Prescribing in Pregnancy

Epilepsy and anticonvulsant drugs

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An epileptic seizure is a paroxysmal discharge of cerebral neurones resulting in a clinical event apparent to the subject or an observer, or both. Tonic-clonic (grand mal) seizures are common and most disruptive of life, but many patients have combinations of complex partial (temporal lobe) seizures and tonic-clonic seizures. Epilepsy, which is best defined as a continuing tendency to epileptic seizures, affects about 0.5% of women of childbearing age.¹ Thus family doctors and obstetric units will from time to time have a pregnant woman with epilepsy under their care. A unit delivering 3000 mothers a year will have about 15 pregnant women with epilepsy on their books at any one time.

It must be remembered that seizures, particularly if they occur in the third trimester, may be due to eclampsia rather than epilepsy. Although modern antenatal care makes it unlikely that eclamptic seizures will occur without previous evidence of pre-eclampsia, many patients presenting with eclampsia have not attended for antenatal care. Furthermore, eclampsia may appear suddenly, particularly during or after delivery.

Epilepsy and oral contraception

Some women with epilepsy may become pregnant unexpectedly while taking oral contraceptives if they are also taking phenytoin. This drug induces hepatic hydroxylating enzymes so that the metabolism of phenytoin itself and many steroids, including oestrogens, is increased. Pregnancy is more likely to occur if a low oestrogen contraceptive is used, but women taking pills containing 50 µg of oestrogen may also become pregnant. Women must be advised of this risk and either use an alternative method of contraception or change their anticonvulsant treatment if they do not wish to become pregnant.

First seizures in pregnancy and epilepsy which begins in pregnancy

The age specific annual incidence of epilepsy is roughly constant at 40-50 cases per 100 000 women throughout the childbearing period.¹ In some women pregnancy and the onset of non-eclamptic seizures will therefore coincide by chance. There is no statistical evidence that pregnancy is likely to precipitate epilepsy. Occasionally, non-eclamptic seizures may occur for the first time in pregnancy, remit after delivery, and then return only in subsequent pregnancies.² Knight and Rhind found only two such patients among 59 epileptic mothers studied during 153 pregnancies.² In

women with pre-existing epilepsy it is unusual for seizures to recur during pregnancy after a prolonged period without seizures. The apparent rarity of such events indicates that pregnancy itself is not a particularly potent epileptogenic agent.

A patient who starts to have seizures during pregnancy should be referred to a neurologist, who will decide whether investigation of the cause is necessary. Investigation is essential if neurological signs develop in association with the seizures or if there are other symptoms such as headache. Seizures with a partial onset also require investigation. An electroencephalogram is unlikely to help in diagnosing the cause but may be helpful in deciding the type of seizure and therefore appropriate anticonvulsant treatment. Computed tomography is required for diagnosing a structural lesion. This is reasonably safe for the fetus, which can be protected from scattered radiation by suitable lead curtains and abdominal screening. Magnetic resonance scanning may be an alternative choice.

Although tumours are rare causes of seizures in women of reproductive age,³ some epileptogenic tumours, such as meningiomas, expand during pregnancy.⁴ Arteriovenous malformations may expand or infarct during pregnancy and, late in pregnancy or in the immediate puerperium, seizures may be due to cortical venous thrombosis.⁵

Frequency of seizures during pregnancy

Schmidt reviewed 27 studies of the effect of pregnancy on the course of epilepsy published between 1884 and 1980 and found considerable variation in the frequency of seizures.⁶ For example, in one study 75% of patients had more seizures and 8% had fewer; in another study 33% had more seizures and 52% had fewer. The average experience from all the studies listed by Schmidt in a total of 2165 women was an increase in frequency of seizures in 24% and a decrease in 22%; in 53% of women the frequency of seizures remained unchanged. Many of these studies are now out of date since increased knowledge of the changes in metabolism of anticonvulsant drugs during pregnancy has enabled better control of oral dosage and serum concentrations.

