

DO THE RESULTS OF PREGNANCY REGISTRIES CONTRADICT ONE ANOTHER?

Malformation Risks of Antiepileptic Drugs in Pregnancy: A Prospective Study from the UK Epilepsy and Pregnancy Register

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OBJECTIVE: To assess the relative risk of major congenital malformation (MCM) from in utero exposure to antiepileptic drug (AED).

METHODS: Prospective data collected by the UK Epilepsy and Pregnancy Register were analyzed. The presence of MCMs recorded within the first 3 months of life was the main outcome measure.

RESULTS: Full outcome data were collected on 3,607 cases. The overall MCM rate for all AED exposed cases was 4.2% (95% confidence interval (CI): 3.6–5.0%). The MCM rate was higher for polytherapy (6.0%) ($n = 770$) than for monotherapy (3.7%) ($n = 2,598$) (crude odds ratio (OR) = 1.63 ($p = 0.010$), adjusted OR = 1.83 ($p = 0.002$)). The MCM rate for women with epilepsy who had not taken AEDs during pregnancy ($n = 239$) was 3.5% (1.8–6.8%). The MCM rate was greater for pregnancies exposed only

to valproate (6.2% (95% CI: 4.6–8.2)) than only to carbamazepine (2.2% (1.4–3.4%)) (OR = 2.78 ($p < 0.001$)); adjusted OR = 2.97 ($p < 0.001$)). There were fewer MCMs for pregnancies exposed only to lamotrigine than only to valproate. A positive dose response for MCMs was found for lamotrigine ($p = 0.006$). Polytherapy combinations containing valproate carried a higher risk of MCM than combinations not containing valproate (OR = 2.49 (1.31–4.70)).

CONCLUSIONS: Only 4.2% of live births to women with epilepsy had an MCM. The MCM rate for polytherapy exposure was greater than for monotherapy exposure. Polytherapy regimens containing valproate had significantly more MCMs than those not containing valproate. For monotherapy exposures, carbamazepine was associated with the lowest risk of MCM.

Maternal Valproate Dosage and Foetal Malformations

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OBJECTIVE: To study the possible dose dependence of the foetal malformation rate after exposure to sodium valproate in pregnancy.

METHODS: Analysis of records of all fetuses in the Australian Registry of Antiepileptic Drugs in Pregnancy exposed to valproate, to carbamazepine, lamotrigine or phenytoin in the absence of valproate, and to no antiepileptic drugs.

RESULTS: The foetal malformation rate was higher ($p < 0.05$) in the 110 fetuses exposed to valproate alone (17.1%), and in the 165 exposed to valproate, whether alone or together with the other antiepileptic drugs (15.2%), than in the 297 exposed to the other drugs without valproate (2.4%). It was also higher ($p < 0.10$) than in

the 40 not exposed to antiepileptic drugs (2.5%). Unlike the situation for the other drugs, the malformation rate in those exposed to valproate increased with increasing maternal drug dosage ($p < 0.05$). The rate was not altered by simultaneous exposure to the other drugs. Valproate doses exceeding 1,400 mg per day seemed to be associated with a more steeply increasing malformation rate than at lower doses and with a different pattern of foetal malformations.

CONCLUSIONS: Foetal exposure to valproate during pregnancy is associated with particularly high, and dose-dependent risks of malformation compared with other antiepileptic drugs, and may possibly involve different teratogenetic mechanisms.

COMMENTARY

There are currently several pregnancy registries monitoring the outcomes of antiepileptic drug (AED)-exposed pregnancies worldwide: the North American Pregnancy Registry, the United Kingdom Epilepsy and Pregnancy Register,

the Australian Registry of Antiepileptic Drugs in Pregnancy, the International Lamotrigine Registry, and the European Pregnancy Registry. The goal of these registries is to gather information about the relative risks of AEDs during pregnancy and particularly to capture outcomes of exposure to the newer AED. According to the similarity of the methods and the reliability of the prospectively obtained results, the findings of these registries should reinforce one other.

The North American Pregnancy Registry was among the first registries to publish findings; data revealed that there was at least a doubled risk of major malformations with phenobarbital monotherapy (1) and valproate monotherapy (2), as compared with a historical control population. The increased risk with valproate has been observed for more than two decades (3) and has been based on several populations, including the two reports discussed here. However, the risk of malformation with phenobarbital may never be confirmed by the UK or Australia registries, because this agent currently is rarely used in either country, or less plausibly, because women taking phenobarbital are systematically not enrolling in these voluntary registries. The UK registry has reported the results of AED monotherapy exposures since December 1996; only AEDs that had a minimum of 25 evaluable births were included. A total of seven AEDs met this criterion, including gabapentin, topiramate, and levetiracetam (each had less than 32 outcomes); however, phenobarbital did not meet the criterion (i.e., <25 evaluable births). Therefore, a risk rate for major malformations from phenobarbital exposure will likely never be determined by the North American Pregnancy Registry and will have to be confirmed in other global regions where phenobarbital is more widely used for epilepsy treatment.

