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COMPARISON OF CARBAMAZEPINE, PHENOBARBITAL, PHENYTOIN, AND PRIMIDONE IN PARTIAL AND SECONDARILY GENERALIZED TONIC–CLONIC SEIZURES

RICHARD H. MATTSON, M.D., JOYCE A. CRAMER, B.S., JOSEPH F. COLLINS, SC.D., DENNIS B. SMITH, M.D., ANTONIO V. DELGADO-ESCUETA, M.D., THOMAS R. BROWNE, M.D., PETER D. WILLIAMSON, M.D., DAVID M. TREIMAN, M.D., JAMES O. MCNAMARA, M.D., CHARLOTTE B. MCCUTCHEN, M.D., RICHARD W. HOMAN, M.D., WAYNE E. CRILL, M.D., MICHAEL F. LUBOZYNSKI, M.D., N. PAUL ROSENTHAL, M.D., AND ASSA MAYERSDORF, M.D.

Abstract We conducted a 10-center, double-blind trial to compare the efficacy and toxicity of four antiepileptic drugs in the treatment of partial and secondarily generalized tonic–clonic seizures in 622 adults. Patients were randomly assigned to treatment with carbamazepine, phenobarbital, phenytoin, or primidone and were followed for two years or until the drug failed to control seizures or caused unacceptable side effects. Overall treatment success was highest with carbamazepine or phenytoin, intermediate with phenobarbital, and lowest with primidone ($P<0.002$).

Differences in failure rates of the drugs were explained primarily by the fact that primidone caused more intolerable acute toxic effects, such as nausea, vomiting, dizziness, and sedation. Decreased libido and impotence were more common in patients given primidone. Phenytoin caused more dysmorphic effects and hypersensitivity. Control of tonic–clonic seizures did not differ significantly with the various drugs. Carbamazepine provided complete control of partial seizures more often than primidone or phenobarbital ($P<0.03$).

Overall, carbamazepine and phenytoin are recommended drugs of first choice for single-drug therapy of adults with partial or generalized tonic–clonic seizures or with both. (N Engl J Med 1985; 313:145-51.)

EPILEPSY is one of the most common disorders of the nervous system. Its prevalence, estimated at over 2 million cases in the United States,[1] is comparable to that of insulin-dependent diabetes mellitus. Complex partial (psychomotor or temporal-lobe), simple partial (focal), and secondarily generalized tonic–clonic (grand mal) seizures account for nearly all adult-onset cases.[1]

Carbamazepine, phenobarbital, phenytoin, and primidone are the most widely used antiepileptic drugs for the treatment of these seizure disorders.[2] These four drugs will probably continue to be the major agents for the treatment of partial and secondarily generalized epilepsy for at least the next decade. Although they have all been moderately effective in managing seizures, each has undesirable side effects. Recent studies have shown that optimal use of single-drug therapy is often as effective as the use of two or more

From the Neurology Services, Veterans Administration Medical Centers at West Haven, Conn., Augusta, Ga., Los Angeles, Boston, Durham, N.C., San Diego, Dallas, Seattle, Minneapolis, and Sepulveda, Calif.; the Departments of Neurology, Yale University School of Medicine, Medical College of Georgia, UCLA School of Medicine, Boston University School of Medicine, Duke University School of Medicine, UCSD School of Medicine, University of Texas Health Science Center, University of Washington School of Medicine, and University of Minnesota School of Medicine; and the VA Cooperative Studies Program Coordinating Center, Perry Point, Md. Address reprint requests to Ms. Cramer at Epilepsy Research/127, VA Medical Center, West Haven, CT 06516.

Supported by the Veterans Administration Medical Research Service Cooperative Studies Program (CS 118).

drugs and is frequently less toxic.[3] Thus, an understanding of the appropriate use of the available drugs is of great importance.

Previous comparisons of the four most widely used antiepileptic drugs in initial, single-drug treatment have not been adequate[2] because of a variety of shortcomings, including failure to use a double-blind randomized protocol; failure to compare all four drugs, failure to monitor serum concentrations of the drugs; a lack of objective measures of specific types of seizures, efficacy, and side effects; a short period of study; and an insufficient sample for statistical analyses.[4]

The Veterans Administration Epilepsy Cooperative Study Group compared the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone in adults with partial or secondarily generalized seizures, in order to determine which single drug best controls these seizures while producing the least side effects. The following is a report of the outcome of this multicenter, randomized, controlled trial.

