Dose-dependent teratogenicity of valproate in mono- and polytherapy

An observational study

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ABSTRACT

Objective: To assess the risk of major congenital malformations (MCMs) in association with maternal use of valproic acid (VPA) in monotherapy or adjunctive therapy, and its relationship with dose.

Methods: The analysis was based on prospectively acquired data from EURAP, a registry enrolling women treated with antiepileptic drugs (AEDs) in early pregnancy, in which the primary outcome is presence of MCMs at 1 year after birth. Exposure was defined as type and dose of AEDs at time of conception. A comparison was made among 3 exposure types: (1) VPA monotherapy (n = 1,224); (2) VPA combined with lamotrigine (LTG) (n = 159); and (3) VPA combined with another AED but not LTG (n = 205).

Results: The frequency of MCMs at 1 year after birth was 10.0% for VPA monotherapy, 11.3% for exposures to VPA and LTG, and 11.7% for exposures to VPA + another (non-LTG) AED. Regardless of exposure group, the frequency of MCMs increased with dose of VPA, being highest at doses ≥1,500 mg/d (24.0% for monotherapy, 31.0% for VPA + LTG, and 19.2% for VPA + other AEDs), and was similar across treatment groups at the lowest VPA dose level of <700 mg/d (5.9% for monotherapy, 7.0% for VPA + LTG, and 5.4% for VPA + other AEDs).

Conclusions: The risk of MCMs associated with VPA exposure increases with increasing VPA dose, both in the presence and in the absence of one concomitant AED, and appears to be related primarily to the dose of VPA. *Neurology*® 2015;85:866–872

GLOSSARY

AED = antiepileptic drug; **CBZ** = carbamazepine; **CI** = confidence interval; **EURAP** = International Registry of Antiepileptic Drugs and Pregnancy; **LTG** = lamotrigine; **MCM** = major congenital malformation; **PB** = phenobarbital; **VPA** = valproic acid.

Publications from different pregnancy registries have consistently demonstrated greater risks for major congenital malformations (MCMs) among the offspring of mothers using valproic acid (VPA) during pregnancy compared with other frequently used antiepileptic drugs (AEDs).[1–3] The same registries[1–3] and other studies[4–7] have shown that this risk is dose-related, with the risk of MCMs increasing with exposure to increasing VPA doses in early pregnancy. The lowest frequencies of MCMs were reported at VPA doses up to 500 mg/d in the North American AED Pregnancy Registry,[2] up to 600 mg/d in the United Kingdom and Ireland Register,[1] and below 700 mg/d in the International Registry of AEDs and Pregnancy (EURAP).[3] For women who require VPA during pregnancy, it is thus essential to keep the dose as low as possible. In some situations, VPA may be prescribed in combination with another AED, possibly in the hope that combination therapy could achieve seizure control with a lower VPA dose and, therefore, reduce exposure of the fetus to this drug. However, to date, no studies have systematically compared the

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frequency of MCMs when different maternal doses of VPA are used alone or in combination with other AEDs. The purpose of the present study was to address this deficiency by assessing prospectively the occurrence of MCMs in the offspring of mothers exposed to mono- and polytherapy with VPA in EURAP.

METHODS

Inclusion criteria and study procedures. A detailed account of the EURAP methodology has been published before,[3] but is summarized in the following. EURAP is an observational study set up in 1999 that relies on the collaboration of investigators from 42 countries from Europe, Asia, Australia, and Latin America (see coinvestigator appendix and appendix e-1 on the *Neurology*® Web site at Neurology.org). Its primary objective is to compare the frequency of MCMs in offspring exposed to AEDs in utero. To be eligible for prospective assessment, women taking AEDs at the time of conception need to be enrolled before gestation week 16 and before fetal outcome is known. At enrollment, 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 at 12 months after birth. Abnormalities in the offspring are recorded descriptively by the reporting physician and classified by an ad hoc independent classification committee that is masked to the type of exposure. MCMs are classified according to the EUROCAT criteria (European Surveillance of Congenital Anomalies; http://www.eurocat-network.eu/homepage). Further methodologic details have been provided in previous publications,[3,8] one of which reported the frequency of MCMs after exposure to the 4 most frequently used AEDs, carbamazepine (CBZ), lamotrigine (LTG), VPA, and phenobarbital (PB), at different dose levels in monotherapy.[3]

