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Review

Is carbamazepine a human teratogen?

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ABSTRACT

The foetal outcomes of 2,635 pregnancies recorded in the Australian Pregnancy Register were studied. In at least the initial 4 months of 515 pregnancies, there had been no intrauterine exposure to antiepileptic drugs, though the women involved in 264 of these pregnancies took antiepileptic drugs in later pregnancies. Compared with these 515 drug-unexposed pregnancies, foetal malformations risks were increased more than five-fold in association with valproate monotherapy, and more than doubled in association with carbamazepine monotherapy ($p < 0.05$). There were no statistically significant increases in malformation rates associated with other more commonly used antiepileptic drugs, while the malformation risk in relation to levetiracetam exposure was lower than that in the drug-unexposed pregnancies. The published literature has rather consistently shown raised malformation rates associated with carbamazepine monotherapy, though only once was it statistically significant. There now appears to be enough evidence to make it likely that carbamazepine possesses some teratogenic capacity. This makes it unwise to employ the malformation rate associated with carbamazepine monotherapy as a comparator when assessing the foetal hazards from exposure to newer antiepileptic drugs. Levetiracetam may prove a better comparator if adequate untreated control material is unobtainable.

1. Introduction

The hazard of potential foetal malformation associated with intrauterine antiepileptic drug (AED) exposure continues to concern women both when they are considering becoming pregnant and while pregnant, and also troubles those responsible for their medical care. A significant amount of relevant information is already available and it has become generally accepted that valproate is a dose related teratogen. There are also published data suggesting that exposure to other AED, for instance phenobarbitone, topiramate and carbamazepine, could be responsible for foetal malformations but the evidence is not yet persuasive [1]. However any teratogenic hazard for which these drugs are responsible appears to be less than that associated with valproate exposure. The situation in relation to carbamazepine is especially important as it remains more widely used than its fellows in managing epilepsy in pregnant women. Also, carbamazepine is usually employed as the standard against which the antiepileptic efficacy of newer AED in focal epilepsies is assessed. It therefore is of some importance to determine whether or not enough evidence is available to settle the issue of carbamazepine's teratogenic hazard. This matter has been examined in the data collected in the Australian Pregnancy Register, as described below.

2. Materials and methods

The nature of the data source, the Australian Pregnancy Register, and its method of information collection and storage have been described in previous publications [2,3]. The Register, which began collecting data in 1999, is estimated to capture some 8% to 9% of all Australian pregnancies in women with epilepsy [4]. In essence, the Register depends on pregnant women, the great majority of whom have epilepsy and take AED, making contact with it after becoming aware of its existence. All further contact between the women and the Register is by telephone, with interviews on four occasions – at recruitment as early in pregnancy as feasible, at 7 months of gestation, during the post-partum month and, whenever possible, 1 year after childbirth. At each interview, information concerning the foetus, details of the woman's epilepsy, the occurrence and type of any epileptic seizures and the AED being taken and their dosages, are recorded. In addition, at the initial interview, details are obtained for all previous pregnancies that have occurred in the woman concerned, the AED taken in each (though not their dosages), and the pregnancy and foetal outcomes. The present paper is based on data from women in the

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Table 1
Malformation rates associated with those individual antiepileptic drugs taken in at least 40 pregnancies, and with no antiepileptic drugs, and calculated malformation risks relative to that associated with no drug exposure, in both the prospective pregnancies and the combined prospective and retrospective pregnancies

	Prospective			Prospective and retrospective		
	Pregnancies	Malf%	RR (95% CI)	Pregnancies	Malf%	RR (95% CI)
No AED	183	2.19		515	2.72	
CBZ	394	5.08	2.32 (0.81–6.70)	528	6.25	2.30 (1.25–4.25)
VPA	272	13.60	6.22 (2.26–17.2)	370	14.32	5.27 (2.97–9.35)
LTG	356	3.65	1.67 (0.55–5.05)	392	4.59	1.69 (0.85–3.35)
LEV	106	1.89	0.86 (0.16–4.63)	121	1.65	0.61 (0.14–2.64)
TPM	51	1.96	0.90 (0.10–7.85)	57	3.51	1.29 (0.30–5.54)
PHT	44	2.27	1.04 (0.12–9.07)	66	6.06	2.23 (0.76–6.57)

AED = antiepileptic drug, CBZ = carbamazepine, CI = confidence interval, LEV = levetiracetam, LTG = lamotrigine, Malf = malformation, PHT = phenobarbitone, RR = relative risk, TPM = topiramate, VPA = valproate.

