Clinical Evaluation of Non-narcotic Substitutive Effects Produced by ANAR during the Therapy of Patients with Heroin Abuse

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The substitutive effects of potentiated ANAR (affinely purified antibodies to morphine hydrochloride in dilutions C30 and C200) used to relieve the opium withdrawal syndrome in 149 patients with heroin abuse were studied in an open standardized clinical trial. Over the first 2 days of therapy the preparation produced the vegetostabilizing, sedative, anxiolytic, neuroprotective, and moderate analgetic effects. During the therapy of patients with opium intoxication ANAR delayed the appearance of symptoms for the opium withdrawal syndrome by 18-30 h. This phenomenon allows us to shorten the period of urgent therapy and decrease doses of symptomatic drugs. Our results show that ANAR possesses substitutive properties and may be used to relieve the opium withdrawal syndrome and post-withdrawal disorders resulting from heroin abuse in remission.

Key Words: *heroin abuse; withdrawal syndrome; ultralow doses; antibodies to morphine*

Recent studies indicate that potentiated neurotropic substances in ultralow concentrations have high biological activity [1,2,6,7,13].

The preparation ANAR was synthesized at the "Materia Medica Holding" Research-and-Production Company and contains homeopathically potentiated and affinely purified antibodies to morphine hydrochloride (PAB-M, mixture of dilutions C30 and C200). Preclinical studies of ANAR during treatment of rats with serious symptoms of the opium withdrawal syndrome (OWS) showed that this preparation activates the system of positive reinforcement and possesses anxiolytic, psychostimulating, and/or antidepressant properties [4,9,10,12,13]. Clinical trials with ANAR on patients with OWS revealed vegetostabilizing, sedative, and analgetic activity. During the therapy of patients with opium intoxication ANAR delayed the appearance of symptoms for OWS by 18-30 h [2,6-8,11,13].

Here we studied the substitutive effects of ANAR during treatment of patients with OWS.

MATERIALS AND METHODS

An open clinical trial was performed on 150 patients with heroin dependence accompanied by mild and moderate OWS. The patients with associated mental disorders (*e.g.*, alcohol dependence) and chronic somatic or neurological diseases in the stage of exacerbation or decompensation were excluded from observations.

Studies were performed at the Department of Mental Disorders Complicated by Pathological Addictions (Moscow Institute of Psychiatry), Department for Therapy of Alcoholism and Drug Abuse (V. P. Serbskii State Research Center for Social and Forensic Psychiatry), Clinical Department of the Institute for Mental Health, Mental Hospital No. 13 (Clinical Department of Drug Addiction, Russian Medical Academy of Postgraduate Education), and Hospital for Drug Abusers No. 17 (Department of Psychiatry and Drug Addiction, Moscow State Medical and Stomatological University).

During ANAR monotherapy the patients sublingually received 1 tablet of the preparation at intervals of 20 (up to falling asleep) and 40 min (after awaking). ANAR was not given during diurnal and nocturnal sleep.

For standardization we used the individual medical history of a patient that included anamnestic and age characteristics, results of somatoneurological and mental examination, and parameters for the severity of OWS symptoms. Twenty symptoms of OWS were analyzed by a 3-point scale (Table 2).

Possible side effects of the preparation were taken into account.

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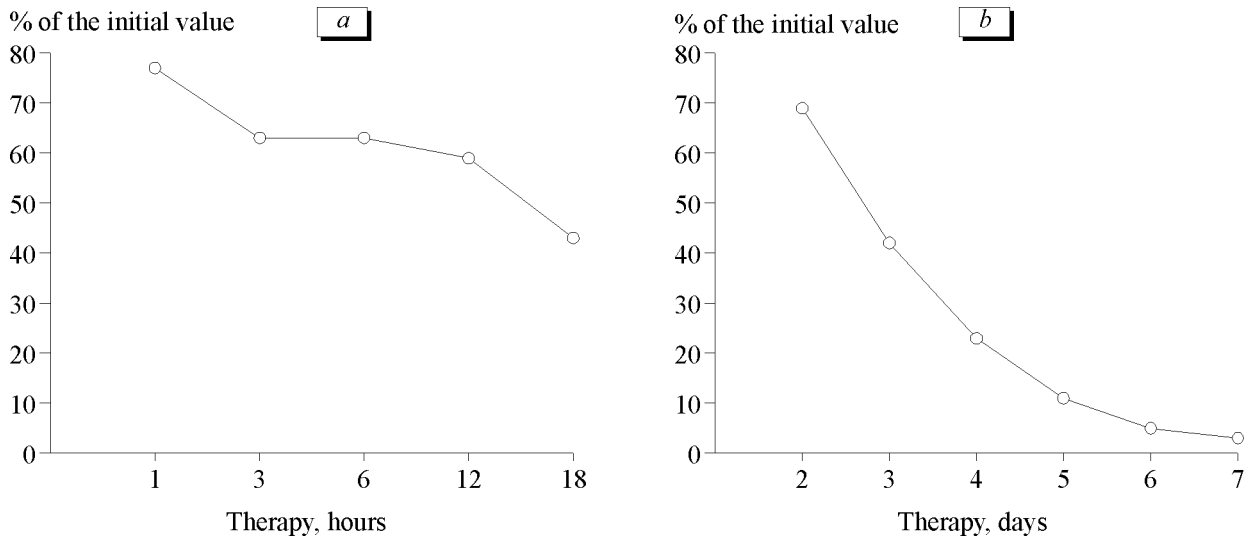

