educativ promovând principiile farmacoterapiei ştiinţifice şi raţionale şi eliminând din mentalul colectiv falsa convingere că antibioticele sunt bune pentru orice afecţiune.

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EFFECTS OF NIACIN-OXYETHYLIDENDIPHOSPHONATO-GERMANATE AND ALPHA-LIPOIC ACID UPON DIABETES-INDUCED OXIDATIVE STRESS IN RETINA

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Summary

Effects of two weeks treatment with niacin-oxyethylidendiphosphonato-germanate (MIGU-4, 2,5; 25,0 mg/kg, i.p.) and alpha-lipoic acid (LA, 5,0 and 50,0 mg/kg, i.p.) as well as their combined usage (MIGU-4 – 2,5, and LA – 5,0 mg/kg) upon antioxidative enzymes and level of malon dialdehyde (MDA) in retina tissue of rats with streptozotocin (STZ)-induced diabetes was determined. It was established that in six weeks after STZ administration superoxiddismutase (SOD) activity decreased by 33,4% (P<0,05), catalase (CAT) – by 28,2% (P<0,05), glutathione peroxidase (GPx) – by 39,8%, glutathione reductase (GR) – by 48,3%, and MDA level raised by 2,65 times when compared with intact rats (P<0,05). MIGU-4 treatment (25,0 mg/kg, i.p.) increased SOD activity by 38,1% (P<0,05), GPx and GR – by 62,9% (P<0,05) and by 35,2% (P<0,05), when compared with diabetes rats. MDA level was reduced by 30,2% (P<0,05) correspondently. The SOD activity under condition of combined MIGU-4 (2,5 mg/kg) and LA (5,0 mg/kg) administration exceeded its level in rats with diabetes by 41,3% (P<0,05), while activity of GPx and GR also was higher by 52,4% and by 47,8% (P<0,05) correspondently. MDA level reduction was higher than in groups which were given MIGU-4 or LA alone (P<0,05). Thus, niacin-oxyethylidendiphosphonato-germanate caused prevention on diabetes-induced deterioration of antioxidant enzymes activity and level of MDA in retina tissue. Combined usage of MIGU-4 and LA was resulted in heightened preventive effects upon manifestations of oxidative stress.

Keywords: *experimental diabetes mellitus, streptozotocin, diabetes retinopathy, niacin-oxyethylidendiphosphonato-germanate, lipoic acid, oxidative stress*

Rezumat

Efectele acidului nicacin-oxetilendendifosfonat germanat şi acidului alfa-lipoic asupra stresului oxidativ indus de diabet în ţesutul retinei

Au fost investigate efectele administrării de două săptămâni a hidroxietilidendifosfonat germanatului (MIGU-4, 2,5; 25,0 mg/kg, i.p.) şi a acidului alfa-lipoic (LC, 5,0 şi 50,0 mg/kg, i.p.) şi efectul utilizării lor combinate (MIGU-4 – 2,5 şi LC – 5,0 mg/kg) asupra activităţii enzimelor antioxidante şi nivelului de malondialdehidă (MDA) în ţesutul retinei şobolanilor cu diabet indus de streptozotocină (STZ). S-a constatat că după 6 săptămâni de la momentul aplicării STZ, activitatea superoxid dismutazei (SOD) a scăzut cu 33,4% (P <0,05), a catalazei (CAT) – cu 28,2% (P <0,05), a glutationperoxidazei – cu 39,8%, a glutationreductazei (GR) – cu 48,3%, cu o creştere a conţinutului de MDA de 2,65 ori, comparativ cu şobolanii intacţi (P <0,05). Odată cu introducerea MIGU-4 (25,0 mg/kg, i.p.), activitatea SOD a fost mai mare cu 38,1% (P <0,05), a HP şi GR – cu 62,9% (P <0,05) şi, respectiv, 35,2% (P <0,05), în comparaţie cu animalele cu diabet zaharat. Nivelul MDA a scăzut cu 30,2% (P <0,05). Eficacitatea MIGU-4 (25,0 mg/kg) a fost comparabilă cu cea a LK utilizată în doză de 50,0 mg/kg. În cazul folosirii combinate a MIGU-4 (2,5 mg/kg) şi a LC (5,0 mg/kg), activitatea SOD a depăşit-o pe cea a şobolanilor cu diabet zaharat cu 41,3% (P <0,05), GP şi GR fiind mai mari cu 52,4% şi, respectiv, cu 47,8% (P <0,05). Scăderea nivelului MDA a fost mai mare decât în cazul grupurilor care utilizează MIGU-4 sau LC (P <0,05). Astfel, administrarea hidroxietildidenfosfonat germanatului previne dereglările activităţii enzimelor antioxidante şi nivelului MDA induse de diabet în ţesutul retinian. Administrarea asociată a MIGU-4

și a LC este însoțită de o acțiune preventivă sporită împotriva manifestărilor stresului oxidativ.

