Anatomical and Behavioral Effects of In Utero Exposure to Antiepileptic Drugs

Increased Rate of Major Malformations in Offspring Exposed to Valproate during Pregnancy

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PURPOSE: To determine the rate of occurrence of major malformations in infants whose mothers had taken the drug valproic acid (VPA) as monotherapy during the first trimester of pregnancy and had enrolled in the North American Antiepileptic Drug Pregnancy Registry.

METHODS: Data were collected from pregnant women throughout the United States and Canada through telephone-based interviews. Each woman was interviewed at enrollment, at 7 months' gestation, and postpartum. With her written permission, the medical records of each mother and her infant were obtained. The major malformations tabulated were those identified at or before age 5 days. The prevalence of congenital malformations among offspring of monotherapy VPA-exposed women was compared with that among infants of women exposed to all other antiepileptic drugs (internal comparison group) and with that among newborns in the Active Malformations Surveillance Program at Brigham and Women's Hospital (external comparison group).

RESULTS: Sixteen affected cases were identified among 149 VPA-exposed women (proportion: 10.7%; 95% CI: 6.3 to 16.9%). The prevalence in the internal comparison group was 2.9% (95% CI: 2.0 to 4.1%; odds ratio: 4.0; 95% CI: 2.1 to 7.4; $P < 0.001$). Assuming a 1.62% prevalence in the external comparison group, the relative risk of having an affected offspring for VPA-exposed women was 7.3 (95% CI: 4.4 to 12.2; $P < 0.001$).

CONCLUSIONS: Maternal exposure to VPA during the first trimester of pregnancy significantly increased the risk of major malformations.

Lamotrigine and the Risk of Malformations in Pregnancy

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PURPOSE: To report the frequency of major malformations in lamotrigine (LTG)-exposed pregnancies from September 1, 1992, through March 31, 2004, in the International Lamotrigine Pregnancy Registry.

METHODS: Health care professionals throughout the world can voluntarily enroll LTG-exposed pregnancies in this observational study. Only pregnancies with unknown outcomes at the time of enrollment were included in the analysis. The percentage of outcomes with major birth defects was calculated as the total number of outcomes with major birth defects divided by the sum of the number of outcomes with major birth defects + the number of live births without defects.

RESULTS: Among 414 first-trimester exposures to LTG monotherapy, 12 outcomes with major birth defects were reported (2.9%, 95% CI 1.6 to 5.1%). Among the 88 first-trimester exposures to LTG polytherapy including valproate, 11 outcomes with major birth defects were reported (12.5%; 95% CI 6.7 to 21.7%). Among 182 first-trimester exposures to LTG polytherapy excluding valproate, 5 outcomes with major birth defects were reported (2.7%, 95% CI 1.0 to 6.6%). No distinctive pattern of major birth defects was apparent among the offspring exposed to LTG monotherapy or polytherapy.

CONCLUSIONS: The risk of all major birth defects after first-trimester exposure to LTG monotherapy (2.9%) was similar to that in the general population and in other registries enrolling women exposed to antiepileptic monotherapy (3.3 to 4.5%). However, the sample size was too small to detect any but very large increases in specific birth defects.

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Critical Relationship between Sodium Valproate Dose and Human Teratogenicity: Results of the Australian Register of Anti-Epileptic Drugs in Pregnancy

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PURPOSE: To compare the incidence of foetal malformations (FMs) in pregnant women with epilepsy treated with different antiepileptic drugs (AEDs) and doses, and the influence of seizures, family and personal history, and environmental factors. A prospective, observational, community-based cohort study.

METHODS: A voluntary, Australia-wide, telephone-interview–based register prospectively enrolling three groups of pregnant women: taking AEDs for epilepsy; with epilepsy not taking AEDs; and taking AEDs for a nonepilepsy indication. Four hundred fifty eligible women were enrolled over a 40-month period. Three hundred ninety-six pregnancies had been completed, with 7 sets of twins, for a total of 403 pregnancy outcomes.

