We acknowledge support for this study from Dr P M Lutterbeck, Merck, Sharp and Dohme Limited.

References

- ¹ Atkinson AB, Brown JJ, Cumming AMM, *et al.* Captopril in renovascular hypertension: long-term use in predicting surgical outcome. *Br Med J* 1982;**284**:689-93,1557.
- ² Atkinson AB, Cumming AMM, Brown JJ, *et al.* Captopril treatment: inter-dose variations in renin, angiotensins I and II, aldosterone and blood pressure. *Br J Clin Pharmacol* 1982;**13**:855-8.
- ³ Heel RC, Brogden RN, Speight TM, Avery GS. Captopril: a preliminary review of its pharmacological properties and therapeutic efficacy. *Drugs* 1980;**20**:409-52.
- ⁴ Patchett AA, Harris E, Tristram EW, *et al.* A new class of angiotensin-converting enzyme inhibitors. *Nature* 1980;**288**:280-3.
- ⁵ Mackay A, Eadie AS, Cumming AMM, Graham AG, Adams FG, Horton PW. Assessment of total and divided renal plasma flow by ¹²⁵I-hippuran renography. *Kidney Int* 1981;**19**:49-57.
- ⁶ Brown JJ, Lever AF, Robertson JIS. Renal hypertension: diagnosis and treatment. In: Black D, Jones NF, eds. *Renal disease*. 4th ed. Oxford: Blackwell, 1979:731-65.
- ⁷ Millar JA, Leckie B, Semple PF, Morton JJ, Sonkodi S, Robertson JIS. Active and inactive renin in human plasma: renal arteriovenous differences and relationships with angiotensin and renin-substrate. *Circ Res* 1978;**43**,suppl 1:120-7.
- ⁸ Waite MA. Measurement of concentrations of angiotensin I in human blood by radioimmunoassay. *Clinical Science and Molecular Medicine* 1973;**45**:51-64.
- ⁹ Atkinson AB, Morton JJ, Brown JJ, *et al.* Captopril in clinical hyper-

tension: changes in components of the renin-angiotensin system and in body composition in relation to fall in blood pressure with a note on measurement of angiotensin II during converting enzyme inhibition. *Br Heart J* 1980;**44**:290-6.

- ¹⁰ Fraser R, Guest S, Young J. Comparison of double isotope derivative and radioimmunological estimation of plasma aldosterone concentration. *Clinical Science and Molecular Medicine* 1973;**45**:411-5.
- ¹¹ Cushman DW, Cheung HS. Spectrophotometric assay and properties of the angiotensin-converting enzyme of rabbit lung. *Biochem Pharmacol* 1971;**20**:1637.
- ¹² Davies DL, Robertson JWK. Simultaneous measurement of total exchangeable potassium and sodium using ⁴³K and ²⁴Na. *Metabolism* 1973;**22**:133-7.
- ¹³ Boddy K, King PC, Tothill P, Strong JA. Measurement of total body potassium with a shadow shield whole-body counter: calibration and errors. *Phys Med Biol* 1971;**16**:275-82.
- ¹⁴ Williams ED, Boddy K, Harvey I, Haywood JK. Calibration and evaluation of a system for total body in vivo activation analysis using 14 MeV neutrons. *Phys Med Biol* 1978;**23**:405-15.
- ¹⁵ Gross DM, Sweet CS, Ulm EH, *et al.* Effect of N- (S)-1-carboxy-3-phenyl propyl- } L-Ala-L-Pro and its ethyl ester (MK421) on angiotensin converting enzyme in vitro and angiotensin I pressor responses in vivo. *J Pharmacol Exp Ther* 1981;**217**:552-7.
- ¹⁶ MacGregor AG, Markandu ND, Bayliss J, Roulston JE, Squires M, Morton JJ. Non-sulphydryl-containing angiotensin-converting enzyme inhibitor (MK421): evidence for role of renin system in normotensive subjects. *Br Med J* 1981;**283**:401-3.
- ¹⁷ Brown JJ, Casals-Stenzel J, Cumming AMM, *et al.* Angiotensin II, aldosterone and arterial pressure: a quantitative approach. *Hypertension* 1979;**1**:159-79.

