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VALPROATE-ASSOCIATED FOETAL MALFORMATIONS –

Rates of occurrence, risks in attempted avoidance

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ABSTRACT

Objectives: To gain insight into the main advantages and disadvantages that might result from valproate being unavailable for women who intend to become pregnant.

Materials and Methods: Analysis of data from the Australian Pregnancy Register concerning pregnancies exposed to valproate (N=501) and pregnancies where previous valproate intake had been ceased before pregnancy (N=101)

Results: The risk of foetal malformation associated with valproate exposure during pregnancy was dose-related, and there was a tendency for the more major malformations, including those often managed by therapeutic abortion e.g. spina bifida, to occur at higher valproate doses. Had there been no exposure to valproate during pregnancy, some 80% of the foetal malformations that occurred might have been avoided.

Cessation of previous valproate therapy before pregnancy was associated with an increased hazard of seizure-affected pregnancy. This was particularly the case for women with generalised epilepsies, in whom the incidence of seizure-affected pregnancy was increased by 50% to nearly 100%.

Conclusions: Avoiding valproate intake during pregnancy is likely to reduce the incidence of foetal malformation, but at a cost of worsened maternal epilepsy control. Individualisation of treatment is particularly important in considering withdrawal of valproate in light of the fact that it is much more widely used in generalised epilepsy, there being fewer alternative drugs than for focal epilepsy and withdrawal is not without risk for both mother and baby. This paper may provide a quantitative basis for assessing the balance between benefit and

disadvantage for individual women with valproate-treated epilepsy who are considering pregnancy.

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Key words: epilepsy control**,** foetal malformations, maternal disadvantages, seizures, spina bifida, valproate

Introduction

In recent years it has become increasingly clear that maternal intake of valproate during pregnancy is associated with an appreciable and dose-related incidence of various foetal malformation[1-4] and also with an increased chance of neurodevelopmental disorder being present in childhood [5,6]. The availability of this knowledge has led to increasing caution in the use of this drug in managing seizure disorders in women who are capable of pregnancy or are already pregnant. Statements to this effect have appeared in the literature and very recently the European Medicines Agency has proposed strengthening its statement regarding the drug in a way that is almost tantamount to prohibiting its use not only in pregnancy but in any female of child-bearing potential unless she is adopting contraceptive measures [7]. This rather absolute prohibition is softened to an extent by an intimation that, in some circumstances, use of the drug might have to be accepted when no satisfactory alternative management is possible.

The strength of this proposed statement, and the medico-legal issues that may arise from its implementation, raise the question of the degrees of hazard that its implementation would hope to avoid. That hazard would involve not only the occurrence of foetal malformation and neurodevelopmental disturbances in childhood, but also maternal hazards. The Australian Register of Antiepileptic Drugs in Pregnancy (APR) contains information about the malformation issue, and some information regarding maternal hazards. It was therefore thought worth investigating the data the APR holds on valproate-associated foetal malformations to obtain insight into the nature and extent of the hazards that the virtual

prohibition of valproate use in a substantial proportion of the Australian female population might avoid, and also regarding possible hazards that this avoidance might produce.

Materials and methods:

The APR collects details of the pregnancies of Australian women who are taking antiepileptic drugs (AEDs), and those of women with epilepsy that was untreated in at least the first half of pregnancy. Detailed information regarding the APR and its recruitment policies and data handling practices has been published previously [8-11]. Inclusion in the APR is entirely at the discretion of pregnant women who become aware of the Register's existence through various means. Once a woman is prepared to be recruited into the APR and meets the criteria set down in the initial sentence of this paragraph, her inclusion in the APR is automatic, no further selection policy of any kind being involved. The APR has been estimated to contain information on about 8.7% of the relevant pregnancies in Australia [12]. All contact between the pregnant women and the APR is via telephone. Data concerning the course of pregnancy are recorded at the time of enrolment, at approximately 28 weeks of pregnancy, within the first month after childbirth and, as far as possible, at one year after birth. The accuracy of the information provided by pregnant women is checked with the women's treating medical practitioners, but no attempt is made to influence clinical management. The APR has been under the ethics oversight of various Melbourne based institutional human ethics committees, with that of the Melbourne Health (The Royal Melbourne Hospital) currently holding the responsibility.

Foetal malformation classified in accord with the Australian Victorian Government criteria [13] and drug therapy data from the APR concerning current and previous pregnancies treated with valproate, as well as seizure control data where previous valproate treatment had been ceased before pregnancy, were transferred to an Excel spreadsheet. This information was then analysed by simple statistical methods (odds ratio calculations [14] and logistic regression, using the Stats Direct program [15]).