RESULTS: The 354 (87.8%) pregnancy outcomes resulted in a healthy live birth; 26 (6.5%) had an FM; 4 (1%), a death in utero; 1 (0.2%), a premature labour with stillbirth; 14 (3.5%), a spontaneous abortion; and 4, lost to follow-up. The FM rate was greater in pregnancies exposed to sodium valproate (VPA) in the first trimester (16.0%) compared with those exposed to all other AEDs (16.0 vs. 2.4%; $P < 0.01$) or no AEDs (16.0% vs. 3.1%; $P < 0.01$). The mean daily dose of VPA taken in pregnancy with FMs was significantly greater than in those without (1975 vs. 1128 mg, $P < 0.01$). The incidence of FM with VPA doses $\geq$1100 mg was 30.2% versus 3.2% with doses $<$1100 mg ($P < 0.01$).

CONCLUSIONS: A dose–effect relation occurs for FM and exposure to VPA during the first trimester of pregnancy, with higher doses of VPA associated with a significantly greater risk than with lower doses or with other AEDs. These results highlight the need to limit, where possible, the dose of VPA in pregnancy.

Neuropsychological Effects of Exposure to Anticonvulsant Medication In Utero

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PURPOSE: To investigate the long-term differential drug effects on cognitive functioning in school-aged children exposed to antiepileptic drugs (AEDs) in utero.

METHODS: Mothers with epilepsy were recruited from specialist epilepsy clinics and obstetric clinics from the Liverpool and Manchester region. The mothers and their children were recruited without prior knowledge of their AED treatment during pregnancy or the health of the offspring. A battery of neuropsychological tests was applied to each mother–child pair to obtain a neuropsychological profile for each child.

RESULTS: Neuropsychological investigation was performed on 249 children between the ages of 6 and 16 years. Children exposed to sodium valproate had a significantly lower verbal IQ when compared with children exposed to other AEDs or not exposed at all. The same children were more likely to have an IQ below 69 and more likely to have memory impairment when compared with the other groups. The mothers' IQs, exposure to sodium valproate, and the number of tonic–clonic seizures during pregnancy were significant predictors of verbal IQ in this population.

CONCLUSIONS: This retrospective study highlights the potential harmful effects of sodium valproate exposure in utero on neuropsychological development.

COMMENTARY

For more than a decade, it has been apparent that the risk of major congenital malformations is higher for children exposed in utero to antiepileptic drug (AED) polytherapy than for children exposed to AED monotherapy or children in the general population. However, it has been unclear whether differential risks for malformations exist across individual AEDs. Further, the risk that in utero AED exposure poses to cognitive and behavioral development of the child is unknown. Understanding the risks of in utero AED exposure on the

TABLE 1. *Anatomic Teratogenicity: Percentage of Major Congenital Malformations (95% Confidence Intervals) from Six Recent Prospective Observational Studies in Women with Epilepsy*

Investigation	AED	%CM	95% CI	Significant Findings
Published Studies				
N. American Registry 2000*	PB	6.5%	2.1–4.5	Greater than general population (1.62%)
Australian Registry 2004†	VPA	14.4%‡	2.25–20.3	Greater no. AED (3.12%) and other AEDs (3.00%)
N. American Registry 2005§	VPA	10.7%	6.3–16.9	Greater than gen pop (1.62%) and other AEDs (2.9%)
International Lamotrigine	LTG	2.9%	1.6–5.1	Monotherapy
Registry 2005‖		2.7%	1.0–6.6	Polytherapy without VPA
		12.5%	6.7–21.7	Polytherapy with VPA
Preliminary Reports				
UK Registry 2005¶	VPA	6.0%	4.4–8.1	Greater than CBZ (2.3%)
NEAD Study 2005#	VPA	14.1%		Greater than other AEDs(1.0–4.9%)

AED, antiepileptic drug; NEAD, neurodevelopmental effects of antiepileptic drugs; PB, phenobarbital; VPA, valproate; CBZ, carbamazepine; LTG, lamotrigine.

*Holmes et al. (2); †Vajda et al.; ‡prospective data only; §Wyszynski et al.; ‖Cunnington and Tennis et al.; ¶Craig et al. (3); #Meador et al. (4).

unborn child and the opposing risks created by seizures during pregnancy is important for women taking AEDs for epilepsy or other indications (e.g., psychiatric conditions or pain). The most recent practice parameters from the American Academy of Neurology, published in 1998, could not provide information on whether AEDs have differential potential for teratogenesis (1). However, a series of reports in the last year now have begun to delineate differential risks of AEDs for the unborn child, which include both anatomic malformations and developmental delay. Tables 1 and 2 provide a summary of these findings.

