Two antiepileptic drugs for intractable epilepsy with complex-partial seizures

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SUMMARY The value of adding a second antiepileptic drug in intractable epilepsy with complex-partial seizures was studied in a long-term prospective trial in 30 adult patients who failed to respond to the maximum use of carbamazepine, phenytoin, phenobarbital or primidone as the first drug. Based on the individual previous history of one-drug treatment, the most promising antiepileptic drug (carbamazepine, clobazam, clonazepam, phenobarbital, phenytoin, primidone, valproic acid) was added, if necessary until clinical toxicity occurred. A reduction of the seizure frequency by more than 75% was seen in only four patients (13%) exposed to a second drug in the event of failure of optimum one-drug treatment. The remaining majority of patients (87%) did not benefit from the second drug; in three patients the seizure frequency increased by more than 100%. The common practice of adding another drug in difficult-to-treat cases may need to be reconsidered until further evidence is presented that two drugs are more beneficial than one drug in the treatment of intractable epilepsy.

One-drug treatment for epilepsy has considerable effectiveness in previously untreated patients.¹ However, one-drug treatment is less promising in chronically treated patients. This was demonstrated recently in a prospective study of phenytoin therapy in a group of 30 patients with frequent complex-partial seizures. In 22 patients (73%) adequate control of the seizures was not obtained despite optimum one-drug treatment with therapeutic drug monitoring.² There remain several options for further treatment in patients in whom adequate one-drug treatment failed. An alternative drug may be chosen or a second drug may be added. Although two or more antiepileptic drugs are used in the majority of chronic patients, there is surprisingly little evidence to evaluate the advantage of using two antiepileptic drugs instead of one.¹

Among the various reasons for giving a patient more than one antiepileptic drug, the apparent lack of response to the first drug, several types of seizures, traditional approaches, personal opinion, and the availability of drugs are most frequently given.

Furthermore, the patient or his relatives may exert pressure on the physician to add another drug in the face of uncontrolled seizures. Yet the most important factor seems to be the concept that adding another drug will improve the therapeutic efficacy of the drug treatment. Unfortunately multiple antiepileptic drug treatment is associated with a number of problems: chronic toxicity, drug interactions, failure to evaluate the individual antiepileptic drug, and possibly the exacerbation of seizures in some patients.³ It may therefore be useful to consider what would be acceptable evidence that two-drug treatment is preferable to one-drug treatment. It is necessary to ensure that the first drug has been used to its maximum capacity—that is, the highest tolerable plasma concentration. Furthermore, therapeutic drug monitoring will have to be employed to detect changes in the plasma concentration of the first drug when the second drug is given. If the plasma concentration of the first drug increases through an interaction with the second drug, the observed clinical effect may also have been produced directly by an increased dose of the first drug. In order to evaluate one-drug versus two-drug treatment, it is necessary to undertake prospective studies in groups of patients who have failed to respond to the optimum use of the first drug as suggested by Reynolds and Shorvon.¹ Such a study has been performed in 30

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patients with complex-partial seizures uncontrolled by one-drug treatment who received a second antiepileptic drug.

Patients and methods

Thirty adult patients with intractable complex-partial seizures were chosen who remained uncontrolled despite one-drug treatment with either phenytoin, carbamazepine, primidone or phenobarbital at the highest tolerable plasma concentrations. It is our policy to increase the dose of the drug if necessary until toxicity occurs. The clinical data of this group of chronic patients are given in table 1. The

highest antiepileptic drug plasma concentration, the number of blood samples, the duration of the one-drug treatment, and the average weekly seizure frequency during one-drug treatment were recorded for each patient. The average seizure frequency during optimum one-drug treatment was 1.0 seizure per week. Patients with additional hysterical seizures, previous neurosurgical therapy or space occupying brain lesions were excluded. The 30 patients were seen by the author every 1–3 months in the Epilepsy Clinic. The type and number of seizures were documented with the help of a seizure calendar, the description of the patient and eye witness reports. The seizures were classified according to the 1981 Revision of the International Classification of Epileptic Seizures.⁴ The plasma concentration of the antiepileptic drug was determined. The patients were asked at every visit about the compliance with the prescribed dose. Most patients used a tablet dispenser to allow self-control of the regular intake of the daily dose. One-drug treatment with phenytoin was ineffective in 19 patients—that is, the epilepsy was uncontrolled despite the onset of nystagmus, tremor or ataxia. In five patients receiving phenobarbital or primidone the seizures were uncontrolled despite sedative side effects, nystagmus or ataxia. Treatment with carbamazepine did not result in seizure control of six patients despite the onset of drowsiness, vertigo, nystagmus and ataxia. The duration of one-drug treatment was 39.6 ± 30 (SD) weeks with a range of 4–115 weeks (tables 2–4).