***Cuvinte-cheie**: diabet experimental, streptozotocin, retinopatie diabetică, niacin-oxietildendifosfonat germanat, acid lipoic, stres oxidativ*

Резюме

Эффекты ниацин-оксиэтилидендифосфонат германата и альфа-липоевой кислоты на диабет-индуцированный оксидантный стресс в ткани сетчатки

Исследовали влияние двухнедельного введения ниацин-оксиэтилидендифосфонат германата (МИГУ-4, 2,5; 25,0 мг/кг, в/бр) и альфа-липоевой кислоты (ЛК, 5,0 и 50,0 мг/кг, в/бр), а также влияние их совместного применения (МИГУ-4 – 2,5, и ЛК – 5,0 мг/кг) на активность антиоксидантних ферментов и уровень малонового диальдегида (МДА) в ткани сетчатки крыс со стрептозотоцин (СТЗ)-индуцированным диабетом. Установлено, что через 6 недель с момента применения СТЗ активность супероксидисмутазы (СОД) уменьшилась на 33,4% (P<0,05), каталазы (КАТ) – на 28,2% (P<0,05), глутатионпероксидазы (ГП) – на 39,8%, глутатион-редуктазы (ГР) – на 48,3% при увеличении содержания МДА в 2,65 раза в сравнении с интактными крысами (P<0,05). На фоне введения МИГУ-4 (25,0 мг/кг, в/бр) активность СОД была выше на 38,1% (P<0,05), ГП и ГР – на 62,9% (P<0,05) и соответственно 35,2% (P<0,05) при сравнении с животными с диабетом. При этом уровень МДА уменьшался на 30,2% (P<0,05). При комбинированном применении МИГУ-4 (2,5 мг/кг) и ЛК (5,0 мг/кг) активность СОД превышала таковую у крыс с диабетом на 41,3% (P<0,05), в то время как активность ГП и ГР была выше на 52,4% и соответственно 47,8% (P<0,05) соответственно. Величина снижения уровня МДА была выше, чем в группах с применением одного МИГУ-4 или ЛК (P<0,05). Таким образом, применение ниацин-оксиэтилидендифосфонат германата предотвращает диабет-вызванные нарушения активности антиоксидантных ферментов и уровня МДА в ткани сетчатки. Совместное введение МИГУ-4 и ЛК сопровождается потенцированным превентивным действием в отношении проявлений оксидативного стресса.

***Ключевые слова:** экспериментальный диабет, стрептозотоцин, диабетическая ретинопатия, ниацин-оксиэтилидендифосфонат германат, липоевая кислота, оксидативный стресс*

Introduction

The intensification of mechanisms of oxidative stress in retinal tissue is regarded as a key mechanism of diabetes retinopathy development [1, 2]. Those drugs, which alleviate diabetes retinopathy manifestations are known as such ones which suppress oxidative stress as well [3].

During last years the pharmacological activity of different derivatives of germanium has been investigated at our laboratory [4, 5]. Among others such one as oxyethylidendiphosphonate germanate: $(NicH)_2$ $[Ge(OH)_2$ $(Oedph)].H_20$ (MIGU-4) with molecular weight of 593 g/M was identified as perspective compound. It was established that MIGU-4 intensify oxidative phosphorilation, prevented discordant state of mitochondrial ATP-ases and heightened mitochondrial resistance to damages. Such pharmacological properties of MIGU-4 led to the stabilization of mitochondrial membrane phospholipids, and suppressed an oxidative stress – both on behalf of enzymatic and antiradical components of defense [5, 6].

That is why it was reasonable to investigate effects of MIGU-4 upon diabetes-induced experimental retinopathy. Hence, the aim of work was to investigate activity of antioxidative enzymes in retina of rats with experimental diabetes under condition of treatment with MIGU-4, and to compare effects with such ones caused by alpha-lipoic acid (LA), which is used for diabetes retinopathy treatment.

