PAPERS AND ORIGINALS

Reduction in polypharmacy for epilepsy

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Summary and conclusions

A two-year prospective study of 40 adult outpatients with chronic epilepsy was carried out in which blood drug concentrations were monitored, and anticonvulsant polypharmacy was reduced to treatment with a single drug in 29 patients (72%). In the year after the reduction of treatment the control of seizures was improved in 16 patients (55%), unchanged in eight (28%), and worse in five (17%). Mental function was improved in 16 (55%). The main reason for failure to reduce to or maintain treatment with a single drug was exacerbation of seizures during the difficult withdrawal period, especially in patients with frequent seizures, taking several drugs, or with additional neuropsychological handicaps.

It is more difficult to reduce polypharmacy than to avoid it in the first place. Polypharmacy may sometimes aggravate control of seizures.

Introduction

Two of the major problems associated with drug treatment of epilepsy are polypharmacy and chronic toxicity.[1] Evidence exists that these could be considerably reduced by more effectively using individual anticonvulsants, with blood-concentration monitoring.[1-4] In a retrospective survey of 50 chronic outpatient epileptics adding a second drug improved seizure control (50% or more reduction in seizure frequency) in the ensuing six months in only 36%.[2] When blood concentrations of the two anticonvulsants were subsequently measured improved seizure control was usually associated with an optimum blood concentration of at least one of the drugs. In two long-term prospective trials in previously untreated adult outpatient referrals with grand mal or partial seizures, or both, given either phenytoin (mean follow-up 32 months) or carbamazepine (mean follow-up 18 months) the failure rate for optimum treatment with a single drug was no higher than 15%.[3,4] Furthermore, among those patients with continuing seizures despite optimum use of a single drug we have no evidence that adding a second drug has improved control, although the numbers are small and this requires further investigation.

In view of the potential for treatment with one drug shown in these studies we have investigated the effects of reducing polypharmacy to single-drug treatment in patients with chronic epilepsy.

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Patients and methods

Forty consecutive adolescent or adult outpatients with grand mal or partial epilepsy, or both, receiving long-term anticonvulsant polypharmacy—that is, two or more drugs—entered the trial. Seventeen attended the specialised epilepsy clinic at the Maudsley Hospital, and 23 attended the neurological outpatient clinic at King's College Hospital.

Table I summarises the age, sex, type of seizure and frequency, duration of epilepsy, associated handicaps, and number of anticonvulsant drugs taken in each case. Subnormality was defined as an overall IQ of less than 85 on the Wechsler Scale. Psychosocial handicaps were defined as those severe enough to warrant referral to a psychiatrist or social worker. Most patients had had seizures since childhood or adolescence, only five having had them for less than 10 years. The Maudsley patients showed trends towards more mixed or partial seizures, more-frequent attacks, more associated handicaps (especially psychosocial), and more drugs.

Each patient was followed up prospectively for 12 months while receiving the original polypharmacy and then, after a variable period when the treatment was reduced, for a further 12 months while receiving only one drug (in the event of successful reduction). These two 12-month periods were compared and form the basis of this report.

Year of polypharmacy—The original regimen of anticonvulsant polypharmacy was maintained. In the event of continuing seizures the dose of each drug was adjusted to maintain optimum blood concentrations, but no drugs were changed or added. Table II shows the drugs used.

