Occasional review

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

D CHADWICK, DM TURNBULL

From the Mersey Regional Department of Medical and Surgical Neurology, Walton Hospital, Liverpool, and the Department of Neurology, University of Newcastle-upon-Tyne, UK

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.¹ 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.²⁻⁴ Since the risks of adverse reactions and chronic toxicity increase when multiple anticonvulsant drugs are administered,^{4,5} 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. Porter⁶ 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.⁷⁻⁹ 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,

Address for reprint requests: Dr D Chadwick, Walton Hospital, Rice Lane, Liverpool L9 1AE, UK.

Received 14 December 1984 and in revised form 14 February 1985. Accepted 16 February 1985

Table 1 Orders of effectiveness against tonic-clonic and partial seizures

Decreasing likelihood of effectiveness	Simple* partial seizures	Complex* partial seizures	Tonic-clonic seizures
1	phenytoin	carbamazepine	phenytoin
2	carbamazepine	phenytoin	carbamazepine
3	primidone	primidone	phenobarbitone
4	phenobarbitone	phenobarbitone	valproate
			(Porter, 1982)*

*as defined in 1981 International Classification of seizures.

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.¹⁰ 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.^{10 11} 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,¹² 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 study¹³ 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,¹⁴ 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

untreated patients who were randomised to different drugs shortly after the diagnosis of epilepsy. Callaghan *et al*¹⁵ 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 (freedom from attacks for a mean of 3 months), than carbamazepine. Loiseau *et al*¹⁶ used a response-conditional cross-over comparative 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 valproate and carbamazepine. Turnbull *et al*¹⁷ compared 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 differentiate 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. Certainly all studies which fail to detect a difference in efficacy between drugs should offer some assessment 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

	Treatment	No	Seizures	Patients	Other drugs	Result
Rajotte <i>et al</i> ²⁰	2 × 6 mth	24	G + P	C	+	C = Phenytoin
Marjerrison <i>et al</i> ²¹	2 × 4 mth	45	G + P	C	+	C = Phenytoin
Cereghino <i>et al</i> ²²	3 × 3 wk	45	G + P	C	—	C = Phenytoin = Phenobarb
Rodin <i>et al</i> ²³	2 × 3 mth	45	P	C	+	C = Primidone
Simonsen <i>et al</i> ²⁴	2 × 4 mth	38	P	C	—	C = Phenytoin
Troupin <i>et al</i> ²⁵	2 × 4 mth	56	P	C	—	C = Phenytoin
Kosteljanetz <i>et al</i> ²⁶	2 × 10 wk	23	G + P	C	+	C = Phenytoin

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

Table 3 Comparison of anticonvulsant efficacy other cross-over studies

	Treatment	No	Seizures	Patients	Other drugs	Result
Gruber <i>et al</i> ²⁷	8 × 3 wk	44	P	C	+	P = Primidone = Phenobarb
White <i>et al</i> ²⁸	10 × 2 wk	20	P	C	—	P = Primidone = Phenobarb
Green <i>et al</i> ¹³	2 × 6 mth	67	P	C	—	P better than Sulthiame
Gibberd <i>et al</i> ²⁹	2 × 6 mth	94	G + P	N	—	P = Pheneturide
Wilensky <i>et al</i> ³⁰	2/4 mth	55	P	C	+	Phenobarb = Clorazepate

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

Table 4 Comparison of anticonvulsant efficacy parallel group randomised studies

	Treatment	No	Seizures	Patients	Other drugs	Result
Ruskin ³¹	24 mth	53	G + P	C	—	P = Pb = M
Bird <i>et al</i> ³²	18 mth	46	G + P	C	—	C = P = Pb = Pr
Millichap & Aymat ³³	?	40	G + P	C + N	+/-	P = Pr
Shakir <i>et al</i> ³⁴	9-48 mth	33	G + P	C + N	—	P = V
Mikkelsen <i>et al</i> ³⁵	6 mth	36	P	N	—	C = Clon
Ramsay <i>et al</i> ³⁶	6-24 mth	87	G + P	N	—	C = P
Wilder <i>et al</i> ³⁷	6 mth	61	G	N	—	P = V