A second drug was added after written consent was obtained. The selection of the second drug depended on the

Table 1 Clinical data of the patients

	n
Complex-partial seizures alone	6
Additional generalised tonic-clonic seizures	24
Age	$36.5 \pm 12^*$
Duration of epilepsy	$18.9 \pm 8^*$
Neurological or psychiatric handicap	23
Febrile convulsions	5
Status epilepticus	
generalised tonic-clonic seizures	3
complex-partial seizures	4
Family history of epilepsy or febrile convulsions	5
Etiology of epilepsy unknown	1
	15

*Mean $\pm$ SD and range in years.

Table 2 No change in seizure frequency despite the addition of a second drug in 12 of 30 patients (40%) with complex-partial seizures uncontrolled by previous one-drug treatment. Primidone treatment was monitored by the plasma concentration of phenobarbital. Abbreviations: Carb = carbamazepine, Clb = clobazam, Clon = clonazepam, DPH = phenytoin, Pb = phenobarbital, Prim = primidone, Val = valproic acid

Patient number	Drug	Plasma concentration (μ g/ml)*	Duration of trial (weeks)	Seizure frequency (weekly)	Drug	Plasma concentration (μ g/ml)*	Duration of trial (weeks)	Seizure frequency (weekly)	Statistical difference
1	DPH	44 (7)	6.0	0.90	DPH	29 (7)	60.0	1.33	NS
9	Carb	15 (2)	15.1	2.30	Carb	7 (5)			
18	Pb	24 (4)	28.0	0.14	Carb	9 (2)	11.9	2.00	NS
24	DPH	33 (11)	26.3	1.86	Prim	18 (2)			
27	DPH	35 (2)	13.6	0.37	Pb	21 (2)	9.8	0.40	NS
32	Carb	12 (11)	44.1	0.50	Carb	6 (1)			
38	Prim	63 (3)	38.5	0.73	DPH	8 (8)	78.4	1.45	NS
42	Prim	49 (7)	36.8	1.49	Pb	32 (8)			
49	DPH	25 (11)	92.4	0.42	DPH	30 (2)	9.9	0.40	NS
50	DPH	33 (4)	17.5	0.57	Carb	6 (1)			
61	DPH	30 (3)	28.0	0.50	Carb	12 (8)	55.0	0.32	NS
73	DPH	49 (6)	4.7	2.80	Pb	21 (7)			
					Prim	42 (4)	11.3	0.53	NS
					DPH	7 (4)			
					Prim	46 (6)	15.0	1.30	NS
					Carb	— (500 mg)			
					DPH	14 (2)	9.4	0.42	NS
					Prim	12 (2)			
					DPH	32 (3)	58.2	0.46	NS
					Clon	— (6 mg)			
					DPH	22 (4)	20.0	3.10	NS
					Val	— (1800 mg)			
					DPH	27 (24)	11.0	1.80	NS
					Prim	54 (22)			

*Highest steady state plasma concentration, number of blood samples in parenthesis.

Table 3 An increase in seizure frequency despite the addition of a second drug in 7 of 30 patients (23%) with complex-partial seizures uncontrolled by previous one-drug treatment. Abbreviations see Table 2

Patient number	Drug	Plasma concentration (µg/ml)*	Duration of trial (weeks)	Seizure frequency (weekly)	Drug	Plasma concentration (µg/ml)*	Duration of trial (weeks)	Seizure frequency (weekly)	Statistical difference (change in percent)
11	DPH	36 (18)	56.7	0.21	DPH	23 (6)	28.2	0.85	+305 [‡]
15	DPH	44 (15)	115.0	0.17	Carb	6 (6)			
21	DPH	16 (5)	71.0	0.70	DPH	42 (7)	44.0	0.39	+129 [‡]
23	DPH	40 (8)	35.4	0.88	Carb	7 (1)			
29	DPH	50 (11)	105.9	1.30	DPH	53 (11)	55.4	1.39	+99 [‡]
45	DPH	45 (17)	94.1	0.57	Val	+ (2700 mg)			
46	DPH	36 (4)	40.0	0.40	DPH	42 (5)	63.0	1.37	+56 [‡]
					Clb	0.24 (4)			
					DPH	48 (4)	20.9	2.90	+123 [‡]
					Pb	18 (4)			
					DPH	26 (6)	23.4	0.94	+65 [‡]
					Carb	6 (4)			
					DPH	21 (10)	123.8	0.64	+60 [‡]
					Carb	7 (10)			