(Accepted 11 October 1982)

Early prognosis of epilepsy

S D SHORVON, E H REYNOLDS

Abstract

In 94 previously untreated new referrals to a neurological clinic with tonic-clonic or partial seizures or both the failure rate for optimum single-drug treatment with phenytoin or carbamazepine after a median of 32 months was 17%. Failure of single-drug treatment was associated especially with the presence of additional neuropsychiatric handicaps but also with partial or mixed seizures, symptomatic epilepsy, and a higher number and frequency of tonic-clonic or partial seizures before treatment. Analysis of the recurrence of seizures suggested that the first year of treatment may be crucial in determining the long-term prognosis.

These findings are in keeping with the concept that seizures may predispose to further seizures, and imply that early, effective treatment may be important to prevent evolution into chronic and more intractable epilepsy.

Introduction

Epilepsy is usually a chronic disorder with a widely varying outcome.¹⁻³ There has been little prospective study, however, of

the factors that influence prognosis.³ Rodin⁴ in his detailed review commented that most reports were retrospective surveys of selected groups of patients with chronic epilepsy who had gravitated to institutions or hospital clinics, often with inadequate documentation and follow-up.

In the past six years we have undertaken studies of single-drug treatment with either phenytoin or carbamazepine, in which we have monitored drug concentrations, in new referrals to a neurological clinic with previously untreated tonic-clonic or partial seizures, or both. In addition to the pharmacological aspects already reported⁴⁻⁷ this has given us the opportunity of studying for the first time, prospectively and from the onset of epilepsy, factors that influence the prognosis for control of seizures.

Patients and methods

We studied 106 consecutive referrals to a neurological clinic with tonic-clonic or partial epilepsy, or both, who had not been treated previously, had no progressive cerebral disorder, and had had two or more recent tonic-clonic seizures or sufficient partial seizures to warrant treatment. Details of the treatment regimen with either phenytoin or carbamazepine and of the blood concentration monitoring have been reported previously.⁴⁻⁶ Our policy was to begin with a small dose of one drug, monitor the blood concentration of the drug at each clinic visit, and increase the dose by small increments, if necessary into the optimum range of blood concentrations for that drug as dictated clinically by the recurrence of seizures, except where there was evidence that the recurrence was due to poor compliance. Two or more seizures despite blood drug concentrations in the optimum range were regarded as evidence of failure of single-drug treatment. Optimum drug concentrations were phenytoin 40-80 µmol/l and carbamazepine 16-32 µmol/l.

University Department of Neurology, King's College Hospital, London SE5 9RS

S D SHORVON, MB, MRCP, honorary registrar (present appointment: senior registrar, National Hospital, Queen Square, London WC1)
E H REYNOLDS, MD, FRCP, consultant neurologist

Four patients were withdrawn (two with tumours and two with skin reactions to carbamazepine); eight were lost to follow-up (after a median of 24 months, range 13-33 months); and 94 (89% of the total) were followed up for a median of 32 months (range 12-70 months). The frequency of clinic visits varied from two-weekly to six-monthly (mean once every 3.4 months). Table I summarises the clinical details of the initial 106 patients and of the 94 patients on whom the data analysis was based. Symptomatic epilepsy was defined as tonic-clonic or partial seizures, or both, associated with a clear history or evidence on examination of a cerebral lesion (for example, perinatal trauma, hemiparesis). A neuropsychiatric handicap was defined as evidence of a cerebral lesion, mental retardation, or psychological or social difficulties of a degree sufficient for referral to a psychiatrist or a social worker.

TABLE I—Details of patients in study

	No (%) of patients initially	No (%) of patients followed up
Male	51 (48)	43 (46)
Female	55 (52)	51 (54)
Median age (range) (years)	23 (6-77)	23 (6-77)
Seizure type:		
Tonic-clonic alone	59 (56)	52 (56)
Partial alone	22 (21)	21 (22)
Mixed	25 (24)	21 (22)
Aetiology:		
Primary generalised	17 (16)	14 (15)
Symptomatic*	29 (27)	27 (29)
Unknown	60 (57)	53 (56)
Timing:		
Nocturnal	28 (26)	27 (29)
Other	78 (74)	67 (71)
Additional neuropsychiatric handicap*:		
Present	50 (47)	41 (44)
Absent	56 (53)	53 (56)
Treatment:		
Phenytoin	61 (58)	54 (57)
Carbamazepine	45 (42)	40 (43)
Total	106 (100)	94 (100)

* See text for definition.

