Seizure 21 (2012) 215–218

Contents lists available at SciVerse ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Valproate and the risk for congenital malformations: Is formulation and dosage regime important?

E. Mawhinney [a], J. Campbell [a], J. Craig [a,*], A. Russell [b], W. Smithson [c], L. Parsons [d], I. Robertson [e], B. Irwin [a], P. Morrison [f], B. Liggan [g], N. Delanty [h], S. Hunt [a], J. Morrow [a]

[a] Department of Neurology, Belfast Health and Social Care Trust, Grosvenor Road, Belfast BT12 6BA, United Kingdom
[b] Dept of Clinical Neurophysiology, Institute of Neurological sciences, Southern General Hospital, 1345 Govan Road, Glasgow, G51 4TF, United Kingdom
[c] Academic Unit of Primary Medical Care, Samuel Fox House, University of Sheffield, Northern General Hospital, Herries Road, Sheffield, S5 7AU, United Kingdom
[d] Neurology Department, Luton & Dunstable Hospitals NHS Trust, Lewsley Road, Luton, LU4 0DZ, United Kingdom
[e] Obstetric & Gynaecology Department, Sharoe Green Unit, Royal Preston Hospital, Presto, United Kingdom
[f] Dept of Medical Genetics, Belfast City Hospital, Lisburn Road, Belfast, BT9 7AB, United Kingdom
[g] RCSI, Beaumont Hospital, Dublin 9, Ireland
[h] Dept of Neurology, Beaumont Hospital, Dublin 9, Ireland

ARTICLE INFO

Article history:
Received 21 September 2011
Received in revised form 16 January 2012
Accepted 18 January 2012

Keywords:
Epilepsy
Pregnancy
Antiepileptic drugs
Valproate
Major congenital malformations

ABSTRACT

Background: Use of valproate in pregnancy, especially in doses over 1000 mg a day, is known to be associated with a higher risk for major congenital malformations compared with other antiepileptic drugs. We sought to investigate whether the increased risk could be minimised by using controlled release or divided daily doses of valproate.
Methods: The UK Epilepsy and Pregnancy Register is a prospective, observational and follow up study set up to determine the risks of major congenital malformations for infants exposed to antiepileptic drugs in utero. In this study we have extracted data for those pregnancies exposed to valproate in monotherapy. We have calculated malformation rates and relative risks as a function of valproate exposure.
Results: Outcome data were available for 1109 pregnancies exposed to valproate in monotherapy. Exposure to 1000 mg a day or more of valproate was associated with almost double the risk of major congenital malformation compared with daily valproate doses below 1000 mg daily (8.86% vs 4.88%, RR: 1.7; 95% CI: 1.1–2.9). There were no differences in the risks for malformations between standard release valproate and controlled release valproate preparations (RR: 1.11; 95% CI: 0.67–1.83) or for those exposed to single or multiple daily administrations (RR: 0.99, 95% CI: 0.58–1.70).
Conclusion: Prescribing controlled release valproate or multiple daily administrations in pregnancy did not reduce the risk for malformations. Higher malformation rates observed with in utero exposure to valproate are more likely related to total daily dose, rather than peak serum levels.

1. Introduction

Prenatal exposure to antiepileptic drugs (AEDs) increases the risk of major congenital malformations (MCMs) from the background risk of 1–2% to between 4% and 9%.[1–4] Previous studies, including those from the UK Epilepsy and Pregnancy Register, have shown that use of valproate, both as monotherapy and as part of a polytherapy regimen, is associated with a higher risk of MCMs than for other AEDs such as carbamazepine and lamotrigine. Several studies have also shown a trend towards a positive dose response for MCMs and valproate, particularly for doses over 1000 mg daily.[4–8]

Animal studies have suggested that the increased rate of MCMs with valproate may be related to peak plasma concentration, as well as the total daily dose.[9] Using a controlled release formulation of valproate results in reduced peak plasma concentration and smaller diurnal fluctuations than standard valproate.[10] Therefore, using a three or four times daily regimen, or use of a controlled release formulation of valproate, to minimise high plasma concentrations has been proposed as possibly being of benefit and has been included in a number of guidelines.[11–14] There have been no published clinical studies investigating the validity of this approach. If confirmed this could have a significant impact on the treatment options available to women of childbearing age with epilepsy, in particular those with

* Corresponding author. Tel.: +44 2890 634590; fax: +44 2890 235258.
E-mail address: john.craig@belfasttrust.hscni.net (J. Craig).