Fig. 1. Changes in the total severity of symptoms for the withdrawal syndrome (% of the initial value) on days 1 (*a*) and 2-7 of therapy (*b*).

The patients were examined before the start of therapy. On day 1 the severity of symptoms was evaluated 1, 2, 3, 4, 6, 12, and 18 h after tretament. Then the patients with OWS were examined daily. The patients were excluded from observations if their health grew worse or ANAR did not produce the therapeutic effect over the first 4 h after the start of therapy.

Most patients were of the male sex (Table 1). By the moment of examination 51% patients were unemployed, 26% patients learned at academic institutions, junior technical colleges, and technical schools, and 23 % patients were employed. Familial alcoholism was revealed of 36% patients. However, most patients were of good families. The patients successfully graduated from secondary schools.

The patients consumed alcoholic beverages and cannabis for the first time in the company of contemporaries. Then they became intranasal and intravenous heroin users. The average duration of OWS surpassed 4 years. The average daily dose of intravenous heroin was 0.5 g. The last intravenous injection of heroin was performed 2-20 h before hospitalization.

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

RESULTS

Changes in the severity of OWS and its individual symptoms and subjective evaluation of the preparation by patients were the main criteria for the efficiency of ANAR monotherapy.

The state of patients was improved over the first 4 h of treatment. The symptoms of OWS were slightly aggravated by day 2, but then reduced. On day 7 of therapy mild symptoms of OWS were revealed only in individual patients (Fig. 1, *a*, *b*). ANAR was as good as standard drugs (Clophelin, Tiapridal, and Tramal) for the reduction of moderate-to-severe OWS symptoms [3,5,6,11]. Only 19 of 150 patients had to take additional drugs due to low efficiency of ANAR. Fifteen patients were excluded from observations in various stages of treatment.

By the end of day 1, 25% patients were sensitive to ANAR (Figs. 2 and 3). Then the number of respondents progressively increased and reached 50% after 4-day therapy. These data indicate that the potentiated preparation ANAR produced a strong substitutive effect during treatment of patients with heroin dependence.

Somatovegetative and neurological symptoms were reduced over the first day of treatment. Pain, anxiety, bustling, and insomnia were resistant to ANAR therapy (Table 2). Diarrhea, hyperthermia, and dyspnea were rarely observed.

Individual symptoms of OWS underwent rapid, but not simultaneous reduction (Table 2). Most sym-

TABLE 1. Age and Anamnestic Characteristics of Patients

Anamnestic parameters	Means and range of individual variations
Age (years)	24.74±1.71 (18-40)
Sex distribution, % patients	
male	128 (86%)
female	21 (14%)
Duration of disease, years	4.34±0.98 (1-8)
Duration of OWS	4.12±0.56
Daily dose of heroin, g	0.65±0.09
Number of patients	135

