Seizure (2008) **17**, 166—171

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Teratogenic effects of antiepileptic drugs

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KEYWORDS
Teratogenic;
Epilepsy;
Antiepileptic drugs;
Malformations

Summary The use of older generation antiepileptic drugs (AEDs) during pregnancy is known to be associated with a two- to threefold increased risk of birth defects in the offspring and possible also other adverse outcomes in the exposed infant. Much less has been known about newer generation AEDs in this respect. Recent studies based on national registries as well as specific epilepsy and pregnancy registries are beginning to provide information on comparative teratogenic effects of different AEDs. Hence, the prevalence of birth defects appears to be higher with exposure to valproate compared with carbamazepine and possibly also in comparison with lamotrigine. Further studies based on larger cohorts are needed to compare AEDs at different dosages and to analyse the possible impact of confounding factors. Furthermore, data is insufficient to assess the human teratogenic potential of other newer generation AEDs than lamotrigine.

Retrospective and a few small prospective studies suggest that exposure to valproate also might be associated with a lower verbal IQ at school age, but further prospective studies are needed to draw firm conclusions.

Introduction

Numerous studies have attempted to assess the teratogenic effects of antiepileptic drugs (AEDs) since the first observations of an association between use of anticonvulsants and an increased risk of birth defects were published 40 years ago.[1] Despite differences in study design and populations, most have confirmed an increased risk of adverse pregnancy outcome with exposure to the older generation AEDs such as phenobarbital, phenytoin, carbamazepine and valproate. Potential adverse fetal effects of these drugs include intrauterine growth retardation, dysmorphisms, major congenital malformations and delay in postnatal cognitive development. Although it is evident that the vast majority of women with epilepsy who are on treatment with these AEDs during pregnancy give birth to perfectly normal children, these potential teratogenic effects are a major concern for all women with epilepsy that are of childbearing potential. Unlike many other medications, antiepileptic drug treatment generally cannot be withdrawn even when pregnancy is planned, since uncontrolled seizures may be harmful to the mother as well as the fetus. The risks associated with uncontrolled seizures thus have to be balanced against the teratogenic risks

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1059-1311/$ — see front matter
doi:10.1016/j.seizure.2007.11.016

imposed by the AEDs. The challenge is to identify the most appropriate AED for the individual patient, with respect to seizure control as well as developmental toxicity, and to use that drug in a way that controls seizures with minimised risks to the mother as well as the fetus.

The number of treatment options has increased substantially with the introduction of several newer AEDs the last 15 years. Furthermore, recent studies have provided new information on the teratogenic potential of the different older and newer generation AEDs thus facilitating more rational approaches to the management of women with epilepsy considering pregnancy. This paper will review such more recent data on teratogenic effects of AEDs with emphasis on major congenital malformations and postnatal cognitive development.

Methodological aspects

Several different methods have been used to assess the teratogenic effects of AEDs. For obvious reasons they all share the limitation of being observational studies rather than randomised trials. The selection of a particular AED, or the dosage, depends on individual factors such as type of epilepsy and seizures, seizure frequency, co-morbidity and socioeconomic circumstances, factors that could be linked to the risk of malformations. An association between a specific treatment and outcome can thus not automatically be interpreted as evidence of a causal relationship. The potential impact of confounding factors needs to be taken into account in the interpretation of the associations.