1059-1311
doi:10.1016/j.seizure.2012.01.005

generalised epilepsy syndromes, where valproate is more effective than other AEDs.[15]

2. Methods

The UK Epilepsy and Pregnancy Register is a prospective, observational, registration and follow-up study that was set up to determine the relative safety of all AEDs taken in pregnancy. In this report we have focussed on all pregnancies that were exposed solely to valproate during the first trimester from December 1996 through April 2010.

Registration and follow up forms as well as the UK Epilepsy and Pregnancy Register computer database were reviewed for all women having registered a pregnancy on valproate monotherapy. Suitable cases were women with epilepsy who became pregnant whilst taking valproate (either standard release valproate or controlled release valproate) in monotherapy and who were referred before the outcome of the pregnancy was known. The main outcome measure was the MCM rate. The rate of minor congenital malformations (mCM) was also recorded. Full methodological details have been published previously.[4] Recording of serum levels of AEDs, including valproate, is not part of the methodology of the UK Epilepsy and Pregnancy Register and were therefore not available for this study. Valproate preparation and dose is recorded at registration only in the majority of cases.

A MCM was defined as an abnormality of an essential embryonic structure requiring significant treatment and present at birth or discovered in the first 6 weeks of life. Disorders not conforming to this definition were assigned as mCMs based on the definitions and lists of disorders in the EUROCAT registry.[16]

MCM and mCM rates were calculated for standard release valproate and controlled release valproate at any dose and at doses below and above 1000 mg daily. We also attempted to estimate the potential influence of peak plasma valproate concentrations by comparing malformation rates in women taking standard release valproate with those taking controlled release valproate or divided doses of standard valproate.

2.1. Statistical analysis

Malformation rates were calculated as [(total number of live births with a malformation) + (total number of pregnancy losses with a malformation)]/[(total number of live births) + (total number of pregnancy losses with a malformation)]. For each malformation rate, 95% confidence intervals (95% CI) were calculated using the traditional method.[17] Relative risks with 95% CI were used to compare groups. Student's *t*-test, ANOVA and Chi-squared tests were used in comparison of characteristics between groups. Significance was determined at $p < 0.05$. Data for drug dose and administration schedule were not recorded for some patients. These patients were excluded from the groups comparing drug dosage and frequency of administration, irrespective of the outcome of the pregnancy.

Table 1
Patient characteristics and pregnancy outcome data.

	All valproate exposures ($n = 1109$)	Standard release valproate exposures ($n = 814$)	Controlled release valproate exposures ($n = 295$)	*p*
Outcome				
Live births	1044 (94.1%)	767 (94.2%)	277 (93.9%)	0.96
Spontaneous abortions	42 (3.7%)	31 (3.8%)	11 (3.7%)	0.95
Still births	12 (1.1%)	9 (1.1%)	3 (1.0%)	0.99
Induced abortions	10 (0.9%)	6 (0.7%)	4 (1.4%)	0.81
Unknown	2 (0.2%)	1 (0.1%)	0 (0%)	0.94
Mean gestational age (weeks)	37.0 (6.0)	38.0 (5.6)	38.0 (6.3)	0.97
M:F ratio	1:1.1	1:1	1:1.3	0.32
Preconceptual folic acid	40.0%	38.3%	44.7%	0.06
Family history MCM	3.1%	2.8%	3.7%	0.43

Table 2
Major congenital malformation (MCM) and minor congenital malformation (mCM) rates.

