findings are encouraging in regard to the relative safety of some new AEDs, they are not strong enough to justify converting women to a different AED in preparation for pregnancy. Clearly, more data are needed to guide treatment of epilepsy in women desiring pregnancy or who have the potential for pregnancy.

The study of Vajda et al., based on the first 30 months of the Australian registry of pregnant women who have epilepsy or are taking AEDs, did not answer most questions it addressed but underlined the promise of this prospective endeavor. The authors were unable to find any significant difference in the incidence of birth defects between women with epilepsy taking VPA, carbamazepine, phenytoin, or lamotrigine (LTG) and women with epilepsy not taking AEDs. This finding occurred because the control group consisted of only 23 women with epilepsy taking no AEDs and having one offspring with a birth defect. Yet enough women were taking VPA to demonstrate a statistically significant difference in the mean VPA dose between women who did and those who did not have offspring with birth defects. Because it may be difficult to recruit women with epilepsy who are not taking AEDs, another control group of women without epilepsy and not taking AEDs should be considered. This group also may be necessary to assess the risk of birth defects imparted by epilepsy in the absence of AEDs and the risk of birth defects imparted by AEDs in the absence of epilepsy.

The authors did not address the incidence of birth defects occurring in association with monotherapy as compared with multiple-AED administration, probably as a result of the small number of subjects. Nevertheless, analyzing the 23 birth defects reported in this study, 14 were associated with VPA monotherapy, 4 with carbamazepine monotherapy, and 1 with phenytoin monotherapy, suggesting that these agents may be potentially teratogenic. No birth defects occurred with LTG monotherapy; in the four birth defects associated with LTG, VPA was coadministered in 3, and phenytoin plus diazepam in 1. It is therefore possible that LTG is safer than the older AEDs, as sug-

gested by recent data (3). With 68 treated women, lamotrigine was the only new AED taken by more than 5% of patients in the current study, but the number of patients receiving LTG monotherapy was not provided.

Despite the limitation of a small number of patients, this study clearly holds much promise for clarifying the specific teratogenicity of new and old AEDs, as well as determining the role of folate supplementation. Once a larger number of subjects have been recruited, the planned analyses will answer many important questions the study posed, including the teratogenicity of AEDs in the absence of epilepsy. Solid evidence of differences in the teratogenicity of AEDs may well change our current practice in the management of epilepsy in women of childbearing potential. If future registry data confirm the current finding that folate supplementation does not protect against AED teratogenicity, then switching to a nonteratogenic AED clearly would be indicated in women of childbearing potential.

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References

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