Anatomic Teratogenesis

Last year, the North American Pregnancy Registry, which has prospectively enrolled more than 3,000 women, reported a 6.5% risk of congenital malformations with phenobarbital (PB) monotherapy during pregnancy (2); this risk is statistically greater than the general-population malformation rate of 1.62%. The malformation rate for PB is higher than the mean combined rate for all other AEDs that are in the registry, but the rate for PB is not statistically greater. Recently, Wyszynski and colleagues reported that the North American Antiepileptic Drug Pregnancy Registry found a 10.7% risk of major malformations in children exposed in utero to valproate (VPA) monotherapy. The risk for VPA was statistically greater than the rates for all other AEDs combined, as well as for the general population.

According to Vajda et al., the Australian Pregnancy Registry, which has assessed more than 400 AED fetal outcomes, also found a significantly greater risk of malformations for children exposed in utero to VPA monotherapy than for children exposed to other types of AEDs or no AED). The increased risk rate was 16.5% overall and 14.4% for their prospective cohort ($n = 336$). Further, the effect of VPA was dose dependent.

TABLE 2. *Behavioral Teratogenecity: Findings in Selected Studies of Developmental Delay in Children of Women with Epilepsy Who Were Exposed In Utero to AEDs*

Investigation	Type of Study	AED	Findings
Denmark, 1995*	Retrospective	PB	Verbal IQ reduced 7 points
Liverpool/Manchester, UK	Retrospective	VPA	1. Increased need for special
2001†, 2004‡, 2005§	(two cohorts)		education in children exposed
			to VPA (30% vs. 3–11%)
			2. Verbal IQ reduced 8–15 points
			3. Increase memory deficits
			4. Delayed developmental in second cohort younger than 6 years
Finland, 2004‖	Prospective	VPA	Verbal IQ reduced 11–12 points for VPA, but no reduction for CBZ.

PB, phenobarbital; VPA, valproate; CBZ, carbamazepine

*Reinisch et al. (6); †Adab et al., 2001 (7); ‡Adab et al., 2004 (8); §Vinten et al.; ‖Gaily et al. (9).

As reported by Cunnington and Tennis, the International Lamotrigine Pregnancy Registry, a pharmaceutical company–based registry, enrolled 414 women taking LTG during the first trimester of their pregnancy. The reported risk for LTG monotherapy was 2.9%. Women receiving polytherapy that included VPA had a higher risk (12.5%) of major malformations in their children than did those patients receiving polytherapy without VPA (2.7%).

Preliminary results from two other prospective studies also point to a greater risk of major congenital malformations in children exposed to VPA compared with other AEDs. The United Kingdom Pregnancy Registry, which includes 2,829 pregnancies, reported a rate of 6.0% for VPA (significantly greater than that for carbamazepine [CBZ]) (3). The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study enrolled 361 mother/child pairs in the United States and the United Kingdom (UK); all mothers were receiving AED monotherapy during pregnancy (4). The NEAD Study is a National Institutes of Health (NIH)-funded investigation designed to examine cognitive and behavioral outcomes of children exposed to AEDs in utero; however, early monitoring already has revealed increased malformations in children exposed to VPA (14.1%) compared with other three AEDs in the study (i.e., CBZ, LTG, phenytoin [PHT]).

In summary, the evidence for AED-induced anatomic teratogenesis includes one prospective study that suggests an increased risk of malformation with PB administration and five prospective studies (three published and two preliminary), indicating an increased risk of major congenital malformations associated with VPA.

Behavioral Teratogenesis

Most investigations have reported an increased risk of developmental delay in children of mothers with epilepsy (5). Multiple factors could contribute to the observed increased risk, but AEDs likely play a major role.

In a retrospective study from Denmark, Reinisch et al. found that prenatal exposure to PB significantly reduced verbal IQ scores (~7 IQ points or 0.5 SD) in two cohorts of men exposed in utero (6). It should be noted that the mothers of these men were not taking PB for seizures but for other indications that were common several decades ago. The study also found that the presence of low socioeconomic status and an "unwanted" pregnancy appeared synergistically to enhance the adverse effects of PB, decreasing the verbal IQ score by approximately 20 points lower than expected in the subset who had all of these risk factors.

