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Effects of Sulthiame Upon Intellectual, Neuropsychological, and Social Functioning Abilities Among Adult Epileptics: Comparison with Diphenylhydantoin

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Since 1960, numerous studies have been done of sulthiame (Conadil®, Ospolot®) as an anticonvulsant. Some investigators have reported enhanced seizure control with this agent (Griffiths and Sylvester, 1964; Smyth, 1964; Liu, 1966; Livingston et al., 1967; Mann et al., 1967), whereas others have come to more reserved conclusions (LaVeck et al., 1962; Liske and Forster, 1963; Fenton et al., 1964; Garland and Sumner, 1964; Gordon, 1964). Nearly all investigators have pointed to such side effects as hyperpnea, paresthesia, weight loss, lethargy, and ataxia, which were believed by most to limit the usefulness of the drug.

Investigators in this area have also reported informal observations of psychological effects of sulthiame, including mental confusion (Fenton et al., 1964; Garland and Sumner, 1964; Gordon, 1964; Mann et al., 1967), depression (Garland and Sumner, 1964; Smyth, 1964; Livingston et al., 1967), and psychotic reactions (Liske and Forster, 1963; Fenton et al., 1964; Garland and Sumner, 1964). However, improvement in behavior (reduction in irritability, hyperactivity, and aggressiveness), at times with an enhancement of interpersonal relationships, has also been reported (Haran, 1962; Ingram and Ratcliffe, 1963; Kneebone, 1968; Moffatt et al., 1970; Al-Kaisi and McGuire, 1974). Still other investigators have noted an improvement in some patients but deterioration of psychological functions in other patients in the same study (Griffiths and Sylvester, 1964; Oettinger et al., 1965). Only Liu (1966) studied changes in intellectual performance before and after the administration of sulthiame, but he was not able to discover any striking differences. There apparently has been no systematic and comprehensive assessment of the effects of sulthiame upon neuropsychological capabilities generally and, other than behavioral rating scales, no objective assessment of social functioning correlates. In addition, previous studies of this drug used patients who were on other anticonvulsants as well, and none employed a double-blind protocol.

The present study is the neuropsychological part of the general clinical study recently reported by Green et al. (1974). It was designed to provide a systematic assessment of the psychological effects of sulthiame in comparison with the effects of diphenylhydantoin (DPH) and, in particular, to assess the effects of sulthiame upon intellectual abilities, neuropsychological abilities, and social functioning.

MATERIALS AND METHODS

A detailed description of the design of the study and of the patients employed is given by

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Green et al. (1974) and will not be repeated here. Briefly, the study had three phases. The first was a 2-month accession period during which the patients were treated and stabilized on DPH alone. This period was followed by two double-blind drug trials of 6 months each. Each patient was assigned randomly to either sulthiame or DPH in the first double-blind period and was then switched to the alternate agent in the second period. All patients were closely followed medically, and those who could not be maintained on a single anticonvulsant with reasonable comfort were removed from the study. Although psychological tests were given at the end of the accession period, those reported here included only the ones given at the end of the 6-month double-blind drug trials.

Twenty-two patients were examined for this study, 20 of whom were included in the original report (Green et al., 1974). The other two patients finished the study after the clinical report went to press. Eleven of the patients were on sulthiame during the first double-blind drug period, and 11 were on DPH. Note should be made that many patients did not complete the study, and their partial results are not included in the present paper. The reasons for their termination are detailed by Green et al. (1974) and will be referred to later. The patients included 11 males and 11 females who had an average age of 25.64 years (SD = 6.86) and an average of 12.41 years of education (SD = 2.32). As their primary seizure diagnoses, 8 had elementary partial seizures, 13 had complex partial seizures, and 1 had akinetic attacks. In addition, 21 of them also had tonic-clonic convulsions. The mean age at onset of their disorders was 10.98 years (SD = 6.96), and the mean duration was 14.66 years (SD = 7.12). In 15 cases, events or conditions in the patients' histories were discovered which were presumed to be etiologically related to the seizure disorders, but in 7 cases no such events or conditions could be detected. Whereas the EEGs of most of these patients have been described elsewhere (Wilkus and Green, 1974), it should be noted that they were abnormal in every case during the accession period, and that they showed activity that was clearly paroxysmal and compatible with a diagnosis of epilepsy in 16 cases.

