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Withdrawal of valproic acid treatment during pregnancy and seizure outcome: Observations from EURAP

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Supplementary Appendix 1 EURAP Coinvestigators
Supplementary Appendix 2 EURAP Contributors

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Summary

Based on data from the EURAP observational international antiepileptic drugs (AEDs) and pregnancy registry, we assessed changes in seizure control and subsequent AED changes in women who underwent attempts to withdraw valproic acid (VPA) during the first trimester of pregnancy. Applying Bayesian statistics, we compared seizure control in pregnancies where VPA was withdrawn (withdrawal group, n=93), switched to another AED (switch group, n=38), or maintained (maintained-therapy group, n=1,588) during the first trimester. The probability of primarily or secondarily generalized tonic-clonic seizures (GTCS) was lower in the maintained-therapy group compared with the other two groups both in the first trimester and for the entire duration of pregnancy. GTCS were twice as common during pregnancy in the withdrawal (33%) and switch groups (29%) compared with the maintained-treatment group (16%). Limitations in the data and study design do not allow to establish a cause-effect relationship between treatment changes and seizure outcome, but these observations provide a signal that withdrawal of, or switch from, VPA during the first trimester could lead to loss of seizure control, and highlight the need for a specifically designed prospective observational study.

Key words: Valproic acid, Pregnancy, Epilepsy, Seizures

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Introduction

The risks to the fetus of maternal use of valproic acid (VPA) during pregnancy is well documented and include increased frequency of major congenital malformations[1], impaired cognitive development of the pre-natally exposed child,[2-4] and possibly also increased risk of autism spectrum disorders[5,6]. These observations have led to a consensus that, whenever possible, VPA should be avoided in women with epilepsy of childbearing potential[7]. It is also generally recommended that any treatment changes for women on VPA should ideally be completed and assessed before conception[7]. However, the strengthened warnings for the use of VPA in girls and women recently issued by the European Medicines Agency[8] could prompt physicians to consider withdrawal of, or switch from, VPA during the course of pregnancy. This strategy has been questioned because potential benefits in terms of reduced teratogenic effects are uncertain, whereas the risk of loss of seizure control can be significant[7]. Recent studies have highlighted the maternal risks associated with epilepsy during pregnancy, which can include epilepsy-related mortality[9,10]. In this context, the lack of data on outcomes of pregnancies where VPA treatment has been withdrawn during pregnancy is highly unsatisfactory. In the present report, data from the observational international antiepileptic drugs (AEDs) and pregnancy registry, EURAP, were analyzed to assess changes in seizure control and subsequent AED changes in women who underwent attempts to withdraw VPA during the first trimester of pregnancy, the period during which concerns about teratogenic risks are greatest.

Methods

Inclusion criteria and study procedures

EURAP is an observational study set up in 1999 which relies on the collaboration of investigators from more than 40 countries from Europe, Asia, Australia, and Latin-America (see Supplementary Appendix 1 and 2)[11]. To be eligible for prospective assessment, women

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taking AEDs at the time of conception need to be enrolled before gestation week 16 and before foetal outcome is known. At enrolment, information is obtained on demographics, type of epilepsy, seizure frequency, comorbidities, parental history of MCMs, drug treatment including folate, smoking habits, alcohol intake, and other risk factors. Follow-up data are collected by the treating physician at each trimester, at birth and 12 months after birth. EURAP's primary objective is to compare the risk of major congenital malformations in offspring exposed to different AEDs in fetal life, but information on seizure control and treatment changes is also obtained prospectively[12].

The present analysis focuses on prospectively assessed pregnancies in women with epilepsy treated with VPA at the time of conception, whose offspring completed one-year postnatal follow-up by May 24, 2013.

The assessed cohorts include 93 pregnancies in which VPA was withdrawn during the first trimester (withdrawal group), 38 pregnancies in which VPA was switched to another AED during the first trimester (switch group), and 1,588 pregnancies in which VPA therapy was maintained during the first trimester (maintained-therapy group). Included in the maintained-therapy group were 145 pregnancies where the VPA dose could have been changed during the first trimester, provided that VPA was not withdrawn. Pregnancies where VPA was withdrawn (n=7) or switched (n=2) *after* the first trimester were also classified as maintained-therapy group. Of the 38 pregnancies in the switch group, two were switched to barbexaclone, four to carbamazepine, four to clobazam, six to clonazepam, one to gabapentin, seven to lamotrigine, one to levetiracetam, 11 to phenobarbital, one to topiramate, and one to oxcarbazepine.

Seizure control (occurrence of primarily or secondarily generalized tonic-clonic seizures (GTCS)) in each of the three groups was assessed for each trimester and for the entire pregnancy.

