Carbamazepine as a single drug in the treatment of epilepsy

A prospective study of serum levels and seizure control

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SUMMARY Serum levels and seizure control were investigated in a prospective study when carbamazepine was given as a single drug to 32 patients with a variety of seizures. The patients included 13 previously untreated patients (group 1), and 19 who were unresponsive to other anticonvulsant drugs used in different combinations or as a single treatment (group 2). Thirteen patients (10 from group 1, and three from group 2) became seizure-free, and a greater than 50% reduction in seizure frequency occurred in 10 patients (nine from group 2, and one from group 1). Less than 50% reduction in seizure frequency occurred in five patients from group 2. As a wide range of serum levels was associated with complete freedom from seizures, or a greater than 50% reduction in seizure frequency, it was not possible to define a therapeutic range for carbamazepine. Side effects occurred at the start of treatment or after a dose increase. A wide range of serum levels was associated with side effects, and some patients could not tolerate levels greater than 42 $\mu\text{mol/l}$.

Carbamazepine is an effective anticonvulsant drug for the treatment of epilepsy in both children (Dalby, 1971; Gamstorp, 1972) and adults (Wolfsohn, 1971; Scheffner and Schiefer, 1972; Hassan and Parsonage, 1976; Sing *et al.*, 1976). Methods are now available for measuring serum levels of the drug (Meijer, 1971; Christiansen, 1973). In most studies dealing with serum levels and seizure control, carbamazepine was added to other anticonvulsant drugs (Parsonage, 1972; Schneider, 1975; Monaco *et al.*, 1976).

Serum levels of anticonvulsant drugs, when used in combination with other anticonvulsants, do not always correspond with the levels for a single drug, and it has been shown that both phenytoin and phenobarbitone alter carbamazepine levels (Christiansen and Dam, 1973). We report a prospective longitudinal study of serum levels and seizure control when carbamazepine was given as a single drug to 32 patients with epilepsy. Two preliminary communications have already been published (Callaghan *et al.*, 1977; Feely, 1977).

Patients and methods

The patients were divided into two groups. Group 1 included 13 previously untreated patients, eight males and five females, mean age 30 years (age range 7-67 years). Group 2 included 19 patients who continued to have frequent seizures on a variety of anticonvulsant drugs. This group included 10 males and nine females, mean age 21 years (age range 12-54 years). The duration of epilepsy for group 1 varied from one week to 13 years (mean of two years); and for group 2 from nine months to 30 years (mean of seven years). Five patients in group 1 had epilepsy of less than six months duration, with an average weekly number of attacks which varied between 0.1 and 10. The other eight patients had a history of epilepsy of between two years and 30 years, with an average weekly attack rate of between 0.08 and 0.77. The mean number of attacks over a period of six months in group 2 was 23, an average of about one per week.

The seizures classified according to a proposal for an international classification (Gastaut, 1969), together with an assessment of their severity, are

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Table 1 Seizure type and severity for group 1

Seizure type	Patients				Severity of attacks
Generalised tonic-clonic	1**	2*	3*	6*	Mild—five patients Severe—two patients
Partial with complex symptomatology	4**	5**	8*		Mild—one patient Severe—two patients
Partial with complex symptomatology, secondarily generalised	9**	10**	11**		All severe

*Mild attacks.

**Severe attacks.

Table 2 Seizure type and severity for group 2

Seizure type	Patients				Severity of attacks
Generalised tonic-clonic	14*	16*	18*	20**	Mild—three patients Severe—five patients
Partial with complex symptomatology	22**	26**	27**	29**	All severe
Partial with complex symptomatology, secondarily generalised	15**	17**	23**		All severe
	32**	30**	31**		
	19**	21**	24**		All severe
	25**	28**			

*Mild attacks.

**Severe attacks.

documented in Tables 1 and 2. Cases 1–13 represent patients in group 1, and cases 14–32 represent patients in group 2. The anticonvulsant drugs which the patients in group 2 were taking before treatment with carbamazepine are documented in Table 3. Serum phenytoin levels were between 40 and 80 $\mu\text{mol/l}$ in five patients (cases 14, 17, 18, 20, and 22), greater than 80 $\mu\text{mol/l}$ in three patients (cases 13, 21, and 28), and between 8 and 40 $\mu\text{mol/l}$ in five patients (cases 15, 16, 26, 27, and 30).

Phenobarbitone levels were greater than 56 $\mu\text{mol/l}$ in nine patients (cases 18, 19, 20, 22, 23, 25, 27, 29, and 30). Phenobarbitone levels relate to levels from ingested phenobarbitone and phenobarbitone derived from primidone.

