

VALPROATE (Commentary)

The challenge of maternal epilepsy

One baby in every two hundred is born to a mother with epilepsy. All the anticonvulsant drugs are potentially teratogenic, yet a severe epileptic attack during pregnancy or delivery can be equally devastating.

Anti-epileptic drug use in women of child-bearing age

Reviewing the need for continued treatment: Two thirds of all children troubled by epilepsy during childhood will find that their disease remits spontaneously before they enter adult life (although the likelihood of this happening is influenced by the nature and the cause of their epilepsy). It becomes extremely important, therefore, to determine whether continued treatment is really necessary. Such a review need to be undertaken at a 'convenient' time in relation to the child's education (specifically, examinations) and to her social and leisure life (eg: not just before she wants to apply for a driving license) or travel abroad. Withdrawal can often be considered when the child has been seizure-free for at least two years. A child's twelfth birthday may often provide the appropriate stimulus to contemplate such a review. Prior EEG information is not usually of sufficient prognostic value to be worth obtaining. A relapse usually occurs during withdrawal or in the first six months after treatment has stopped, but relapses can still occur after this. If treatment withdrawal fails there is only a 20% chance of it being successful if attempted a second time.

Several small UK studies have shown that, at the present time, a third of women who started taking anticonvulsant medication in early childhood are still taking the same drug fifteen years later and are only, belatedly, recognized to be taking treatment unnecessarily after they become pregnant. As treatment with valproate becomes more and more widely used, and as doubts about whether valproate is the optimum drug to use in pregnancy grow, there is an increasingly pressing need for paediatricians to take the lead in ensuring that treatment is only continued into adult life when it is really necessary.

Starting treatment during adolescence or later: Many of the problems that can be confused with epilepsy, including anxiety attacks, pseudo-epileptic seizures and vasovagal (syncopal) fainting attacks, are particularly common in young women. It is, therefore, particularly important to be sure of the diagnosis before putting any woman of child-bearing age on anticonvulsant medication. Specialist referral is, therefore, always indicated. True epilepsy coming on for the first time during adolescence seldom remits quickly. Only half of all adults with continuing epilepsy first developed this problem during childhood.

Contraception: Women taking one of the enzyme-inducing anticonvulsants (including carbamazepine, phenytoin, and topiramate) need to take a high dose oral contraceptive. A pill with 50 micrograms of oestrogen will normally suffice. A few need to take two 30 microgram pills. Break through bleeding shows the dose is too low, but the converse does not always hold and it may be wise to check whether the normal ovulatory rise in plasma progesterone is still occurring at 21 days.

The effect of seizures during pregnancy and child birth

There are significant risks to the fetus if the woman has tonic-clonic seizures including the physical effects of falling because of seizures and also because of hypoxic-ischaemic damage during a prolonged tonic-clonic seizure (including status epilepticus) and also during delivery, when maternal death may occur. It is unclear whether repeated, but brief (<5 minutes) tonic-clonic seizures may also affect the fetus, particularly but not exclusively during the first trimester through repeated periods of mild hypoxia and/or lactic acidosis. Risks to the fetus during maternal absence and myoclonic seizures are likely to be far less, although falls and physical injuries may still occur. Maternal complex partial seizures are also reported to be associated with significant risks (although fewer than with tonic-clonic seizures), with at least one case report of maternal complex partial seizures during labour being associated with foetal heart rate decelerations and prolonged uterine contractions. However, the risk to the fetus of complex partial seizures is likely to be very small and possibly of no clinical significance.

A tonic-clonic seizure may occur during labour in 1–2% of women with epilepsy and within the first 24 hours after delivery in another 1–2%. This is a considerably greater risk than the average probability of a seizure during the preceding pregnancy. The effects on the fetus of a maternal seizure during labour include bradycardia and late fetal heart decelerations for approximately 30 minutes following the seizure.

