Maintenance of Homeostasis of Endogenous Ethanol as a Method for the Therapy of Alcoholism

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We propose a new method for the therapy of alcoholism based on maintenance of homeostasis of endogenous ethanol and inhibition of alcohol dehydrogenase with emetine. After the standard antialcohol therapy, activity of this enzyme remained high or even increased, and pathological alcohol addiction also increased. Emetine normalized activity of alcohol dehydrogenase and suppressed pathological alcohol addiction. After this therapy more than 50% patients achieved stable remissions from alcoholism over 1 year, which indicated high efficiency of the proposed method.

Key Words: *alcoholism; alcohol dehydrogenase; ethanol homeostasis; emetine*

Modern therapy of alcoholism includes conditioned reflex, sensitizing [6,9,13], and psychopharmacological approaches [2] based on the development of unstable aversive, phobic, and antidepressive reactions inhibiting pathological alcohol addiction (PAA) [13]. The efficiency of new methods, including narcopsychotherapy of alcoholism, remains unclear [7]. The search for new approaches to the treatment of PAA is still in progress.

Alcohol dehydrogenase (ADH) is a cytosolic enzyme catalyzing conversion of acetaldehyde into endogenous ethanol [5,11]. Blood content of endogenous ethanol is low, but relatively stable. In alcoholics, ADH activity in the blood is high during both alcohol abuse and remissions [3]. However, high ADH activity shifts the reaction towards the formation of acetaldehyde from ethanol [5,11] and its accumulation in the organism. These processes trigger cascade biochemical reactions leading to generation and accumulation of psychotropic substances and the development of alcohol abstinence syndrome (AAS) and PAA [14].

We hypothesized that normalization of ADH activity in patients with alcohol dependence (after withdrawal of exogenous ethanol) would recover homeostasis of endogenous ethanol and acetaldehyde and, therefore, prevent PAA. Emetine used as an emetic drug during conditioned reflex therapy of alcoholism is proposed as the inhibitor of ADH [6,9,13]. *In vitro* experiments showed that emetine in therapeutic doses decreases plasma ADH activity in patients with high enzyme activity. These data provided a basis for the use of emetine in clinical practice.

MATERIALS AND METHODS

We examined 170 men aging 23-65 years and suffering from alcohol dependence for 2-34 years (Department for the Therapy of Alcohol Dependence). The patients were hospitalized with symptoms of severe alcohol intoxication and AAS (alcohol abuse) or during remission.

Over the first 1-3 days after hospitalization the patients were examined by the method described elsewhere [1], and PAA was expressed in points. The blood from the cubital vein was taken from fasting patients. Plasma ADH activity was measured spectrophotometrically [4,8]. In group 1 patients (n=85), severe alcohol intoxication was not accompanied by subjective feelings of PAA; ADH activity did not exceed the normal (0.96-1.18 U/liter) [4,13,14]. Group 2 included patients (n=68) with symptoms of AAS. Patients hos-

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TABLE 1. Somatic and Autonomic Components of PAA

Parameter		Intoxication (*n*=85)	AAS (*n*=68)	Remission (*n*=17)
ADH activity, U/liter		0.68±0.42	6.46±1.13	12.4±0.1
PAA components	autonomic	1.47	2.9	2.66
	ideomotor	1.42	2.7	2.83
	sensory	0.94	2.3	2.5
Behavior		1.36	2.7	2.66
Total score		5.19	10.6	10.65

pitalized during remission with symptoms of PAA comprised group 3 (*n*=17). Group 1 and 2 patients were subjected to traditional detoxification and symptomatic therapy. Groups 2 and 3 practically did not differ by the level of PAA. Group 3 patients were treated with emetine.

