EFFECT OF TRANQUILIZERS OF BLOOD ENDOGENOUS ETHANOL LEVEL IN ALCOHOLICS

Yu. V. Burov, V. G. Treskov,
É. S. Drozdov, and A. E. Kovalenko

UDC 616.89-008.441.13-07:616.153.
262-02:615.214.22

KEY WORDS: alcoholism; tranquilizers; endogenous ethanol.

The level of endogenous ethanol (EE) and acetaldehyde is regarded as a factor which controls many of the homeostatic mechanisms that determine states of comfort and discomfort [4, 6]. Experimental investigations have shown that factors which increase ethanol utilization (stress, hunger, thiamine deficiency) lower the EE level [5]. Meanwhile, in recent years psychotropic drugs have been used successfully for the treatment of alcoholism; tranquilizers, in particular, reduce the pleomorphic psychopathological disorders found in alcoholics that lie at the basis of the alcohol motivation, and they thereby reduce alcohol consumption [1-3]. Since the psychotropic activity of ethanol itself has a broad spectrum [7], differential treatment of alcoholism by courses of psychotropic drugs would appear to be a kind of replacement therapy.

It was accordingly decided to investigate whether the psychotropic effect of tranquilizers is linked with the EE level.

EXPERIMENTAL METHOD

Men aged 28-42 years in stage II-III of chronic alcoholism took part in the investigation on the 20th-25th days after admission to the clinic, when withdrawal symptoms had cleared up. They received no drugs during the 4-5 days before the investigation. Blood was taken from the cubital vein (2-3 ml) at the same time of day (from 9:30 to 11 a.m., 1.5-2 h after breakfast). Each patient was investigated once only. After initial blood sampling and 15, 30, 60, and 120 min after administration of a single dose of the tranquilizers the psychopathological investigation was carried out and a further blood sample taken. In series I a total of eleven patients was studied after administration of 1.5 g mebicar,* a saturated bicyclic bis-urea derivative; in series II nine patients were studied after receiving 50 ml of a 5% syrup of sodium hydroxybutyrate (a γ-hydroxybutyric acid derivative); in series III the eleven patients received 20 mg seduksen (a 1,4-benzodiazepine derivative). The EE concentration was determined by gas–liquid chromatography on an LKhM-8MD (model 5) chromatograph (USSR). Polyethylene-glycol 1500, equal to 15% of the weight of the solid carrier, was used as the stationary phase; the solid carrier was Celite C-22; the column temperature was 50°C, the vaporizer temperature 75°C, the detector current 140 mA, and the carrier gas was helium. To 0.5 cm^3 blood were added 0.5 cm^3 of 50% TCA and 0.5 cm^3 of 1% isopropyl alcohol, which was the internal standard. The flask was sealed and 0.25 cm^3 of 30% $NaNO_2$ introduced into it by means of a syringe. The contents of the flask were shaken and the gaseous phase withdrawn from the flask by means of a syringe and led into the chromatograph. Student's and Fischer's tests were used for the statistical analysis of the data.

*2,4,6,8-Tetramethyl-2,4,6,7-tetra-azobicyclo-(3,30)-octadione-3,7.

Laboratory for the Search for and Study of Substances for Prevention and Treatment of Drug Addiction, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow.
(Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 95, No. 1, pp. 60-62, January, 1983. Original article submitted July 19, 1982.

0007-4888/83/9501-0081$07.50

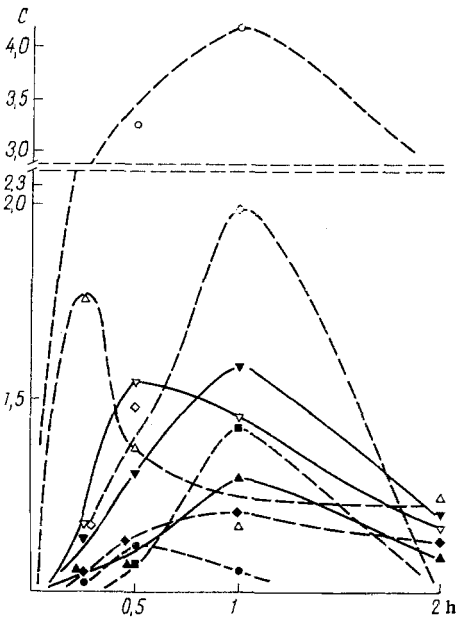

Fig. 1

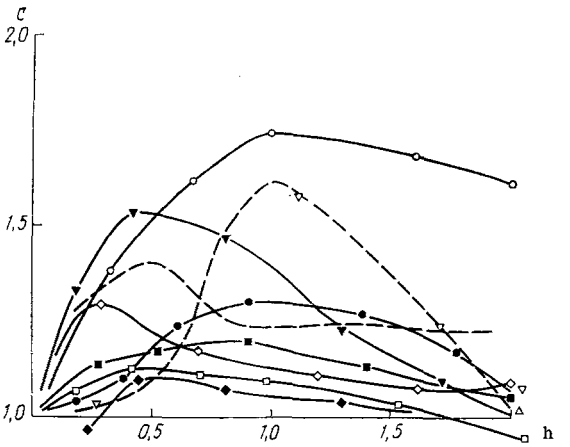

Fig. 2

Fig. 1. Individual features of the time course of EE in the blood of alcoholics after taking mebicar. Abscissa, time (in h); ordinate, relative concentration (C). Broken line indicates time course of EE in patients with no visible clinical effect; continuous line shows time course of EE in patients with a clinical effect.