Statistical methods

Proportions of women with GTCS in the three groups were compared by using Bayesian statistics. In the Bayesian modeling paradigm, all parameters are considered to be random variables and are given a prior distribution (prior belief). All inference about these parameters is made from their posterior distribution obtained by applying Bayes's theorem to combine the information given in the observed data with the information given in the prior distribution[13]. These posterior distributions[†] can be summarized by calculating the Bayesian

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Credible Interval (BCI), which resembles a traditional frequentist confidence interval, and can be used to compute the probability that the proportions differ across groups[14]. All statistical computations were performed using R software version 3.2.3 and the Inequality Calculator software version 3.0 (M.D. Anderson Department of Biostatistics – University of Texas)

†When the parameter of interest is a proportion, the posterior distribution obtained by applying the Bayes's theorem is a *Beta* probability function parameterized with $a = [x + 0.01]$ and $b = [(n - x) + 0.01]$ where: x is the number of events (number of women with GTCS), (n – x) is the number of non-events (number of women without GTCS) and 0.01 is the value used here to express the lack of prior information through a non-informative *Beta* prior distribution i.e. B(0.01, 0.01).

Results

Demographic and clinical data for the three cohorts are shown in Table 1. At conception, VPA was used as monotherapy in 39/93 pregnancies (41.9%) in the withdrawal group, in none of the 38 pregnancies in the switch group, and in 1,224/1,588 pregnancies (77%) in the maintained-therapy group. The mean VPA dose at conception was lower (688.1 mg/day) in the withdrawal group than in the switch (830.6 mg/day) or maintained-therapy group (845.3 mg/day). Women wih juvenile myoclonic epilepsy were under-represented in the withdrawal group compared with the other two groups (Table 1).

Frequencies of women with GTCS during pregnancy with associated 95% Credible Intervals in each of three groups are shown in Table 1, with their posterior probability distribution being illustrated in Figure 1. Compared with the other two groups, the proportion of women with GTCS was lower in the maintained-therapy group both in the first trimester (Fig. 1a) and for the entire duration of pregnancy (Fig. 1d) and the probability that such differences are real and not attributable to chance is high ranging from 0.85 (Fig. 1c) to 0.99 (Fig. 1a, 1b, 1d). When assessed over the entire pregnancy, the frequency of women with GTCS were about twice as common in the withdrawal and switch groups as in the maintained-therapy group. The proportion of women with GTCS in the maintained-therapy group was also lower than in the withdrawal group during the second trimester, and lower than the switch group during the third trimester with high probabilities that such findings are real and not attributable to chance.

In the withdrawal group, VPA was reintroduced after the first trimester in 13/93 pregnancies (14%), four on polytherapy and nine on monotherapy, while a different AED was introduced

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in 5/93 (5.4%). In the switch group, VPA was reintroduced after the first trimester in 3/38 pregnancies (7.9%). Changes in VPA treatment after the first trimester were rare in the maintained-therapy group. Such changes included VPA withdrawal in 7/1,588 pregnancies (0.5%) and switch from VPA to another AED in 2/1,588 pregnancies (0.1%).
Seizure control during the second and third trimester was also assessed for women who were seizure free during the first trimester. Within this population, GTCS occurred in 9/70 (12.9%) women in the withdrawal group, in 4/31 (12.9%) women in the switch group, and in 125/1,424 (8.8%) women in the maintained-therapy group (Table 1, Fig. 1e).
Status epilepticus occurred in 2/93 pregnancies in the withdrawal group (2.2%, both non-convulsive), in none of the 38 pregnancies in the switch group, and in 8/1,588 pregnancies in in the maintained-therapy group (0.5%, three convulsive and five non-convulsive).

Discussion

In the current analysis we applied Bayesian statistics because when dealing with small and unbalanced cohorts, as in our case, it provides more meaningful and intuitive inferences compared to classic frequentist statistics.[13]. Based on this analysis, women who had their VPA treatment withdrawn or switched to another AED during the first trimester were found to have a higher probability of experiencing GTCS during pregnancy compared with those who remained on a maintained treatment with VPA throughout the first trimester. Furthermore in almost 20% of pregnancies in which VPA was withdrawn during the first trimester, VPA was reintroduced later in pregnancy or another AED was added. VPA was also re-introduced in 8% of pregnancies in which an attempt had been made to switch to another AED during the first trimester.

