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Is lamotrigine a significant human teratogen? Observations from the Australian Pregnancy Register

F.J.E. Vajda [a,*], J.E. Graham [a], A.A. Hitchcock [a], T.J. O'Brien [a], C.M. Lander [b], M.J. Eadie [b]

[a] Department of Medicine and Neurology, Royal Melbourne Hospital and University of Melbourne, Parkville, Victoria 3050, Australia
[b] Royal Brisbane and Women's Hospital and University of Queensland, Brisbane, Queensland 4027, Australia

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ABSTRACT

Lamotrigine (LTG) is increasingly being prescribed in pregnancy for women with epilepsy in place of valproate (VPA), because of the teratogenic risks associated with the latter. It is therefore important to know the teratogenic hazard associated with LTG, relative to VPA and to other commonly used antiepileptic drugs (AEDs). Data from the Australian Register of Antiepileptic Drugs in Pregnancy was examined to determine the incidence of teratogenicity determined 1 year from completion of pregnancy in women who took AEDs in monotherapy during pregnancy. Compared with a 3.4% malformation incidence in women who took no AEDs ($N = 118$), the incidences for LTG ($N = 243$), carbamazepine (CBZ) ($N = 302$) and VPA ($N = 224$) were, respectively, 4.9%, 5.3% and 15.2%, the latter statistically significantly greater than the risk for no AED therapy in pregnant women with epilepsy. Logistic regression analysis showed no tendency for foetal hazard to increase with increasing LTG dose in pregnancy, unlike the situation for VPA. However, seizure control in pregnancy tended to be not as good in the women taking LTG compared with those taking VPA, though the data examined were not adequate to permit definite conclusions regarding this matter. We conclude that LTG monotherapy in pregnancy is safer than valproate monotherapy from the point of view of foetal malformations, and no more hazardous in this regard than therapy with other commonly used AEDs.

1. Introduction

Although several antiepileptic drugs (AEDs) are more or less equally effective in preventing the seizures of the partial epilepsies, valproate (VPA) is widely accepted as the most effective therapy for achieving seizure control in the primary generalised epilepsies. The increasing evidence that valproate is an important human teratogen[1–4] has therefore produced a considerable dilemma for the management of women with primary generalised epilepsy who wish to become pregnant, or are already in early pregnancy. There is now some evidence that, on a milligram (mg) for mg dosage basis, VPA may be less teratogenic when combined with other AEDs.[5] In patients in whom it is decided to replace valproate with another AED, whenever feasible before pregnancy commences, at the present time lamotrigine (LTG) often seems to be the drug chosen. However, this choice raises two questions, viz. (i) to what extent is LTG itself a teratogen and (ii) how effective is LTG in controlling maternal seizures during pregnancy. In the present paper data from the Australian Pregnancy Register of Antiepileptic Drugs have been examined with the aim of answering these questions.

2. Materials and methods

The Australian Pregnancy Register of Antiepileptic Drugs was established in 1999 to collect information concerning pregnant women with epilepsy, whether treated with AEDs or not, and also in pregnant women with disorders other than epilepsy who are treated with AEDs. Recruitment is nationwide and entirely voluntary, potentially eligible women becoming aware of the Register by various means, though most often by their treating medical practitioners, nurses or allied health professionals, or by other pregnant women. All contact with the Register is by telephone. Relevant details are obtained from pregnant women on recruitment (as far as possible in the first or second trimester), at 7 months of pregnancy, within the first post-natal month and at the end of the first post-natal year and are entered into a database. Treating medical practitioners are contacted to confirm details. The foetal malformation classification used is that of the Birth Defects Registry of Victoria.[6] The Register database was housed initially at St. Vincent's Hospital, Melbourne, then at Monash University, Melbourne, and is currently at the Royal Melbourne Hospital. The

* Corresponding author. Tel.: +61 398193056; fax: +61 398193056.
E-mail address: vajda@netspace.net.au (F.J.E. Vajda).

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Table 1
Incidences of pregnancy with foetal malformation associated with exposure to monotherapy with each of the more commonly used AEDs. The malformation rates at 1 year are calculated relative to the number of pregnancies present at the end of the first post-natal month, not the first post-natal year.

