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

- uni- or bilateral visual impairment;
- pain and double vision;
- numbness and tingling in the fingers;
- reduce 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 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 - is means of pathogenetic, symptomatic and reparative therapy. In recent years, significant progress in pathogenetic therapy of MS, which is aimed at preventing the destruction of brain tissue activated by T- cells of the immune system and toxic substances.

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

The aim of the current study was the experimental evaluation of analgesic, anti-depressive, hypnotic's 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

The study was conducted as part of research work of the Department of Pharmacology and Clinical Pharmacology of State Establishment "Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine" "non-opioid analgesics Systemic pharmacology and medical facilities protect the brain under conditions of pathological conditions" (DR № 0114U000935). The experiment was performed on 48 white purebred rats weighing 180-230 g, are kept in standard vivarium conditions SE "DMA Ministry of Health of Ukraine". [6] By random sampling rats were divided into 6 groups (n = 8): I - active control (EEMS); II - methylprednisolone (methylprednisolone EEMS + (M) at a dose of 3.4 mg / kg); 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). For playback of EEMS applied input encephalitogenic emulsion in a base of rat's tail [7]. Evaluation of antinociceptive activity of antidepressants was carried out by electrical stimulation of the root of the tail of rat [10]. Assessment of pain sensitivity was performed by the reaction of vocalizations (central component forming nociceptive response) in the initial state and on 90 minutes after a single oral administration of antidepressants research. Study of anti-depressant activity performed in the test - model of Porsolt (test of forced or compulsory swimming) [9]. Analysis hypnagogic action performed on two indicators: 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 processed in conventional biomedical research methods of statistical analysis using standard software packages. Mathematical treatment involves taking the average values of (M), their errors (± m). Authentication of intergroup differences in pain threshold values of the indicator reaction was performed using parametric Student's t-test, Wilcoxon test rank sums (Wilcoxon Rank-Sum test), Mann-Whitney and method of univariate analysis of variance (ANOVA). The differences are considered statistically significant at the level pd"0,05. Before using parametric criteria audited hypothesis of normal distribution of random variables [5].

Results and discussion

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 receiving methylprednisolone (M) at 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 tail root in the initial state (5-day introduction M) and 90 minutes after the use of antidepressants.

Established that in the initial state the conditions prevailing EEMS against the background of basic therapy methyl-prednisolone response to electrical stimulation in the rat tail all groups been registered at the level of 1.35 ± 0.12 (group V) and 1.48 ± 0.1 (group IV). Under these conditions treated with antidepressant agents intragastrointestinaly once into groups. The results are presented in Fig. 1. Established that the studied potential analgesic drugs was quite high. Thus, the maximum analgesic activity was observed against the background of the introduction of fluoxetine and tryttiko that manifested an increase in pain threshold 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, registered moderate analgesic effect of methylprednisolone passive control group (II) against the background of its 5-day administration (+ 39.2%; $p \geq 0,05$) indicators on the initial state.

Comparative analysis antinociceptive potential anti-depressants 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.),