Valproate exposure	MCM rate (95% CI)	Minor CM rate (95% CI)	Mean dose mg (SD)
Total valproate exposures ($n = 1085$)	6.7% (5.2–8.2)	7.7% (6.1–9.3)	939.6 (509.5)
<1000 mg total daily dose ($n = 584$)	4.9% (3.1–6.7)	5.8% (3.8–7.7)	569.6 (196.7)
≥1000 mg total daily dose ($n = 501$)	8.9% (6.3–11.4)	9.1% (6.5–11.7)	1362.4 (425.0)
Total standard release exposures ($n = 791$)	6.5% (4.7–8.2)	7.4% (5.5–9.2)	930.0 (509.9)
<1000 mg total daily dose ($n = 429$)	4.7% (3.0–7.1)	5.4% (3.6–8.0)	561.0 (200.7)
≥1000 mg total daily dose ($n = 362$)	8.0% (5.6–11.3)	9.1% (6.5–12.6)	1365.1 (413.9)
Standard release valproate (single daily dose) ($n = 251$)	6.5% (4.8–8.2)	7.5% (5.5–9.0)	782.9 (501.4)
<1000 mg total daily dose ($n = 158$)	2.5% (0.7–6.5)	4.4% (2.0–9.0)	465.2 (216.9)
≥1000 mg total daily dose ($n = 94$)	11.8% (6.5–19.9)	11.8% (6.5–19.9)	1322.6 (367.8)
Standard release valproate (divided daily dose) ($n = 538$)	6.5% (4.8–8.2)	7.2% (5.5–9.0)	997.0 (501.0)
<1000 mg total daily dose ($n = 271$)	5.9% (3.6–9.4)	5.9% (3.6–5.4)	617.0 (167.2)
≥1000 mg total daily dose ($n = 268$)	6.7% (4.2–10.4)	8.2% (5.4–12.1)	1379.9 (428.4)
Valproate controlled release ($n = 294$)	7.1% (4.1–10.2)	8.6% (5.3–11.9)	965.2 (510.8)
<1000 mg total daily dose ($n = 154$)	5.2% (2.5–10.1)	6.5% (3.4–11.7)	593.5 (184.7)
≥1000 mg total daily dose ($n = 140$)	8.6% (4.9–14.5)	9.4% (5.4–15.4)	1355.4 (453.8)
Valproate controlled release (single daily dose) ($n = 95$)	6.3% (2.7–13.4)	11.6% (6.4–19.7)	849.6 (531.3)
<1000 mg total daily dose ($n = 58$)	8.6% (3.3–19.1)	10.3% (4.5–21.1)	537.9 (205.1)
≥1000 mg total daily dose ($n = 37$)	2.7% (0.01–15.1)	13.5% (5.4–28.5)	1337.8 (517.7)
Valproate controlled release (multiple daily doses) ($n = 198$)	7.1% (4.2–11.6)	6.1% (3.4–10.4)	1005.6 (492.3)
<1000 mg total daily dose ($n = 96$)	3.1% (0.6–9.2)	4.2% (1.3–10.6)	627.1 (155.2)
≥1000 mg total daily dose ($n = 103$)	10.8% (5.9–18.3)	7.8% (3.8–14.8)	1361.8 (431.0)

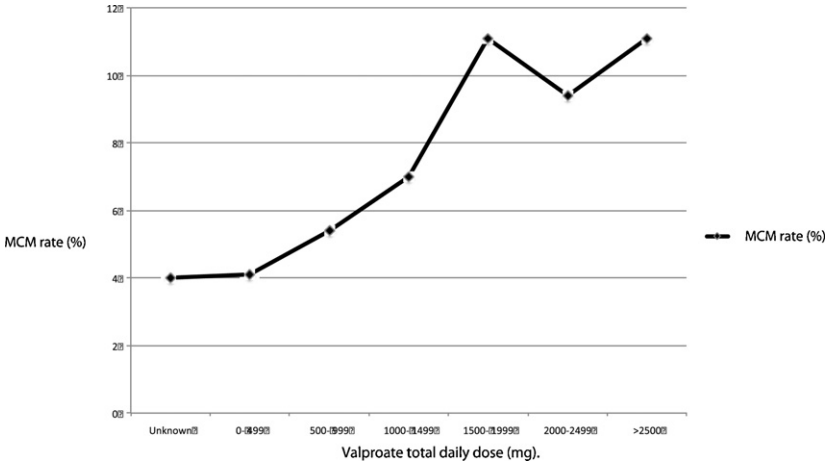

Fig. 1. MCM rate according to valproate total daily dose (mg).

