



EFFECTS OF IN UTERO ANTIEPILEPTIC DRUG EXPOSURE

Kimford J. Meador, MD

Department of Neurology, University of Florida, McKnight Brain Institute, Gainesville, Florida, USA

Recent studies demonstrate an increased teratogenic risk for valproate and a probable increased risk for phenobarbital. Carbamazepine and lamotrigine appear relatively safe; however, results are inconclusive concerning a specific risk for cleft lip/palate for both drugs as well as a dose-dependent effect for malformations associated with lamotrigine. Data regarding teratogenic risks for other antiepileptic drugs are inadequate. Additional studies are needed to delineate further the risks for all antiepileptic drugs and determine the underlying mechanisms.

Although the majority of children born to women with epilepsy are normal, they are at increased risk for malformations as well as for poor neuropsychological outcomes (1,2). Antiepileptic drugs (AEDs) have the potential to affect fetal development throughout pregnancy. In the United States alone, at least 45,000 children are exposed to AEDs during pregnancies of mothers with epilepsy (2). Given that less than half of AEDs are prescribed for epilepsy and that the majority are prescribed for psychiatric and pain indications, the total number of children exposed to this category of drugs is substantially higher. The risk of in utero exposure has to be measured against the risk of the underlying disease. For most women with epilepsy, the risks imposed by seizures affecting both the mother and child usually outweigh the risks of drug exposure. Women should not discontinue AEDs without discussion with their physicians, as trauma is the leading cause of nonobstetrical death in pregnant women with epilepsy (3). In a UK survey, the death rate during pregnancy for women with epilepsy was increased tenfold compared to the general population, primarily as a result of seizures

(4). Thus, understanding the magnitude and differential effects of AEDs on teratogenesis is important.

Anatomical Teratogenesis

AEDs had been used for a 100 years when the thalidomide tragedy in the mid-20th century raised concerns about the potential teratogenic effects of all drugs. Shortly thereafter, the first report of AED-induced birth defects was published (5). Within a decade, estimates were that AED exposure raised the risk of malformation two- to threefold (6). Subsequently, this risk has been confirmed in human and animal studies (7–9). The risk increases with higher AED dosages, higher AED serum levels, or polytherapy. For example, a recent study found major malformations in 4.5% of children exposed to AED monotherapy but in 8.6% of children exposed to AED polytherapy (10). This study also suggested that the risk of malformation is similar for children whose mothers did not have epilepsy yet took AEDs for other indications. The most common major malformations associated with AED exposure include cardiac (e.g., ventricular septal defect), orofacial (e.g., cleft lip with or without cleft palate), urological (e.g., hypospadias), skeletal (e.g., radial ray defects, phalangeal hypoplasia), and neural tube defects (e.g., spina bifida) (1,7). In addition to the risk of major malformations, in utero AED exposure may impact long-term intellectual development (2,9). Many questions remain unanswered; however, recently there has been an increase in information concerning the teratogenic effects of AEDs, which is due in large part to the establishment of multiple pregnancy registries.

The most striking new information arising from these registries is that valproate poses a greater risk for major congenital malformations compared with other AEDs. As outlined in Table 1, the Australian Pregnancy Registry (11), Finnish National Medical Birth Registry (12), International Lamotrigine Pregnancy Registry (13), Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study (14), North American Pregnancy Registry (15), Swedish Medical Birth Registry (16), and United Kingdom Pregnancy Registry (17) have all reported that valproate exposure is associated with an increased risk for malformations. Although a risk for spina bifida (~1.5%) has been known for years, the defects associated with valproate identified in these recent studies were seen across multiple body systems. In most of the registry studies, the adverse effects of valproate were dose dependent (see Table 2). A recent meta-analysis found that the risk of major malformations in children exposed to valproate was 10.73% (95% CIs: 8.16, 13.29), which is statistically higher than the risk associated with several other

