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Pharmacological Correction of Neurological Disorders in Case of Multiple Sclerosis

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Abstract. The article analyzes the possibility of drug correction of common neurological disorders (pain, anxiety, depression, insomnia) using antidepressants under the conditions of experimental equivalent of multiple sclerosis on the background of basic drug therapy with methylprednisolone.

Assessment of antidepressants antinociceptive potential identified "a range of activity" of the mentioned medicines (analgesic activity of classical amitriptyline antidepressant was accepted as conventional unit): paroxetine (0.9 c.u.), amitriptyline (1 c.u.), fluoxetine (1.11 c.u.) and trittico (1.16 c.u.).

Comparative analysis of the duration of animals' fading in the water at the forced swimming (Porsolt forced swimming test) found that the ability to weaken the level of anxiety and concern was the most significant for trittico and paroxetine groups. Immobilization time was 1.7 ($p \leq 0.05$) and 1.6 ($p \leq 0.05$), respectively, which was shorter than the corresponding figures of the active control group. The effect of antidepressants on latency, sleep duration when administered on a background of basic drug therapy with methylprednisolone was characterized by the following indicators: trittico (-66.5% and + 133.45%)≥fluoxetine (-60.5% and + 117.79%)≥paroxetine (-61.8% and + 93.59%)≥amitriptyline (-52.75% and + 81.85%).

Thus, trittico and paroxetine were reasonable to administer under the experimental equivalent of multiple sclerosis taking into account the basic hormonal therapy as a means of drug correction of pain, anxiety, depression and sleep disorders.

Keywords: multiple sclerosis; pain; antidepressants; depression; sleep.

Problem statement and analysis of the recent research

Multiple sclerosis (MS) is a disease with a chronic progressive course characterized by the formation of demyelination foci in the brain and spinal cord as a result of an autoimmune response to myelin implemented by T-lymphocytes. Site of inflammation is formed at the site of scar tissue. These plaques on nerve fibers conduct impulses break from the brain to executive powers: it complicates voluntary movements and speech, reduced sensitivity [2, 11]. The earliest signs of MS appear when about 50% of the nerve fibers are already affected. At this stage of disease the following complaints appear in patients:

- uni- or bilateral visual impairment;
- pain and double vision;
- numbness and tingling in the fingers;
- reduced skin sensitivity;
- muscle weakness;
- movement coordination disorders.

The main effort in the treatment of MS should be aimed at reducing the severity of the process, the effective prevention of relapses, prolongation of remission, slowing the rate of disability and thus increase in functional activity and quality of life of patients. MS treatment at this stage is based on the appointment of immunotropic means [4]. Medications used in the treatment of MS are means of pathogenetic, symptomatic and reparative therapy. In recent years, significant progress in pathogenetic therapy of MS aimed at preventing the destruction of brain tissue activated by T-cells of the immune system and toxic substances has been made.

According to the recommendations of the "Protocol of Management of Patients with Multiple Sclerosis" MS therapy should be started with hormones. Glucocorticoids are the main tools in the treatment of MS exacerbations. The most effective drug of this group is methylprednisolone for intravenous use (level of evidence A) [1, 8]. This remains a problem of correction of neurological disorders (pain, depression, sleep disorders, etc.) in patients with multiple sclerosis whose prevalence for this disease is quite widespread. [1]

The objective of the research was the experimental evaluation of analgesic, anti-depressive, hypnotic action of antidepressants (amitriptyline, fluoxetine, paroxetine and tryttiko) in rats with experimental equivalent of MS (EEMS) on a background of drug therapy by methylprednisolone.

Materials and methods of the research

The study was conducted as part of research work of the Department of Pharmacology and Clinical Pharmacology at Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine. The research work was "non-opioid analgesics in Systemic pharmacology and medical facilities to protect the brain under conditions of pathological conditions" (DR № 0114U000935). The experiment was performed on 48 white purebred rats weighing 180-230 g kept in standard vivarium conditions SE "DMA Ministry of Health of Ukraine". [6] By random sampling rats were divided into 6 groups (n = 8): group I - active control (EEMS); group II - methylprednisolone (methylprednisolone EEMS + (M) in a dose of 3.4 mg / kg); group III - EEMS + M + amitriptyline (10 mg / kg); IV - EEMS + M + fluoxetine (25 mg / kg); V - EEMS + M + tryttiko (40 mg / kg) and VI - EEMS + M + paroxetine (8 mg / kg). Input encephalitogenic emulsion in a base of rat's tail was applied for reproduction of EEMS [7]. Evaluation of antinociceptive activity of antidepressants was conducted by electrical stimulation of the rat's tailhead [10]. Assessment of pain sensitivity was performed by the reaction of vocalizations (central component forming nociceptive response) in the initial state and in 90 minutes after a single oral administration of antidepressants study. Study of anti-depressant activity was performed using Porsolt forced swimming test (test of forced or compulsory swimming) [9]. Analysis of hypnagogic action was performed on two indicators, namely time falling asleep animals (latent period) and sleep duration; sleep medication caused by the introduction of thiopental sodium (30 mg / kg) [3]. All the data were processed in conventional biomedical research with the use of methods of statistical analysis using standard software packages. Mathematical treatment involved taking the average values (M), their errors (± m). Authentication of intergroup differences in pain limit values of the indicator reaction was performed using parametric Student's t-test, Wilcoxon Rank-Sum test, Mann-Whitney test and method of analysis of variance (ANOVA). The differences were considered statistically significant at the level of $p \leq 0.05$. Before using parametric criteria audited hypothesis of normal distribution of random variables [5].

