concentration when initiating treatment with continuous subcutaneous insulin infusion or multiple injections. We do not know whether this will occur if the blood glucose concentration is reduced at a slower rate. So far we have examined the effect of lowering the blood glucose concentration over several months, and after the initial deterioration retinopathy seems to improve. The study is continuing to see if this improvement remains.

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Which drug for the adult epileptic patient: phenytoin or valproate?

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Abstract

A series of 140 previously untreated patients with tonic-clonic or partial seizures were randomised to receive either phenytoin or sodium valproate. There was no difference between the treatment groups in pretreatment variables that might influence outcome.

Sodium valproate and phenytoin in the treatment of tonic-clonic or partial seizures showed no difference in efficacy as regards time to two year remission or time to first seizure. When the possible prognostic factors were studied, including history and results of clinical examination and investigations before treatment; the only factor which influenced the proportion of patients achieving two year remission was type of seizure. Patients with a

clinical history of partial seizures did significantly less well than those with a history of tonic-clonic seizures only.

This study showed no major difference in efficacy between sodium valproate and phenytoin in adults with recent onset of epilepsy, irrespective of the type of seizures that the patient suffered.

Introduction

The overall prognosis for the remission of epilepsy appears good, up to 70% of patients in a community based study achieving long term remission of their epilepsy,¹ compared with the more pessimistic outlook for patients drawn from hospital based populations with chronic epilepsy, in whom roughly 30% achieve remission.² The more optimistic outlook is supported by several studies of previously untreated patients, which suggest a high rate of success irrespective of which single anticonvulsant drug is used.³⁻⁷

The success of monotherapy in these studies demands a serious appraisal of which single anticonvulsant drug should be prescribed first to the patient presenting with epilepsy,^{7a} and the need for carefully controlled, long term comparisons of anticonvulsant drugs is plain.⁸ We report the results of a randomised, controlled clinical trial comparing the efficacy of sodium valproate and phenytoin in newly diagnosed adult epileptic patients followed up for between two and four years.

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Methods

The clinical trial was conducted in the Department of Neurology, Royal Victoria Infirmary, Newcastle upon Tyne. Recruitment began in October 1978, ended in December 1980, and follow up of patients continued until February 1983. The patients included in this study were over 16 years of age at the time of diagnosis and had received no previous anticonvulsant treatment. All had a history of two or more seizures in the previous three years and were started on treatment within three months after their last seizure. Patients were randomised to receive either sodium valproate or phenytoin after being stratified for age, sex, and type of seizure. The age groupings were 16-25, 26-65, and 66 or older. Patients were allotted to a non-partial, tonic-clonic seizure group if there was no positive clinical evidence of focal onset or aftermath to the seizure, or to a group consisting of patients with partial (simple or complex) seizures with or without secondary generalised seizures. Inclusion in the first group did not indicate that patients had "primary generalised epilepsy"; indeed, some patients showed focal abnormalities on electroencephalography.

A detailed history was taken and full neurological examination performed on all patients entering the study. The presence or absence of other possible prognostic factors was recorded. All patients underwent skull radiography and electroencephalography, and other neurological investigations were performed when clinically indicated. Before treatment a full blood count, red blood cell and serum folate concentrations, serum calcium concentration, alkaline phosphatase and aspartate aminotransferase activities, and bilirubin, urea, creatinine, albumin, globulin, and immunoglobulin concentrations were estimated. These investigations were repeated at six month intervals throughout.

After randomisation the patients began either phenytoin (100 mg three times a day) or sodium valproate (200 mg thrice daily). If the patients remained seizure free they were reviewed at three month intervals, but were seen more often if they had further seizures or if there were other clinical indications. At each follow up appointment the number and type of seizures since the last visit, blood anti-convulsant concentration, weight, and incidence of adverse effects were documented.

If further seizures occurred medication was increased. Phenytoin was increased according to the plasma concentration: if less than 10 mg/l the dose was increased by 50 mg/day, and if greater than 10 mg/l it was increased by 25 mg/day. Doses were further increased until either seizures stopped or adverse effects were seen, irrespective of serum concentration. For patients receiving valproate dosage was increased regardless of the serum concentration, the increments being to 1200 mg, 2100 mg, and 3000 mg/day given in three divided doses. A patient was considered to have failed on monotherapy and

withdrawn from the study only if seizures continued despite sufficient medication to cause either dose related or other adverse effects or, in the case of valproate, if a maximum dose of 3 g daily was ineffective. Patients withdrawn from the initial treatment because of adverse reactions, or lost to follow up, were regarded as treatment failures and analysed as such.