Address correspondence to Kimford J. Meador, MD, Department of Neurology, University of Florida, McKnight Brain Institute (L3-100), 100 South Newell Drive, P.O. Box 100236, Gainesville, FL 32610-0236. E-mail: kimford.meador@neurology.ufl.edu

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TABLE 1. Rates for Major Congenital Malformations across Recent Studies

Australian Registry (Monotherapy)
Valproate = 16.8%, Carbamazepine = 3.8%,
Lamotrigine = 0%, Phenytoin = 5.9%
RR = 5.6 (2.42–12.92) for valproate vs other AEDs
Reference: Vajda et al. (11)

Finnish Birth Registry (Monotherapy)
Valproate = 10.7%; OR = 4.18 (2.31–7.57) vs controls
Carbamazepine = 3.5%
Reference: Artama et al. (12)

European Surveillance of Congenital Anomalies (EUROCAT) (Monotherapy)
No evidence of increased isolated orofacial clefts relative to other malformations for lamotrigine monotherapy.
Reference: Dolk et al. (22)

International Lamotrigine Registry (Polytherapy)
12.5% with valproate vs 2.7% no valproate
RR = 4.55 (1.63–12.69)
Reference: Cunnington et al. (13)

Neurodevelopmental Effects of Antiepileptic Drugs (NEAD Study) (Monotherapy: major malformations and fetal deaths)
Valproate = 20.3%, Carbamazepine = 8.2%,
Lamotrigine = 1.0%, Phenytoin = 10.7%
RR = 4.59 (2.07–10.18) for valproate vs other AEDs
Reference: Meador et al. (14)

North America Registry (Monotherapy)
Phenobarbital = 6.5%; RR = 2 (0.9–4.5) vs other AEDs
Valproate = 10.7%, OR = 4.0 (2.1–7.4) vs other AEDs
Other AEDs = 2.9%
General population = 1.62%
Lamotrigine 2.7% (cleft lip/palate 0.73%)
Carbamazepine 2.6% (cleft lip/palate 0.023%; neural tube 0.014%)
Reference: Wyszynski et al., Holmes et al., Holmes et al., Hernandez-Diaz et al. (15,19,22,23)

Swedish Birth Registry (Monotherapy)
Valproate = 9.7%, Carbamazepine = 4.0%
OR = 2.51 (1.43–4.86) for valproate vs carbamazepine
Reference: Wide et al. (16)

UK Registry (Monotherapy)
Valproate = 6.2%, Carbamazepine = 2.2%,
Lamotrigine = 3.2%
OR = 2.97 (1.65–5.35) for valproate vs carbamazepine
Reference: Morrow et al. (17)

AEDs or the risk for children in the general population (18) (see Table 3).

For some women, valproate may be the only AED that can control their seizures. Thus, a balance of the risks has to be considered on an individual patient basis. Valproate is especially effective for generalized epilepsies, but which women will respond only to valproate cannot be predicted. Similarly, which children will suffer valproate-induced teratogenesis can-

TABLE 2. Valproate Dose Effects across Recent Studies

Australia Registry
Significant
34.5% malformations >1,400 mg/day vs 5.5% at ≤1,400 mg/day
Reference: Vajda et al. (11)

Finish Birth Registry
Significant
23.8% for doses >1,500 mg/day vs 9.5% for doses ≤1,500 mg/day
Reference: Artama et al. (12)

Finish Cognition Study
Significant
Reduce VIQ 20 points >1,500 mg/day, 16.6 at 800–1,500 mg/day, 4.2 <800 mg/day
Reference: Gaily et al. (29)

Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study
Significant for both birth defects and 2 y/o cognitive outcomes
24.2% malformations for doses ≥900 mg/day vs 9.1% <900 mg/day
References: Meador et al. (14, 20)

North America Registry
Not significant
1033 mg/day (±434) with malformations vs 983 mg/day (±431) without
Reference: Wyszynski et al. (15)

