Epilepsia, 30(4):453–457, 1989
Raven Press, Ltd., New York

Motor Speed Is a Contaminating Factor in Evaluating the "Cognitive" Effects of Phenytoin

Carl B. Dodrill and Nancy R. Temkin

Regional Epilepsy Center, University of Washington School of Medicine, Seattle, Washington, U.S.A.

Summary: Many studies suggestive of adverse effects of phenytoin (PHT) on mental abilities have used testing procedures which have timed or motor speed elements. Therefore, to what degree the motor speed element alone may have resulted in attributing adverse higher level intellectual or cognitive effects to PHT instead of the identified construct to be measured (e.g., memory, abstraction, decision making) is not clear. To help distinguish "motor" effects from these more complex "cognitive" effects, neuropsychological data on 70 adult PHT monotherapy patients were reanalyzed. Initially, a series of statistically significant differences favored the low serum level group over the high serum level group in neuropsychologic performance. However, when a simple measure of motor speed (Finger Tapping Test) was covaried out, all statistically significant differences between the groups disappeared. Thus, losses in cognitive abilities could not be associated with PHT even though markedly elevated blood levels had been achieved. **Key Words:** Phenytoin—Epilepsy—Drug-induced abnormalities—Neuropsychology—Cognition—Motor activity.

The possible adverse effects of antiepileptic drugs (AEDs) on memory, ability to think, and other cognitive functions have received much attention in recent years (Evans and Gualtieri, 1985; Reynolds and Trimble, 1985; Trimble, 1987; Vining, 1987; Dodrill, 1988). A perusal of these reviews in connection with phenytoin (PHT) discloses a tendency to ascribe various adverse cognitive effects to this agent, including impairment in memory, concentration, problem solving, and speed of response. However, a closer examination of the investigations on which these conclusions are based reveals that most of the tests used to measure various higher level cognitive constructs (e.g., memory, problem solving, attention) were timed tasks obviously dependent on speed of motor response; e.g., the work of Thompson as summarized by Trimble (1987) showed six statistically significant differences associated with PHT. All differences were for tasks in which responses were timed or in which the stimulus delivery was timed. Therefore, whether "memory," "concentration," and "decision-making" were being measured or whether the primary factor being evaluated on many tests might not have pertained to speed of response may be questioned.

In 1975, Dodrill reported a series of 70 adults with epilepsy who were stabilized with PHT monotherapy and who had been administered a broad battery of clinically relevant neuropsychological tests. He demonstrated that patients with high serum PHT levels (mean 43 mg/L) performed more poorly on eight test variables than did patients with low serum levels (mean 17 mg/L). However, all eight had obvious motor components; the interpretation therefore offered was that PHT had primarily motor effects. Because some of the test variables appeared to have other elements as well, such as visual-spatial skills and intelligence, the study has been interpreted by other investigators as supportive of a broader range of adverse effects (Reynolds and Trimble, 1985). This is indeed a possibility which could not be ruled out based on the previous analysis. Furthermore, since side effects of these agents are believed to have great significance on the quality of life for our patients and since toxic effects represent a point on which drug selection may hinge, further evaluation of the data appeared to be in order.

The question advanced in this investigation pertains to whether evidence representing genuine differences in performance between the groups in the

Received September 1988; revision accepted December 1988.
Address reprint requests to Dr. C. B. Dodrill at Regional Epilepsy Center (ZA-50), Harborview Medical Center, 325 Ninth Ave., Seattle, WA 98104, U.S.A.

previous study exists for factors other than motor speed (Dodrill, 1975). This question is addressed by a reanalysis of the data in such a way that simple motor speed is covaried out of test scores; the differences between the groups are then reevaluated.

METHODS

Subjects

Subjects for the study were 70 adults (45 males, 25 females) having an average age of 28.14 years (SD 8.81) and an average of 12.41 years of education (SD 2.00). All had uncontrolled seizure disorders, and all were participants in a larger program of AED evaluation for which informed consent was obtained. Primary seizure diagnoses were as follows: complex partial 48, elementary partial 18, and generalized convulsive/nonconvulsive 4. In addition, 58 patients also had secondarily generalized tonic-clonic seizures. The mean age at onset was 12.95 years (SD 8.63 years). Etiology was known in 39 cases and was most frequently traumatic or infectious. EEGs taken within 30 days of neuropsychological testing were available for 68 patients, with 66 showing definite abnormalities, including 49 with clearly paroxysmal activity compatible with a diagnosis of epilepsy.

