

Psychometric Study of Children with Learning Problems and 14-6 Positive Spike EEG Patterns, Treated with Ethosuximide (Zarontin) and Placebo*

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The electroencephalogram denoting a 14-6 cycles per second positive spike pattern is seen in EEG readings just before a patient drops off to sleep and again upon awakening (Kellaway, Crawley, and Kagawa, 1959). The montage used for the tracing on which the 14-6 cycles per second pattern appears is a monopolar one, connecting the occipital, temporal (posterior and mid), and central leads to the same side ear. Though not all neurologists agree on the significance of this pattern, it is seen by many as abnormal and as indicative of a cerebral dysfunction of the diencephalon (Chao, Druckman, and Kellaway, 1958; Hughes, Means, and Still, 1965). Additionally, patients with this pattern often have a history of irritability, stomach-aches, headaches (Chao *et al.*, 1958), and, in the authors' experience, of being management problems to their parents and teachers.

Over the past year, a number of children were referred by paediatricians for electroencephalograms and psychological testing at Porter Memorial Hospital, Denver, Colorado. All these children had initially been brought to the attention of their parents by teachers who indicated that they were having learning problems and were often difficult to manage in the classroom. The parents, in these cases, took their children to the family paediatrician who subsequently requested electrograms and psychological evaluations.

For the subjects in this study, their physicians prescribed anticonvulsant medication (ethosuximide) after the initial neuro-psychological evaluations, and the children were re-examined after treatment. Ethosuximide is an anticonvulsant medication usually regarded as efficacious in the treatment of *petit mal* seizures.

It was found in a preliminary study that the Wechsler IQ scales reflected changes while the subjects were being treated with ethosuximide. The mean verbal IQ change was 10.9 increase, which yields a 't' of 6.903 ($p < 0.0005$). The change in performance IQ scales was non-significant 't' = 0.731 ($p < 0.50$). The change in the full-scale IQ was 7.100, 't' = 9.2328 ($p < 0.0005$). It was found that psychomotor and personality tests did not change from pre- to post-medication testing. Thus the performance IQ scores of the Wechsler tests did not significantly change nor did quantitative Rorschach test scores or Raven progressive matrices test scores. From these results it appeared that the next step would be to compare psychometric tests on patients who were being treated with ethosuximide but who would be receiving both the drug and a placebo within a double-blind series. This is the report of this latter investigation.

Material and Methods

Ten patients (ranging in ages from 8 to 14), 8 males and 2 females, were subjects in this investigation. All were being treated with ethosuximide up to the time of this study, and 6 of them were involved in the initial study. In this study, all subjects were patients of the three referring paediatricians who administered the medication in an investigational sequence. Thus each subject received a supply of medication which would last for three weeks. The subject received either ethosuximide or a placebo, depending upon the random packaging of the preparations. The administration of the drug was on a double-blind basis, and neither the physician nor the investigators who tested these patients knew whether they were receiving placebo or ethosuximide. Each subject received a three-week supply of medication with instructions to take one 250 mg. capsule once a day. At the end of the three weeks, the subject received a battery of psychological tests; the subject was then crossed over to

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either the active medication or placebo, depending on the first preparation administered. At the completion of the investigation, the code was broken, and test scores obtained while the subject was taking a placebo were compared with scores while he was receiving ethosuximide.

Test employed. Measures were selected to determine changes in functioning in the following areas. (1) *Intellectual functioning*: Wechsler-Bellevue forms I and II, Wechsler intelligence scale for children. (2) *Perception*: Raven's progressive matrices (revised order, 1956). (3) *Personality*: Rorschach inkblot test.

All the above measures have been used in studies of cerebral dysfunction (McFie, 1960) as well as in the areas for which they were originally standardized. Consequently, these devices give a cross-check upon certain cerebral dysfunctions in addition to their specific uses.

