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Baclofen administration for the treatment of affective disorders in alcoholic patients

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Ninety alcoholic patients with the secondary affective disorders (anxiety, depression) were divided into four groups. Patients in the first group received $GABA_B$ receptor ligands (baclofen), those in the second group, diazepam, those in the third group, amitriptyline and those in the fourth group, placebo. The results of clinical, psychological (tests of Spielberger, Zung and MMPI), and electrophysiological (superslow ω-potential) investigations showed that baclofen is an effective drug for affective disturbances in alcoholic patients, with efficacy superior to placebo and equal to diazepam and amitriptyline. At the same time baclofen does not have the side-effects and complications of the latter. Significant changes in platelet MAO_B activity and the dopamine, serotonin and GABA concentrations in blood after treatment were not found in the four patient groups. The peripheral metabolism of GABA and monoamines do not seem to be related to the development of secondary affective disorders [redacted] receptor ligands.

Key words: alcoholism; anxiety; depression; baclofen

Introduction

Affective disturbances (anxiety, depression) are a typical part of the clinical picture of alcoholism. Affective disturbances may precede the development of alcoholism ('initial' affective disturbances), but more often 'secondary' affective disturbances take place. They appear after the alcohol withdrawal syndrome (AWS) has developed (Bokij, 1983; Schuckit and Monteiro, 1988). Affective disorders occurring in alcoholics in remission have a frequency of 5–30% [redacted] Schuckit and Monteiro, 1988). The diagnosis and adequate therapy of affective disturbances are an important aspect of the prevention of alcohol relapses (Erishev et al., 1988). Benzodiazepine tranquilizers are often used for the treatment of anxious and depressed alcoholic patients and antidepressants have a role to play (Linnoila, 1989; Meyer, 1989). Some authors consider that the administration of benzodiazepine tranquilizers for the treatment of affective disorders in alcoholics is inexpedient because of the high probability of developing dependence on these drugs (Miller and Gold, 1990), and also because of their side-effects (depriming action, stimulat- [redacted] post-stress adaptation, etc.) (Hallstrom, 1989). The lesions of the parenchymal organs, cardiovascular system and CNS, because of chronic alcohol intoxication, essentially increase the likelihood of antidepressant side-effects (Schuckit, 1986). Besides this, there is a high

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probability of serious complications induced by alcohol or disulfiram administration against the background of antidepressant treatment (Pary et al., 1988). All of this is relevant in the search for psychotropic drugs for treating affective disturbances in alcoholic patients. The investigation of drugs acting on the GABA-receptors independently of the benzodiazepine receptors is, in our opinion, valid. The rationale for this is the presence of common GABAergic links in neurobiological mechanisms of anxiety and depression (Paul, 1988). These concepts are suggested by a putative antidepressant action of diazepam (Tiller et al., 1989) and the suggestion that GABA is involved in the mechanism of action antidepressants (Lloyd et al., 1987; Mata

Baclofen is a selective ligand of $GABA_B$ receptors and does not act on benzodiazepine receptors and $GABA_A$ receptors complex (Feltz et al., 1987). It has been shown that baclofen has

1989) and in patients with panic disorders (Breslow et al., 1989). Baclofen therapy for affective disorders in alcoholic patients is especially interesting in view of its lack of addictive potential. The comparative investigation of anxiolytic action of ligands acting on $GABA_B$ receptors (baclofen) and benzodiazepines, whose action is mainly mediated by chloride channels of the $GABA_A$ receptor, is also of interest from a theoretical view.

Methods

The investigation was carried out on 90 alcoholic in patients with secondary affective disorders. All patients were abstinent for at least 3–4 weeks, i.e. their affective disturbances were not AWS symptoms. The affective disorders in all patients comprised mainly a combination of anxiety and subdepression, which is typical of the affective pathology in alcoholic patients. The patients were randomly divided into four groups (see Table I). For 3 weeks the

baclofen — 37.5 mg/day (first group), diazepam — 15 mg/day (second group), amitriptyline — 75 mg/day (third group), and placebo tablets by name (described B') (for the

The low doses of the amitriptiline were used because the affective disorders in all patients were not severe and had a subclinical nature. There were no significant differences in age, the duration of addiction, length of sobriety period, or the character of the leading syndrome.