Methods

Design

The study methods have been reported in detail.[4-6] Patients with previously untreated or undertreated simple or complex partial or secondarily generalized tonic–clonic seizures were randomly assigned to therapy with carbamazepine, phenobarbital, phenytoin, or primidone and followed in a double-blind, prospective study conducted at 10 Veterans Administration Medical Centers — in Augusta (Georgia), Boston, Dallas, Durham (North Carolina), Los Angeles, Minneapolis, San Diego, Seattle, Sepulveda (California), and West Haven (Connecticut) — using the same protocol. Separate randomization schemes were used for each seizure type. Assignment of seizure type was based on descriptions of previous and recent seizures. Some patients had more than one seizure type (e.g., frequent partial seizures with rare tonic–clonic seizures); other patients initially reported only tonic–clonic seizures but on follow-up study were found to have a history or recent onset of simple or complex partial seizures as well. The initial categorization for purposes of randomization indicated a predominant seizure type, but it was not unusual for other seizure types to appear over time or to be modified by drug therapy.

Patients were followed for one to six years. Evaluations were performed at 1 and 2 weeks and at 1, 2, 3, 4, 6, 9, and 12 months during the first year, quarterly during the second year, semi-annually thereafter, and at unscheduled visits when clinically appropriate. Patients continued to take the original study drug until the end of the project unless the drug failed to control their seizures or caused unacceptable side effects, or unless the patient left the study for reasons unrelated to the treatment.

Criteria for Entry

We studied men and women who were 18 to 70 years of age and had simple or complex partial seizures or secondarily generalized tonic–clonic seizures as defined in a modification of the International Classification of Epileptic Seizures.[7] The criteria for exclusion were a documented previous therapeutic failure with, or hypersensitivity to, any of the four study drugs; alcohol or drug abuse; known noncompliance with treatment programs; severe psychiatric problems; low intelligence (IQ less than 85); a progressive neurologic disorder; and a serious, unstable medical disorder. Patients with alcohol-related seizures were specifically excluded.[5]

Drug Treatment

Patients were randomly assigned to treatment with one of the four active preparations: carbamazepine (Tegretol), 200-mg tablets, phenobarbital (generic), 32-mg capsules, phenytoin (generic), 100-mg capsules, or primidone (Mysoline), 250-mg tablets. In addition, a blank tablet or capsule was provided so that the treatment was not distinguishable. Initial doses of drugs were planned in accordance with expected initial side effects and pharmacologic differences.[5] For example, primidone was begun at a dose of 125 mg daily (at bedtime), which is only a sixth of the usual maintenance dose recommended by the manufacturer. Whenever initial use of a drug caused dose-related side effects, the medication was withheld or the dosage decreased immediately, in order to allow time for tolerance to develop. Every effort was made by the investigator and study assistant to assist the patient in adapting to the antiepileptic treatment.

Doses were increased to attain serum concentrations in the "mid" to "high" therapeutic range, as specified by the study protocol.[5] If seizures were not controlled, the dose was increased until toxicity occurred and was then reduced. If seizures were controlled but unacceptable side effects were apparent, the dose was reduced to try to eliminate the problem without recurrence of seizures. If the lowered dose still produced unacceptable side effects and blood levels were below the therapeutic range, the drug was withheld. Thus, treatment failure was designed to result from a combination of side effects and seizures, as would be found in standard clinical practice. Patient compliance was monitored by measurement of serum concentrations of the drug and by pill counts at each follow-up visit.

Assessments

Rating scales of seizure frequency, systemic toxicity, and neurotoxicity were designed for this study[6] and completed at each visit. These scales provided a numerical assessment of clinical progress during the course of the study. At each visit, the evaluating physician reviewed the patient's seizure record as documented by the patient and family, together with the results of recent hematology and serum chemistry tests and the serum drug concentrations reported as being in the "sub," "low," "mid," "high," or "very high" therapeutic range.[5] The frequency and severity of each of the three types of seizures (simple partial, complex partial, and tonic–clonic) were tabulated and scored on a rating scale that assigned a numerical value to each type.[8] These rating scales were designed and tested so that a combined composite score (seizure frequency plus systemic toxicity plus neurotoxicity) of 0 to 20 points corresponded with a good clinical response, a score of 20 to 35 represented a satisfactory but suboptimal response, a score of 35 to 49 represented a fair to poor but not clearly unacceptable outcome, and a score of 50 or more represented an unacceptable outcome requiring a change in therapy.