Tests administered

The complete neuropsychological battery originated by Halstead and developed by Reitan (Reitan and Wolfson, 1985) was administered. These tests are well established clinically with respect to reliability and validity and have been shown relevant to the daily life performance of adults with epilepsy (Dodrill and Clemmons, 1984). The tests were administered by highly trained technicians who did not have access to blood level data and who were not aware of the purposes of the study. Because motor effects were suspected, the Marching Test of the Reitan-Indiana Neuropsychological Battery for Children was also administered (Reitan and Davidson, 1974).

Procedure

Approximately 60 days before testing, efforts were made to stabilize each patient with PHT alone, with all other AEDs phased out over the next 30 days. In most instances, only minor changes in PHT dosage were made in the 30 days before testing. At the time of testing, the average dosage was 439 mg/day (SD 100). The patients were divided into a low serum level group ($n = 34$) with serum levels ≤ 30 mg/L (mean 17.44, SD 7.78) and a high serum level group ($n = 36$) with serum levels ≥ 31 mg/L (mean 43.14, SD 9.80). These extremely high serum levels were the product of vigorous monotherapy treatment under blinded conditions so that the attending physicians were not aware of the levels. The serum level groups did not differ from each other with respect to the variables of age, years of education, age at onset of seizure disorder, or duration of disorder ($p > 0.10$).

Data analysis

To facilitate analysis and presentation of results, the raw score values for each variable were ranked for all subjects and converted into normalized *T* scores with a mean of 50 and an SD of 10 so that in each case higher scores represented better performances. Student's *t* statistic was then individually applied to each variable across the two groups. These analyses were performed for the original article (Dodrill, 1975). Analysis of covariance was then applied, by which the variance in test scores between the groups which could be attributed to the most simple measure of motor speed (Finger Tapping Test, preferred hand) was factored out. The groups were then again compared on each test variable as originally accomplished in search of drug effects attributable to factors other than simple motor speed.

RESULTS

Figure 1 shows the results of the original analyses comparing the test performances of the low serum level and the high serum level groups. A series of statistically significant differences were found, all of which favored lower serum PHT levels. The means and SD of the raw data were published in the original report (Dodrill, 1975).

Figure 2 shows the results of the same analyses after the variance in test scores attributable to a simple measure of motor speed (Finger Tapping Test) had been covaried out. All statistically significant differences disappeared. Thus, no differences between the groups remained which could be attributed to a factor other than motor speed.

DISCUSSION

This study failed to provide support for the postulation that PHT had adverse cognitive effects beyond that of motor speed. The Finger Tapping Test evaluates the speed with which an individual can propel a typewriter-like key up and down. It is not considered to have any significant intellectual or cognitive (thinking, memory, problem solving) component, and motivational factors are reduced by the method of administration. It therefore appears to be a fairly pure measure of motor speed.

