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Major malformations in infants exposed to antiepileptic drugs *in utero*, with emphasis on carbamazepine and valproic acid: a nation-wide, population-based register study

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Aim: Antiepileptic drugs (AEDs) are known teratogens. Some specificity between different AEDs has been noted in the literature. The aim was to compare the teratogenic effect of valproic acid (VPA) and carbamazepine (CBZ) in monotherapy. *Methods:* Infants exposed to AEDs ($n = 1398$) in early pregnancy were identified from the Swedish Medical Birth Registry. The number of infants with congenital malformations and exposed to AED was compared with the expected number estimated from all infants born ($n = 582\,656$). *Results:* 90% (1256) of the AED exposed children were exposed to AEDs in monotherapy, 56% were exposed to CBZ and 21% to VPA. The odds ratio (OR) for having a malformation in the AED exposed group was 1.86 [95% confidence interval (95% CI) 1.42–2.44]. Exposure to VPA in monotherapy compared with CBZ in monotherapy gave OR = 2.51 (95% CI 1.43–4.68) for a neonatal diagnosis of malformations. However, there is no information available on the number of therapeutic abortions, or the different types of epilepsy or drug dosage in the two treatment groups.

Conclusion: There was a small increase in the risk of having a major malformation after exposure to AEDs in monotherapy. Exposure to VPA seems to carry a higher risk than exposure to CBZ.

Key words: *Antiepileptic drugs, folic acid, major congenital malformations, pregnancy, valproic acid*

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Maternal treatment with antiepileptic drugs (AEDs) during pregnancy is associated with an increased risk of major congenital malformations in the infants. Polytherapy seems to increase the risk more than monotherapy. A drug specificity has been noted for different types of malformation, e.g. valproic acid (VPA) and carbamazepine (CBZ) have been associated with an increased risk of spina bifida (1–4).

The aim of the study was to evaluate the teratogenic potential of the present AED use in Sweden by using information from the Swedish health registries. Special emphasis was placed on possible differences between the two major drugs, VPA and CBZ.

Material and methods

Since 1994, the Swedish Medical Birth Registry (5) has contained information on drug use reported by the pregnant women in early pregnancy. The Swedish personal identification number, which is unique to each person in Sweden, enables linkage between different registries.

Infants born from 1 July 1995 to 31 December 2001, whose mothers had reported the use of AEDs, were identified in the Medical Birth Registry and further analysed for the presence of congenital malformations

Information on congenital malformations was partly based on ICD (International Classification of Diseases) codes recorded in the Medical Birth Registry, and partly on information obtained by record linkage with the Swedish Register of Congenital Malformations (6) and information from the Hospital Discharge Registry (for hospitalizations up to and including 2000)

Malformation distribution and the total risk of any type of malformation are presented according to number of AEDs used. The risk estimates were based on Mantel–Haenszel estimates of odds ratios (OR), adjusting for year of birth, maternal age, parity and smoking in early pregnancy. A test-based method was used to estimate the 95% confidence interval (95% CI) of the OR.

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Table 1. Antiepileptic drugs to which infants had been exposed in monotherapy in early pregnancy.

		No. malformed	
Drug used	No. exposed	Total	"Severe"
Phenobarbital	7	1	1
Primidone	3	0	0
Phenytoin	103	11	7
Ethosuximide	8	0	0
Clonazepam	48	3	2
Carbamazepine	703	46	28
Oxcarbamazepine	4	0	0
Valproic acid	268	35	26
Vigabatrin	3	0	0
Lamotrigine	90	5	4
Topiramate	1	0	0
Gabapentin	18	0	0
Total	1256	101	68

Number of exposed infants are given and number of infants with a congenital malformation diagnosis, irrespective of source of malformation information. "Severe" malformations exclude the following conditions: preauricular tag, patent ductus arteriosus in preterm infant, congenital laryngeal stridor, undescended testicle, hip dislocation, pes calcaneovalgus, unspecified foot deformity, facial asymmetry and naevus.

To compare the malformation rate of infants exposed to AED with that of all infants in the population, only malformations identified in the Medical Birth Registry were used.

For comparisons within the group of AED-exposed infants, all malformation diagnoses irrespective of source were used. In the definition of "severe" malformations, the following conditions were excluded: preauricular tag, patent ductus arteriosus in preterm infant, congenital laryngeal stridor, undescended testicle, hip dislocation, pes calcaneovalgus, unspecified foot deformity, facial asymmetry and naevus.

Results

During the study period 582 656 infants were reported to the Swedish Medical Birth Registry and 1398 infants were exposed to AEDs. Monotherapy was present in 1256 infants, two drugs had been used in 130 infants, 11 infants were exposed to three AEDs, and 1 infant had been exposed to four AEDs. Table 1 lists the monotherapy exposures.