These findings raise important concerns, as well as interpretative questions. Interpretation of the data should take into account the fact EURAP is an observational study and women were not randomized to different treatment strategies. Baseline demographic and clinical characteristics of the three groups differed in potentially important variables such as epilepsy syndrome, VPA dose at conception, and proportion receiving VPA monotherapy. Information on pre-conception seizure frequency is not collected in the registry, and the reason(s) for making treatment changes in the first trimester are not recorded, nor do we know exactly how quickly VPA was withdrawn. Alterations in concomitant AED medication could have had an impact on the observed seizure control, as could the fact that withdrawal of VPA may have

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altered the serum concentration of concomitant AEDs. In particular, available information does not permit to determine whether the seizures reported during the first trimester occurred before or after the treatment changes. Therefore, it is unclear whether some treatment changes (e.g. a switch to another AED) were made in response to a poor seizure control, or whether the seizures were caused by the treatment changes, or were unrelated to the changes. Inclusion in the maintained therapy group of some pregnancies where the VPA dose was changed (but not withdrawn) could also affect our comparisons. However, to the extent that these patients may represent failed withdrawal attempts, their inclusion in the maintained therapy group is likely to reduce the difference in the comparison with the withdrawal and switch groups.

In conclusion, although this study does not establish a definite cause-effect relationship between treatment changes and seizure outcome, it does provide a signal that withdrawal of or switch from VPA during the first trimester could lead to loss of seizure control. Due to the small numbers with status epilepticus, we cannot conclude if there is a difference in this risk. The signal regarding seizure control should stimulate the development of well designed observational studies to evaluate the precise indications for and the exact timing of treatment changes, along with information on seizure occurrence before and after the change.

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Disclosure of conflicts of interest

DB has received speaker's fees from UCB Pharma. EB has received consultancy fees from Italfarmaco, Zambon, Polichem, Roche and Sanofi-Aventis. JC received research grants and speaker's fees from UCB Pharma, Eisai, GSK, Sanofi-Aventis, Pfizer, and Janssen-Cilag. DL received research grants from Janssen-Cilag, GSK, Pfizer, and Netherlands Epilepsy Foundation. AS received consultancy or lecture fees, and has received travel support from Eisai Denmark, GSK, and UCB Nordic. EP received research funds from the European Union, the Italian Ministry of Health, the Italian Ministry for Education and University, and

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FV and SVT report no disclosure.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Legend to Fig. 1.

Posterior distributions of the proportion of women with primarily or secondarily generalized tonic-clonic seizures (GTCS) during the first trimester (Fig. 1a), during the second trimester

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(Fig. 1b), during the third trimester (Fig. 1c), and during the entire pregnancy (Fig. 1d). Figure 1e shows posterior distributions of the proportion of women with GTCS during the entire pregnancy among those seizure free during the first trimester.

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Table 1. Demographic data and seizure control (n=1,719)

	VPA withdrawn without any switch during first trimester (n=93)		**VPA switched to other AED during first trimester (n=38)**		**VPA maintained during the first trimester (n=1,588)[a]**	
Three most common concomitant AEDs	lamotrigine, carbamazepine, levetiracetam		phenobarbital, lamotrigine, clonazepam		lamotrigine, carbamazepine, phenobarbital	
	mean	**range**	**mean**	**range**	**Mean**	**range**
Maternal age at time of enrolment (years)	26.9	(15.1-38.1)	26.4	(17.8-38.9)	28.9	(14.1-45.8)
Duration of pregnancy at time of enrolment (weeks)	8	(3-16)	7	(4-13)	8	(2-16)
VPA daily dose at conception (mg)	688.1	(100-2,000)	830.6	(266-3,000)	845.3	(100-3,000)
VPA intake duration since conception (days)	45.1	(4-92)	46.5	(7-87)	VPA throughout pregnancy	
	n	**percentage**	**n**	**percentage**	**N**	**percentage**
Type of epilepsy						
other idiopathic generalized epilepsy	39	41.9%	12	31.6%	710	44.7%
juvenile myoclonic epilepsy	12	12.9%	10	26.3%	395	24.9%
localisation-related epilepsy	27	29.1%	13	34.2%	323	20.3%
undetermined/unclassifiable	15	16.1%	3	7.9%	160	10.1%
VPA dose groups						
VPA < 700 mg	55	59.1%	16	42.1%	648	40.8%
VPA ≥ 700 mg	34	36.6%	19	50.0%	755	47.5%
VPA ≥ 1,500 mg	4	4.3%	3	7.9%	185	11.7%
Number of AEDs taken during the first trimester						
1	39	41.9%	-		1,224	77.1%
2	40	43.0%	33	86.9%	364	22.9%
3 or higher	14	15.1%	5	13.1%	-	
Parity						
0	65	69.9%	27	71.1%	1,007	63.4%
1	21	22.6%	6	15.8%	451	28.4%

