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Comparative Risk of Major Congenital Malformations With 8 Different Antiepileptic Drugs: A Prospective Cohort Study of the EURAP Registry

Teratogenesis of 8 Antiepileptic Drugs in Multinational Experience

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Background: Evidence for the comparative teratogenic risk of antiepileptic drugs is insufficient, particularly in relation to the dosage used. Therefore, we aimed to compare the occurrence of major congenital malformations following prenatal exposure to the 8 most commonly used antiepileptic drugs in monotherapy. Methods: We did a longitudinal, prospective cohort study based on the EURAP international registry. We included data from pregnancies in women who were exposed to antiepileptic drug monotherapy at conception, prospectively identified from 42 countries contributing to EURAP. Follow-up data were obtained after each trimester, at birth, and 1 year after birth. The primary objective was to compare the risk of major congenital malformations assessed at 1 year after birth in offspring exposed prenatally to 1 of 8 commonly used antiepileptic drugs (carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate) and, whenever a dose dependency was identified, to compare the risks at different dose ranges. Logistic regression was used to make direct comparisons between treatments after adjustment for potential confounders and prognostic factors. Findings: Between June 20, 1999, and May 20, 2016, 7555 prospective pregnancies met the eligibility criteria. Of those eligible, 7355 pregnancies were exposed to 1 of the 8 antiepileptic drugs for which the prevalence of major congenital malformations was 142 (10·3%) of 1381 pregnancies for valproate, 19 (6·5%) of 294 for phenobarbital, 8 (6·4%) of 125 for phenytoin, 107 (5·5%) of 1957 for carbamazepine, 6 (3·9%) of 152 for topiramate, 10 (3·0%) of 333 for oxcarbazepine, 74 (2·9%) of 2514 for lamotrigine, and 17 (2·8%) of 599 for levetiracetam. The prevalence of major congenital malformations increased with the dose at time of conception for carbamazepine ($P = .0140$), lamotrigine ($P = .0145$), phenobarbital ($P = .0390$), and valproate ($P < .0001$). After adjustment, multivariable analysis showed that the prevalence of major congenital malformations was significantly higher for all doses of carbamazepine and valproate as well as for phenobarbital at doses of more than 80 mg/d than for lamotrigine at doses of 325 mg/d or less. Valproate at doses of 650 mg/d or less was also associated with increased risk of major congenital malformations compared with levetiracetam at doses of 250 to 4000 mg/d (odds ratio [OR]: 2.43, 95% confidence interval [CI]: 1·30-4·55; $P = .0069$). Carbamazepine at doses of more than 700 mg/d was associated with increased risk of major congenital malformations compared to levetiracetam at doses of 250 to 4000 mg/d (OR: 2.41, 95% CI: 1.33-4.38; $P = .0055$) and oxcarbazepine at doses of 75 to 4500 mg/d (OR: 2.37, 95% CI: 1.17-4.80; $P = .0169$). Interpretation: Different antiepileptic drugs and dosages have different teratogenic risks. Risks of major congenital malformation associated with lamotrigine, levetiracetam, and oxcarbazepine were within the range reported in the literature for offspring unexposed to antiepileptic drugs. These findings facilitate rational selection of these drugs, taking into account comparative risks associated with treatment alternatives. Data for topiramate and phenytoin should be interpreted cautiously because of the small number of exposures in this study.

Commentary

The teratogenic risks of phenytoin and valproate in humans and mice were first reported decades ago.[1-4] New data on the risks of all antiepileptic drugs (AEDs) are welcomed by clinicians and patients, particularly when they include information about the comparative risks of different medications. These data are important because the number of cases ascertained in the past was limited, and because the number of AEDs available in most countries has increased dramatically over the last 25 years. The latter has resulted in a shift toward the use of newer

AEDs for which we have few or no data on the risk of human teratogenesis.

Most women with epilepsy (WWE) and their providers are aware that AEDs as a group carry an increased risk of major congenital malformations (MCMs), yet some lack the most up-to-date information about risks specific to the AED and the dose being used in their pregnancy. As a result, some pregnancies are being managed today on the basis of older, possibly inaccurate or incomplete information. Given that AEDs are used not only for epilepsy but also to treat chronic migraine, bipolar disorder, neuropathic pain, fibromyalgia, and sometimes off-label for other conditions, the number of potential parents and their offspring who may benefit from updated information is quite large. For these reasons it is important to provide access to accurate and current risk data not only to neurology providers but also to all health-care practitioners in order to reduce the risks of a lifetime of morbidity caused by the use of AEDs during pregnancy. To address these concerns, several international AED pregnancy registries were established approximately 2 decades ago.