Reporting and recall bias are other important sources for misinterpretations when retrospective data are used. As an example, the spontaneous reporting of pregnancy outcome to manufacturers of AEDs are likely to suffer from selective reporting of adverse outcomes. Case-control designs may be useful for uncommon outcomes but is associated with the risk of recall bias. Existing registries of e.g., drug prescriptions and cross-linkage with registries of birth defects has been useful. Some such registries are nationwide and population-based. Unfortunately, they generally lack detail and information on other factors that could contribute to the outcome. Cohort studies are another common approach. Such studies can be retrospective or prospective. Retrospective identification of the cohort is associated with the risk of selection bias, whereas prospective studies ideally identify and enrol women with epilepsy before any information on pregnancy outcome is known, thus avoiding the risk of selection bias. A special type of cohort studies, antiepileptic drugs and pregnancy registries, has been established lately. These registries are prospective observational studies enrolling women with epilepsy early in pregnancy collecting information on drug exposure and other potential risk factors before outcome of the pregnancy is known. Outcome in terms of occurrence of birth defects in the offspring is recorded. These registries can collect high numbers of pregnancies, the type of drug exposure is ideally recorded in an unbiased way without prior knowledge of teratogenic outcome, and detailed data on other relevant patient characteristics could be obtained. The internal validity of the risk assessments is high but it is essential that the impact of possible confounders is included in the analyses. A potential problem with the pregnancy registries is the generalizability of the observations, which will depend on how pregnancies were enrolled.

Cohort studies of long-term postnatal outcome pose additional methodological challenges. In addition to the difficulties in keeping drop-out rates low the impact of environmental confounding factors will increase with the duration of follow-up.

It is thus important to pay attention to methodological issues such as statistical power, reliability of collected data, and attempts to control for appropriate confounding factors in the analyses, rather than to just compare rates of adverse pregnancy outcome in published studies.

Major malformations

Most studies report a two- to threefold increase in risk of major malformations among the offspring of women that are treated for epilepsy during pregnancy.[2–5] The pathogenesis is likely to be multifactorial, including genetic predisposition, socioeconomic circumstances, seizures and epilepsy, and it has long been debated whether maternal epilepsy *per se* is associated a greater risk of malformations in the offspring. However, a recent meta-analysis suggested that the malformation rate among offspring of women with untreated epilepsy was similar to that among non-epilepsy controls.[6] The available data thus strongly suggests that AEDs are the major cause for the increased risk of these adverse outcomes.

Polytherapy with AEDs has in general been associated with a higher malformation rate than monotherapy.[3,5,7–11] This has been a consistent finding throughout most studies. However, different AED combinations are likely to vary in their teratogenic potential. Some have been suggested to be associated with particularly high malformation rates,

e.g., the combination of carbamazepine, phenobarbital and valproate among older generation AEDs.[12] More recent studies have also indicated a considerable risk with valproate in combination with lamotrigine.[11,13] The International Lamotrigine Pregnancy Registry reported major malformations in 12.5% of children exposed to this specific combination compared with 2.9% in lamotrigine monotherapy.[13] Morrow et al. found birth defects among 9.6% of the offspring of mothers treated with valproate and lamotrigine combined, versus in 3.2% associated with lamotrigine monotherapy and 6.2% in monotherapy with valproate.[11] Although interesting, these observations need to be interpreted with great caution since factors such as differences in drug dosages and severity of the maternal epilepsy may contribute.

A dose–effect relationship of valproate teratogenicity has been reported in several studies. Dosages above 800–1000 mg/day have been associated with significantly higher malformation rates than lower dosages.[3,5,7,10,14] One recent study also reported a positive dose response for major congenital malformations with lamotrigine exposure. Doses above 200 mg/day were associated with higher risks.[11] This, however, was not confirmed in the manufacturer's own lamotrigine pregnancy registry.[15]

A major concern for women with epilepsy considering pregnancy, and for their physicians, is if AEDs differ with respect to fetal risks. Here data are less conclusive. However, the pattern of malformations varies. Heart defects seem to dominate among children exposed to barbiturates, and to some extent phenytoin and carbamazepine, whereas neural tube defects and hypospadia are more common among offspring of mothers taking valproate during pregnancy. The risk of neural tube defects in association with valproate has been estimated to 1–2% of exposed infants.[16] Valproate has also been associated with skeletal abnormalities.[17] An increased risk of neural tube defects of 0.5–1%, has also been reported after carbamazepine exposure.[18] Recently, lamotrigine has been reported to be associated with a significant increase in the risk of non-syndromic oral clefts.[19]