Results and discussion of the research

The first stage of the study was to create EEMS: changes in animals' peak formed on 7th day of the study; for the next 5 days, rats received methylprednisolone (M) in a dose of 3.4 mg / kg as a means of basic pathogenetic therapy. Under these conditions indicators registered nociceptive response to gradually increasing electrical stimulation in the rat headtail in the initial state (5-day introduction M) and 90 minutes after the use of antidepressants.

In the initial state the conditions prevailing EEMS against the background of basic therapy methylprednisolone response to electrical stimulation in the rat's tail all groups were registered at the level of 1.35 ± 0.12 (group V) and 1.48 ± 0.1 (group IV). Under these conditions animal were treated with antidepressant agents intragastrointestinally once. The results are presented in Fig. 1. The studied potential of analgesic drugs was quite high. Thus, the maximum analgesic activity was observed against the background of the introduction of fluoxetine and tryttico that manifested an increase in pain limit of 2.7 ($p \leq 0.05$) and 3.1 ($p \leq 0.05$) times compared to those of the initial state; with analgesic potential of amitriptyline for 90 minutes amounted to 166.2% ($p \leq 0.05$). In addition, moderate analgesic effect of methylprednisolone passive control group (II) against the background of its 5-day administration (+ 39.2%; $p \geq 0.05$) indicators was registered on the initial state.

Comparative analysis of antinociceptive potential of antidepressants identified "a number of activity" of these facilities (analgetic classical antidepressant activity of amitriptyline taken as a conventional one), paroxetine (0.9 c.u.), amitriptyline (1c.u.), fluoxetine (1.11 c.u.) and tryttiko (1.16 c.u.).

In the active control group of animals duration of sinking in water at forced swimming (Porsolt test) was the highest and constituted 209.4 ± 11.9 seconds (Fig. 2) which corresponded to a high level of anxiety and concern. When using antidepressants, immobilization time decreased in the amitriptyline group to 27.75% ($p \leq 0.05$), for fluoxetine to 33.43% ($p \leq 0.05$), for tryttiko to 48.05% ($p \leq 0.05$) and paroxetine to 46.7% ($p \leq 0.05$). The ability to weaken the level of

anxiety and concern was the most significant for groups of tryttiko and paroxetine, immobilization time was in 1.7times ($p \leq 0,05$) and 1.6 ($p \leq 0,05$) according shorter compared to the active control group index . Many patients with multiple sclerosis observed sleep disorder usually caused by secondary factors such as stress, spasticity, limited physical activity or depression. So, the next stage of work was to evaluate the hypnagogic action of antidepressants in rats with EEMS, the results of which are presented in the Table 1.

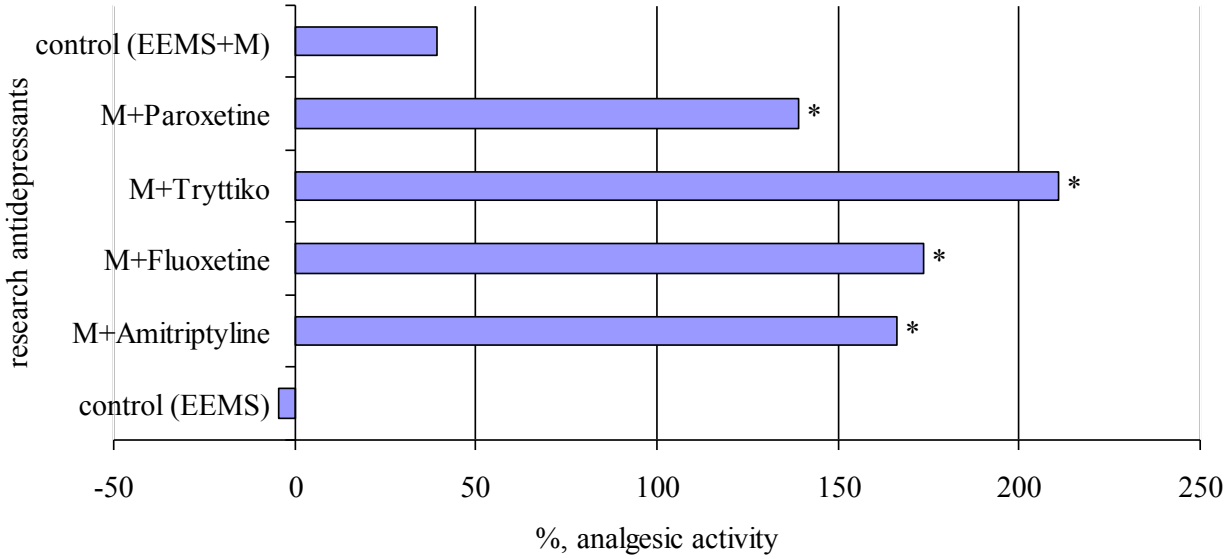

Fig. 1. Antinociceptive potential of antidepressants in electrical stimulation of rats' headtail under EEMS (90 mins) against pharmacotherapy methylprednisolone.