Results

To analyse factors influencing control of seizures we combined the data obtained in the two drug groups since our own and other studies have failed to show any important differences in the anticonvulsant efficacy of phenytoin and carbamazepine either in new referrals^{5,6} or in patients with chronic epilepsy.^{8,9} Patients were classified into five groups on the basis of overall control of seizures according to criteria defined previously (table II).^{4,5} Monotherapy was successful in 72 patients (groups 1-3) and failed in 16 (group 5). Six patients (group 4) continued to have seizures without achieving optimum drug concentrations, probably due to poor compliance. Of the eight patients lost to follow-up, four were in group 1, two in group 4, and two in group 5 when last seen.

Table III summarises the clinical characteristics of the 72 patients whose seizures were controlled with single-drug treatment (groups 1-3) and the 16 patients whose seizures were not controlled with optimum single-drug treatment (group 5). The most striking difference was in the relative excess of neuropsychiatric handicaps in patients in group 5 ($p < 0.001$, $df = 1$, $\chi^2 = 14.0$). Patients in group 5 tended to have more partial or mixed seizures, more symptomatic epilepsy or disease of unknown aetiology, fewer nocturnal seizures, and a history of a greater number and more frequent tonic-clonic or partial seizures before treatment. Due probably to the small number of

TABLE II—Overall outcome

Group	Outcome	No in group
1	Seizures controlled with suboptimum drug concentrations	24
2	Seizures controlled with optimum drug concentrations	22
3	Seizures uncontrolled with suboptimum but controlled with optimum drug concentrations	26
4	Seizures uncontrolled with suboptimum drug concentrations (optimum concentrations not achieved)	6
5	Seizures uncontrolled with optimum drug concentrations	16
Total		94

TABLE III—Comparison of patients whose seizures were controlled (groups 1-3) and uncontrolled (group 5) with single-drug treatment (figures are numbers (%) of patients)

	Controlled	Uncontrolled
Total No of patients	72	16
Seizure type:		
Tonic-clonic alone	42 (86)	7 (14)
Partial or mixed	30 (77)	9 (23)
Aetiology:		
Primary generalised	12 (92)	1 (8)
Other	60 (80)	15 (20)
Timing of seizures:		
Nocturnal	24 (92)	2 (8)
Other	48 (77)	14 (23)
Neuropsychiatric handicap:		
Present	22 (63)	13 (37)
Absent	50 (94)	3 (6)

No and frequency of seizures before treatment

Median No of tonic-clonic seizures (range)	3.0 (2-26)	4.0 (2-20)
Median frequency of tonic-clonic seizures (attacks/month) (range)	0.38 (0.07-2)	0.84 (0.09-1.6)
Median No of partial seizures (range)	20 (2-180)	73 (30-960)
Median frequency of partial seizures (attacks/month) (range)	1.67 (0.33-30)	10.6 (2-30)

Comparisons between groups made using χ^2 test and Wilcoxon's rank sum test—see text.

patients in group 5 these trends did not reach significance at the 1% level. When these factors were combined, however, the differences became even more evident: thus of the nine patients who had tonic-clonic seizures without additional handicaps, all were controlled with treatment; and of the 20 patients who had partial or mixed seizures, symptomatic epilepsy, and additional handicaps, seven remained uncontrolled with optimum monotherapy ($p < 0.001$, $df = 1$, $\chi^2 = 4.15$). There were no differences between the patients whose seizures were and were not controlled with respect to age, sex; age at onset of epilepsy; perinatal, childhood, or family history; or electroencephalographic findings.

