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Original Research Article

Fetal outcome following maternal treatment with antiepileptic drugs

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Abstract: To estimate the risk of congenital malformation with antiepileptic drugs exposure during pregnancy reported to the UK National Teratology Information Service (NTIS). Only limited local guidelines are available to clinicians as to which drugs are most appropriate for women of childbearing age. Using standardised procedures, NTIS, has provided prospective fetal risk assessment and collected outcome data in 184 women (115 monotherapy, 69 polytherapy) taking antiepileptic drugs (AEDs) throughout pregnancy. The results are in both groups, the majority of live born babies were normal (91.8% monotherapy, 85.7% polytherapy). The incidence of malformations was higher than expected; (8.1% monotherapy, 14.3% polytherapy vs 2-3% expected). The incidence of miscarriage (12.1% and 1.4% vs 10-20%) and elective terminations (14.7% and 8% vs 23%) was within the expected range. The wide range of congenital malformations was observed including cardiac malformations and facial clefts. There were no neural tube defects (NTDs) in either group. The majority of live born babies in these high risk groups were normal. The incidence of malformations in women treated with old and newer AEDs was higher than expected, with a higher incidence observed in the polytherapy group. A range of malformations was reported, but no NTDs were observed following valproate and carbamazepine exposures.

Keywords: antiepileptic drugs (AEDs), congenital malformation, monotherapy, polytherapy.

INTRODUCTION

Epilepsy is one of the most common neurological disorders (Shehata and Nelson –Piercy, 2001). In the past, women with epilepsy have been discouraged from marrying and having children because of the increased risk of congenital malformations, which is twice that of the general population [1, 2]. However, the great majority of women with epilepsy who become pregnant have normal pregnancies and 90% deliver healthy infants [3]. Nevertheless, exposure to antiepileptic drugs in the first trimester may put the offspring of epileptic mothers at an increased risk of a variety of congenital malformations (NICE, 2004) while later exposure may increase the risk of developmental delay and neonatal haemorrhage [4].

The most commonly used antiepileptic drugs are proven human teratogens. The frequency of congenital malformations in women with epilepsy in the absence of drug treatment is about 4%, higher than that for the general population which is 2-4%. This rate increases further still to 6-11% for women using an antiepileptic treatments [5] and further still to 23% for women taking four or more anti-epileptic drugs medications [6]. There is disagreement among experts about which of commonly prescribed antiepileptic drugs is the most suitable for use during pregnancy [7]. One recent opinion holds that the antiepileptic drug(s) most effective for the type of epilepsy and seizure control for individual women should be used [8]. To assess prospectively the risks of fetotoxic effects of maternal treatment with antiepileptic drugs during pregnancy. Also determine whether certain antiepileptic drugs or combination of drugs are associated with greater risk. And to compare risks between established and new antiepileptic drugs.

METHODS

The UK National Teratology Information Service (NTIS) collects prospective follow-up data on the outcomes of pregnancy reported where there has been exposure to antiepileptic drugs. This includes women with epilepsy and non-epileptic women who are taking antiepileptic drugs for other reasons, e.g. bipolar effective disorder, depression, mood disorders, pain relief etc., in which exposure occurred between January 1985 and May 2003. The present study used data collected by UK NTIS without identifiers and its use therefore did not require ethical approval.

For each patient the enquirer was asked to provide information on the type of drug exposure, the gestational age at time of enquiry, the mother's expected date of contacting the enquirer or mother's general practitioner after expected date of delivery. This was done by sending standardised data collection forms

seeking information on the mode of delivery, the baby's gender, gestational age at the time of birth, birth weight, Apgar score, length and OFC, the results of physical examination, including the presence and types of any congenital malformations. Details of treatments given drug doses and postnatal complications were also sought. If the outcome of pregnancy was spontaneous abortion, therapeutic abortion (most of which were for social reasons) or stillbirth, this was also noted.

