EXPERIMENTAL STUDY OF THE PERIPHERAL COMPONENT OF THE ANALGESIC ACTIVITY OF PHARMACEUTICAL COMPOSITIONS OF COXIBS WITH CAFFEINE

Syrova Ganna
Doctor of Pharmaceutical Sciences, Professor
Kharkiv National Medical University
Kharkiv, Ukraine
Zavada Oksana
PhD (Pharmaceutical Sciences)
Kozub Svitlana
PhD (Technical Sciences), Associate Professor
Kharkiv National Medical University
Kharkiv, Ukraine

Introduction. In connection with the importance and relevance of anesthesia, modern medicine and pharmacy have a large arsenal of means and methods of fight against pain syndrome. It is well known that the nociceptive system is an interesting physiological apparatus, and pain is considered as an evolutionarily formed process under the action of nociceptive damaging factors (or a process that occurs when the pain-relieving system is suppressed). It is also known that drugs that affect transduction processes (local anesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs) [1]), block transmission (local anesthetics), affect modulation processes (opioid analgesics, stimulants) are used as painkillers central alpha 2-adrenoreceptors) that affect perception processes (opioids, barbiturates, tranquilizers, neuroleptics, inhalation anesthetics, ketamine, sodium oxybutyrate), which stimulate antinociceptive mechanisms (opioids, tranquilizers, ketamine, sodium oxybutyrate). Therefore, NSAIDs act on the processes of pain transduction, they suppress the synthesis of prostaglandins, which is due to a decrease in the activity of cyclooxygenase (COX) - the key enzyme in the metabolism of arachidonic acid, therefore NSAIDs block pain, fever, hyperthermia; in addition, NSAIDs inhibit the migration of neutrophils and reactivate lymphocytes, which explains their anti-

inflammatory and analgesic effects [2]. It is known that physiological prostanoids are produced by COX-1, therefore they protect gastric mucosa, vascular and platelet homeostasis, renal regulation of sodium-hydrogen balance, and pathological prostanoids are produced by COX-2, they affect inflammatory processes. It is also known that according to the mechanism of action, NSAIDs can be classified into four main groups [3]: 1. Selective inhibitors of COX-1 (small doses of aspirin), 2. Non-selective inhibitors of COX-1 and COX-2 (sodium diclofenac, ibuprofen, indomethacin, piroxicam, ketoprofen, etc.), 3. Selective COX-2 inhibitors (meloxicam, nimesulide), 4. Specific COX-2 inhibitors (celecoxib, rofecoxib, etoricoxib). The last group, according to the literature, is an effective and relatively safe NSAIDs (however, we know about their side effects: instability of blood pressure from the side of the cardiovascular system, risk of myocardial infarction), so we were interested in investigating their analgesic effect on laboratory animals. Due to the fact that the reception, transmission and analysis of nociceptive information and the formation of the feeling of pain are provided by both central and peripheral neuronal formations, it is advisable to study both the central and peripheral components of the pain-relieving reaction of substances - potential analgesics.

One of the directions of modern pharmacy and medicine is the creation of pharmaceutical compositions, which is justified by the possibility of achieving a pronounced analgesic effect, strengthening it when using an adjuvant [4-7]. Experimental, preclinical and clinical research confirm the advantages of pharmaceutical compositions over monopreparations in the pharmacotherapy of pain [8]. Knowing the physiological, biochemical, and pharmacological features of caffeine, its introduction into combined pharmaceutical preparations based on NSAIDs is expedient on the basis of the possibility of enhancing their pain-relieving effect with caffeine.

Materials and methods. Study of the effect of coxibs 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-pyrazol-1-yl]benzenesulfonamide (celecoxib) and 4-(4-(methylsulfonyl)phenyl)-3-phenylfuran-2(5H) -one (rofecoxib) and their pharmaceutical compositions with 1,3,7-trimethylxanthine (caffeine) were carried out

on white, sexually mature male rats of the WAG line with an average weight of 190-220 g. The source of obtaining and location of the laboratory animals is the vivarium of the KhNMU (air temperature 23 -25°C, lighting in the room 100 lux, in the cage - 20–40 lux). Acclimatization period of animals was 2 weeks; the main diet is vegetables, fodder beets; the source of water is settled tap water. Rats were kept in a vivarium in accordance with the rules of humane treatment of laboratory animals.

The research was carried out in accordance with the methodological recommendations of the State Pharmacological Center of the Ministry of Health of Ukraine. When choosing the number of animals and dividing them into groups, an economical approach, bioethical rules and statistical requirements were taken into account [9, 10]. The research was conducted in compliance with the principles of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Scientific Purposes" (Strasbourg, 1986) and the resolution of the Third National Congress on Bioethics (Kyiv, 2007) [11].

The experiments were conducted in the early hours of the day, which is according to the literature in consistent with the dependence of the main pharmacological parameters and the pharmacological activity of the drugs accepted for the study on circadian rhythms [12].