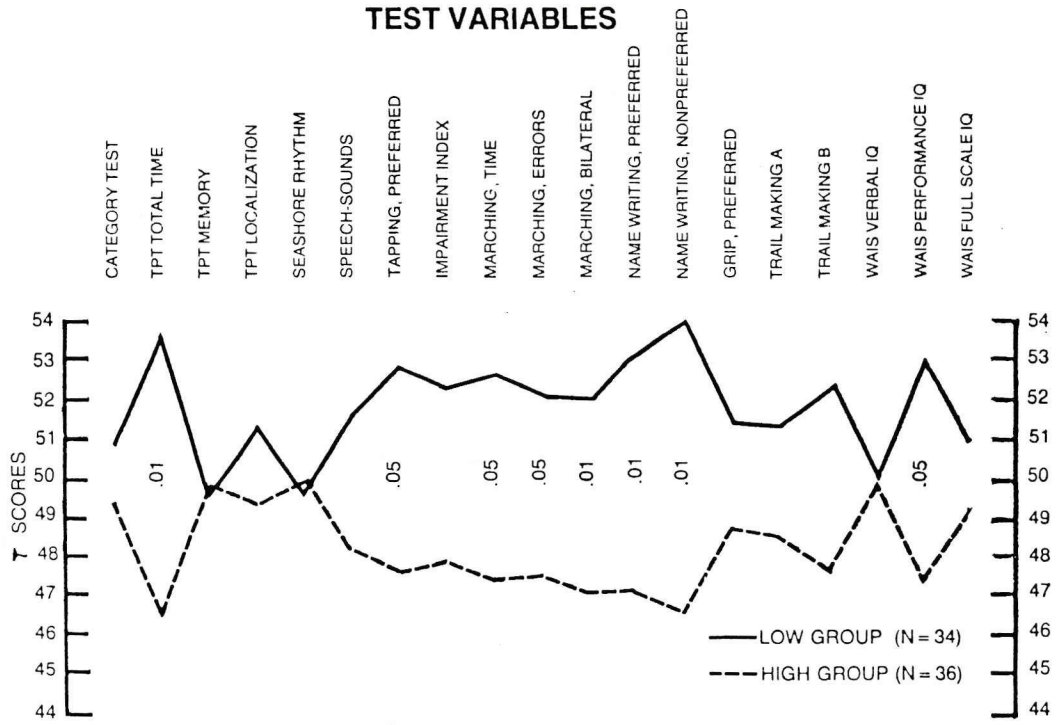

FIG. 1. Performances of low and high serum level groups before analysis of covariance.

A review of the changes on the particular tests is of interest. Motor speed is known to be a factor in the WAIS Performance Scale. When this element is removed, the initially noted difference between the groups (Fig. 1) disappears. Thus, it is the motor speed element and not the larger intellectual element which is associated with the drug effect. Likewise, when the motor speed element is removed from the complex Tactual Performance Test (TPT), in which a person is blindfolded and places blocks

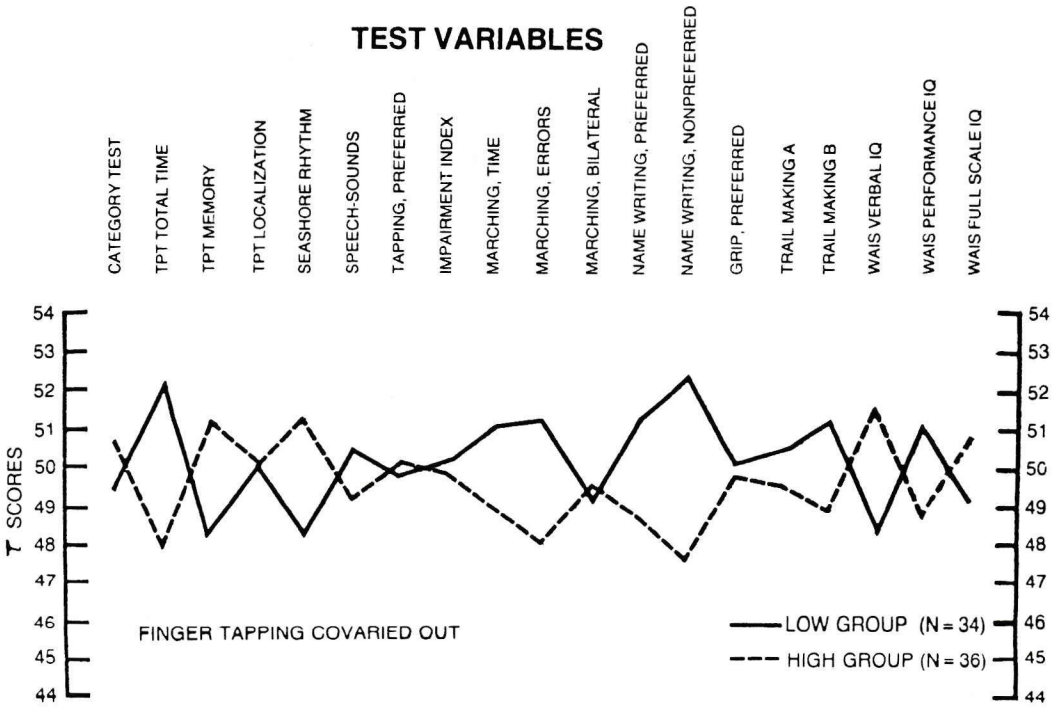

FIG. 2. Performances of low and high serum level groups after analysis of covariance.

in an upright board as quickly as possible, any effects of the drug on other elements (general problem-solving ability, ability to discern block shapes, memory for block shape and location) are not sufficient, even when considered as a whole, to result in a statistically significant difference. This does not prove that PHT might not have some adverse effects in these areas, but does raise the possibility that the effects in these areas may be less than has commonly been supposed because of the contaminating factor of motor speed.