The follow up period was divided into three month periods during which each patient was designated as being free of or suffering from tonic-clonic or partial seizures. Two variables were used to describe success or failure of treatment: "time to two year remission of seizures" was the time between enrolment in the study and the achievement of a two year remission, and "time to first seizure" was the time between enrolment and the first seizure during treatment. The rates at which these events occurred were estimated by an actuarial method.⁹ Comparison of these rates for the two groups of patients was by a log rank test leading to a χ^2 LR statistic.¹⁰ The criterion two year remission may seem to be more useful as a clinical indicator of success, but time to first seizure gives a more powerful test. Power calculations leading to approximate estimates of the difference in rates which would have a high chance of being found significant were performed using the equation given by Freedman.¹¹

Baseline variables for the two groups were compared by the Mann-Whitney test (continuous variables) and χ^2 test (discrete variables). The numbers of patients displaying idiosyncratic adverse effects were compared by Fisher's exact test.

Results

SEIZURE CONTROL

One hundred and forty patients were randomised to receive either phenytoin or sodium valproate (table I). The length of history, time in the trial and number of seizures in the previous 12 months, electroencephalographic findings, and age were not significantly different between the two groups before treatment ($p > 0.05$) whether or not patients with tonic-clonic and partial seizures were analysed separately (table I). Table II and the figure (A) summarise the outcome in the 140 patients. Six patients (4%) died during the study, one from a myocardial infarction, one from a stroke, one from an accident, and three from intracranial tumours diagnosed after randomisation. Three patients (2%) were non-compliant, with persistent absence of anticonvulsant in the serum and admitted failure to take their medication regularly. Fifteen patients (11%) failed to return despite repeated reminders (eight randomised to valproate, seven to phenytoin).

All statistical analyses are based on the groups as randomised,

TABLE I—Pretreatment values

	Tonic-clonic		Partial seizures		All patients	
	Valproate	Phenytoin	Valproate	Phenytoin	Valproate	Phenytoin
No of patients	37	39	33	31	70	70
Age (years) { Median	25	26	35	33	30	30
Range	16-69	16-70	16-65	17-66	16-69	16-70
Sex { F	20	20	16	11	36	31
M	17	19	17	20	34	39
Seizure history (months) { Median	8	7	12	9	12	9
Range	1-120	1-160	1-132	1-360	1-132	1-360
No of seizures in previous year:						
Partial { Median	—	—	8	7	—	—
Range	—	—	1-120	1-120	—	—
Generalised { Median	3	2	2	2	2	2
Range	1-8	1-6	0-8	0-10	0-8	0-10
Electroencephalogram { Normal or non-specific	28	29	16	15	44	44
Generalised spike and wave	5	5	0	0	5	5
Focal	4	5	17	16	21	21
Neurological/psychiatric handicap { Yes	2	2	7	8	9	10
No	35	37	26	23	61	60

TABLE II—Results of treatment and deviations from protocol

	Tonic-clonic		Partial seizures		All patients	
	Valproate	Phenytoin	Valproate	Phenytoin	Valproate	Phenytoin
No of patients	37	39	33	31	70	70
No achieving 2 year remission	27	22	9	9	36	31
No controlled for < 2 years	3	6	9	5	12	11
No continuing to have seizures	1	2	9	9	10	11
Idiosyncratic adverse effect requiring drug withdrawal	0	4	0	1	0	5
Death	1	0	2	3	3	3
Non-compliant or lost to follow up	5	5	4	4	9	9

including those patients who did not complete two years of follow up. When the results for all patients randomised are considered (table II; figure (A)), allowing for stratification for seizure type there was no significant difference between the two therapeutic groups in time to two year remission ($\chi^2_{LR}=1.13$; $df=2$; $p=0.3$) or time to first seizure ($\chi^2_{LR}=0.94$; $df=2$; $p=0.5$).

Tonic-clonic seizures—Seventy six patients had only tonic-clonic seizures. Table II and the figure (B) summarise the outcome. If all patients with non-partial tonic-clonic seizures who were randomised

The poorer outlook in this group of patients was due to continued partial seizures. Further tonic-clonic seizures (presumably secondary generalised) were as uncommon in this group of patients as they were in the group of patients with a previous history of tonic-clonic seizures only (see below).