All medications were administered by the referring physicians. Both sets of tests were administered by the same investigator. The subjects were randomly assigned to one of the two investigators. As the subject was accompanied by a parent (usually the mother) to the test session, the investigator would question the parent as to any observed behavioural changes in the weeks preceding the examination. In all cases, the parents had been in contact with the subjects' teachers and reported the teachers' impressions as well. All psychological testing was done in the Cortical Function Laboratory at Porter Memorial Hospital, Denver, Colorado. The subjects in this study came from a middle-class and upper middle-class socioeconomic background. None of them received any other type of medical or psychological treatment during the course of this study. However, all subjects had been receiving ethosuximide before the start of this investigation and were taking the medication up to the beginning of the project. They were then given the investigation medicine (or placebo) without any interruption. Whether or not the subject received a placebo or the drug in the initial part of the study depended on the randomization of the packaging of the preparations. For the second three weeks, the subjects were crossed over to the alternate preparation depending on the packaging sequence.

Results

Raven test scores did not change significantly. The Rorschach test was scored quantitatively (Klopfer *et al.*, 1956) and χ^2 analysis did not reveal significant changes. Scanning the Rorschach test responses qualitatively did not indicate obvious differences between the two testings. However, significant variations between placebo and drug treatment testings did occur on the intelligence measures.

It can be seen in Table I that highly significant changes of verbal IQ scores occurred when comparing the score attained on the the placebo with

that reached on ethosuximide. It should be noted that the means for the Weschler IQ scales were quite different in the preliminary study and the present study. It was necessary to replace 4 of the subjects in the preliminary study with different subjects, all previously on ethosuximide, to complete the present study due to errors in prescribing dosage. As the Table indicates, all but Case 3 had an increase in verbal IQ scores while on ethosuximide. Since these subjects were being treated with the drug up to the initiation of the study, one could interpret Table I as demonstrating a decrease in verbal IQ scores while on the placebo, since the subjects received the latter in accordance with a randomized drug administration.

TABLE I

Comparison of Verbal IQ Scores of 10 Patients on Ethosuximide and Placebo Treatment

Case No.	Placebo	Ethosuximide	Difference
1	97	113	16
2	106	113	7
3	106	101	-5
4	95	119	24
5	102	111	9
6	111	122	11
7	115	121	6
8	104	106	2
9	90	110	20
10	96	126	30
Means	102.2	114.2	

Difference between means, 12.00.
 $t = 3.5853$; $p = 0.005$.

Table II depicts significant increases in full-scale IQ scores in all but Case 8. Of course, the increase in verbal IQ scores is responsible for this, since no increase in performance IQ scores occurred, as seen in Table III. 2 subjects (Case 1 and 7) did show large increases in performance IQ scores, but this was not sufficient to influence the group statistics. Case 1 showed increases of 21 points in both verbal and performance scores.

Discussion

The data in this study have demonstrated the efficacy of ethosuximide in its ability to increase verbal cognitive functions in this particular patient population. To attribute these changes to extraneous factors appears out of the question, since the subjects randomly received the drug and placebo, and a statistically significant decrease in verbal IQ scores took place while on the placebo. These data become even more impressive when one considers the fact that 6 of these subjects had received the

TABLE II

Comparison of Full-scale IQ Scores of 10 Patients on Ethosuximide and Placebo Treatment

Case No.	Placebo	Ethosuximide	Difference
1	103	124	21
2	121	121	0
3	116	121	5
4	101	115	14
5	119	124	5
6	126	136	10
7	109	125	16
8	114	113	-1
9	103	115	12
10	103	122	19
Means	111.5	121.6	

Difference between means, 10.1.
 $t = 4.1666$; $p = 0.005$.

same tests employed here in our earlier study, and yet the only changes that occurred were decreases of verbal functions while on placebo and increases on ethosuximide. There is a general assumption in intelligence testing that learning gains do take place with performance items though not noticeably in verbal items (Guertin *et al.*, 1962; Littell, 1960). Even this did not occur in our study population, with tests being administered three weeks apart and, as mentioned above, six subjects had received these tests in our earlier investigation. Consequently, any distortion of results on the basis of learning factors was not evident in this investigation.