Drug	*N*	Malformation (by 1 month)	%	Malformation (by 1 year)	%	Odds ratio: by 1 year data *versus* no AED	95% C.I.
No AED	118	4	3.4	4	3.4		
CBZ	302	8	2.7	16	5.3	1.59	0.52, 4.97
LTG	243	7	2.9	12	4.9	1.48	0.47, 4.69
VPA	224	30	13.4	34	15.2	4.99	1.73, 14.44*
PHT	34	1	2.9	1	2.9		
LEV	33	0	0	0	0		
TPM	34	1	2.9	1	2.9		
CZP	24	0	0	0	0		
GPT	14	0	0	0	0		
OxCBZ	8	0	0	0	0		

PHT: phenytoin; LEV: levetriacetam; TPM: topiramate; CZP: clonazepam; GPT: gabapentin; OxCBZ: oxcarbazepine.
* $P < 0.05$.

Register has been consecutively under the ethical oversight of the Research Ethics Committees of the above institutions.

All pregnancies in the Register that had gone to term live, or had been terminated because of detected foetal abnormality, were initially included in the analysis. Spontaneous abortions, stillbirths and intrauterine deaths were excluded. Data relating to pregnancies in which more than one AED was taken simultaneously during the first trimester of pregnancy were then excluded from further consideration, because of the uncertainty in assigning roles in the production of malformations and in achieving seizure control when more than one active substance was involved.

All results were expressed in terms of pregnancies, not of offspring, and a pregnancy involving one malformed twin was regarded as a pregnancy with a malformation. The presence of foetal malformations was determined on the basis of the information available at the end of the first post-natal month and of the first post-natal year, though some women included in the analysis were lost to follow up by the end of the first year, and others had not reached that stage at the time of data analysis. The presence or absence of seizure control in the pre-pregnancy year and during pregnancy was noted at each times of interview, but a more detailed study of seizure behaviour was not carried out because not all women involved in the study keep daily seizure diaries, and also had not kept them for their pre-pregnancy years.

The relationship between AED dosage and malformation risk was assessed by means of logistic regression analysis. Statistical significances of differences were assessed using confidence interval analysis.

3. Results

3.1. Pregnancies with malformations—incidence

There were 1052 pregnancies exposed to AED monotherapy and 118 pregnancies in women who had not taken AEDs in at least the first trimester of their pregnancies. Table 1 sets out the risk of malformation associated with monotherapy with the more commonly prescribed AEDs, and with epilepsy unexposed to any AED. The risks at the end of 1 year post-natally are likely to be underestimates, because the rate has been expressed without allowance for pregnancies untraceable by this stage and pregnancies which had not reached the 12-month time-point. The risk of malformation occurring in pregnancies exposed to VPA was significantly greater than the risk when any other AED had been used in monotherapy in pregnancy. However the odds ratios for the risks associated with exposure to the other commonly used AEDs (CBZ and LTG) were also greater than 1.0, though not significantly so. The numbers associated with the other AEDs were too small for useful analysis.

3.2. Pregnancies with malformations—dose-related risk

If an AED is a teratogen, it might be anticipated that the risk of foetal malformation in pregnancy would increase in relation to increasing dosage exposure to that AED. Accordingly, logistic regressions for the risk of pregnancy with malformation on AED dose were calculated for the 3 AEDs commonly used in monotherapy. The logistic regression equations were:

- LTG: logit risk = −2.698683 − 0.000962 dose; *P* intercept = <.0001, *P* slope = .638
- CBZ: logit risk = −3.535977 + 0.001017 dose; *P* intercept = <.0001, *P* slope = .1644
- VPA: logit risk = −3.031384 + 0.001193 dose; *P* intercept = <.0001, *P* slope = .0001

The only statistically significant regression was that for VPA, though the regression for CBZ did show a tendency for the risk to increase with increasing dosage. The risk for LTG tended to diminish slightly as dose increased, but this did not approach significance. To enable the risks relative to dosage to be compared visually, on a common dosage basis, Fig. 1 has been drawn to show the logistic regressions for risk on dose for the 3 main AEDs after drug dosage was converted to a multiple of the WHO defined daily doses for each drug (LTG 300 mg, CBZ 1000 mg, and VPA 1500 mg).

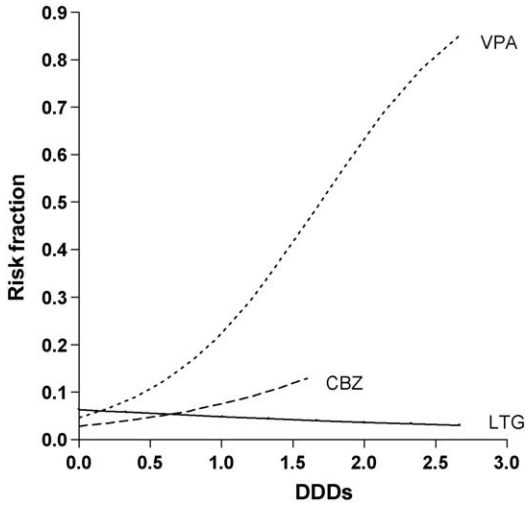

Fig. 1. Logistic regressions for the fraction of pregnancies associated with foetal malformation relative to drug doses for LTG, CBZ, and VPA, with doses of these drugs being expressed as multiples of their WHO defined daily doses (DDDs).

