statistics and epidemiology at the London School of Hygiene and Tropical Medicine, for his advice on statistics.

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One drug for epilepsy

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Summary and conclusions

We performed prospective trials of phenytoin and carbamazepine, assisted by blood level monitoring, in untreated patients newly referred with grand mal or partial seizures, or both, to a neurological clinic. At the time of follow-up (mean 28·5 months for phenytoin; 12 months for carbamazepine) 76-88% of patients were completely controlled. Twelve per cent of the patients on each drug had further seizures, despite an optimum blood level. When the blood drug concentration was in the optimum range there was a 98% reduction in grand mal attack rate and 92-93% reduction in partial seizure rate.

These results suggest that polypharmacy is largely, and possibly totally, unnecessary in newly diagnosed adult epileptics.

Introduction

Epileptic patients are usually treated with several drugs. A survey conducted in four European countries showed that each patient received an average of 3·2 drugs, of which 84·3% were anticonvulsants.[1] This polypharmacy is unsatisfactory because (*a*) it increases the risks of chronic toxicity,[2] (*b*) with the availability of blood level monitoring any individual anticonvulsant can now be used more effectively,[3–5] and (*c*) we are unaware of any satisfactory evidence that two (or more) drugs are more effective than one, used efficiently, in controlling any type of seizure.

In a retrospective survey[6] of 50 chronic epileptics who were attending a neurological clinic and who were each taking two anticonvulsants we found that seizure control was improved in only 36% of patients in the six months after the addition of the second drug. It is questionable whether this rate of improvement is significantly better than that which would be produced by giving a placebo. Furthermore, when serum concentrations of the two drugs were subsequently measured we found a significant correlation between improved control and optimum levels of at least *one* drug.

We have already described[5] a prospective study of 31 untreated outpatients with grand mal or partial seizures, or both, who were treated initially with phenytoin with the guidance of blood level monitoring. After a mean follow-up of 14·7 months only 10% of these patients needed a second drug because of continuing seizures despite an optimum blood level. We have followed up 26 of these patients for a mean of 28·5 months and have performed a similar study with carbamazepine in a further 25 patients, who have been followed for a mean of one year. We report here our findings.

Patients and methods

We studied consecutive patients (table I) referred to the neurology clinic, King's College Hospital, who (*a*) had a history of two or more recent tonic-clonic seizures or sufficient partial seizures to warrant treatment; (*b*) had had no anticonvulsant treatment; and (*c*) had no progressive neurological disease.

TABLE I—*Details of patients in both prospective trials*

	Phenytoin	Carbamazepine
No of patients	26*	25
Sex	12 F; 14 M	11 F; 14 M
Mean age (years)	32·5 (14–75)	31·9 (10–66)
Follow-up (months)	28·5 (12–41)	12·0 (5–28)
Seizure classification (No of patients):		
Tonic-clonic (grand mal)	14	12
Tonic-clonic with partial origin	3	4
Tonic-clonic and partial seizures	5	6
Partial seizures (simple and complex)	4	3
Associated neuropsychiatric handicaps (No of patients):		
Mental retardation	2	3
Depression, psychoneurosis, behavioural disturbance	7	3

*Of the original 31 patients, one was excluded when a cerebral tumour (glioma) was discovered and four were lost to follow-up.

Each patient was treated initially with phenytoin 200-300 mg/day or carbamazepine 200-400 mg/day in two divided doses. Serum concentrations were measured at each outpatient visit (between 10 00 am and 12 noon), which took place every two weeks to three months, depending on clinical progress. Patients and relatives were asked to record carefully any seizures and this information was documented at each outpatient visit. If seizures continued the dose of the drug was increased if necessary to obtain an optimum serum concentration. Only if seizures continued in spite of an optimum level was a second drug or placebo added and single drug treatment considered to have failed. The optimum ranges used were: phenytoin 10-20 mg/l, and carbamazepine 4-8 mg/l.

Serum phenytoin was measured by the gas chromatographic

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technique of Kupferberg[7] and serum carbamazepine by the method of Toseland *et al.*[8]

Results

Seizure frequency was related to serum concentrations in three ways.

Firstly, the patients were grouped according to their response to treatment at the end of follow-up. Table II shows that 77-88% were completely controlled at this time. In both trials only three patients had one or more seizures despite optimum drug concentrations. These failures on a single drug were usually associated with partial seizures, poor compliance, or additional neuropsychiatric handicap. A further three patients on phenytoin had additional seizures but single drug treatment was not considered to have failed because their blood phenytoin concentrations had never reached optimum levels owing to poor compliance or attendance.