Seizures—G = generalised (tonic-clonic), P = partial. Patients—C = chronically treated. N = newly diagnosed. Drugs—C = carbamazepine, P = phenytoin, Pb = phenobarbitone, Pr = primidone, V = valproate, M = mesantoin, Clon = clonazepam.

symptomatic rather than an ideopathic epilepsy, and the presence or absence of clustering of seizures in temporal patterns.^{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 *et al*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.¹² Annegers *et al*¹⁰ 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 Gowers¹⁸ 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.^{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.¹⁹ 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.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 anti-convulsant 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

- 1 Reynolds EH, Shorvon SD. Monotherapy or polytherapy for epilepsy? *Epilepsia* 1981;**22**:1–10.
- 2 Shorvon SD, Reynolds EH. Unnecessary polypharmacy for epilepsy. *Br Med J* 1977;**1**:1635–7.
- 3 Schmidt D. Reduction of two-drug therapy in intractable epilepsy. *Epilepsia* 1983;**24**:368–76.
- 4 Schmidt D. Two antiepileptic drugs for intractable epilepsy with complex-partial seizures. *J Neurol Neurosurg Psychiatry* 1982;**45**:1119–24.
- 5 Reynolds EH. Chronic antiepileptic toxicity: a review. *Epilepsia* 1975;**16**:319–52.
- 6 Porter RJ. Clinical efficacy and use of antiepileptic drugs. In: Woodbury DM, Penry JK, Pippenger CE, eds. *Antiepileptic Drugs*. New York: Raven Press, 1982:167–77.
- 7 Coatsworth JJ. *Studies on the Clinical Efficacy of Marketed Antiepileptic Drugs*. Bethesda NINDS Monograph No. 12 1971.
- 8 Gram L, Bentsen KD, Parnas J, Flachs H. Controlled trials of epilepsy: a review. *Epilepsia* 1982;**23**:491–519.
- 9 Mattson RH. The design of clinical studies to assess the efficacy and toxicity of antiepileptic drugs. *Neurology (NY)* 1983;**33**:Suppl 1:2–37.
- 10 Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. *Epilepsia* 1979;**20**:729–37.
- 11 Shorvon SD, Reynolds EH. The early prognosis of epilepsy. *Br Med J* 1982;**285**:1699–701.
- 12 Rodin EA. *The Prognosis of Patients with Epilepsy*. Springfield Thomas, 1968.
- 13 Green JR, Troupin AS, Halpern LM, Freil P, Kanarek P. Sulthiame: Evaluation as an anticonvulsant. *Epilepsia* 1974;**15**:329–49.
- 14 Houghton GW, Richens A. Phenytoin intoxication induced by sulthiame in epileptic patients. *J Neurol Neurosurg Psychiatry* 1974;**37**:275–81.
- 15 Callaghan N, Kenny RA, O'Neill B, Crowley M, Groggini. A comparative study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy. A preliminary communication. *Br J Clin Pract* 1983;**Suppl 27**:7–9.
- 16 Loiseau P, Cohadon S, Jogeix M, Legroux M, Artigues J. Efficacité du valproate de sodium dans les epilepsies partielles. *Rev Neurol (Paris)* 1984;**140**:434–7.
- 17 Turnbull DM, Rawlins MD, Weightman D, Chadwick DW. Which drug for the adult patient with epilepsy: phenytoin or valproate? *Br Med J* 1985;**290**:815–9.
- 18 Gowers W. *Epilepsy and Other Chronic Convulsive Diseases*. London: Churchill Livingstone, 1881.

