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Aprotinine (Contrykal®) in the Differential Pharmacotherapy of the Opiate Withdrawal Syndrome

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Case studies in heroin addicts with opiate withdrawal syndrome (OWS) had shown good therapeutic effects after infusions (i.v.) of peptidase inhibitor aprotinine in some but not all patients. This study aims to reveal possible relationships between the pattern of OWS and the therapeutic efficacy of aprotinine. Two groups of heroin addicts with OWS – group 1 (70 patients) and group 2 (50 patients) – received standardized pharmacotherapy. Complementary, group 1 received one i.v. infusion of aprotinine and group 2 received i.m. injections of tramadol hydrochloride. At baseline and then daily for 5 days the severity of OWS symptoms was estimated by a 4-score scale in both groups. The treatment was more effective in group 1 (aprotinine). Within this group three subgroups were distinguished according to high, intermediate and low effectiveness of the aprotinine therapy. The effectiveness of aprotinine therapy was higher the more pronounced algesic and autonomic symptoms and the less depressive symptoms there were. Accordingly, a predominance of depressive disorders could correlate with less favourable treatment results. *J Clin Basic Cardiol 2000; 3: 187–9.*

Keywords: aprotinine, opiate withdrawal syndrome, complementary therapy, differential pharmacotherapy

Withdrawal syndrome in patients with heroin addiction and its control is the subject of great therapeutic efforts concerning the search for non-narcotic remedies for its elimination, in order to avoid treatment programs which include opiates or their derivates. The pattern of the opiate withdrawal syndrome (OWS) presents algesic, autonomic, emotional, psychopathic, hypochondriac, dyssomnic and other symptoms.

Our preliminary clinical observations based on the experimental data by S. K. Sudakov [1] have shown a good therapeutic effect after infusions (i.v.) of the peptidases inhibitor aprotinine in cases where algesic and autonomic disorders dominated in the OWS. In other patients the use of aprotinine was less effective or ineffective. The present study is aimed to reveal possible reasons for the differences in therapeutic effectiveness of aprotinine and to differentiate clinical indications for its use.

Material and Methods

One hundred and twenty (120) heroin addicted in door-patients (80 men, 40 women), were included in the present study. Prevailing ages were 18–20 years (31 patients), 21–23 years (39 patients) and 24–26 years (27 patients). The duration of the disease was to 1 year in 31 patients, from 1 to 2 years in 40 patients, from 2 to 3 years in 36 patients, from 3 to 4 years in 10 patients, and over 4 years in 3 patients. All patients had clear signs of OWS. Patients with other major mental, neurologic and somatic diseases were not included in the study.

The patients were included on the day after admission to the hospital and randomly allocated to either group 1 (70 patients) or group 2 (50 patients). The groups were comparable by age, gender and duration of the disease. All patients received a standardized treatment for elimination of the withdrawal symptoms. The treatment included theralene, clonidine, pyrroxane, thiapridal, diazepam, potassium and magnesium salts, vitamins, non-narcotic analgetics. The patients in group 1 were given a single infusion (i.v.) of aprotinine (Contrykal®, ASTA Medica AG) at a dose of 30.000 antitripsine units, and the patients in group 2 were given injections (i.m.) of analgetic tramadol hydrochloride prescribed at doses of 50–100 mg 3–4 times a day for 2–4 days.

Patients' condition was examined dynamically, on a basis of quantification of the OWS symptoms by a 4-score scale ("0" – no symptoms, "3" – maximal intensity of symptoms). Algesic conditions (including painful senestopathia), autonomic symptoms (chill, sweating, sneezing, rhinorrhea, anorexia, nausea, diarrhea, cyanosis), depression (including dysphoric and apathic conditions) and craving for drug (subjective desire, narcotic night dreams, torturing feeling of discomfort) were scored separately. The general withdrawal index was calculated as a sum of scores of the separate scales. The patients were evaluated before treatment (baseline), at 1 hour, at 5 hours, at 1 day and then daily for 5 days during treatment. The statistical significance of differences between groups was tested with the Student's test for either paired or unpaired data (comparison between group 1 and group 2 at baseline and after treatment and between subgroups of group 1). Probability values less then 0.05 were regarded as statistically significant.