Table 3
Types of MCMs for all valproate, standard release valproate and controlled release valproate exposures.

Type of MCM	All valproate monotherapy exposures ($n = 1109$)	Standard release valproate monotherapy exposures ($n = 814$)	Valproate controlled release monotherapy exposures ($n = 295$)	p-Value standard release vs controlled release
Neural tube defect	13 (1.2%)	10 (1.2%)	3 (1.0%)	0.98
Clefting disorder	12 (1.1%)	11 (1.4%)	1 (0.3%)	0.44
Hypospadias/GIT	12 (1.1%)	7 (0.9%)	5 (1.7%)	0.99
Cardiac	10 (0.9%)	7 (0.9%)	3 (1.0%)	0.90
Other/skeletal	24 (2.2%)	16 (2.2%)	8 (2.7%)	0.98
Unknown	5 (0.5%)	4 (0.5%)	1 (0.3%)	0.70
Total	76 (6.7%)	55 (6.5%)	21 (7.1%)	0.99

3. Results

Through April 2010, outcome data were available for 1109 pregnancies exposed to valproate as monotherapy. Of these, 1044 pregnancies (94.1%) resulted in a live birth and 65 (5.9%) a pregnancy loss. Seven additional pregnancies were lost to follow up and are not included in analysis. Valproate dose and administration schedule was not recorded in 24. Patient characteristics and pregnancy outcome data are outlined in Table 1. Eight hundred and fourteen patients (73.4%) were exposed to standard release valproate and 295 (26.6%) to controlled release valproate. There were no statistical differences between the groups in terms of mean gestational age, preconceptual folic acid intake and family history of MCMs (Table 1).

The total MCM rate for all valproate exposures was 6.7% (95% CI: 5.2–8.2%) and for mCMs 7.7% (95% CI: 6.1–9.3%) (Table 2). Forty-six point two percent were exposed to a total daily dose of 1000 mg or more and 53.8% to less than 1000 mg a day. The risk of MCM increased with total daily dose (Fig. 1) with the risk in the high dose group being almost double that of the low dose group (8.9% vs 4.9%; RR 1.8 (95% CI: 1.1–2.9)). This pattern was also seen for mCMs (9.1% with total daily doses at or above 1000 mg vs 5.8% for total daily doses less than 1000 mg; RR 1.2 (95% CI: 1.0–2.5)).

The risk for MCMs and mCMs did not vary depending on whether valproate was prescribed as standard or controlled release. The relative risk (RR) for MCMs for those exposed to controlled release valproate compared with standard release valproate was 1.1 (95% CI: 0.7–1.8). The proportion of those exposed to a total daily dose of 1000 mg or more was similar for the standard and controlled release groups. No significant difference in the risk of MCMs was noted between these groups (RR 1.2 (95% CI: 0.6–2.1)).

Two hundred and fifty one patients took standard release valproate once daily with 832 either taking controlled release valproate or standard release valproate, administered twice daily or more (divided dose group). MCM rates were no different for those pregnancies exposed to once daily standard valproate compared with those taking either controlled release valproate or standard release valproate in divided doses (RR 1.0 (95% CI: 0.6–1.7)). This was also the case when pregnancies exposed to less than 1000 mg a day or to 1000 mg a day or more were considered (RR 0.6 (95% CI: 0.3–1.1)).

Overall there were no significant differences between the types of MCMs seen in those exposed to standard release and controlled release valproate ($p = 0.99$) (Table 3). Clefting abnormalities, however, were almost five times more common in those exposed to standard release valproate, with hypospadias and other disorders of the genitourinary tract being almost twice as likely in those exposed to controlled release valproate.