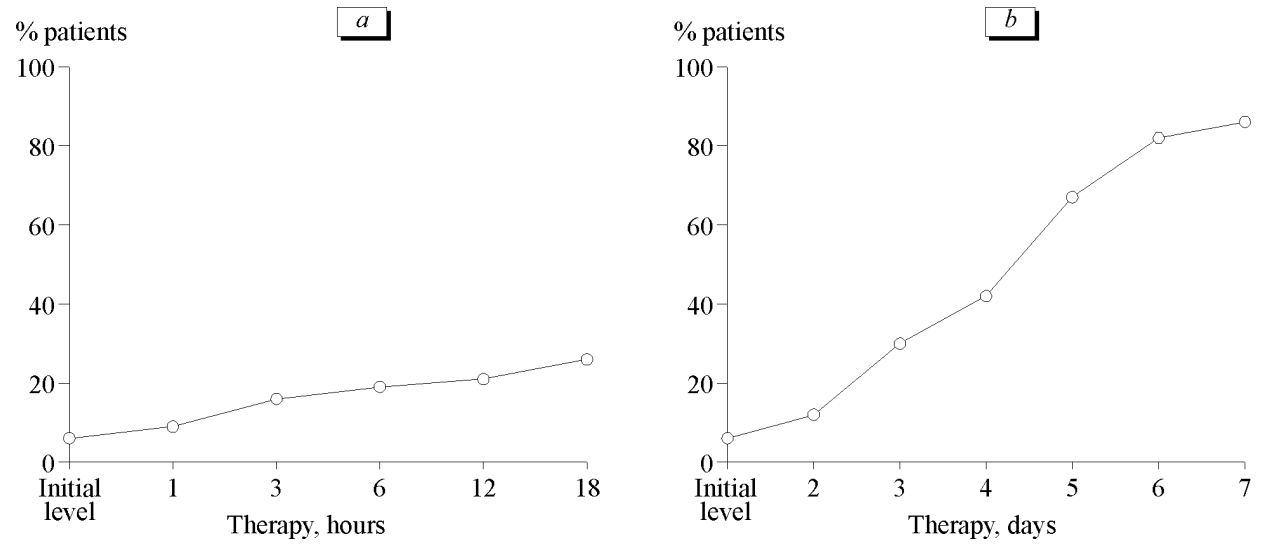

Fig. 2. Changes in the number of patients (%) sensitive to treatment during the first day (*a*) and first week of therapy (*b*).