Results:

Foetal malformations:

At the end of 2017 the APR contained records of 501 current pregnancies which had been exposed to valproate throughout. There was a family history of various types of foetal malformation in 14.0% of these pregnancies, and in 14.6% of pregnancies exposed to other

antiepileptic drugs (AEDs) only. Valproate had been taken as the sole AED in 290 pregnancies, and in combination with other AEDs in 211. Foetal malformation had been present in 63 of the 501 pregnancies (12.6%), with occurrence rates of 14.8% in the monotherapy pregnancies and 10.9% in the polytherapy ones. Logistic regression analysis (Fig 1) showed apparently lower dose-related rates of foetal malformation when valproate was used as part of AED polytherapy. However, the difference was not statistically significant at the P <.05 level (logit malformation risk = -2.690748 + 0.000941 VPA dose – 0.514645 polytherapy; P = 0.083 for the polytherapy effect). Because the polytherapy effect had a probability close to the P<.05 level, a multiple variable logistic regression was calculated for the relationship between the malformation risk and dosages of all the commonly used AEDs. Except for valproate, no AED had any statistically significant partial regression coefficient and apart from valproate, oxcarbazepine and clobazam all the coefficients had negative values. Because of these results, monotherapy and polytherapy pregnancies were not analysed separately beyond this point.

There were 66 individual malformations recorded in the 43 monotherapy pregnancies (an occurrence rate of 1.53 per pregnancy) and 30 in the 20 polytherapy pregnancies (rate 1.50 per pregnancy). The natures of the individual malformations, arranged in order of increasing valproate dosage, are shown in Table1**, i**n which the monotherapy pregnancies and also pregnancies ending in therapeutic abortion are identified. Logistic regressions for the risk of the more commonly occurring malformations on valproate dose are shown in Fig 2. There was no statistically significant regression for the occurrence of facial clefts on drug dose, but the incidences of spina bifida, hypospadias and malformations of the heart and great vessels, and digits, were dose-related. There is an overall impression that those managed by therapeutic abortion, and other more severe, often untreatable, malformations had tended to be associated with higher valproate dosages, particularly in the monotherapy data, but there clearly were exceptions. For the 40 pregnancies in which only a single malformation was recorded, the threshold daily dosages of valproate associated with malformation occurrence were: spina bifida - 1000mg; heart and great vessels - 400mg; hypospadias – 400mg; facial clefts – 500mg; digit abnormalities – 400mg. For all the pregnancies, the mean doses associated with these abnormalities, shown in the same order, were: 2000, 1387, 1623, 1067, and 1562 mg per day.

Therapeutic abortion, apparently carried out because of detection of devastating and essentially un-correctable foetal malformations, had been carried out in 0.5% of pregnancies

where the maternal valproate dose was below 800 mg/day, in 1.03% when the dose was below 1000 mg/day but, at doses of 1000mg/day and above, in 3.8%.

Seizure control:

Valproate had been taken throughout pregnancy to treat generalised epilepsies in 72.7% of the 501 current pregnancies, and in focal epilepsies in 20.2%, the seizure disorder type being uncertain in the remainder. In the APR database, there were also records of 236 previous pregnancies that had been treated with valproate, but where the women concerned were no longer taking the drug. Valproate intake had been ceased before the current pregnancy in 101 of these pregnancies (61 in women with generalised epilepsies, and 36 in women with focal epilepsies, the type of seizure disorder being unclear in the remainder). At the outset of these pregnancies AED polytherapy had been employed in 5 of the 61 generalised epilepsy pregnancies, the individual AEDs taken in this sub-group being: lamotrigine 23 instances, levetiracetam 10, carbamazepine 5, clonazepam 3, and topiramate and clobazam each once, with 23 pregnancies being untreated. For the 36 focal epilepsy pregnancies, the corresponding figures were: polytherapy 3 instances, lamotrigine 17, levetiracetam 5, carbamazepine 7, gabapentin 2, and phenytoin and oxcarbazepine each once, with 6 pregnancies being untreated).

