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# Section 2. Medico-biological sciences

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# How meloxicam, caffeine and their pharmacological composition influence the emotional-behavioral reactions in rats under formalin edema

**Introduction.** While studying the pharmacological effect of pharmaceutical drugsit is vital to explore their influence on behavioral characteristics in animals. That we have no verbal contact with animals limits the range of possible tests. The so-called “open-field test” is still the most wide-spread and informative one in studying the influence of medicines on emotional-behavioral reactions (EBR) [[1]](#footnote-1). Medical practice often resorts to combined pharmacotherapy to improve the efficiency of a medicines [[2]](#footnote-2). Modern medical practice has an urgent necessity in medicines with rather a wide range of pharmacological actions in considerably smaller doses and, at the same time, with low toxicity and minimal side effects. Such advantages are known to pertain to combination drugs as compared to mono-medicines [[3]](#footnote-3). The analysis of references testifies that analgetics rather often contain caffeine, whereas meloxicam is a well-known nonsteroid anti-inflammatory drugs (NSAIDs) of oxicams. There is no information on the present pharmacological composition of meloxicam and caffeine.

**The purpose of our research** was to study the influence of meloxicam, caffeine and their pharmacological composition on the EBR in rats by testing in the “open field” under formalin edema as compared to the reference medicine (diclofenac sodium).

The following tasks were solved in accordance with the given purpose: to study and analyse EBR in rats in “the open field” test by injecting meloxicam, caffeine and their composition under formalin edema as compared to the reference medicine (diclofenac sodium).

**Materials and methods of the research**. How meloxicam, caffeine and their composition influence EBR in rats was studied under formalin edema. An experimental study was conducted on WAG-line rats with an average weight of 180–220 g. The animals were divided in 6 groups with 6 rats in each group. The animals of group 1st were a control group, receiving 3% starch mucilage one time by oral intragastric administration (2 ml per 200g rat). Formalin edema in the animals of group 2nd was modeled by sub-plantar injection of 2% formalin solution in the rat’s hind leg along with intragastric injection of 3% starch mucilage (2 ml per 200g rat) [[4]](#footnote-4). The experimental products and their composition were injected one time intragastrically as a suspension with 3% starch mucilage to the animals of 3rd through 6th group. Thus, the animals from group 3rd received meloxicam in the dose of 0,6 mg/kg, caffeine (0,6 mg/kg) was injected to animals from group 4, the fifth group received the pharmacological composition of meloxicam (0,6 mg/kg) with caffeine (0,6 mg/kg) and diclofenac sodium (8 mg/kg) as a reference medicine was injected to the 6th group. Maximum development of formalin edema can be observed in a four-hour period after its modeling [[5]](#footnote-5). The medicines and their pharmacological composition, as well as 3% starch mucus were injected an 1 hour prior to this moment taking into consideration pharmacokinetic peculiarities of the experimental products.

The influence of the medicines and their combination on the animals’ behavioral characteristics was assessed by comparing groups 3–5 with the control one (group 1), with that under formalin edema (group 2) and with the reference medicine (group 6), as well as by comparing group 3 and 4 with group 5 (a medical composition). Parameters of the rats’ reference and research activity were observed during 3 minutes in the “open field” [[6]](#footnote-6) test and by the multi-parameter method of assessing alarming and phobic states according to the generally established methods [[7]](#footnote-7).

The parameter of the rats’ reference and research activity in the “open field” test is characterized by a series of dimensions: the number of intersected squares (horizontal motion activity (HMA)), upright postures (vertical motion activity (VMA)), observed openings, washings (grooming), urinations and defecations according to the generally established methods [[8]](#footnote-8).

**Results of our experiment.** *The influence of experimental medicines and their composition on the rats’ HMA and VMA.* The analysis of the rats’ reference and exploratory behaviour in the open field test concerning HMA and VMA characteristics exposed a motivational component in the rats’ characteristic. At the same time they tried to come into indirect contact with the objects, located at some distance by sniffing at the objects beyond “the open field”.

Modelling of the formalin edema (group 2) contributed to decrease in the HMA by 1,1 times and in the VMA by 1,5 times in the rats relative to the control group (table 1). Mono-injection of meloxicam under formalin edema, contributed to decrease in the HMA and VMA as compared to the animals from group 2 (by 1,1 times) and relatively to the control group (by 1,3 times and 1,7 times correspondingly), by 1,3 times (HMA) and by 2,1 times (VMA) as compared to the reference medicine. While resorting to mono-injection of caffeine, we observed increase of the HMA by 1,2 times and the VMA by 1,4 times relatively to group 2. Meanwhile, the received data did not differ from reference quantities statistically veritably (group 1) the same as by HMA from the reference medicine. While injecting the meloxicam-caffeine composition, we observed the following: increase of the HMA (by 1,3 times) and VMA (by 1,6 times) in the rats relative to group 2, as well as increase of the HMA in the rats relatively to all the experimental groups, and the VMA in the rats relative to groups 1–4, which did not differ from the reference medicine statistically veritably (see table 1).