Testing of psychological abilities focused upon three areas. The first area was intellectual abilities, as assessed by the Wechsler Adult Intelligence Scale (WAIS). The second included a broad range of neuropsychological abilities evaluated by a group of tests having well-established relationships with brain function. These tests included Halstead's Neuropsychological Battery, the Trail Making Test, strength of grip (in kilograms), the Marching Test, and a series of perceptual examinations. The latter provided error scores and included tests of unilateral and bilateral simultaneous tactile, auditory, and visual perception plus tests of finger agnosia, agraphagnosia, and astereognosis (coin recognition and Tactile Form Recognition). In addition, the time required to complete the Tactile Form Recognition task with both hands was also recorded. All of these tests are described in detail by Reitan and Davison (1974) and many are described by Halstead (1947) and Reitan (1966). The final area evaluated was social functioning, as assessed by the Heimler Scale of Social Functioning (HSSF, Heimler, 1967). This orally administered instrument inquires about satisfactions in five important areas (work, finance, friends, family, and personal-sexual) and about signs of frustrations or difficulties manifesting themselves in five important ways (paralysis of activity, somatic concerns, feelings of persecution, signs of depression, and use of methods of escape from frustration). Five questions in each of the 10 areas are answered "Yes," "Perhaps," or "No" and are scored 4, 2, and 0, respectively. When the scores for the questions relating to satisfactions are added, a Total Positive score results; the same procedure applied to signs of frustration renders a Total Negative score. In addition, five questions (scored 1 to 20) give an overall index of optimism toward life and are expressed as Synthesis Total. Finally, the Frustration Ratio (Total Negative/Total Positive) takes into account the number of satisfactions and the number of frustrations in a single score.

All testing was complete except for two instances in which the Tactual Performance Test could not be administered because of time limitations and one case in which a burn prevented the use of one arm on one occasion. The affected tests were excluded from the data

analyses for the patients involved under both drug conditions so that comparability across drugs was maintained.

To facilitate the presentation and examination of the results, the raw score values for each variable under both drug conditions combined were ranked and converted into normalized T scores having a mean of 50 and a standard deviation of 10. These scores were transformed so that the higher scores represented the better performances in every instance. The t statistic for dependent data was then obtained and two-tailed tests were applied. Means and standard deviations of the raw score data were also computed and involved the commonly used raw score units, except that the maximal scores for the Time component of the Tactual Performance Test and for Part B of the Trail Making Test were set at 60 min and 5 min, respectively.

RESULTS

The first part of the study concerned the assessment of intellectual abilities by means of the WAIS. Table 1 summarizes the raw score data and Fig. 1 presents the parallel standard score (T score) data. As indicated above, all t scores were computed on the basis of T scores. Furthermore, all positive t-score values favored DPH, while all negative t-score values favored sulthiame. On every subtest of the WAIS the scores favored DPH even when not statistically different from sulthiame, and the statistically significant differences found were particularly substantial for the Verbal Scale.

The second area assessed was that of general neuropsychological functions. The standard score results are presented in Fig. 2, while the raw score results are presented in Table 2. Substantial differences were found here also, although they were not as consistently significant as those in the more homogenous intellectual area. However, in every instance the statistically significant differences favored DPH. The Perceptual Errors variable represented the total errors on the several perceptual tasks described above. Because a significant difference was found on this variable overall, separate analyses were run for each of the perceptual tasks to obtain more detailed information about those which might be contributing to the overall result. These analyses revealed statistically significant differences on only two variables: (1) number of errors on unilateral tactile, auditory, and visual stimulation, with fewer errors on DPH ($t = 2.17$, $p < 0.05$); and

