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Influence of the 4-thiazolidinone derivative Les-6490 on the inflammatory process in rats compared to nimesulide

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Nonsteroidal anti-inflammatory drugs, which are used to treat numerous diseases, can cause a number of side effects. Therefore, the development of new molecules with anti-inflammatory and antimicrobial properties is an important task of modern medicine and veterinary medicine. A promising group of drugs with the above-described action are derivatives of 4-thiazolidinones. The thiazolidinone ring is a part of many existing potential antimicrobial and anti-inflammatory agents. The combination with a pharmacophore pyrazole moiety in the same structure, may result in enhanced therapeutic benefit. **Aim.** To assess the effects of the 4-thiazolidinone derivative Les-6490 and the conventional anti-inflammator y agent Nimesulide on hematological and biochemical parameters in rats within the context of an induced inflammatory process. **Methods.** The inflammatory process in animals was modeled with complete Freund's adjuvant. (CFA). The assessment of changes in the animal body was carried out by the biochemical indicators of blood serum: activity of transaminases and alkaline phosphatase, indicators of total protein and albumin content, creatinine and urea levels, indicators of lipid metabolism (total cholesterol and triglycerides), quantitative levels of phosphorus and calcium as markers of mineral exchange. **The results.** The compound Les-6490 slows down the development of the inflammatory process in the AF inflammation model. It was determined that

the development of the CFA-induced inflammatory process was not accompanied by significant changes in the concentration of total protein and albumin. Nimesulide caused a significant 22.7 % ($p < 0.001$) decrease in the albumin concentration, whereas no changes were observed with the compound Les-6490 against the background of FA. The self action of Les-6490 was accompanied by a significant decrease of urea compared to the control. The introduction of Les-6490 against the background of the inflammatory process led to a 9.9 % ($P < 0.001$) increase in the level of creatinine in the blood and a decrease in the activity of transaminases. It was confirmed that the action of Nimesulide is accompanied by a decrease in the amount of phosphorus and calcium in the serum, whereas Les-6490 does not show such effect. **Conclusions.** The studied compound Les-6490 is not inferior to the level of anti-inflammatory activity of Nimesulide in markers of the inflammatory process; the research of influence of the compound Les-6490 on the markers of liver diseases in comparison with the action of Nimesulide did not reveal a significant hepatotoxic effect of the substance; the compound Les-6490 showed a hypolipidemic effect that was similar to the effects of Nimesulide, both under the conditions of self-administration and when modeling the inflammatory process; the investigated compound can be considered promising for further research as a substance with an anti-inflammatory effect. The compound Les-6490 slows down the development of the inflammatory process in the AF inflammation model.

Keywords: NSAIDs, Nimesulide, Freund's adjuvant, inflammatory process, 4-thiazolidinones, protein, albumin, creatinine, leukocytes, lipid metabolism, triglycerides.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs), used in the treatment of numerous diseases, can cause a number of side effects, the main of which is an ulcerogenic effect on the mucous membranes of the gastrointestinal tract. NSAIDs can also cause side effects in the hepato-biliary, cardiovascular, excretory systems, affect the functioning of the liver and lungs [1]. The mechanism of action of NSAIDs is based on the inhibition of the activity of cyclooxygenase (COX), which exists in two main isoforms COX-1 and COX-2, differ structurally and functionally [2, 3]. COX-1 is a constitutive isoform that is expressed throughout the body and synthesizes prostaglandins involved in numerous physiological processes. In particular, with the participation of COX-1, prostaglandins are formed. They regulate the secretion of hydrochloric acid and stimulate the formation of protective mucus in the stomach, influence the process of proliferation and intercellular integration in various organs, regulate vascular homeostasis, platelet aggregation, and kidney function. COX-2 is an inducible form of the enzyme, which expression increases during inflammation, ensuring the synthesis of relatively large concentrations of prostaglandins, that act as the inflammation mediators [4, 5].

Considering the numerous side effects of currently existing NSAIDs, the development of new anti-inflammatory drugs devoid of side effects is actively underway. In this sense, the compounds capable of simultaneous inhibiting the cyclooxygenase and lipoxygenase (LOX) pathways of arachidonic acid metabolism are of significant interest. Dual-acting COX/LOX inhibitors could provide multiple advantages

of anti-inflammatory activity, improved protection, and a safer cardiovascular profile compared to conventional NSAIDs. The promising drugs with the above-described effect are the numerous derivatives of 4-thiazolidinones. They have an anti-inflammatory effect and at the same time show reduced gastro- and enterotoxicity [6–11]. Given that the search for new derivatives of 4-thiazolidinones with an anti-inflammatory action continues, we chose the newly synthesized compound Les-6490 for the analysis.