Prognostic factors—The pretreatment history and results of clinical examination and investigation were studied to see if it is possible to predict which newly diagnosed epileptics are likely to respond poorly to treatment. These factors included the presence or absence

Actuarial percentages of patients in two year remission. Numbers of patients at risk shown at each time point. A: All patients. B: Non-partial tonic-clonic seizures. C: Partial seizures. D: Partial and non-partial tonic-clonic seizures (phenytoin and valproate treatment groups combined for each seizure type).

are included there was no significant difference between the two therapeutic groups in time to a two year remission ($\chi^2_{LR}=0.47$; $df=1$; $p=0.5$) or time to first seizure ($\chi^2_{LR}=0.36$; $df=1$; $p=0.6$).

Partial seizures—There were 33 patients treated with valproate, of whom seven had only partial seizures and 26 partial seizures with generalisation. Four patients had simple partial symptoms, the rest complex partial symptoms. Thirty one patients received treatment with phenytoin, 10 of whom had only partial seizures and 21 partial seizures with generalisation. Twenty seven had complex partial symptoms and four simple partial seizures. Table II and the figure (C) summarise the outcome. Including all patients with partial seizures who were randomised there was no significant difference between the two therapeutic groups in time to a two year remission ($\chi^2_{LR}=0.66$; $df=1$; $p=0.4$) or time to first seizure ($\chi^2_{LR}=0.58$; $df=1$; $p=0.4$).

of neurological or psychiatric deficit or disease, the length of history, the number and type of seizures in the 12 months before treatment, radiological abnormalities of the skull, and electroencephalographic findings. Several measures of performance were studied. The only factor which influenced the proportion of patients achieving two year remission was the type of seizure. When all patients with a clinical history of tonic-clonic seizures only (irrespective of treatment) were compared with all those with partial seizures (figure (D)) there was a significantly poorer response in the partial seizure group as measured by time to two year remission ($\chi^2_{LR}=5.35$; $df=1$; $p<0.025$) and time to first seizure ($\chi^2_{LR}=38.4$; $df=1$; $p<0.001$). The generalised seizures which occurred in the group with partial seizures, however, responded as well to treatment as did those occurring in patients with symptoms of tonic-clonic seizures only, both in time to two year remission

($\chi^2_{LR}=0.48$; $df=1$; $p=0.5$) and in time to first seizure ($\chi^2_{LR}=1.00$; $df=1$; $p=0.3$). Thus both anticonvulsant drugs were relatively ineffective against partial seizures but appeared to suppress primary and secondary generalised seizures with equal efficacy. In addition to type of seizure there was a significant difference in the time to first seizure between those with low and high frequencies of partial seizures before treatment (≤ 6 or >6 in one year) ($\chi^2_{LR}=5.41$; $df=1$; $p<0.025$). There was, however, no such significant difference in time to two year remission between these two groups. None of the other prognostic factors examined appeared to be of any value.

ADVERSE EFFECTS

Type A: dose related—During the study nine patients treated with valproate were withdrawn because of dose related adverse effects (tremor, irritability and restlessness, and alopecia). The clinical manifestations and relation to serum concentration have been reported.¹² Eleven patients were withdrawn because of dose related adverse effects of phenytoin. These were nystagmus, ataxia, tremor, diplopia, and mental change.

Type B: idiosyncratic—Five patients were withdrawn from the study because of idiosyncratic adverse effects. All patients were taking phenytoin, and four developed a skin eruption within the first month of beginning this drug. The fifth patient developed erythroderma and jaundice. In all five patients the adverse effect cleared completely on withdrawal of phenytoin and all subsequently received valproate. The number of patients who were withdrawn due to idiosyncratic adverse effects in the phenytoin treated group compared with the valproate treated group just failed to reach significance ($p=0.06$).

WEIGHT AND HAEMATOLOGICAL AND BIOCHEMICAL VARIABLES

The effect of the different anticonvulsants on weight and haematological and biochemical variables was determined by analysis of variance using pretreatment and two year treatment values. All tests of significance were at the 5% level. The analysis was performed on only 40 patients from both therapeutic groups because the two year values were not available for those patients who were lost to follow up, failed to comply, or died. In 10 patients pretreatment values were incomplete, and these patients were therefore excluded from analysis.

The following values did not change significantly over the two year treatment period: white blood cell count; platelet count; bilirubin, globulin, IgG, IgM, urea, and creatinine concentrations; and weight. For those patients in whom a change occurred it was possible to split the variables into those for which all patients were affected to a similar extent regardless of which drug was taken (table III) and those for which the change depended on the drug taken by the patient (table IV). For one variable, red blood cell folate, the size of the change depended on the sex of the patient and the drug taken (table V), male patients taking phenytoin showing the largest decrease.