The quantitative assessment of affective dis-

Table I. Characteristics of patients.

Group	Drug	Number of patients	Data about patients					
			Age	Duration of abstinence from alcohol (days)	Long duration of AWS (years)	Character of leading syndrome		
						Anxiously-depressive (%)	Astheno-depressive (%)	Depressive (%)
1	Baclofen (37.5 mg/day)	29	36.6 ± 1.1	45.1 ± 2.6	9.3 ± 1.1	51.7	34.5	13.8
2	Diazepam (15 mg/day)	20	38.3 ± 1.8	43.0 ± 2.2	9.8 ± 1.7	50	40	10
3	Amitriptyline (75 mg/day)	18	36.3 ± 1.9	40.9 ± 4.3	9.7 ± 1.4	55.5	22.3	22.2
4	Placebo	23	37.5 ± 1.7	40.7 ± 3.3	11.0 ± 0.9	56.6	30.6	13

orders, and thereby the evaluation of therapy, was measured on the Zung's test and depressive scale of MMPI (adapted by L.N. Sobchik in Russia (Sobchik, 1990)), which are valid methods for the diagnosis of depressive disturbances in alcoholic patients (Lippman et al., 1987; Tamkin et al., 1987), Spielberger's test (adapted by Yu.L. Khanin in Russia (Khanin, 1976)) for the evaluation of anxiety and also Taylor's anxiety scale of MMPI were used for the investigation of anxiety disorders in alcoholic patients (Erishev et al., 1988). All patients were tested before and after a 3-weeks course of pharmacotherapy.

In all patients blood platelet MAO-B activity and plasma levels of dopamine, serotonin, and GABA (the metabolic disturbances of which are associated with the development of affective disorders (Lidberg et al., 1985; Lloyd et al., 1987; Orlikov, 1991)) were determined before and after treatment. The dopamine concentration in blood was determined by Kogan's spectrofluorimeter method (Kogan and Netchayev, 1979); serotonin by the spectrofluorimeter method of Loboda and Makarov (Kolb and Kamyshnikov, 1976); GABA by the spectrofluorimeter method of Sutton and Simmond (Sutton and Simmonds, 1974); MAO_B activity was determined by the

Moskvitina 1988). Additional objective estimates of anxiety disturbances used the superslow electrophysiological processes, the ω-potential. This was measured by discrete omegametry. It has been shown that the values of ω-potential correlate with the severity of anxiety in alcoholic patients (Grinenko et al., 1989). The discrete omegametry was carried out by V.A. Illiukhina's method (Illiukhina, 1986). The ω-potential value was estimated over 5 min with a special amplifier and liquid chlorid/silver electrodes in vertex (once a minute) allowing for calculation of the average ω-potential

before and after treatment.

As a rule there is a peculiar dissociation between the expression of secondary affective disorders in alcoholic patients and the subjective

poor self-recognition of affective disorders) (Markovskaja, 1991). This often results in the absence of requests for therapy in alcoholic patients with secondary affective disorders. In order to minimize the placebo-effect we did not emphasise the treatment of the affective disturbances, but we told the patients that this pharmacotherapy was a component of the whole course of anti-alcohol treatment. All patients gave an informed consent to participate in the study, and the study conformed to local ethical practice.