An investigational group from Liverpool/Manchester, UK, has conducted several large, retrospective studies of cognitive outcomes in children born to women with epilepsy and published their results in prior articles (7,8) as well as in the recent article by Vinten and colleagues. Their first study assessed 594 school-age children and found that 30% of the children exposed in utero to monotherapy VPA required special education compared with 3% to 6% for other AED monotherapy groups. In a follow-up study, they examined development in one cohort of children 6 to 16 years old ($n = 249$) and in another cohort of children younger than 6 years old ($n = 119$). Approximately half of the children in the cohort of older children were included in the prior study on the need for special education. IQ was assessed in the children 6 to 16 years old. Multivariate analyses revealed that the verbal IQ of the children was significantly affected by maternal IQ and seizure frequency during pregnancy. In addition, an independent effect of in utero AED exposure was noted. IQ was lower in the children whose mothers had more than four convulsions during the pregnancy. Children exposed to monotherapy VPA had a mean verbal IQ that was significantly lower than children not exposed to AEDs (−7.9 verbal IQ points) and to children exposed to CBZ monotherapy (−10.5 verbal IQ points) or to PHT monotherapy (−14.9 verbal IQ points). The effect of VPA was found to be dose dependent. The percentage of children with mental retardation (i.e., verbal IQ <70) was 7% in the unexposed children, 8% in the CBZ monotherapy group, and 22% in the VPA monotherapy group. In comparison, the percentage of children with mental retardation in the general population is 2.5%. Although analyses of IQ were limited to children 6 to 16 years old, the same investigators also examined cognitive outcomes in a second cohort of children who were younger than 6 years old, by using an age-appropriate developmental scale. A greater proportion of children exposed to VPA in this younger cohort exhibited developmental delay. Thus, VPA produced worse outcomes in both the younger and older cohorts studied by Liverpool/Manchester, UK, investigational group.

Last year, a prospective study from Finland also reported a greater risk for impaired cognition in children exposed in utero to VPA (9). The study included 182 children of mothers with epilepsy (107 monotherapy, 30 polytherapy, and 45 no AED) and 141 control children of healthy mothers. Overall, verbal IQ was reduced with polytherapy and VPA exposure compared with the healthy controls and children exposed to CBZ monotherapy. Verbal IQ (mean, 96) for children exposed to CBZ did not differ from that of healthy controls (verbal IQ, 95). Verbal IQ was 82 for the VPA monotherapy group. The sample size for the monotherapy VPA group was small, but the magnitude of decline in verbal IQ is similar to the UK findings previously described.

In summary, the evidence for AED-induced behavioral teratogenesis includes one retrospective study with two cohorts, suggesting an increased risk of cognitive impairment with in utero PB use and one retrospective study with two cohorts as

well as one prospective study indicating an increased risk of cognitive impairment after in utero VPA exposure.

Conclusions

None of the individual studies discussed qualifies as class I evidence, and class I studies are unlikely to ever be conducted in this population, for both pragmatic and ethical concerns. The findings regarding PB raise concerns and suggest that it may pose a greater risk than other AEDs. However, taken together, the eight studies examining the effects of in utero VPA exposure provide strong evidence that VPA poses a distinctly greater risk to the unborn child. The probability is very small that eight investigations with different cohorts, geographic locations, designs, and outcome measures would all demonstrate differentially greater adverse effects for VPA by chance. In view of these findings, it seems appropriate to recommend that VPA not be used as a first-line drug in women of child-bearing potential, whether VPA is used for seizures or for other indications (e.g., psychiatric conditions or pain). This recommendation does not imply that VPA should never be used in women of childbearing age. Consideration of VPA use in this population must be measured against risk of the disease and availability of alternative therapies. Further, women receiving or starting VPA need to be advised of the increased risk of anatomic malformations and developmental delay to an unborn child.

The treatment of women with epilepsy involves hard choices. The newly published findings will help clinicians and patients make better choices but do not resolve all the conflicts. The risks of AED-associated teratogenic effects have to be balanced against the risk of seizures. The risk of maternal death during pregnancy is elevated more than 10-fold for women with epilepsy, and the increased risk appears to be due mainly to seizures (8). In addition, children of women who experienced more than four convulsions during pregnancy have impaired cognitive outcomes (8).

Further research in this area is critically needed. The adverse effects of in utero AED exposure are not uniform across all children. Most of the children born to women with epilepsy are normal, but the human and financial costs of adverse outcomes in the subset who are affected is staggering. Delineating the underlying mechanisms may assist in understanding individual variability, predicting the effects of specific AEDs on individual patients, and improving patient care.

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