Schmidt *et al* studied the course of 23 pregnancies in women who were not taking anticonvulsant drugs.⁷ The number of seizures increased in only eight pregnancies, and in six of these the authors thought that deprivation of sleep was important. The definition of deprivation of sleep, however, was only "a delay of more than two hours from the usual working day onset of sleep." The increase in frequency of seizures occurred most often in the first two trimesters. This proportion—one third of women having an increased frequency of seizures during pregnancy—is in accord with the wider review of Schmidt.⁶ The evidence suggests that untreated epileptic pregnant women are about equally likely to experience fewer seizures as more seizures during pregnancy.

Remillard *et al* analysed the effects of pregnancy on the different types of epileptic seizure.⁸ Women with secondary generalised and complex partial seizures were most likely to have an increase in

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frequency of seizures during pregnancy (83% and 67% of mothers respectively). Only 29% of those with primary generalised epilepsy showed such an increase.

In a prospective study of patients receiving anticonvulsant treatment during pregnancy Schmidt *et al* found that the frequency of seizures increased in one third of pregnancies.⁷ In two thirds of these cases the increase was associated with either poor compliance with anticonvulsant treatment or deprivation of sleep. Good compliance with anticonvulsant treatment is not easily attained. Pregnant women in developed countries are increasingly aware of the teratogenic effects of anticonvulsant drugs (see below), and they may therefore reduce or stop the prescribed regimen in an attempt to reduce the chances of having an abnormal baby.

Among pregnant epileptic women as a group, whether receiving anticonvulsant treatment or not, those who had not had a tonic-clonic seizure in the year before pregnancy, who had only one type of seizure, and who had primarily generalised epilepsy were the least likely to have an increase in frequency of seizures during pregnancy.⁷ These factors are similar to those which favour good prognosis for seizures in men and non-pregnant women.⁹

Metabolism of anticonvulsant drugs during pregnancy

The writings of many authors in the United Kingdom and the United States have encouraged physicians to simplify anticonvulsant regimens to avoid adverse effects and interactions between drugs.¹⁰ In a typical recent study nearly half of the pregnant women with epilepsy were taking only one drug.¹¹ The drugs most widely used are phenytoin, carbamazepine, and sodium valproate. Published work is extensive, and much of it has been collected in a monograph.¹² Only examples will be given here.

ABSORPTION

Absorption of anticonvulsant drugs from the bowel may be reduced during pregnancy. Ramsey *et al* reported a pregnant woman with seizures who had low serum concentrations of phenytoin, complicated by the occurrence of status epilepticus, until the oral dosage of phenytoin was increased to 1200 mg a day.¹³ Metabolic studies showed that the proportion of unmetabolised phenytoin in the urine remained unchanged but a large proportion (56%; normal range 5-15%) was excreted in the stool. This proportion fell to 23% after delivery. The malabsorption was not specific for phenytoin, also affecting xylose and dietary fat.

DISTRIBUTION

During pregnancy fluid retention and the volume of fetal tissues and placenta increase the available volume for distribution of anticonvulsant drugs. This dilution tends to lower the serum concentration if the oral dose is not changed. The figure shows the fall in serum phenytoin concentration which may occur during pregnancy, although this is not due to dilutional effects alone (see below). In a recent study Jensen showed that the increase in the volume of distribution of both carbamazepine and phenytoin could not be accounted for by weight gain alone, which suggests some increased tissue affinity for these drugs during pregnancy (Jensen NO, International League against Epilepsy, York 1986).

PROTEIN BINDING

Ruprah *et al* found that binding of phenytoin to plasma proteins was considerably reduced in the last trimester.¹⁴ A reduction in binding changes the relation between the serum concentration of phenytoin and its therapeutic effect since a greater proportion of the drug is free and pharmacologically active. The clinical value of measuring phenytoin concentrations in whole serum is therefore greatly reduced unless serum binding capacity is also measured. It is

insufficient to judge the extent of protein binding by measuring the concentration of plasma albumin because this correlates poorly with protein binding. Direct measurement of protein binding is time consuming and requires a considerable volume of blood. Knott *et al* found, however, that the concentration of phenytoin in saliva measured during the pregnancies of 11 epileptic mothers correlated with the fraction of phenytoin that was unbound.¹⁵ The correlation was sufficiently close to allow the ratio of saliva and plasma phenytoin concentration measured at the same time to be used as an index of the free fraction. The figure shows the fall in saliva phenytoin concentration during pregnancy, and hence the reduced biological effect, despite an increase in the saliva to plasma ratio, indicating reduced binding. The concentration of phenytoin can be measured in very small volumes of saliva. Some workers believe that citric acid crystals should not be used as a sialagogue if the drug is assayed by an enzyme multiplied immunoassay technique as the enzyme used in the assay may be inhibited by the resulting low pH.¹⁶