In terms of the changes of verbal functions, it appears that ethosuximide has some influence on specific functions. If we consider the work of some other investigators in the light of our findings, we have some interesting speculations. McFie (1960), who used the Wechsler intelligence tests on a large number of subjects with various types of brain injuries, concluded that verbal cognitive functions were localized in the left hemisphere of the brain. He carried this even further by showing that patients with left temporal brain trauma experienced the greatest loss of verbal functions regardless of dominance of handedness. By working backwards from McFie's work to our own group who manifested initial reductions in verbal skills before treatment, it seems that ethosuximide has some effect on left hemisphere functions, and that the effect is more specific rather than secondary to some over-all general effect. If it were a more general influence of the drug, changes would be seen at other levels, such as in the personality tests or in performance items and psychomotor skills. Generally, in about 80% of

TABLE III

Comparison of Performance IQ Scores of 10 Patients on Ethosuximide and Placebo Treatment

Case No.	Placebo	Ethosuximide	Difference
1	107	128	21
2	126	126	0
3	127	137	10
4	108	108	0
5	132	131	-1
6	135	138	3
7	114	125	11
8	122	119	-3
9	116	116	0
10	110	113	3
Means	119.7	124.1	

Difference between means, 4.4.
 $t = 1.8739$; p n.s.

the 78 cases studied, increases in functioning are seen in verbal symbolic abilities which are directly related to left hemisphere functions. In the remaining 20%, an increase is seen in visual motor spatial configuration abilities which are tied up with right hemisphere functions in about three-quarters, with the remainder showing no change.

It should be noted that the mean difference for the present study on the Wechsler is higher than that for the preliminary study. There are two possible explanations for this finding. One of these is due to the mild sedative effect of ethosuximide. Since all the subjects had been taking the drug regularly before the study was begun, one might expect a 'let-down' when the subjects were placed on a placebo. This would tend to make the mean differences somewhat larger than in the preliminary study where no placebo was used. This, incidentally, indicates a difficulty with the double-blind cross-over method. A second explanation for the larger difference between the means is a possible cumulative effect of ethosuximide. From the authors' experience, it is felt that the drug has a slight cumulative effect. This does not remain through the three-week placebo period but could make the differences between test results greater in the double-blind study than when comparing test results in the preliminary study. In the preliminary study the subjects were uniformly on the drug for three weeks.

There is another aspect of this study that poses a question for future investigations. It was our belief that the EEG 14-6 positive spike pattern had something to do with verbal deficiency of these subjects before they received therapy. With the disagreement over the meaning of this particular EEG pattern, one could take a different view and

reason that these subjects were experiencing verbal difficulties and/or other problems, and the presence of the 14-6 c.p.s. positive spike EEG pattern only served to exacerbate their already difficult situation. No doubt many of our subjects had had some problems, especially relating to school work, for some time, months or possibly years. However, if this were the case, it would be difficult to explain how an anticonvulsant medication increased verbal function and decreased it when it was stopped.

Based on the results of this study and additional research in our laboratory (Smith and Weyl, 1968), it is our feeling that the 14-6 pattern is associated with a minimal brain dysfunction that interferes with verbal skills. That is, the verbal skills are present but are 'short-circuited' by this type of diencephalic dysfunction which responds in some way to the medication used in this study.

Summary

Ten subjects, ranging in age between 8 and 14, all with 14-6 positive spike EEG patterns and all having learning and management problems, were treated with ethosuximide. All were placed

on the drug and placebo in a double-blind series. While on placebo, their verbal and full-scale IQ scores decreased. While receiving ethosuximide, these same scores increased to a statistically significant level (0.005). Personality and performance-motor tests did not significantly change.

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