TABLE 1. *Raw score comparison of diphenylhydantoin and sulthiame on the Wechsler Adult Intelligence Scale*

Test variable	Diphenylhydantoin		Sulthiame		
	Mean	SD	Mean	SD	t
Information	10.59	3.03	10.18	3.05	1.30
Comprehension	10.32	2.50	9.55	3.29	2.16[a]
Arithmetic	8.73	3.13	8.00	3.67	2.05
Similarities	11.68	2.38	10.32	3.48	3.39[b]
Digit Span	9.55	3.39	7.27	3.55	4.59[c]
Vocabulary	10.32	2.53	9.41	3.11	2.89[b]
Digit Symbol	8.14	2.17	6.86	2.57	3.33[b]
Picture Completion	10.27	2.43	9.59	2.44	2.44[b]
Block Design	10.50	3.17	8.36	3.47	4.15[c]
Picture Arrangement	8.91	2.71	7.82	2.97	1.94
Object Assembly	9.55	2.87	8.64	3.32	1.77
Verbal IQ	101.68	12.91	94.95	15.69	5.76[d]
Performance IQ	97.36	14.55	89.32	16.78	3.67[b]
Full-Scale IQ	100.29	13.03	92.24	16.15	5.33[d]

[a] $p < 0.05$, $t > 2.08$.
[b] $p < 0.01$, $t > 2.83$.
[c] $p < 0.001$, $t > 3.82$.
[d] $p < 0.0001$, $t > 4.78$.

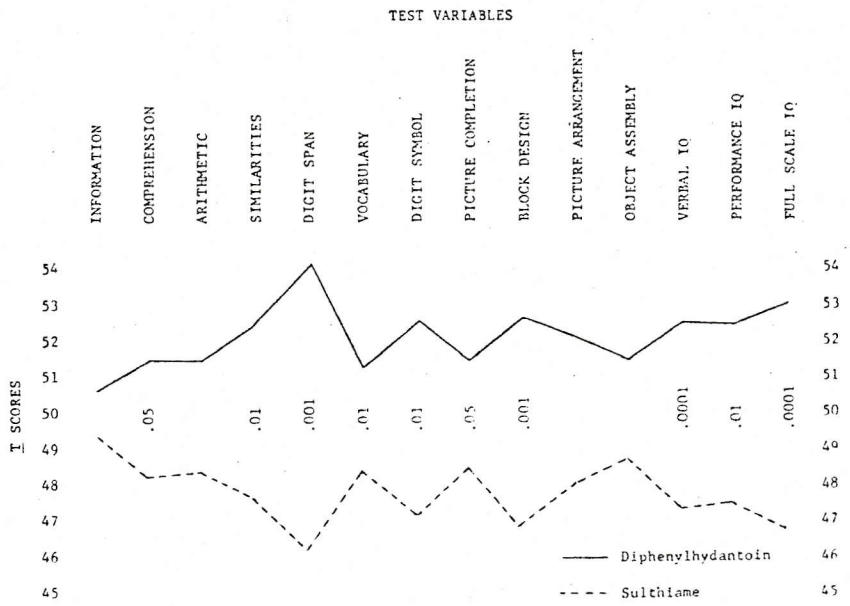

FIG. 1. Intellectual performances of patients on diphenylhydantoin and on sulthiame.

(2) number of errors on the agraphagnosia task with fewer errors on DPH ($t = 3.13, p < 0.01$). These perceptual tasks are among those most clearly calling for concentration and sustained attention to the task.