*Highest steady state plasma concentration, number of blood samples in parenthesis.

[‡]p < 0.05.

^{‡‡}p < 0.01.

Table 4 An improvement in seizure frequency following the addition of a second drug in 11 patients uncontrolled by previous one-drug treatment. In 5 of 30 patients (17%) the seizures decreased by more than 75%. None of the patients became seizure-free. Abbreviations see Table 2

Patient number	Drug	Plasma concentration (µg/ml)*	Duration of trial (weeks)	Seizure frequency (weekly)	Drug	Plasma concentration (µg/ml)*	Duration of trial (weeks)	Seizure frequency (weekly)	Statistical difference (change in percent)
5	Carb	14 (2)	4.1	2.93	Carb	15 (6)	7.0	0.43	-85 [‡]
8	Carb	12 (4)	59.2	0.34	Pb	36 (4)			
12	Carb	9 (3)	43.3	2.20	Carb	7 (6)	147.9	0.22	-35 [‡]
14	DPH	40 (5)	19.9	0.85	Prim	47 (9)			
16	Carb	12 (16)	21.0	0.80	DPH	30 (9)	36.6	1.40	-36 [‡]
22	DPH	19 (5)	6.4	2.34	Carb	— (1200 mg)			
28	DPH	35 (12)	26.9	1.34	DPH	29 (6)	21.6	0.46	-46 [‡]
35	DPH	35 (11)	47.4	0.60	Carb	8 (5)			
37	DPH	50 (3)	23.1	2.22	Carb	5 (5)	9.0	0.10	-87 [‡]
54	Prim	35 (5)	36.0	1.00	DPH	31 (3)			
55	Prim	60 (12)	32.7	1.44	DPH	39 (23)	86.0	0.47	-80 [‡]
					Prim	52 (22)			
					DPH	32 (9)	105.1	1.26	-6 [‡]
					Pb	50 (9)			
					DPH	19 (3)	22.3	0.09	-85 [‡]
					Clb	—			
					DPH	47 (2)	6.3	0.28	-87 [‡]
					Pb	13 (3)			
					Prim	33 (4)	64.7	0.53	-47 [‡]
					DPH	16 (4)			
					Prim	46 (17)	39.3	1.09	-24 [‡]
					DPH	43 (15)			

*Highest steady state plasma concentration, number of blood samples in parenthesis.

[‡]p < 0.05.

^{‡‡}p < 0.01.

previous drug regimen of the individual patient. The policy was to select one of the standard drugs (phenytoin, carbamazepine, or primidone/phenobarbital) which had previously not been shown to be ineffective in a controlled fashion (that is with monitoring of plasma concentrations) in our Epilepsy Clinic or elsewhere. In four patients phenytoin was added, in 10 patients carbamazepine and in 11 patients primidone or phenobarbital were given as the

second drug. In five patients none of these four drugs seemed promising; in these cases valproic acid or clobazam were added in two patients and clonazepam was introduced as secondary antiepileptic drug in one patient. In subsequent visits clinical parameters were monitored in a protocol identical to that during the previous one-drug treatment. The second drug was slowly increased in dose until seizure control or clinical toxicity was seen. The dose

of the first drug was reduced individually until clinical toxicity disappeared before the second drug was introduced.

Clinical toxicity of valproic acid was indicated by tremor, that of benzodiazepines by drowsiness, sedation or irritability.⁵ During the initial phase of the two-drug treatment it was necessary to reduce the dose of the first drug in two patients due to side effects. The highest steady state plasma concentration of the two antiepileptic drugs, the duration of treatment and the mean weekly seizure frequency were recorded. The average duration of the two-drug treatment was 41.8 ± 37 weeks, with a range of 6–147.9 weeks (tables 2–4). The average duration of the total study with one-drug treatment and subsequent two-drug treatment was 81.0 ± 48 (SD) weeks, with a range of 11–207 weeks.

