Occasional review

The comparative efficacy of antiepileptic drugs for partial and tonic-clonic seizures

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SUMMARY Studies of the efficacy of anticonvulsant drugs are difficult to undertake and historically have been of poor quality. Randomised comparisons of drugs are few in number, and have failed to detect significant differences between drugs. This is surprising in view of the strong feelings that many clinicians have about the relative efficacy of the drugs they use. A review of the literature emphasises the need for further studies in this field.

Recent studies have emphasised that the majority of patients with the onset of epilepsy in adult life can satisfactorily be managed by using a single anticonvulsant drug. There is little definite evidence that adding a second anticonvulsant drug improves seizure control in patients who have received an optimal dose of a single drug. Since the risks of adverse reactions and chronic toxicity increase when multiple anticonvulsant drugs are administered, monotherapy has become increasingly popular. This poses a question that has not previously demanded serious investigation, namely: which anticonvulsant drug to choose for an individual patient?

Three major factors are likely to influence the choice of an anticonvulsant: efficacy, toxicity and cost. In clinical practice assumptions made about comparative efficacy of anticonvulsants have been of major importance in this choice, and it is the purpose of this review to question the basis for these assumptions.

The desire to adopt a universally acceptable classification of both seizures and epilepsy stems in part from the assumption that there is a different response of individual seizure types and epilepsies to different anticonvulsant drugs. There is some evidence to support this contention in that, until the introduction of sodium valproate, drugs effective against petit mal absence seizures in childhood (for example ethosuximide and trimethadione), were ineffective against tonic-clonic and partial seizures whilst drugs such as phenytoin and carbamazepine which are effective against the latter are ineffective against petit mal absence seizures. However, it has also been assumed that different drugs are to be preferred depending on whether a patient has tonic-clonic seizures, or a partial epilepsy. Porter has recently reviewed the subject and suggested that there is an order of preference for drugs which depends on seizure type (table 1). This ranking of anticonvulsant efficacy conforms to generally accepted clinical practice and would not be regarded as controversial by many neurologists. However, it is uncertain on what evidence these preferences are based as the literature relating to the efficacy of anticonvulsant drugs is unsatisfactory. Few studies have included such basic requirements as a randomised design and adequate statistical analysis in comparing anticonvulsant drugs. These omissions are compounded by two further problems: a lack of a generally accepted definition for "control" of epilepsy, and problems in the selection of patients.

Control of epilepsy

Response to an anticonvulsant drug is most commonly described using arbitrary definitions of poor, good or excellent control. These terms are usually defined by comparing pre-test seizure frequency,
with seizure frequency following the initiation or change of therapy, and using percentage change to define the response as "good", "poor" etc. However, there may be inherent difficulties in such comparisons. Patients rarely have a stable seizure threshold and seizures not infrequently occur in clusters. Thus when a patient presents with a flurry of four seizures within one week and has his or her treatment amended it might be assumed that the pre-treatment seizure frequency might amount to some 16 seizures per month. However the patient may only experience one such flurry of seizures in a year, in which case when treatment is started the apparent monthly seizure frequency might well fall from twelve seizures per month, to 0-35 seizures per month even if the drug treatment had no effect on seizure frequency. It is therefore necessary in assessing treatment to ensure that the period of observation prior to treatment is prolonged and identical to the period following the change before comparisons of seizure frequency can be derived.

In previously untreated patients it may be difficult to withhold a treatment to establish a pretreatment seizure frequency so that other means of assessing seizure response become necessary in such patients. Here it seems preferable to adopt definitions of control of epilepsy which describe periods entirely free from seizures. In this instance control of epilepsy may be defined in terms of the number of patients entering remissions lasting, one, two or more years. Such a definition is more clinically relevant than any assessment based on comparisons of seizure frequencies, clinicians and patients aiming for complete cessation of attacks, rather than reduction of say 50% from four seizures per day, to two.

**Patient selection**

Studies of anticonvulsant efficacy have usually been undertaken in chronic epileptic patients who have proved themselves resistant to therapy over many years, and who often continue with their previous medication during the drug study. The long-term remission rates in such patients are always likely to remain low, in contrast to the prognosis for newly diagnosed patients with epilepsy in whom the prognosis is considerably better. Indeed when a trial drug is given as add-on therapy to patients with chronic epilepsy, whose seizures continue in spite of one, two, or more drugs in combination, the lack of response to an additional drug may not imply a lack of anticonvulsant properties. It may simply be an indication that the trial drug is no more effective than the previously administered drugs, or that the trial drug has a similar mechanism of action to the concurrently administered drugs.

These considerations make it essential that comparative studies of the efficacy and toxicity of anticonvulsant drugs should rely on trial designs which include a randomisation procedure with prolonged follow-up. Multiple drug therapy should be avoided, and the population of patients should be defined in terms of those factors known to influence prognosis. The number of prospective randomised comparative studies has increased over the past decade but the numbers still remain small, and many are still open to criticism.