At least two possible alternative explanations of the present results should be considered. First, the battery of tests used may have been insufficiently sensitive to drug effects. This possibility has been advanced by Alpherts (1988), Trimble (1987), and other investigators and is definitely worthy of consideration. These investigators have suggested that computerized testing may offer increased accuracy and increased sensitivity to drug effects. They have therefore developed series of tests which are administered with the assistance of a computer and they are in various stages of application of these measures to patients with epilepsy. The critical study however, one that compares computer-based tests with standardized neuropsychological tests (such as those used in the present study) with respect to both drug sensitivity and relevance to performance in life, has not yet been done. Until this study is completed, an adequate response cannot be given to the criticism of possible insensitivity of standard neuropsychological tests to drug effects.

A second alternative explanation for the lack of drug effects beyond motor speed demonstrated in this study pertains to the serum drug levels. In any study, one can argue that not enough drug was present to result in a broader drug effect. In the present investigation, this argument appears to have little merit. Serum drug levels were available for every patient, and very close quality control was maintained by the chemist who performed the serum levels by gas liquid chromatography. The neurologists were blinded to the drug levels and tended to increase PHT dosages to the point of intolerable (rather than detectable) toxicity if improvement in seizure control was experienced. Had the drug levels been available to the neurologists, the medication would never have been elevated to the levels obtained. Indeed, to our knowledge, no one else has ever reported neuropsychological studies of a group of patients with such high serum drug levels. Thus, inadequate serum levels do not appear to constitute a reasonable explanation for the lack of higher level cognitive effects associated with PHT.

This investigation illustrates how speed of response factors may complicate the assessment of higher level intellectual and cognitive effects of AEDs. The study does not prove that such effects do not exist, but it does raise the possibility that in previous studies adverse cognitive effects attributed to PHT may have been more accurately identified as one aspect or another of motor speed. Further evaluation of this possibility is of great importance in the accurate assessment of adverse effects not only with PHT, but with other AEDs as well.

Acknowledgment: This research was supported by NIH Grants No. NS 17111 and NS 17277 awarded by the National Institute of Neurological and Communicative Disorders and Stroke, PHS/DHHS.

REFERENCES

Alpherts WCJ. Computers as a technique for neuropsychological assessment in epilepsy. In: Aldenkamp AP, Alpherts WCJ, Meinardi H, Stores G, eds. *Education and epilepsy*. Amsterdam: Swets & Zeitlinger, 1988:101–9.

Dodrill CB. Diphenylhydantoin serum levels, toxicity, and neuropsychological performance in patients with epilepsy. *Epilepsia* 1975;16:593–600.

Dodrill CB. Effects of antiepileptic drugs on abilities. *J Clin Psychiatry* 1988;49(suppl):31–4.

Dodrill CB, Clemmons DC. Use of neuropsychological tests to identify high school students with epilepsy who later demonstrate inadequate performances in life. *J Consult Clin Psychol* 1984;52:520–7.

Evans RW, Gualtieri T. Carbamazepine: a neuropsychological and psychiatric profile. *Clin Neuropharmacol* 1985;8:221–41.

Reitan RM, Davidson LA. *Clinical neuropsychology: current status and applications*. Washington, D.C.: WH Winston, 1974.

Reitan RM, Wolfson D. *The Halstead-Reitan neuropsychological test battery*. Tucson, AZ: Neuropsychology Press, 1985.

Reynolds EH, Trimble MR. Adverse neuropsychiatric effects of anticonvulsant drugs. *Drugs* 1985;29:570–81.

Trimble MR. Anticonvulsant drugs and cognitive function: a review of the literature. *Epilepsia* 1987;28(suppl 3):S37–45.

Vining EPG. Cognitive dysfunction associated with antiepileptic drug therapy. *Epilepsia* 1987;28(suppl 3):S18–22.

