Proproten-100 in the Therapy of Patients with the Alcohol Withdrawal Syndrome

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The efficiency of Proproten-100 containing antibodies to S100 protein in ultralow doses and used to relieve somatovegetative and psychoneurological manifestations of the alcohol withdrawal syndrome was studied in a double-blind, placebo-controlled clinical trial. The preparation possessed anxiolytic, sedative, hypnagogic, and vegetostabilizing properties. Proproten-100 more rapidly relieved the alcohol withdrawal syndrome than standard drugs (by 2 times). Proproten-100 may used in combination with detoxicating and symptomatic drugs to treat patients with severe disorders. The preparation did not cause side effects. Our observations indicate that Proproten-100 may be used alone (monotherapy) or in combination with standard pharmaceutics for treatment of patients with the alcohol withdrawal syndrome.

Key Words: *alcohol withdrawal syndrome; ultralow doses; antibodies to S100 protein; Proproten; vegetostabilizer*

Elaboration of new pharmacotherapeutic methods for rehabilitation of patients with various pathological addictions is an urgent problem. Preparations with ultralow doses of the active substance are important for pharmacotherapy of drug addiction. New hypothesis regarding the mechanisms of their therapeutic activity were developed in recent years [7,9-11].

A new preparation Proproten-100 was synthesized at the "Materia Medica Holding" Research-and-Production Company and contains antibodies to brain-specific S100 protein in ultralow doses [10,11].

Here we evaluated the efficiency of Proproten-100 in relieving the alcohol withdrawal syndrome (AWS). The major manifestations of AWS develop very rapidly, undergo diurnal variations, and have the individual spontaneous dynamics. It is difficult to differentiate the actual therapeutic and placebo effects of test preparations. In the present work we performed a double-blind, placebo-controlled clinical trial of Proproten-100.

MATERIALS AND METHODS

Therapeutic effectiveness of Proproten-100 was studied at the Department of Mental Disorders Complicated by Pathological Addictions (Moscow Institute of Psychiatry), Basic Clinical Departments of Drug Addiction (Laboratory of Drug Addictions, Russian State Medical University), and Department of Narcology (Russian Medical Academy of Postgraduate Education).

We examined 172 patients with moderate drug addiction and severe somatovegetative and psychoneurological symptoms of AWS. The diagnosis was verified by criteria for disorders associated with pathological dependence (International Classification of Diseases, 10th Edition). Clinical observations were performed on patients without associated chronic somatic, neurological, and mental diseases in the stage of exacerbation or decompensation. The age of patients was no more than 65 years.

Proproten-100 or placebo in a single dose of 1 tablet was given sublingually up to complete dissolution (2 tablets at a 30-min interval and 3 tablets at 1-h intervals). If required, the patients were repeatedly treated after 2-3 h. Proproten-100 or placebo was prescribed as monotherapy. Standard disintoxication and general improving health therapy was performed when the effect did not develop over 5-6 h after treatment. In this instance the patients continued to take test preparations under similar regimen. The efficiency of Proproten-100 was evaluated in the acute stage of AWS (first 3-4 days).

On day 1 the patients were examined 3 times after intake of preparations. Then examination of patients

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TABLE 1. Demographic and Anamnestic Characteristics of Patients

Parameter		Proproten-100 (*n*=87)	Placebo (*n*=85)
Age (years)		41.80±1.11	43.50±1.12
35-45 years, % patients		49	49
Sex, % patients	men	90	87
	women	10	13
Duration of disease, years		13.70±0.87	13.50±0.70
Duration of the last drinking bout, days		9.60±0.71	8.60±0.77
Periodic drinking bout, % patients		83	76
Continuous drinking bout, % patients		17	24
Doses, % patients	low	5	4
	medium	45	59
	high	43	34
	ultrahigh	7	3

was performed at the same time. The medical history of a patient included demographic data, anamnesis, and results of daily examination. We also analyzed 37 major somatovegetative, neurological, and psychopathological symptoms of AWS. The state of health in patients and severity of AWS symptoms were determined by a 3-point scale [3].