The efficacy of two-drug treatment was evaluated by comparison of the average weekly seizure frequency with the previous one-drug treatment period. The total number of seizures (complex-partial seizures, isolated auras, and generalised tonic-clonic seizures) during the one-drug and the two-drug treatment period were compared for each patient with the Fischer-Yates adaptation of the chi square test for small numbers. Each patient served as his own control for comparison with the variable two-drug treatment period. At *p* values of 0.05 or less, statistical significance was assumed. In addition, a per cent change of the average weekly seizure frequency was given. A change by more than 75% was arbitrarily considered to be clinically relevant.

The plasma concentrations of phenytoin, phenobarbital, valproic acid and carbamazepine were determined in duplicate by the enzyme immunoassay EMIT. Primidone treatment was monitored by the plasma concentration of phenobarbital. Quality control included multiple determinations of control samples with a coefficient of variation of less than 3% and external quality control in the European Antiepileptic Drug Quality Control Program organised by Prof Richens. The plasma concentrations of clobazam and its *N*-desmethyl-metabolite were kindly determined by Hoechst AG.

Results

In 12 out of the 30 patients (40%) uncontrolled by one-drug treatment the second antiepileptic drug did not significantly influence the seizure frequency (table 2). The highest plasma concentration of the second drug ranged from 6–8 µg/ml carbamazepine, 7 µg/ml phenytoin, and 12–54 µg/ml phenobarbital (derived from primidone treatment in some patients). A further increase in the dose of the second drug was not possible because of clinical toxicity. The seizure frequency was increased in seven patients (23%) despite the introduction of the second drug (table 3). In three patients the increase in seizure frequency was more than 100%. The highest steady state plasma concentrations of the second drug reached 6–7 µg/ml carbamazepine, 18 µg/ml phenobarbital and 0.24 µg/ml clobazam. In one patient (No 11) the addition of

carbamazepine led to a decrease in the phenytoin plasma concentration from 36 to 23 µg/ml and a subsequent increase in seizure frequency. In patients Nos 45 and 46 the dose of phenytoin was reduced due to side effects after carbamazepine was added. It is remarkable that in patients Nos 15, 21 and 23 the seizure frequency increased even though the plasma concentration of the first drug did not change or even increase during the concomitant treatment.

In 11 patients the seizure frequency decreased, in five patients by more than 75% (table 4). No patient was seizure-controlled by the addition of a second drug. The expected result that the seizure frequency is significantly reduced by the second drug was confirmed in only five out of 30 patients (17%). In one of the five patients (No 22) it remained unclear whether the addition of the second drug was in fact responsible for the improved seizure control. The plasma concentration of phenytoin as the first drug increased from 19 to 39 µg/ml during two-drug treatment which suggests that a higher dose of the first drug alone could have achieved the same clinical improvement. As a result, improved seizure control can be ascribed in only four out of 30 patients (13%) to the second drug. The five patients complained about side effects (nystagmus, vertigo, drowsiness, ataxia) during one-drug and two-drug treatment.

Discussion

The addition of a second drug for epilepsy uncontrolled by one-drug treatment is based on the widely accepted concept that the second drug increases the therapeutic efficacy of the drug treatment. This concept may be based on a pitfall in interpretation of the common clinical impression that seizure control may improve when a second drug is added. If the first drug was not given in sufficiently high dosage, the improved seizure control cannot be reliably attributed to the second drug as optimum use of the first drug alone may have achieved the same therapeutic result. The clinical experience shared by many physicians does therefore not provide conclusive evidence in favour of two-drug treatment. In fact, this study indicates that the desired therapeutic result is reached in only 13% of the patients exposed to a second drug in the event of failure of optimum one-drug treatment. The remaining great majority of patients did not benefit from the two-drug treatment and in three patients (10%) the epilepsy even increased in seizure frequency more than 100% despite the second drug treatment.