RÉSUMÉ

De nombreuses études évaluant les effets secondaires de la phénytoine (PHT) sur les performances mentales ont utilisé des tests intégrant des éléments chronométrés ou utilisant la vitesse motrice. Le degré de responsabilité de l'élément "vitesse motrice" seul dans l'attribution d'effets secondaires intellectuels ou cognitifs plus importants à la phénytoine n'est donc pas tout à fait clair, il a pu masquer la grandeur mesurée (par exemple: mémoire, abstraction, prise de décision, etc.). Afin de distinguer les effets moteurs de ces effets cognitifs plus complexes, les auteurs ont réanalysé les données neuropsychologiques recueillies chez 70 patients adultes recevant une monothérapie par PHT. Initialement, une série de différences statistiquement significatives dans les performances neuropsychologiques aviat été trouvée, avec des résultats meilleurs dans le groupe des patients à taux sanguins bas par rapport au groupe de patients à taux sanguins élevés. Cependant, si l'on enlève comme covariant un test simple de vitesse motrice (le test du Finger Tapping), toute différence statistiquement significative entre les groupes disparaît. Ainsi, les déficits dans les performances cognitives ne

peuvent pas être associés à la PHT, même chez les patients pour lesquels des taux sanguins très élevés étaient observés.

(P. Genton, *Marseille*)

RESUMEN

Muchos estudios que sugieren efectos adversos de la fenitoina (PHT) sobre las facultades mentales han utilizado solamente procedimientos de medición del tiempo o de la velocidad de los movimientos. Por lo tanto no queda claro hasta que grado puede el elemento de velocidad motora solamente ser responsable de los efectos adversos que la fenitoina pueda ejercer sobre niveles intelectuales más elevados o sobre las funciones cognitivas en vez de identificar para su medida un esquema construido (por ejemplo: memoria, abstracción, capacidad de decisión, etc.). Para facilitar la selección de efectos "motores" de los efectos "cognitivos" más complejos se ha reanalizado la información neuropsicológica en 70 pacientes adultos con monoterapia de PHT. Inicialmente se encontró una serie de diferencias estadísticamente significativas en los resultados neuropsicológicos que favorecían el grupo de niveles séricos bajos sobre el grupo de niveles séricos altos. Sin embargo, cuando se obtuvo una covariación de la simple medida de la velocidad motora (test de percusión digital) todas las diferencias estadísticamente significativas entre los grupos desaparecieron. Así pués, la pérdida de las habilidades cognitivas pueden no estar asociadas con la PHT a pesar de que se alcancen nivels séricos marcadamente elevados.

(A. Portera-Sánchez, *Madrid*)

ZUSAMMENFASSUNG

In vielen Studien, wo eine Beeinträchtigung mentaler Fähigkeiten durch Phenytoin vermutet worden war, wurden Testverfahren gewählt mit Zeitmessungen oder Elementen motorischer Geschwindigkeit. Es ist daher nicht klar in welchem Ausmaß die motorische Geschwindigkeit alleine die unerwünschte Nebenwirkungen von Phenytoin auf intellektuelle und kognitive Bereiche beeinflußt hat und somit nicht die betroffenen Items wie Gedächtnis, Abstraktion, Entscheidungsprozeß etc. gemessen wurden. Um "motorische" Effekte aus den komplexeren kognitiven Leistungen auszusondern, wurden die neuropsychologischen Daten von 70 erwachsenen Patienten unter Phenytoinmonotherapie noch einmal analysiert. Zunächst wurden eine Serie statistisch signifikanter Unterschiede in den neuropsychologischen Leistungen gefunden, welche zugunsten einer Gruppe niedriger Serumspiegel gegenüber hoher Spiegel ausfiel. Wurde jedoch ein einfacher Test für motorische Geschwindigkeit (Fingertipp-Test) herausgenommen, verschwanden alle statistisch signifikanten Unterschiede zwischen beiden Gruppen. Auf diese Weise konnte Phenytoin keine kognitive Verschlechterung angelastet werden, trotz vorliegender deutlich erhöhter Blutspiegel.

(C. G. Lipinisk, *Heidelberg/Neckargemünd*)

Neuropsychological effects of carbamazepine and phenytoin: A reanalysis

Article abstract—We previously reported that carbamazepine had fewer adverse neuropsychological effects than phenytoin, but it is now clear that our patients had much higher phenytoin than carbamazepine serum levels. When persons with high initial phenytoin levels were excluded, the statistical significance of all neuropsychological differences between the drugs disappeared.

NEUROLOGY 1991;41:141-143

Carl B. Dodrill, PhD, and Allan S. Troupin, MD

We previously evaluated the psychotropic effects of carbamazepine in comparison with phenytoin using patients with chronic uncontrolled partial seizures.[1] These subjects were stabilized on phenytoin monotherapy for a 2-month baseline period, and then randomized to either 4 months of phenytoin monotherapy followed by 4 months of carbamazepine monotherapy, or to 4 months of carbamazepine monotherapy followed by 4 months of phenytoin monotherapy. Seizure control was equivalent for the drugs, but slightly better performances with carbamazepine administration were noted on 4 cognitive and 1 personality measure. We concluded that there were selective improvements with carbamazepine.