**Randomised comparative studies**

Two differing designs have been used. Most have employed a double blind cross-over design (tables 2 and 3), which necessitates short periods of patient observation which may not provide information that can readily be applied to longer-term clinical management. Drugs such as benzodiazepines, whose anticonvulsant effects show tolerance, are likely to be unduly favoured by such designs. Other studies have undertaken randomisation with a longer-term parallel-group follow-up (table 4). However, these usually give no information to confirm that the groups as randomised are comparable for those factors known to influence the prognosis of epilepsy, essential for this particular type of design, which lacks a cross-over. In spite of these difficulties it is nevertheless quite striking that only one study suggests that one of the anticonvulsant drugs tested was superior to another, phenytoin being preferred to sulthiame. As some of the antiepileptic properties of sulthiame may be due to its ability to inhibit phenytoin metabolism, it is perhaps not surprising that the drug is inferior when compared to phenytoin.

Three recently reported studies demand further comment, as they were undertaken in previously

<table>
<thead>
<tr>
<th>Decreasing likelihood of effectiveness</th>
<th>Simple* partial seizures</th>
<th>Complex* partial seizures</th>
<th>Tonic-clonic seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>phenytoin</td>
<td>carbamazepine</td>
<td>phenytoin</td>
</tr>
<tr>
<td>2</td>
<td>carbamazepine</td>
<td>phenytoin</td>
<td>carbamazepine</td>
</tr>
<tr>
<td>3</td>
<td>primidone</td>
<td>primidone</td>
<td>phenobarbitone</td>
</tr>
<tr>
<td>4</td>
<td>phenobarbitone</td>
<td>phenobarbitone</td>
<td>valproate</td>
</tr>
</tbody>
</table>

*as defined in 1981 International Classification of seizures.
untreated patients who were randomised to differ-
ent drugs shortly after the diagnosis of epilepsy. Cal-
laghan et al15 compared phenytoin, carbamazepine,
and valproate in 181 adult patients with tonic-clonic
or partial seizures who were followed up for a mean
of 20 months. Whilst the criteria for seizure control
were inadequate (see above), the drugs were found
equally effective with the exception that phenytoin
therapy was more likely to result in excellent control
of tonic-clonic seizures (independence of attacks for
a mean of 3 months), than carbamazepine. Loiseau et
al16 used a response-conditional cross-over con-
structive study of carbamazepine and valproate in 31
patients with newly diagnosed partial epilepsy.
Whilst the numbers are small and follow-up short no
differences were detected between efficacy of val-
proate and carbamazepine. Turnbull et al17 com-
pared phenytoin and valproate in 140 patients with
adult onset epilepsy. Follow up was for up to 4 years
and actuarial analyses were used to assess the rates
at which patients achieved 2 year remissions. No
differences in efficacy were detected against either
tonic-clonic or partial seizures, and the study was
the first to have sufficient power to exclude clinically
meaningful differences in efficacy in a parallel group
design.

Why, then, should this array of data fail to dif-
ferentiate between the efficacy of anticonvulsant
agents? It is possible that the samples of patients
studied have been too small to detect reliably
significant differences, or that other methodological
inadequacies are obscuring real differences. Cer-
tainly all studies which fail to detect a difference in
efficacy between drugs should offer some assess-
ment of the statistical power of the trial. However,
we should perhaps consider the possibility that, as
suggested by the available (although inadequate)
randomised studies, the choice of anticonvulsant
makes little contribution to the prognosis for control
of epilepsy. There is evidence which suggests that
the ultimate prognosis for remission of epilepsy can
be predicted at the presentation of epilepsy. Factors
which adversely affect outcome are classification of
epilepsy (those patients with partial seizures having
a much poorer outlook than those with only tonic
clonic seizures), the length, duration and frequency
of seizures prior to treatment, the presence of
neurological or psychiatric deficit indicative of a

### Table 2 Comparison of anticonvulsant efficacy cross-over studies, carbamazepine vs other drugs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No</th>
<th>Seizures</th>
<th>Patients</th>
<th>Other drugs</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rajotte et al10</td>
<td>2 × 6 mth</td>
<td>24</td>
<td>G + P</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Marjerrison et al11</td>
<td>2 × 4 mth</td>
<td>45</td>
<td>G + P</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Cereghino et al12</td>
<td>3 × 3 wk</td>
<td>45</td>
<td>G + P</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Rodin et al13</td>
<td>2 × 3 mth</td>
<td>45</td>
<td>P</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Simonsen et al14</td>
<td>2 × 4 mth</td>
<td>38</td>
<td>P</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Troupin et al15</td>
<td>2 × 4 mth</td>
<td>56</td>
<td>P</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Kosteljanetz et al16</td>
<td>2 × 10 wk</td>
<td>23</td>
<td>G + P</td>
<td>C</td>
<td>+</td>
</tr>
</tbody>
</table>

Seizures—G = generalised (tonic-clonic), P = partial. Patients—C = chronically treated. N = newly diagnosed