Results and Discussion

The results of this clinical-psychological investigation showed that all four groups of patients showed a high level of reactive and personal anxiety on the Spielberger-Khanin test, anxiety on Taylor's scale of the MMPI, and also mild depression (subdepression) by Zung's test and MMPI depression scale. There were no differences between patient groups. Three weeks' treatment with baclofen, diazepam, and amitriptyline resulted in a statistically significant decrease in anxiety and depression scores (see Table II). Moreover, the results of all tests of the

from the placebo group in which no significant decrease in anxiety and depression were noted (Table II). The considerable clinical improvement in the active treatment groups corresponded to the positive results in the psychological tests (the patients became more tranquil, well-balanced, active and their mood was improved). Moderate sedative effects (sleepiness, flabbiness, etc.) were observed in some patients taking diazepam and amitriptyline, whereas our clinical observations found that baclofen administration was not accompanied by any side-effects. The clinically observed changes were in-

Thus, the anxiolytic and antidepressant action of baclofen in alcoholic patients with secondary affective disorders was similar to such typical tranquilizers and antidepressants as diazepam

ment with the previous data of Breslow et al.

Table II. Expressivity of affective disorders in alcoholic patients.

Group	Drug	Results of psychological test before and after treatment (mean ± S.E.)									
		Spielberger's test (reactivity anxiety)		Spielberger's test (personality's anxiety)		Zung's test		MMPI depressive scale		MMPI Taylor's anxiety scale	
		B	A	B	A	B	A	B	A	B	A
1	Baclofen	51.8 ± 1.5	40.4 ± 2.3$^{+,***}$	54.3 ± 1.4	44.1 ± 1.7$^{+,***}$	53.0 ± 1.4	40.5 ± 1.1$^{+++,***}$	86.7 ± 2.0	66.7 ± 2.5***	25.8 ± 1.7	16.3 ± 1.8$^{+++,**}$
2	Diazepam	51.8 ± 1.5	39.7 ± 1.9$^{+,***}$	51.2 ± 1.7	42.3 ± 1.4$^{+,***}$	54.2 ± 0.6	41.5 ± 1.7$^{+++,***}$	81.1 ± 3.3	68.2 ± 4.4*	27.0 ± 1.7	18.6 ± 2.1**
3	Amitriptyline	51.9 ± 2.6	39.4 ± 3.1**	53.3 ± 2.2	45.8 ± 2.5*	55.6 ± 1.2	44.7 ± 1.9$^{++,***}$	82.1 ± 1.5	67.1 ± 4.2**	25.5 ± 1.9	17.3 ± 2.4$^{+,*}$
4	Placebo	52.5 ± 2.9	47.1 ± 2.4	52.8 ± 1.9	49.7 ± 2.2	55.3 ± 1.0	53.2 ± 1.8	81.3 ± 3.9	76.1 ± 5.4	28.0 ±2.0	24.9 ± 2.5

Notes: (1) Difference between before and after treatment (Student's *t*-test): $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.
(2) Difference between group taken placebo and other ones: $^{+}P < 0.05$; $^{++}P < 0.01$; $^{+++}P < 0.001$.
(3) B: before treatment; A: after treatment.

Table III Biochemical indices in alcoholic patients with affective disorders (mean ± S.E.).

Group	Drug	MAO-B in blood platelets *nmol/mg.h*		GABA *(ng/ml)*		Serotonine *(μg/ml)*		Dopamine (ng/ml)	
		B	A	B	A	B	A	B	A
1	Baclofen	98.51 ± 7.1	103.16 ± 4.9	38.84 ± 2.7	42.27 ± 2.1	0.049 ± 0.003	0.039 ± 0.003	117.49 ± 8.1	103.13 ± 8.1
2	Diazepam	92.83 ± 5.1	108.81 ± 7.1	43.78 ± 2.9	44.36 ± 3.8	0.041 ± 0.003	0.044 ± 0.004	106.88 ± 8.7	104.83 ± 4.5
3	Amitriptyline	99.34 ± 5.3	106.58 ± 8.7	41.41 ± 1.8	45.08 ± 3.1	0.045 ± 0.003	0.048 ± 0.003	131.15 ± 11.4.	110.42 ± 6.3
4	Placebo	90.72 ± 4.1	94.88 ± 5.6	42.27 ± 3.6	39.59 ± 2.1	0.045 ± 0.002	0.046 ±0.003	129.59 ± 7.5	124.76 ± 11.6

Notes: (1) B: before treatment; A: after treatment.