Recently, Meador et al[2] reviewed our work and noted that our patients averaged much higher phenytoin than carbamazepine serum levels. They hypothesized that "the observed differences may have been due to differences in drug concentrations rather than differential drug effects on cognitive mechanisms" (p 391). The present paper constitutes a test of this hypothesis through a reanalysis of our original data.

Methods. Of the 46 subjects with complete data, it was found that the average phenytoin serum level at the end of baseline was 35.19 μg/ml, that 67% of patients had serum levels greater than 30, and that 37% had serum levels greater than forty. Since by today's standards these levels are too high, the 17 persons with serum levels greater than 40 were first eliminated (average serum level of remaining cases, 26.17 μg/ml) and the neuropsychological testing was reanalyzed. The same procedure was repeated with the removal of 14 others with baseline serum phenytoin levels greater than 30 (average serum level of remaining cases, 16.75).

The following variables were reanalyzed, each of which had shown a statistically significant difference in the original paper: (1) receptive errors on Reitan's Aphasia Screening Test; (2) a rating of constructional dyspraxia or distortion in pencil and paper drawings; (3) errors on the high interference condition of the Stroop Color Word Test; (4) errors on the Wonderlic Personnel Test, a general measure of problem-solving ability; and (5) the Minnesota Multiphasic Personality Inventory (MMPI) F Scale. Statistical analyses consisted of comparing means across drugs for each test variable using the Student *t* statistic for paired data.

Results. All serum level data are given in table 1. The procedure of eliminating patients based upon high baseline phenytoin serum levels had the desired result of lowering the phenytoin levels during the double-blind phenytoin study period, but the carbamazepine levels did not change significantly.

The neuropsychological results are presented in table 2. When patients with phenytoin levels greater than 40 at baseline were eliminated, the number of statistically significant differences was reduced from 5 to 2. When patients whose serum levels were greater than 30 were eliminated, no statistically significant differences remained.

It was noted that 15 patients had baseline Wechsler Adult Intelligence Scale Full Scale IQ scores less than 90, 13 of whom had levels greater than thirty. Thus, although in our original study carbamazepine had the most favorable effects on patients with low intelligence and substantial emotional problems, it is now evident that these conditions are correlated with initial phenyt-

Table 1. Serum level data on reanalysis of 1977 study of Dodrill and Troupin comparing phenytoin and carbamazepine

Drug period	All patients (n = 46)	Patients with baseline phenytoin levels no greater than 40 μg/ml (n = 29)	Patients with baseline phenytoin levels no greater than 30 μg/ml (n = 15)
Baseline period phenytoin levels			
Mean	35.19	26.17	16.75
SD	16.02	11.61	8.28
Range up thru 20.0	9 (20%)	9 (31%)	9 (60%)
20.1-30.0	6 (13%)	6 (21%)	6 (40%)
30.1-40.0	14 (30%)	14 (48%)	0 (0%)
40.1 and up	17 (37%)	0 (0%)	0 (0%)
Study period phenytoin levels			
Mean	30.57	26.76	18.10
SD	14.66	13.15	10.83
Range up thru 20.0	11 (24%)	8 (28%)	8 (53%)
20.1-30.0	12 (26%)	10 (34%)	6 (40%)
30.1-40.0	11 (24%)	7 (24%)	1 (7%)
40.1 and up	12 (26%)	4 (14%)	0 (0%)
Study period carbamazepine levels			
Mean	9.27	8.99	8.17
SD	3.80	3.67	4.05
Range up thru 6.0	8 (17%)	6 (21%)	5 (33%)
6.1-12.0	30 (65%)	18 (62%)	7 (47%)
12.1 and up	8 (17%)	5 (17%)	3 (20%)

Table 2. Neuropsychological data comparing phenytoin and carbamazepine in the double-blind study periods