Some anticonvulsant drugs are present in fetal blood in lower concentrations than in maternal blood, but others may accumulate in the fetus so that fetal blood concentrations exceed those of the mother. Some of the difference may be accounted for by higher concentrations of drug binding proteins on one side of the placenta. Krauer measured changes in serum albumin and α_1 -acid glycoprotein in paired maternal and fetal blood and showed differential changes in the ratios during pregnancy.¹⁷ Difficulties in analysing these changes are compounded by the changes in maternal blood free fatty acids, which displace some drugs from proteins in maternal serum. Increased concentrations of drugs in fetal blood can therefore result from decreased concentrations of drug binding proteins in the mother or increased concentrations of displacing agents. The increased concentration of free fatty acids in both mother and child at birth can result in decreased protein binding of diazepam and valproic acid,^{18,19} but the importance of the increased drug concentrations at this time is uncertain. Changes during early pregnancy may well be important, however, because an increase in the free fraction of anticonvulsant drugs in the fetus may lead to a greater risk of fetal abnormality. For example, Krauer *et al* have shown that the free fraction of diazepam in fetal serum is considerably increased in early pregnancy.²⁰

CLEARANCE

The maternal liver usually develops an increased capacity for hydroxylation of some anticonvulsant drugs such as phenytoin.²¹ Lander *et al* found that in pregnant women the clearance of phenytoin after intravenous injection was roughly twice the rate found in non-pregnant patients.²² In five patients studied before and during pregnancy Jensen found increases in urinary excretion of parahydroxyphenytoin—the principal metabolite of phenytoin—ranging from 16% to 143% compared with values before pregnancy, and body clearance increased by 13% to 73% (International League against Epilepsy, York 1986). In Jensen's study the patients had been taking phenytoin for at least one year before the first estimation (while not pregnant), and so the results could not be due to the induction of hydroxylating enzymes by phenytoin itself but must represent a change associated with pregnancy. Jensen also reported increases in the clearance of carbamazepine of up to 30% in six patients and increases in the urinary excretion of trans-10,11-dihydroxycarbamazepine, the principal metabolite of carbamazepine, of 32-138%. Bardy *et al*, on the other hand, did not find significant changes in the clearance of carbamazepine, though the clearance of phenobarbitone was considerably increased.²³ There were striking variations within and between individuals in the clearance of primidone, but overall no significant changes were found.

The increased clearance of anticonvulsant drugs and the changes in volume of distribution may well result in a fall in serum concentration (figure). It must, however, be remembered that such a fall does not necessarily reflect changes in free concentration of anticonvulsant drugs such as phenytoin due to changes in protein binding. Any woman with active epilepsy who becomes pregnant

will therefore need regular estimations of concentrations of anti-convulsant drugs in serum and saliva with appropriate adjustment, usually an increase, of oral dosage. Close liaison between the obstetrician, neurologist, and mother is advisable. If the oral dosage of an anticonvulsant drug is increased during pregnancy appropriate adjustments must be made after delivery in order to avoid intoxication.

Concentrations of phenytoin in saliva and plasma and (top) ratio between the two (saliva:plasma). Although saliva and plasma concentrations roughly follow each other, there is a significant increase in ratio throughout pregnancy, reflecting increased amount of drug which is not bound to plasma protein. Probably only the unbound fraction of the drug is pharmacologically active. Asterisks indicate seizures. The break in the abscissa indicates delivery.

Data reproduced by kind permission from Knott C, Williams CP, Reynolds F. Phenytoin kinetics during pregnancy and the puerperium. *Br J Obstet Gynaecol* 1986;93:1030-7.