Period of withdrawal—We decided which anticonvulsants to withdraw on an empirical basis depending on the drug combination, the dose and serum concentration of each drug, and side effects. The duration of withdrawal varied between three weeks and seven months (mean 2·8 months) depending on the original number, doses, and serum concentrations of the drugs. Each drug was withdrawn slowly by small weekly or fortnightly decrements. The drug to be continued

TABLE I—*Details of patients studied at Maudsley and King's College hospitals*

	Maudsley	King's College	Total
No of patients	17	23	40
Mean age (years)	28·8	25·0	26·9
Sex:			
Men	7	13	20
Women	10	10	20
Type of seizure:			
Grand mal	3	8	11
Partial	4	4	8
Mixed	10	11	21
No of seizures*†:			
None	1	7	8
1-10	4	5	9
11-100	5	7	12
Over 100	7	4	11
Mean duration of history (years)	19·9	16·5	18·0
Associated handicap:			
None	4	7	11
Subnormality	6	10	16
Neurological	1	4	5
Psychosocial	8	5	13
No of drugs prescribed*:			
2	11	18	29
3	5	5	10
4	1	0	1

*In year of polypharmacy.
†Grand mal and partial attacks combined.

TABLE II—*Numbers of patients receiving each of the drugs prescribed, according to whether they attended Maudsley or King's College Hospital*

	Year of polypharmacy (n=40)			Year when single drug prescribed (n=29)		
	Maudsley	King's	Total	Maudsley	King's	Total
Phenytoin	14	18	32	1	9	10
Phenobarbitone	3	15	18	2	1	3
Primidone	11	8	19	1	2	3
Carbamazepine	9	2	11	5	6	11
Sulthiame	1	3	4			
Valproate	0	3	3	0	1	1
Clonazepam	2	0	2			
Mesantoin	0	1	1	0	1	1
Pheneturide	0	1	1			
Troxidone	1	0	1			

was maintained, if necessary, in the optimum range. Facilities for urgent consultation were always available, and if the seizures became more frequent the process of withdrawal was halted. Unless the serum concentration of one of the remaining drugs was shown to be suboptimum (in which case the appropriate dose adjustment was made) the patient resumed the original polypharmacy and was withdrawn from the trial.

Year of single drug treatment—Those patients who successfully reduced to a single drug were followed up for a further 12 months. Table II lists the drugs used in these patients. If seizures continued then the dose of the anticonvulsant was adjusted, if necessary, to maintain an optimum blood concentration. If the seizures became more frequent, despite an optimum concentration, polypharmacy was reconsidered.

Intervals between outpatient visits varied between two weeks and three months, depending on clinical progress. Seizure frequency was recorded by the patient or a relative on standard forms. Side effects, including mental symptoms, were recorded by us on questionnaires, at three- to six-monthly intervals. Serum concentrations of phenytoin, phenobarbitone, primidone, carbamazepine, and valproate were measured at each outpatient visit (between 10 00 am and noon) by standard gas chromatographic techniques.[3 4] Optimum ranges of serum concentrations were: phenytoin 10-20 μg/ml, phenobarbitone 20-40 μg/ml, carbamazepine 4-10 μg/ml, and valproate 40-100 μg/ml; primidone was monitored with the derived phenobarbitone.

Results

Twenty-nine patients (72%) successfully reduced to and maintained treatment with a single drug (group A), but the remaining 11 patients (group B) failed to do so. Table III compares the two groups. There were no significant differences in age, sex, duration of history, or type of seizure. Patients in group B had significantly more severe epilepsy ($P<0·01$), more drugs per patient ($P<0·01$), and a trend to more additional handicaps. These differences may explain why patients from King's College Hospital (87% in group A) did better than those from the Maudsley Hospital (53% in group A). Success or failure to reduce treatment was not clearly influenced by the type of drug withdrawn.

OUTCOME IN GROUP A

Seizure frequency—In 16 patients (55%) a 50% or more reduction in seizure frequency occurred during the year when they received only one drug compared with the year of polypharmacy; in eight patients (28%) there was no change, and in five (17%) a 50% or more increase in seizure frequency occurred. Table IV compares these three groups. No significant differences were noted in age, sex, duration of history, type or severity of epilepsy, or number of drugs taken, although there was a trend to fewer handicaps in the improved subgroup.

