ADVANCES OF SCIENCE

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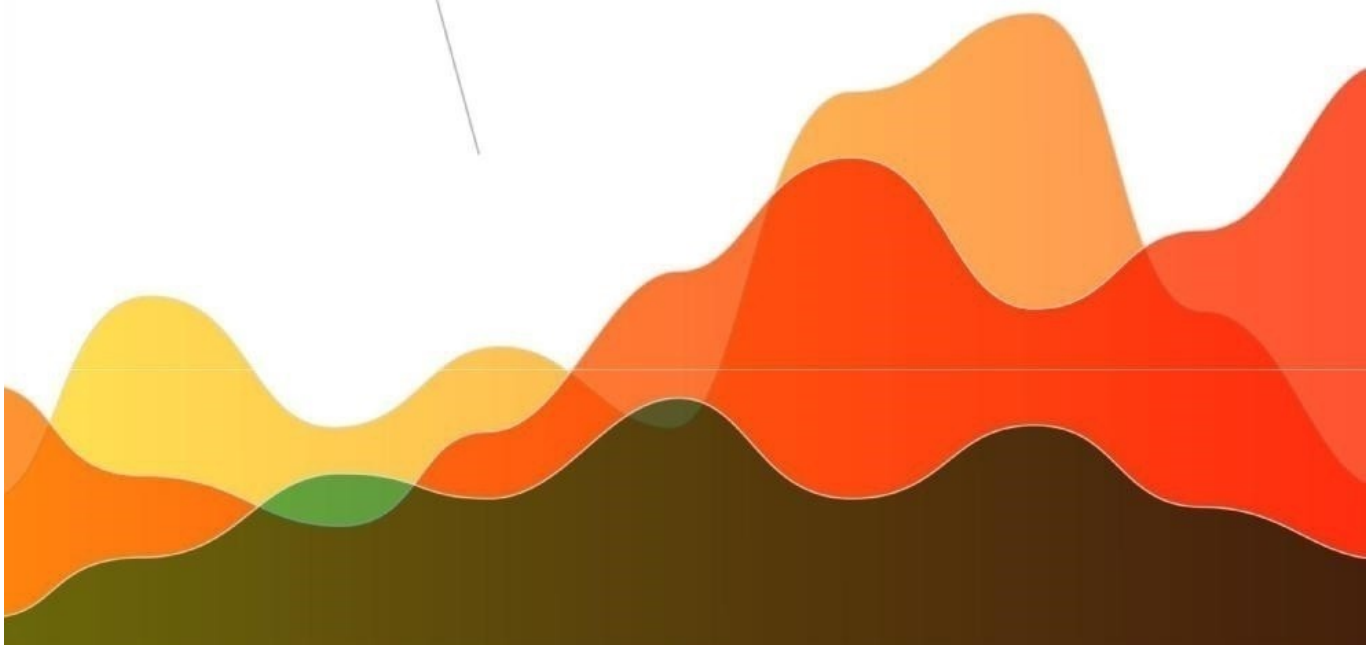

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COMPARATIVE ANTIPYRETIC ACTIVITY OF OXICAMS OF DIFFERENT CHEMICAL STRUCTURE

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At present time, there is a significant arsenal of modern nonsteroidal anti-inflammatory drugs (NSAIDs) and non-narcotic analgesics that are used to treat many diseases. NSAIDs are a group of drugs of different chemical structure (mainly derivatives of organic acids): salicylates, derivatives indoloacetic and phenylacetic

acids, oxicams, and others [1]. They are applied in many branches of modern medicine due to their anti-inflammatory, analgesic, antipyretic and other actions [2, 3]. But the development of undesirable effects (peripheral edema, gastro-, hepato-, oto-, cardio-, nephrotoxicity, hypersensitivity, skin manifestations, neurological symptoms) complicates their use [4, 5]. The antipyretic properties of NSAIDs allow to use them in fever. There are two ways of hypothermic action of NSAIDs. The first one is associated with inhibition of the prostaglandin biosynthesis (and as a consequence, a blockade of hyperthermic action of pyrogens), and the second is an active effect directly on pyrogens [6-9].

Earlier we have investigated various types of pharmacological activity of NSAIDs of various chemical structure [10-15]. 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 oxicams group (piroxicam and meloxicam) using intragastric route of administration [16-22]. They are derivatives of pyridine-2-ilamide and, besides the anti-inflammatory action, have a sufficiently pronounced analgesic activity and are used to treat rheumatic diseases, neuralgia and other diseases [23-28]. We have selected 2 representatives of oxicams as research objects.

Our purpose was an experimental study of the effect of oxycams of different chemical structure (piroxicam and meloxicam) on antipyretic activity for rats.

Diclofenac sodium (sodium salt of 2-[(2,6-dichlorophenyl)amino]phenylacetic acid) is the leading compound among the most effective NSAIDs due to the combination of anti-inflammatory and analgesic action with satisfactory tolerance. Since diclofenac sodium has an anti-inflammatory, analgesic and antipyretic effect [29-31] it was chosen as a reference drug.

The antipyretic effect was studied on the model of milk-fever. 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 [32]. 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 during 24 hours of observation (after 1, 2, 3 hours and at the end of the experiment). 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 4 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 2-4 were exposed one-time to suspension of experimental drugs in 3 % starch mucus: 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 – 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 [32]. The number of animals and their distribution into groups were chosen in consideration of the economical approach, bioethical rules and statistical requirements. Doses for rats were recounted from human ones using a coefficient of specific sensitivity according to Rybolovlev Yu.R. [33].

The work was carried out on laboratory animals from the experimental-biology clinic of the Kharkiv national medical university, taking into account the norms of storage, care and feeding (air temperature – 23-25 °C, lighting – in the room 100 Lx, in a cage – 20-40 Lx). Length of stay of laboratory animals – 1.5 months; period of acclimatization – 2 weeks; main ration – vegetables, fodder beets; water source – tap water. The rats were kept in vivarium in accordance with the rules of humane treatment to laboratory animals. The research was carried out in accordance with the principles of the "European Convention for the Protection of Vertebrate Animals

used for Experimental and Scientific Purposes" (Strasbourg, 1986) [34] and the Decree of the First National Congress on Bioethics (Kyiv, 2007) [35]. Experiments were carried out in the first half of the day, which, according to literature data, is consistent with the dependence of the main pharmacological parameters and pharmacological activity of the circadian rhythms taken for the study of drugs [36-38].

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 [39].

Rats' milk-fever was detected by an increase of body temperature (38,8-39,8) °C. The maximum increase is observed on the 4th h of the experiment. Hyperthermia remains in the control group for 7 h of observation, decreasing to 36,72 ± 0,21 °C at the end of the experiment (within a day).

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 h. 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 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).

Thus, comparing the antipyretic activity of oxycams, we can select the leader – meloxycam, 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 during the whole experiment (72.78 %). The

maximum decreasing of temperature was observed in 3 hours after administration of piroxicam (38,20 ± 0,10). The antipyretic activity of piroxicam was lower (54.43 %) than for the reference drug.

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