Area of assessment/test variable		All patients (n = 46)	Patients with baseline phenytoin levels no greater than 40 μg/ml (n = 29)	Patients with baseline phenytoin levels no greater than 30 μg/ml (n = 15)
Cognitive functions				
Receptive aphasia, errors				
Phenytoin study period	Mean (SD)	1.72 (1.56)	1.62 (1.50)	1.27 (1.28)
Carbamazepine study period	Mean (SD)	1.30 (1.33)	1.41 (1.30)	1.33 (1.23)
	t (prob.)	2.01 ($p = 0.05$)*	0.78 ($p = 0.44$)	0.23 ($p = 0.82$)
Constructional dyspraxia, rating				
Phenytoin study period	Mean (SD)	1.94 (1.22)	1.90 (1.08)	1.67 (0.90)
Carbamazepine study period	Mean (SD)	1.46 (1.15)	1.34 (1.14)	1.47 (1.12)
	t (prob.)	3.38 ($p = 0.002$)*	3.29 ($p = 0.003$)*	0.82 ($p = 0.42$)
Stroop Test, interference errors				
Phenytoin study period	Mean (SD)	9.28 (11.34)	6.44 (5.17)	5.62 (2.66)
Carbamazepine study period	Mean (SD)	6.85 (8.64)	5.65 (4.37)	4.54 (4.43)
	t (prob.)	2.34 ($p = 0.03$)*	1.34 ($p = 0.20$)	0.80 ($p = 0.44$)
Wonderlic Personnel Test, errors				
Phenytoin study period	Mean (SD)	8.32 (5.46)	8.94 (6.18)	8.39 (5.97)
Carbamazepine study period	Mean (SD)	6.37 (4.88)	6.91 (5.69)	5.08 (3.25)
	t (prob.)	2.24 ($p = 0.04$)*	1.13 ($p = 0.28$)	1.26 ($p = 0.24$)
Emotional adjustment				
MMPI F Scale				
Phenytoin study period	Mean (SD)	63.00 (12.00)	61.93 (11.60)	60.23 (10.47)
Carbamazepine study period	Mean (SD)	59.95 (10.89)	59.86 (11.97)	59.57 (11.13)
	t (prob.)	3.07 ($p = 0.004$)*	2.46 ($p = 0.02$)*	1.11 ($p = 0.29$)

* Note: All statistically significant differences favored carbamazepine.

oin levels and that the carbamazepine advantage with these subgroups was lost.

Discussion. We confirmed the hypothesis of Meador et al[2] that the neuropsychological differences that we originally reported were in all likelihood due to disproportionately high phenytoin levels rather than to differential drug effects on cognitive mechanisms. As reanalyzed, our study shows no statistically significant differences between the drugs favoring either agent. This, of course, does not *prove* that such a difference does not exist, nor does it conclusively demonstrate that the drugs are "the same." It can be said that statistically reliable evidence for a difference between the drugs was not forthcoming.

The loss of statistical significance did not appear to be due to a smaller number of subjects in the successive analyses since differences in mean scores between the groups became noticeably smaller in 4 of 5 cases (table 2). The 1 exception (Wonderlic Personnel Test, errors) should not be overinterpreted in view of the fact that 35 variables were originally evaluated; the findings may be due to chance factors.

The only test of abilities that continued to show a statistically significant difference after the first elimination of subjects was the measure having the strongest motor component (constructional dyspraxia rating). Slight adverse motor effects have been associated with phenytoin, at least at high serum levels.[3] This effect persisted until the serum level cutoff fell below 30 μg/ml, whereupon the statistically significant difference also disappeared. The MMPI F Scale behaved in a similar way.

The results of this study are in agreement with those of two other recent investigations[2,3] that found no definite adverse cognitive effects relatable to phenytoin. This conclusion is incongruent with a sampling of previous studies[4-7] of patients with epilepsy. Such studies have even led to the conclusion that "phenytoin is associated with maximal impairments" (page S44 in reference 8). Comment concerning this major discrepancy is required.

First, studies reporting significant adverse cognitive effects of phenytoin on patients with epilepsy routinely evaluate cognitive correlates of drug changes made for clinical reasons rather than changes made on a randomized or experimental basis. Since these patients represent a subset of persons who are often doing poorly on their present drugs, and since the drugs selected for change are based upon other patient needs and characteristics (eg, the ability to comply with multiple dosing regimens), biases are introduced. As has now been demonstrated,[9] these biases can result in the complete reversal of the findings of a study and they are *not* necessarily eliminated by matching for age, education, seizure type, and so on.