Material and methods

Investigations were performed on 94 Wistar male rats with body weight of 170- 240 g, which were kept under standard conditions at Odessa National Medical University (ONMedU) vivarium. Animals were randomly allocated to the following conditions**:** a constant temperature of 23°C, relative humidity of 60%, 12 h dark/light cycles, a standard diet, and tap water were given *ad libitum* in accordance to international laws and policies (EU Council Directive 86/609, OJ L 358, 18/12/1986 P.0001-0028; National Institute of Health Guide for Care and Use of Laboratory Animals, US National Research Council, 1996, p. 21-55) and in strict accordance to prescriptions issued by Commission on Bioethic at ONMedU (Protocol no 84, 10th October, 2008).

Experimental diabetes was induced via i.p. streptozotocin (STZ, *Sigma Aldrich.ru* RF) administration (55,0 mg/kg) which was dissolved in sodium-citrate buffer solution (pH 4,5). The level of glucose was determined in vein blood in one week from the moment of STZ administration and those rats with level not less than 300 mg/dL have been included into observation [1, 3]. Measurements were performed at 9.00 AM under conditions of free access to water and food during night time. Insulin administration (0,2 IU, subcutaneously, two-five times per week) was performed during all period of observation [1, 3].

The treatment with MIGU-4 and LA was performed during fifth-sixth weeks from the moment of diabetes modeling via STZ administration. Both drugs were administered daily and tissues for measurement of enzyme activity and MDA level were got

in 24 h from the moment of last (14th) administration. After euthanasia was performed retina was got and kept in liquid nitrogen.

Retina tissue washed out from blood remnants with a buffer solution was homogenized in 0,1M phosphate buffer solution (pH 7,0) at the ratio of 1:20 (weight of tissue/volume of homogenate). Homogenized samples were centrifugated during 15 min at velocity of 13.000 rotations/min at + 4°C.

SOD activity was determined in accordance to [7], CAT – [8], GPx – [9], and GR – [10] methods.

MDA was determined with spectrophotometric method [11]. The incubation of homogenate was performed at high temperature with thiobarbituric acid and gained pink solution was investigated at 532 nm length of wave. The tetraoxypropane solution was used as a standard. The MDA level was expressed as nmoles/mg of proptein. The protein level was determined in accordance to Lowery method [11].

Results of investigation were statistically analyzed using ANOVA method and followed with Newman-Keuls test.

Results and discussion

Effects of MIGU-4 administrations. Obtained data revealed that in rats with diabetes the significant reduction of investigated enzymes activity was detected (*table 1*). Thus, Superoxide dismutase (SOD, EC 1.15.1.1) was reduced by 33,4% (P<0,05), CAT (EC 1.11.1.6) – by 28,2% (P<0,05), Glutathione peroxidase (GPx, EC 1.11.1.9) and Glutathione reductase (GR, EC 1.8.1.7) – by 39,8% and by 48,3% (P<0,05) pertained to corresponded data registered in control rats. Besides, the increased level of MDA, which exceeded such one in the control group by 2,65 times was also observed (P<0,05).

In the group of rats treated with MIGU-4 in lower dosage (2,5 mg/kg, i.p.) SOD activity increased by 7,6% when compared with such one in the rats with diabetes (P>0,05), and CAT activity also have been raised by 5,2% (P>0,05). Meanwhile the GPx activity exceeded initial value by 15,8% (P>0,05), while GR activity also raised by 17,6% (P>0,05). MDA level was higher when compared with the initial one by 6,8% (P>0,05).

MIGU-4 (25,0 mg/kg, i.p.) administration was followed by SOD activity increasing by 38,1% when compared with diabetes rats (P<0,05) and was not differ from such one registered in the control group (P>0,05). The CAT activity also increased by 32,0% (P<0,05), while GPx and GR activity exceeded initial values by 62,9% (P<0,05) and by 35,2% (P<0,05) correspondently. CAT and GPx activity was not differ from control values, and GR activity remained reduced by 30,1% (P<0,05). The MDA level was less when compared with diabetes rats by 30,2% (P<0,05) and continued to be reduced when compared with the control group – by 85,0% (P<0,05) (*table 1*).

