LITERATURE CITED

1. N. G. Aleksidze, in: Advances in Neurochemistry [in Russian], Leningrad (1974), p. 132.
2. N. G. Aleksidze, R. G. Akhalkatsi, M. V. Balavadze, et al., Soobshch. Akad. Nauk Gruz. SSR, No. 3, 701 (1974).
3. N. I. Maisov, Yu. G. Sandalov, R. N. Glebov, et al., Byull. Éksp. Biol. Med., No. 1, 45 (1976).
4. N. I. Maisov, N. S. Tolmacheva, and K. S. Raevskii, Farmakol. Toksikol., No. 5, 537 (1975).
5. K. S. Raevskii and N. I. Maisov, Byull. Éksp. Biol. Med., No. 6, 63 (1975).
6. J. Davis and G. Johnston, J. Neurochem., 2, 931 (1974).
7. D. G. Grahame-Smith et al., J. Neurochem., 17, 1339 (1970).
8. F. A. Henn, M. N. Goldstein, and A. Hamberger, Nature (London), 249, 633 (1974).
9. L. L. Iversen and J. S. Kelly, Biochem. Pharmacol., 24, 933 (1975).
10. O. H. Lowry, N. J. Rosebrough, A. L. Farr, et al., J. Biol. Chem., 193, 265 (1951).
11. M. C. W. Minchin and P. M. Beart, Brain Res., 83, 437 (1975).
12. S. P. R. Rose, Biochem. J., 102, 33 (1967).
13. D. Schubert, Brain Res., 84, 87 (1975).
14. M.-L. Valvelainen and S. S. Oja, Brain Res., 40, 477 (1972).

EFFECT OF DERIVATIVES OF GAMMA-AMINOBUTYRIC ACID ON SLEEP DISTURBANCES IN NEUROSES

N. A. Vlasov

UDC 616.85+616.891]-06:616.8-009.836-085.31:547.466.3

Electropolygraphic investigations revealed a tendency in patients with sleep disturbances associated with various forms of neuroses for the total duration of sleep to increase under the influence of derivatives of γ-aminobutyric acid (GABA), on account of an increase in the principal stages of sleep (second stage, Δ sleep, and fast sleep) and a statistically significant decrease in the number of spontaneous awakenings, in the total duration of wakefulness at night, and in the activation index of movements. Analysis of some of the electrographic indices within the stages of sleep revealed a tendency for the number of sleep spindles to increase in the second stage, an increase in the Δ index in the third and fourth stages of sleep, and an increase in the mean numerical indices of rapid eye movements in the absence of significant changes in their specific occurrence per unit time. GABA derivatives in the doses used cause on the whole similar changes in the structure of sleep in its various disturbances, with sodium hydroxybutyrate having a relatively stronger action.

KEY WORDS: sleep disturbance; stages of sleep; sodium hydroxybutyrate; fenibut.

The wide-spread occurrence of sleep disorders in neuroses and the lack of any sufficiently effective drugs with a soporific action necessitate the search for new ways and means of correcting such disturbances. The attention of research workers has been drawn to biologically active substances and, in particular, to γ-aminobutyric acid (GABA) which, according to experimental data, plays an active role in the regulation of sleep.

Because of the difficulty with which GABA passes through the blood–brain barrier, its analogs sodium hydroxybutyrate and fenibut (beta-phenyl-gamma-aminobutyric acid) are used. According to the information published, in experiments on animals sodium hydroxybutyrate promotes the appearance of phases of slow [5-7] and rapid sleep – RS [1, 3]. The phase of sleep which develops has been shown to depend on the dose of the drug [2].

Department of Pathology of the Autonomic Nervous System, I. M. Sechenov First Moscow Medical Institute.

(Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 85, No. 2, pp. 174-177, February, 1978. Original article submitted June 10, 1977.

TABLE 1. Changes in Structure of Sleep under the Influence of GABA Derivatives

Preparation	Duration of sleep, min	Time of going to sleep, min	Stages of sleep, min				Number of spontaneous awakenings	AIM, %
			I	II	III+IV	RS		
Sodium hydroxybutyrate								
Sessional dose	+26	−3,7	−5,6	+13,3	+8,9	+9,7	−0,89	−6,2
Weekly dose	+42	−12,6	+1,1	+16,1	+14,1	+11,4	−1,12	−13,2
Fenibut:								
Sessional dose	+27	−3,4	−1,2	+3,7	+8,7	+6,3	−0,8	Not tested
Weekly dose	+39	−9,7	−2,1	+18,2	+12,5	+13,3	−0,9	−8,1

Legend. Underlining of numbers denotes significant increase (+) or decrease (−) in indices.

The object of this investigation was to study the effect of sodium hydroxybutyrate and fenibut on the structure of sleep in patients with sleep disturbances associated with neuroses.

EXPERIMENTAL METHOD

Electropolygraphic investigations, including continuous recording of the EEG (central and fronto-central leads), the electrooculogram, the electromyogram of the submental muscles, and the EKG, were carried out over a period of several nights (before and after each dose of the drugs and the weekly course). The electropolygraphic data were analyzed in accordance with the international classification [4]. To prolong the analysis of the principal stages of sleep the total number of sleep spindles and of rapid eye movements per unit time (1 min) was counted and the index of Δ activity was analyzed.

The data were analyzed on the Minsk-32 computer. Altogether 34 patients with various forms of neuroses, one of the manifestations of which was disturbance of sleep, were studied. Of the 34 patients 13 took 1.5 g sodium hydroxybutyrate before sleep and 21 took 1 g fenibut. Control tests were carried out on 8 healthy persons.