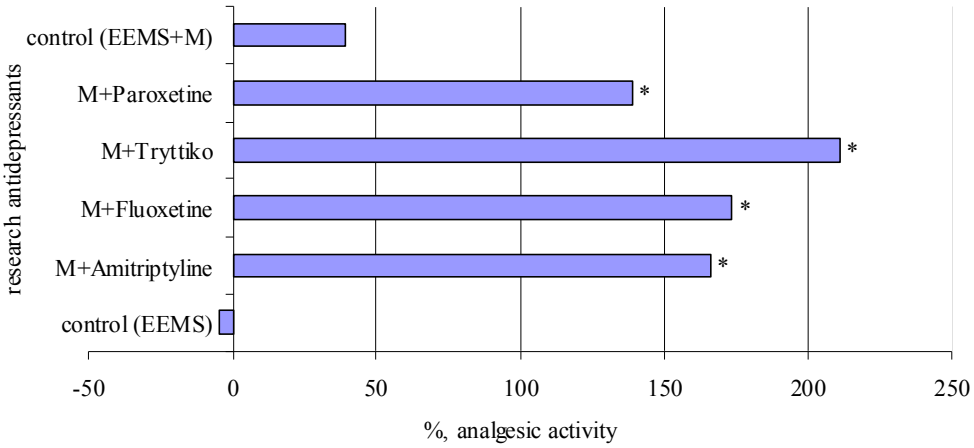

Fig. 1. Antinociceptive potential antidepressants in electrical stimulation of root tail rats under EEMS (90 mins) against pharmacotherapy methylprednisolone.
Note: * - p≤0,05 performance against original state

fluoxetine (1,11 c.u.) and tryttiko (1.16 c.u.).

It is shown in the active control group of animals length sinking in water at forced swimming (Porsolt test) was the highest - 209.4 ± 11.9 s (Fig. 2), which corresponded to a high level of anxiety and concern. When using antidepressants decreased immobilization time in the amitriptyline group to 27.75% (p≤0.05) for fluoxetine to 33.43% (p≤0.05) for tryttiko to 48.05% (p≤0.05) and paroxetine to 46.7% (p≤0.05). The ability to weaken the level of anxiety and concern was most pronounced for groups of tryttiko and paroxetine, immobilization time was in 1.7times (p≤0.05) and 1.6 (p≤0.05) according shorter compared to the active control group index . Many patients with multiple sclerosis observed sleep disorder that is usually caused by secondary factors: 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

It is shown that 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).

When using antidepressants to hormone therapy observed background basic one-way speaker with methylprednisolone reducing latency and increasing sleep duration. So, against the backdrop of the introduction of amitriptyline and paroxetine sleep in rats was longer EEMS to 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 most pronounced - in 1.74 (p≤0.05) and in 1.86 (p≤0.05) times of the performance group II. Thus, the influence of antidepressants on latent period and duration of sleep when administered on a background of basic drug therapy methylprednisolone 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. Given 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 the basic hormone therapy of EEMS as a means of pharmacological therapy of pain, anxiety, depression and sleep disorders most appropriate to appoint tryttiko and paroxetine.

Perspectives of further researches

In this study seems appropriate to further define the features of the influence of antidepressants to approximately research function of the central nervous system to improve adjuvant analgesic therapy of nociceptive displays in multiple sclerosis.

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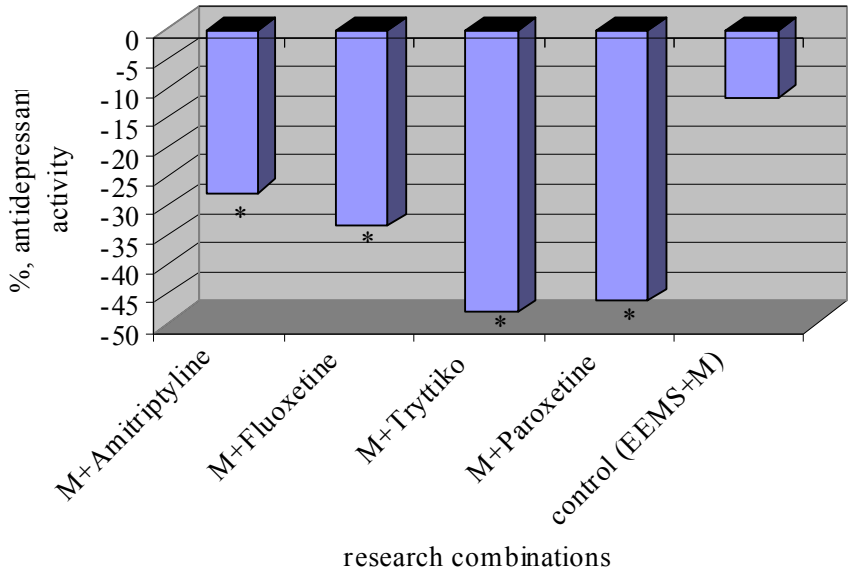