- ¹⁹ Chadwick D. When can anticonvulsants be stopped? In: Garfield J, Warlow C, eds. *Neurological Controversies*. Edinburgh: Churchill-Livingstone, 1983;133-44.
- ²⁰ Rajotte P, Jilek W, Jilek L, et al. Propriétés antiepileptiques et psychotropes de la carbamazépine. *Union Med Can* 1967;**96**:1200-6.
- ²¹ Marjerrison G, Jedlicki SM, Keogh RP, Hrychuk W, Poulakakis GM. Carbamazépine: behavioural, anticonvulsant, and EEG effects in chronically hospitalized epileptics. *Dis Nerv Syst* 1968;**29**:133-66.
- ²² Cereghino JJ, Brock JT, Van Peter JC, Penry JK, Smith LD, White BG. Carbamazépine for epilepsy: a controlled prospective evaluation. *Neurology (Minneapolis)* 1974;**24**:401-10.
- ²³ Rodin EA, Kitano H, Lewis R, Rennick PM. A comparison of the effectiveness of primidone versus carbamazépine in epileptic outpatients. *J Nerv Ment Dis* 1976;**163**:41-6.
- ²⁴ Simonsen N, Zander-Olsen P, Kuhl V, Lund M, Wendelboe J. A comparative controlled study between carbamazépine and diphenylhydantoin in psychomotor epilepsy. *Epilepsia* 1976;**17**:169-76.
- ²⁵ Troupin AS, Ojemann LM, Halpern L, et al. Carbamazépine—a double-blind comparison with phenytoin. *Neurology (Minneapolis)* 1977;**27**:511-9.
- ²⁶ Kosteljanetz M, Christiansen J, Dam AM, Hansen BS, Lyon BB, Pedersen H. Carbamazépine vs phenytoin. *Arch Neurol* 1979;**36**:22-4.
- ²⁷ Gruber CM, Brock JT, Dyken M. Comparison of the effectiveness of phenobarbital, mephobarbital, primidone, diphenylhydantoin, ethosin, metharbital, and methylphenyl-ethylhydantoin in motor seizures. *Clin Pharm Ther* 1962;**3**:23-8.
- ²⁸ White PT, Plott D, Norton J. Relative anticonvulsant potency of primidone. *Arch Neurol* 1966;**14**:31-35.
- ²⁹ Gibberd FB, Park DM, Scott G, et al. A comparison of phenytoin and pheneturide in patients with epilepsy: a double-blind cross-over trial. *J Neurol Neurosurg Psychiatry* 1982;**45**:1113-8.
- ³⁰ Wilensky AJ, Ojemann LM, Temkin NR, Toupin AS, Dodrill CB. Clorazépine and phenobarbital as antiepileptic drugs: a double blind study. *Neurology (NY)* 1981;**31**:1271-6.
- ³¹ Ruskin DB. Comparative results in seizure control using phenobarbital, dilantin, and mesantoin. *Am J Psychiatry* 1950;**107**:415-21.
- ³² Bird CAK, Griffin BP, Miklaszewska JM, Galbraith AW. Tegretol (carbamazépine): A controlled trial of a new anticonvulsant. *Br J Psychiatry* 1966;**112**:737-42.
- ³³ Millichap JG, Aymat F. Controlled evaluation of primidone and diphenylhydantoin sodium: comparative anticonvulsant efficacy and toxicity in children. *JAMA* 1968;**204**:738-9.
- ³⁴ Shakir RA, Johnson RH, Lambie DG, Melville ID, Nanda RN. Comparison of sodium valproate and phenytoin as single drug therapy in epilepsy. *Epilepsia* 1981;**22**:27-33.
- ³⁵ Mikkelsen B, Berggreen P, Joensen P, Kristensen O, Kohler O, Mikkelsen BO. Clonazépine and carbamazépine in psychomotor epilepsy: A randomised multicenter trial. *Epilepsia* 1981;**22**:415-20.
- ³⁶ Ramsay RE, Wilder BJ, Berger JR, Bruni J. A double-blind study comparing carbamazépine with phenytoin as initial seizure therapy in adults. *Neurology (NY)* 1983;**33**:904-10.
- ³⁷ Wilder BJ, Ramsay RE, Murphy JV, Karas BJ, Marquardt K, Hammond EJ. Comparison of valproic acid and phenytoin in newly diagnosed tonic-clonic seizures. *Neurology (NY)* 1983;**33**:1474-6.