Table 3 Previous treatment for patients in group 2

Single drugs	Number of patients	Combinations of drugs	Number of patients
Phenytoin	2	Phenytoin + phenobarbitone	4
Phenobarbitone	2	Primidone + phenytoin	3
Primidone	1	Sulthiame + beclamide	1
		Phenytoin + beclamide + ethosuximide	2
		Carbamazepine + primidone + sulthiame	
		Phenytoin + primidone + sulthiame	2

Agreement to take part in the study was obtained from patients or their parents.

Patients in group 2 who were taking more than one anticonvulsant drug were admitted to hospital for the purpose of discontinuing their other drugs, and introducing carbamazepine. Carbamazepine was given initially in a dosage of 600 mg daily to adults, and in a dosage of 10–20 mg/kg body weight to children. The dose was introduced at 200 mg, and was increased over a period of five days to 600 mg daily for adults. The initial dose was also introduced gradually in children. Further dose increases were carried out, when necessary, in order to control seizures. Patients were seen initially at the end of one week when blood was taken for carbamazepine levels. They were then seen at intervals of four weeks or more frequently, if required, depending upon the severity of seizures. Patients who were making satisfactory progress after nine months were seen at intervals of three months, and all other patients continued to be seen at frequent intervals.

At each visit, blood was taken by venesection for estimation of carbamazepine levels, and details of seizure frequency and side effects were documented, based on information obtained from the patients and their relatives. As many of the patients lived a long distance from the hospital, it was impossible to obtain blood levels at a specific time at each visit. The patients were, therefore, seen at the most convenient time possible for them to attend, either in the morning or afternoon. Blood was taken at intervals which varied between one and eight hours after the last dose of carbamazepine. Patients were taking carbamazepine twice or three times daily. Serum levels of carbamazepine were measured by gas liquid chromatography according to the method of Roger *et al.* (1973).

Results

Four patients who were included in the study initially were withdrawn. They included two patients from group 1 (cases 7 and 11) and one patient from group 2 (case 28) who developed side effects on starting treatment, and one other patient from group 2 (case 31) who was withdrawn from the study when a second drug was added to carbamazepine after seizures at another hospital.

The results will, therefore, deal with 11 patients from group 1, and 17 patients from group 2.

Ten patients from group 1 (cases 1, 2, 3, 4, 5, 8, 9, 10, 12, and 13), and three patients from group 2 (cases 14, 16, and 18), became seizure-

free. A reduction in seizure frequency which was greater than 50% occurred in nine patients from group 2 (cases 20, 22, 26, 27, 15, 17, 23, 19, and 21), and one patient from group 1 (case 6). All of these patients continued to take carbamazepine as a single drug. Some improvement occurred in five other patients from group 2 (cases 29, 32, 30, 24, and 25), but the reduction in seizure frequency was less than 50%, and in two patients (cases 24 and 25) a decrease in partial seizures with a complex symptomatology was associated with an increase in generalised tonic-clonic seizures. As these five patients continued to have frequent and severe attacks on the maximum dose of the drug which they could tolerate, a second drug was added to the carbamazepine.

The range of carbamazepine levels and doses related to seizure control are summarised in Table 4. Because of frequent dose adjustments in an attempt to control seizures, it was not possible to obtain mean levels for all of the five patients with a less than 50% reduction in seizure fre-

quency, and the levels, therefore, refer to three patients only from this group.

We observed fluctuations in serum levels in all patients. This is illustrated for a single patient on a fixed dose in Fig. 1 which shows that the patient remained seizure-free during the period of observation. A wide range of levels was observed on a fixed dose for all patients. This is summarised in Fig. 2 for the 13 patients who became seizure-free.

Side effects occurred at the start of treatment, or after a dose increase. The side effects and associated mean serum levels are summarised in Table 5. The drug was discontinued in two patients who developed a rash, and in one who developed ataxia. The rash occurred within 10 days in one patient, and after six weeks in one other patient.

The ataxia occurred on the initial minimal dose of the drug. Side effects, which occurred in five patients after a dose increase, persisted until the dose was reduced, and were associated with serum levels greater than 42 $\mu\text{mol/l}$. They included three patients who developed drowsiness, one who developed diplopia, and one with an unpleasant facial sensation. The mild sedation which occurred at the start of treatment was transient.

Carbamazepine successfully replaced polypharmacy in nine patients (cases 14, 16, 20, 22, 26, 27, 29, 15, and 17). Improvement in seizure control also occurred in three patients who were not controlled on other drugs used as a single treatment (cases 18, 23, and 21). The drugs included phenytoin in one patient, and phenobarbitone in two patients. All patients who failed to achieve a greater than 50% reduction in seizure frequency were previously taking more than one drug. Two patients withdrawn from the study had treatment with a single drug before taking carbamazepine.

