Antiepileptic drugs in pregnancy and lactation

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Summary

No antiepileptic drug is completely safe to use in pregnancy as the risk of fetal abnormality is increased. Valproate should be avoided if possible because of the risk of major malformations. Ideally a plan for managing the woman's epilepsy during pregnancy should be prepared before conception. The occurrence of an unexpected pregnancy should not trigger sudden cessation or alteration of antiepileptic drug treatment without medical advice. The smallest effective dose of a drug with a low risk of teratogenicity should be used. Doses may need adjustment as the pharmacokinetics of some drugs change during pregnancy. Data are limited, but most antiepileptic drugs seem to have little effect on full-term breastfed babies.

Key words: birth defects, folate, valproate, vitamin K.

(Aust Prescr 2008;31:70–2)

Introduction

Uncontrolled epilepsy in a pregnant woman is a serious and potentially life-threatening condition for both mother and child. Most pregnant women with epilepsy will need to take at least one antiepileptic drug. The goal for all concerned is a healthy, seizure-free mother and an undamaged child. The following somewhat contradictory issues need to be considered concurrently.

- The optimum treatment of the mother's epilepsy requires that the most appropriate antiepileptic drug be used in effective doses throughout pregnancy. This requires knowledge of specific epileptic syndromes and also antiepileptic drug pharmacokinetics before, during and after pregnancy.
- Any adverse effect that the antiepileptic drug could have on the developing child needs to be avoided or minimised during pregnancy and lactation.

Fetal abnormality

Women with epilepsy taking antiepileptic drugs have a greater (2–3 times) risk than other women of having a baby with a fetal abnormality. Taking more than one antiepileptic drug carries a higher risk than monotherapy. Major malformations, such as congenital heart disease, neural tube defects, urogenital defects and cleft lips or palates, occur in about 3–7% of women with epilepsy who take antiepileptic drugs, although a substantially higher risk is attributed to high doses of valproate (greater than 1400 mg/day).

For more than 30 years, a gradually increasing body of literature has attributed a 'fetal anticonvulsant syndrome' and increased malformation rate to all the 'old' antiepileptic drugs – barbiturates, phenytoin, carbamazepine and valproate. Some data are now available for lamotrigine, but very little is known of the risk of the 'new' antiepileptic drugs such as levetiracetam, topiramate, oxcarbazepine, gabapentin, pregabalin, tiagabine and zonisamide.

Problems may emerge in childhood. Numerous small studies have suggested cognitive and language impairment and an increase in autistic spectrum disorder in children who have been exposed to antiepileptic drugs *in utero*.[1] Recent reports suggest that these problems may be highest in children who have been exposed to valproate.

In order to better understand the extent of the teratogenic risks of all antiepileptic drugs, observational pregnancy registers have been established around the world including Australia.* These registers contain useful information about the most commonly used antiepileptic drugs. From these registers, consistent warnings about the increased risk of structural birth defects have been issued for valproate. The North American Pregnancy Register has published specific concerns with respect to phenobarbitone and lamotrigine.

Management of women with epilepsy

Before conception, a comprehensive management plan is desirable. The diagnosis of epilepsy needs to be validated, the epilepsy syndrome elucidated, 'optimal' antiepileptic drug treatment established and folate supplements given. Potential parents should understand that there are no 'safe' antiepileptic drugs in pregnancy. The balance of risks, as presently known, should be explained to them. All risk of harm cannot be eliminated.

Women with epilepsy who are considering pregnancy should be treated with the least teratogenic but most efficacious

* Australian Pregnancy Register for women on anti-epileptic medication. Phone 1800 069 722.

antiepileptic drug for their particular type of epilepsy at the lowest effective dose. Pregnancy counselling and planning are strongly advised. When an unexpected pregnancy happens and embryogenesis has already occurred, there is usually little to gain and there may be substantial risk in stopping or changing antiepileptic drugs. Early monitoring for an adverse fetal outcome and appropriate counselling are advisable.

Folate and vitamin K_1

All women are recommended to take folate supplements before pregnancy. It is reasonable practice to recommend routine folate supplementation, 0.5–1.0 mg/day, to all potentially reproductive women with epilepsy taking antiepileptic drugs even if they are not contemplating pregnancy. It is currently recommended that a woman with epilepsy takes folate 5 mg/day for three months before conception and for at least the duration of the first trimester. There is good evidence that folate supplementation reduces the risks of spina bifida and other malformations in large population studies, but there is no documented evidence that it further reduces teratogenic risk in women taking antiepileptic drugs.

National Health and Medical Research Council Guidelines (2000) recommend that all babies at birth are given 1 mg intramuscular vitamin K_1 or a course of oral vitamin K_1. Maternal oral vitamin K_1, for example 10 mg/day for one month prepartum, has been recommended when enzyme-inducing antiepileptic drugs are prescribed because the drugs may potentially predispose the baby to haemorrhagic disease of the newborn. However, reports suggest that this risk is practically negligible.[2]

Specific epilepsy syndromes

Two major groups of epilepsies need to be distinguished because they typically respond differently to different drugs. Localisation-related or partial epilepsies respond to most antiepileptic drugs. For idiopathic generalised epilepsy valproate is usually the most effective drug. Often, especially in juvenile myoclonic epilepsy, seizures can be controlled with a reasonably low valproate dose, for example 800 mg/day or less. Lamotrigine may be helpful but often is not as effective as valproate and sometimes worsens the myoclonic seizures of juvenile myoclonic epilepsy. Topiramate and levetiracetam may be effective in idiopathic generalised epilepsy while carbamazepine, tiagabine, oxcarbazepine, phenytoin and gabapentin may worsen some seizure types, especially myoclonic and absence seizures. For some women with idiopathic generalised epilepsy syndromes, there may be no effective alternative to valproate.