The final area assessed was that of social functioning. The standard score results on the HSSF variables are presented in Fig. 3, while the raw score results are presented in Table 3. All statistically significant differences here

TABLE 2. *Raw score comparisons of diphenylhydantoin and sulthiame on various neuropsychological measures*

Test variable	Diphenylhydantoin		Sulthiame		
	Mean	SD	Mean	SD	t
Category Test	48.91	33.86	47.23	32.45	−0.55
TPT, Total time	24.75	19.57	34.42	19.96	3.72[b]
TPT, Memory	7.42	1.80	7.53	2.09	−0.60
TPT, Localization	2.89	2.56	2.79	2.72	0.33
Seashore Rhythm	24.14	4.11	18.73	6.63	4.39[c]
Speech Perception	7.00	4.12	11.41	11.97	2.80[a]
Tapping	45.68	7.65	46.00	7.11	−0.66
Impairment Index	0.51	0.28	0.60	0.27	2.04
Trail Making, Part A	37.05	19.70	55.82	33.43	3.45[b]
Trail Making, Part B	95.95	50.83	182.73	92.83	5.28[d]
Dynamometer	83.18	28.66	82.88	28.28	0.90
Tactile Form Recog.	27.39	23.95	34.33	34.05	2.35[a]
Marching, Time	27.39	4.41	31.50	8.94	2.36[a]
Marching, Bilateral	82.41	2.43	78.06	12.04	1.10
Perceptual Errors	14.40	16.34	19.00	19.15	2.48[a]

[a] $p < 0.05, t > 2.08$.
[b] $p < 0.01, t > 2.83$.
[c] $p < 0.001, t > 3.82$.
[d] $p < 0.0001, t > 4.78$.

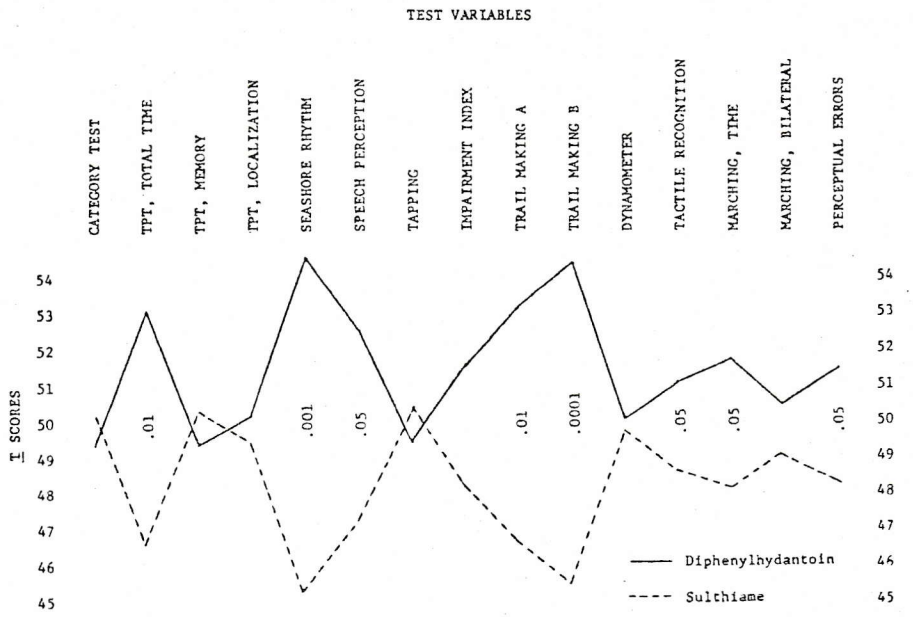

FIG. 2. Neuropsychological performances of patients on diphenylhydantoin and on sulthiame.

favored DPH once again, but they were much more sparse and they were seen only with those variables relating to reports of satisfaction and general optimism and not with signs of difficulties and frustrations.