Of the 94 patients, 47 experienced at least one further seizure during follow-up. In 40 of these the seizure occurred within the first 12 months of treatment. The figure shows a life-table calculation of the proportion of patients at risk who were seizure free at successive monthly intervals of treatment. Fifty-seven per cent of patients were

Life table showing proportion of patients who were seizure free throughout the study, calculated by actuarial methods. n = adjusted number at risk.

seizure free at 12 months, and this proportion had fallen by only a further 7% at 36 months. Of 25 patients who had at least one seizure in the first 12 months and were followed up for at least two years, 11 had a further seizure during the second year; in contrast only four of the 39 patients who were free of seizures during the first year had a seizure in the second year ($p < 0.01$, $df = 1$, $\chi^2 = 9.67$).

Discussion

These findings in 94 patients followed up for a median of 32 months confirm our earlier observations^{4,5} in smaller numbers

followed up for shorter periods and suggest that in new, previously untreated referrals to a neurological clinic the prognosis for control of tonic-clonic or partial seizures, or both, with phenytoin or carbamazepine is fairly good. Complete control was achieved in 72 patients, the failure rate for optimum single-drug treatment was 17%, and in a further 6% of patients seizures remained uncontrolled and were associated with low blood drug concentrations, probably due to poor compliance.

In this report we were mainly concerned to examine the clinical features associated with a successful or unsuccessful response to single-drug treatment. The most striking association with failure of treatment was the presence of an additional neurological or psychosocial handicap. The mechanism of this effect may be partly mediated by the influence of cerebral lesions as there was also an association between poor control, partial or mixed seizures, and symptomatic epilepsy. Thus in patients with combined partial or mixed seizures, symptomatic epilepsy, and additional neuropsychiatric handicaps the failure rate for optimum single-drug treatment rose to 35%. These observations are in accord with the finding by Rodin¹ in patients with chronic epilepsy of an adverse influence of psychomotor or mixed seizure types, an abnormal neurological or mental state on examination, or a low IQ. A further interesting observation is that failure of monotherapy was associated with a greater number and frequency of both tonic-clonic and partial seizures before treatment. This also agrees with Rodin's conclusions¹ that the longer the history of epilepsy and the more seizures experienced the less likely will be complete seizure control. Other factors that so far we have not found to exert any appreciable influence on outcome are age, sex, age at onset of epilepsy, perinatal, childhood, or family history, and electroencephalographic findings.

We also examined in detail the recurrence of seizures during carefully monitored anticonvulsant treatment. The remarkable finding was that in patients followed up for three years most (85%) of the relapses occurred in the first year, with only 15% of patients relapsing for the first time during the second and third years of treatment (figure). Furthermore, patients who had a seizure within the first year had a significantly higher chance of having seizures in future years compared with patients in whom the first year was seizure free. Probably many factors determine the prognosis for control of seizures from the onset of treatment, including those we have studied and possibly others. One possibility is that during the first year of treatment more "severe" cases of epilepsy are sorted out from milder forms of the disorder. Another possibility, however, was suggested by Gowers¹⁰ in 1881 when he noted that "the effect of a convulsion on the nerve centres is such as to render the occurrence of another more easy, to intensify the predisposition that already exists. Thus every fit may be said to be, in part, the result of those which have preceded it, the cause of those which follow it." The implication of Gowers's concept is that the more seizures that have occurred the more difficult they may be to control, and that the earlier seizures are suppressed the better the prognosis. Some of our observations lend support to Gowers's view: the greater the number and frequency of seizures before treatment the worse the prognosis; the prognosis for control of seizures in new referrals is fairly good compared with our own and common experience¹ that chronic seizures are more difficult to control; and good control during the first year of treatment implies a better prognosis than if seizures recur in this period.

Retrospective community surveys² show a rather better long-term prognosis for remission of seizures than hospital-based studies,¹ although the former have also confirmed that the longer seizures have continued the lower the remission rate. The differences in outcome between community- and hospital-based studies may be due to the inclusion of all cases from the inception of epilepsy in community studies and the tendency for more resistant cases of chronic epilepsy to be treated in hospital clinics. The present study is the first to attempt to evaluate prospectively the factors influencing prognosis from the onset of epilepsy in a hospital setting. To what extent the patients in this study are representative of patients in the community is uncertain, but

further long-term investigations of this kind, including children, may resolve the discrepancies between hospital- and community-based surveys. There is also clearly a need for more investigation into the early years of treatment of epilepsy, which has been surprisingly neglected.⁷⁻¹¹ The present evidence suggests that patients with a poorer prognosis may be identified fairly early in the course of treatment. The first year may be crucial in determining the future course and prognosis of what is often a chronic and sometimes a lifelong disorder.