Statistical Considerations

The primary end point for evaluating the efficacy and toxicity of the study drugs was patient retention (length of time that the patient continued to take the randomly assigned drug). Composite scores, total seizure control, the seizure rate, and the incidence of side effects were other important outcomes. The recruitment goals of the study, based on the largest sample size required for any of the primary end points, were 250 patients for the secondarily generalized tonic–clonic seizure group and 200 patients for the complex partial and simple partial seizure groups. Separation of patients with partial seizures into two groups (those with simple and those with complex seizures) proved to be difficult because of overlap. Drug randomization was designed to permit analyses with both categories combined to form a single group with partial seizures. Sample sizes for all end points for groups with secondarily generalized tonic–clonic or partial seizures were based on important clinical differences in the outcome measures, with a power of 0.80 and a significance level of 0.05, as described elsewhere.[5]

Patient retention in the study, the primary end point, was analyzed with the actuarial life-table method, as time to drug failure. The generalized Wilcoxon statistic was used to determine statistical significance. Kaplan–Meier analyses also gave the same results. The composite scores and seizure rates were subjected to analyses of variance when possible or Kruskal–Wallis tests when the assumptions for analysis of variances were not valid. All tests were two-

tailed. Chi-square determinations were used to analyze total seizure control and the incidence of side effects. Analyses were performed separately for data on each seizure type and with data on all randomized patients combined for as long as patients were active in the study.

All analyses that involved drug failures as end points were performed both including patients who left the study for reasons not related to the drug and excluding them as withdrawals. Inclusion of the non-drug–related losses allowed the use of data on every patient entered into the study for all analyses, under the assumption that all losses were treatment failures. Such analyses guarded against the possibility that an unrecognized drug-related difference in dropout rate existed but was undetected. The analyses that considered the non-drug–related losses as withdrawals allowed the use of a patient's data only until the time when he or she was lost. In these analyses, the patient's data were considered to be censored at the time of loss and not to represent a treatment failure. These analyses assumed that the reason for loss was not related to the treatment — e.g., was caused by severe medical problems unrelated to the study drug or the patient's moving because his job required it — and that the drug should therefore not be considered responsible.

To ensure that the determination of non-drug–related losses was as valid as possible, the investigators were required to reassess every loss four to six months after termination and to interview the patient if possible. In addition, the study chairman reviewed every case in a blinded fashion to confirm the reason for early termination. If there was any indication that the loss was drug-related, the case was considered a drug-related loss. Most important, the statistical significance of the failures in the trial proved to be essentially the same for the analyses with and without the non-drug–related losses.

Description of Patients

During the five-year patient-enrollment period, 622 patients qualified, agreed to enter the trial, and were randomly assigned to the group with their predominant seizure type: 357 were in the secondarily generalized tonic–clonic seizure group (94 received carbamazepine, 86 phenobarbital, 96 phenytoin, and 81 primidone), and 265 were in the partial seizure group (61 received carbamazepine, 69 phenobarbital, 69 phenytoin, and 66 primidone). Four hundred twenty-one patients either continued to take the drug until the two-year end point or were removed from the study because of drug failure. In 223 of the 421 patients, a drug failed because seizures persisted or the side effects were intolerable, but more often because both problems occurred (Table 1). One hundred ninety-eight patients remained in the study until its conclusion and averaged 36 months of follow-up treatment, with some followed for as long as six years. Two hundred one patients left the study before two years of follow-up for reasons unrelated to seizure frequency or drug toxicity — e.g., they moved or were lost to follow-up[8] (37 per cent of the carbamazepine group, 41 per cent of the phenobarbital group, 36 per cent of the phenytoin group, and 31 per cent of the primidone group). These losses were not significantly different among the drug groups.

Fifty-eight per cent of the patients had never received antiepileptic drug treatment before the event that brought them into the study; 21 per cent had taken antiepileptic drugs at some time in the past, and 21 per cent were receiving an antiepileptic drug at very low, subtherapeutic doses and blood levels,[5] so that they were considered essentially untreated at the time of entry.