The North American AED Pregnancy Registry (NAAPR) began enrollment in February 1997. Pregnant women taking AEDs for any reason may enroll prior to delivery, preferably prior to any prenatal screening. The AEDs taken in the first trimester are studied. Women register themselves, and outcome is verified shortly after delivery by obtaining the medical records of the mother and infant. Additionally, an internal control group of pregnant women who were not taking AEDs is enrolled. Rates of major malformations are assessed; excluded are minor anomalies, such as preauricular sinus, simian creases, hemangiomata, congenital skin moles, undescended testes, patent ductus arteriosus, Down syndrome, achondroplasia, hip dysplasia with breach, and unilateral renal agenesis seen only on ultrasound.[5]

The most recent NAAPR results were updated on October 31, 2018 and are available online via open-access.[6] For the 8 most-commonly used AEDs in North America, 5925 pregnant WWE have provided pregnancy outcome data for monotherapy use. The incidence of MCMs (numbers in parentheses are 95% confidence intervals [CI]) were 8.2% (5.5-11.9%) for valproate, 6.1% (3.3-10.7%) for phenobarbital, 5.3% (3.6-7.9%) for topiramate, 2.8% (1.9-4.0%) for carbamazepine, 2.6% (1.4-4.7%) for phenytoin, 2.6% (1.2-5.6%) for oxcarbazepine, 2.1% (1.5-2.8%) for lamotrigine, and 2.0% (1.3-3.1%) for levetiracetam. The MCM rate for the internal control group of 745 unexposed women was 1.2% (0.6%-2.4%).

Enrollment in the NAAPR by year for specific AEDs has changed dramatically. In 1999, the proportion of mothers receiving carbamazepine was ~45%, phenytoin was ~20%, valproate was ~15%, and phenobarbital was ~10%. In 2018, lamotrigine was 40%, levetiracetam was ~35%, gabapentin was ~8%, and others were each 5% or less (valproate was ~0%). There is no doubt that early results from the NAAPR and other international registries informed changes in the prescribing choices of providers.

The UK and Ireland Epilepsy and Pregnancy Registers, established in December 1996, also enroll pregnant women taking AEDs and WWE who were not taking medication prior to delivery. Pregnancy, epilepsy, and outcome information are obtained at the time of registration and also at 3 months postpartum. Eligible pregnant women are referred by their health-care provider or by themselves. Outcomes are classified as: no birth defects, MCMs, or other defects (minor defects, chromosomal disorders, and single gene defects). A 2014 publication[7] reported 15 years of data regarding the occurrence of MCMs in 5206 women exposed to monotherapy valproate (n = 1290), carbamazepine (n = 1718), and lamotrigine (n = 2198). The MCM risk with monotherapy valproate was 6.7% (CI = 5.5%-8.3%) versus 2.6% with carbamazepine (1.9%-3.5%), and 2.3% with lamotrigine (1.8%-3.1%). A significant dose-effect was seen with valproate ($P = .0006$) and carbamazepine ($P = .03$). A non-significant trend toward higher MCM rate with increasing dose was found for lamotrigine, but the MCM rate for high-dose lamotrigine (>400 mg/d) was still lower than the rate for low-dose valproate (<600 mg/d; 3.4% vs 5.0%, respectively; N.S.).

The Australia Register of AEDs in Pregnancy (ARAP) began in 1999, and reported its first 15 years of experience in 1461 pregnancies with AED monotherapy and 484 pregnancies with AED polytherapy.[8] The ARAP found that MCM rates decreased from 1999 to 2014 in monotherapy but increased in polytherapy pregnancies despite less frequent use and lower doses of valproate. The MCMs became more frequent in polytherapy pregnancies around 2005 when topiramate and levetiracetam use increased. When pregnancies involving valproate were excluded, MCM rates were still higher in the remaining polytherapy pregnancies than the monotherapy ones (6.90% vs 3.64%; odds ratio 1.96, 95% CI: 1.23-5.10). Levetiracetam in polytherapy did not result in increased malformation rates. Topiramate in polytherapy had a positive dose-relationship with teratogenicity risk ($P = .025$). The methodology for ARAP is similar to the NAAPR.