Anti-epileptic drug use in pregnancy

Long established drugs: Use during pregnancy appears to be associated with a 2 or 3 fold increase in the risk of major congenital malformations in women with epilepsy. All the drugs in common use between 1950 and 1990 have been implicated. The risk of malformation seems to be higher in women taking more than one anticonvulsant, and also seems to be higher in women on high dose treatment. However, while drug use is generally blamed for any malformation, epilepsy itself may be a contributory factor: genetic inheritance may play a part, and seizures themselves may also cause damage). Specific defects that occur

more frequently than normal include neural tube defects (particularly in the lower thoracic and lumbo-sacral region), where the risk appears to be particularly high if the woman is taking valproate or carbamazepine. Clinicians often stress the risk of oro-facial clefting (with or without palate involvement), but the risk of this only seems to be convincingly increased in women taking phenobarbital and, even here, the increase in risk is not great (odds ratio about 3). Radial ray (limb) defects and genito-urinary malformations may be marginally commoner. Many reports speak of congenital heart disease as being commoner but there is, in fact, no good evidence that this is true. Minor anomalies, such as hypoplastic digits and/or nails (particularly with phenytoin) and dysmorphic facial features (eg: broad nasal bridge, short nose, flat philtrum), almost certainly occur more frequently but often go under-recognised. It does a disservice to families to mention such things when counselling parents as they are of little clinical importance.

The facial appearance in children born to mothers who have taken sodium valproate is said to be more distinctive, and includes a thin upper lip, anteverted lower lip, grooves under the eyes, incomplete medial borders of the eyebrows and prominence of the mid-line metopic suture of the forehead. Collectively, all of these features are often referred to as the 'fetal valproate syndrome'. However, this specific syndrome is not seen in the majority of babies where the woman has been taking sodium valproate and tends to show a dose-dependent relationship – being more likely to occur where the dose exceeds 1.0–1.5 grams per day. In addition, when present, the features of the 'fetal valproate syndrome' are rarely obvious at birth and usually only recognisable after the first year of life.

Recent studies have suggested that some antiepileptic drugs may have an additional adverse effect on the child's development and/or the older child's co-ordination, intellectual functioning and communication skills, including autistic spectrum disorder, even where there are no dysmorphic features. Sodium valproate is the drug that has most frequently caused concern in this regard. Carbamazepine, in contrast, has come out of most of these observational studies with a reasonably clean 'bill of health' to date. It has to be stressed, however, that these developmental and/or cognitive outcomes may well represent the cumulative, or additive, effect of an underlying genetic susceptibility at least as much as an effect of the medication itself.

The nearest we yet have to a study that has allowed for these factors is an elegant ten year study from Finland (Artama, *et al.* 2005) where the number of easily recognizable congenital malformations in the 1,411 children of mothers who continued taking antiepileptic medication during the first trimester of pregnancy was compared with that found in 939 children who had stopped taking medication. This study seems to have shown, fairly convincingly, that the risk of malformation was increased **four** fold in children whose mothers continued to take valproate in early pregnancy. The number of pregnancies terminated because of fetal abnormality is not known, but spina bifida only accounted for 6 of the 65 defects seen in the children born to women taking valproate. Polytherapy seemed to increase the risk, as did high dose monotherapy. Indeed the risk of a malformation was ten fold higher in babies whose mothers took more than 1,500 mg of valproate a day. No such risk was seen in those who only took carbamazepine, oxcarbazepine or phenytoin.

In a further recently published study, in which an attempt was made to control for social and genetic factors by testing the mother as well as the child (Vinten, *et al.* 2005), there was evidence that maternal valproate treatment during pregnancy also has an impact on cognition in school-age children. No such association was seen with other anticonvulsant medication. More comparative studies looking at the use of different drugs during pregnancy are urgently needed to unravel what fraction of cognitive impairment is genetic in origin, and what fraction is drug related. National and international prospective research is now underway to address these issues (see below).

Newer drugs: Gabapentin, lamotrigine, levetiracetam and tiagabine do not seem to be teratogenic in animals; vigabatrin has been associated with oro-facial clefting in New Zealand white rabbits and topiramate causes limb and digit reduction in a number of animal species. However, there is, as yet, very little information on the occurrence of major structural malformations, minor anomalies and even less information on the later developmental and cognitive development in children exposed to these newer drugs. This is, in part, due to the fact that these drugs have only come into common usage in the last decade, and to the fact that, in the early years, these newer drugs were used as "add on" treatments when older drugs proved inadequate on their own. This makes it very difficult to decide whether any abnormality noted was due to the older drug, the newer drug, or the combined use of both. Despite this, some clinicians do use one of the newer drugs (usually lamotrigine) rather than one of the older drugs (and, in particular, sodium valproate) when treating teenage girls and women of child-bearing age. Only time will tell whether this turns out to have been a wise move.