The patients in the four drug groups did not differ in mean age (41 years), sex distribution (87 per cent male), mean Wechsler Adult Intelligence Scale IQ (100), education (13 years), or cause of seizures (trauma in 34 per cent, stroke in 14 per cent, other reasons in 18 per cent, and unknown in 34 per cent). Most patients were veterans at Veterans Administration Medical Centers. Ten per cent of the study patients were not veterans but entered the study through special sharing agreements with other medical centers.

Serum drug concentrations were within the therapeutic range throughout the study, indicating continuing good compliance. Mean levels of carbamazepine, phenobarbital, phenytoin, primidone, and derived phenobarbital at 24 months were 8.4, 25.8, 14.0, 11.4, and 16.3 μg per milliliter, respectively — all in the mid to high therapeutic range.[5]

Table 1. Reasons for Drug Failure in the Four Treatment Groups.*

Reason	Treatment Group†				All Patients
	CBZ	PB	PHT	PRM	
	N = 101	N = 101	N = 110	N = 109	N = 421
Toxicity alone	12	19	18	36	85
Toxicity plus seizures	30	33	29	35	127
Seizures alone	3	4	1	3	11
Total failures	45	56	48	74	233

*Treatment failure because of seizures with or without side effects was similar with all drugs. The inability to continue treatment because of adverse effects alone was greatest with PRM.

†CBZ denotes carbamazepine, PB phenobarbital, PHT phenytoin, and PRM primidone. The table excludes the 201 patients who withdrew from the trial for non-drug–related reasons.

Results

Retention Time (Life Table)

The number of patients remaining active in the study was assessed with life-table analyses. The decreasing retention of patients over time represented an inability to manage seizures, unacceptable toxicity, or both. Figure 1 shows data on all seizure types through 36 months of follow-up. The data on all patients were combined because 53 per cent had more than one type of seizure. Both the carbamazepine and phenytoin groups had significantly better retention than the primidone group ($P<0.001$). The phenobarbital group had an intermediate retention, which was also significantly better than retention in the primidone group ($P<0.02$). No significant difference was found between the carbamazepine, phenytoin, and phenobarbital groups. The carbamazepine and phenytoin groups also had significantly better retention than the primidone group when non-drug–related losses were included as drug failures in the analyses ($P<0.05$).

The 36-month retention for the group with tonic–clonic seizures showed that phenobarbital was as successful as carbamazepine and phenytoin, whereas primidone remained significantly less so ($P<0.01$) (Fig. 2). Analyses of the group with partial seizures showed somewhat different results. There was a higher retention rate among patients with partial seizures given carbamazepine or phenytoin than among those given phenobarbital or primidone ($P<0.02$) (Fig. 3). Most of the primidone and phenobarbital failures occurred early in treatment. Analyses for both seizure types also showed statistically significant differences when non-drug–related losses were counted as failures (tonic–clonic, $P<0.02$; partial, $P<0.01$).

Reasons for Drug Failure

Drug treatments were termed failures when seizure control was unacceptable, untoward side effects developed, or both (Table 1). Lack of seizure control required dose increments that resulted in unacceptable toxicity during titration, causing combined failure, in 127 patients. Drug failure occurred in 85

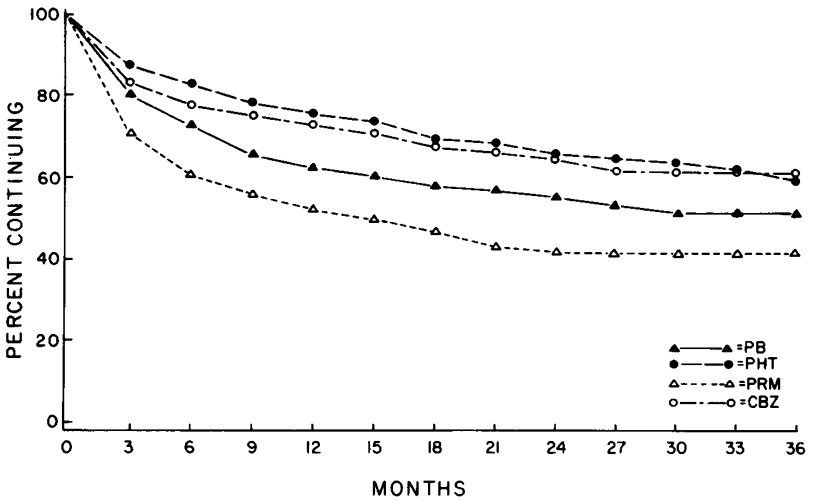

Figure 1. Cumulative Percentage of Patients Successfully Treated with Each Drug during 36 Months of Follow-up.