EXPERIMENTAL RESULTS

According to the results of the electropolygraphic investigations, a reduction in the duration of nocturnal sleep, an increase in the period of going to sleep, an increase in the number of spontaneous awakenings and in the duration of wakefulness in the course of the night, a decrease in the representation of deep Δ sleep, and a decrease in the total number and relative number per unit time (1 min) of sleep spindles in the phase of slow sleep and of rapid eye movements in the phase of RS were found in the patients before treatment. The activation index of movements (AIM), reflecting the ratio between the number of movements with activation on the EEG and the total number of movements of the body during sleep, was considerably increased compared with its value in healthy subjects.

It can be concluded from the analysis of the data that the sleep disturbances in neuroses are based on a change in the relations between synchronizing (somogenic) and desynchronizing (activating) brain systems, with a definite increase in the activity of the so-called arousal or activating system, as is shown by the increase in AIM, the increase in the number of spontaneous awakenings and the duration of wakefulness in the course of the night, and the increase in the heart rate during the various phases and stages of sleep.

The longer period of going to sleep in the patients tested at the beginning of the night and during awakening in the various stages of sleep, the decrease in the relative occurrence of deep slow sleep (Δ sleep), and readiness for awakening also reflect the increased activity of this system. Close correlation exists between the activation changes observed and the emotional disturbances characteristic of neuroses.

Under the influence of the various substances tested an increase was observed in the duration of nocturnal sleep on account of an increase in its principal stages: the stage of "sleep spindles" (II), Δ sleep (III+IV, statistically significant after taking sodium hydroxybutyrate) and RS (Table 1).

The increase in the duration of nocturnal sleep was particularly marked in the patients with an initially low occurrence of the stages of slow and rapid sleep, probably on account of the regulatory influence of the GABA derivative on both phases of sleep. The results of a detailed analysis of certain electrographic indices within the stages of sleep are also evidence of the beneficial effect of GABA derivatives on the phases of slow

TABLE 2. Dynamics of Occurrence of Sleep Spindles

Preparation	Number of sleep spindles with undermentioned amplitude						
	15 μV	15–40 μV	40–60 μV	60–80 μV	80 μV	total	per minute
Before treatment	21,6	150,1	183,8	82,2	11,9	449,8	3,06
Sodium hydroxybutyrate	21,4	158,4	227,1	92,5	14,0	513,5	3,09
Before treatment	31,7	119,6	252,3	122,4	3,5	529,8	3,07
Fenibut	19,7	197,0	301,0	87,0	—	604,7	3,04

and rapid sleep. For instance, an initially reduced number of sleep spindles had a tendency to increase under the influence of these substances (Table 2). The increase (not statistically significant) took place mainly on account of spindles with an amplitude of 16-60 μV.

The study of the principal index of stages III and IV (the Δ index) revealed a small increase in its value under the influence of sodium hydroxybutyrate and fenibut, mainly on account of an increase in the proportion of low-amplitude Δ waves.

In the RS phase the number of rapid eye movements increased under the influence of the drugs, although their frequency per unit time showed no significant change.

Under the influence of sodium hydroxybutyrate ($P < 0.01$) and fenibut ($P < 0.001$) a decrease in the number of spontaneous awakenings and in the duration of wakefulness in the course of the night was observed. AIM fell significantly under the influence of sodium hydroxybutyrate ($P < 0.005$) and of fenibut ($P < 0.01$).

Mathematical analysis with the aid of the computer of the results of electropolygraphic investigation revealed a decrease in the dispersions of most indices studied. An increase in dispersions affected only the number of rapid eye movements under the influence of both compounds tested, whereas after taking sodium hydroxybutyrate there was an increase in the individual dispersion of Δ sleep. Correlation analysis showed similar and different correlations between certain electropolygraphic indices of sleep in both groups of patients tested. Both preparations strengthened correlation between the duration of sleep and Δ sleep (more in case of sodium hydroxybutyrate). Besides their general action, the preparations also showed some specific features in their action: Sodium hydroxybutyrate weakened correlation between the duration of RS and the number of rapid eye movements, whereas fenibut strengthened correlation between these indices.

Under the influence of GABA derivatives, in patients with neuroses accompanied by sleep disturbances a reduction in activation shifts was thus accompanied by improvement of the objective indices (shortening of the time taken in going to sleep, a reduction in the number of spontaneous awakenings and in the duration of wakefulness in the course of the night, an increase in the duration of Δ sleep, slowing of the heart rate), which correlates with improvement of sleep as shown by the patients' subjective reports after final awakening in the morning. The preparations used in the investigation in the doses specified give rise on the whole to similar changes in the structure of nocturnal sleep in its various disturbances, and the action of sodium hydroxybutyrate is relatively stronger.

LITERATURE CITED

1. M. Matsuzaki, H. Takagi, and T. Tokizane, Science, 146, 1328 (1964).
2. M. Matsuzaki and H. Takagi, Brain Res., 4, 206 (1967).
3. M. Matsuzaki and H. Takagi, Brain Res., 4, 223 (1967).
4. A. Rechtschaffen and A. Kales (eds.), A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects, Bethesda (1968).
5. F. Rinaldi, F. M. Puca, F. Mastrosimone, et al., Acta Neurol. (Naples), 22, 65 (1967).
6. B. Vern and J. Hubbord, Electroenceph. Clin. Neurophysiol., 31, 573 (1971).
7. Y. Yamada, I. Yamamoto, A. Fujuki, et al., Electroencephalogr. Clin. Neurophysiol., 22, 558 (1967).