The present analysis focuses on pregnancies exposed to VPA as monotherapy or in combination with a second AED (polytherapy), and is based on an updated database. The analysis includes prospective pregnancies in women with epilepsy treated with VPA at the time of conception, whose offspring completed 1-year postnatal follow-up by May 24, 2013. We excluded cases in which pregnancies ended prematurely due to spontaneous abortions or stillbirths (n = 183), teratogenic outcome was impossible to classify (n = 12), the offspring was considered to have chromosomal or genetic abnormalities (n = 22), the woman had a concomitant disease or concurrent medication considered to be associated with teratogenic risks (n = 71), or a change in AED treatment during the first trimester was made that involved switching between AEDs or adding or withdrawing an AED (n = 203). AED exposure was classified based on type of drugs and the dose at conception. Details for these exclusion criteria have been described previously.[3] Pregnancies for which VPA was combined with more than one AED were also excluded from the present analysis (n = 77).

In total, 1,224 pregnancies with VPA monotherapy and 364 with VPA polytherapy met eligibility criteria and were included in the analysis. The polytherapy group was divided into VPA + LTG (n = 159), which was the most common combination, and VPA + any other AED (n = 205). The latter included 16 different combinations, the most common of which comprised CBZ (n = 61), PB (n = 26), topiramate (n = 26), levetiracetam (n = 21), clonazepam (n = 19), and oxcarbazepine (n = 14). Frequencies of MCMs were analyzed by the 3 VPA dose categories at time of conception, which had been defined by our previous analysis of the dose-dependency of VPA teratogenic effects.[3]

Statistical methods. The primary endpoint was the occurrence of any MCM, expressed as proportions with 2-sided 95% confidence intervals (CIs). Other endpoints included VPA dose at conception, frequency of any MCM stratified for VPA dose range, and occurrence of specific malformations. The distribution of demographic and anamnestic data across the 3 exposure groups were evaluated descriptively by computing absolute and relative frequencies for categorical variables and medians with interquartile ranges for continuous variables.

Differences in primary endpoint across exposure groups were evaluated using Pearson χ^2, whereas VPA doses at conception were compared across groups using the Kruskal–Wallis test. The presence of a dose-response relationship across the VPA dose-range categories was investigated overall and for each exposure group by using the Cochran-Armitage linear trend test. Results were considered statistically significant for 2-sided p values <0.05. All statistical computations were performed using SAS JMP 10.8.3 (SAS Institute, Cary, NC) for Macintosh.

Standard protocol approvals, registrations, and patient consents. The protocol was approved by ethics committees of participating centers and informed consent was obtained from all women, in writing or orally depending on the requirements in the different countries.

RESULTS

Demographic and clinical data for the 3 exposure groups are shown in table 1. Maternal age, parity, parental history of MCMs, parental educational level, and folic acid use were similar across groups, whereas the VPA + other AEDs group included a slightly higher proportion of mothers with focal epilepsy. Table e-1 provides the same information for the different dose categories of VPA.

Mean VPA dose at conception was significantly higher for the VPA + other AEDs group than for the 2 other groups ($p < 0.0001$ vs monotherapy and $p < 0.05$ vs VPA + LTG) (table 2). Overall frequencies of MCMs were similar across the 3 exposure groups (table 2). The frequency of MCMs at the lowest VPA dose (<700 mg/d) was similar across all groups, and increased with increasing VPA dose in all groups, with such relationship being statistically significant for the monotherapy group and the VPA + LTG group (table 3). The mean VPA dose in pregnancies resulting in MCMs was 992 ± 489 mg/d in the monotherapy group, 1,217 ± 656 mg/d in the VPA + LTG group, and 1,275 ± 536 mg/d in the VPA + other AEDs group (table 2). In each of the treatment groups, VPA doses for pregnancies associated with MCMs were significantly higher than those for pregnancies not associated with MCMs.