The results were analyzed by the sign test, Student's *t* test, and Student's ratio test. The differences were significant at $p \leq 0.05$.

RESULTS

During the first examination of patients we revealed various symptoms of AWS. The major psychoneurological and somatovegetative manifestations of AWS were pathological alcohol addiction, troubled sleep and nightmares, partial or complete insomnia, asthenia, depression, petulance, dysphoria, anxiety, headache, tremor, sweating, nausea, tachycardia, and arterial hypertension. Hypobulia, anhedonia, bustling, psychomotor excitation or depression, elementary illusory or hallucinatory disorders, apathy, feeling of fear, and chill were rarely observed. These general symptoms correspond to the major manifestations of AWS [3,8].

Depending on the efficiency of treatment over the first 5-6 h, the patients were divided into 2 groups. Group 1 included patients (*n*=87) with a pronounced effect of the preparation. If the preparation did not produce considerable changes the patient was attributed to group 2 (*n*=85). Group 1 patients demonstrated positive changes associated with the effect of Proproten-100. Over the first 5-6 h we revealed no therapeutic effect in 85 patients of group 2 receiving placebo. Therefore, the patients were naturally divided into 2 groups by the end day 1. Beginning from the evening of day 1 the patients of group 1 received Proproten-100 monotherapy. Group 2 patients treated with disintoxication and general improving health preparations constituted the control group. Therapeutic activities of Proproten-100 and standard pharmaceutics were compared from day 2 of examination.

TABLE 2. Initial Total Severity of AWS Symptoms (Points, % of Maximum Value)

Group	Parameter	
	score	%
Proproten-100 (*n*=87)	1891 (4959)	38
Placebo (*n*=85)	1751 (4845)	36

Note. Maximum values are shown in brackets.

We revealed no significant between-group differences in the general demographic and anamnestic characteristics (Table 1). It should be emphasized that the average age of patients was relatively high. It was probably associated with the imperfect system for revealing and therapy of patients with alcoholism. These patients are hospitalized in later stages of the disease.

TABLE 3. Changes in Total Severity of AWS Symptoms (Points and Percents of Initial Values)

Group	Days		
	2	3	4
Proproten-100	739 (39**)	304 (16*)	100 (5*)
Placebo	1080 (62)	656 (38)	376 (22)

Note. *p<0.01 and **p<0.05 compared to the initial value. Percent of the initial value is shown in brackets.

TABLE 4. Changes in the Severity of Major AWS Symptoms (Points and Percents of Initial Values)

Symptom			Initial value	Days		
				2	3	4
Addiction	Proproten-100	score	206	80 (39**)	21 (10)	5 (2)
		number of patients+	87	56	15	4
	placebo	score	179	104 (58)	58 (32)	37 (21)
		number of patients+	78	68	39	27
Sleep disorders	Proproten-100	score	124	53 (43**)	25 (20)	4 (3)
		number of patients+	51	44	20	2
	placebo	score	128	93 (73)	66 (52)	34 (27)
		number of patients+	61	63	45	25
Insomnia	Proproten-100	score	101	37 (37)	9 (9)	—
		number of patients+	44	23	7	—
	placebo	score	93	41 (44)	28 (30)	19 (20)
		number of patients+	43	27	19	14
Asthenia	Proproten-100	score	171	79 (46)	40 (23)	18 (11)
		number of patients+	62	52	35	9
	placebo	score	155	97 (63)	82 (53)	45 (29)
		number of patients+	64	63	54	37
Depression	Proproten-100	score	120	40 (33*)	18 (15)	7 (6)
		number of patients+	67	37	17	8
	placebo	score	108	67 (62)	49 (45)	31 (29)
		number of patients+	53	37	23	18
Dysphoria	Proproten-100	score	145	67 (46)	28 (19)	7 (5)
		number of patients+	66	55	28	3
	placebo	score	123	70 (57)	53 (43)	27 (19)
		number of patients+	57	51	40	19
Anxiety	Proproten-100	score	127	42 (33**)	16 (13)	3 (2)
		number of patients+	73	24	12	2
	placebo	score	99	58 (59)	37 (37)	20 (20)
		number of patients+	62	36	24	13
Tremor	Proproten-100	score	195	90 (46*)	36 (19)	15 (8)
		number of patients+	85	67	24	5
	placebo	score	167	116 (70)	76 (46)	43 (26)
		number of patients+	78	79	59	32
Sweating	Proproten-100	score	164	68 (41*)	18 (11)	5 (3)
		number of patients+	77	45	8	2
	placebo	score	134	89 (66)	41 (31)	20 (15)
		number of patients+	71	57	31	16
Tachycardia	Proproten-100	score	153	53 (35*)	17 (11)	7 (5)
		number of patients+	84	45	12	7
	placebo	score	134	96 (72)	47 (35)	23 (17)
		number of patients+	76	59	33	23
Arterial hypertension	Proproten-100	score	118	47 (40**)	25 (21)	9 (8)
		number of patients+	67	25	15	8
	placebo	score	104	71 (68)	40 (39)	19(18)
		number of patients+	65	46	27	12