Register who had, or by the time of subsequent pregnancies had developed, known epileptic seizure disorders.

Ethical oversight of the Register has been the responsibility, successively, of the Ethics Research Committees of St. Vincent's Hospital, Melbourne, the Monash Medical Centre, and (at present) the Royal Melbourne Hospital, the Register's site of housing having changed with the passing of time.

Because of the availability in the Register of data from previous pregnancies, the material available for assessment has comprised both prospective and retrospective pregnancies. If a given woman had a second pregnancy included in the Register, the former prospective one should have become a retrospective one once the later pregnancy was entered. However, this newly retrospective pregnancy continued to be regarded as a prospective one for the purposes of the present study. This study considered only the outcomes of pregnancies where the presence or absence of foetal malformation had been determined, so that, for instance, pregnancies ending in spontaneous abortions, abortions carried out for maternal rather than foetal reasons, and stillbirths, were excluded from consideration. Results are expressed in relation to numbers of pregnancies, not numbers of offspring of the pregnancies. The classification of foetal malformation employed was that of Riley and Halliday [5].

Data for individual pregnancies were transferred from a Microsoft Access database to an Excel spreadsheet (Microsoft, Redmond, WA, USA), and there related to individual women's names by linking separate databases so that the same pregnancy was not included in both the prospective and retrospective groups. Confidence interval (CI) analysis methods and logistic regression were used in assessing the outcomes.

3. Results

The study involved 2,638 pregnancies in 1,521 women, 1,895 of the pregnancies being prospective and 743 retrospective (the latter in 374 women). As mentioned above, AED dosage data were available only for the prospective pregnancies. Some 264 of the 515 pregnancies that were not associated with AED exposure in at least the initial 4 months of pregnancy had occurred in 158 women who took AED during their subsequent pregnancies.

Table 1 shows the rates of occurrence of foetal malformations of any kind associated with no AED therapy, and with exposure to the individual AED used in monotherapy for both the prospective pregnancies and for all pregnancies. Valproate monotherapy was associated with a five or six-fold risk of foetal malformation relative to that in pregnancy not exposed to AED. The risk associated with carbamazepine monotherapy was a little over two-fold increased, and was statistically significant in relation to the combined prospective and retrospective pregnancies. The higher malformation rate associated with carbamazepine monotherapy in the prospective pregnancies, relative to that in all the pregnancies not exposed to AED was almost statistically significant (relative risk = 1.87: 95% CI 0.96–3.65). There were no other statistically significant differences in relative risks for other AED taken as monotherapy. However, it was noticeable that the relative risk associated with lamotrigine exposure appeared to be higher, and that associated with levetiracetam exposure lower, than the risk in AED unexposed pregnancy. Multiple different malformations sometimes occurred in the one malformed foetus, and a wide range of different types of malformations occurred in the population studied, but no single malformation was present frequently enough to warrant its individual further study.

Logistic regression analysis of the effect of drug dosage on malformation risk for the prospective pregnancies (no dosage data being available for the retrospective ones) showed statistically significant positive effects for valproate dosage ($p < 0.0001$) and topiramate dosage ($p < 0.007$), but not for carbamazepine dosage ($p = 0.201$). The mean carbamazepine monotherapy dose in malformation associated pregnancy was 730 ± standard deviation (SD) 357.3 mg/day, and in pregnancy without malformation 638.4 ± SD 492.3 mg/day, the difference of 91.6 mg/day not being statistically significant (95% CI −128 to 311 mg/day). Assuming that the non-statistically significant logistical regression for malformation risk on carbamazepine dose was representative of the true situation, increasing the carbamazepine dose from 200 mg a day to 1600 mg a day would have increased the average malformation risk by 2.4%.

4. Discussion

The present analysis has produced evidence, some of it statistically significant, that carbamazepine when employed in AED monotherapy has some teratogenetic capacity. To our knowledge only one of a number of previously published individual studies of the use of the drug in monotherapy during pregnancy, that of Samren et al. [6], has produced similar statistically significant evidence, though all but one of these studies, that of Morrow et al. [7], found increased relative risk or odds ratio values for the use of the drug when compared with variously collected populations of pregnancies in which the drug had not been in use (Table 2). However, several meta-analyses based on some of these individual studies, together with other published data, have shown that the drug had a statistically significant teratogenetic capacity. These meta-analyses have involved substantially larger comparator groups than the individual studies, as well as larger AED unexposed comparator groups, and therefore were better powered to demonstrate differences. However combining the individual studies into meta-analyses involves limitations, most notably that in various studies different criteria were used to determine the existence of malformations; malformation rates were expressed in relation to