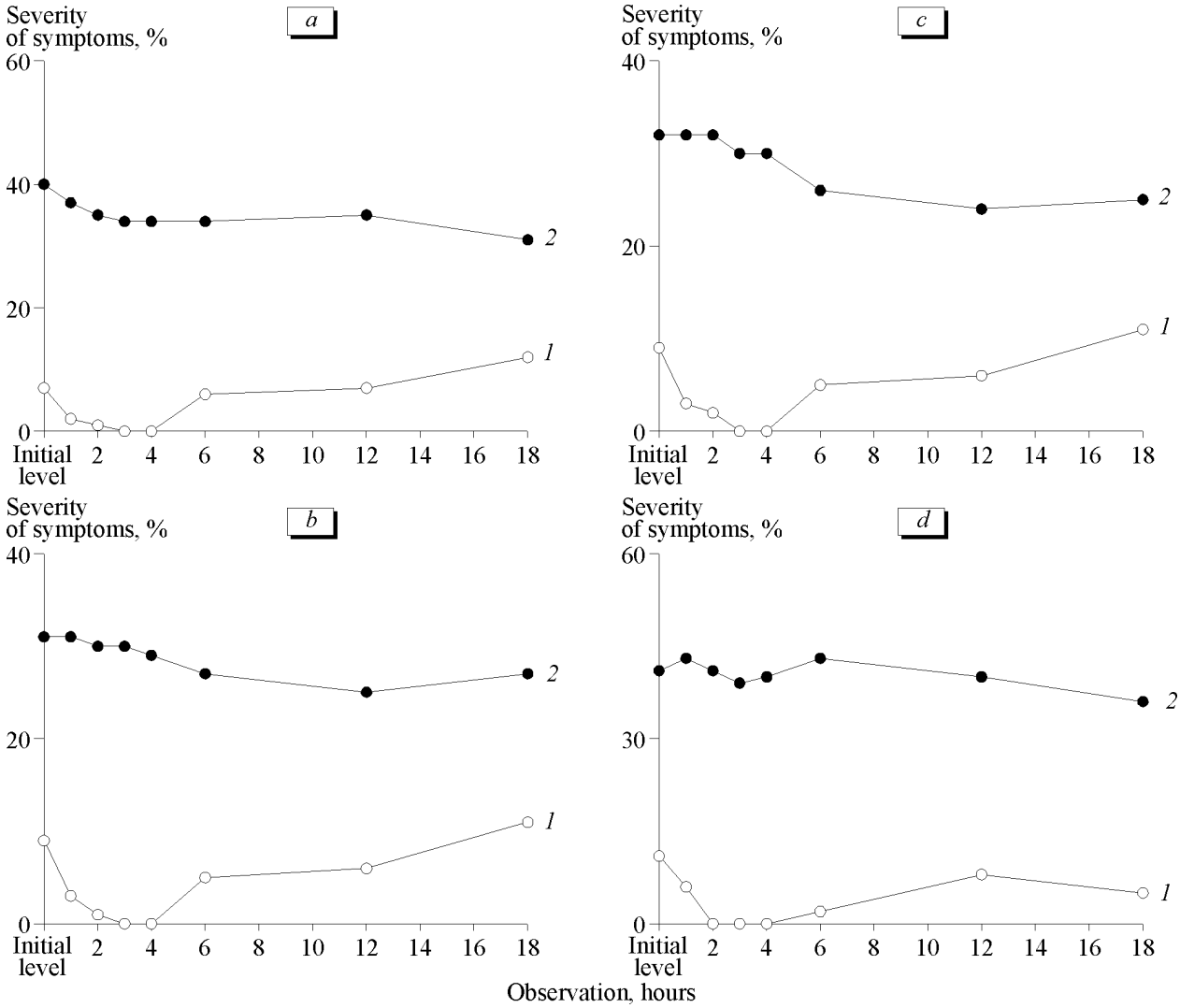

Fig. 3. Changes in the severity of somatovegetative (*a*), psychopathological (*b*), neurological, and pain symptoms (*c*) and drug addiction (*d*) over the first day of therapy. Here and in Fig. 4: ordinate, severity (% of maximum value). Group 1: opium intoxication during hospitalization (*1*). Group 2: opium withdrawal (*2*).

TABLE 2. Changes in the Severity of Main OWS Symptoms during 7-Day Therapy (%)

Symptom	Day 1, hour					Therapy, days					
	1	3	6	12	18	2	3	4	5	6	7
Yawning	74	44*	46	46	40	60	30	9	5	2	1
Watery eyes	72	60**	58	44	31	60	26	9	3		
Salivation	75	53**	65	61	34	59	28	3	1		
Sneezing	70	47**	40	38	29	52	28	6	2	1	
Sweating	84	70**	53	50	41	70	47	17	14	4	2
Tremor	85	51*	37	38	47	51	27	8	5	3	
Chill	97	72**	58	46	44	64	39	18	11	1	
Gooseflesh	79	40*	40	24	27	49	16	8	3	2	
Anorexia	92	77**	66	64	63	60	39	23	12	4	2
Dyspnea	ND	ND	ND	ND	ND	60	34	17	17	9	4
Tachycardia	ND	ND	ND	ND	ND	49	41	30	31	15	9
Hypertension	ND	ND	ND	ND	ND	48	129*	38	31	15	14
Anxiety and bustling (day 1)	77	64	72	72	51**	84	50	35	17	4	2
Pain in muscles and joints	85	77	80	77	59**	108**	64	39	14	8	2
Petulance	82	66**	64	65	49	87	71	49	25	15	12
Sleep disorders	91	80	86	103	87	107	67	44	28	10	8
Addiction	102	87**	102	101	67	97	65	45	30	17	13

Note. *p<0.01 and **p<0.05 compared to the initial level. ND: not determined.