Table 1

The activity of antioxidative enzymes in retinal tissue (6 weeks from the moment of STZ-administration) under conditions of MIGU-4 treatment (M±m)

	Control group (intact rats, vehicle i.p.) (n=11)	*STZ-diabetes (n=11)*	*STZ-diabetes + MIGU-4 (2,5 mg/kg) (n=10)*	*STZ-diabetes + MIGU-4 (25,0 mg/kg) (n=10)*
Superoxide dismutase (% of blocking of nitroblue tetrazolium reduction)	121,3±5,56	80,80± 6,53*	86,97±6,59*	111,6± 7,71#
CAT (H_2O_2/ (min.mg of protein)	3,48±0,23	2,50±0,18*	2,63±0,24*	3,30± 0,27#
Glutathione peroxidase (GSH/(min. mg of protein), nM)	1,03±0,07	0,62±0,05*	0,78±0,08	1,01± 0,09#
Glutathione reductase (NADPH/ (min.mg of protein), nM)	12,84±0,61	6,64±0,56*	7,81±0,55*	8,98±0,44*#
Malon dialdehyde (nM/mg of protein)	2,00±0,18	5,30±0,43*	4,94±0,41*	3,70± 0,25*#

Notes. * – P<0,05 when compared with the data in the control group (intact false operated rats); # – P<0,05 when compared with the data in diabetes rats. Method ANOVA + Newman-Keuls test were used.

Alpha-lipoic acid (LA) effects. LA administration in a lower dosage (5,0 mg/kg, i.p.) was followed by the tendency of the antioxidant enzymes increasing with the GR activity heightened by 35,0% as a greatest one (P<0,05) (*table 2*). At the same time the SOD activity raised by 22,7% (P>0,05), while CAT activity increased only by 2,8% (P>0,05). Meanwhile, both SOD and CAT activity continued to be less when compared with control data – by 32,7% (P<0,05) and by 23,8% (P<0,05) correspondently. The MDA level decreased by 9,9% when compared with diabetes rats (P>0,05).

LA administered in a dosage of 50,0 mg/kg, i.p. caused more pronounced effect when all investigated indices – activities of enzymes were did not differ

from the corresponded data in the control group (P>0,05). Besides, SOD and GR activity exceeded the value of analogous indices in the control group by 37,2% and by 43,9% (P<0,05) correspondently. The MDA level also was reduced when compared with the control group by 42,1% (P<0,05) and continued to be greater than such one in rats with diabetes by 1,65 times (P<0,05) (*table 2*).

Table 2

Antioxidative enzymes activity in rat retina (six weeks from the moment of diabetes modeling via STZ administration) under conditions of alpha-lipoic acid treatment (M±m)

	Control group (intact rats, vehicle i.p.) (n=11)	*STZ-diabetes (n=11)*	*STZ-diabetes + LA (5,0 mg/kg) (n=10)*	*STZ-diabetes + LA (50,0 mg/kg) (n=10)*
Superoxide dismutase (% of blocking of nitroblue tetrazolium reduction)	111,39±7,44	61,06±6,69*	74,93±6,94*	97,22±7,77#
CAT (H_2O_2/ (min.mg of protein)	3,32±0,21	2,46±0,19*	2,53±0,24*	3,10±0,26
Glutathione peroxidase (GSH/ (min. mg of protein), nM)	1,04± 0,07	0,69±0,07*	0,75±0,08	0,98±0,12
Glutathione reductase (NADPH/ (min.mg of protein), nM)	13,21±0,99	8,74±0,81*	11,80±1,10#	12,58±1,21#
Malon dialdehyde (nM/mg of protein)	1,96±0,14	5,58±0,52*	5,03±0,46*	3,23±0,25#*

Notes. The same as in table 1.

Effects of combined usage of MIGU-4 and LA. Combined administration of MIGU-4 and LA in lower dosages (2,5 mg/kg and 5,0 mg/kg correspondently) resulted in SOD activity increasing by 41,3% pertained to the level observed in rats with diabetes (P<0,05) (*table 3*). Besides, the activity of GPx and GR have been increased also when compared with the data in rats with diabetes – by 52,4% and by 47,8% correspondently (P<0,05). It should be stressed that in this session of experimental observation LA administration (5,0 mg/ kg, i.p.) effectively prevented GPx activity decreasing, which significantly exceeded the corresponded value in rats with diabetes – by 52,4% (P<0,05). There were any significant differences between enzymatic activity in groups with separate and combined usage of MIGU-4 and LA (P>0,05).