How consistent are the results that are emerging from the various AED pregnancy registries? When the recent findings of the UK and the Australian pregnancy registries are compared, there are both consistencies and inconsistencies. As mentioned, the elevated malformation rate associated with valproate monotherapy as compared to other AED monotherapies was found in both studies. However, the UK registry reports a malformation rate with valproate monotherapy of 6.2% of 715 fetuses and the Australian registry reports a rate of 17.1% of 110 fetuses. The higher rate of malformation associated with valproate found in the Australian registry may partly be explained by a longer follow-up period than that used in the UK registry. Patients in the Australian registry enroll voluntarily and were contacted by phone between 1 and 2 months after delivery and again at 1 year after delivery. Therefore, the reported major malformation rate was obtained at the 1-year contact point. In contrast, the UK registry defines malformations as those present at birth or occurring in the first 6 weeks of life. It is clear from general population surveys that major malformation rates are significantly higher at 1 year than at birth, which is due to the

fact that some birth defects are overlooked at birth (e.g., rectal atresia) (4). Furthermore, the optimal surveillance period for assessing birth defects in the general population has not been determined or standardized, which makes it difficult to compare data sets (4)—a fact that clearly makes it difficult to accurately compare AED-associated malformation risk rates across the various pregnancy registries. So presumably, the higher malformation rate with valproate in the Australian registry could be because of the longer follow-up.

Using this explanation of the difference in malformation rates, one would expect that rates with the other AEDs likewise would be higher in the Australian registry than in the UK registry; however, this is not the case. Excluding valproate, the malformation rate for all AED monotherapy exposures in the Australian registry is 2.4%; while in the UK registry, the malformation rates range from 2.2% to 3.7% for evaluable monotherapies, again, excluding valproate. It is possible, therefore, that a greater number of subjects were needed to obtain an accurate valproate malformation rate than were available for the Australian registry. After 149 valproate-exposed pregnancies, the North American Pregnancy Registry reported a 10.7% rate of major malformations detected in the first 5 days of life (2). The North American Pregnancy Registry methodology was designed with the strict criterion that any AED reported to be correlated to an increased risk of malformation must have a risk rate twice that of the control population rate. Therefore, it is possible that the number of valproate monotherapy exposures (i.e., 110) obtained in the Australian registry actually may have been too low to provide an accurate rate of birth defects, in spite of the reported 17.1% malformation rate.

The most provocative difference in the findings between these two articles is the dose-response relationships for malformations reported for lamotrigine and valproate. A dose-response relationship for malformations was found in the UK registry for lamotrigine but not for valproate. In contrast, a dose-response relationship for malformations was found in the Australian registry for women taking valproate but was not found for lamotrigine. This disparity likely is explained by dissimilar analytic methods and a discrepancy between the valproate doses used in the United Kingdom and Australia. Furthermore, the UK pregnancy registry is much larger than the Australian registry; there were 647 lamotrigine and 715 valproate monotherapy births available for assessment in the United Kingdom, compared with 128 lamotrigine and 110 valproate monotherapy births available for assessment in Australia.

In the UK study, dose-response rates for malformations were determined in two ways. First, the doses of exposure to AEDs that resulted in malformations were compared with the doses that did not result in malformations. This method showed no dose-response risk for carbamazepine or valproate, although the malformations were associated with slightly higher doses.

However, a dose response was found for lamotrigine, with a mean daily dose of 350 mg in the malformation group and 250 mg in the group without malformation. Although interesting, the finding is not helpful information to the clinician, since during pregnancy the levels of lamotrigine can decrease markedly (5,6), and a dose increase of 100 mg within a week is a frequent occurrence. In fact, dose is not a good surrogate for level with lamotrigine, and levels during pregnancy need to be assessed to evaluate the risk of exposure. A more definite lamotrigine risk dose or, better yet, level is needed to help manage patients.

The second method used by the UK registry to calculate dose-response rates was to divide the monotherapy groups into roughly equal proportions, based on dose. For example, for the valproate group, one third of the patients took <600 mg per day, one third took 600 to 1,000 mg per day, and one third took >1,000 mg per day. Similarly, the doses for lamotrigine were <100 mg per day, 100 to 200 mg per day, and >200 mg per day. Using the Mann-Whitney *U* test, a significant difference was found in the risk of major malformation between a lamotrigine dose of >200 mg per day (5.4%) and lower doses; although the exact malformation rate of the lamotrigine comparison group is not given, it is somewhere between 1.3% and 1.9% ($p = 0.006$). As mentioned, the finding of the increased risk for lamotrigine at doses >200 mg per day is not very useful in clinical management because level is a more accurate measure and because most women will be taking more than 200 mg per day during pregnancy; however, it does point to the relative risk of lamotrigine compared with other AEDs. The authors state that no dose response was revealed for valproate by this method, but they do not report the values that were used for the Mann-Whitney *U* test that yielded this result.

The Australian investigators performed logistic regression on the AED dose and the percentage of malformation rates at each dose. Very simply, a logistic regression analysis can be thought of as a model that is capable of identifying associations (derived from the actual values of variables) that are occurring in relationship to the primary data obtained. Using this method, the Australian investigators found a dose relationship for malformations with valproate, particularly at doses >1,400 mg per day. The cutoff point of 1,400 mg per day was determined from their data, based on the slope of the logistic regression curve. No dose relationship for malformations was found with other AEDs using this method.

The challenge is to find the truth in these data and, furthermore, to have the data be clinically useful. Although logistic regression may be a more speculative analysis than evaluating malformation rates within an exact dose range and although some transformation of the data were performed by the Australian investigators to create a variable (i.e., the percentage rate of malformations at each dose), logistic regression nonetheless may be a method to determine whether there is a dose relationship in the risk of major malformations for a particular AED. If the dose of 1,400 mg per day can be confirmed as an accurate cutoff point for risk of malformation by performing subsequent prospective studies, this finding will be clinically useful. Valproate doses could be adjusted before pregnancy in situations for which the drug must be continued.

The results from these two pregnancy registries, therefore, are reinforcing, and the contradictions in the findings are less profound when the size of the data sets and statistical methods are considered. The investigators and subjects of the pregnancy registries should be highly lauded as they continue to help us provide better care for epilepsy patients.

by Cynthia L. Harden, MD

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