Various models are used to test the anti-inflammatory effects of drugs, among which we chose the model of the inflammatory process induced by complete Freund's adjuvant (CFA) [12, 13]. The NSAID Nimesulide (selective COX-2 inhibitor), which belongs to the group of methanesulfonanilides, was chosen as the drug for comparing the effects of Les-6490. The data on the pharmacological properties, metabolism and side effects of Nimesulide are well known [14, 15], but information about the potential hepato- and nephrotoxicity of Les-6490 is practically absent. Considering the above, the aim of the study is to compare the effects of Les-6490 and Nimesulide on the blood parameters of rats under the conditions of their self administration and against the background of modeling the inflammatory process by CFA.

Materials and Methods

1. Chemistry

1.1. General remarks

The melting points were measured in open capillary tubes on a BÜCHI B-545 melting point apparatus (BÜCHI Labortechnik AG, Flawil, Switzerland) and were uncorrected. The elemental analyses (C, H, N) were performed using the Perkin-Elmer 2400 CHN analyzer (PerkinElmer, Waltham, MA, USA) and were within ±0.4 % of the theoretical values. The 500 MHz ^{1}H and 100 MHz ^{13}C NMR spectra were recorded on a Varian Unity Plus 500 (500 MHz) spectrometer (Varian Inc., Paulo Alto, CA, USA). All spectra were recorded at room temperature, except where indicated otherwise, and were referenced internally to solvent reference frequencies. Chemical shifts (δ) are quoted in ppm and coupling constants (*J*) are reported in Hz. LC-MS spectra were obtained on a Finnigan MAT INCOS-50 (Thermo Finnigan LLC, San Jose, CA, USA). The reaction mixture was monitored by thin layer chromatography (TLC) using commercial glass-backed TLC plates (Merck Kieselgel 60 F254, Merck, Darmstadt, Germany). Solvents and reagents that are commercially available were used without further purification. The thiazolidine-2,4-dione **(*i*)** and 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **(*ii*)** and were prepared according to the methods described in [16, 17] respectively.

1.2. General procedure for the synthesis of 5-(1,3-diphenyl-1H-pyrazol-4-ylmethylene)-thiazolidine-2,4-dione Les-6490

A mixture of 0.01 mol of thiazolidine-2,4-dione **(*i*),** 0.011 mol of 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **(*ii*)** and 0.015 mol of ammonium acetate in 20 ml of toluene was heated under reflux for 5 h. Yellow crystalline precipitate was filtered off, washed with hexane, and recrystallized from a mixture of DMF-ethanol (1:2). Yield: 85 %, yellow crystal powder, mp 278–280 °C (DMF-EtOH (1:2)).

LC-MS (ESI+): *m/z* 348.0 (100.0 %, $[M+H]^+$). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.40 (t, J = 7.4 Hz, 1H arom.), 7. 47 — 7. 59 (m, 6H, arom. + CH=), 7.63 (d, J = 7.3 Hz, 2H arom.), 8.00 (d, J = 8.0 Hz, 2H, arom.), 8.68 (s, 1H, CH, pyrazole), 12.52 (s, 1H, NH, thiazolidinone). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 115.9, 119.8, 122.5, 123.1, 127.9, 128.4, 129.2, 129.4, 130.1, 131.8, 154.1, 167.5 (C=O), 167.9 (C=O).

2. Animals. Modeling of the inflammatory process

In order to induce the inflammatory process, experimental animals were injected with Freund's adjuvant (AF) in a volume of 0.1 ml subcutaneously in the plantar part of the hind limb [18]. The development of the inflammatory process was evaluated in points: 0 points — no erythema or edema; 1 point — mild erythema or edema; 2 points — moderate edema and erythema in the area from the ankle to the metatarsal bones; 3 points — severe edema and erythema in the area from the ankle to the metatarsal bone; 4 points — edema, erythema, limitation of passive mobility — inability to bend the ankle to the lower leg.