The Kerala (India) Registry of Epilepsy and Pregnancy, established in 1998, published its findings of 1021 monotherapy and 368 dual AED exposures in pregnancy through 2013.[9] The AEDs used most commonly were carbamazepine, valproate, phenobarbital, and clobazam. The MCMs occurred in 70 (6.8%) of monotherapy and 44 (11%) of dual therapy exposed pregnancies. Valproate had a higher rate of MCMs than other monotherapies. The excess risk of dual therapy over monotherapy (relative risk = 1.6, $P = .0015$) was largely contributed by topiramate or valproate.

The International Registry of AEDs and Pregnancy (EURAP), established in 1999 in Europe, is now a consortium of 44 countries from Europe, Oceania, Asia, Latin America, and Africa. Pregnant WWE are included if they are exposed to AEDs at conception, are enrolled by their health-care provider by gestational week 16, and have known fetal outcome and outcomes reported by their provider at the end of each trimester, and at birth, 2 months, and 1 year of age. Exclusion criteria are women without epilepsy, cases in which data were not reported

within preset deadlines, pregnancies in which AEDs were withdrawn or switched during the first trimester, AED polytherapy, exposure to other teratogenic drugs, spontaneous abortions, abortions induced for etiologies other than fetal malformations, and offspring with genetic or chromosomal abnormalities.

The current EURAP report by Tomson et al summarizes its most current findings on the teratogenic risks of the 8 AEDs most commonly used in monotherapy. 7335 of prospective pregnancies met inclusion criteria and were exposed. The prevalence of MCMs was greater for 7 of the 8 monotherapy AEDs than in the recent NAAPR update. The only exception was the rate for topiramate, which was lower in the EURAP than the NAAPR registry. Differences in registry methodologies likely account for the generally higher rates in EURAP. The NAAPR ascertains women using self-referral, and obtains pregnancy outcome data shortly after delivery. By contrast, EURAP enrolls women via their health-care provider, and final outcome assessment is at 1 year. As a result of having women self-enroll in NAAPR, a bias toward inclusion of women who are more motivated regarding their pregnancy and have better prenatal care may occur, thereby including women who may have a lower chance for a malformation. Likewise, by obtaining MCM outcome data at 1 year of age of the infant, the EURAP study may have a greater chance to detect birth defects which were missed shortly after birth.

Considering only these 5 international registries, and not including others,[10] more than 20 000 WWE taking or not taking AEDs, and women taking AEDs for other conditions, have contributed vitally important data with which we can better counsel future patients. Although the exact prevalence rates of MCMs for each of the major AEDs reported vary somewhat across the registries, most likely due to differences in enrollment criteria and follow-up methodologies, the relative risks are generally consistent.

It's abundantly clear that of the AEDs studied in large numbers, valproate carries the highest risk of MCMs. Furthermore, valproate exposure has been linked with a higher incidence of developmental intellectual disability, and in some studies autism.[11] This has led the US Food and Drug Administration and the European Medicines Agency to issue mostly concordant warnings and contraindications to the prescribing information for valproate. In response, on 12 May 2017, the American Epilepsy Society created a position statement about the use of valproate by women of childbearing potential and can be found at *www.aesnet.org*.

In summary, the monotherapy MCM prevalence rate with valproate is highest, the rates with topiramate and phenobarbital are moderately high, the rates with carbamazepine, oxcarbazepine, and phenytoin are intermediate, and the rates with levetiracetam and lamotrigine are lowest, but all have higher risk than the NAAPR internal control rate of 1.2%. Higher doses correlate with higher MCM rates with valproate and carbamazepine in monotherapy, and with topiramate in polytherapy. Higher dose lamotrigine monotherapy has a nonsignificant trend toward a higher MCM rate. Polypharmacy results in higher prevalence rates of MCMs, particularly when these regimens include valproate or topiramate.

The results of these studies provide extremely helpful information to guide the management of the pregnant woman taking AEDs. These important registries must continue to enroll more patients in order to provide needed information about the risk of human teratogenesis with the use of the newest medications.

By David G. Vossler

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