We are grateful to Parke-Davis, Ciba-Geigy, and the Medical Research Council for financial support; Drs A Galbraith, D Chadwick, and C Dellaportas for clinical help; Mr L Vydelingum and Mr M Laundry for technical help; and Dr A L Johnson for statistical advice.

Reprint requests to EHR.

References

- Rodin EA. *The prognosis of patients with epilepsy*. Springfield, Illinois: Thomas, 1968.
- Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. *Epilepsia* 1979;20:729-37.
- Ounsted C, Lindsay J. The long-term outcome of temporal lobe epilepsy in childhood. In: Reynolds EH, Trimble MR, eds. *Epilepsy and psychiatry*. Edinburgh: Churchill Livingstone, 1981:185-215.
- Reynolds EH, Chadwick D, Galbraith AW. One drug (phenytoin) in the treatment of epilepsy. *Lancet* 1976;i:923-6.
- Shorvon SD, Chadwick D, Galbraith AW, Reynolds EH. One drug for epilepsy. *Br Med J* 1978;ii:474-6.
- Shorvon SD, Galbraith AW, Laundry M, Vydelingum L, Reynolds EH. Monotherapy for epilepsy. In: Johannessen SI, Morselli PL, Pippenger CE, Richens A, Schmidt D, Meinardi H, eds. *Antiepileptic therapy: advances in drug monitoring*. New York: Raven Press, 1980:213-20.
- Reynolds EH, Shorvon SD. Monotherapy or polytherapy for epilepsy? *Epilepsia* 1981;22:1-10.
- Troupin AA, Green JR, Halpern LM. Carbamazepine (Tegretol) as an anticonvulsant. A controlled double-blind comparison with dilantin. *Acta Neurol Scand [Suppl]* 1975;60:13-26.
- Simonsen N, Olesen PZ, Kuhl V, Lund M, Wendelhoe J. A comparative controlled study between carbamazepine and diphenylhydantoin in psychomotor epilepsy. *Epilepsia* 1976;17:169-76.
- Gowers WR. *Epilepsy and other chronic convulsive diseases*. London: Churchill, 1881.
- Shorvon SD, Johnson AL, Reynolds EH. Statistical and theoretical considerations in the design of anticonvulsant trials. In: Dam M, Gram L, Penry JK, eds. *Advances in epileptology*. New York: Raven Press, 1981:123-8.

(Accepted 14 September 1982)

QUACKS AND QUACK REMEDIES I have considered this matter as far as lies in my power; and I do not think it possible that any Act of Parliament can prevent a man from acting as a quack . . . if the College of Surgeons were to endeavour to bring such a Bill into the House of Commons, we should be beat, head over heels, upon that very point, of preventing people from practising who wish to practise for the public advantage. We should have gentlemen rising up on all sides saying, "I was cured by Mr St John Long: I was cured by Morrison's pills, when the regular doctors could not do it." I know therefore that any such attempts on our part would utterly fail . . . I have no objection to a man selling, if he pleases, quack medicines. In the first place, I know people will have them. It is like brandy, and French gloves and other things. It will only become a surreptitious trade if you do not permit it; but I would have a tax put on such things.—GEORGE JAMES GUTHRIE, PRCS. (Select Committee on Medical Education. *Parliamentary Papers* 1834.)

MEDICINES APPROPRIATED TO THE TEETH—Vehement heat, and vehement cold, are inimical to the teeth, but they are most of all offended by sharp and sour things, and the reason is, because they have neither skin nor flesh to cover them, they delight in such medicines as are cleansing and binding, because they are troubled with defluxions and rheums upon every light occasion; and that's the reason the common use of fat and sweet things, soon rots the teeth. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)