The OR for AED-exposed infants ($n = 1398$) to have a congenital malformation was 1.86 (95% CI 1.42–2.44), after adjustment for year of birth, maternal age, parity and smoking in early pregnancy. If exposed to AEDs in monotherapy ($n = 1256$), the OR was 1.61 (95% CI 1.18–2.19) and if exposed to AEDs in polytherapy ($n = 142$) it was 4.20 (95% CI 2.42–7.49). These two ORs differ significantly ($z = 3.0$, $p < 0.01$).

A total of 121 infants had a congenital malformation identified (8.7%), of whom 87 had a relatively severe malformation (6.2%).

In Table 1, the numbers of all malformations and of severe malformations are shown for each specific AED in monotherapy. The rates of severe malformations differed significantly ($p = 0.02$, Fisher's exact test), with a much higher rate after VPA than after the other drugs. The OR for a severe malformation after VPA compared with after CBZ was 2.59 (95% CI 1.43–4.68).

Table 2 compares the exposure rate for VPA, for CBZ, and for the other AEDs for some major groups of congenital malformations (polytherapy included). Three of four infants with spina bifida and 11 of 16 with hypospadias were exposed to VPA. Thus, among 310 infants exposed to VPA (42 of them in polytherapy), 1.0% had spina bifida and 3.5% had hypospadias; two infants had both malformations.

Discussion

The present study is based on a nation-wide medical birth registry. The incidence of epilepsy during pregnancy has been estimated to be 3–4 per 1000, which would mean that approximately 70% of all cases were identified. The majority of the missing cases are probably due to a lack of reporting or recording of AED use at the first antenatal visit. As the information on drug use is recorded before anything is known about

Table 2. Some major groups of congenital malformations, irrespective of the presence of other malformations, with antiepileptic drug (AED) exposure, including AEDs in polytherapy ($n = 1231$).

	VPA ($n = 310$)		CBZ ($n = 783$)		Other ($n = 396$)		Total
Malformation group	mono ($n = 268$)	poly ($n = 42$)	mono ($n = 703$)	poly ($n = 80$)	mono ($n = 285$)	poly ($n = 111$)	
Neural tube defect	2	1	1	1	0	0	4
Cardiac defect	7	5	7	1	3	6	24
Orofacial cleft	4	0	1	0	1	0	6
Hypospadias	7	4	3	1	2	3	16
Alimentary tract atresia	1	0	1	0	1	0	3
Diaphragmatic hernia	1	1	0	2	0	1	3
Carniosynostosis	1	1	1	1	1	0	4

VPA: valproic acid; CBZ: carbamazepine; mono: monotherapy; poly: polytherapy.

the outcome of the pregnancy, this will hardly affect the risk estimates.

The recording of congenital malformations was done by the examining paediatrician at the routine examination, and even though the information on maternal drug use was available at that time it is unlikely that maternal use of AEDs could have biased malformation recording, apart from in some mild cases. The use of multiple sources for malformation identification also reduced the risk of a bias in malformation recording.

Selectively aborted foetuses are not included because Swedish regulations prohibit data collection for pregnancies that do not end with a birth. This will affect estimates of total malformation rates and may slightly reduce risk estimates after AED exposure, if prenatal diagnosis is more thorough when the mother has used AEDs. It is not likely that this will affect a comparison between different AED regimens. It will mean, however, that malformations that are nearly always detected and aborted, e.g. anencephaly, cannot be studied.

It is difficult to compare the rates found here with rates published in the literature owing to different definitions of malformations and different methods of identifying the AED-treated mothers, and possibly different strategies for identifying and aborting malformed foetuses. However, the risk estimates on the total malformation rate in the newborn infants are of the same magnitude as reported in other recently performed studies (3, 7, 8).

This study verified the previously described higher congenital malformation risk after AEDs in polytherapy than in monotherapy. The degree of severity and nature of the epilepsy may, however, bias this result.

In this study there was a significantly higher malformation rate among infants exposed to VPA than in infants exposed to other AEDs and notably to CBZ, which was the most common drug in the data set. There is a well-known, specifically high risk of spina bifida (10–13) associated with VPA, but also of hypospadias (4, 12, 13). CBZ has also been associated with spina bifida (14, 15) and all four infants with this malformation were exposed to either VPA or CBZ, or both. The increase in risk for spina bifida is probably higher than seen from these figures because prenatal diagnosis followed by selective abortion is widely used in Sweden and is probably intensified after maternal exposure to VPA or CBZ. CBZ and VPA are partly used for different types of epilepsy; this does not necessarily mean that the epilepsies treated with VPA are more severe, but that different genetic factors may influence the malformation rates differently for the two drugs.

In conclusion, this study verifies the teratogenic effects of AEDs, with a higher risk with polytherapy than with monotherapy, and a significantly higher risk with VPA than with other AEDs and notably CBZ. The treatment of women of childbearing age with epilepsy must be carefully evaluated in each individual case with consideration to the type of epilepsy, the possible AEDs, and the dosages. This is especially important for VPA.

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