For statistical analysis, first we estimated the incidence of malformation in the total group and for each drug. The calculation of risk did not include either spontaneous or therapeutic abortion due to a lack of data on necropsy results; only the number of live-born infants was used as the denominator. Standard statistical tests were applied to the data allowing calculation of risk. Results were presented with 95% confidence intervals.

RESULTS

Table 1 provide data on the outcomes of the 115 monotherapy exposed pregnancies in comparison with 69 polytherapy exposed pregnancies. There were no differences in stillbirth rate between the two groups. A higher rate of both elective termination and miscarriage was observed in the monotherapy exposed group when compared with polytherapy exposed group.

The mean length of gestational age was 38.2 weeks for the monotherapy exposed group and 39 weeks for the polytherapy exposed group. There is no difference in gestational age between each antiepileptic drug. The mean birth weight was 3252g for offspring exposed to monotherapy. Phenobarbitone monotherapy was associated with lowest values for weight and head size (mean weight 2740g, OFC 32.4cm). The mean weight for polytherapy exposed group was 3352g and OFC 35 cm. all women in both groups were exposed to antiepileptic drugs from the first trimester. The rate of congenital malformation was higher in the offspring of the polytherapy exposed group (14.3% versus 8.1% RR 1.77, 95% CI 0.84, 2.7 Table 1).

Table1: Outcomes of the monotherapy exposed pregnancies in comparison with polytherapy exposed pregnancies

Maternal exposures	Liveborn normal	Liveborn malformation	Spontaneous abortion	Elective termination	stillbirth
Monotherapy n = 115	79/86 91.8%	7/86 8.1%	13 11.1%	17 14.7%	1 0.9%
Polytherapy n= 69	54/63 85.7%	9/63 14.3%	1 1.4%	4 5.8%	1 1.4%

Amongst the 86 live birth (including two sets of twins) in offspring of monotherapy exposed women, there were 79 normal infants (91.8%), while 7 infants *8.1%, 95% CI 2,4%, 13.8%) had a variety of congenital malformations. Of the 79 live births without malformations, there were 55 normal babies (63.9%) and 24/86 infants who had neonatal complications (27.9%) Of 63 live born offspring of women exposed to polytherapy, there were 54 infants without and 9 infants (14.3%, 95% CI 9.9%-18.7%) with congenital malformations. Among the 54 live born infants without a malformation, there were 42 normal babies (66.7%) and 12 babies (19%) who experienced neonatal complications.

Table 2, 3 lists the congenital malformations in offspring from monotherapy and polytherapy exposed groups. We found a higher percentage of skeletal anomalies and congenital heart defects in mono-therapy group. In contrast there was a higher percentage of cleft lip and palate in the poly-therapy group. Three of nine malformed infants were exposed to 3 antiepileptic drugs and 6 were exposed to two antiepileptic drugs.

Table 2: The congenital malformations in offspring from monotherapy exposed groups.

DRUGS	LB	Cleft p&Lip	CHD	Skeletal malformation	Genitourinary	GIT	heart	Minor	Total
monotherapy									
carbamazepine	30	0	1	0	0	1	0	0	2
Sodium valproate	18	0	1	1	1	1	0	0	4
clobazam	1	0	0	1	0	0	0	0	1
Total		0	2	2	1	2	0	0	7

Table 3: The congenital malformations in offspring from polytherapy exposed groups.