DRUG INTERACTIONS

Phenytoin interacts with many other drugs.²⁴ For example, benzodiazepines, which may be given to anxious pregnant women with epilepsy, lower the serum concentration of phenytoin.

Epilepsy and fetal abnormality

EFFECTS OF THE SEIZURES

Apart from the possibility of a genetic association between epilepsy and the risk of fetal abnormality (see below), seizures could cause fetal damage through hypoxia or associated trauma.

Fetal monitoring during a maternal tonic-clonic seizure lasting three minutes showed that the onset of the seizure was immediately followed by fetal bradycardia lasting about 15 minutes.²⁵ Prolonged maternal seizures, or status epilepticus, could therefore harm the fetus. Suggested regimens for managing status epilepticus in pregnancy have been published,²⁶ but, with the exception of the need for fetal monitoring, they do not differ appreciably from usual medical management. In one study the highest malformation rate was for pregnancies in which seizures had occurred despite drug treatment, though the numbers were insufficient to make this association significant.²⁷ Although a fall during a seizure could damage the fetus, such an event must be extremely rare. There is

also no evidence to suggest that obstetric complications, such as pre-eclampsia, accidental haemorrhage, or hyperemesis, are more common in epileptic mothers.^{28, 29}

One Scandinavian study suggested that obstetricians may be more likely to attempt potentially harmful obstetric intervention, such as induction of labour and instrumental delivery, in pregnant women with epilepsy,³⁰ although this is seldom indicated. Another study, however, did not show an excess of such interventions.²⁵

GENETIC ASSOCIATION OF EPILEPSY AND FETAL ABNORMALITY

Facial clefts and cleft palate are among the most common fetal abnormalities associated with epilepsy and its treatment. The role of treatment in causing such abnormalities is considered below, although genetic factors could be responsible for both the epilepsy and the malformations. Alternatively, the increased risk of fetal abnormality may be limited to families with a genetic predisposition to malformations. A recent study from Denmark showed that epileptic men did not have more children with facial clefts than men in the general population,³¹ which is in contrast to results of some earlier studies. Epileptic women, however, did have more children with facial clefts (with or without cleft palates) than women in the general population, but this increased incidence occurred only after the onset of epilepsy. Genetic factors linking epilepsy and facial clefts were largely excluded by this study. The authors concluded that epilepsy itself contributes to facial clefts in offspring; the ratio between the number of observed cases and expected cases was zero for children born before the onset of epilepsy and 2.4 for children conceived after the onset of epilepsy and where no anticonvulsant treatment had been given during the pregnancy. The ratio was 4.7 if the fetus had been exposed to anticonvulsant drugs. Although this was a large scale survey, the numbers of affected children were small, and lower confidence limits for these ratios were not given.

EFFECTS OF ANTICONVULSANT DRUGS ON THE FETUS

In 1968 Meadow reported six infants with cleft lip and palate born to mothers with epilepsy who had taken anticonvulsant drugs during pregnancy.³² Four of the children also had cardiac lesions. All of the children had an unusual facial appearance with short neck, low hairline at the back, widely spaced eyes, and minor deformities of the pinna. This report led to a large number of publications, which have been reviewed elsewhere.^{12, 27} Overall, results showed that children of epileptic mothers taking drugs have roughly twice as many malformations as children of mothers in the population as a whole. Since about 3% of all newborn babies have a significant congenital abnormality the chance of the child of a mother with epilepsy having a significant abnormality are about 6%. It is probably more encouraging to talk to the mother in terms of a 94% chance of having a normal child.

If anticonvulsant drugs are necessary in early pregnancy the smallest dose that is compatible with control of seizures should be used. Factors other than the serum concentration of unbound drug may, however, be important in teratogenesis. There is good evidence of a genetic predisposition to congenital abnormalities induced by phenytoin. The most striking example is a case report of fraternal heteropaternal twins born to a mother treated with phenytoin.³³ One twin had many features of the fetal hydantoin syndrome³⁴ and the other none. Strickler *et al* found that a genetic defect in detoxification of arene oxides, intermediate metabolites of phenytoin metabolism, is correlated with major congenital defects in infants born to mothers treated with phenytoin.³⁵