(1989) on the anxiolytic action of baclofen in patients with panic disorders.

Baclofen compared favourably with the drugs by its absence of undesirable side-effects and complications connected with benzodiazepine tranquilizers and antidepressant administration.

The results of the biochemical investigations, unlike clinical-psychological ones, did not reveal significant changes (Table III). One must conclude that there is no relationship between the clinical expression of secondary affective disturbances in alcoholic patients and peripheral indices of disorders of the neuromediators studied in this work. The relationship previously discovered between affective pathology and metabolic disturbances of GABA (Lloyd et al., 1987, 1989), monoamine (Markelova et al., 1986; Orlikov, 1991) and MAO_B activity (Lidberg et al., 1985; Perris et al., 1984) is probably caused by differences of pathogenesis for the secondary affective disorders in alcoholic patients and in patients with affective disturbances of other aetiology. The correlation noted in our preceding work (Krupitsky et al., 1991) between the increase of MAO-B activity in blood platelets and GABA concentration in blood on the one hand and reduction of secondary affective disturbances in alcoholic patients induced by treatment with transcranial electrostimulation on the other hand, can be explained by the peculiarities of transcranial electrostimulation and its action on the central nervous system. At the same time, because of the results obtained in this work, this correlation can not be considered as evidence of direct pathogenetic reciprocity of GABA disturbances and monoamine metabolism with secondary affective disorders in alcoholic patients.

The investigation of superslow electrophysiological processes in vivo by discrete omegametry carried out in all four patient groups has shown that all active pharmacological treatments significantly decreased the values of the ω-potential by several mV, whereas these significant changes were not registered in the group of patients who took placebo (Table IV). Since it was shown earlier (Grinenko et al., 1989) that there is a correlation between the expression of reactive and personal anxiety by the Spielberger-Khanin test on the one hand, and value of ω-potential on the other hand, the data obtained in this work can be considered as objective electrophysiological confirmation of the positive clinical-psychological dynamics of anxiety observed in the active treatment groups.

Thus, the data of this clinical-psychological and electrophysiological investigation have shown that baclofen is an effective drug for the treatment of the secondary affective disturbances in alcoholic patients (anxious and depressive disorders) when compared to the action of diazepam and amitriptyline traditionally used in the treatment of anxiety and depression.

Table IV Dynamics of ω-potential in alcoholic patients with affective disorders.

Group	Drug	Value of ω-potential (mV) (mean ± S.E.)			
		D		S	
		B	A	B	A
1	Baclofen	23.74 ± 1.0	20.27 ± 1.5*	25.32 ± 1.2	21.44 ± 1.4*
2	Diazepam	28.78 ± 2.6	18.88 ± 2.5*	27.33 ± 2.8	18.30 ± 2.9*
3	Amitriptyline	23.58 ± 1.5	18.84 ± 2.1*	25.00 ± 1.5	19.25 ± 2.3*
4	Placebo	22.60 ± 3.6	22.20 ± 2.3	22.24 ± 3.4	22.20 ± 2.2

Notes: (1) B: before treatment; A: after treatment.
(2) D: right back of the hand; S: left back of the hand.
(3) See Table II (1).

Baclofen does not have the side-effects and complications of antidepressants and benzodiazepine tranquilizers (especially symptoms of dependence), which is a very important feature of baclofen allowing wider use in the therapy of alcoholic patients.

The results of this investigation have also shown that the action of selective ligands of $GABA_B$ receptors (baclofen) in alcoholic patients have comparable efficacy to diazepam, the action of which is mediated through the chloride channel of $GABA_A$ receptors. This opens new avenues in the search for drugs among $GABA_B$ receptor ligands for treatment of affective pathology.

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