Too Complicated or So Simple: AED Type and AED Dose Matter for Pregnancy

Dose-Dependent Risk of Malformations With Antiepileptic Drugs: An Analysis of Data From the EURAP Epilepsy and Pregnancy Registry.

Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, Perucca E, Vajda F; for the EURAP Study Group. *Lancet Neurol* 2011;10(7):609–617.

BACKGROUND: Prenatal exposure to antiepileptic drugs is associated with a greater risk of major congenital malformations, but there is inadequate information on the comparative teratogenicity of individual antiepileptic drugs and the association with dose. We aimed to establish the risks of major congenital malformations after monotherapy exposure to four major antiepileptic drugs at different doses. METHODS: The EURAP epilepsy and pregnancy registry is an observational cohort study representing a collaboration of physicians from 42 countries. We prospectively monitored pregnancies exposed to monotherapy with different doses of four common drugs: carbamazepine, lamotrigine, valproic acid, or phenobarbital. Our primary endpoint was the rate of major congenital malformations detected up to 12 months after birth. We assessed pregnancy outcomes according to dose at the time of conception irrespective of subsequent dose changes. FINDINGS: After excluding pregnancies that ended in spontaneous abortions or chromosomal or genetic abnormalities, those in which the women had treatment changes in the first trimester, and those involving other diseases or treatments that could affect fetal outcome, we assessed rates of major congenital malformations in 1402 pregnancies exposed to carbamazepine, 1280 on lamotrigine, 1010 on valproic acid, and 217 on phenobarbital. An increase in malformation rates with increasing dose at the time of conception was recorded for all drugs. Multivariable analysis including ten covariates in addition to treatment with antiepileptic drugs showed that the risk of malformations was greater with a parental history of major congenital malformations (odds ratio 4·4, 95% CI 2·06–9·23). We noted the lowest rates of malformation with less than 300 mg per day lamotrigine (2·0% [17 events], 95% CI 1·19–3·24) and less than 400 mg per day carbamazepine (3·4% [5 events], 95% CI 1·11–7·71). Compared with lamotrigine monotherapy at doses less than 300 mg per day, risks of malformation were significantly higher with valproic acid and phenobarbital at all investigated doses, and with carbamazepine at doses greater than 400 mg per day. INTERPRETATION: The risk of major congenital malformations is influenced not only by type of antiepileptic drug, but also by dose and other variables, which should be taken into account in the management of epilepsy in women of childbearing potential.

Commentary

Approximately one-quarter of patients with active epilepsy are females of childbearing age, necessitating treatment with medications that are known teratogens during this vulnerable life stage. However, most women with epilepsy require chronic treatment with an antiepileptic drug (AED) to maintain seizure control. Pregnancy registries over the last 2 decades have provided incremental advances in our knowledge quantifying the teratogenic risks, but the most useful information to the prescribing clinician is findings that delineate differential risks amongst the AEDs. Several pregnancy registries consistently report that of the AEDs analyzed thus far, valproic acid has the highest risk for major congenital malformations (MCM) and poor neurodevelopmental outcomes (1–3). The AAN/AES practice parameter update concluded that it is highly probable that intrauterine first-trimester valproic acid monotherapy exposure has a higher risk of MCMs compared with carbamazepine and possibly compared with phenytoin or lamotrigine (1). However, evidence necessary to direct the care of women with epilepsy planning and during pregnancy is still inadequate, with AED-specific risk profiles for many of the medications still unknown.

Most AED pregnancy registries prospectively follow a cohort of women on AEDs across several sites and record outcomes. Given the low incidence of MCMs (1.6–2.1% in the general population and 4–8% in women with epilepsy on AED monotherapies [4]), it is difficult to gain enough statistical power to ascertain differential risks between different doses for the same drug or between dose ranges of different drugs.

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The one exception is for valproic acid, with findings from several studies supporting an association between dose and risk of MCMs (5, 6). One study also reported a dose-associated risk for lamotrigine (3), but another study did not find an effect of maximal first-trimester dose level despite a large number of outcomes (7). It is less clear if there is a dose-related risk for other AEDs.