Although AEDs apparently vary in the spectrum of malformations that they are associated with, earlier studies have failed to demonstrate differences in the overall teratogenic potential between different AEDs. This may be explained by methodological shortcomings and in particular lack of statistical power due to insufficient numbers of pregnancies. Large studies with thousands of pregnancies are needed considering the number of treatment options that are available and the potential confounding factors that need to be taken into account. Population-based national registries have been utilized to analyse the risk of birth defects with different AEDs. The Swedish Medical Birth Registry recently published a report based on 1398 pregnancies with exposure to AEDs.[9] The risk for a severe malformation in the offspring was greater after exposure to valproate (n = 268) compared with carbamazepine monotherapy (n = 703), odds ratio (OR) 2.59 (95% CI: 1.43–4.68).[9] The Finnish drug prescription database and the National Medical Birth Registry were utilized to identify 1411 pregnancies with AED exposure.[10] The risk of malformations was higher in children exposed to valproate monotherapy (malformation rate 10.7%; OR = 4.18; 2.31–7.57) than of untreated patients. In contrast, the risk of malformations was not elevated in association with exposure to carbamazepine, oxcarbazepine, or phenytoin monotherapy.

However, realising that even larger studies are needed, epilepsy and pregnancy registries have been established in different regions of the world. These are prospective observational studies aiming to enrol large numbers of AED exposed pregnancies and providing outcomes assessment in terms of birth defects in the offspring. Using slightly different methodologies such registries have been established in North America, the UK, Australia, and Europe. The European registry (EURAP) has been enlarged to include also collaborators in Asia, Oceania, South America, and Australia.[20] EURAP has not yet released outcome data in relation to individual AEDs, whereas the other registries have published such information. Table 1 provides a summary of malformation rates in association with exposure to different AEDs in monotherapy from the pregnancy registries and other major studies in recent years. Malformation rates with carbamazepine exposure have ranged from 2.2 to 7.9%, with lamotrigine from 0 to 4.4%, phenobarbital from 2.9 to 10.4%, phenytoin from 0.7 to 9.1%, and with valproate from 5.7 to 16.8% (Table 1). The wide ranges in malformation rates reflect differences in study populations but probably most importantly differences in methodology. Methods for follow-up and recording of outcomes vary as well as the criteria for malformations. Prevalences of malformations with different AEDs should therefore not be compared across studies. The so far largest cohort with data on different AEDs is the report from the UK Register, which demonstrated a greater risk for malformations with valproate compared to carbamazepine.[11] However, even within-study comparisons should be interpreted with caution considering the possible effects of confounding factors.

The manufacturer GlaxoSmithKline has set up a separate registry for lamotrigine pregnancies.

Table 1 Malformation rates (%) with exposure to antiepileptic drugs in monotherapy in comparatively recent studies (*N* = offspring with malformations)

Study	Carbamazepine			Lamotrigine			Phenobarbital			Phenytoin			Valproate		
	Total outcomes	*N*	%	Total outcomes	*N*	%	Total outcomes	*N*	%	Total outcomes	*N*	%	Total outcomes	*N*	%
Artama[10]	805	22	2.7							38	1	2.6	263	28	10.6
Holmes[21]	58	3	5.2				64	3	4.7	87	3	3.4			
Holmes[22]							77	5	6.5						
Kaneko[5]	158	9	5.7				79	4	5.1	132	12	9.1	81	9	11.1
Morrow[11]	927	20	2.2	684	21	3.1				85	3	3.5	762	44	5.8
Samren[7]	280	22	7.9				48	5	10.4	141	9	6.4	184	16	8.7
Samren[3]	376	14	3.7				172	5	2.9	151	1	0.7	158	9	5.7
Vajda[14]	155	6	3.9	61	0	0.0				17	1	5.9	113	19	16.8
Wide[9]	703	28	4.0	90	4	4.4				103	7	6.8	268	26	9.7
Holmes[19]				564	15	2.7									
Hernandez-Diaz[24]	873	23	2.6												
Wyszynski[23]													149	16	10.7