### Table 3 Comparison of anticonvulsant efficacy other cross-over studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No</th>
<th>Seizures</th>
<th>Patients</th>
<th>Other drugs</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gruber et al17</td>
<td>8 × 3 wk</td>
<td>44</td>
<td>P</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>White et al18</td>
<td>10 × 2 wk</td>
<td>20</td>
<td>P</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Green et al19</td>
<td>2 × 6 mth</td>
<td>67</td>
<td>P</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Gibberd et al20</td>
<td>2 × 6 mth</td>
<td>94</td>
<td>G + P</td>
<td>N</td>
<td>-</td>
</tr>
<tr>
<td>Wilensky et al21</td>
<td>2/4 mth</td>
<td>55</td>
<td>P</td>
<td>C</td>
<td>+</td>
</tr>
</tbody>
</table>

Seizures—G = generalised (tonic-clonic), P = partial. Patients—C = chronically treated. N = newly diagnosed

### Table 4 Comparison of anticonvulsant efficacy parallel group randomised studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No</th>
<th>Seizures</th>
<th>Patients</th>
<th>Other drugs</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruskin11</td>
<td>24 mth</td>
<td>53</td>
<td>G + P</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Bird et al12</td>
<td>18 mth</td>
<td>46</td>
<td>G + P</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Millichap &amp; Aymat13</td>
<td>?</td>
<td>40</td>
<td>G + P</td>
<td>C + N</td>
<td>+/-</td>
</tr>
<tr>
<td>Skaklen et al14</td>
<td>9–48 mth</td>
<td>33</td>
<td>G + P</td>
<td>C + N</td>
<td>-</td>
</tr>
<tr>
<td>Kikken et al14</td>
<td>6 mth</td>
<td>36</td>
<td>P</td>
<td>N</td>
<td>-</td>
</tr>
<tr>
<td>Ramsay et al22</td>
<td>6–24 mth</td>
<td>87</td>
<td>G + P</td>
<td>N</td>
<td>-</td>
</tr>
<tr>
<td>Wilder et al23</td>
<td>6 mth</td>
<td>61</td>
<td>G</td>
<td>N</td>
<td>-</td>
</tr>
</tbody>
</table>

symptomatic rather than an ideopathic epilepsy, and the presence or absence of clustering of seizures in temporal patterns.\textsuperscript{11, 12, 16} The suggestion that these factors have greater importance in the ultimate prognosis of epilepsy than the selection of drug therapy is supported by the study of Turnbull \textit{et al}\textsuperscript{17} and a number of other lines of evidence.

In spite of the introduction of many antiepileptic agents there is little evidence to suggest any major improvement in the prognosis for long-term remission of epilepsy in hospital based populations during the course of this century.\textsuperscript{12} Annegers \textit{et al}\textsuperscript{16} did not find any improvement in the long-term remission of epilepsy in the years 1945–1959, compared to 1960–1974 in a community based study of the prognosis of epilepsy in Rochester, Minnesota. Indeed over a hundred years ago Gowers\textsuperscript{18} commented that 83% of his patients presenting with a history of epilepsy of less than one year’s duration would be “cured” by treatment with bromides. This is strikingly similar to claims made for drug therapy at present.\textsuperscript{11, 17} Furthermore, there is a striking similarity between those factors which predict the onset of remission of epilepsy during drug therapy and those factors which predict the likelihood of continued remission if anticonvulsants are withdrawn after a prolonged period of seizure control.\textsuperscript{16} One possible explanation of this might be that onset of remission is to some degree co-incidental to drug therapy in those patients who continue in remission after the withdrawal of drugs.

In essence it seems that epilepsy has a spectrum of severity. At one extreme are patients with only a few tonic-clonic seizures as part of an idiopathic epilepsy, who will respond well irrespective of the potency of the chosen drug. Indeed, some patients may arguably not require drug therapy. At the other extreme are patients with partial or secondary generalised epilepsies, symptomatic of cerebral disease, and complicated by neuropsychiatric handicap who are unlikely to be controlled by any available antiepileptic drug or combinations of drugs. There may only be a small number of patients between these extremes in whom the choice of drug influences outcome. As such patients cannot presently be identified, comparative studies of antiepileptic drugs will have to include larger numbers of patients to detect differences in efficacy.

There is an obvious need for further large, long-term randomised comparisons of anticonvulsant drugs, preferably in previously untreated patients. One adequate study has recently been reported.\textsuperscript{17} Similar studies have been commenced in both this country and the USA, and the results will be of considerable importance.

In conclusion, at present it is impossible, on the basis of controlled randomised comparisons of anticonvulsant drugs, to suggest that any individual drug is to be preferred in terms of its therapeutic efficacy against tonic-clonic or partial seizures in adult patients. In these circumstances the choice of drug should be determined by the comparative toxicity, and the cost of drug therapy.

References

The comparative efficacy of antiepileptic drugs for partial and tonic-clonic seizures


The comparative efficacy of antiepileptic drugs for partial and tonic-clonic seizures.
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