Seizures had occurred during pregnancy in 26 of the 61 pregnancies (42.6%) in the generalised epilepsies subgroup, but in 111 of the 364 generalised epilepsy pregnancies in the APR (30.5%) where valproate use had been continued through pregnancy (Odds Ratio 1.69, 95% C.I. = 0.97, 2.95). However, in the valproate withdrawn subgroup, valproate intake had been re-instituted during the course of 13 of the 61 pregnancies, in 5 of these even though there had been no recurrence of seizures. If these 5 pregnancies are excluded, the seizure-affected pregnancy occurrence rate in the valproate withdrawn pregnancies became 26 in 56 (46.4%) and the Odds Ratio 1.91 (95% C.I. = 1.08, 3.37). In contrast, rates of pregnancies during which seizures occurred were quite similar in the valproate-withdrawn focal epilepsy subgroup (17 in 36 pregnancies, i.e. 47.2%) and in the focal epilepsy pregnancies where valproate intake continued during pregnancy (48 in 101, i.e. 47.5%).

When considering only generalised epilepsy associated pregnancies where the woman involved had been seizure-free for at least a year prior to pregnancy, seizures had occurred during 9 of 36 pregnancies (25%) in the valproate-withdrawn sub-group, and in 44 of the 245 APR pregnancies (18.0%) where valproate had been taken through pregnancy (Odds Ratio

1.52, 95% C.I. = 0.67, 3.46). For the analogous previously controlled partial epilepsies, where earlier valproate therapy had already been withdrawn, the seizure-affected pregnancy rate was 6 in 20 (30%), as compared with 12 in 52 (23.1%) in pregnancies where valproate exposure continued (Odds Ratio 1.43, 95% C.I. = 0.45, 4.53). In the above comparisons, events in the 12 months or longer before pregnancy are compared with events in the shorter 9 months duration of pregnancy, so that the comparisons may be biased against rates of loss of seizure control during pregnancy.

Overall, it seems that substituting other AEDs for valproate had proved disadvantageous in relation to seizure control during pregnancy, and especially so when the drug had previously been used to treat generalised epilepsies. Sufficient data were not available to assess the situation in relation to subtypes of generalised epilepsy. It is also worth mentioning that, in the valproate withdrawn generalised epilepsy subgroup, one foetus died in utero during a severe seizure.

DISCUSSION

The present paper is based on a relatively small collection of foetal malformation data so that conclusions drawn from it need to be treated cautiously. However, so far as we are aware, no similar collection of individual malformation data related to valproate exposure during pregnancy is available in the literature. Because valproate use in pregnancy is diminishing in Australia, and when the drug is being used in pregnancy its dosage has been decreasing, associated with a fall in annual foetal malformation occurrence rates [16], it is unlikely that any significantly larger collection of relevant material will be accumulated in the APR within a reasonable period of time. Consequently, it has not seemed worth delaying an analysis of the material on hand to attempt to gain a contemporary insight into the extent of a major aspect of the problem related to the valproate-foetal malformation issue, despite the obvious desirability of having a larger collection of data to permit more secure interpretations.

Assuming that the general population foetal malformation rate of around 2.5 to 3% would still apply if the 63 pregnancies with foetal malformations analysed in the present study had not been exposed in pregnancy to valproate, it seems that some 50 pregnancies carrying abnormal foetuses may not have occurred. However if, for instances, valproate had been used but in doses below 800 mg a day, there would have been perhaps 6 drug-related

malformation-bearing pregnancies, and in many of these the malformations would have been comparatively mild and, for the most part, treatable.

Clearly avoiding all of the malformations due to valproate, as distinct from those related to other factors, would have been desirable, but would this avoidance entail disadvantages? Leaving aside the situation of women with pregnancy potential who might otherwise have been treated with valproate, a population for which the APR contains no data, the present analysis shows that ceasing valproate intake before pregnancy was associated with an increased chance of seizure-affected pregnancy. This was particularly the case in relation to pregnancies in women with generalised epilepsies where, assuming equal competence in those managing AED therapy in the groups compared, the chance of seizure-affected pregnancy was 50% to almost 100% higher when valproate therapy had been discontinued before pregnancy. This was probably the case because, overall, valproate seems the most effective available AED for managing generalised epilepsies, whereas several other AEDs are available that appear no less effective in controlling focal epilepsies. Since it was not practicable to have seizures diaries kept by the women involved both before and during pregnancy, it was not possible to know whether already active epilepsy before pregnancy might have worsened or improved during pregnancy. However, loss of previous full seizure control would be expected to have adverse consequences for affected women, one obvious one being in relation to holding a vehicle driver's licence. The APR contains little information as to whether altered maternal seizure control in pregnancy had adverse effects on the mother's health, quality of life, and the well-being of her family, including the foetus resulting from her pregnancy. Though no data have been collected, one can speculate concerning other adverse consequences that might occur, recognising that these would probably vary between individuals. Certainly, the possibilities cannot be ignored that accidents involving mother or offspring, or physical injury to either or both, or even unexpected death during or in relation to seizures, [17] may occur.