Among 802 prospective monotherapy exposures, major birth defects occurred in 22 (2.7%; 1.8—4.2%),[15] but the registry lacks an internal comparison. With the exception of lamotrigine, information on the newer generation AEDs is particularly scarce. In one case-series, all of 35 pregnancies with oxcarbazepine monotherapy enrolled at any stage prior to birth had normal outcome, while 1 of 20 pregnancies with oxcarbazepine as combination therapy resulted in a cardiac malformation.[25] In the drug-prescription registry-based study from Finland, Artama et al reported one uro-genital malformation among 99 pregnancies with oxcarbazepine monotherapy.[10] Of 16 retrospectively or prospectively enrolled women taking gabapentin as monotherapy from onset of pregnancy, one resulted in an infant born with one kidney.[26] The UK Register has published separately on outcome in association with levetiracetam exposure.[27] Three of 117 infants of women treated with levetiracetam during pregnancy had major congenital malformations, 2.7% (95% CI: 0.9—7.7%). None was among the 39 exposed to levetiracetam in monotherapy. These studies are clearly too small to allow firm conclusions as to the teratogenic potential of levetiracetam, oxcarbazepine or gabapentin.

Postnatal cognitive development

The possibility that AED exposure during pregnancy may adversely affect postnatal development of the offspring has previously been assessed in several small-scale studies. In a Cochrane review, Adab concluded that the majority of these studies are of limited quality and that there is little evidence about which drugs carry more risks than others to the development of children exposed.[28] Since then, a few studies have been published indicating that exposure *in utero* to valproate might be associated with specific adverse cognitive effects in the child.[29—31] A retrospective study from the UK found significantly lower verbal IQ in 41 children exposed to valproate monotherapy than in un-exposed and in children exposed to carbamazepine (*n* = 52) or phenytoin (*n* = 21).[29] Multiple regression analysis identified exposure to valproate, five or more tonic—clonic seizures in pregnancy and low maternal IQ to be associated with lower verbal IQ also after adjustment for confounding factors. Valproate doses above 800 mg/day were associated with lower verbal IQ than lower doses. These important signals still have to be interpreted with some caution given the small numbers, the retrospective nature of the study and the fact that only 40% of eligible mothers agreed to participate.

A small prospective population-based study from Finland found a lower verbal IQ in children exposed *in utero* to valproate and to polytherapy in general compared with non-exposed children or children exposed to carbamazepine.[30] However, this study could not demonstrate an independent effect of valproate because of small numbers (13 children exposed to valproate monotherapy) and since the results were confounded by low maternal education and polytherapy. Another small prospective population-based Finnish study signals a similar trend for worse outcome in verbal IQ in children exposed to valproate.[31]

Although conclusive evidence is lacking, the signals concerning potential adverse effects on postnatal development of particularly valproate need to be considered seriously and adequately sized prospective studies are urgently needed.

Conclusions

Although the majority of women with epilepsy give birth to healthy children, there is a two- to three-fold increase in the risk of major congenital malformations in the offspring. This increase is mainly due to the teratogenic effects of AEDs. Recent studies suggest that the prevalence of birth defects might be higher with exposure to valproate compared with carbamazepine and possibly also in comparison with lamotrigine. Further studies based on larger cohorts are needed to compare AEDs at different dosages and to analyse the possible impact of confounding factors. Data is insufficient to assess the human teratogenic potential of other newer generation AEDs.

Important signals indicate that exposure to valproate *in utero* may be associated with a lower verbal IQ at school age, but further prospective studies are needed.

While the observations of potential differences between AEDs in teratogenic potential are relevant for treatment decisions, these must be weighed against possible differences in effectiveness against the seizure disorder. The overall aim of the treatment should be to use the AED that can control tonic–clonic seizures with minimised risks to the mother as well as the fetus.

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