Serum anticonvulsant concentrations—During the year of polypharmacy six patients had consistently suboptimum concentrations of all their drugs. Four of these had improved seizure frequency in the year when they took only one agent (three with optimum blood concentrations), and in the other two seizure frequency increased (associated with suboptimum concentrations). During the year when they took only one drug three patients had consistently suboptimum concentrations but were seizure free. Eight further patients had transiently suboptimum concentrations, of whom three were seizure free, three had seizures in this range but were seizure free in the

TABLE III—*Comparison of patients who were successful (group A) or unsuccessful (group B) in reducing to a single drug*

	Group A	Group B
No in group	29	11
Associated handicap:		
Present	20	9
Absent	9	2
No of seizures*:		
Nil	7	1
1-10	8	1
11-100	10	2
Over 100†	4	7
No of drugs*:		
2‡	25	4
3	4	6
4		1
Hospital attended:		
Maudsley	9	8
King's	20	3

*In year of polypharmacy.
†Significantly more patients in group B ($P<0·01$).
‡Significantly more patients in group A ($P<0·01$).

TABLE IV—*Effect of reducing treatment on seizure frequency in patients who successfully reduced to a single drug (group A; n=29)*

	Improved*	Unchanged	Worse†
No of patients	16	8	5
Associated handicap:			
Present	10	6	4
Absent	6	2	1
No of seizures‡:			
Nil	—	5	2
1-10	4	1	3
11-100	10	0	0
Over 100	2	2	—
No of drugs‡:			
2	13	8	4
3	3	0	1
Hospital attended:			
Maudsley	5	3	1
King's College	11	5	4

*A 50% or more reduction in seizure frequency.
†A 50% or more increase in seizure frequency.
‡In year of polypharmacy.

TABLE V—*Details of improvement in mental function that occurred in 16 patients*

	No of patients	Drug withdrawn		
		Barbiturate (n=12)	Phenytoin (n=8)	Others (n=3)
More alert	10	9	3	1
Less depressed or anxious	9	6	4	3
More sociable	5	4	2	1
Less fatigued	5	5	2	2
Improved behaviour	3	3		
Improved intellectual function	2	2	1	

*Drugs withdrawn in the 16 patients were a barbiturate (phenobarbitone or primidone) in 12, phenytoin in eight, carbamazepine in one, sulthiame in one, and valproate in one.

optimum range, and two had seizures with both suboptimum and optimum concentrations.

Side effects—Sixteen patients (55%) reported a moderate or considerable improvement in mental function; 12 (41%) were unchanged; and one experienced an increase in anxiety and tension when a barbiturate was withdrawn. Table V summarises details of the group with improved function. Improvement was not correlated with improved seizure frequency.

OUTCOME IN GROUP B

Five patients experienced an exacerbation of seizures during the withdrawal period, one requiring admission to hospital for frequent partial attacks, which responded to the original drug regimen. In three polypharmacy was reintroduced by us after five, six, and eight months of receiving a single drug because of continuing seizures—although at a rate no greater than that in the year of polypharmacy. In two cases polypharmacy was reintroduced by other doctors, again without evidence of more-frequent seizures. One patient, who had a personality disorder, failed to co-operate with the study.

Discussion

We reduced polypharmacy to a single drug, which was maintained for one year, in 72% of our patients. The main reasons for returning to polypharmacy in the remainder were (1) clear exacerbation of seizures during the difficult withdrawal phase and (2) pressure on the attending doctors to take some further action in the face of continuing seizures, although there was no evidence that these were more frequent. In three patients we succumbed to these pressures ourselves, but in two patients the drugs were reintroduced by others.

Among the 29 patients successfully maintained on a single drug a surprising finding was that the seizure frequency was improved by over 50% in as many as 16 (55%). In nine the reduction was striking (over 80%), and six (21%) became seizure free. We were unable to identify the factors associated with this improvement. There was no clear relation to seizure type or frequency, individual drugs, or drug concentrations, but a trend to fewer handicaps was observed. During the year when a single drug was prescribed there was no change in seizure frequency in eight (28%) patients but, disconcertingly, the number of seizures increased in five (17%). In all five we were able to maintain the drug either because the recurrence or increase was associated with suboptimum blood concentrations or because side effects were appreciably reduced.