Monitoring blood levels: Anticonvulsant blood levels nearly always fall during pregnancy (usually by 10–12 weeks), returning to what they were earlier 4–6 weeks after pregnancy is over. There are many reasons why plasma levels might fall during pregnancy, including increased renal or hepatic clearance, increased plasma volume, reduced plasma albumin and reduced protein-binding capacity,

increased vomiting (and therefore reduced drug absorption) and decreased compliance. Decreased blood levels are seldom associated with deteriorating seizure control or with increased drug toxicity. If monitoring is called for, it is the unbound rather than the total protein-bound fraction that should be measured. There is, as yet, little evidence that routine monitoring is beneficial. Monitoring will sometimes show that the women has decided that, despite advice to the contrary it would be better to stop treatment during pregnancy. One recent study found, when they analysed samples of hair, that this was commoner than was generally admitted (Williams *et al.*, 2002).

Supplementary folate: Women with epilepsy are generally advised to take supplemental folic acid (q.v.), especially if they are on an anticonvulsant drug. A daily 0.4 mg supplement is generally recommended, although it is often argued that a 4–5 mg supplement is more appropriate if there is a past family history of neural tube defects. Organisations in the US, Canada and the UK have all issued similar advice. There is no proof that folate supplementation works. The recommendations are, however, based on three interrelated observations: first, that it reduces the frequency of neural tube defects in the normal population; second, that some anti-epileptic drugs (specifically, phenytoin, phenobarbital and carbamazepine) are known to reduce blood folate levels; and, third, that some other anti-epileptic drugs (specifically, sodium valproate and carbamazepine) seem to increase the risk of neural tube defects. Valproate is considered to increase this risk by inhibiting glutamate formyl transferase, an enzyme mediating the pathway that produces folinic acid. The potential combination of reduced serum and red cell folate levels and an inherent increase in the risk of neural tube defects would suggest that folate supplementation is a reasonable recommendation. However such use **must** be started prior to conception, and preferably from the time that a woman becomes sexually active; folate started more than 25 days after conception does not seem to have any neuro-protective effect.

Vitamin K: It is *not* necessary for mothers to take vitamin K before delivery, as often advised, but the babies of mothers taking one of the enzyme-inducing anticonvulsants (carbamazepine, phenobarbital, phenytoin or topiramate) should be given IM vitamin K at birth as advised in the main monograph on this vitamin and its associated web commentary.

Anti-epileptic drug use during lactation

Use of any of the anticonvulsants listed in this compendium is generally considered safe during lactation, although little is known about safety of some of the more recently introduced drugs. Nevertheless it has to be recognised that the babies of mothers taking ethosuximide and phenobarbital will sometimes have drug levels in their blood not dissimilar to those of their mothers (a situation that can, if the mother so wishes, be avoided after birth even though it could not be avoided before birth. Most would hold that, because of the known advantages associated with breast feeding, nothing should be done to dissuade a mother from breast feeding if she so wishes merely because she is taking a reasonably well studied anticonvulsant drug. Most of the evidence currently available is summarised in two extensive reviews by Hägg and Spigset (2000) and by Barr-Oz *et al.* (2000).

The future

Regional and national databases of registers already exist for anti-epileptic drugs and pregnancy in many countries, including the UK, Australia, India and the USA. An International Anti-Epileptic Drug and Pregnancy register is currently being developed in conjunction with the European Epilepsy Academy (EUREPA) and the International League Against Epilepsy (ILAE). Such an international register may well be launched soon. To be unbiased it is important to have as much as possible of the information obtained by these registers documented prospectively.

UK register: www.epilepsyandpregnancy.co.uk

US register: www.aedpregnancyregistry.org

International register: www.eurepa.de

More information about the UK register can be obtained from Dr J Morrow, The Royal Victoria Hospital, Belfast, BT12 6BA. Freephone: 0800 389 1248.

Further reading

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