The study of inflammation was performed in the three groups of animals, 6 individuals each: group A (control) — animals were injected with an adjuvant into the pad of the foot of the hind paw, group AL — the adjuvant was injected against the background of the administration of the compound Les-6490, group AN — the adjuvant was injected against the background of nimesulide administration. Observations of the animals began on the first day of the experiment (with an interval of two days) and were carried out until its completion (the 14th day). The circumference of the foot in the zone of maximum expression of the inflammatory process was measured using a flexible ruler with a millimeter scale.

3. Biochemistry

The experimental work was performed on sexually mature non-linear white rats of an initial weight of 220±5.1 g, obtained from the vivarium of the Danylo Halytsky Lviv National Medical University. Research was conducted in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 2005), Directive 2010/63/EU of the European Parliament and of the Council and the Law of Ukraine No. 3447-IV "On the Protection of Animals from Cruelty" as amended from January 14, 2020 No. 440-IX, according to the minutes of the meeting of the commission on the ethics of scientific research, experimental developments and scientific works of Danylo Halytsky LNMU.

The animals were kept on a standard diet for rodents, with free access to water at constant air temperature (20±4 °C) and humidity (50–60 %), and a 12-hour light/dark cycle. Rats were acclimatized for 14 days before experiments.

The inflammatory process in animals was modeled with complete FA, administered according to the generally accepted method, by subcutaneous injection of 0.1 ml into the plantar part of the hind limb [19, 20]. Nimesulide and compound Les 6490 were given to the animals intragastrically using a non-traumatic probe.

60 animals were used in the research and 6 groups of 10 animals each were formed:

1st group (K) — control (intact animals); 2nd group (N) — animals were administered with Nimesulide (dissolved before administration in Tween 80) in a volume of 1 ml at a dose of 15 mg/kg, daily for 14 days; animals of the 3rd group (L) received the newly synthesized compound Les-6490 (dissolved in Tween 80) in a volume of 1 ml at a dose of 10 mg/kg daily for 14 days; animals of the 4th group (A) were injected with FA to induce an inflammatory process; animals of the 5th group (AL) against the background of the inflammatory process induced by FA, were administered with the drug Les 6490 in a volume of 1 ml at a dose of 10 mg/kg; the animals of the 6th group (AN) received Nimesulide (1 ml at a dose of 15 mg/kg) administered against the background of the inflammatory process. Collection of material (blood and blood serum) for research was carried out on the 14th day after the administration of drugs.

To assess the changes in the animal body and compare the effects caused by Nimesulide and the compound Les-6490 under the conditions of an experimental inflammatory process, a number of biochemical indicators of the blood serum of experimental animals were used: activity of transaminases and alkaline phosphatase, indicators of total protein and albumin content, creatinine and urea levels, indicators of lipid metabolism (total content of cholesterol and triglycerides), quantitative level of phosphorus and calcium as markers of mineral metabolism. The blood serum research was carried out in the biochemical laboratory of the Institute of Animal Biology of the National Academy of Sciences of Ukraine (biochemical analyzer Humalyzer 2000 (Human; automatic type).

The development of the inflammatory reaction was monitored by indicators of the quantitative content of leukocytes, ESR, as well as by recording the edematous and exudative effect at the injection site.

Results and discussion

Chemistry

The 4-thiazolidinone-bearing derivative Les-6490 **(iii)** has been synthesized by Knoevenagel condesation of 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **(i)** and thiazolidine-2,4-dione **(ii)** with satisfactory yield (85 %) and purity (Fig. 1).

The structure of the synthesized compound Les-6490 was confirmed by ^{1}H, ^{13}C NMR, and LC-MS spectra. In the ^{1}H and ^{13}C NMR spectra, the signals of all the atoms appear in the relevant magnetic field with an appropriate spectral pattern. The molecular ion peak observed at the *m/z* value of 348.0 $[M+H]^+$ in the positive ionization mode in the mass spectrum

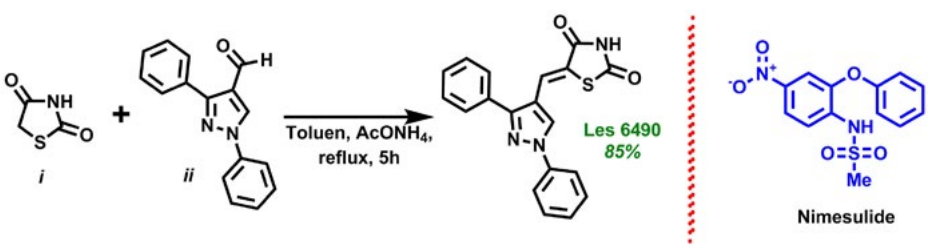

Fig. 1. Scheme of 5-(1,3-diphenyl-1*H*-pyrazol-4-ylmethylene)-thiazolidine-2,4-dione, Les-6490 synthesis and Nimesulide structure.