PB denotes phenobarbital, PHT phenytoin, PRM primidone, and CBZ carbamazepine. There were 275 patients at 12 months, 164 at 24 months, and 97 at 36 months.

patients because side effects were intolerable, even though no seizures had occurred as of the preceding two visits. Some cases of toxicity-associated failure (e.g., acute vomiting or impotence) were due to unwillingness by the patient to continue treatment at a lower dose even though seizures had not recurred. Acute primidone-induced toxicity was especially common and was associated with a constellation of problems, including nausea, vomiting, dizziness, ataxia, and somnolence, causing early discontinuation of the drug. Many patients refused to allow the physician to reinstitute or continue with primidone after their initial adverse experience. Other toxicity-associated failures in patients without seizures were due to non-dose–related problems, such as hypersensitivity, which necessitated a drug change because of the risk of serious systemic effects.

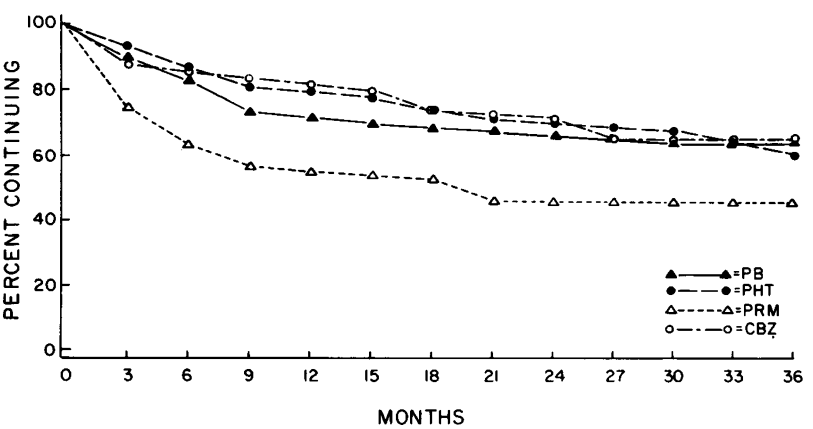

Figure 2. Cumulative Percentage of Patients with Tonic–Clonic Seizures Successfully Treated with Each Drug during 36 Months of Follow-up.

There were 170 patients at 12 months, 97 at 24 months, and 60 at 36 months. The abbreviations are defined in the legend to Figure 1.

Composite Scores

The composite score provided a method to compare seizures and side effects among patients taking each drug, a method differing from the all-or-nothing end point of success or failure obtained in life-table analyses. These ratings were analyzed in two ways.

First, we used end-point analyses (50 points assigned at time of failure) of overall outcome, which showed significantly worse composite scores for primidone and phenobarbital at 12 and 24 months of follow-up (both $P<0.01$) for the entire population (Table 2). Analyses were performed for all patients eligible to be followed for the specific periods and included patients still receiving one of the drugs and patients in whom the drug had failed earlier. The lowest composite scores — i.e., the best overall effectiveness — were achieved with carbamazepine, phenytoin, and phenobarbital ($P<0.05$ as compared with primidone) at 12 months in the group with secondarily generalized tonic–clonic seizures. At 12 months patients in the partial-seizure group who were given phenytoin had lower composite scores than those given phenobarbital or primidone ($P<0.05$). With non-drug–related losses included with failures and 50 points assigned as a failure score, differences among drugs for all patients were also statistically significant at 12 months ($P<0.05$).

We also examined composite scores among patients still in the study (i.e., continuing to take the original drug at 12, 24, and 36 months) without carrying forward failure scores. This provided a measure of relative treatment adequacy in patients remaining in the long-term follow-up study. These scores indicated that patients who continued to take the initial drug (i.e., those in whom the drug did not fail) had comparable amounts of side effects and seizure activity regardless of which drug they received. Scores at 24 months were 11 with carbamazepine, 13 with phenobarbital, 12 with phenytoin, and 9 with primidone (difference not significant).