DRUGS	LB	Cleft p&Lip	CHD	Skeletal malformation	Genitourinary	GIT	head	Minor	Total
polytherapy									
Carbamazepine+ Lamotrigine+ phenobarbitone	-	1	0	0	0	0	0	0	1
S. valproate+ Carbamazepine+ clonazepam	-	0	0	0	0	0	0	1	1
Carbamazepine+ Gabapentin+DZP	-	0	1	0	0	0	0	0	1
PHENYTOIN+ vigabatrin	-	0	0	0	1	0	0	0	1
Phenytoin+ gabapentin	-	1	0	0	0	0	0	0	1
S. valproate+ lamotrigine	-	0	1	1	0	0	0	0	2
Carbamazepine+ vigabatrine	-	0	0	0	0		1	0	1
Carbamazepine+ clonazepam	-	0	0	0	0	0	1	0	1
Total		2	2	1	1	0	2	1	9

DISCUSSION

We studied prospectively pregnancy outcome of 184 women treated with the antiepileptic drugs all women were exposed from the first trimester. We found that exposure to antiepileptic drugs prenatally was associated with increased risk of a variety of congenital anomalies (including minor types), particularly when exposure was to polytherapy (14.3%) compared with monotherapy (8.1%). Our results are consistent with previous reported rates of congenital malformations 7% and 15% in populations exposed to monotherapy and polytherapy respectively [9]. A recent study from the UK Epilepsy and Pregnancy Register (2003) reported malformation rates of 3.4% for monotherapy and 6.5% for polytherapy. The higher incidence of malformations in our study may relate to a higher chance of advice being sought from NTIS when the pregnancy is considered high risk, or because of less like hood of complete follow up data being received if the offspring is normal. It should be stressed that in the present study there is at least an 85.7% chance of having a normal baby with poly-therapy and 91.8% with mono-therapy.

We found no congenital malformations among the offspring of non-epileptic women receiving antiepileptic drugs for other conditions, although the numbers involved were very small. Whether malformations in the offspring of epileptic women are directly attributed to antiepileptic drug exposure in pregnancy, as several studies suggest [10] or due to the underlying genetic defects associated with epilepsy [11] or combination of both cannot be determined using our data. Several mechanisms have been postulated to explain the teratogenicity of antiepileptic drugs. Some antiepileptic drugs may be teratogenic because the generate free radicals (arene oxide) intermediates. Higher concentrations of oxide metabolites are associated with a greater risk of fetal malformations [12, 9] Folic acid deficiency is also a possible mechanism of teratogenicity for phenytoin, carbamazepine, phenobarbitone and sodium valproate [13].

Our data provides evidence suggesting a possible association between antiepileptic drugs and congenital heart defects, oral clefts and skeletal malformations (radial ray aplasia and polydactyly). Previous studies have found that the most common malformations in infants exposed to antiepileptic drugs during pregnancy were CHD, oral clefting, urogenital defects and neural tube defects [14, 5].

Neural tube defects were not observed in this study. It is possible that thus is due to either the increased pre-conception use of folic acid by women taking antiepileptic drugs [16] or prenatal diagnosis leading to elective termination of pregnancy. The overall frequency of therapeutic abortion among pregnant women receiving antiepileptic drugs was similar to non-exposed women (vs. 22-24%). Also, the incidence of spontaneous abortion (12.5% vs. 10-20%). This finding consists with previous study [17]. It is difficult to obtain reliable information about this from NTIS data because initial enquiries may not be made until a stage of pregnancy when the risk of abortion has already passed. In the present study, carbamazepine, lamotrigine, sodium valproate and gabapentin were the most widespread antiepileptic drugs used for treatment of epileptic women during pregnancy in the UK, either as monotherapy or as part of a polytherapy regimen.

The only drugs for which sufficient data was collected to draw any conclusions with respect to safety in pregnancy were carbamazepine, lamotrigine, sodium valproate. For all other drugs, fewer than 10 women were exposed to monotherapy.

Carbamazepine;

The incidence of malformation in our study was 2/30 (6.7%) live birth with Carbamazepine monotherapy, but higher in polytherapy regimens incorporating other antiepileptic drugs to be more teratogenic that Carbamazepine 5/36. 14%). Matalon *et al.;* in 2002 [18] also found combination therapy with other antiepileptic drugs to be more teratogenic than carbamazepine monotherapy. Oral clefts were the commonest congenital malformations occurring with either monotherapy or polytherapy with carbamazepine. One case of congenital cataract with polytherapy was found in our study. Sutcliffe *et al.;* in 1998 [19] have shown that there is an association between Carbamazepine exposure during pregnancy and an increased risk of congenital eye defects. However, this has not been confirmed by a more recent study [20].