Note. +Number of patients with the symptom. Percent of the initial value is shown in brackets. *p<0.01 and **p<0.05 compared to the placebo group.

Patients of the placebo group were older than patients of the main group. The period of a drinking bout in patients receiving Proproten-100 was longer than in placebo patients. In the main group the number of patients consuming high and ultrahigh doses of alcoholic beverages during the last drinking bout was greater than in the placebo group.

The patients of both groups often had associated and background diseases, including coronary heart disease (n=24), arterial hypertension (n=14), peptic ulcer of the stomach or duodenum (n=15), and craniocerebral injury with concussion of the brain (n=10). Some patients of the main (n=6) and placebo group (n=5) previously suffered from depressive disorders (cyclothymia or slow progredient schizophrenia). Alcohol dependence in these patients may be classified as actual secondary alcoholism. By the moment of examination these diseases were not in exacerbation.

It should be emphasized that patients of both groups had serious symptoms of chronic intoxication with alcohol. The patients were characterized by long duration of the disease and sever hangover. During hospitalization the state of 82% patients was moderate-to-severe or severe. The initial severity of AWS did not differ between patients (Table 2). This parameter was expressed in percents of the maximum total severity for AWS symptoms estimated during the first examination. The initial total severity of AWS symptoms did not differ between patients admitted to 3 hospitals.

The total severity of symptoms observed in the acute stage of AWS markedly decreased in patents receiving Proproten-100 (Table 3).

Differences in the severity and persistence of main AWS symptoms in patients receiving Proproten-100 and placebo were revealed over the first 2-6 h of examination (Table 4). In 40% patients the severity of tachycardia and sweating decreased 2-3 h after treatment with Proproten-100. In this period the degree of anxiety, alcohol addiction, tremor, and arterial hypertension were reduced in 30% patients receiving Proproten-100. In 60% patients the severity of sweating decreased 4-6 h after the start of therapy. Finger tremor of the extended hands disappeared in 50% patients. Alcohol addiction and arterial hypertension markedly decreased in 40% patients.

Between-group differences in the severity of AWS symptoms were more significant on day 2 of therapy. In patients receiving Proproten-100 manifestations of wistful depression, melancholy, finger tremor of the extended hands, and tachycardia were relieved more rapidly than in control patients. The degree of alcohol addiction, asthenia, and anxiety markedly decreased in patients of the main group. Sleep and appetite were improved in patients treated with Proproten-100. Blood pressure returned to normal in 50% patients (except for 8 patients with arterial hypertension).

On day 3-4 differences in AWS symptoms in patients of the main and control groups were less significant. Proproten-100 did not produce side effects.

These data show that Proproten-100 produces a strong therapeutic effect, relieves somatovegetative and psychoneurological manifestations of AWS, affects alcohol addiction, and possesses antidepressant, anxiolytic, hypnagogic, and vegetostabilizing properties. Proproten-100 may be used to relieve symptoms of AWS during the therapy of patients with alcohol dependence.

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