4. Discussion

The MCM rate observed for valproate exposed pregnancies in this study at 6.7% was lower than that reported by other groups, where rates ranging between 8.3%[9] and 16.8%[6] have been recorded. A trend towards increasing MCM risk with higher total daily valproate dose has been previously observed in studies by the UK Epilepsy and Pregnancy Register, EURAP, the North American AED Pregnancy Registry and the Australian Epilepsy and Pregnancy Registry.[4–8] In keeping with this, we found a statistically significant positive dose response with almost a doubling of risk for those exposed to more than 1000 mg per day compared with those on less than 1000 mg per day (8.9% vs 4.9%). Use of controlled release valproate did not significantly alter the risk for MCMs, irrespective of total daily dose. Likewise, the risk for MCMs and mCMs was not affected by the number of daily administrations of valproate. This was demonstrated by the similar rates of MCMs, irrespective of total daily dose, for pregnancies exposed either to a single dose of valproate and those exposed to divided daily doses of controlled release valproate. The types of MCMs were similar for those

exposed to standard and controlled release valproate. Clefting abnormalities, however, were almost five times more likely in those exposed to standard release valproate and hypospadias and other disorders of the genito-urinary tract almost twice as common in those exposed to controlled release valproate. These findings were not statistically significant and demonstrate the very large number of pregnancies that would be required to detect such differences, if they exist.

One obvious criticism of our study is that we did not record serum valproate levels. None of the national or international epilepsy and pregnancy registries record this information.[18] Conducting such a study where valproate levels were recorded would be difficult since it would require repeated trough and peak serum valproate levels to be recorded throughout the pregnancy. Considering MCMs only and taking into account the different periods that are important for organogenesis would clearly require very detailed study in the first trimester.

That peak serum levels of valproate may be an important determinant for the risk of MCMs has been shown in a mouse model which compared the effects of a conventional injection regime of valproate and a steady drug infusion delivered by implanted mini-pumps. In this study, a 10 times higher dose was required in the infusion regimen to produce neural tube defect rates at a rate similar to that observed in the injection regimen (up to 60% of foetuses). Higher rates of embryolethality and foetal weight retardation were noted however with the implanted minipumps.[9]

Prescribing valproate as a continuous infusion is clearly not feasible in humans were the only practical means available to minimise peak valproate concentrations are to reduce the dose, split it into multiple daily administrations or prescribe controlled release valproate. Our results, in contrast to the study in mice,[9] showed that attempting to minimise peak serum concentrations has no significant effect on MCM risk and that it is only by reducing the total daily dose of valproate that the risk for MCMs and mCMs can be lowered. We have therefore not been able to substantiate the advice that for women planning pregnancy, or who become pregnant, while taking valproate, that the daily dose should be split and controlled release valproate prescribed.[11–14] In the absence of any definite harm we would however still advocate this approach. Clearly in some women increasing the frequency of drug administration can reduce adherence, and discussion of the risks and benefits is vital before recommending multiple daily administrations. This is the first report to study the effects of formulation and dosage administration schedule for valproate in pregnancy and there will be an opportunity for the other epilepsy and pregnancy registers to do the same. Furthermore, with increasing evidence that valproate can have an even more significant effect on cognitive development and behaviour,[19–26] which also appears to be dose related, further work is clearly needed to determine the importance of drug formulation and dosage regime.

