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EXPERIMENTAL STUDY OF THE ANTIPYRETIC EFFECT OF OXICAMS AND THEIR COMPOSITIONS WITH CAFFEINE

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Abstract. *The experimental study of the influence of caffeine on the antipyretic activity of oxicams in rats was carried out. Meloxicam, piroxicam and their adjuvant caffeine were selected as drugs. According to the results of experimental studies, it was found that meloxicam has the highest antipyretic activity (89,24 %) in 3 hours after administration and exceeded the antipyretic activity of the reference drug. Addition of caffeine to meloxicam did not promote increasing of the meloxicam antipyretic activity, so this composition is considered inappropriate in relation to its antipyretic effect. The antipyretic activity of piroxicam was lower comparing to the reference drug diclofenac sodium. Addition of caffeine to piroxicam promotes increasing of the piroxicam antipyretic activity in 3 hours after administration of the drug. This exceeded the piroxicam antipyretic activity in 1,3 times but did not reach diclofenac sodium activity. The results of experimental studies can become the basis for the creation of new domestic combined medicines.*

Keywords*: meloxicam, piroxicam, caffeine, antipyretic effect, pharmaceutical composition.*

Introduction. Despite the richness of the pharmaceutical market in Ukraine by the nonsteroidal anti-inflammatory drugs (NSAIDs) and non-narcotic analgesics (NNA), the search for new drugs and modifications of already known medicines of these groups is the subject of preclinical research of modern scientists [1].

Combined pharmacotherapy with the addition of caffeine, which is the most commonly used psychotropic substance in the world and an adjuvant to NSAIDs, is often used in medical practice. A lot of pharmaceutical compositions of NSAIDs and NNAs with caffeine are known, but there are no oxicam compositions in pharmacy practice. Oxicams are NSAIDs, derivatives of pyridine-2-ylamide-3-carboxylic acid. They include piroxicam, isoxicam, sudoxicam, meloxicam, tenoxicam and lornoxicam [2, 3]. The mechanism of oxicams action, like other NSAIDs, is in inhibition of the cyclooxygenase enzyme (COX), which provides the transformation of arachidonic acid to prostaglandins (PG), as well as a decrease of the thromboxane synthesis, which leads to inhibition of the development of inflammatory process, reduction of pain, and can lead to decreasing the body temperature. We have previously studied various types of pharmacological activity and quantum-chemical properties of NSAIDs (oxicams) [4-16].

The purpose of our study was to investigate the influence of caffeine on the specific pharmacological effect of NSAIDs (oxicams) of different chemical structures. Possibility to achieve a stronger pharmacological action (analgetic and anti-inflammatory) for composition comparing with a single drug became the basis of our study.

We chose two drugs of different chemical structure and their composition with caffeine.

Piroxicam (4-hydroxy-2-methyl-N-2-pyridinyl-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide) has anti-inflammatory, analgesic and antipyretic effects (fig. 1). An anti-inflammatory effect of piroxicam exceeds such for a significant number of other anti-inflammatory drugs.

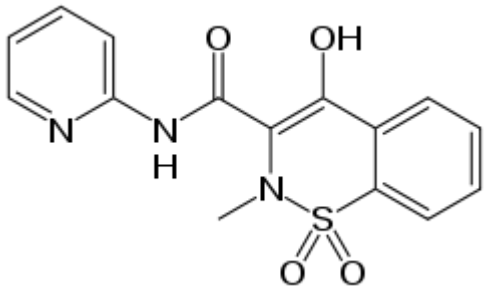

Fig. 1. Piroxicam
(4-hydroxy-2-methyl-N-2-pyridinyl-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide)

Piroxicam inhibits the activity of both COX-1 and COX-2, reduces the synthesis of PG, including PGE_1, PGE_2, $PGE_{2\alpha}$ and thromboxanes, and inhibits phagocytosis, platelet aggregation. Piroxicam is a nonselective COX inhibitor, which causes a greater number of side effects from the digestive system (including gastrointestinal bleeding), comparing to other NSAIDs [17-20].

Meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide) has anti-inflammatory, analgesic and antipyretic actions (fig. 2).