Because pregnancies outcomes were not followed for more than a year after childbirth, the present analysis is incapable of throwing light on the issue of subsequent valproate-associated neurodevelopmental abnormality, and there does not yet seem to be sufficient information in the literature to estimate what degree of advantage might accrue in this regard from avoiding valproate exposure in pregnancy.

Until more extensive information becomes available, it is hoped that data such as that provided in this paper may help inform those responsible for advising women on issues relating to the question of valproate and existing or future pregnancy. Given advice on the advantages and disadvantages of avoiding valproate use in pregnancy, different women, even in apparently reasonably similar life situations, may have quite different attitudes towards their personal balances between the potential foetal disadvantages associated with intrauterine valproate exposure, particularly at lower drug doses, and the disadvantages in relation to their own epilepsies and the effects those epilepsies may have on their foetuses. It may prove regrettable, and possibly be a source of harm, if official policies that considerably restrict the use of valproate come to be applied in an unthinking way, and as a result tend to deny the opportunity for, or distort, balanced assessments of the situations of individual women whose need for valproate therapy might be better evaluated on a less restrained and adequately informed basis.

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Disclosure of conflict of interest

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C M Lander, JE Graham, AA Hitchcock and M J Eadie have no relevant conflicts of interest to declare. No personal funding from outside bodies has been involved in their roles in this paper.

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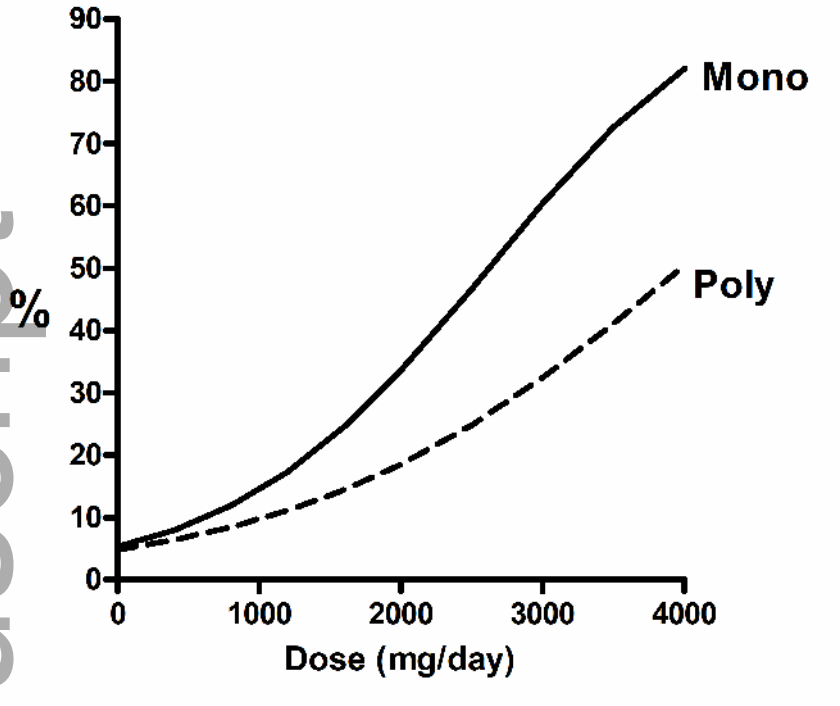
VPA Dose mg/day	Monotherapy	MALFORMATION(s)	
		Rate	Nature
200		**1/43 = 2.3%**	***anencephaly***
400			Dandy-Walker syndrome, talipes
400	M		plagiocephaly
400			microcephaly
400		**7/73 = 9.6%**	VSD, hypospadias, craniosynostosis
400	M		polydactyly, crossed toes
400	M		polydactyly
400	M		ear deformity
500	M		VSD, hypospadias, craniosynostosis
500	M	**3/30 = 10%**	cleft lip
500			undescended testis
600	M		cleft palate. Pierre Robin syndrome
600		**4/41 = 10%**	talipes
600	M		hydronephrosis
600	M		polydactyly
700	M	**2/10 = 20%**	Sturge-Weber syndrome
700	M		PFO
800	M		cleft palate
800	***M***		***Dandy-Walker syndrome, talipes***
800	M		craniosynostosis
800	M		talipes equinovarus
800	M		VSD
800		**11/80 = 13.8%**	***hydrocephalus***
800			hypospadias