UK Registry
Significant (reanalyzed by Cochran-Armitage Trend Test)
9.1% >1,000 mg/day, 6.1% 600–1,000 mg/day, 4.1% <600 mg/day
[UK Registry reported no significant effect of valproate but reanalyzed by Cochran-Armitage Trend Test is significant. UK Registry found significant dose effect for lamotrigine, but the International Lamotrigine Registry (see below) did not.]
Reference: Morrow et al. (17)

UK Cognition Study
Significant
Reduce VIQ 15 points >1,500 mg/day, 9.9 at 801–1,500 mg/day, 2.2 ≤800 mg/day
Reference: Adab et al. (4)

International Lamotrigine Registry and Swedish Birth Registry
Not analyzed for valproate dose effect.
References: Cunnington et al. (13); Wide et al. (16)

not be predicted; however, it is more likely to occur at higher doses (>~1,000 mg/day; see Table 2) and blood levels (>~40 mcg/mL) (19). Since there are numerous alternative effective AEDs, it would seem prudent to try others before prescribing valproate for women of childbearing potential.

The North American Registry also has reported an increased risk of malformations for phenobarbital (6.5%) (20).

TABLE 3. Monotherapy Results of a Recent Meta-Analysis

Monotherapy Treatment	Malformations	
	Number of Fetuses	Percent (95% Confidence Interval)
None (women without epilepsy)	108,084	3.27 (1.37–5.17)
Carbamazepine	4,411	4.62 (3.48–5.76)
Lamotrigine	1,337	2.91 (2.00–3.82)
Phenobarbital	945	4.91 (3.22–6.59)
Phenytoin	1,198	7.36 (3.60–11.11)
Valproate	2,097	10.73 (8.16–13.29)

Reference: Meador et al. (18)

Another study from the same registry found no increased risk of malformations overall for lamotrigine, but a specific increased risk for cleft lip/palate (0.73%) was noted (21). In contrast, the European Surveillance of Congenital Anomalies (EUROCAT) study found no evidence of increased isolated orofacial clefts relative to other malformations for lamotrigine (22). The UK Registry reported a dose-dependent effect for malformations overall with lamotrigine use, yet the pattern was not seen in the North American Registry or the International Lamotrigine Registry (13,17,21). It is now known that lamotrigine clearance increases during the second and third trimesters of pregnancy (which occurs with other AEDs, although to a lesser degree); regardless, it is unlikely that lamotrigine clearance would be a major factor in malformations, as they occur in the first trimester. A report from the North American Registry has cited an increased risk for cleft lip/palate (0.023%) and neural tube defect (0.014%) associated with carbamazepine (23). A preliminary study with levetiracetam did not show increased risk (24), and preliminary studies with topiramate have had conflicting results (25,26). However, the sample sizes in these studies are too small to permit confidence in the results (24–26).

Behavioral Teratogenesis

Animal studies have demonstrated that AEDs can produce cognitive deficits at dosages less than those required for anatomical teratogenesis (8). Several human studies also have raised concerns over AED behavioral teratogenesis (see Table 4). A retrospective Danish study examined two separate cohorts of adult men exposed to phenobarbital during their mothers' pregnancies; each cohort was administered a different cognitive measure. Regardless of the cognitive measure used, data indicated that in utero phenobarbital exposure was associated with reduced IQ (27). Retrospective studies from a center in the UK found that children exposed in utero to valproate had increased de-

TABLE 4. Cognitive Effects of In Utero Antiepileptic Drugs in Recent Studies

UK (2 retrospective cohorts)

Valproate vs other monotherapy or no AED

Special education: 30% of the valproate group vs 3–6% other groups

Valproate 6–16 years old group had reduced VIQ (10–14 points) vs other groups

Valproate <6 years old group had greater delay on Schedule of Growing Skills II

Reference: Adab et al. (4), Adab et al. (28)

Finland (prospective)

Valproate group had reduced VIQ (12 points) vs carbamazepine

Carbamazepine group did not differ from control group

Reference: Gaily et al. (29)

Neurodevelopmental Effects of Antiepileptic Drugs

(NEAD) Study: USA & UK (prospective preliminary results)

Valproate group was reduced 9–11 points vs carbamazepine, lamotrigine, or phenytoin on the Bayley Mental Development Scale at 2 years old.