Before the pathogenetic mechanism for this surprising lack of efficacy of two-drug treatment is considered, it may be useful to review the literature

for acceptable evidence how often a second drug was successful when optimum one-drug treatment failed. In a retrospective survey of 50 chronic patients on two antiepileptic drugs, the addition of a second drug was associated with a reduction of seizure frequency by 50% or more in only 36% of the patients, and when it did occur, it was usually associated with optimum blood levels of at least one of the drugs.⁶ In prospective trials of mostly pretreated chronic patients with complex-partial seizures the addition of a second drug⁷ either carbamazepine,^{8,9} primidone,^{9,10} or phenobarbital¹¹ did not result in complete seizure control when the first drug was given in sufficiently high dose. In one recent study, the number of seizures decreased by more than 50% in 12 of 20 patients with intractable epilepsy when carbamazepine was added.¹² In one double-blind study carbamazepine was added as a second drug to patients uncontrolled by phenytoin or phenobarbital at plasma concentrations of 10–15 µg/ml. The therapeutic effect of the second drug is difficult to evaluate in this study, as it may also have been achieved by the first drug at higher plasma concentrations.¹³ Gallagher *et al*¹⁴ showed in two studies that the addition of etobarb was beneficial to patients uncontrolled by phenytoin at an average plasma concentration of 15 µg/ml and 20 µg/ml. During the etobarb treatment, the plasma concentration of phenytoin increased in the patients with significant improvement, consequently it is difficult to assess the efficacy of the second drug. Furthermore, there is surprisingly little experimental data on the increase of the therapeutic effect when a second drug is added. Leppik and Sherwin¹⁵ showed that the anticonvulsant action of phenobarbital and phenytoin when given individually or in various combinations could be accounted for by the sum of concentration of the individual drugs in the brain. Whether this concentration was reached by one drug or both drugs did not influence the therapeutic effect. Earlier experimental data suggested that the combination of phenytoin and phenobarbital were up to 1.35 times more potent than calculated on the basis of similar joint action of the component parts of the mixture.¹⁶ This apparent potentiation of anticonvulsant activity when these drugs were administered simultaneously was re-examined by Leppik and Sherwin.¹⁵ They found that brain concentrations of phenytoin relative to the dose employed were significantly higher when phenobarbital was administered concurrently than when phenytoin was given alone. Consequently there is no sound experimental evidence that a combination of both drugs is more efficacious than one drug given in a sufficiently high dose.

In conclusion, there does not seem to be sound

experimental or clinical evidence which suggests that a second drug leads to seizure control when a first standard drug failed. The explanation why the second drug was not successful in most chronic patients with an intractable epilepsy is difficult to give from a clinical point of view. The selection of the patients in this report was biased towards a hard core group of chronic intractable epilepsy with a high frequency of partial seizures and neurological or psychiatric handicaps. These factors are known to be prognostically unfavourable in regard to seizure control.¹ It may be suggested, however, that once the available receptor sites for the therapeutic effect are occupied regardless of the type of antiepileptic drug, any further drug cannot exert an additional antiepileptic effect. In the patients with an increase in seizure frequency, the plasma concentration of the first drug dropped either due to drug interaction, when carbamazepine was added to phenytoin as recently reviewed³ or because the dose of the first drug was reduced. In some patients there is no drop in plasma concentration which could explain the worsening in seizure control. Curiously, all patients who had an increase in seizures on two drugs were on phenytoin as the first drug. It seems possible that the two-drug therapy aggravated the epilepsy in these cases. Our data do not allow us to incriminate a specific drug as there was no randomisation in the choice of the drug in this trial. The disturbing fact that anticonvulsant toxicity may aggravate epilepsy has recently been reviewed extensively.¹ In fact, improvement in seizure control has been shown following reduction of polypharmacy.^{1,17} The number of patients with a change in seizure frequency by more than 75% (either increase or decrease) was 13% and 17%, respectively. This suggests that the changes in seizure frequency could be due to the spontaneous course of the disease independent of the therapeutic or toxic effects of the drug treatment. A placebo-controlled trial of the addition of a second drug may be helpful for further studies. The result of this study may justify the following preliminary clinical conclusions. A second drug should not be added unless the first drug has failed despite optimum dose guided by response and drug monitoring. In the event of failure of a first drug, the second drug is beneficial in only about one out of six patients with intractable complex-partial seizures. The widespread practice of adding another drug in difficult-to-treat cases may need to be reconsidered until further evidence is presented that two drugs are more beneficial than one drug in the treatment of intractable epilepsies.

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