Fig. 2. Changes of immobilization time against the backdrop of the introduction of antidepressants in rats with EEMS against the backdrop of pharmacotherapy by metlprednizolone
Note: * - p≤0.05 performance against original state

Table 1. Assessing of the impact of antidepressants on sleep medication parameters in rats with EEMS against the backdrop of pharmacotherapy by methylprednisolone

Research groups	Time to sleep (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

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Фармакологічна корекція неврологічних розладів при розсіяному склерозі

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Резюме. В статті проаналізовані можливості медикаментозної корекції розповсюджених неврологічних розладів (біль, тривога, депресія, інсомнії) антидепресантами за умов експериментального еквіваленту розсіяного склерозу на тлі базової фармакотерапії метилпреднізолоном.

Оцінкою антиноцицептивного потенціалу антидепресантів визначений «ряд активності» зазначених засобів (аналгетична активність класичного антидепресанту амітриптиліну прийнята за умовну одиницю): пароксетин (0,9 ум.од), амітриптилін (1ум. од), флуоксетин (1,11 ум. од) та триттіко (1,16 ум.од.).

Порівняльним аналізом тривалості завмирання тварин у воді при примусовому плаванні (тест Порсолта) встановлено, що здатність ослабляти рівень тривожності та занепокоєння була найбільш вираженою для груп триттіко та пароксетину: час іммобілізації був у 1,7 (p≤0,05) та у 1,6 (p≤0,05) відповідно коротшим у порівнянні з відповідним показником групи активного контролю. При цьому вплив антидепресантів на латентний період та тривалість сну при введенні на тлі базової фармакотерапії метилпреднізолоном характеризувався наступними показниками: триттіко (-66,5% та +133,45%) ≥ флуоксетин (-60,5% та + 117,79%) ≥ пароксетин (-61,8% та + 93,59%) ≥ амітриптилін (-52,75% та +81,85%).

Таким чином, за умов експериментального еквіваленту розсіяного склерозу з урахуванням базової гормональної терапії в якості засобів медикаментозної корекції болю, тривоги, депресії та розладів сну доцільно призначати триттіко та пароксетин.

Ключові слова: розсіяний склероз, біль, антидепресанти, депресія, сон.

Нефедов А.А., Мамчур В.И.

Фармакологическая коррекция неврологических расстройств при рассеянном склерозе

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Резюме: В статье проанализированы возможности медикаментозной коррекции распространенных неврологических расстройств (боль, тревога, депрессия, инсомнии) антидепрессантами в условиях экспериментального эквивалента рассеянного склероза на фоне базовой фармакотерапии метилпреднизолоном.

Оценкой антиноцицептивного потенциала антидепрессантов определен «ряд активности» указанных средств (анальгетическая активность классического антидепрессанта амитриптилина принята за условную единицу): пароксетин (0,9 у.е.), амитриптилин (1 у.е.), флуоксетин (1,11 у.е.) и триттико (1,16 у.е.).

Сравнительным анализом продолжительности замирания животных в воде при принудительном плавании (тест Порсолта) установлено, что способность ослаблять уровень тревожности и беспокойства была наиболее выраженной для групп триттико и пароксетина: время иммобилизации был в 1,7 (p≤0,05) и в 1,6 (≤0,05) соответственно короче по сравнению с соответствующим показателем группы активного контроля. При этом влияние антидепрессантов на латентный период, длительность сна при введении на фоне базовой фармакотерапии метилпреднизолоном характеризовался следующими показателями: триттико (-66,5% и + 133,45%) ≥ флуоксетин (-60,5% и + 117,79%) ≥ пароксетин (-61,8% и + 93,59%) ≥ амитриптилин (-52,75% и + 81,85%).

Таким образом, в условиях экспериментального эквивалента рассеянного склероза с учетом базовой гормональной терапии в качестве средств медикаментозной коррекции боли, тревоги, депрессии и расстройств сна целесообразно назначать триттико и пароксетин.

Ключевые слова: рассеянный склероз, боль, антидепрессанты, депрессия, сон.

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