The analgesic effect of peripheral genesis was studied by the peripheral component of the nociceptive reaction. Comparative characteristics of the analgesic effect of coxibs, caffeine and their pharmaceutical compositions were carried out according to the screening model of "acetic acid writhings". In the mechanism of the development of pathology under the influence of acetic acid, the activation of the kallikrein-kinin system, prostaglandins, biogenic amines, leukotrienes, which are endogenous mediators of inflammation and contribute to the development of abdominal muscle writhings, accompanied by stretching of the hind limbs and bending of the back, occurs. Writhings were induced by a single intra-abdominal injection of 0.6% acetic acid solution. The researched pharmaceutical drugs and their compositions, as well as 3% starch mucus, were administered intragastrically (intravenously) 1 hour before phlogogen administration. The animals were observed

for 20 minutes after the introduction of acetic acid and the number of writhings in rats was counted [8]. The animals were divided into 7 groups and each group consist of 6 animals. The animals of the 1st group were the control, they were given a single intravenous injection of 3% starch mucus (2 ml per 200 g of rat). The animals of the 2nd-7th groups were administered experimental pharmaceuticals and their compositions once intravenously in the form of a suspension on 3% starch mucus: animals of the 2nd group - rofecoxib (1.5 mg per 1 kg of rat weight), 3rd group - celecoxib (5 mg per 1 kg of rat weight), 4th group - caffeine (0.6 mg per 1 kg of rat weight), 5th group - rofecoxib composition (1.5 mg per 1 kg of rat weight) with caffeine (0.6 mg per 1 kg of animal weight), the 6th group - a composition of celecoxib (5 mg per 1 kg of rat weight) with caffeine (0.6 mg per 1 kg of animal weight), the 7th group - [2- (2,6-Dichloroanilino)phenyl]acetic acid (diclofenac sodium) (8.0 mg per 1 kg of animal weight). Analgesic activity (AA) was evaluated by the ability of coxibs (celecoxib and rofecoxib), caffeine, their pharmaceutical compositions and diclofenac sodium to reduce the number of writhings in the experimental groups of animals compared to the control and was expressed as a percentage according to the formula:

$$AA = \frac{Cc - Ce}{Cc} \cdot 100\%,$$

where AA – the analgesic activity, %;

C_c – the average number of writhings in the control group;

C_e – the average number of writhings in the examined group [13].

AA of coxibs and caffeine when administered alone were also compared with AA when administered in combination (celecoxib+caffeine and rofecoxib+caffeine) and with the reference drug. Statistical processing of the obtained data was carried out using generally accepted methods of statistical analysis (mean, error of the mean, Fisher-Student probability criterion) using MS Excel and Stat Graphics Plus 2.1 programs [14].

Results and discussion. Experimental studies of the peripheral component of AA showed its presence in experimental coxibs: when rofecoxib was

mono-administered (group 2), the reduction in writhings reached 9.67±0.21, and when celecoxib was mono-administered (group 3) – 11.17±0.31, against 22, 00±0.86 in control. Adjuvant caffeine (group 4) reliably reduced the number of writhings to 7.81±0.48 compared to the control group and was the leader of the study, but its data were inferior to the reference drug (group 7), which reduced the number of writhings in animals to 7.20 ± 0.17 this experiment. The researched pharmaceuticals can be ranked according to the effectiveness of the peripheral component of AA: sodium diclofenac (67,3 %) > caffeine (64,5 %) > rofecoxib (55,9 %) > celecoxib (49,1 %) (Fig. 1). Addition of the adjuvant caffeine to rofecoxib and celecoxib contributed to a statistically significant reduction in the number of writhings compared to the coxib monoadministration groups: when the pharmaceutical composition of rofecoxib with caffeine (group 5) was administered, a statistically significant decrease in the number of writhings was observed to 7.0 ± 0.43 compared to group 2, while administration of the pharmaceutical composition of celecoxib with an adjuvant (group 6) also observed a statistically significant decrease in the number of writhings to 7.63 ± 0.43 compared to group 3. The analgesic effect of the pharmaceutical compositions was 67.8% (group 5), 65.3%, respectively (group 6), therefore, the pharmaceutical composition of rofecoxib with caffeine turned out to be the leader of our study - according to AA, it surpassed the reference drug diclofenac sodium (67.3%) - group 7 (Fig. 1).

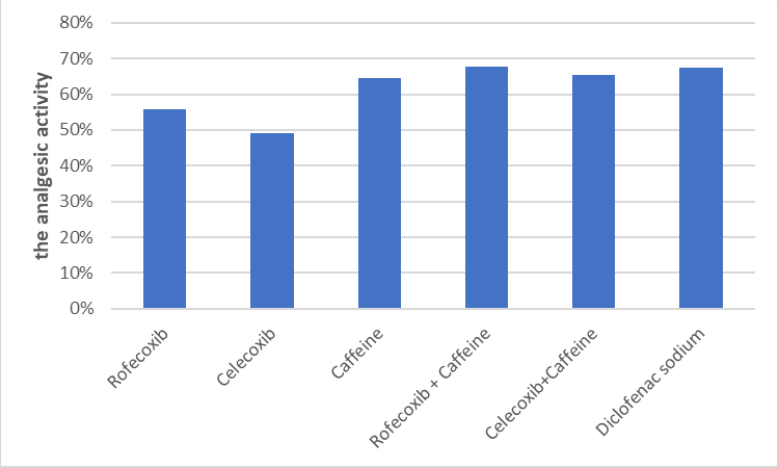

Fig. 1. The results of experimental studies of the peripheral component of the analgesic activity of coxibs and their pharmaceutical compositions with caffeine

Conclusions

1. Analysis of the results of experimental studies of the peripheral component of pain-relieving activity shows that the studied pharmaceutical drugs for AA can be placed in the following series: Diclofenac sodium (67,3 %) > Caffeine (64,5 %) > Rofecoxib (55,9 %) > Celecoxib (49,1 %)

2. The creation of pharmaceutical compositions based on coxibs with caffeine is advisable to confirm the strengthening of their AA: caffeine has confirmed its role as an adjuvant.

3. In an experiment on laboratory rats, the pharmaceutical composition of rofecoxib with caffeine was the leader in the study of the peripheral component of AA; according to the investigated indicator, pharmaceutical compositions can be arranged in a series: Rofecoxib+caffeine (67,8 %) > diclofenac sodium (67,3 %) > celecoxib+caffeine (65,3 %)

4. We consider the pharmaceutical compositions of coxibs with caffeine studied by us to be promising for further study.

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