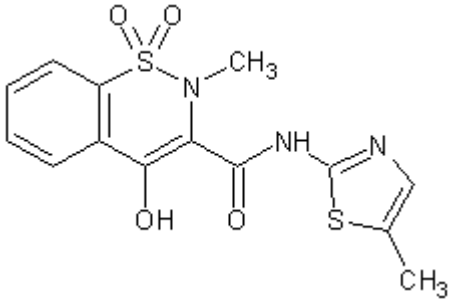

Fig. 2. Meloxicam
(4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide)

In contrast to piroxicam, meloxicam is a selective inhibitor of COX-2 isoform, regulating the synthesis of PG at the inflammation cell, which contributes to a reduction of the amount of side effects from the digestive and urinary systems, but the anti-inflammatory and analgesic effects of the drug are not reduced. Meloxicam increases activity of COX-1, which participates in the synthesis of PG and regulation of blood flow in kidneys, in much more less degree and protects the mucous membrane of the stomach. The selectivity of meloxicam may decrease if it is administrated in high doses, used during long terms and because of individual peculiarities of the organism [22, 23].

Caffeine (1,3,7-trimethylxanthine) is an alkaloid which is in composition of coffee beans, tea leaves, nuts, squill, and is a purine derivative (fig. 3).

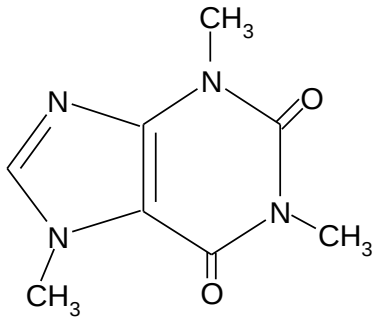

Fig. 3. Caffeine (1,3,7-trimethylxanthine)

It is known that caffeine blocks the central and peripheral adenosine receptors, inhibits the activity of phosphodiesterase, and promotes the stabilization of the transfer of nerve impulses. It regulates and enhances the processes of excitation in the cerebral cortex, respiratory and vascular centers, activates conditioned reflexes, motor activity, stimulates the central nervous system. In

previous studies we carried out an animal study (mature male WAG lines rats) of pharmacological activity (analgesic of peripheral and central genesis, anti-inflammatory) of the NSAIDs of oxicam group (piroxicam and meloxicam) with potentiating action of caffeine using intragastric route of administration [10, 11, 15, 16].

A derivative of acetic acid – diclofenac sodium (Sodium salt of 2-[(2,6-dichlorophenyl)-amino]-phenylacetic acid, D-Na), which according to the literature data shows anti-inflammatory, analgesic and antipyretic effects, was selected as a reference drug (Fig. 4). D-Na has stronger anti-inflammatory and analgesic effects than acetylsalicylic acid, butadione, etc. [24-26].

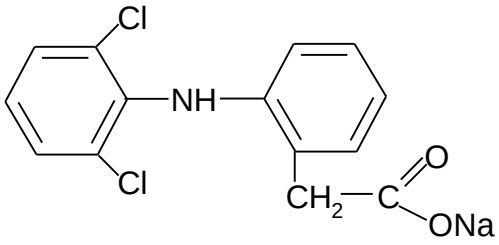

Fig. 4. Diclofenac sodium (Sodium salt of 2-[(2,6-dichlorophenyl)-amino]-phenylacetic acid)

Study of antipyretic activity was carried out on the model of milk-fever in laboratory animals – mature male white WAG lines rats of both sexes. Pasteurized and warmed up to 37-40 °C cow's milk was used as a protein pyrogen. It was administered intramuscularly in a dose of 0,5 mL per 100 g of animal weight [27]. The maximum temperature rise was observed in 4 hours after injection of milk. Drugs (piroxicam, meloxicam and diclofenac sodium) were administered 1 hour before the maximum rise of temperature (preventive administration). Registration of rectal temperature was carried out in dynamics by electrothermometer in 1, 2, 3 and 24 hours after administration of the drug.