Table 3

Antioxidant enzymes activity in retina tissue (6 weeks from the moment of STZ – administration) under conditions of treatment with MIGU-4 and alpha-lipoic acid (M±m)

	Control (intact rats, vehicle i.p.) (n=11)	*STZ-diabetes (n=10)*	*MIGU – 4 (2,5 mg/kg) (n=11)*	*LA (5,0 mg/kg) (n=10)*	*MIGU-4 + LA (n=10)*
Superoxide dismutase (% of blocking of nitroblue tetrazolium reduction)	120,5±6,4	74,3±5,9*	86,97± 6,59*	78,12+ 7,88*	105,03± 9,62#
CAT (H_2O_2/ (min.mg of protein)	3,28±0,20	2,33±0,22*	2,63±0,24	2,87±0,25	3,08± 0,26
Glutathione peroxidase (GSH/ (min.mg of protein), nM)	1,07±0,07	0,63±0,05*	0,75± 0,06*	0,89±0,07#	0,96±0,08#
Glutathione reductase (NADPH/ (min.mg of protein), nM)	14,49±0,80	9,37±0,64*	11,06±1,16*	12,13±0,86	13,85±0,93#
Malon dialdehyde (nM/mg of protein)	1,96+0,14	5,54±0,60*	5,30±0,43*	4,95± 0,27*	3,09±0,21#*

Notes. The same as in table 1.

MDA level was reduced by 44,2% (P<0,05) pertained to rats with diabetes and exceeded the corresponded level in control group by 57,6% (P<0,05). It should be stressed that MDA level in rats given combined treatment was significantly less when compared with such one in the groups treated with MIGU-4 – by 41,7%, (P<0,05) and LA – by 37,6%, (P<0,05) (*table 3*).

Hence, gained data are in favor that in six weeks from the moment of experimental diabetes modeling via STZ administration the net reduction of antioxidant enzymes activity is registered in rat's retina. Namely, SOD activity decreased by 33,4% (P<0,05), CAT – by 28,2% (P<0,05), GPx – by 39,8% and GR – by 48,3% when compared with corresponded data in the control group (P<0,05). Besides, MDA level raised by 2,65 times pertained to control data (P<0,05). Such data are in correspondence with other investigations [1].

MIGU-4 (25,0 mg/kg, i.p.) administration performed during fifth-sixth weeks from the moment of STZ administration prevented the mentioned reduction of antioxidant enzymes activity reduction and raising of MDA level. Thus, SOD activity increased

by 38,1% (P<0,05), GPx and GR – by 62,9% (P<0,05) and by 35,2% (P<0,05), when compared with corresponded data in rats with diabetes. At the same time MDA level was reduced by 30,2% (P<0,05) when compared with diabetes rats. The pronounced tendency to GPx activity raising was also noted in diabetes rats treated with MIGU-4 in lower dosage (2,5 mg/kg, i.p.). Such effectiveness was also observed for Ge- containing compounds in case of other types of oxidative stress [12, 13].

Obtained data were in favor for the effectiveness of LA treatment against STZ-diabetes-induced oxidative stress in retina tissue. Thus, even lower dosage of LA (5,0 mg/kg, i.p.) prevented diabetes-induced decreasing of GR activity, which exceeded such one in rats with diabetes by 35,0% (P<0,05), and in higher dosage (50,0 mg/ kg, i.p.) such difference raised up to 43,9% (P<0,05). Besides, higher dosage of LA effectively prevented SOD activity decreasing, and it's activity exceeded control value by 37,2% (P<0,05). At the same time the MDA level decreased by 42,1% pertained to level in diabetes rats (P<0,05).

The comparison of the pronouncement of protective effects of MIGU-4 revealed that in dosage of 25,0 mg/kg they are equal to such one caused by LA administered in a dosage of 50,0 mg/kg. But in lower dosages LA administration (5,0 mg/kg) was followed by more pronounced effects than MIGU-4 (2,5 mg/kg). Such differences might be explained by realization of LA protective action via influence upon glutamate turnover, which plays an important role in diabetes retinopathy [1, 2].

Combined administration of MIGU-4 (2,5 mg/kg) and LA (5,0 mg/kg) caused the prevention of diabetes-induced SOD activity decreasing: it exceeded by 41,3% similar index in rats with diabetes (P<0,05). The activity of GPx and GR also exceeded such ones in rats with diabetes – by 52,4% and by 47,8% correspondently (P<0,05). The absence of differences between enzymatic activity in groups with separate and combined usage of MIGU-4 and LA was in favor for the summation as a main mechanism of their combined therapeutic preventive action.

It should be stressed that MDA level in rats given combined treatment was significantly less when compared with such one in the groups treated with MIGU-4 – by 41,7%, (P<0,05) and LA – by 37,6%, (P<0,05). This fact is in favor for potentiating as the main mechanism of MIGU-4 and LA interaction with respect to prevention of MDA level increasing in STZ-induced diabetes. But, absence of mentioned differences in the case of effects upon enzymatic activity assumes summation of preventive activity of MIGU-4 and LA as well.