Adverse Effects

Various systemic and neurotoxic effects occurred with all four drugs, but some were significantly more or less common with specific drugs. Adverse effects were evaluated both as causes of failure and as chronic problems persisting throughout the study.

Carbamazepine caused no side effects that were significantly worse than those associated with the other drugs. Phenobarbital was associated with the lowest incidence of motor disturbance (ataxia, incoordination, nystagmus, and tremor) early in treatment (carbamazepine, 33 per cent; phenobarbital, 24 per cent; phenytoin, 28 per cent; and primidone, 37 per cent; $P<0.05$), as well as the fewest gastrointestinal problems (carbamazepine, 27 per cent; phenobarbital, 13 per cent; phenytoin, 24 per cent; and primidone, 30 per cent; $P<0.01$). Phenytoin caused more dysmorphic and idiosyncratic side effects — including gum hypertrophy, hirsutism, acne, and rash — than the other drugs (carbamazepine, 14 per cent; phenobarbital, 11 per cent; phenytoin, 22 per cent; and primidone, 10 per cent; $P<0.01$). Finally, reports of decreased libido or impotence were most frequent among patients given primidone (carbamazepine, 13 per cent; phenobarbital, 16 per cent; phenytoin, 11 per cent; and primidone, 22 per cent; $P<0.05$).

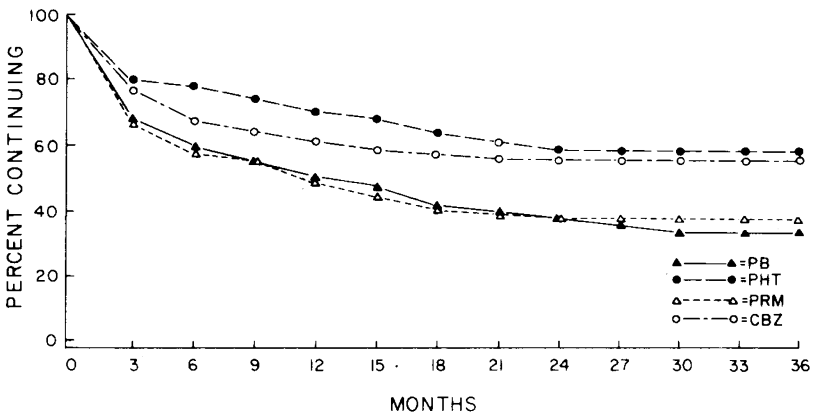

Figure 3. Cumulative Percentage of Patients with Partial Seizures Successfully Treated with Each Drug during 36 Months of Follow-up.
There were 105 patients at 12 months, 67 at 24 months, and 37 at 36 months. The abbreviations are defined in the legend to Figure 1.

Serious Side Effects

Potentially life-threatening side effects were very infrequent. Each occurrence was assumed to be associated with the study drug, which was withdrawn. Although all serious problems were scored as drug-related failures, a causal relationship could usually not be proved. One case of confirmed lymphoma occurred after approximately a year of treatment with phenytoin. A lupus-like syndrome that began with a rash improved rapidly upon discontinuation of phenytoin. Two cases of transient psychosis that occurred during early treatment with primidone cleared after discontinuation of the treatment.

Eighteen patients died during the course of the project, but no deaths were caused by a study drug. There were nine deaths from cardiac disease, four accidental deaths, one death from systemic neoplastic disease, and four pulmonary-related deaths, equally distributed across the drug therapies.

Laboratory Tests

Several laboratory test results changed during drug therapy. Mean alkaline phosphatase levels increased between the base-line and 12-month test in patients given phenytoin (from 86 to 112 IU per liter) or phenobarbital (from 79 to 97) ($P<0.01$) but remained within the normal range. Mean white-cell counts decreased by one month in patients given carbamazepine (from 7500 to 6900) or primidone (from 7800 to 7100) ($P<0.01$). Smaller decreases occurred with phenytoin (from 7300 to 7000). Thereafter, mean white-cell counts stabilized at values that were lower than those at base line but in the normal range in all treatment groups. One hundred sixty-six patients (52 given carbamazepine, 46 phenobarbital, 46 phenytoin, and 22 primidone) had a white-cell count of 3000 to 5000 at some time during the first six months of treatment. Eight patients had one or more counts between 2000 and 3000 (four given carbamazepine, two phenytoin, and two primidone). Drug treatment was not stopped because of low white-cell counts in any patient. There were no clinically important changes associated with these laboratory findings.