Results

The data reflecting the intensity of OWS in the two groups of patients indicated more effective treatment in group 1 (Table 1). Algesic and autonomic symptoms were found to be especially sensitive to the therapeutic effect of aprotinine. Less distinct were the differences between the two groups regarding the dynamics of depression symptoms.

The analysis of the treatment related dynamics of the integral OWS index in group 1 revealed four sub-groups: in subgroup 1 (19 patients) the effect of aprotinine infusion was distinctly positive, ie, arresting the symptoms of the OWS. The effects of sedation and relaxation appeared quickly; painful sensations, chill, sweating, feeling of discomfort completely disappeared; a grayish-pale color of the skin changed into normal. Generally, patients fell asleep during the infusion of aprotinine already and slept up to 5 hours. After waking up a restoration of appetite, even mood, and absence of craving for drug was observed. During the next day algesic

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symptoms usually reappeared but in a less severe form – flying, unstable arthralgias or the feeling of "tiredness" in muscles. Patients described the condition as "tolerable". These residual symptoms were controled by non-narcotic analgetics. Autonomic disorders did not reappear on the next day, the only persistent complaint was the unstable sleep. The behaviour and emotional state of the patients did not present any special therapeutic problems during the first five days.

In subgroup 2 (30 patients) the direct effect of the aprotinine infusion manifested by marked decrease of algesic and autonomic symptoms, general relaxation, relief of the sense of indisposition, disappearance of behavioural deviations – importunity, capriciousness, hypochondria. Yet the depressed mood remained in those patients and prevented them from the positive estimation of the evident improvement of their condition. During the observation period, craving for drug, light depression, sleeplessness reappeared. This was the reason to prescribe the administration of antidepressants on the 5th or 6th day following the treatment with aprotinine which proved to be effective.

In subgroup 3 (16 patients) the direct effect of the aprotinine infusion was not so apparent and consisted only in modification of pains into unpleasant and vague sensations similar to the feeling of muscular discomfort and general indisposition. During the entire period of observation, a dysphoric depression, craving for drugs, insomnia, hypochondria, tendency to conflicts, discontent on every occasion, insubordination prevailed in those patients. This required prescribing a complementary combined therapy with neuroleptics, antidepressants, anticonvulsants and tranquilizers.

In subgroup 4 (5 patients) the patients' condition at baseline was determined by psychopathic, depressive-dysphoric symptoms and craving for drug. Algesic and autonomic symptoms were not so pronounced. In these cases the aprotinine infusion did not have any noticeable positive effect.

In the subsequent analysis the 3rd and 4th subgroup were pooled together into one subgroup 3, characterized by the predominance of depressive-dysphoric symptoms combined with craving for drug in the pattern of OWS. In this combined group aprotinine had no satisfactory therapeutic effect.

Contrary to this, the aprotinine infusion had a very good therapeutic effect in subgroup 1 with predominance of algesic and autonomic symptoms in the OWS pattern. In subgroup 2, with algesic and depressive symptoms in the pattern of OWS the aprotinine infusion had only limited therapeutic effect.

The craving for drug symptom estimated at baseline by scores was pronounced in the three subgroups nearly equally (subgroup 1: 2.1 ± 0.6; subgroup 2: 2.1 ± 0.8; subgroup 3: 2.2 ± 0.8) and so could not be used for differentiating. During 3rd–5th day following the treatment with aprotinine, though, considerable inter-group differences in the intensity and dynamics of craving for drug occured: in subgroup 2 there was an increase in craving for drug almost up to baseline values after a transitional lowering, and in the subgroups 1 and 3 the craving for drug dynamics had an undulating nature and decreased in general to the 5th day (Table 2).

Hence, the initial predominance of depressive symptoms in the pattern of OWS was the unfavourable prognostic sign in regard to the effect of aprotinine on the integral OWS index and especially on the craving for drug symptom.