EURAP (An International Registry of Antiepileptic Drugs and Pregnancy) is an observational cohort study with sites spanning 42 countries, generating outcomes for a large number of pregnancies. Of the eligible pregnancy outcomes, 86% were exposed to one of four common AEDs (carbamazepine, lamotrigine, valproic acid, phenobarbital). The rate of MCMs with lamotrigine <300 mg/d was so low (2.0%, 95% confidence interval [CI]: 1.19–3.24), that it was used as the comparator for other lamotrigine doses and other AEDs at various doses. This modest rate of MCMs is not unlike rates published from other AED pregnancy registries that included all lamotrigine doses, with 1.9% (95% CI: 1.3–2.8) MCM rate in the North American AED Pregnancy Registry and 2.2% (95% CI: 1.6–3.1) MCM rate in the International Lamotrigine Pregnancy Registry (7, 8). Compared with lamotrigine <300 mg/d, MCM rates were higher for valproic acid and phenobarbital at all doses and for carbamazepine at doses >400 mg/d (odds ratios [OR] of 2.5–16); for each AED, the OR increased with the higher dose ranges. MCM rates were modestly low for carbamazepine <400 mg/d (3.4%, 95% CI: 1.11–7.71) similar to other registry findings (1), but with fairly wide confidence intervals. Other notable findings were the high overall MCM rate (24%) and the neural-tube defects rate (2%) for valproic acid >1,500 mg/d.

Perhaps the most novel results are the significantly higher odds ratios for MCMs across all the drugs studied with internal daily dose range comparisons: carbamazepine (≥1,000 vs <400 mg/d; OR, 2.9; 95% CI: 1.04–8.0), lamotrigine (≥300 vs <300 mg/d; OR, 2.2; 95% CI: 1.12–4.35), phenobarbital (≥150 vs <150 mg/d; OR, 3.2; 95% CI: 1.11–9.45), valproic acid (≥700 to <1,500 vs <700 mg/d; OR, 2.1; 95% CI: 1.25–3.43), valproic acid (≥1,500 vs <700 mg/d; OR, 5.8; 95% CI: 3.07–10.92).

The AED doses utilized in this study were specific to the time of conception. This study did not take into account any subsequent dosage changes, and thus this is not an analysis of dose or level of exposure throughout pregnancy or even the first trimester. These findings should not be extrapolated to maintaining the lowest daily doses studied throughout pregnancy (phenobarbital <150 mg, carbamazepine <400 mg, lamotrigine <300 mg, and valproic acid <700 mg). Drug clearance markedly increases for many AEDs during pregnancy, and dosage adjustments are necessary to avoid seizure worsening (9). This is especially true for AEDs that have markedly increased clearance during pregnancy such as lamotrigine (10). Uncontrolled seizures have been associated with fetal loss, fetal hypoxia, and even poor neurodevelopment (11). Women with active epilepsy need not only effective treatments but effective management of their AEDs during pregnancy to optimize maternal and fetal outcomes. Tomson et al. reported on the percentage of women that were seizure free throughout pregnancy, and similar ranges of 62 to 71 percent were seen for all AEDs. However, the authors correctly emphasize that this is not a direct comparison, as patient groups differed in seizure types and severity at baseline, thus dictating their specific AED type and dose entering pregnancy.

This analysis of outcomes by type of AED monotherapy and by dose of AED *at time of conception* offers important information for management of women with epilepsy during the entire span of childbearing years. Clinicians cannot wait until the diagnosis of pregnancy to determine the optimal lowest dose for the individual patient. Nor should they wait until the patient's decision to become pregnant as 50% of pregnancies are unplanned in women with epilepsy (12). However, if a patient does decide to stop an estrogen-containing contraceptive, this provides a window of opportunity to lower fetal risk by adjusting the AED dose downward if she is on an AED with a metabolic route that is induced by estrogens (for example, lamotrigine, valproic acid).

The general principle that teratogens act in a dose-dependent manner for MCMs likely holds true for other effects of in utero AED exposure such as brain development. The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study group reported that performance at 3 years old was negatively associated with maternal valproic acid dose for both verbal and nonverbal abilities and negatively associated with carbamazepine dose for verbal abilities (2). Future research should include other fetal outcomes such as neurodevelopment and intrauterine growth as well as maternal outcomes of seizure control and obstetric complications. Dose is only a surrogate marker of fetal exposure, especially with the variability that occurs with clearance alterations during pregnancy. Studies, ideally, would include serum concentrations of mother and newborn and key phenotype, pharmacodynamic, and pharmacogenetic factors, with the ultimate goal of a personalized profile that balances maternal health and fetal exposure risk throughout pregnancy.

In summary, this report from EURAP provides another important incremental advance in the management of women with epilepsy during the reproductive years; the clinician should not only consider AED type but also daily dose. Too complicated? Not really, as the message is so simple.

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