800			undescended testis, hydrocele however,
800	M		undescended testis
800	M		hypospadias
800	M		hypospadias undescended testis
1000	M		Fallot tetralogy
1000	M		polydactyly, crossed toes
1000	M		VSD, ASD, digits
1000	***M***		***spina bifida***
1000	***M***	**10/107 = 9.3%**	***trisomy 21***
1000			PDA
1000			fused lambdoid suture
1000			VSD
1000	M		hypospadias, talipes
1000			undescended testis
1400	M		trigger thumb
1400	M	**3/13 = 23.1%**	cleft lip
1400	M		cleft palate, Pierre Robin syndrome
1500	M		hypospadias, hypertelorism
1500	M		spina bifida, ASD, VSD
1500	M		hypospadias, hypertelorism
1500	M	**7/37 = 18.9%**	ASD
1500	***M***		***holoprosencephaly, club feet***
1500			craniosynostosis
1500	***M***		***spina bifida***
1700	M	**1/2 = 50%**	cleft palate
2000	***M***		***spina bifida, hydrocephalus:*** plagiocephaly, polydactyly #
2000			hypospadias, hypertelorism
2000			VSD, hypospadias, craniosynostosis

2000		**7/22 = 31.8%**	spina bifida, hydrocephalus
2000	M		hypospadias
2000			***spina bifida, Arnold-Chiari malformation***
2000			sacral groove
2500	M	**1/4 = 25%**	hypospadias, digits
3000	M		polydactyly, crossed toes
3000	***M***		***spina bifida***
3000	M	**5/10 = 50%**	peno-scrotal fusion
3000			***spina bifida***
3000	M		PDA, digits
5000	M	**1/1 = 100%**	bulbus cordis, ear deformity

Table 1: Details of individual foetal malformations related to increasing maternal valproate dosages, with risk of some malformation occurring at each dosage shown. Malformations associated with pregnancies terminated by therapeutic abortion are shown in bold italics. ASD = atrial septal defect; PDA = patent ductus arteriosus; PFO = patent foramen ovale; VSD = ventricular septal defect.

A twin pregnancy with one twin aborted, the other found malformed at term



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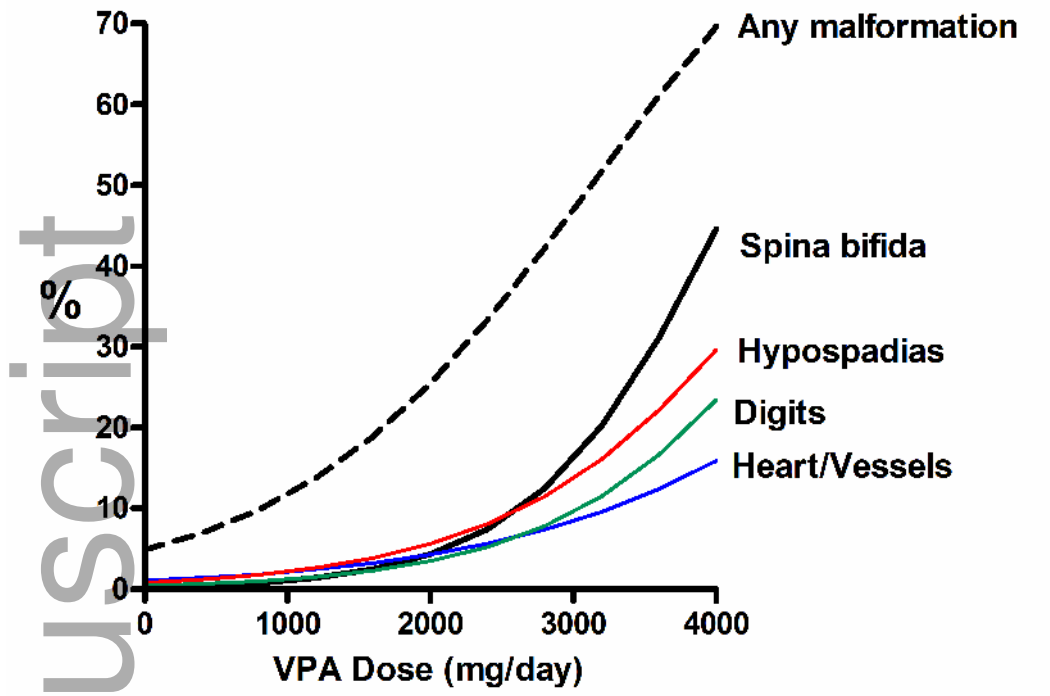

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