The duration of follow-up for the patients who remained on carbamazepine alone, and who did

Table 4 Range of mean serum carbamazepine levels $\pm$ SD with range of single levels and mean dose range

Patients	Range of mean levels ($\mu\text{mol/l}$)	Range of single levels ($\mu\text{mol/l}$)	Mean dose range (mg/kg)	Response
13	5-34 + + - - 4 7	0-84	6.25-15.38	No seizures
10	24-53 + + - - 7 20	14-96	8.24-31.25	> 50% reduction
5	31-86* + + - - 8 19	33-116**	14.00-28.25	< 50% reduction

* = three patients.

** = five patients.

Fig. 1 Relationship of fluctuating blood levels to seizure control on a fixed dose of carbamazepine.

Fig. 2 Range of serum levels, mean levels, and corresponding doses for the 13 patients who became seizure-free.

not require a second drug, was 7–32 months, with a mean of 14 months; for the five patients who could not be controlled on carbamazepine as a single drug it was 10–21 weeks, with a mean of 16 weeks.

Discussion

Our findings were in keeping with the results of previous studies (Dalby, 1971; Wolfsohn, 1971; Gamstorp, 1972; Scheffner and Schiefer, 1972; Hassan and Parsonage, 1976; Sing *et al.*, 1976; Shorvon, 1977). The drug controlled attacks in previously untreated patients, and successfully replaced other drugs given in a variety of combinations in chronic epileptic patients with uncontrolled seizures.

Table 5 Side effects and mean serum levels of carbamazepine

Side effects	Number of patients	Onset	Serum levels ($\mu\text{mol/l} \pm \text{SD}$)
Rash	2	At start of treatment	14–22
Ataxia	1		+ +
Mild sedation	8		– – 6 7
Headache	1	After dose increase	42–86
Diplopia	2		+ +
Sedation	3		– –
Unpleasant facial sensation	1		8 19

There is no agreed therapeutic range for serum levels of carbamazepine. Schneider (1975) suggested a range of 19.3–27.3 $\mu\text{mol/l}$, Monaco *et al.*, (1976) a range of 16.8–42 $\mu\text{mol/l}$, and

Dam and Christiansen (1976) a level greater than $16.8 \mu\text{mol/l}$.

In this study, the patients who derived most benefit from carbamazepine were those who achieved either complete freedom from seizures or a greater than 50% reduction in seizure frequency. Because of the wide range of serum levels observed in these patients, it was not possible to define a lower limit of carbamazepine which provided the greatest protection from seizures. Therefore, in keeping with the findings of Parsonage (1972), we were unable to define a therapeutic range for the drug.

We observed wide fluctuations in serum levels of carbamazepine on a fixed dose in all patients. This has already been described (Morselli *et al.*, 1975; Monaco *et al.*, 1976). It has been suggested that such fluctuations may be related to alterations in absorption of the drug, (Morselli *et al.*, 1975), or a shorter half-life after long-term treatment (Strandjord and Johannessen, 1975).

Failure of compliance may also result in fluctuating levels, and minor fluctuations may have clinical significance in relation to seizure control (Rodin *et al.*, 1976). We were unable to establish an association between fluctuating levels and poor control, but it is possible that poor compliance by some patients, and a variation of the time in taking blood samples from all patients, contributed to our findings.

Side effects were associated with a range of serum levels. Ataxia occurred with low levels, diplopia with high levels, and sedation with low and high levels. Sedation which occurred with low levels was transient, but persisted with high levels until the dose was reduced. A wide individual variation of serum levels in association with side effects has already been described (Meinardi, 1973).

Our findings support the observations of Reynolds *et al.* (1976) and Shorvon *et al.* (1978) who have shown that, with careful dose adjustments aided by blood monitoring, most patients can be controlled satisfactorily with one drug. The replacement of multiple drug treatment by the single drug carbamazepine in some patients is in keeping with the observations of Hassan and Parsonage (1976). A tendency to polypharmacy for the treatment of epilepsy has been shown (Penry, 1971). It has been established that the hazards of long-term treatment with anticonvulsant drugs are increased when many drugs are used in combination (Reynolds, 1975). Polypharmacy did not benefit the patients in group 2 who continued to have frequent seizures on multiple drugs. In view of our findings with carbamazepine, the value of

other drugs as a substitute for polypharmacy in patients with controlled seizures needs to be clarified. As we found a wide range of serum levels in association with seizure control, we suggest that monitoring of carbamazepine levels is not necessary in all patients. We agree with the recent suggestion (Schain *et al.*, 1977), that serum levels are best used to test compliance and to detect overdosage which may be associated with serum levels greater than $42 \mu\text{mol/l}$.

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