Troxidone, now seldom used, was found to be strongly teratogenic in one multicentre study.²⁷ Affected children have low set, backwards sloping ears, V shaped eyebrows, anomalies of the palate, irregular teeth, and developmental delay.³⁶ A fetal hydantoin (phenytoin) syndrome has also been reported,³⁴ the affected children suffering from craniofacial abnormalities, mental retardation, and limb defects such as digital hypoplasia. Similar dysmorphic features, however, have been seen in the children of

epileptic mothers treated with other anticonvulsant drugs or not treated at all,³⁷ and the specificity of these "syndromes" is in doubt.³⁸ There is little doubt, however, that sodium valproate is particularly likely to result in neural tube defects.³⁹ All 10 cases reported by Lindhart and Meinardi had open defects that probably would have been detected by measuring α -fetoprotein concentration in amniotic fluid and by ultrasound scanning.³⁹

There have been few reports of fetal abnormality associated with carbamazepine, but this may reflect merely the fact that this drug has come into extensive use only in the past 12 years or so.

Other metabolic disturbances induced by anticonvulsant drugs

SERUM FOLATE CONCENTRATION

Treatment with anticonvulsant drugs may result in decreased serum folate concentrations and, occasionally, megaloblastic anaemia. Hiilesmaa *et al* measured serum folate concentrations in 150 pregnancies of 137 epileptic mothers who received small (about 500 μ g) folic acid supplements.⁴⁰ Maternal serum folate concentrations correlated inversely with serum concentrations of phenytoin and phenobarbitone but not with those of carbamazepine. Folate values usually remained well within the normal range. There was no suggestion that a low folate concentration resulted in an increased frequency of seizures. A low dose of folate supplement therefore seems to be sufficient for pregnant women with epilepsy, despite the effect of phenytoin and phenobarbitone on folic acid.

VITAMIN D METABOLISM

Long term treatment with phenytoin and phenobarbitone has been shown to induce clinical osteomalacia and rickets and, more commonly, hypocalcaemia without clinical evidence of bone disease. Phenobarbitone and phenytoin increase the hepatic metabolism of vitamin D and 25-hydroxyvitamin D with depletion of vitamin stores. It has also been suggested that these drugs may modify the metabolism of dihydroxyvitamin D or inhibit intestinal absorption of minerals through mechanisms independent of any effect on vitamin D metabolism. Markestad *et al* showed that pregnant epileptic women who were taking anticonvulsant drugs and receiving 400 IU of vitamin D₃ a day had lower median concentrations of 25-hydroxyvitamin D and 1,25 dihydroxyvitamin D and higher median 25,26 dihydroxyvitamin D concentrations than a control group of pregnant women who also received 400 IU of vitamin D₃ each day.⁴¹ Serum calcium concentrations tended to be lower in the women with epilepsy, but it is unlikely that these metabolic effects would be clinically important in developed countries. Asian epileptic mothers who have migrated to less sunny climates may be at risk, however, as may their babies.

THYROID FUNCTION

Although the thyroxine concentration of cord serum is significantly reduced in the infants of epileptic mothers treated with anticonvulsant drugs, this effect is entirely due to altered protein binding.⁴² Phenytoin competes for thyroxine binding sites on thyroxine binding globulin.

VITAMIN K METABOLISM

Neonates born to mothers with epilepsy who have been treated with anticonvulsant drugs are at increased risk of haemorrhage. The mechanism of this has been partly illuminated by studies on prothrombin and vitamin K. The carboxylation of an inert precursor of prothrombin in the liver is carried out by a vitamin K dependent enzyme, γ carboxylase. In the absence of vitamin K, or in the presence of vitamin K antagonists, γ carboxylase is inhibited and the inert precursor—known as protein induced by vitamin K

absence (PIVKA)—appears in the serum. Davies *et al* have shown that concentrations of protein induced by vitamin K absence are raised in men and women with epilepsy treated with phenytoin, carbamazepine, sodium valproate, and phenobarbitone without any biochemical evidence of hepatic dysfunction.⁴³ Neonatal haemorrhage can be prevented by giving women vitamin K during pregnancy.⁴⁴

NEONATAL PERIOD

The rate of clearance of anticonvulsant drugs from newborn babies has been reviewed by Bossi.⁴⁵ The half life of sodium valproate is 14-88 hours, primidone 7-60 hours, phenobarbitone 40-500 hours, phenytoin 15-105 hours, and carbamazepine 8-28 hours.