DISCUSSION

The most striking finding of this study related to the substantially poorer performance seen in a number of instances while the patients

TABLE 3. *Raw score comparison of diphenylhydantoin and sulthiame on the Heimler Scale of Social Functioning*

Test variable	Diphenylhydantoin		Sulthiame		
	Mean	SD	Mean	SD	*t*
Work	14.73	3.68	11.55	3.90	3.28[b]
Finance	12.27	5.80	8.18	6.23	2.67[a]
Friends	17.91	2.51	15.64	4.69	2.06
Family	14.45	5.01	15.73	5.36	−1.94
Personal	16.45	2.39	16.91	2.45	0.86
Total Positive	75.82	10.49	68.00	12.69	3.06[b]
Activity	5.82	3.59	4.64	4.42	−1.20
Somatic	6.82	4.48	6.73	4.07	−0.10
Persecution	7.27	5.54	7.00	5.37	−0.28
Depression	9.09	5.12	10.36	5.74	0.58
Escape Routes	6.27	3.22	6.00	4.90	−0.32
Total Negative	35.27	13.29	34.73	15.26	−0.23
Synthesis Total	70.45	13.82	60.73	19.83	2.18[a]
Frustration Ratio	0.48	0.20	0.54	0.26	0.85

[a] $p < 0.05$, $t > 2.08$.
[b] $p < 0.01$, $t > 2.83$.

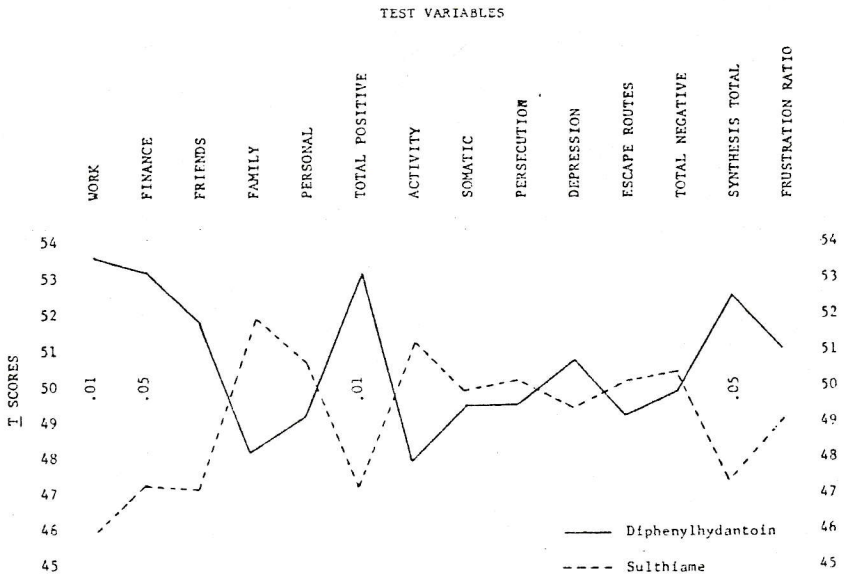

FIG. 3. Social functioning status of patients on diphenylhydantoin and on sulthiame.

were on sulthiame rather than on DPH. Many of the decrements seen were sufficiently marked so that they had an impact on ability to function in daily life. Furthermore, it seemed very likely that the individuals examined here represented a biased sample of those persons beginning the study as some 25 individuals were dropped due to increased seizures or toxicity or both while on sulthiame, whereas only 11 were dropped for similar reasons while on DPH (Green et al., 1974). Hence, the results of this study are likely to be biased to some degree toward a more *favorable* outcome with sulthiame than might otherwise be warranted.

The deficits shown on the intellectual and neuropsychological tests were seen in a number of areas. Intellectual abilities were poorer with sulthiame on both the Verbal and Performance Scales of the WAIS, and although some subtests of the WAIS showed more drug effect than others, the fact that every subtest was performed more poorly with sulthiame suggested a generalized effect. Also substantially affected were the more complex tasks calling for sustained attention and concentration. The Seashore Rhythm Test was a good example of this, as was Part B of the Trail Making Test. A similar pattern was seen in a study by Matthews and Harley (1975) where toxic patients on multiple anticonvulsant drug regimens were compared with nontoxic patients. However, this was not seen by Dodrill (1975) when increasing serum drug levels were related to performance among patients on DPH alone. Furthermore, the very strong motor deficits due to DPH therapy (Dodrill, 1975) were seen in the present study only on relatively complex psychomotor tasks such as the Tactual Performance Test, the Block Design subtest of the WAIS, and Part B of the Trail Making Test. Simple motor abilities such as finger tapping speed were not affected in the present study as they were in connection with DPH. However, verbal intellectual abilities were substantially affected by sulthiame, but almost not at all by DPH. Therefore, the drugs apparently have effects that can be differentiated by certain tests.