The antipyretic activity was calculated according to the formula:

$$A = \frac{B - C}{B} \cdot 100\%,$$

where A – antipyretic activity, %;
B – change of temperature in control group;
C – change of temperature in test group.

Animals were divided into 7 groups of 6 animals in each. Animals of the 1st group were the control group, they were exposed one-time to 3 % starch mucus injected intragastric (2 mL per 200 g of rat). Animals of groups 2-7 were exposed one-time to suspension of experimental drugs and their compositions in 3 % starch mucus 1 hour before the maximum rise of temperature (preventive administration): animals of the 2nd group – piroxicam (1,3 mg per 1 kg of animal weight); animals of the 3rd group – meloxicam (0,6 mg per 1 kg of animal weight); animals of the 4th group – adjuvant caffeine (0,6 mg per 1 kg of animal weight); animals of the 5th group – pharmaceutical composition of piroxicam (1,3 mg per 1 kg of animal weight) with caffeine (0,6 mg per 1 kg of animal weight); animals of the 6th group – pharmaceutical composition of meloxicam (0,6 mg per 1 kg of animal weight) with caffeine(0,6 mg per 1 kg of animal weight); animals of the 7th group – reference drug diclofenac sodium (8,0 mg per 1 kg of animal weight). The research was carried out in accordance with the methodological recommendations of the State Pharmacological Center of the Ministry of Health of Ukraine [27]. The number of animals and their distribution into groups were chosen in consideration of the economical approach, bioethical rules and statistical requirements [28]. Doses for rats were recounted from human ones using a coefficient of specific sensitivity according to Yu. R. Rybolovlev [29].

Statistical analysis of the obtained data was carried out using generally accepted methods of statistical analysis (average, average error, probability criterion of Fisher-Student) using the programs MS Excel and Stat Graphics Plus 2.1 [30].

Research results. Milk-fever in rats is declared by an increasing of the body temperature (38,8-39,8) °C. The maximum temperature rise is observed at 4th hour of the experiment after the injection of milk. Hyperthermia remains in the control group for 7 hours of observation, decreasing to 36,72 ± 0,21 °C at the end of the experiment (in 24 hours) (Table 1).

Table 1. Study of the effect of oxicams, caffeine and their pharmaceutical compositions on rectal temperature in rats (n = 6)

№	Groups of animals	Measures of rectal temperature, before and after drug administration, °C				
		initial	in 1 hour	in 2 hour	in 3 hour	in 24 hours
1.	Control	36,42±0,20	38,08±0,19	38,03±0,17	38,02±0,18	36,72±0,21
2.	Piroxicam	37,48±0,15*	38,78±0,14 */***/****/*****/ *******/********	38,57±0,14 ***/****/******/ *******/*********	38,20±0,10 ***/****/******/ *******/**********	37,67±0,10*
3.	Meloxicam	37,38±0,12*	37,88±0,11 **/*****/*******/********	37,73±0,11 **/******/*********	37,55±0,12 **/*****	37,40±0,11*
4.	Caffeine	37,37±0,17*	38,10±0,09 **/********	37,98±0,05 **/*********	37,88±0,06 **/*******/**********	37,42±0,10*
5.	Piroxicam + caffeine	37,18±0,14*	38,48±0,13 ***/******/********	38,25±0,10 ***/*******/ *********	38,10±0,11 ***/******/ *******/**********	37,33±0,15
6.	Meloxicam + caffeine	37,37±0,10*	38,00±0,09 **/*****/********	37,78±0,08 **/******/*********	37,60±0,07 **/****/*****	37,43±0,08*
7.	Diclofenac sodium	37,25±0,11*	38,28±0,10 **/***/********	37,95±0,09 **/*********	37,68±0,09 **/*****/**********	37,35±0,11*

Notes: * – the probability of the results towards the control group, P < 0,05;
** – the probability of the results towards the administration of piroxicam, P < 0,05;
*** – the probability of the results towards the administration of meloxicam, P < 0,05;
**** – the probability of the results towards the administration of caffeine, P <0,05;
***** – the probability of the results towards the administration of the composition of piroxicam with caffeine, P < 0,05;
****** – the probability of the results towards the administration of the composition of meloxicam with caffeine, P < 0,05;
******* – the probability of the results towards the administration of the reference drug diclofenac sodium, P < 0.05.
******** – the probability of the results in 1 hour after the administration of the drug towards the initial temperature, P < 0.05.
********* – the probability of the results in 2 hours after the administration of the drug towards the initial temperature, P < 0.05.
********** – the probability of the results in 3 hours after the administration of the drug towards the initial temperature, P < 0.05.