Sodium valproate

In our Study sodium valproate was associated with 4 congenital malformations out of a total of 18 live births. This number is higher than would be expected for the unexposed population, although interpretation is limited by the small numbers involved. The malformations included 1 infant with skeletal abnormalities, one with abdominal well defect and 1 infant with CHD and 1 with an ovarian cyst. Sodium valproate polytherapy was also associated with a higher risk of malformations (3/13, 23%).

Canger and colleagues (1999) [21] have also found a higher prevalence of malformations among infants exposed to sodium valproate (10/77, 13%) than with other antiepileptic drugs in a prospective study. Malformations reported included CHD and digit anomalies (polydactylyl and radial ray aplasia). There was one female infant with bilateral ovarian cysts, a diaphragmatic hernia, and dysmorphism. Attention was also drawn to the increased risk of sodium valproate in a recently published (NICE, 2004).

Lamotrigine

In the current study, no congenital malformations were documented amongst 20 live births following exposure to lamotrigine monotherapy. The incidence of congenital malformation with lamotrigine polytherapy was (3/13, 25%). The 3 cases observed were of multiple congenital anomalies (CHD, oral clefts and diaphragmatic hernia). Previously, Sabers *et al.;* in 2004 [22] reported a malformation rate of 2 % in offspring exposed to lamotrigine in utero. An important finding was the higher incidence of major malformations in infants exposed to the combination of drugs lamotrigine plus sodium valproate (17%), compared with other polytherapy (8%) not including sodium valproate. This finding supports previous observations that a combination of sodium valproate and lamotrigine carries the highest rate of malformations [23].

Other antiepileptic drugs

An important finding was that only a small number of pregnant women were exposed to phenytoin or phenobarbitone. One explanation could be a change in prescribing patterns as result of the side effects of these agents e.g. gum hyperplasia with phenytoin [24] however, these drugs may also be avoided in women of childbearing age because of apparent fetal adverse effects.

There were two pregnancies exposed to phenytoin monotherapy. One resulted in a spontaneous abortion and the other in a preterm delivery of a set of twins. Following exposure to phenytoin as part of polytherapy, there 2/7 live births with a congenital malformation (29%). One infant had hypospadias and other had a cleft lip and palate. Dessens *et al.;* in 2001 [25] have reported an increased risk of genital tract malformations in the offspring of mothers exposed to phenytoin. There was also one stillbirth 38 weeks of gestation with polytherapy that included phenytoin.

CONCLUSION

The majority of live born babies in these high-risk groups were normal. The incidence of malformations in women treated with established and new antiepileptic drugs was higher than would be exposed in general population. The highest incidence of malformations with antiepileptic drug polytherapy, in particular with the combinations of sodium valproate with lamotrigine and carbamazepine and lamotrigine or vigabatrin polytherapy.

For monotherapy with antiepileptic drugs, the data suggests that sodium valproate carries the highest risk, there is an intermediate risk with carbamazepine and lamotrigine appears relatively safe. However patient numbers are small and some caution is needed in drawing conclusions. Our data is consistent with the findings of the UK National Institute for Clinical Excellence (2004). Malformations can be prevented by improvements in drug regimen, and avoiding by polytherapy wherever possible. Sodium valproate monotherapy should only be used in women of childbearing age when there is no satisfactory alternative. The benefits of therapy must be weighed very carefully against the risks. Although the numbers in this series are small, the incidence and types of malformation are similar to those reported from larger studies worldwide, although no neural tube defects were observed following valproate or carbamazepine in the current study.

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