Fig. 2. Individual time course of EE in blood of alcoholics after taking sodium hydroxybutyrate syrup. Legend as to Fig. 1.

EXPERIMENTAL RESULTS

Three of nine patients, 5-20 min after taking mebicar, had a sensation of mild, subjectively pleasant intoxication, slight dizziness, internal relaxation, and rest. An almost imperceptible level of general animation was observed. This state lasted 30-50 min, and it was followed by imperceptible reversion to the initial state. A clinically noticeable effect after a single dose of mebicar largely depended on the patients' initial state. It was exhibited in those patients who had asthenoneurotic disorders at the time of investigation. In the patients with psychopathic symptoms and patients without any psychopathological disorders, no clinical manifestations were observed after a single dose of mebicar.

Seven of the nine patients 15-30 min after taking sodium hydroxybutyrate noticed a sensation of slight intoxication with mild dizziness, minor disturbances of the accuracy of movements, and a sensation of heaviness or weakness in the lower limbs. After 15-20 min the not always subjectively pleasant state was replaced by one definitely pleasant, with a slightly elevated mood and a sensation of rest (four subjects) or with some degree of apathy and relaxation (three cases). The state reverted to its initial character after 1.5-2 h. No clinical effect was exhibited in patients with psychopathic disorders.

Patients taking seduksen were aware after 20-30 min of a feeling of apathy, dizziness, mild disturbance of movement coordination, and weakness of the whole body, especially the lower limbs. After 1.5-2 h this state was followed by sleepiness. The clinical effect in this series of cases was only a little dependent on the patients' initial state, but a marked degree of apathy and drowsiness could be noted in patients with asthenoneurotic symptoms.

The time course of the EE concentration (C) in each patient after taking the drugs is illustrated in Figs. 1-3 as a function of C_t/C_0 on time, where C_t is the EE concentration at a given moment and C_0 the initial EE concentration. It will be clear from Figs. 1-3 that the EE concentration rose in each subject after taking the tranquilizer. The greatest increase in EE concentration was observed in most patients 60 min after taking mebicar and sodium hydroxybutyrate and 15-30 min after taking seduksen (except two patients, whose EE concentration continued to rise until the end of the second hour). The maximal rise of the EE level after administration of mebicar averaged 75%, compared with 32% after sodium

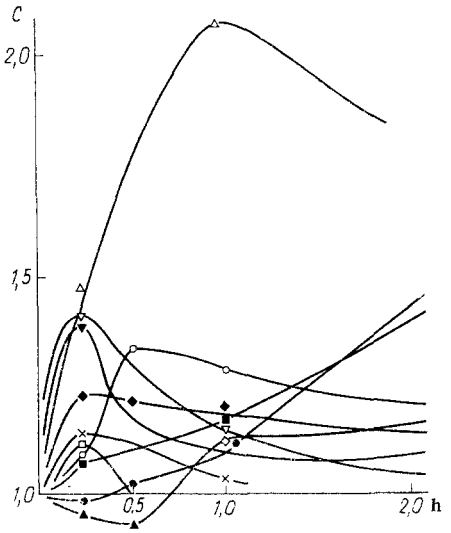

Fig. 1. Individual time course of blood EE levels in alcoholics after taking seduksen. Legend as to Fig. 1.

hydroxybutyrate and 15-20% after seduksen. The EE level after 2 h was almost back at its initial value in the first two series of cases but remained high after administration of seduksen. The dynamics of the EE concentration coincided on the whole in time with manifestation of the psychotropic effect of the drugs. However, no correlation could be found between the EE concentration and the intensity of the clinical effect.

In absolute terms, incidentally, the increase in EE concentration was an order of magnitude less than that observed in the presence of the mildest clinical features of alcoholic intoxication.

It can be postulated on the basis of these results that the EE level is under central control. Meanwhile, by virtue of its physicochemical properties, EE may influence the functional state of the receptor apparatus of the CNS, modifying effects not only of neurotransmitters and neuromodulators, but also of any drugs which may also be used.

LITERATURE CITED

1. Yu. A. Aleksandrovskii, V. G. Treskov, and É. S. Drozdov, in: New Soviet Drugs for Use in Psychiatry and the Treatment of Addiction and the Theoretical Basis of Their Development [in Russian], Moscow (1982), pp. 42-49.
2. V. B. Al'tshuler, Zh. Nevropatol. Psikhiat., No. 2, 269 (1978).
3. A. L. Gamburg, A. G. Aranovich, and V. L. Vol'fson, Zh. Nevropatol. Psikhiat., No. 2, 264 (1978).
4. G. I. Ezrielev, New Aspects of the Pathogenesis of Alcoholism [in Russian], Leningrad (1975).
5. Yu. M. Ostrovskii, M. N. Sadovnik, and V. I. Sotanovskaya, Dokl. Akad. Nauk BSSR, 22, 1125 (1978).
6. Yu. M. Ostrovskii et al., Ethanol and Metabolism [in Russian], Minsk (1982), pp. 6-47.
7. V. G. Treskov, in: First Congress of Neuropathologists and Psychiatrists of Moldavia [in Russian], Vol. 2, Kishinev (1981), p. 169.