Table 2
Showing the rates of occurrence of seizures during pregnancy for LTG and VPA monotherapy in those free from seizures, and those experiencing seizures, in the pre-pregnancy year. Results are shown for all women with epilepsy and, separately, for those with primary generalised and with partial epilepsies.

Drug	Seizures in year before pregnancy	*N*=	Seizures in pregnancy	%	Difference %	95% C.I. %
All epilepsy						
LTG	Free	134	36	26.9	10.8	1.4, 20.2*
VPA	Free	162	26	16.0		
LTG	Present	116	93	80.1	20.8	6.75, 34.8*
VPA	Present	64	38	59.4		
Primary generalised						
LTG	Free	61	16	26.2	9.56	−3.18, 22.3
VPA	Free	132	22	16.7		
LTG	Present	42	28	66.7	3.88	−16.4, 24.2
VPA	Present	43	27	62.8		
Partial						
LTG	Free	67	20	29.9	10.8	−9.25, 30.9
VPA	Free	21	4	19.0		
LTG	Present	69	60	87.0	22.3	−1.82, 46.3
VPA	Present	17	11	64.7		

* $P < 0.05$.

3.3. Seizure control

In relation to seizure control, the clinical issue is whether LTG monotherapy can achieve as good seizure control in pregnancy as that produced by VPA, particularly in managing the primary generalised epilepsies. Table 2 compares seizure control in the pre-pregnancy year with control during pregnancy for LTG and VPA, each used in monotherapy, in all women with epilepsy and, separately, in those with diagnosed primary generalised and partial epilepsies.

In all comparisons, seizure control relative to the pre-pregnancy situation were better with VPA than with LTG, but the differences were significant only for all types of epilepsy taken together, and not for the partial or the primary generalised epilepsy subpopulations alone. Interestingly, 71.7% of those on VPA had at least 1 year's seizure control before pregnancy began, compared with 53.6% for LTG. Not unexpectedly, those women with seizures in the pre-pregnancy year were more likely to continue to experience seizures during pregnancy. The overall 36% incidence of uncontrolled epilepsy in the pre-pregnancy year raises unanswerable questions regarding the adequacy of treatment provided, and of patient compliance.

4. Discussion

The present analysis has shown no statistically significant difference between the risk of foetal malformation and exposure to LTG monotherapy in pregnancy, and that which applied when pregnant women with epilepsy took no AEDs. This finding is consistent with the findings of other studies which have also shown no enhanced hazard for malformations in relation to the use of LTG in pregnancy[3,7] though Morrow et al.[3] did find a higher mean LTG dose taken in pregnancies associated with foetal malformation. The present study, employing logistic regression analysis, has shown no evidence of an increased malformation risk as LTG dose in pregnancy increases. It therefore seems that, at least from the foetal point of view, LTG monotherapy in pregnancy is probably distinctly safer than VPA monotherapy, and no less safe than CBZ monotherapy.

Unfortunately, the present study does not definitely answer the question of whether LTG monotherapy is as satisfactory as VPA monotherapy in controlling seizures during pregnancy. The data of Table 2 suggest that it is not, in keeping with the conclusion of Mazurkiewicz-Bledzinska et al.[8]. However, the data available to the present study have rather substantial limitations. No standardised seizure diaries were kept by the women studied, either before or during pregnancy. Therefore information concerning the occurrence of seizures was retrospectively acquired and highly dependent on the accuracy of the women's recall. Given that 36% of the women in their pre-pregnancy year had seizures that were not controlled by AED monotherapy, and yet did not receive AED polytherapy, one must wonder how adequate had been their management. One might also wonder whether the same inadequacy of management may have continued in pregnancy and, in particular, whether the considerably increased clearance of LTG in this situation[9,10] had been taken into account in determining drug dosages. There the allocation of drugs to the pregnant women was not random, and there was no matching of the patients or their epilepsies. Consequently it may be unwise to draw firm conclusions about comparative drug efficacy from the seizure data from this analysis in the present study. Nonetheless, the impression remains that women who want to avoid the foetal hazards of VPA monotherapy by taking LTG may trade an increased risk of seizures during pregnancy, with the social and psychological consequences that may entail, for a greater margin of safety for their babies.

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