TABLE II—*Overall outcome of treatment*

	No (%) on phenytoin	No (%) on carbamazepine
Controlled with suboptimum levels	9 (35)	5 (20)
Controlled with optimum levels	3 (12)	16 (64)
Uncontrolled with suboptimum levels but controlled with optimum levels	8 (31)	1 (4)
Uncontrolled, but levels always suboptimum	3 (12)	0 (0)
Uncontrolled with optimum levels	3 (12)	3 (12)

Secondly, taking the duration of follow-up and serum concentrations into account, we calculated the seizure frequency (attacks per month) in the pretreatment, suboptimum, and optimum phases. A few patients briefly had serum concentrations in the supraoptimum range and these data were included in the optimum phase. The pretreatment phase was the time from the first seizure to the start of treatment. Table III shows that for grand mal there was a striking fall in the attack rate of tenfold or more even in the suboptimum range and a further fall in the optimum range. Indeed, in the optimum range only five attacks occurred in 16 patients on phenytoin over a mean of 16 months, and the corresponding figures for carbamazepine were seven attacks in 17 patients over a mean of seven months. In the few patients with partial seizures there was also a considerable fall in attack rate in the optimum range with both drugs. There was, however, a slightly greater tendency for some attacks to continue in the optimum range, but the pretreatment attack rate was much greater than for grand mal.

Thirdly, the percentage reduction in seizure frequency for each patient in the suboptimum and optimum phases was estimated and the mean of these reductions calculated. There was a fall in the frequency of grand mal attacks in the suboptimum range of 87% on carbamazepine and 92% on phenytoin and a further remarkable 98% reduction on either drug in the optimum range. The reduction in partial seizures was slightly less impressive: the frequency of seizures fell by 80% on suboptimum concentrations of phenytoin (there were insufficient data on suboptimum concentrations of carbamazepine) and by 93% on optimum concentrations of phenytoin and 92% on optimum concentrations of carbamazepine.

Discussion

Both prospective trials showed that a single anticonvulsant used in conjunction with serum drug concentration monitoring was highly effective in controlling tonic-clonic or partial seizures in untreated patients newly referred to a neurological outpatient clinic. Our earlier promising results with phenytoin[5] have been maintained for a mean of 28·5 months, and carbamazepine seems to be equally effective after a mean of 12 months. On either drug 76-88% of our patients were completely controlled at the time of follow-up. Only 12% continued to have seizures with an optimum serum drug concentration and could therefore be considered to have failed on single-drug therapy. This failure was usually associated with partial seizures, poor compliance, or additional neuropsychiatric handicap.

The efficacy of the drugs was emphasised by the mean reduction in the frequency of monthly tonic-clonic seizures by 87-92% in the suboptimum range and 98% in the optimum range. Partial seizures were slightly more difficult to treat, the reduction being 92-93% in the optimum range. There was no significant difference between the two drugs as anticonvulsants in these comparable groups of previously untreated patients, as noted in earlier comparative studies on chronic patients.[9 10] Although carbamazepine more readily achieved an optimum blood concentration early in the course of treatment, phenytoin was easier to fine tune with its much wider range of measurable blood concentrations. The choice of drug in any individual patient will therefore be determined by considerations of toxicity and economic costs.

The excellent results achieved in our patients with a single drug contrast with the much poorer prognosis found generally[11] and the widespread practice of polypharmacy. There are several possible reasons for this.

Firstly, the main reason for the effectiveness of our treatment has undoubtedly been the availability of regular blood concentration monitoring in our clinic. The recent growth in our knowledge of the clinical pharmacology of anticonvulsant drugs[12 13] has already resulted in improved seizure control in prospective studies of chronic patients with grand mal[4] and petit mal[3] on multiple drugs, and we have now confirmed this in our untreated patients with grand mal and partial seizures. Indeed, a measure of the value of the blood level monitoring in our patients is our estimation that without it 60-70% of them would now be taking more than one drug. Many of our patients have continued to have seizures but they have almost invariably been associated with suboptimum blood levels, and it is easy to see how the practice of polypharmacy has evolved without the guidance of blood levels.