After normalization of these disorders (at the end of the first or in the beginning of the second week of therapy), ADH activity in the blood was measured 1-2 times a week. In the majority of patients, these tests were repeated 3-6 times. At each stage of observations, enzyme activity was measured at least in 10 patients. Liver functions were repeatedly estimated (2-3 times) by blood alanine aminotransferase (ALT) activity [8]. After disappearance of acute postintoxication disorders (from the second week of treatment), group 1 and 2 patients were treated with emetine in a dose of 0.005-0.010 g 2-4 times a day for 15-20 days. This dose of emetine was much lower than that used during conditioned reflex therapy. PAA was periodically estimated. The data on ADH activity were analyzed by Student's *t* test.

RESULTS

Group 1 patients were characterized by moderate somatic, autonomic, and psychic components of PAA, which corresponded to their subjective feelings (Tables 1 and 2). In group 2 patients, practically all PAA parameters 2-fold surpassed those in group 1 patients. Blood ADH activity in group 2 and 3 patients far surpassed the control and was higher than in group 1 patients. During the first days after hospitalization ALT activity was increased only in 61% patients. We found no correlation between ALT activity, patient's state and age, and duration of alcohol abuse.

Detoxification and general therapy increased ADH activity in group 1 and 2 patients during the first week of treatment (Fig. 1). Patients of both groups were characterized by pronounced subjective feelings of PAA. Emetine rapidly decreased blood ADH activity in group 3 patients (over the first week of therapy). ADH activity decreased slowly in group 1 and 2 patients treated with emetine at later stages than group 3 patients.

Emetine progressively decreased PAA. By the end of therapy, PAA disappeared in the majority of patients, while others had no subjective feelings of PAA. In some patients emetine in a dose of 0.01 g produced side effects (including nausea and vomiting) that disappeared after reducing the dose of the drug. In patients hospitalized with high ALT activity, this parameter returned to normal by the end of treatment without hepatotropic therapy. In other patients, ALT activity did not increase which indicated that emetine in these doses normalized liver functions and produced no hepatotoxic effects.

We revealed a correlation between increased ADH activity and psychosomatic indexes of PAA. In patients with high ADH activity, the reaction catalyzed by this enzyme was shifted towards the formation of acetaldehyde (precursor of morphine-like compounds probably responsible for PAA).

The decrease in blood ADH activity after emetine therapy was accompanied by suppression of PAA, which was probably associated with restoration of homeostasis of endogenous ethanol and acetaldehyde and normalization of metabolic processes in the central nervous system. This therapeutical procedure produced stable effects: more than 50% patients achieved stable remissions for 1 year. It should be emphasized that other antialcoholic methods are efficient only in 24% patients [3].

TABLE 2. Psychic Components of PAA (Score)

Component	Intoxication (*n*=85)	AAS (*n*=68)	Remission (*n*=17)
Subdepression	1.36	2.7	2.2
Anxiety	1.05	2.5	2.3
Emotional lability	0.73	1.8	1.75
Dysphoria	1.1	2.6	2.41
Euphoria	0.68	1.0	1.33
Apathy	1.63	2.6	2.16
Total points	6.55	13.2	12.15

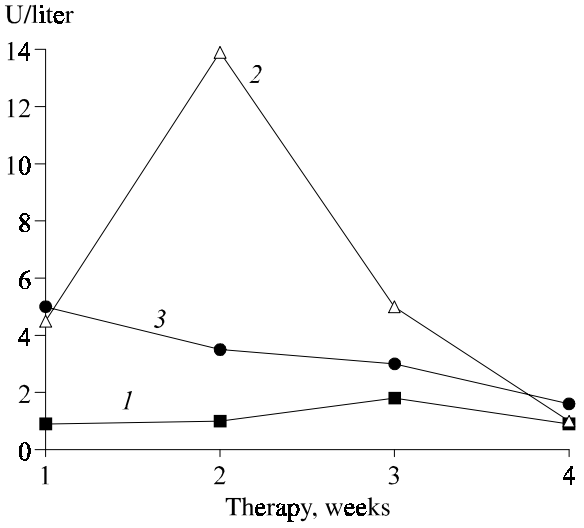

Fig. 1. Alcohol dehydrogenase activity during therapy of patients with alcohol dependence hospitalized at the stage of intoxication (*1*), alcohol abstinence (*2*), or remission (*3*).

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