Parenthetically, one might note that these patients routinely reported a subjective improvement in alertness while on sulthiame (Green et al., 1974). The fact that just the opposite was demonstrated here by these datum points to the value of objective assessment of functioning abilities in connection with anticonvulsant evaluation. It is likely, of course, that the patients themselves were less able to make judgments about their own

alertness, and the value of an objective assessment of abilities is apparent.

The assessment of social functioning by the HSSF represented a limited approach to that area. The mixed reports in the literature about the psychotropic effects of sulthiame were consistent with the results shown in Table 3. Reports of increased satisfactions occurred only in some areas during DPH administration, although the patients seemed to have a more positive outlook on life while on this drug. There was no real difference with respect to somatic concerns, feelings of persecution, signs of depression, etc. These latter findings are of interest although, of course, the responses of individual patients may vary substantially.

One source of complication with respect to interpreting the results of this study related to seizure frequency and to the possible effects that seizures themselves may have had upon performance. Of the 20 patients on whom the seizure records were reasonably complete, six by their own report had a total of nine generalized clonic-tonic attacks in the 30 days prior to testing while on DPH, and five patients had a total of eight such attacks in the corresponding 30 days while on sulthiame. With respect to other types of seizures, however, more were reported while on sulthiame (N = 333) than while on DPH (N = 229). Furthermore, it is possible that the patients could have been less able to recall and to report their seizures while on sulthiame and, if so, the number of seizures on sulthiame may have been underestimated. Hence, one could not rule out the possibility that the greater number of seizures on sulthiame may itself have had an impact upon performance, and it may have interacted with other effects of this agent as well.

One such effect of sulthiame related to the EEG correlates of the drug. Wilkus and Green (1974) studied the same subjects employed in this investigation and found that while the administration of sulthiame was associated with an increase in frequency of the waking parieto-occipital EEG rhythm, it was also associated with an increase in the number of epileptiform discharges as compared to recordings taken while the patients were on DPH. As is well known, the generalized 3/sec bilaterally synchronous spike-and-wave patterns associated with absence seizures (petit mal) are related to substantial decrements in attentional abilities (Mirsky and Van Buren, 1965; Mirsky, 1969; Goode et al., 1970). However, this has not been demonstrated with patients having focal rather than generalized epileptiform discharges, at least with simple tasks such as the Continuous Performance Test (Mirsky, 1969). It may be, of course, that the complex neuropsychological procedures employed in this study are sensitive to the effects of focal epileptiform activity, and a systematic investigation of this possibility is underway (Wilkus and Dodrill, *in preparation).* The faster waking rhythms, of course, may have been related to the patients' reports of subjectively increased alertness, but this finding was not related to actual improvements in performance.

A final point worthy of reiteration is that this study evaluated sulthiame as a sole anticonvulsant, rather than as an agent added to an existing drug regimen. What might occur in the latter circumstance cannot be concluded from this study. Whether sulthiame-related decrements in performance would also occur when the drug is used as an adjunct medication is open to conjecture. Nevertheless, the present study not only provides data about the psychological effects of sulthiame, but it also points to a need for objective assessment of the psychological impacts of anticonvulsant medications. Conclusions drawn concerning the total effects of these drugs without such an assessment may be in error.