*The number of the surveyed holes*. A variation of the rats’ reference and exploratory behaviour is the number of surveyed holes, an indicator of the hole reflex, which shows the animal’s ability to explore the “open field”, in particular, to peep into apertures. The number of the surveyed holes characterizes the rats’ cognitive activity. Modelling of the formalin edema contributed to a decrease in the number of the surveyed apertures by 2,7 times relatively to the control group. Mono-injection of meloxicam contributed to the increasing number of the surveyed holes with rats relatively to group 2 by 3,3 times, while mono-injection of caffeine increased the aforesaid by 2 times. Caffeine, added to meloxicam, significantly improved the rats’ cognitive activity by 2,7 times relatively to group 2. Though similar to the control group from the viewpoint of statistical authenticity, these indicators were different from those of the reference product (see table 1).

*The rats’ cosmetic behaviour*. Grooming (cosmetic behaviour) in rats is an important feature of the animals’ behavior in the “open field”.

Traditionally, rats spend the best part of their time on combing out their bodies as compared to their spatial motion.

Table 1 – Indices of the rats’ behavioral activity under formalin edema according to “the open field” method (n = 6)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Rats’ groups** | **The number of interjections**  **(HMA)** | **The num-**  **ber of sets**  **(VMA))** | **The number of the surveyed holes** | **The number of washing**  **(grooming)** | **The number of urination** | **The number of defecation** |
| Control | 45,33 ± 7,03 | 6,67 ± 1,09 | 1,33 ± 0,49 | 7,5 ± 2,58 | 1,00 ± 0,00\*\*\*\* | 2,0 ± 0,78 |
| Formalin edema | 41,50 ± 0,50 | 4,50 ±  0,72\*\*\*\*\*\* | 0,50 ±  0,32\*\*\*\*\*\* | 3,50 ± 0,56 | 0,50 ±  0,23\*\*\*/\*\*\*\*\* | 1,00 ± 0,45 |
| Meloxicam | 36,17 ± 3,81 | 4,00 ±  1,53\*\*\*\*\*\* | 1,67 ± 0,56 | 3,33 ± 2,39 | 1,33 ±  0,21\*\*/\*\*\*\* | 1,67 ± 0,49 |
| Caffeine | 50,67 ± 12,62 | 6,33 ± 2,26 | 1,00 ±  0,45\*\*\*\*\*\* | 8,00 ± 3,67 | 3,50 ± 0,44  \*/\*\*\*/\*\*\*\*\*/\*\*\*\*\*\* | 1,17 ± 0,17 |
| Meloxicam + caffeine | 55,33 ± 7,89 | 7,17 ± 1,30 | 1,33 ±  0,21\*\*\*\*\*\* | 4,00 ± 2,46 | 1,50 ± 0,22  \*\*/\*\*\*\* | 2,50 ± 0,67 |
| Diclofenac sodium | 48,33 ± 7,73 | 8,50 ± 0,76\*\*/\*\*\* | 3,17 ±  0,54\*\*/\*\*\*\*/\*\*\*\*\* | 4,50 ± 2,31 | 1,00 ± 0,00\*\*\*\* | 1,33 ± 0,87 |

*Remarks (average ± error of mean):*

*\* – veracity of the results relative to the control group, P < 0,05;*

*\*\* – to the rats under formalin edema, P < 0,05;*

*\*\*\* – to the rats, subjected to mono‑injection of meloxicam, P < 0,05;*

*\*\*\*\* – to the rats, subjected to mono‑injection of caffeine, P < 0,05;*

*\*\*\*\*\* – to the rats, injected with the caffeine+meloxicam composition, P < 0,05;*

*\*\*\*\*\*\* – to the rats, subjected to mono‑injection of diclofenac sodium, P < 0,05;* Grooming is closely correlated with motion activity. Therefore, when studying medicines, we find this behavioral characteristic of special interest.

Modeling of the formalin edema led to diminishing washings by 2,1 times relative to the control group 1. Mono-injection of meloxicam exerted no influence on grooming under formalin edema. Mono-injection of caffeine increased washings in the rats relatively to group 2 by 2,3 times. While injecting the meloxicam-caffeine composition against formalin edema, we could observe increased grooming by 1,1 times relative to group 2 with no statistically veritable difference from the reference medicine (see table 1).

*Diuresis, defecation*. It should be noted that the number of urination and defecation is significant to indicate the rats’ emotional status. The level of the rats’ emotional state of is evaluated by the number of these indicators. Modeling of formalin edema (group 2) decreased diuresis and the number of defecation twice relative to the control group. Mono-injection of meloxicam under formalin edema showed increasing diuresis and the number of defecation relative to group 2 by 2,7 times and by 1,2 times respectively. Mono-injection of caffeine contributed to the statistically veritable increase in diuresis by 7 times relative to group 2. The injected meloxicam-caffeine composition increased diuresis statistically veritably by 3 times relative to group 2, similar to the reference product in that respect. The experimental composition having no influence on the number of defecations, we could observe their increase by 2,5 times relative to group 2, with no statistically veritable difference from group 1 and the reference product (see table 1).