The clinical signs of barbiturate withdrawal in the neonate are hyperexcitability, occasional seizures, tremulousness, and impaired suckling.⁴⁶ Kaneko *et al* found less efficient suckling and slower weight gain in the infants of epileptic mothers than in the infants of normal mothers.⁴⁷ Expectant supervision of such children is usually adequate, but if tremulousness or, in particular, seizures occur, small doses of phenobarbitone (3-5 mg/kg/day) may be given.

BREAST FEEDING

Most mothers taking anticonvulsant drugs may safely breast feed their children. Significant amounts of these drugs do, however, pass into the milk.⁴⁷⁻⁴⁸ The ratio between the concentration in breast milk and serum concentration is 0.19 for phenytoin, 0.41 for carbamazepine, 0.36 for phenobarbitone, and 0.70 for primidone.⁴⁷ In practice, phenytoin and carbamazepine have little clinical effect on the neonate.

Conclusions

An epileptic woman of childbearing age who has had no seizures for two or three years should have anticonvulsant treatment gradually withdrawn before any planned pregnancy. For a woman who needs anticonvulsant drugs the dose should be as low as possible. Serum or saliva concentrations of anticonvulsant drugs should be monitored during pregnancy because there are considerable changes in pharmacokinetics. There is a risk of teratogenesis; the risk seems to be least for carbamazepine. Readjustment of dosage is necessary in the puerperium. Mothers taking anticonvulsant drugs may safely breast feed their children.

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Portraits from Memory

7—Dr E C (Ted) Smith (d 1943)

JAMES HOWIE

Ted Smith, a medical graduate of Dublin, was a first rate microbiologist; director of the Medical Research Institute at Yaba, Ebute Metta, Lagos, Nigeria; a real gentleman, a bachelor, a lover of animals, music, and flowers; and a most effective supporter of the British army pathologists who were posted to Nigeria during the period 1941-3.

I was in charge of the first of the laboratories that was set down in Nigeria as part of 56 General Hospital in Ibadan in May 1941. Very soon after my arrival I was summoned to a military-civilian conference in Lagos to discuss the problems that had arisen from the possibility that yellow fever might well be exported by aircraft from west Africa to Egypt and India, where the disease did not exist but the transmitting mosquito did. After the fall of France in 1940, and the failure in September 1940 to capture Dakar in French West Africa, the only means of rapid communication between Britain and Egypt and India was by air via Sierra Leone, the Gold Coast, Nigeria, and the Sudan or east Africa. The risk of spreading yellow fever by this air route was well understood and was guarded

against by so called anti-maryll precautions worked out in the 1930s by the League of Nations Health Organisation in Geneva. These precautions required the elimination of all mosquito breeding areas within a quarter of a mile range of airfield buildings and runways, that distance being regarded as the greatest a mosquito could fly. Yellow fever in an African could be a very mild infection so that a carrier state could not be excluded. No unimmunised person, therefore, was allowed within the anti-maryll area. So, the calculation went, no passenger or mosquito carrying the virus could reach Egypt, east Africa, or India by the air route. But runways up to 10 times the lengths originally legislated for made it impossible to keep the zone mosquito free. Moreover, the danger of enemy airborne invasion from adjacent Vichy French territories was a real threat and it became necessary to station unimmunised African troops on the four trans-African airfields in Nigeria. Rotation of duties meant that these troops could come from any of the regiments scattered throughout that vast area—six times the size of England and Wales.

Knowing nothing about yellow fever except from textbooks, I was now called on to advise the military how best to respond to the urgent civilian representations that "something must be done." It seemed to me that, with plenty of energy and good organisation, it would surely be possible to immunise all the African troops who might be liable for airfield protection duty.

How little I knew of the vaccine, as I was promptly told. It was expensive and scarce, especially after the bombing of the one laboratory in England that could make it. Moreover, it had to be

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