Reference: Meador et al. (19)

Denmark (two retrospective cohorts tested with different measures)

Phenobarbital reduced VIQ scores (Wechsler Adult Intelligence Scale [Danish version] or Danish Military Draft Board Intelligence Test) by ~0.5 standard deviation or ~7 VIQ compared with general population.

Reference: Reinisch et al. (27)

VIQ = verbal intelligence quotient

velopmental delays among a cohort of children ≤ 6 years old, increased special education needs in a cohort of ≥ 6 year olds, and reduced verbal IQ in a cohort of children ≥ 6 years old (4,28). A prospective Finnish study demonstrated reduced verbal IQ for valproate but not for carbamazepine, although the monotherapy valproate sample was small (29). Preliminary results from the prospective NEAD Study in the USA and UK have demonstrated a dose-dependent (see Table 2) developmental delay in children exposed in utero to valproate (19).

Possible Mechanisms of AED Teratogenesis

Anatomical and behavioral teratogenesis likely differ in mechanisms since first trimester AED exposure poses the highest risk for anatomical malformations, while third trimester exposure appears to be associated with the highest risk for adverse behavioral effects (7,9). Various mechanisms have been proposed for the teratogenicity of AEDs, including folate-related actions, ischemia, neuronal suppression, reactive intermediates (e.g., free radicals), and AED-induced neuronal apoptosis (30). All of these mechanisms remain hypothetical. For example, there is

not any evidence that folate supplementation can reduce the risk of AED-induced malformations. In regard to anatomical teratogenesis, reactive intermediates may be the most likely candidate. These agents bind to DNA, proteins, and lipids, affecting cell development. Regarding behavioral teratogenesis, several AEDs (i.e., clonazepam, diazepam, phenobarbital, phenytoin, vigabatrin, and valproate) have been shown to induce widespread neuronal apoptosis in immature animal brains, in a manner similar to ethanol (31–33). Of note, valproate-induced apoptosis occurs at relatively lower therapeutic concentrations compared with other AEDs. Similar apoptotic effects were not seen for carbamazepine, levetiracetam, lamotrigine, or topiramate monotherapy, although all of these AEDs, except levetiracetam, are capable of enhancing phenytoin-induced apoptosis in polytherapy (34–37). Considerable variability exists in both anatomical and behavioral outcomes for individual children exposed in utero to a specific AED, even when similar dosages are employed during pregnancy. Teratogens interact with susceptible genotypes (7), which may explain the individual variance. Additional research is needed to demonstrate the risks for all AEDs, determine the underlying mechanisms, and delineate reasons for individual variance in outcomes.

Conclusions

Human studies of AED teratogenesis are not double-blind randomized trials; consequently, the most definitive findings are those that are replicated across numerous investigations. Over recent years, the combined results of multiple anatomical and behavioral studies of AED teratogenesis provide compelling evidence that valproate poses a special risk to the unborn child. The occurrences of various different malformations and of impaired cognitive function are increased by valproate in a dose-dependent manner. Although less data are available, phenobarbital also appears to pose a risk for both anatomical and behavioral impairments. The overall risks for carbamazepine and lamotrigine appear relatively low; but, as discussed, one registry reported a dose-dependent effect for lamotrigine, and another registry reported a specific risk of cleft lip/palate for both carbamazepine and lamotrigine. However, evidence from other registries is contradictory or completely absent, which leaves the validity of these observations in doubt. Information on other AEDs is inadequate. Although many questions remain unanswered, the recent increase in information is helpful to physicians and patients in making informed treatment decisions. Further studies are critical to delineating the risks for specific deficits associated with individual AEDs. An understanding the mechanisms underlying these defects may help explain the considerable individual variance in outcomes for children exposed to the same AED. More importantly, this knowledge could lead to preventative measures.

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