Discussion

The data presented here have shown the clinical heterogeneity of OWS in the process of treatment of heroin addicted patients with aprotinine. That, in turn, could determine the differentiation of the OWS treatment. A presence and an intensity of depressive disorders in the pattern of OWS, and their relationship to algesic and autonomic syndromes appeare to be of special relevance. It has been known that the OWS symptoms are diametrically opposite to the symptoms of the direct pharmacological effect of opiates. Therefore, different patterns of OWS suggest different clinical effects of opiates. This has been illustrated [2] in rats of two different, genetically pure lines. According to these data the analgesic effect of morphine, which corresponds to the algesic syndrome in the pattern of OWS, was prominent in the one line of rats and was very weak in the other one. Besides, rats not responding to the analgesic effect of morphine were distin-

Table 1. Integrated OWS index and its main components in patients of both groups (therapeutic dynamics by scores (mean ± SD))

	Baseline		During treatment									
			1st hour		5th hour		1st day		3rd day		5th day	
	group 1	group 2	group 1	group 2	group 1	group 2	group 1	group 2	group 1	group 2	group 1	group 2
OWS index	1.6 ± 0.3	1.6 ± 0.3	0.9 ± 0.2	1.6 ± 0.3*	0.7 ± 0.2	1.3 ± 0.3*	0.9 ± 0.2	1.1 ± 0.2*	0.8 ± 0.3	1.0 ± 0.2*	0.7 ± 0.3	1.0 ± 0.2*
Algesic component	1.9 ± 0.2	1.9 ± 0.2	0.9 ± 0.3	1.9 ± 0.2*	0.6 ± 0.3	1.9 ± 0.2*	1.0 ± 0.4	1.5 ± 0.3*	0.8 ± 0.4	1.5 ± 0.2*	0.5 ± 0.4	1.0 ± 0.1*
Autonomic component	1.6 ± 0.4	1.6 ± 0.4	0.8 ± 0.3	1.5 ± 0.2*	0.5 ± 0.2	1.5 ± 0.2*	0.7 ± 0.3	1.4 ± 0.2*	0.3 ± 0.1	1.0 ± 0.2*	0.2 ± 0.1	0.8 ± 0.1*
Depressive component	1.6 ± 0.2	1.6 ± 0.2	1.0 ± 0.2	1.5 ± 0.2*	0.9 ± 0.2	1.5 ± 0.2*	0.9 ± 0.2	1.5 ± 0.2*	0.8 ± 0.2	1.3 ± 0.2*	0.8 ± 0.2	1.3 ± 0.2*
Craving for drug	2.1 ± 0.6	2.1 ± 0.6	1.2 ± 0.6	2.1 ± 0.5*	1.6 ± 0.6	2.0 ± 0.5	1.5 ± 0.5	2.0 ± 0.4	1.4 ± 0.6	1.8 ± 0.5	1.2 ± 0.4	1.9 ± 0.4*

The statistical significance was determined by comparison with baseline values; * $p < 0.05$

Table 2. Craving for drug in group 1 (aprotinine) according to therapeutic effect (estimation by scores (mean ± SD))

Subgroups	Baseline	1st hour	5th hour	1st day	3rd day	5th day
Subgroup 1 (n = 19)	2.1 ± 0.6	1.2 ± 0.6*	1.5 ± 0.6*	1.5 ± 0.6*	1.3 ± 0.6*	1.0 ± 0.6*
Subgroup 2 (n = 30)	2.2 ± 0.8	0.8 ± 0.8*	1.4 ± 0.8*	1.4 ± 0.8*	1.7 ± 0.8	1.7 ± 0.8
Subgroup 3 (n = 21)	2.1 ± 0.8	1.6 ± 0.8*	1.8 ± 0.5	1.7 ± 0.8	1.1 ± 0.8*	0.8 ± 0.8*

The statistical significance was determined by comparison with baseline values; subgroup 1: high therapeutic effect; subgroup 2: intermediate therapeutic effect; subgroup 2: low therapeutic effect; * $p < 0.05$

guished by a lower activity of the serotonine system. This fact becomes especially meaningful in the light of the data regarding the role of the serotonine system in the pathogenesis of depressions [3–5]. Although the results of animal experiments cannot be transferred unconditionally to a clinical setting, they might show a possibility of the existence of genetically determined differences in OWS pattern which should be studied and taken into account when developing differentiated treatment programs for opiate addicted patients. It is quite possible that these differences relate not only to OWS but also to the symptoms of other stages of the disease.

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