Risk-Benefit Assessment of Anticonvulsants in Women of Child-Bearing Potential

Peter G. Cleland
Sunderland District General Hospital, Sunderland, and Newcastle General Hospital, Newcastle upon Tyne, England

Summary

Problems with anticonvulsants in women of child-bearing potential include potential adverse effects on appearance, contraception and pregnancy. These effects must be weighed against the overwhelming benefits of anticonvulsant treatment in the majority of women with epilepsy.

Coarsened features, hirsutism and acne may occur in both men and women, particularly if they are exposed to phenytoin. Valproic acid may cause weight gain and hair loss, while carbamazepine treatment carries a significant risk of skin rashes. Anticonvulsants which are liver enzyme inducers (phenytoin, phenobarbital, primidone and carbamazepine) reduce the efficacy of the oral contraceptive pill. No 'pill failure' has been reported with valproic acid.
There is a risk of increased seizure frequency in pregnancy irrespective of whether anticonvulsant treatment is taken. Individual seizures carry little risk to the mother or fetus but status epilepticus has a significant maternal and fetal mortality. The risk of status epilepticus must be taken into account when deciding whether to stop anticonvulsant treatment before pregnancy.

There is a 2 to 3 times increased malformation rate in the offspring of epileptic women on treatment. This is primarily due to the drug treatment, but epilepsy itself may also increase the malformation rate. Most malformations are mild and include facial clefts, congenital heart disease and skeletal abnormalities. Valproic acid, however, carries a 1% risk of causing neural tube defects: women receiving this drug who become pregnant should have an ultrasound and α-fetoprotein estimation at 16 to 18 weeks of pregnancy. If any abnormality is detected then amniocentesis should be carried out.

Women with epilepsy should be counselled before conception and during pregnancy. Before achieving pregnancy a woman should be on optimum treatment, preferably on one anticonvulsant. Consideration should be given to withdrawal of anticonvulsant drugs in any woman who has been seizure free for 2 years or who has only mild and infrequent seizures. Folate supplementation should be started prior to conception and should continue during pregnancy. There is a tendency for anticonvulsant drug concentrations to fall during pregnancy, and the dose may need to be increased if clinically indicated. Over 90% of epileptic women who become pregnant will have uneventful pregnancies and will produce healthy infants.

Epilepsy is a common condition with a prevalence of about 1 in 200; the cumulative incidence (i.e. the lifetime incidence of ever having recurrent seizures) is even higher at around 3% (Hauser et al. 1983). A little under half the epileptic population are female, and many are women of child-bearing potential. There has been interest in epilepsy in women for many hundreds of years: Hippocrates, for example, stated that ‘cessation of menstrual flux is a cause of seizures’, which led to the belief that ‘a good menses would prevent epilepsy’ (Temkin 1971). Over the past 30 years attention has focused on the side effects of anticonvulsants in women, particularly in relation to fetal malformations. In table I the potential side effects of anticonvulsants are listed.

This article does not discuss in detail the benefits of anticonvulsant treatment, for these are self-evident. There are situations in which anticonvulsants may be withheld, for example in patients with very mild or infrequent seizures. Withdrawal of anticonvulsant drugs should always be considered after a seizure-free interval of 2 years: the results of the recent British Medical Research Council trial of anticonvulsant drug withdrawal will be published shortly and should permit an accurate assessment of the risk of recurrence.

1. Side Effects of Anticonvulsant Drugs

The main concern about anticonvulsants centres around pregnancy, and in particular the risk of malformations in the offspring of women with epilepsy. However, there are other aspects to be considered and these include their effects on appearance, contraception and fertility.

1.1 Appearance

Both epilepsy and anticonvulsants may affect appearance, which is a concern to many individuals, and the details are listed in table II.

Table I. Appearance in patients with epilepsy

<table>
<thead>
<tr>
<th>Effect</th>
<th>Anticonvulsants</th>
<th>Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Child care</td>
<td>o</td>
<td>+</td>
</tr>
<tr>
<td>Contraception</td>
<td>+</td>
<td>o</td>
</tr>
<tr>
<td>Fertility</td>
<td>o</td>
<td>+</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

Key: + = adverse effect; o = no effect or beneficial effect.