Efficacy of Seizure Control

The drugs were compared in terms of efficacy by several measures. The mean and median frequency of seizures per month in each patient were analyzed as a seizure rate with 1-month to 60-month periods of assessment. The numbers of seizures in all patients in each drug group were totaled for 12, 24, and 36 months. Seizure control was also assessed with a rating scale that allowed for gradation according to severity and interference with everyday life.[6] The interval between the time therapeutic drug levels were achieved and the first recurrence of seizures was also analyzed. No statistically significant differences among drugs were found for any of the above measures.

The drugs were also compared in terms of prevention of all seizures after one month of treatment to allow drug levels to reach the therapeutic range. The probability of obtaining complete seizure control was analyzed for all patients at various times, and the analysis included all patients who had any seizures before failure or non-drug–related loss. Overall, total seizure control was only 39 per cent at 12 months and was similar with the drugs tested (carbamazepine, 47 per cent; phenobarbital, 36 per cent; phenytoin, 38 per cent; and primidone, 35 per cent). The prognosis for complete control of tonic–clonic seizures with the four

Table 2. Composite Scores for Seizure Frequency and Toxicity at 12, 24, and 36 Months.*

Treatment Group	Score at 12 mo	Score at 24 mo	Score at 36 mo
Carbamazepine	22	27	31
Phenobarbital	26	31	33
Phenytoin	21	24	29
Primidone	31	35	36
Total	457	374	255

*Mean composite scores were obtained with end-point analysis, with 50 points assigned to patients whose drug failed. Differences among drugs were significant at 12 and 24 months for all seizure types combined ($P<0.01$); lower scores indicate a better outcome.

drugs was also similar (carbamazepine, 48 per cent; phenobarbital, 43 per cent; phenytoin, 43 per cent; and primidone, 45 per cent. Carbamazepine provided significantly better total control of partial seizures (43 per cent) than did phenobarbital (16 per cent) or primidone (15 per cent) ($P<0.03$ at 18 months), and phenytoin provided intermediate control (26 per cent). Carbamazepine also provided the best complete control of partial seizures at every 6-month point during the 36 months of follow-up.

The probability that patients receiving long-term treatment (i.e., not lost or removed because of drug failure) would be totally seizure-free was also analyzed at specific times during the follow-up period. Complete control of tonic–clonic seizures for 12 months was possible for 55 per cent of the patients remaining in the carbamazepine group, 58 per cent in the phenobarbital group, 48 per cent in the phenytoin group, and 63 per cent in the primidone group (difference not significant). Control of partial seizures was significantly better with carbamazepine (65 per cent) than phenobarbital (33 per cent), phenytoin (34 per cent), or primidone (26 per cent) ($P<0.05$) at 18 months. As in the analysis of all patients, carbamazepine provided better complete control of partial seizures at 12 to 36 months of follow-up.

Eighty-two patients whose first drug failed (because of seizures and concomitant side effects) had seizures that were so frequent or severe that they were given a two-drug combination. Although 32 patients had fewer seizures and continued to take two drugs for a year, only 9 (11 per cent) remained completely free of seizures. In addition, scores for side effects were higher among those taking two drugs.

Discussion

The results indicated that carbamazepine and phenytoin are most likely to be successful overall when used as the initial, single antiepileptic drug in adults with partial seizures or secondarily generalized tonic–clonic seizures or both. The choice between carbamazepine and phenytoin requires consideration of other criteria. Dysmorphic side effects occurred significantly more often with phenytoin. Carbamazepine might be preferable in children, adolescents, or women, for whom the dysmorphic potential of phenytoin could be of greater importance than it was in the predominantly adult male population in this study. Reports of difficulty with cognition were more common with phenytoin. Although the differences did not reach statistical significance in this study, such findings have been reported by other investigators.[9,10] Complete control of partial seizures was significantly better with carbamazepine than primidone or phenobarbital. The advantages of phenytoin include its availability in a parenteral formulation for intravenous use, which is especially valuable for rapid initiation of treatment of acute seizures.