Discussion

The choice of an anticonvulsant agent will be determined by the efficacy, safety, and cost of the drug. Perhaps the most difficult of these to examine is efficacy, because of the problem of defining what is meant by "control" of epilepsy. There has been no uniform agreement on this in anticonvulsant studies, which commonly use terms such as "excellent," "good," or "poor" control, based on comparing frequencies of seizures in different treatment periods. Such terms are almost meaningless and control in this study is defined as absence of seizures for a two year period after entry. The choice of two years to define control is arbitrary but may be defended; many clinicians will begin to consider withdrawing anticonvulsant drugs after such a period.

This study represents the first long term randomised clinical trial comparing the efficacy of monotherapy in more than 100 previously untreated adult patients. Our aim was to compare the efficacy of sodium valproate, an antiepileptic drug thought to be most effective against generalised seizures and with less effect against partial seizures, with phenytoin, an established

drug effective against both tonic-clonic and partial seizures.¹³ The treatment groups as randomised did not differ in pretreatment variables that might influence outcome. We were unable to differentiate between the efficacy of valproate and phenytoin in all the patients randomised or in the two main subgroups.

If the measure of efficacy is defined as the proportion of patients who were seizure free in their first two years in the trial, and if testing is at the 5% level of significance, then there is roughly a 60% chance of detecting a 20% improvement over phenytoin and an 85% chance of detecting a similar decrease in efficacy. Thus while we can exclude a large, clinically significant difference in efficacy between the two drugs, the numbers of patients in each subgroup do not allow us detect to reliably small differences in efficacy. These observations illustrate that large numbers of patients need to be studied to reliably detect moderate differences between the efficacy of anticonvulsant drugs. They emphasise the problems in drawing conclusions from studies which have examined small populations of patients.^{7,14}

Possibly the difficulty in detecting differences is due to the fact that the outcome for patients presenting with epilepsy is as much determined by natural history as by the drug treatment. Thus most patients with only tonic-clonic seizures may become seizure free when treated with drugs even if these are of relatively low anticonvulsant potency. Some patients with partial seizures are resistant to any known anticonvulsant. There may be relatively few patients within a population of previously untreated epileptics in whom the potency and dosage of the drug will be critical in determining the response. Clearly if these patients could be defined they would represent a valuable population for study.

Probably, therefore, the initial choice of anticonvulsant is more likely to be determined by relative toxicity than efficacy. Both drugs used in this study possessed dose related toxicity—valproate giving rise to tremor, alopecia, weight gain, and mental change with irritability and occasionally frank confusion,¹²

TABLE III—Variables that changed significantly with treatment in all patients ($n=40$ for both groups)

	Mean pretreatment value	Mean change	(SE)
Haemoglobin (g/dl)	14.4	-0.3	(0.1)
Mean cell volume (fl)	90	+2	(0.3)
Aspartate aminotransferase (U/l)	13	+3	(0.6)
Albumin (g/l)	46	-1	(0.4)
Calcium (mmol/l)	2.4	-0.08	(0.01)

Conversion: SI to traditional units—Calcium: 1 mmol/l $\approx$ 4 mg/100 ml.

TABLE IV—Variables for which size of change varied with drug group ($n=40$ for both groups)

	Mean pretreatment value (all patients)	Mean Change (SE)			
		Valproate group		Phenytoin group	
Serum folate (μ g/l)	4.7	+1.3	(0.4)	-1.0	(0.3)
Alkaline phosphatase (U/l)	66	+7	(1)	+19	(4)
IgA (g/l)	2.05	-0.25	(0.1)	+0.09	(0.09)

TABLE V—Variable for which size of change varied with sex and drug taken ($n=40$ for both groups)

	Mean pretreatment value (all patients)	Mean change (SE)			
		Valproate		Phenytoin	
		M	F	M	F
Red blood cell folate (μ g/l)	268	-59 (46)	+62 (43)	-118 (35)	-61 (39)

and phenytoin causing characteristic ataxia, dysarthria, nystagmus, and drowsiness. It is difficult to compare symptomatic chronic toxicity of these two drugs with a relatively short two to four year follow up. Both drugs seem to have similar effects on biochemical and haematological variables, although phenytoin but not valproate is associated with decreased red cell folate concentrations. We did not undertake psychometric testing in our patients, but other evidence suggests that phenytoin has a greater effect on cognitive function than does valproate.¹⁴ During this study none of the rarer and more serious adverse reactions to valproate occurred. In particular no patient developed evidence of hepatotoxicity related to valproate. The only serious adverse effect occurred in the phenytoin group and consisted of erythroderma and hepatitis in one patient.