Although we did not include formal psychometric studies, an improvement in mental function (alertness, mood, sociability) was a striking feature in 16 (55%) of the patients who succeeded in reducing treatment. This observation was most commonly associated with the withdrawal of barbiturates. Very often the adverse effects of drug treatment had not been reported by the patient during the year of polypharmacy, in keeping with the evidence that anticonvulsants are commonly an unrecognised cause of mental symptoms.[5]

The fact that we were able to reduce to and maintain treatment with a single drug in 72% of our patients supports our view that there is much unnecessary polypharmacy in the treatment of epilepsy.[2–4] Clearly, however, such reduction is not without its risks, mainly owing to exacerbation during the period of withdrawal. One of our patients required admission to hospital for frequent partial seizures, and although we did not observe status epilepticus, we appreciate that this might occur, especially when patients are not carefully supervised. The patients most at risk of exacerbation are, not surprisingly, those with most frequent seizures, most handicaps, and who are receiving most drugs. It would be difficult to disentangle the separate influences of these three factors, which often go together and probably accounted for our much higher failure rate in patients treated at the Maudsley Hospital. To what extent the exacerbation observed during withdrawal is the result of "withdrawal" seizures or release of the underlying epilepsy is uncertain. Interestingly, however, once the difficult withdrawal period has been negotiated the risks are smaller. Nevertheless, caution is still required, especially in patients who were previously seizure free or had infrequent attacks, who accounted for most of those with late exacerbations when receiving a single drug and who have most to lose socially from this.

Our observations are in keeping with those of the Milano collaborative group,[6] whose patients, who were mainly in institutions, were probably more handicapped and had more frequent seizures than our series at the Maudsley Hospital. In 44 such patients followed up for 16 months they succeeded in reducing treatment from a mean of 2·5 to 2 drugs, while at the same time halving seizure frequency (six patients became seizure free) and appreciably improving mental function, especially alertness and psychomotor performance.

Thus provided close, careful supervision is possible, with the help of blood drug concentration monitoring, there is a case for simplifying and rationalising treatment in even the most difficult of chronic patients. Both our own and the Milano studies suggest that if withdrawal can be achieved the benefits for some patients may be striking, in terms of both seizure control and, especially, reduction of toxicity. The evidence also suggests that in some patients polypharmacy actually exacerbates seizures.

Our studies suggest that it is more difficult to reduce polypharmacy in chronic patients than to maintain patients on a single drug, assisted by drug concentration monitoring, from the start of treatment.[3 4] Thus polypharmacy should be avoided in the first place if possible. Probably the main reasons for the traditional and widespread practice of polypharmacy are (1) failure to use individual drugs to their maximum potential,[1] a problem that is often compounded by poor compliance by patients, who are thus exposed to withdrawal seizures; and (2) lack of knowledge of the *limits* to effective anticonvulsant treatment, so that there is frequent pressure to add more drugs in the face of continuing attacks (as occurred in five of our patients in group B). Our studies suggest that there is probably no case for more than two drugs for each type of seizure, and some uncertainty still exists about the value of a second drug if seizures are still occurring despite the optimum use of one drug.[2–4] Further studies with different drugs and in different patient populations are, therefore, required to clarify the limits to effective drug treatment.

There is, of course, a contrast between the continuing seizures of chronic patients, whether receiving one or several drugs with optimum blood concentrations, and the more effective seizure control in patients receiving a single drug with blood-concentration monitoring from the start of treatment.[2–4] This, however, probably reflects the more resistant nature of chronic seizures[7] and is not a justification for using more and more drugs. It emphasises the need for more attention to careful and effective treatment at the onset of seizures in order to avoid the evolution into more resistant chronic seizures.

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