After administration of piroxicam a peak of temperature rise was observed and it gradually decreased during 1, 2, 3 hours. However, it wasn't observed any positive antipyretic effect (38,20 ± 0,10 °C). The temperature reached the initial values 24 hours later (37,67 ± 0,12 °C).

Analysis of the dynamics of meloxicam antipyretic effect has shown that the hypothermic action of this drug had started in 1 hour after administration (up to 37,88 ± 0,11 °C). Then the effective temperature decreasing was observed during 3 hour. Administration of the drug 1 hour before the maximum of the temperature rise didn't give the expected peak of the temperature, which proves the effectiveness of its antipyretic effect.

After administration of caffeine a peak of temperature rise was reached (38,10 ± 0,09 °C) and no significant decrease of the temperature was observed in 1, 2, 3 hours after the administration of the drug. The temperature reached the norm after 24 hours of the experiment

When added caffeine to piroxicam there was a slight decrease of a peak of temperature rise: after 1, 2, 3 hours the temperature decreased insignificantly (38,10 ± 0,11 °C) comparing to the administration of piroxicam, therefore this composition is considered inappropriate in relation to the antipyretic effect.

When added caffeine to meloxicam a peak of temperature rise (38,00 ± 0,09 °C) was observed in 1 hour after the administration of the composition, then it was a gradual decreasing of temperature in 2 and 3 hours after the administration of the composition of drugs (37,60 ± 0,07 ^{0}C). The rectal temperature practically did not differ from the initial one (37,43 ± 0,08 ^{0}C) in 24 hours after the injection of milk.

After administration of the reference drug diclofenac sodium, the temperature rise was (38.28 ± 0,10 °C) and it gradually decreased in 1, 2, 3 hours after administration of the drug (up to 37,70 ± 0,10 °C). And it reached the initial value in 24 h of the experiment (37,35 ± 0,11 °C).

Comparing the antipyretic activity of oxicams, caffeine and their pharmaceutical compositions we can select the leader – meloxicam, which had the highest antipyretic activity in 3 hours after administration (89.24 %) and this trend persisted during the experiment. This exceeded the antipyretic activity of the reference drug (Table 2). However, the addition of caffeine to meloxicam did not increase these measures, therefore we consider their pharmaceutical composition inappropriate.

Table 2. Comparative characteristics of the antipyretic activity of oxicams, caffeine and their pharmaceutical compositions

№	Groups of animals	Antipyretic activity, %			
		in 1 hour	in 2 hour	in 3 hour	in 24 hour
1.	Piroxicam	21,69	32,30	54,43	36,67
2.	Meloxicam	69,88	78,26	89,24	93,33
3.	Caffeine	56,02	59,01	58,86	83,33
4.	Piroxicam + caffeine	21,69	33,54	68,99	50,00
5.	Meloxicam + caffeine	62,05	74,53	85,44	80,00
6.	Diclofenac sodium	37,95	56,52	72,78	66,67

The antipyretic activity of piroxicam was lower than that of the reference drug diclofenac sodium during the experiment. Addition of caffeine to piroxicam contributed to an increase of the antipyretic activity of piroxicam in 3 hours after the administration of the drug (68,99 %), which exceeded the antipyretic activity of pure piroxicam in 1,3 times but did not reach the antipyretic activity of diclofenac sodium.

Conclusions. It was found that meloxicam is a leader. Addition of caffeine to meloxicam is not feasible. Caffeine has increased the antipyretic activity of piroxicam, but obtained data are statistically significantly different from meloxicam, diclofenac sodium, and therefore addition of caffeine to piroxicam is also considered inappropriate in relation to the antipyretic effect.

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