The Use of Naloxone in Small Doses in Complex Therapy of Postabstinent Heroin Syndrome: Enkephalinase Mechanisms

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The use of naloxone hydrochloride (0.2-0.4 mg) in complex therapy of adolescent heroin addicts significantly prolonged the half-life of serum leu-enkephalin, slightly elevated the thresholds of thermal nociceptive reactions, and improved some clinical indices (considerably reduced drug addiction, eliminated affective disorders, *etc.*), which are important for deactualization of drug addiction and promoting remission.

Key Words: *naloxone hydrochloride; enkephalinase activity; heroin addiction; thermal nociception*

Exogenous morphine or morphine-like agents (*e.g.*, heroin) potentiate the release of endogenous opioids such as β-endorphin in the plasma, cerebrospinal fluid (CSF), and brain structures [13,15] and met-enkephalin and dynorphin in CSF [14]. At the same time, morphine-tolerant animals are characterized by low content of endogenous opioids in cerebral structures, pituitary, and plasma [12]. This phenomenon can be explained by sharp activation of endopeptidases (in particular, enkephalinase A, EC 3.4.24.11) in response to enhanced release of endogenous opioids [4]. Since re-uptake of endogenous opioids was never demonstrated, their content is assumed to be controlled by respective peptidohydrolases [1]. Low content of endogenous opioids characteristic of tolerant state leads to disappearance of analgesic effect of narcotic preparations. This is the reason for increasing the dose for attaining analgesia and a motivation-forming factor and neurochemical basis of drug abuse. Animal experiments showed that naloxone in low doses inhibited enkephalinase [6,7] and suppressed morphine intake in experimental animals in a free choice paradigm [3]. In this connection, it was interesting to study the possibility of using naloxone in low doses in the complex therapy of postabstinent heroin syndrome for correction of opioid synthesis and catabolism disturbed by chronic drug intake. This approach is based on firmly established biochemical determinancy of psychiatric pathologies and drug addiction [8]. The necessity to study fundamental neurobiological mechanisms underlying symptoms of drug abuse and the possibility of their correction at the level of neurotransmitter and enzyme systems is acknowledged by most authorities [2]. Only this approach can underlie the pathogenically based therapy that can be recommended for clinical application.

MATERIALS AND METHODS

We examined 14-18-year-old male adolescents admitted to Children and Adolescent Department, Research Institute of Drug Abuse. All patients were opioid addicts with formed abstinent syndrome. The severity of abstinent syndrome, the time course of drug addiction, and the severity of postabstinent disorders were scored before and after treatment. Starting from day 15 after heroin withdrawal, the patients of the main group (n= 11, heroin addicts for 1 year and longer) received daily intravenous injections of naloxone hydrochloride in

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doses of 0.2-0.4 mg (depending on the threshold of the thermonociceptive reactions) for 10 days. General state of the patients and thresholds of thermonociceptive reactions (reflecting the state of endogenous opioid system [5]) were daily assessed. The total serum enkephalinase activity (EA) was measured by M. V. Gabaeva and O. Yu. Sokolov (Laboratory of Pathophysiology, Research Center of Mental Health, Russian Academy of Medical Sciences). The blood was drawn on days 1, 5, and 10 of naloxone treatment. EA was assessed by measuring radioactivity of ^{3}H-leu-enkephalin degradation products isolated by thin layer chromatography [9]. Apart from naloxone, the patients received standard therapy (neuroleptics, antidepressants, and tranquilizers). The control group patients (n=18) received the same standard therapy without naloxone. Serum EA in 6 age-matched students of Moscow Medical Academy never used narcotics was taken as the control. The results were analyzed by Student's t and Wilcoxon's tests using STADIA software.

RESULTS

In the control group (patients not treated with naloxone) leu-enkephalin half-life ($T^1/_2$) markedly decreased to hospital day 15 (detoxification period). In 70% patients this decrease correlated with a decrease in thermonociception threshold. Clinically, these patients were characterized by actualization of drug addiction. To hospital day 30, $T^1/_2$ of leu-enkephalin continued to decrease (p<0.001, Fig. 1) and serum EA increase. The most drastic decrease in $T^1/_2$ was found in 5 patients (from 1.25 to 0.17 min, from 1.36 to 0.4 min, and from 2.86 to 0.45 min, *etc*.).