Details of specific MCMs are shown in table 4. For both the monotherapy and the polytherapy exposures, the most common MCMs were cardiac defects, hypospadia, neural tube defects, and multiple MCMs. The mean VPA dose at conception in pregnancies

Table 1 Demographics and clinical data of pregnancies included (n = 1,588) in the cohorts exposed to VPA monotherapy, VPA + LTG, and VPA + another AED different from LTG

	VPA (n = 1,224)	VPA + LTG (n = 159)	VPA + other AED (n = 205)
Maternal age at time of enrollment, y	29.1 (14.1–45.8)	29.2 (18.7–41.8)	28.6 (17.1–40.9)
Duration of pregnancy at time of enrollment, wk	8 (2–16)	8 (2–16)	8 (2–16)
Parental history of major congenital malformations			
Negative	1,207 (98.6)	157 (98.7)	203 (99.0)
Positive	14 (1.1)	2 (1.3)	1 (0.5)
Information missing	3 (0.3)	0 (0)	1 (0.5)
Parity			
0	785 (64.1)	102 (64.2)	120 (58.5)
1	337 (27.5)	47 (29.5)	67 (32.7)
2	84 (6.9)	7 (4.4)	12 (5.9)
≥3	18 (1.5)	3 (1.9)	6 (2.9)
Type of epilepsy[a]			
Idiopathic generalized	921 (75.2)	85 (53.4)	99 (48.3)
Localization-related	191 (15.6)	55 (34.6)	77 (37.6)
Undetermined/unclassifiable	112 (9.2)	19 (12.0)	29 (14.1)
Occurrence of convulsive seizures during the first trimester			
No seizures	1,155 (94.4)	134 (84.3)	167 (81.5)
Seizures present	69 (5.6)	25 (15.7)	38 (18.5)
Educational level of the father[a]			
Low	198 (16.2)	21 (13.2)	31 (15.1)
Medium or high	888 (72.5)	107 (67.3)	146 (71.2)
Information missing	138 (11.3)	31 (19.5)	28 (13.7)
Educational level of the mother[a]			
Low	195 (15.9)	30 (18.9)	39 (19.0)
Medium or high	925 (75.6)	103 (64.8)	146 (71.2)
Information missing	104 (8.5)	26 (16.3)	20 (9.8)
Folic acid use[a]			
Appropriate	437 (35.7)	63 (39.6)	75 (36.6)
Inappropriate	785 (64.1)	96 (60.4)	130 (63.4)
Information missing	2 (0.2)	—	—
Sex of the infant			
Female	616 (50.4)	66 (41.5)	97 (47.3)
Male	588 (48.0)	89 (56.0)	103 (50.2)
Information missing	20 (1.6)	4 (2.5)	5 (2.5)

Abbreviations: AED = antiepileptic drug; LTG = lamotrigine; VPA = valproic acid.
Data are median (range) or n (%).
[a] Localization-related is equivalent to "focal" and "idiopathic generalized" is in most cases equivalent to genetic generalized epilepsy in the new terminology. Educational level is low when referring to an illiteracy or primary level and medium or high when referring to secondary or tertiary level. Folic acid is appropriate if taken continuously at least from 3 months before conception up to 3 months after conception; otherwise, it is inappropriate.

associated with specific MCMs was 1,001 ± 515 mg/d for cardiac malformations, 1,108 ± 511 mg/d for hypospadia, 1,258 ± 492 mg/d for neural tube defects, and 1,382 ± 625 mg/d for multiple MCMs.

There was no apparent relationship between appropriate use of folate (defined as folate intake initiated at least 3 months before conception and maintained throughout the first trimester irrespective of dose) and frequency of MCMs. MCMs were reported

Table 2 Frequency of MCMs and dose of VPA in pregnancies resulting in offspring with and without MCMs after exposure to VPA monotherapy, VPA + LTG, and VPA + another AED