References

1. Olafsson E, Hallgrimsson JT, Hauser WA, Ludvigsson P, Gudmundsson G. Pregnancies of women with epilepsy: a population-based study in Iceland. *Epilepsia* 1998;**39**:887–92.
2. Holmes LB, Harvey EA, Coull BA, Huntington KB, Khoshbin S, Hayes AM, et al. The teratogenicity of anticonvulsant drugs. *N Engl J Med* 2001;**344**:1132–8.
3. Kaneko S, Battino D, Andermann E, Wada K, Kan R, Takeda A, et al. Congenital malformations due to anti-epileptic drugs. *Epilepsy Res* 1999;**33**:145–58.
4. Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2006;**77**:193–8.
5. Vajda FJE, Hitchcock A, Graham J, Solinas C, O'Brien TJ, Lander CM, et al. Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. *Eur J Neurol* 2006;**13**:645–54.
6. Vajda FJ. The Australian pregnancy register of antiepileptic drugs: 10 years of progress. *J Clin Neurosci* 2010;**17**(December (12)):1485–8.
7. Diav-Citrin O, Shechtman S, Bar-Oz B, Cantrell D, Amon J, Omoy A. Pregnancy outcome after in utero exposure to valproate: evidence of dose relationship in teratogenic effect. *CNS Drugs* 2008;**22**(4):325–34.
8. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Dose dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy pregnancy registry. *Lancet Neurol* 2011;**10**:609–17.
9. Nau H. Teratogenic valproic acid concentrations: infusion by implanted mimipumps vs conventional injection regimen in the mouse. *Toxicol Appl Pharmacol* 1985;**80**:243–50.
10. Kondo T, Tokinaga N, Suzuki A, Ono S, Yabe H, Kaneko S, et al. Altered Pharmacokinetics and metabolism of valproate after replacement with the slow release formulation in epileptic patients. *Pharmacol Toxixol* 2002;**90**:130–8.
11. Delgado-Escuera AV, Janz D. Consensus guidelines preconception counselling, management and care of the pregnant woman with epilepsy. *Neurology* 1992;**42**(Suppl. 5):149–60.
12. Scottish Obstetric Guideline and Audit Project. *The management of pregnancy in women with epilepsy, No. 5.* SPCERH Publications; 1997.
13. Crawford P, Appleton R, Betts T, Duncan J, Guthrie E, Morrow J. The women with epilepsy guidelines development group. Best practice guidelines for the management of women with epilepsy. *Seizure* 1999;**8**:201–17.
14. Crawford P. Best practice guidelines for the management of women with epilepsy. *Epilepsia* 2005;**46**(Suppl. 9):117–24.
15. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, et al., for the SANAD Study group. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007;**369**:1016–26.
16. De Wals P, Mastroiacovo P, Weatherall JAC, Lechat M, editors. *EUROCAT guide for the registration of congenital anomalies.* Brussels: European Union; 1984.
17. Wilson EB. Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc* 1927;**22**:209–12.
18. Tomson T, Battino D, Craig J, Hernandez-Diaz S, Holmes LB, Lindhout D, et al. Pregnancy registries: differences, similarities, and possible harmonization. *Epilepsia* 2010;**51**:909–15.
19. Adab N, Kini U, Vinten J, Ayres J, Baker G, Clayton-Smith J, et al. The longer term outcome of children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry* 2004;**75**:1575–83.
20. Adab N, Jacoby A, Smith D, Chadwick D. Additional educational needs in children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry* 2001;**70**:15–21.
21. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med* 2009;**360**:1597–605.
22. Meador KJ, Baker GA, Browning N, Cohen MJ, Clayton-Smith J, Kalaylian LA, et al., for the NEAD Study Group. Foetal antiepileptic drug exposure and verbal versus non-verbal abilities at three years of age. *Brain* 2011;**134**:396–404.
23. McVearry KM, Gaillard WD, Van Meter J, Meador KJ. A prospective study of cognitive fluency and originality in children exposed in utero to carbamazepine, lamotrigine, or valproate monotherapy. *Epilepsy Behav* 2009;**16**:609–16.
24. Bromley RL, Mawer G, Love J, Kelly J, Purdy L, McEwan L, et al. Early cognitive development in children born to women with epilepsy: a prospective report. *Epilepsia* 2010;**51**:2058–65.
25. Nadebaum C, Anderson VA, Vajda F, Reutens DC, Barton S, Wood AG. Language skills of school-aged children prenatally exposed to antiepileptic drugs. *Neurology* 2011;**76**:719–26.
26. Cummings C, Stewart M, Stevenson M, Morrow J, Nelson J. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child* 2011;**96**(7):643–7.