Secondly, our trial has been the first to study untreated new referrals. Although phenytoin has been used since 1938 and carbamazepine since 1962 we are unaware of any trials of these drugs (or other anticonvulsants) in untreated patients, even before the availability of blood level monitoring. This seems an extraordinary omission and reflects the generally poor quality of anticonvulsant trials, as emphasised by Coatsworth.[14] New drugs always seem to be evaluated in patients with continuing seizures on other drugs, thus perpetuating the phenomenon of polypharmacy. It has been suspected at least since Gowers[15] that each seizure may to some extent facilitate the occurrence of a further attack, and certainly there is good evidence that the longer the duration of epilepsy the worse are the results of treatment.[11] Early and effective treatment, assisted by blood level monitoring, may therefore improve the long-term results

TABLE III—*Seizure frequency related to serum levels. Results are means ± SE*

	Phenytoin			Carbamazepine		
	No of patients	No of attacks/month	Duration of treatment (months)	No of patients	No of attacks/month	Duration of treatment (months)
Tonic-clonic seizures:						
Pretreatment	22	0·94 ± 0·35	15·0	22	1·20 ± 0·46	18·3
At suboptimum concentrations	20	0·08 ± 0·03	18·5	9	0·18 ± 0·18	7·3
At optimum concentrations	16	0·02 ± 0·01	16·1	17	0·03 ± 0·02	7·1
Partial seizures:						
Pretreatment	9	9·71 ± 4·10	29·3	9	10·11 ± 3·04	23·3
At suboptimum concentrations	8	2·21 ± 1·30	16·0	3	Insufficient data	
At optimum concentrations	8	0·71 ± 0·26	16·0	8	0·59 ± 0·29	12·1

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of treatment. We suggest that more attention should be directed to evaluating new or old anticonvulsants in newly diagnosed untreated patients.

Finally, our results may have been influenced by the relative lack of associated neuropsychiatric handicaps (table I), which have been shown to be associated with a generally poorer prognosis.[11] On the other hand, although we excluded patients with obviously progressive neurological diseases, our patients are typical of those referred to a neurological clinic and representative of most adult epileptic patients. Further studies of this type should certainly be undertaken in a more brain-damaged population and also in children, in whom epilepsy is so common.

Whether those patients who continue to have seizures despite an optimum blood concentration of one drug will be improved by the addition of another drug is still uncertain. We have not observed any further improvement in the few patients who failed on a single drug but the numbers were too small to draw firm conclusions. In our retrospective study of chronic patients,[6] however, the addition of a second drug was not usually associated with improved control, but when control did improve it was usually associated with an optimum blood level of one of the drugs. It is at least possible, therefore, that polypharmacy is totally unnecessary and we may have to adjust to the idea that some patients will continue to have attacks with one drug instead of continuing to have them, as is usually the case, with multiple drugs. Only further studies will clarify this.

We conclude from our two prospective trials and retrospective study that there is now considerable potential for improving the quality and results of treatment of epileptic patients. In the population we studied polypharmacy appears to be largely unnecessary and most patients can be satisfactorily treated from the beginning with one drug, assisted by blood level monitoring. An added advantage of this policy will be the associated reduction in chronic toxicity and economic costs.

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Cellular hyperviscosity as a cause of neurological symptoms in leukaemia

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Summary

Six patients with various forms of leukaemia had neurological signs and symptoms associated with an extremely high white blood cell count and increased whole blood (but not plasma) viscosity. All were treated by leucapheresis with an Aminco Celltrifuge. Rapid and complete reversal of all symptoms occurred in three patients and partial recovery in one. One patient died shortly after leucapheresis and another (from cerebral intravascular coagulation) two days later.

It is concluded that a cellular hyperviscosity syndrome may cause neurological dysfunction in patients with extremely high white cell counts, and that leucapheresis, in carefully selected patients, can be an effective method of treatment.

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Introduction

The hyperviscosity syndrome is a symptom complex of neurological dysfunction, visual disturbances, and a haemorrhagic tendency caused by increased blood viscosity. It is classically associated with Waldenström's macroglobulinaemia, and is a more recently recognised complication of myelomatosis—in both cases the symptoms resulting from increased plasma viscosity produced by the abnormal circulating paraprotein.[1 2] Generally, however, the packed cell volume is the most important factor affecting blood viscosity, and the symptoms resulting from abnormal viscosity in polycythaemia vera are well recognised. Though white blood cells on the other hand normally contribute little to whole blood viscosity, patients with leukaemia may develop the hyperviscosity syndrome as a direct consequence of a grossly raised white blood cell count. We report studies on six patients and the results of treating them with leucapheresis.

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