In the control group, the thresholds of thermonociceptive reactions decreased to hospital day 30. In 69% patients the nociceptive threshold decreased compared to days 1 and 15. These changes and increase in EA attest to hypofunction of the endogenous opioid system. Correction of this hypofunction is a prerequisite for successful treatment and long-term remission, because hypofunction of the opioid system determining extremely low opioid content in the major behavior-forming brain structures is a motivation factor of addiction relapse. An increase in leu-enkephalin $T^1/_2$ on hospital days 15-30 was observed in some patients (30%) with shorter history of drug abuse, although only in 3 of them this index approximated the normal, whereas in others it tended to increase but remained 2-3 times below the normal.

In the experimental group, the time course of total EA was opposite (Fig. 1). Starting from hospital day 15 (first naloxone injection), leu-enkephalin $T^1/_2$ gradually increased in all patients (p<0.001) and EA returned to normal. On hospital day 30, $T^1/_2$ remained below the normal in only 2 patients (1.15 and 1.00 min, respectively). However, it should be taken into account that leu-enkephalin $T^1/_2$ in these patients before naloxone treatment was extremely low (0.50 and 0.28 min, correspondingly). Therefore, even in these patients this parameter increased by 2-4 times and EA decreased. The thresholds of thermonociceptive reactions in these patients also increased.

In parallel with the above changes, the patients of the experimental group demonstrated improvement in some clinical indices starting from day 2 of naloxone treatment. The patients reported mood improvement and appearance of physical comfort. At discharge, all patients of this group demonstrated pronounced reduction of drug addiction and disappearance of affective disorders. On the whole, small doses of naloxone hydrochloride were highly efficient in the treatment of postabstinent state in heroin addicts. The dynamics of leu-enkephalin $T^1/_2$ attests to the necessity of earlier inclusion of naloxone in low doses in the therapy of early stages of heroin abstinence. This regimen can prevent the decrease in leu-enkephalin content observed on hospital day 15 and accelerate remission without abstinence aggravation on days 14-15. Traditional concept on the use of naloxone in high doses for correction of acute intoxication is based on its antagonism with opioids. It was also reported that single intravenous injections of naloxone (0.4 and 1.92 mg) abolished symptoms of acute intoxication in addicts [10, 11]. In animal experiments we showed that naloxone in low doses (0.1-0.7 mg/kg) produces an analgesic effect via inhibition of enkephalinase, which restores the disturbed balance between the synthesis

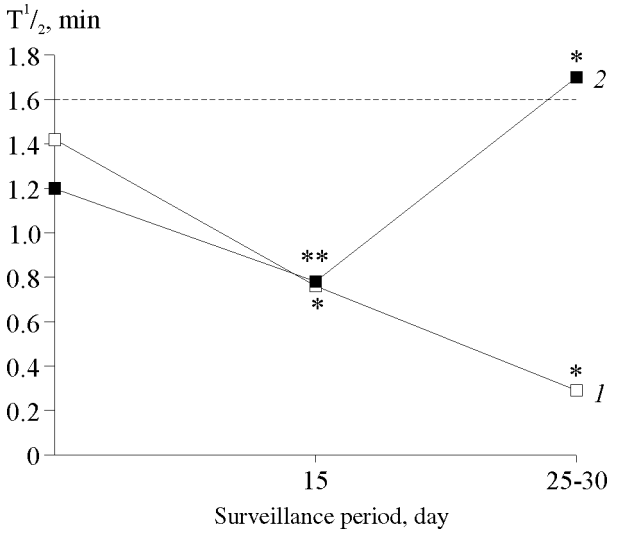

Fig. 1. Half-life ($T^1/_2$) of leu-enkephalin in serum of heroin addicts not treated (*1*) and treated with naloxone (*2*) as a component of complex therapy. The first naloxone injection was made on observation day 15. *p<0.001 and **p<0.01 compared to the initial values at admission. Dashed line shows the normal.

and degradation of endogenous opioids. It also activates the synthesis of endogenous opioids in the CNS and suppresses the motivation-forming factor of drug addiction relapse [4]. When used in doses equal or above 0.7 mg/kg, naloxone produces hyperalgesia and acts as an opioid antagonist. In the doses used in this study (0.1-0.4 mg), naloxone does not potentiate abstinence and improves therapeutic efficiency.

Therefore, in contrast to available published data [10,11], our findings suggest that efficiency of naloxone in low doses as a component of complex therapy of heroin addiction is determined by inhibition of enkephalinase, which advances new neurobiological arguments for application of naloxone in clinical practice.

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