Second, a number of these studies report very few statistically significant findings relative to a large num-

ber of statistical tests. Drug effects are typically limited in magnitude, but the studies frequently do not highlight this fact. In one case,[4] 32 statistical tests were run at the 0.05 level of confidence; 3 favored carbamazepine and 1 favored phenytoin. This near-chance set of findings does not provide a basis for the inference that either drug is better than the other.

Third, many of these studies reporting adverse cognitive effects of phenytoin used computerized tests and other procedures that are heavily loaded with motor speed. However, it has now been shown in one study[3] that when the phenytoin's motor speed element is factored out, the "cognitive" effects also disappear. Thus, studies reporting adverse "cognitive" effects of phenytoin may be reporting one measure or another of motor speed.

Finally, the contrast in findings is remarkable between the studies just discussed and those investigations that have used *random* assignment of drugs under double-blind conditions. Three such studies exist, which compare the neuropsychological effects of phenytoin and carbamazepine in people with epilepsy. These include the study of Meador et al,[2] which found no statistically significant differences, the present investigation which, as reanalyzed, found no statistically significant differences, and the Veterans Administration Cooperative Study.[10] This latter investigation, not yet fully reported, resulted in test scores that were often slightly better for carbamazepine than phenytoin when a number of statistical calculations were undertaken, but apparently the differences between means only occasionally attained statistical significance. Taken together, these investigations show fewer adverse cognitive effects of phenytoin than reported in the less well-controlled studies. Although carbamazepine is at times reported clinically to have fewer adverse cognitive effects than phenytoin, quantitative studies do not consistently confirm this qualitative impression drawn from experience with individual patients.

The results of the present study cannot be interpreted to prove that there are no adverse cognitive effects of phenytoin. They do, however, raise the possibility that many such effects that have at times been attributed to the pharmacologic characteristics of this drug may ultimately be found to be related to other factors.

From the Regional Epilepsy Center (Dr. Dodrill), University of Washington School of Medicine, Seattle, WA; and the Department of Neurology (Dr. Troupin), Louisiana State University, New Orleans, LA.

Supported by grants NS 24823 and NS 17111 awarded by the National Institute of Neurological Disorders and Stroke, PHS/DHHS. Ciba-Geigy assisted in the support of the original investigation. Warner-Lambert provided partial support of several research projects currently under way at the Regional Epilepsy Center in Seattle.

Received May 15, 1990. Accepted for publication in final form September 26, 1990.

Address correspondence and reprint requests to Dr. Carl B. Dodrill, Regional Epilepsy Center, Haborview Medical Center, Seattle, WA 98104.

References

1. Dodrill CB, Troupin AS. Psychotropic effects of carbamazepine in epilepsy: a double-blind comparison with phenytoin. Neurology 1977;27:1023-1028.
2. Meador KJ, Loring DW, Huh K, Gallagher BB, King DW. Comparative cognitive effects of anticonvulsants. Neurology 1990;40:391-394.
3. Dodrill CB, Temkin NR. Motor speed is a contaminating variable in evaluating the "cognitive" effects of phenytoin. Epilepsia 1989;30:453-457.
4. Andrewes DG, Bullen JG, Tomlinson L, Elwes RDC, Reynolds E. A comparative study of the cognitive effects of phenytoin and carbamazepine in new referrals with epilepsy. Epilepsia 1986;27:128-134.
5. Corbett JA, Trimble MR, Nichol TC. Behavioral and cognitive impairments in children with epilepsy: the long-term effects of anticonvulsant therapy. J Am Acad Child Psychiatry 1985;24:17-23.
6. Duncan JS, Trimble MR, Shorvon SD. The effects of phenytoin, carbamazepine and valproate withdrawal on cognitive function. Neurology 1989;39(suppl 1):149.
7. Thompson PJ, Trimble MR. Comparative effects of anticonvulsant drugs on cognitive functioning. Br J Clin Pract 1982;18 (sym. suppl):154-156.
8. Trimble MR. Anticonvulsant drugs and cognitive function: a review of the literature. Epilepsia 1987;28(suppl 3):S37-S45.
9. Dodrill CB. Cognitive effects of anti-epileptic drugs. J Clin Psychiatry 1988;49(suppl):31-34.
10. Smith DB, Mattson RH, Cramer JA, Collins JF, Novelly RA, Craft B, and the Veterans Administration Epilepsy Cooperative Study Group. Results of a nationwide Veterans Administration cooperative study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. Epilepsia 1987;28(suppl 3):S50-S58.

Reprinted from NEUROLOGY, Volume 41, Number 1, January 1991