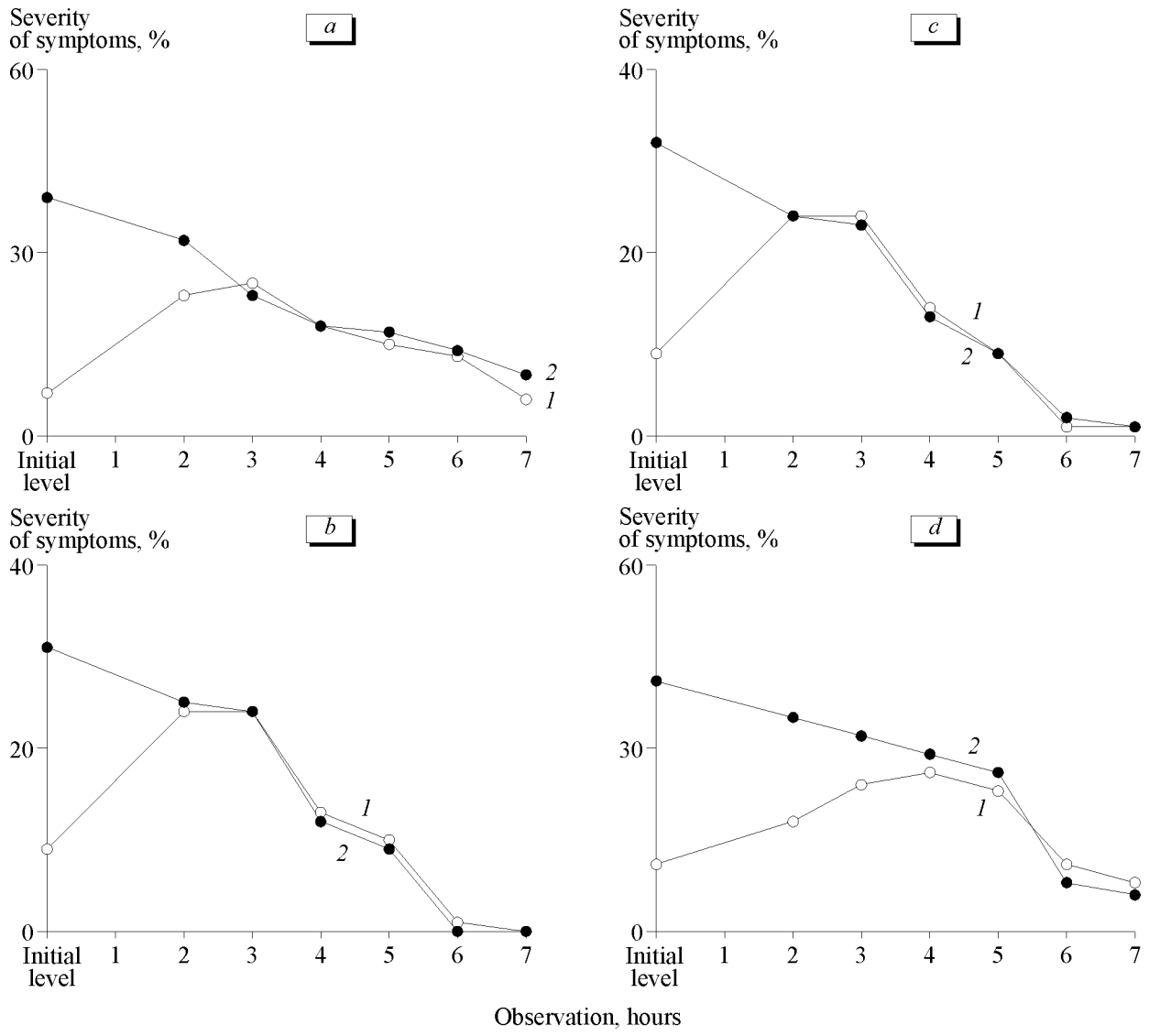

Fig. 4. Changes in the severity of somatovegetative (*a*), psychopathological (*b*), neurological, and pain symptoms (*c*) and drug addiction (*d*) during 7-day therapy.

ptoms disappeared over the first 4 days of therapy (yawning, watery eyes, salivation, sneezing, tremor, and gooseflesh). Sweating, anxiety, bustling, and pain in muscles and joint were reduced by days 6-7. ANAR improved sleep and appetite. Petulance, tachycardia, and drug addiction persisted for a longer time. On day 2 we observed a significant increase in blood pressure.

The patients were divided into 2 groups depending on their state before treatment. Group 1 included 34 patients with mild symptoms of OWS. The patients with moderate-to-severe or severe symptoms of OWS constituted group 2.

In patients of groups 1 and 2 the symptoms of OWS were present or absent during hospitalization. Group 1 patients took heroin immediately before hospitalization and were characterized by opium intoxication during the first examination. Group 2 patients with OWS symptoms consumed heroin in the earlier period. These observations indicate that in group 1 and 2 patients ANAR therapy started in the stage of opium intoxication and manifestation of OWS symptoms, respectively.

Changes in the total severity of OWS symptoms in patients of groups 1 and 2 reflected substitutive activity of ANAR [2,6,7]. The appearance of OWS symptoms in group 1 patients was delayed (Fig. 3, *a-d*). The first somatovegetative, psychopathological, neurological, and lobar symptoms of OWS and drug addiction were observed only 18-30 h after the start of therapy. It should be emphasized that in 18 patients of group 1, 2-3 treatments with ANAR were followed by long sleep (6-20 h). These changes also reflect the substitutive effect of ANAR. OWS symptoms were progressively reduced in group 2 patients (Fig. 4, *a-d*).

The differences between patients of various groups were less significant on day 3 of therapy. ANAR did not cause side effects.

Clinical studies showed that ANAR is potent in reliving somatovegetative and neurological symptoms in patients with heroin abuse accompanied by OWS.

The efficiency of ANAR is highly competitive with that of various pharmacological preparations, including Clophelin, Tiapridal, papaverine, and Pyrroxan. ANAR produces a less pronounced sedative effect and moderately affects drug addiction. ANAR delays the development of OWS in patients with opium intoxication by 18-30 h, which is of considerable practical importance. This phenomenon reflects the nonnarcotic substitutive effect of ANAR. ANAR holds much promise for the therapy of patients with postwithdrawal disorders and delayed OWS.

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