SUMMARY

This report presented results of psychological studies done during a double-blind study which compared sulthiame with diphenylhydantoin as primary agents in the treatment of uncontrolled epileptics. Assessments of intellectual, neuropsychological, and social functioning abilities were made with 22 adult epileptic patients. The results showed significantly less impairment with treatment by diphenylhydantoin than by sulthiame, and substantial differences were revealed on intellectual tasks, on tasks calling for sustained concentration and attention, and on psychomotor problem-solving tasks. The results could not be explained on the

basis of increased tonic-clonic seizures while on sulthiame. However, an increase in other types of seizures was noted, as was an increase in EEG epileptiform discharges. Possible mechanisms for the decrement in performance were discussed, and the value of an objective assessment of the psychological effects of anticonvulsant agents was noted.

RÉSUMÉ

Le travail présente les résultats d'études psychologiques faites en double aveugle, qui comparent le sulthiame et le diphénylhydantoine dans le traitement d'épileptiques non contrôlés.

Une évaluation des conditions intellectuelles, neuropsychologiques, et sociales étaient faites chez 22 épileptiques adultes. Les résultats montraient de façon significative une atteinte moindre avec le traitement par le diphénylhydantoine que par le sulthiame et des différences importantes se sont révélées dans les tests intéllectuels et dans des situations demandant une concentration et une attention soutenues et dans des tests de performance psychomotrice.

Les résultats ne pouvaient pas être expliqués sur la base d'une augmentation des crises tonico-clonique pendant le traitement par le sulthiame Cependant on a observé une augmentation des autres types de crises et des décharges épileptiformes â l'EEG. On discute les mécanismes possibles de l'évaluation objective des effets psychologiques des agents anticonvulsivants.

(C. A. Tassinari, *Marseilles*)

RESUMEN

Se presentan los resultados de los estudios psicológicos practicados con método doble ciego y que comparan las acciones del "sulthiame" y de la difenilhidantoina como agents primarios en el tratamiento de los epilépticos no controlados. Se realizaron determinaciones de las funciones intelectuales neurofisiológicas y sociales de 22 epilépticos adultos. Los resultados revelaron menores alteraciones con la utilización de la difenilhidantoina que con el "sulthiame" y las diferencias más sustanciales aparecieron en las actividades intelectuales, en las actividades que requieren atención y concentración mantenidas y en la resolución de problemas psicomotores. No fué posible achacar estos resultados al aumento de los ataques clónico—tónicos que ocurrió durante el tratamiento con "sulthiame." Sim embargo se observó un aumento de otro tipo de ataques asociado a un incremento de las descargas epileptiformes en el EEG. Se han discutido los posibles mecanismos responsables de la disminución de la "performance" y se ha verificado el valor del análisis objetivo de los efectos psicológicos de los agentes anticonvulsivos.

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ZUSAMMENFASSUNG

Darstellung der Ergebnisse psychologischer Studien während eines Doppelblindversuchs in dem Sulthiame mit Diphenylhydantoin als Medikament der ersten Ordnung in der Behandlung unkontrollierter Anfallskranker verwendet wurde. Die intellektuelle und neuropsychologische Untersuchung und die Bestimmung des Sozialverhaltens wurde an 22 erwachsenen anfallskranken Patienten durchgeführt. Die Ergebnisse zeigen eine signifikant geringere Beeinträchtigung unter der Therapie mit Diphenylhydantoin verglichen mit Sulthiame; wesentliche Unterschiede zeigten sich in den intellektuellen Aufgaben, bei Aufmerksamkeits- und längeren Konzentrationstests und bei Aufgaben zur Lösung psychomotorischer Probleme. Die Ergebnisse lassen sich nicht durch die vermehrten tonisch-klonischen Anfälle unter Sulthiame erklären. Es liess sich jedoch eine Zunahme anderer Anfallstypen erkennen die einhergingen mit einer Zunahme epileptiformer Entladungen im EEG. Die möglichen Mechanismen für die Verhaltensänderung werden diskutiert und die Bedeutung einer objektiven Untersuchung der psychologischen Effekte antikonvulsiver Mittel wird betont.

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