Phenobarbital was as successful as carbamazepine and phenytoin in the patients with predominantly tonic–clonic seizures. However, the failure rate of phenobarbital in management of partial seizures was significantly worse than that of carbamazepine or phenytoin. Because more than half the patients had both partial and secondarily generalized tonic–clonic seizures or later acquired a second seizure type, selecting a drug with the greatest success rate for both types of seizures seems most logical. However, in some patients there may be reasons to choose phenobarbital for initial treatment — e.g., the minimal gastrointestinal and motor-system toxicity, the availability of a parenteral formulation, and the very low cost.

The worst outcome was found in the patients treated with primidone, which was included in the trial in an effort to learn whether it was different from phenobarbital and whether it should be considered for initial use as an anticonvulsant. Most commonly, primidone has been used as an alternative or adjunctive therapy for epilepsy rather than as a drug of first choice. The minimal success achieved with primidone was largely attributable to acute side effects that occurred despite administration of the drug at very low doses, as recommended by the manufacturer. Primidone failures continued to occur during initiation of therapy throughout the study. Such problems with the use of this drug were noted in initial clinical trials.[11-13] Sciarra et al.[13] reported that 82 per cent of patients placed on primidone had side effects. In our trial, the rate of acute side effects from primidone was strikingly different from the rate seen with phenobarbital, demonstrating that the two drugs have different actions despite the considerable conversion of primidone to phenobarbital. Gallagher et al.[14] showed that acute side effects at the start of primidone treatment occurred before notable quantities of the metabolites phenylethylmalonamide and derived phenobarbital were detectable in the blood.

Although primidone was associated with a higher failure rate and lower retention of patients in all seizure groups, the patients who were able to use this drug had equivalent overall seizure and side-effect scores (composite ratings) when compared with the other groups. Consequently, primidone can be considered an acceptable alternative drug in patients who can tolerate the side effects.

The data on seizure control showed that carbamazepine was significantly more effective than phenobarbital or primidone for total control of partial seizures. Other measures of control of tonic–clonic or partial seizures did not show greater efficacy for any one drug — consistent with previous studies that have evaluated pairs of drugs in smaller populations.[2]

Although carbamazepine and phenytoin were associated with the most successful outcomes in this population, the study did not sequentially compare the four drugs in any given patient. Consequently, it is quite possible that any of the drugs may prove satisfactory as an alternative if the initially chosen drug has failed. On the basis of these data, we suggest that if either carbamazepine or phenytoin is selected for treatment but fails, then the other drug should be tried. Alternatively, treatment with one of the barbiturates could follow.

Overall, the adequacy of seizure control in this group of patients given single-drug therapy was suboptimal even with expert neurologic care. Although more than three quarters of the patients were successfully treated with carbamazepine or phenytoin for a year, the percentage maintaining complete seizure control decreased over time, as might be expected.[15] These data agreed exactly with those of Elwes et al.,[16] who also found that only 39 per cent of patients had complete seizure control at one year. Interval analyses suggest that most patients who lose seizure control will be identified within the first half year of follow-up. This prognostic pattern may be useful in making decisions concerning the appropriateness of driving motor vehicles or of similar hazardous activities.

The relatively unsatisfactory degree of complete seizure control cannot be explained as an inadequacy of single-drug therapy.[3] When patients were placed on a combination of two drugs, seizure frequency or severity (or both) decreased, but only at the cost of greater toxicity. It is important to note that only 11 per cent of the patients placed on two drugs because of inadequate seizure control remained entirely free of seizures for the next 12 months. For some patients this added control may justify the possibility of greater toxicity.

The outcome of this project underscores the unsatisfactory status of antiepileptic therapy with the medications currently available. Most patients whose epilepsy is reasonably controlled must tolerate some side effects. These observations emphasize the need for new antiepileptic drugs and other approaches to treatment, as well as efforts aimed at prevention of epilepsy and seizures.

On the basis of this long-term comparative assessment of the four major antiepileptic drugs, we recommend carbamazepine or phenytoin for the initial antiepileptic treatment of adolescents and adults with partial or secondarily generalized tonic–clonic seizures or both types.

We are indebted to the Operations Committee (F.E. Dreifuss, chairman, J.K. Penry, O.D. Williams, and C.J. Klett) for expert monitoring of the project, to the study assistants at each site, and to the VA Cooperative Studies Program staff.

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