**Conclusions.** Analysing the results of the influence of meloxicam, caffeine and their composition on the rats’ EBR under formalin edema, we can state the following:

1. Caffeine potentiates the effect of meloxicam relatively to HMA and VMA and grooming in rats under formalin edema.
2. Injection of meloxicam, caffeine and their composition improves rats’ cognitive activity under formalin edema. However, addition of caffeine to meloxicam does not contribute to improving rats’ cognitive activity in experimental conditions from the point of statistical significance.
3. Injection of the meloxicam-caffeine composition normalizes diuresis and the number of defecation in rats under formalin edema.

The pharmacological meloxicam-caffeine composition is expedient and promising concerning the exploration of the central component with analgetic action.

**Contents**

## Section 1. Clinical medicine . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 3

*Akbarov Avzal*

Evaluation of immunological indices in the dynamics of topical application of “Fargals” at patients during the process of adaptation to complete removable plate prosthesis depending on age . . . . . . . . . . . . . . . . . . . . . . . . . 3

*Alzhanova Svetlana Vasilevna, Tazhibay Gulmira Tazhibaykyzy,*

*Zhussupbekova Lazzat, Yeshmuratov Baurzhan Kuralovich,*

*Nurakhmetova Aya Sagatpekovna*

Analysis of the state of coronary vessels in myocardial infarction

depending on sex and age. . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 7

*Berihanova Rumisa Ramzanovna*

Analysis of the quality of life of patients with a metabolic syndrome

on the background of a non-drug correction of climacteric disorders. . . . . . 12

*Duzhyi Igor Dmytrovych, Gresko Igor Yaremovych,*

*Kravets Oleksandr Valeriyovych, Mischenko Yurii Oleksandrovych* Modern surgical possibilities of tuberculosis pneumoempyema

treatment. . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 16

*Karataeva Lola Abdullaevna, Arifdjanova Jonona Farrukh qizi,*

*Son Tatyana Ruslanovna*

Morphogenetic aspects of the study of Vessena-Tebezia vessels . . . . . . . . . 21

*Polyakova Olga Leontievna*

Dentistry, which defines odontometrical and odontoscopied

characteristics of the permanent teeth’s crowns . . . . . . . . . . . . . . . . . . . . . . 26

*Simonyan Lilit Hektor*

Changes in clinical parameters depends of several types therapy at

chronic obstructive pulmonary disease . . . . . . . . . . . . . . . . . . . . . .. . . . . . . . 31

*Sabirov Maksud*

Correction of markers of osteoporosis in patients with CKD 3rd stage . . . . . 39

*Yumashev Aleksej Valerievich, Utyuzh Anatolij Sergeevich,*

*Admakin Oleg Ivanovich, Samusenkov Vadim Olegovich,*

*Nefedova Irina Valerievna*

Complex stability study and analysis of osseointegration

of dental implants . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 42

## Section 2. Medico-biological sciences. . . . . . . . . . . . . . . . . . . . . . . . . . . . . 48

*Lukianova Larysa Vladimirovna, Syrovayа Anna Olegovna,*

*Andreeva Svetlana Viktorovna, Krasnikova Yuliya Nikolaevna,*

*Issaaka Adamu*

How meloxicam, caffeine and their pharmacological composition influence the emotional-behavioral reactions in rats

under formalin edema . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 48

*Uruzbaev Rinat Maratovich, Bychkov Vitaliy Grygorevich,*

*Yuzhakova Ekaterina Andreevna*

The effect of NiTi alloy supernatant on the proliferative activity of skin elements in a burn wound . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 53

## Section 3. General biology . . . . . . . . . . . . . . . . . . . . . . . . . . . . . .. . . . . . . . 55

*Mirkhamidova Parida*

A suppression of toxic actions of pesticides by antioxidantive preparations . 55

## Section 4. Preventive medicine. . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 57

*Mamedova Guzalya Bakirovna, Maksudova Nargiza Adilovna,*

*Sapiohunova Hilola Muminovna*

Development the marketing department in medical institutions . . . . . . . . . . 57

## Section 5. Physiology. . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 60

*Mamedov Arif Mamed oglu, Ganiyeva Fidan Ilgarov qızı*

The distribution of coherence relations of the rapher nucleus and

structures the visual system of quiet wakefulness in rabbits . . . . . . . . . . . . . 60

*Nifontova Oksana Lvovna, Setyaeva Natalya Nikolaevna,*

*Kostokmaeva Mariyam Kodkhodmaevna*

Evaluation of physical development of primary schoolchildren

(Khants) living in conditions equal to the Far North . . . . . . . . . . . . . . . . . . . 63

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