Drug exposure and effects

The pharmacokinetics of antiepileptic drugs may change in pregnancy. Doses have to balance the risk of seizures with minimising the risk of harming the fetus.

Valproate

Four pregnancy registers and numerous smaller studies have warned that there is a substantial risk of major malformations including spina bifida when valproate is used as monotherapy or with other drugs. The Australian Pregnancy Register[3] has reported the risk to be as high as 16% for first trimester fetal exposure to valproate at doses above 1400 mg/day, compared with 6% at doses below 1400 mg/day. Others have reported higher risk when plasma valproate concentrations are consistently high (more than 70 mg/L). Valproate should therefore be avoided in reproductive women wherever possible. When it is unavoidable, the lowest effective dose should be used. It should not exceed 1000 mg/day in divided doses. The woman needs to be warned of the risk of seizures and she should avoid seizure triggers such as sleep deprivation. While she is taking a reduced dose she may have to restrict her driving.

If the valproate dose has been reduced to a minimum during pregnancy in order to reduce teratogenesis, the prepartum effective dose may need to be re-established before the onset of labour. This is a time of increased seizure risk especially in patients with idiopathic generalised epilepsy who are very sensitive to sleep deprivation.

Breastfeeding is considered compatible with valproate therapy. Valproate concentrations in breastfed babies are low.

Lamotrigine

The North American Pregnancy Register has reported that exposure to lamotrigine in the first trimester may cause an increased risk of oral clefts (a rate of 8.9 per 1000, as compared to 0.37 per 1000 in the reference population).[4] Significant dose-related teratogenesis with lamotrigine exceeding 200 mg/day has been reported.[5]

Lamotrigine clearance increases steadily through to 32 weeks of pregnancy. Plasma concentrations of lamotrigine fall early in pregnancy so dose increases may be necessary to control seizures. A trough plasma lamotrigine concentration before pregnancy, at the onset of the second trimester of pregnancy and every two months during pregnancy may help to guide any necessary increase in lamotrigine dose. Postpartum, the lamotrigine concentration rises within a few days and prompt dose reduction may be required to prevent toxicity.[6]

Lamotrigine is excreted in considerable amounts into breast milk. Early reports show that most full-term babies seem to have little problem with breastfeeding, but close monitoring for toxicity, especially in small or preterm babies, is advised.

Carbamazepine

For almost 20 years reports have associated carbamazepine with an increased risk of structural birth defects including spina bifida. However, no pregnancy register has yet shown any statistically significant increase in risk relative to the

total population. In the Australian Pregnancy Register, the malformation rate with carbamazepine cannot be distinguished from that of women with epilepsy who are not taking antiepileptic drugs.

Modest pharmacokinetic changes occur during late pregnancy, but dose changes are not usually required. Carbamazepine is compatible with breastfeeding in the full-term infant.

Phenytoin

Phenytoin is now used less frequently in women with epilepsy. It has been reported to produce an increase in major malformations.

A marked increase in the clearance of phenytoin in pregnancy is associated with a fall in plasma concentrations and possible loss of seizure control. Regular monitoring of plasma concentrations throughout pregnancy helps to determine when a higher dose is required. Postpartum monitoring helps prevent phenytoin toxicity. The pharmacokinetic changes of early pregnancy and postpartum occur more slowly with phenytoin than with lamotrigine. Breastfeeding is acceptable with phenytoin.

Levetiracetam

Levetiracetam has been used in few pregnancies. Its teratogenic risk is unknown.

There appears to be a substantial increase in clearance during pregnancy and an associated fall of blood concentrations.[7] It is not yet known if this is associated with a loss of epilepsy control. Serum monitoring is not currently available, but may prove helpful in clinical practice.

Although levetiracetam is secreted into breast milk, recent data suggest that the neonatal concentrations are low. Breastfeeding is probably acceptable in full-term neonates, but close clinical monitoring is advisable.

Clonazepam

Clonazepam is used as an adjunctive antiepileptic drug. No particular pregnancy risks have been associated with it, but it may cause drowsiness in the breastfed neonate. Withdrawal effects can occur if breastfeeding ceases suddenly.

Oxcarbazepine, topiramate, ethosuximide

Only a few pregnancies have been documented, so the teratogenic risks of these drugs are unknown. Oxcarbazepine clearance seems to increase significantly in pregnancy, but the clinical importance of this is uncertain.

These drugs are excreted in breast milk, but the very limited data available suggest that neonatal drug concentrations are usually low. Breastfeeding is probably acceptable with clinical monitoring.

Phenobarbitone

Phenobarbitone is rarely used now in Australia in reproductive women with epilepsy. The North American Pregnancy Register suggests that it may carry a significant teratogenic risk. A marked increase in plasma clearance occurs in pregnancy. Phenobarbitone in breast milk may cause neonatal drowsiness and apathy.

Conclusion

In women with epilepsy treated with antiepileptic drugs, there is a better than 90% chance that the child will be normal. The most specific therapeutic dilemma and the highest risk is in women who need to take valproate to control their epilepsy. Most infants whose mothers are taking antiepileptic drugs can be successfully breastfed without complications.

Editorial note: Some antiepileptic drugs are used in the management of bipolar disorders. See: Sved Williams A. Antidepressants in pregnancy and breastfeeding. Aust Prescr 2007;30:125–7.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 83)

5. Valproate increases the risk of spina bifida if taken during pregnancy.
6. The dose of lamotrigine may need to be increased during pregnancy.