Conclusions

1. Retinopathy in STZ-induced diabetes is characterized by reduction of antioxidants enzymes – superoxiddismutase, catalase, glutathione peroxidase, glutathione redusctase activity and accumulation of malon dialdehyde in retina tissue.

2. Niacin-oxyethylidendiphosphonato-germanate (25,0 mg/kg, i.p.) caused preventive effects upon diabetes-induced oxidative stress in retina tissue, and pronouncement of activity is comparable with such one induced with alpha-lipoic acid used in a dosage of 50,0 mg/kg, i.p.

3. Combined usage of niacin-oxyethylidendiphosphonato-germanate and alpha-lipoic acid are followed with strengthened protective effects which might be regarded as effect of summation in case of correction of antioxidant enzymes activity and as potentiating in case of correction of MDA accumulation.

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CERCETĂRI FARMACOLOGICE EXPERIMENTALE PRIVIND EFECTELE ADVERSE ALE ASOCIERII ALPRAZOLAM+BROMAZEPAM

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Rezumat

În lucrarea de față ne-am propus cercetarea preclinică a potențialului farmacotoxicologic al asocierii dintre două benzodiazepine: alprazolam și bromazepam. Cercetările noastre s-au efectuat la șoareci prin teste farmacologice specifice de evaluare a efectului miorelaxant (testul rotarod) și a efectului asupra memoriei și achiziției spațiale (labirintul acvatic Morris). Dozele administrate au fost. alprazolam 0,5 mg/kg corp și bromazepam 0,75 mg/kg corp. În urma cercetărilor efectuate, putem afirma că cele două benzodiazepine studiate, alprazolam și bromazepam, la dozele administrate, singure sau în asociere, nu influențează în sens negativ abilitatea șoarecilor de a se menține pe axul în rotație sau capacitatea de a învăța și de a memora poziția platformei în testul labirintului acvatic Morris.

***Cuvinte-cheie**: alprazolam, bromazepam, testul rotarod, labirintul acvatic Morris*

Summary

Pharmacological experimental research on the adverse effects of alprazolam+bromazepam association

In the present paper we have researched, through experimental pharmacology studies, the pharmacotoxicological potential of the association between two benzodiazepine drugs: alprazolam and bromazepam. Our research has performed using specific pharmacological tests to evaluate the effect of miorelaxant (rotarod test) and effect on memory and spatial acquisition (Morris aquatic labyrinth). The doses administered were alprazolam 0.5 mg/kg body weight and bromazepam 0.75 mg/kg body weight. Based on our research, we can state that the studied benzodiazepines, alprazolam and bromazepam, at the doses administered alone or in combination, do not adversely affect the ability of mice to maintain on the rotating spindle or the ability to learn and to remember platform position in the Morris aquatic labyrinth test.

***Keywords:** alprazolam, bromazepam, rotarod test, aquatic labyrinth Morris*

Резюме

Фармакологические экспериментальные исследования побочных эффектов ассоциации алпразолам+бромазепам

В этой статье мы поставили себе цель провести доклинические исследования фармакотоксикологического потенциала ассоциации между двумя бензодиазепинами: альпразоламином и бромазепамом. Наши исследования проводились на мышах с помощью специфических фармакологических тестов для оценки влияния миорелаксанта (тест ротарода) и влияния на память и пространственное поглощение (водный лабиринт Морриса). Доза альпразолама была 0,5 мг/кг массы тела и бромазепа – 0,75 мг/кг массы тела. Основываясь на наших исследованиях, мы можем констатировать, что два исследуемых бензодиазепина, альпразолам и бромазепам в указанных дозах, вводимых отдельно или в комбинации, не оказывают отрицательного влияния на способность мышей поддерживать ось вращения или способность учиться и помнить позицию платформы в тесте водного лабиринта Морриса.

***Ключевые слова**: альпразолам, бромазепам, тест ротарода, водный лабиринт Морриса*

Introducere

De la descoperirea lor la începutul anului 1960 și până în prezent, benzodiazepinele s-au numărat printre cele mai prescrise medicamente datorită multiplelor acțiuni farmacologice (anxiolitică, hipnoinductoare, anticonvulsivantă, miorelaxantă), care le-au conferit o importantă valoare terapeutică și le-au permis folosirea într-o varietate de afecțiuni. Utilizarea lor pe scară largă se datorează într-o mare măsură tolerabilității și siguranței acestora. În comparație cu alte medicamente deprimante ale sistemului nervos