Table 1. **Development of the inflammatory process induced by Freund's adjuvant**

Groups of animals	Observation days/points						
	1	3	5	7	9	11	13
A	0	1	2	3	4	4	4
AL	0	0	1	1	2	3	3
AN	0	1	1	2	3	4	4

A — Freund's adjuvant; AL is an adjuvant against the background of the introduction of compound Les-6490; AN is an adjuvant against the background of nimesulide administration

confirmed the formation of the compound Les-6490. A study of the development of the inflammatory process induced by Freund's adjuvant can be seen in Table 1.

The observation results indicate a slight slowdown in the development of the inflammatory process under the influence of the studied compound Les-6490 and nimesulide. In the control group, the first signs of the inflammatory process (erythema) — 1 point — appeared from the third day of observation, swelling — from the 5th day (2–3 points), and severe swelling with limitation of passive mobility (4 points) from the 9th day. In the AL group, the first signs of inflammation were noted on the 5th day of observation; no four-point development of the inflammatory process was found in this group. In the AN group, the maximum development of the inflammatory process was detected 2–3 days later. Therefore, the compound Les-6490 caused a slowdown in the development and intensity of manifestations of the inflammatory process compared to other observation groups.

When observing the development of the inflammatory process, quantitative indicators were simultaneously evaluated based on the circumference of the paw in the zone of maximum expression of the inflammatory process (Fig. 2A). The results are shown in Fig. 3.

In group A, the increase in quantitative indicators of inflammation was observed from the third day after the administration of the adjuvant. On the seventh day, the circumference of the affected area increased by 1.5 times, on the 9th day by 1.7 times, and by the end of the study (day 13) by 1.9 times. During the action of the compound Les-6490 in the same time intervals, the increase of this indicator was 1.1; 1.2 and 1.6 times, respectively. That is, there was a decrease in indicators of the development of the inflammatory process compared to group A. When nimesulide was applied, the circumference of the affected area was 1.2 times larger on the se-

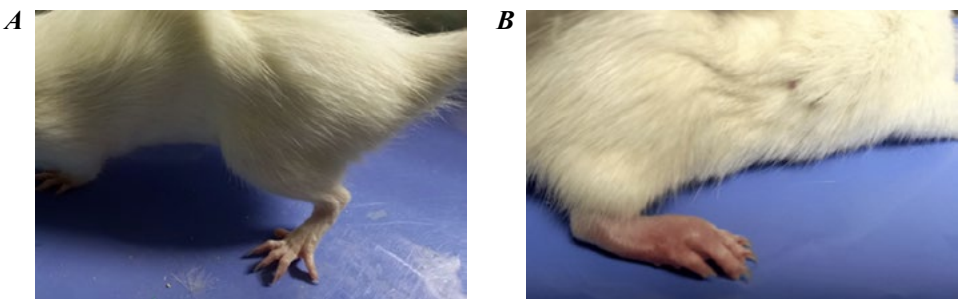

Fig. 2. Paw of a rat without inflammation (*A*) and with an induced inflammatory process (*B*).

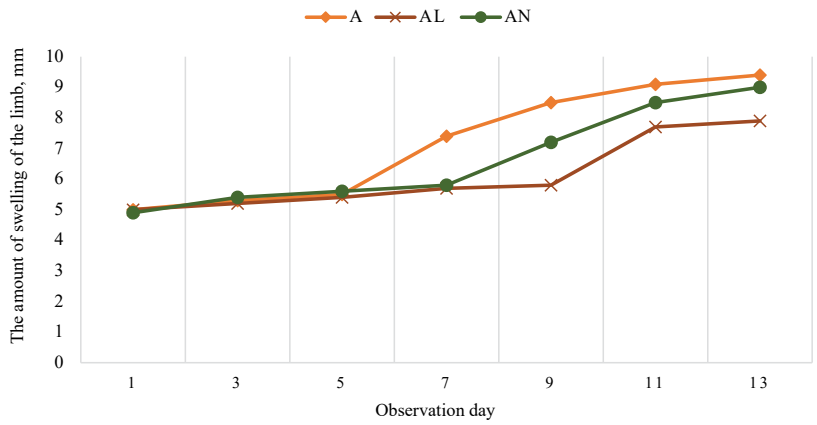

Fig. 3. Effect of the compound Les-6490 and nimesulide on the paw diameter of rats with AF-induced inflammation, mm (M±m, n = 6). **Note.** The difference between the indicators of groups A and AL on the 11th and 13th day is statistically significant (value $p < 0.01$) and between the indicators of groups AL and AN (value $p < 0.05$).

venth day, 1.5 times on the 9th day, and 1.8 times on the 13th day. The difference between the indicators of groups A and AL on the 11th and 13th day is statistically significant (value $p < 0.01$) and between the indicators of groups AL and AN (value $p < 0.05$).