Type of treatment	No.	Mean VPA dose ± SD, mg/d	Frequency of MCMs; 95% CI (n) of MCMs	Mean VPA dose ± SD (mg/d) for pregnancies resulting in MCMs	Mean VPA dose ± SD (mg/d) for pregnancies not resulting in MCMs	p[a]
VPA monotherapy	1,224	814 ± 378	10.0; 8.4–11.8 (122)	992 ± 489	794 ± 359	<0.0001
VPA + LTG	159	863 ± 514	11.3; 7.3–17.2 (18)	1,217 ± 656	817 ± 477	<0.05
VPA + other AED	205	1,022 ± 479	11.7; 8.0–16.8 (24)	1,275 ± 536	988 ± 462	<0.05

Abbreviations: AED = antiepileptic drug; CI = confidence interval; LTG = lamotrigine; MCM = major congenital malformation; VPA = valproic acid.
[a] The *p* values refer to comparison of VPA doses between pregnancies resulting in MCMs and those not resulting in MCMs.

in 66 of 575 or 11.5% (95% CI 9.1–14.3) of cases with appropriate folate use vs 98 of 1,011 or 9.7% (95% CI 8.0–11.7) of cases with inappropriate folate use (not significant).

DISCUSSION The European Medicines Agency has recently strengthened the warnings on the use of VPA in women and girls because of the risk of congenital malformations and developmental disorders in offspring exposed prenatally to VPA.[9] The new Summary of Product Characteristics introduces severe restrictions for the use of VPA in female children and adolescents, women of childbearing potential, and pregnant women with no consideration of differences in risks depending on the dose of VPA.[9]

However, as confirmed in the present prospective study, the risk of MCMs associated with VPA exposure in utero is strongly dose-dependent. Our findings demonstrate that such dose-dependency occurs irrespective of whether VPA is used in monotherapy or in combination with another AED. The overall risk of MCMs was comparable across the 3 exposure groups, despite a significantly higher mean VPA dose in the group exposed to VPA in combination with another AED different from LTG. This observation could be explained by the fact that a large majority of mothers in the latter group was receiving an enzyme inducer such as CBZ or PB, which would be expected to reduce significantly maternal serum VPA concentrations and fetal VPA exposure. Of note, frequencies of MCMs at the lowest dose level (<700 mg/d) were similar across the monotherapy and the polytherapy groups, whereas at the highest VPA doses (≥1,500 mg/d), there was a trend toward a lower MCM risk in the VPA + other AEDs group (19.2%) relative to VPA monotherapy (24.0%) and VPA + LTG (31.0%) (table 3).

Taken together, our results suggest that the risk of MCMs associated with combination therapy is determined primarily by VPA, and that use of concomitant AEDs seems to have no major influence on such risk, although the small numbers of exposures to the highest dose levels call for caution in interpretation. Earlier reports from the Australian registry[10,11] also suggested that the teratogenicity risk associated with polytherapies seems to relate more to the inclusion of VPA in the combination than to the number of AEDs that the fetus is exposed to, an observation subsequently confirmed by the North American registry.[12] Although numbers of specific MCMs in our study were relatively small, our findings also suggest that the pattern of malformations in the polytherapy groups is similar to that reported with VPA monotherapy (table 4), an observation that supports a dominating role of VPA in the etiology of the MCMs.

To provide a deeper assessment of the pattern of MCMs associated with VPA exposure, frequencies of specific malformations identified in our study and in 3 other major AED pregnancy registries are compared in table 5. Although classification criteria for MCMs and time windows for assessing abnormalities vary somewhat among registries,[13] the pattern of

Table 3 Frequency of MCMs at different dose categories of VPA, in association with VPA in monotherapy or 2 different types of AEDs polytherapy

	VPA dose			
Type of treatment	<700 mg/d	≥700 to <1,500 mg/d	≥1,500 mg/d	p
VPA monotherapy	5.9; 4.2–8.3 (31/522)	11.0; 8.8–13.8 (66/598)	24.0; 16.8–33.1 (25/104)	<0.0001
VPA + LTG	7.0; 3.0–15.4 (5/71)	6.8; 2.7–16.2 (4/59)	31.0; 17.3–49.2 (9/29)	<0.01
VPA + other AEDs	5.4; 1.9–14.9 (3/55)	11.2; 6.4–19.0 (11/98)	19.2; 10.8–31.9 (10/52)	0.084
Total	6.0; 4.4–8.1 (39/648)	10.7; 8.7–13.1 (81/755)	23.8; 18.2–30.4 (44/185)	<0.0001

Abbreviations: AED = antiepileptic drug; LTG = lamotrigine; MCM = major congenital malformation; VPA = valproic acid.
Data represent frequency of MCMs; 95% confidence interval (n) of MCMs at indicated dose categories of VPA.