There are few studies of the factors predicting the outcome of treatment in previously untreated patients. It is therefore of interest that the most dominant factor in outcome in both this study and that of Shorvon and Reynolds¹⁵ was the history of partial seizures. Shorvon and Reynolds also found that the presence of a neurological, psychiatric, or social disability had an adverse effect on prognosis. We did not find this to be the case, possibly due to the difference in definitions used.

Overall, there seems little evidence of any major difference in efficacy between valproate and phenytoin in adult patients with recent onset of epilepsy, irrespective of the type of seizures that the patients suffered. This study does not disclose any difference in the symptoms of toxicity between the two drugs. Although the five cases of early idiosyncratic reactions which required drug withdrawal were all in the phenytoin group, this was not statistically significant at the 5% level. The unusual pharmacokinetic properties of phenytoin make it a more difficult drug for routine use, necessitating small dosage increments and frequent assays of serum drug concentration. In comparison, the relation between dose and serum concentration for valproate is linear, and regular blood monitoring of monotherapy does not

seem to be critical. In women patients of childbearing age the choice of anticonvulsant drug remains difficult since both drugs appear to be teratogenic.¹⁶

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SHORT REPORTS

Necrotising tongue and skin lesions in temporal arteritis: follow up of a case with a possible iatrogenic factor

Temporal arteritis is a generalised vascular disease characterised by formation of granulomas (giant cell arteritis) which gradually constrict the lumen.¹ Arteries of medium and small size are those mainly affected, the site of predilection being within the cranial vascular territory. Cases with necrotising lesions of the scalp, skin, and tongue have been reported, probably resulting from massive disease of branches of the external carotid artery. We describe these complications in a patient with histologically proved disease² and review published work to see how often they have been reported and under which circumstances they occurred.

Case report

A previously well 69 year old woman was admitted to hospital with a two month history of muscular pain, particularly in the shoulders, neck, and jaw. On examination she appeared fit and did not have headache or visual disturbances. The temporal arteries were slightly tender. Pulsation was normal. Sedimentation rate and plasma fibrinogen concentration were substantially increased. Ophthalmological findings were normal. A biopsy sample was taken from the right temporal artery under local anaesthetic containing a vasoconstrictor. Six hours later she complained of hypoaesthesia of the tongue and interior right side of the jaw and impaired movement of the tongue. A nasogastric tube was inserted because of difficulty with swallowing. She was given large doses of corticosteroids and improved within 24-48 hours.

The histological picture was giant cell arteritis. During the following days she developed anaesthesia of the right lower lip, inferior gingiva, and tongue, which became cyanotic. After nine days most of the tongue was necrotic

together with the right lower lip. Tracheostomy was performed to prevent aspiration of the sloughing tongue. Revision of the tongue was postponed until demarcation had taken place six weeks later. Most of the alveolar process of the mandible was also necrotic. In addition, she developed necrotic lesions on the scalp, which were left to heal spontaneously.

The necrotic area of the right lower lip healed with severe shrinkage of the lip and fixation to the floor of the mouth. The lip was corrected by an Abbé operation and two months later a sulcoplasty was performed with a free graft of split skin. The patient was given a new denture for the lower jaw. Later the prosthetic treatment was completed with a tongue obturator fixed to a palatal plate. By these means she could speak adequately.

Four months later the patient was in excellent health and the tracheostomy was closed. Problems with swallowing still necessitated a feeding tube, but after a year this was removed; she remained, however, able to take only a blended diet. She was followed up regularly as an outpatient for five and a half years and felt well taking a continual low dose of prednisone (5 mg daily).

Comment

Forty nine cases of necrotising lesions of the scalp, facial skin, and tongue have been reported, and in 29 of these there was histological proof of giant cell arteritis. In two of these cases the necrotising lesions within the cranial vascular territory developed shortly after biopsy under local anaesthesia.³⁻⁵

Plainly, necrotising lesions may develop spontaneously in cases of advanced vascular changes of a constrictive-thrombotic nature. It seems reasonable to assume that tissues relying on a critical blood supply may undergo necrosis after an arterial spasm, retrograde in character, with thrombotic occlusion of all collateral and communicating vessels triggered by the vasoconstrictor in a local anaesthetic. Our patient showed symptoms from the cranial vascular territory with pain in the neck and jaw. The diagnosis was plain clinically, and the delay in instituting steroid treatment was probably an important factor in the development of severe necrosis.