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2 or higher	7	7.5%	5	13.1%	130	8.2%
Type of delivery						
caesarean section	27	29.7%	21	55.3%	495	31.7%
other instrumental deliveries	9	9.9%	2	5.2%	103	6.6%
non-instrumental	55	60.4%	15	39.5%	956	61.1%
information missing	-		-		9	0.6%
	Median (95% CI) [Ratio]*		**Median (95% CI) [Ratio]***		**Median (95% CI) [Ratio]***	
Proportion of women with GTCS during the first trimester	0.235 (0.156 - 0.328) [22/93]		0.179 (0.080 - 0.320) [7/38]		0.083 (0.07 - 0.097) [132/1,588]	
Proportion of women with GTCS during the second trimester	0.172 (0.104 - 0.257) [16/92]		0.125 (0.046 - 0.254) [5/38]		0.075 (0.063 - 0.089) [120/1,586]	
Proportion of women with GTCS during the third trimester	0.118 (0.063 - 0.195) [11/91]		0.179 (0.080 - 0.320) [7/38]		0.086 (0.072 - 0.1) [133/1,550]	
Proportion of women with GTCS during whole pregnancy	0.332 (0.242 - 0.432) [31/93]		0.286 (0.159 - 0.441) [11/38]		0.163 (0.145 - 0.181) [257/1,580]	
Proportion of women with GTCS during whole pregnancy among those seizure free during the first trimester	0.125 (0.062 - 0.216) [9/70]		0.121 (0.038 - 0.266) [4/31]		0.088 (0.074 - 0.103) [125/1,424]	

[a]VPA was withdrawn after the first trimester in 7/1,588 pregnancies and switched to another AED in 2/1,588

* Median and 95% Credible Intervals in parentheses are derived from the respective Posterior Distributions. Ratio indicates the observed proportions expressed as ratios (i.e. number of women with GTCS / total number of women with information available in the respective subgroup).

GTCS, primarily or secondarily generalized tonic-clonic seizures.

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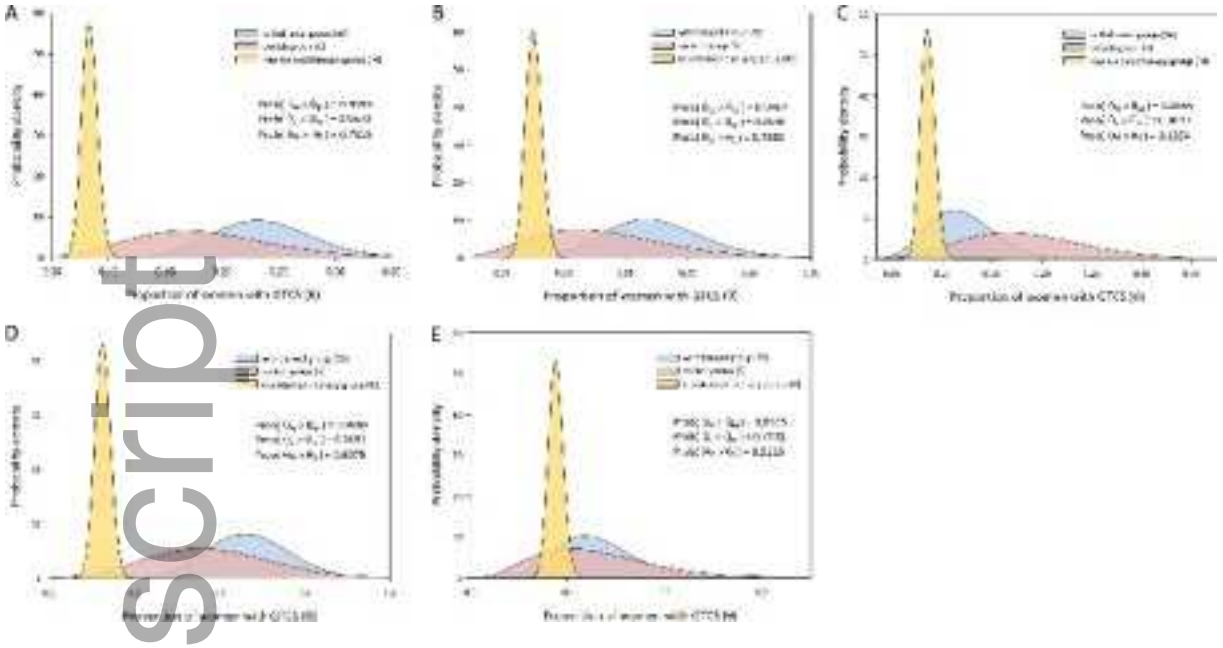

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