Table 4 Frequency of some specific MCMs at different dose categories of VPA for all pregnancies combined, VPA monotherapy, and VPA polytherapy

	No. exposed	Cardiac	Oral clefts	Hypospadia	Neural tube defects	Polydactyly	Multiple	Other malformations
VPA for all pregnancies combined								
MCMs at VPA doses <700 mg/d	648	1.8 (12)	0.5 (3)	0.6 (4)	0.3 (2)	0.3 (2)	0.3 (2)	2.2 (14)
MCMs at VPA doses ≥700 to <1,500 mg/d	755	1.7 (13)	0.3 (2)	1.9 (14)	1.3 (10)	1.2 (9)	1.2 (9)	3.2 (24)
MCMs at VPA doses ≥1,500 mg/d	185	5.9 (11)	0.5 (1)	3.8 (7)	4.3 (8)	0	5.9 (11)	3.2 (6)
Total	1,588	2.3 (36)	0.4 (6)	1.6 (25)	1.3 (20)	0.7 (11)	1.4 (22)	2.8 (44)
VPA monotherapy								
MCMs at VPA doses <700 mg/d	522	1.5 (8)	0.6 (3)	0.8 (4)	0.4 (2)	0.2 (1)	0.4 (2)	2.1 (11)
MCMs at VPA doses ≥700 to <1,500 mg/d	598	2.2 (13)	0.2 (1)	2.0 (12)	1.5 (9)	1.0 (6)	1.0 (6)	3.2 (19)
MCMs at VPA doses ≥1,500 mg/d	104	6.7 (7)	0	4.8 (5)	1.9 (2)	0	7.7 (8)	2.9 (3)
Total	1,224	2.3 (28)	0.3 (4)	1.7 (21)	1.1 (13)	0.6 (7)	1.3 (16)	2.7 (33)
VPA polytherapy								
MCMs at VPA doses <700 mg/d	126	3.2 (4)	0	0	0	0.8 (1)	0	2.4 (3)
MCMs at VPA doses ≥700 to <1,500 mg/d	157	0	0.6 (1)	1.3 (2)	0.6 (1)	1.9 (3)	1.9 (3)	3.2 (5)
MCMs at VPA doses ≥1,500 mg/d	81	4.9 (4)	1.2 (1)	2.5 (2)	7.4 (6)	0	3.7 (3)	3.7 (3)
Total	364	2.2 (8)	0.5 (2)	1.1 (4)	1.9 (7)	1.1 (4)	1.6 (6)	3.0 (11)

Abbreviations: MCM = major congenital malformation; VPA = valproic acid.
Data are % (n) unless otherwise indicated.

MCMs is rather consistent across studies. Cardiac malformations, hypospadia, and neural tube defects are the most frequently reported abnormalities. We also identified a relatively high frequency (up to 1.6%) of multiple malformations (table 5). Since it is unclear how multiple MCMs were accounted for in the other registries, no meaningful comparison can be made for this finding. The Australian registry reported higher mean doses of VPA (mono- and polytherapy combined) in mothers whose offspring had spina bifida and hypospadia compared with other malformations.[14] The mean VPA dose in pregnancies associated with neural tube defects and hypospadia in our study was considerably lower than that reported by the Australian registry (1,257 ± 492 mg/d vs 2,000 ± 707 for neural tube defects, and 1,108 ± 511 vs 2,417 ± 1,323 for hypospadias, respectively). These differences could be related to variability in prescribing practices across regions. There is also some overlap between EURAP and the Australian registry, because the latter contributes some of its pregnancies (those who meet EURAP eligibility criteria) to the EURAP database.[13] In the present analysis, the Australian registry accounted for 100 of the 1,224 VPA monotherapy exposures, 26 of 159 VPA + LTG exposures, and 19 of 205 VPA + other AED exposures. Exclusion of the Australian pregnancies in a secondary analysis, however, did not change our results (data not shown).