Note. * - $p \leq 0.05$ performance against original state.

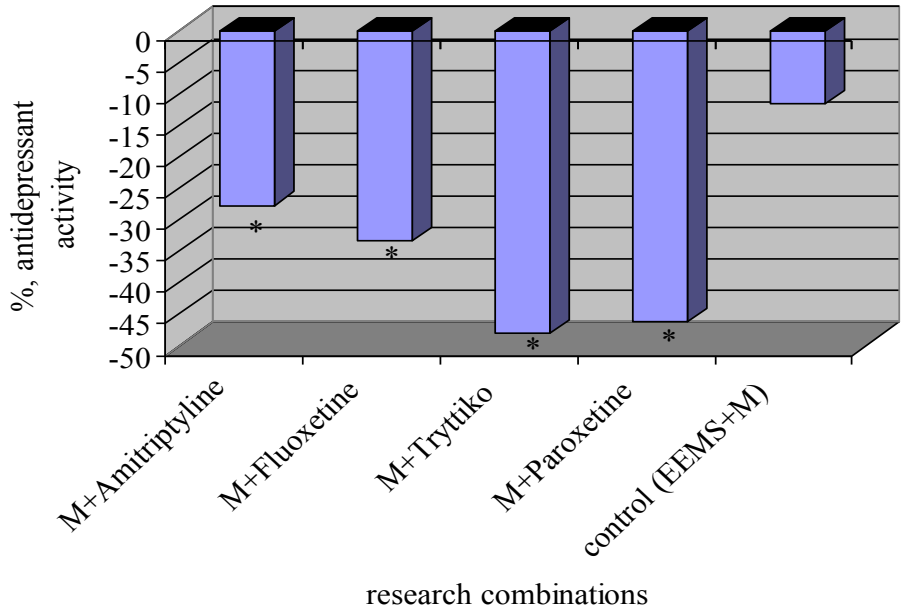

Fig. 2. Changes of immobilization time against the background of the introduction of antidepressants in rats with EEMS against the background of pharmacotherapy by metlprednizolone

Note. * - $p \leq 0.05$ performance against original state

Table 1

Assessment of the impact of antidepressants on sleep medication parameters in rats with EEMS against the background of pharmacotherapy by methylprednisolone

Research groups	Sleep Time (latent period)	Sleep Time (duration of sleep)
EEMS (active control)	61.8±13.1	28.1±3.65
EEMS + M	55.6±12.0	35.1±3.34
EEMS + M + Amitriptyline	29.2±5.56	51.1±5.40
EEMS + M + Fluoxetine	24.4±5.78	61.2±7.81
EEMS + M + Tryttiko	20.7±3.25	65.6±8.28
EEMS + M + Paroxetine	23.6±4.21	54.4±6.87

Note. * - p≤0.05 relative performance of active control

The active control group duration slumber was 61.8 ± 13.1 sec; group II (EEMS + methylprednisolone 3.4 mg / kg) and rats fell asleep concerned, but rather (55.6 ± 12.0 seconds). Thus, the sleep in the first group compared with group II was shorter by 24.9% (p≥0.05).

Using antidepressants to hormone therapy background basic one-way speaker with methylprednisolone reducing latency and increasing sleep duration was observed. So, against the background of the introduction of amitriptyline and paroxetine sleep in rats was longer EEMS by 81.85% (p≤0.05) and 93.59% (p≤0.05) respectively compared to the control group.

When using fluoxetine and tryttiko a parameter was the most significant, namely in 1.74 (p≤0.05) and 1.86 (p≤0.05) times in group II performance. Thus, the influence of antidepressants on latent period and duration of sleep when administered on a background of basic drug therapy methylprednisolone was characterized by the following indicators: tryttiko (-66.5% and + 133.45%) ≥ fluoxetine (-60.5% and + 117.79%) ≥ paroxetine (-61.8% and + 93.59%) ≥ amitriptyline (-52.75% and + 81.85%).

Conclusions

1. The experimental equivalent of MS antidepressants retain specific pharmacological activity, show a strong analgesic effect and help to increase the duration of sleep medication.
2. Subject of the basic hormone therapy of EEMS as a means of pharmacological therapy of pain, anxiety, depression and sleep disorders are the most appropriate to appoint tryttiko and paroxetine.

Prospects for further research involve further defining of the features of antidepressants influence on approximately research function of the central nervous system to improve adjuvant analgesic therapy of nociceptive displays in multiple sclerosis.

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