Strengths of the EURAP collaboration include the size of the cohort, which is larger than any other similar study published to date, the strict eligibility

Table 5 Frequency of different types of major congenital malformations with exposure to VPA in different registries

Registry	Exposure (n)	Cardiac	Oral clefts	Hypospadia	Neural tube defects	Polydactyly	Multiple
EURAP	VPA monotherapy (1,224)	28 (2.3)	4 (0.5)	21 (1.7)	13 (1.1)	7 (0.6)	16 (1.3)
EURAP	VPA polytherapy (364)	8 (2.2)	2 (0.3)	4 (1.1)	7 (1.9)	4 (1.1)	6 (1.6)
North American[2]	VPA monotherapy (323)	8 (2.5)	4 (1.2)	5 (3.1)	4 (1.2)	NA	NA
UK and Ireland[1]	VPA monotherapy (1,220)	14 (1.1)	13 (1.1)	15 (1.2)	13 (1.1)	NA	NA
Australian[14]	VPA mixed (262 monotherapy; 147 polytherapy)	11 (2.7)	5 (1.2)	6 (1.5)	8 (2.0)	NA	NA

Abbreviations: EURAP = International Registry of Antiepileptic Drugs and Pregnancy; NA = not available; VPA = valproic acid.
Data are n (%) unless otherwise indicated.

criteria for prospective assessment, the unambiguous definition of AED exposure, the systematic collection of information about potential risk factors other than the AEDs, and the extended follow-up (1 year after birth), which allows identification of many MCMs that are typically missed at birth. These strengths permitted a detailed evaluation of the dose-dependency of VPA teratogenicity in the presence and in the absence of concomitant AEDs. Although the nonrandomized design is an unavoidable limitation in studies of human teratogenicity, the clinical characteristics of our cohort showed no major differences across the 3 exposure groups for potentially confounding risk factors such as maternal age, parental education, parity, family history of MCMs, or use of folate. Because of statistical power limitations related to small size of subgroups, we did not consider doses of concomitant medications in the polytherapy groups. However, this is probably of less importance because the results indicate a dominating role of VPA for teratogenic outcome. A further limitation is that our analysis relies on drug doses rather than serum concentrations that might better reflect fetal exposure. Such information is not obtained in EURAP and it is also difficult to determine how to best utilize serum drug concentrations for this purpose (total or unbound concentrations, trough or peak concentrations, and optimal time of gestation for sampling).

The evidence concerning the risks of in utero VPA exposure for the offspring is overwhelming. The risks are not restricted to MCMs but also include adverse effects on cognitive as well as behavioral development.[15–18] Although IQ was no different from controls in children exposed to less than a 1,000 mg/d[17] or 800 mg/d,[18] one study reported impaired verbal abilities and increased educational interventions among children exposed to these lower doses.[18]

These data led to the recommendation that VPA should be avoided whenever possible when pregnancies are planned.[9] However, studies have also indicated that the chance of remaining seizure-free throughout pregnancy might be higher with VPA than with some other AEDs,[2,19] and for some women with generalized epilepsies, seizures cannot be controlled with AEDs other than VPA. In such cases, the VPA dose should be kept as low as possible. One way of achieving seizure control at a lower VPA dose might be to combine with another AED, in particular the combination of VPA and LTG has been suggested to have synergistic efficacy.[20,21] In that perspective, our results may have important implications in demonstrating that the risk of MCMs, particularly at low to intermediate doses of VPA, appears not to be affected by comedication with LTG or another AED. Overall, MCM frequencies as well as risk of specific MCMs seem to be comparable between VPA mono- and polytherapy, and lower at VPA doses less than 700 mg/d than at larger doses.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the design of the study. E.B. conducted the statistical analysis. All authors contributed equally to the interpretation of the data. T.T. and D.B. drafted the first version of the manuscript, and all authors contributed equally to input of the first draft and the finalization of the submitted manuscript.

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DISCLOSURE

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