Biochemistry

The administration of AF was accompanied by a significant increase in the number of leukocytes in the blood of the test animals by 70 % and ESR values by 62.4 % ($p < 0.001$), respectively, compared to the control. Indicators of the above named markers of the inflammatory process were correlated with changes in the FA injection site.

The independent action of Nimesulide and Les-6490 did not significantly affect the level of leukocytes and ESR compared to the values of control animals, however, when they were used against the background of FA-induced inflammation, the number of leukocytes decreased by 36,6 %, and when exposed to the drug Les-6490 — by 34/8 % ($p < 0.01$). Also, the value of ESR decreased to almost the same extent, both in the AN and in the AL groups (Table 2). This may indicate that the anti-inflammatory properties of Les-6490 are not inferior to those of Nimesulide.

The levels of total protein, albumin and urea are the markers of protein metabolism that respond to the hepatotoxic effects of drugs and

Table 2. **Peripheral blood indicators of animals under the condition of FA-induced inflammation and the effect of Nimesulide and the compound Les-6490, n = 10, M±m**

Indicators	The groups of experimental animals					
	1	2	3	4	5	6
	K	N	L	A	AL	AN
Leukocytes, 10^9 /l	10,03±0,8	10,55±1,0	9,55±2,5	17,15±0,7	11,4±1,8*	11,1±1,9*
ESR, mm/hour	1,64±0,5	2,10±0,20	1,9±0,18	4,36±0,32	1,72±0,3*	1,8±0,4*

Note. * — Indicators are significantly different ($p < 0,01$) between groups A and AL, AN.

their changes demonstrate a violation of the protein-synthesizing function of the liver and the ability to detoxify ammonia. The quantitative level of total protein in the serum of animals of all studied groups was not significantly different, although the introduction of Nimesulide, as expected, showed a tendency to decrease this indicator (Table 3). In general, the content of albumin correlated with the indicators of total protein. An increase in the concentration of prostaglandins during inflammation cause a moderate hepatotoxic effect, manifested in 1–5 % of patients by an increase in the activity of transaminases and some deviation from the norm of alkaline phosphatase activity [21, 22].

The development of the FA-inflammatory process in our experiments was not accompanied by significant changes in the concentration of total protein and albumin compared to the parameters of intact animals. Nimesulide, on the other hand, caused a significant 22,7 % ($p < 0,001$) decrease in albumin concentration. No significant changes in protein and albumin parameters were registered when using the drug Les-6490 against the background of FA. At the same time, it is worth noting that the independent action of the drug Les-6490 was accompanied by a significant decrease in the urea content compared to the control. The studied compound is poorly soluble in water and belongs to typical xenobiotics, it can be assumed that the process of biotransformation of Les-6490, which takes place in the liver, partially affects the functioning of the ornithine cycle of urea formation. It is also noteworthy that the introduction of Les-6490 against the background of the inflammatory process led to a 9,9 % ($P < 0,001$) increase in the level of creatinine in the blood, which indicates changes in the glomerular filtration process.

To gain a deeper understanding of the potential hepatotoxicity of the studied drugs, the activity of marker enzymes of hepatocyte function was determined. It is known that long-term use of Nimesulide can lead to a violation of hepatocyte functions and is accompanied by an increase in the activity of transamina-

Table 3. **Separate biochemical indicators of blood serum of animals under the condition of FA-induced inflammation and the action of Nimesulide and the drug Les-6490, n = 10, M±m**

Indicators	Groups of experimental animals					
	1	2	3	4	5	6
	K	N	L	A	AL	AN
Protein, g/l	77,75±6,57	69,75±5,06	74,67±3,93	79,45±3,35	75,92±4,76	75,42±4,67
Albumin, g/l	27,02±2,69	21,23±4,43	23,63±2,05	23,25±1,92	24,9±2,12	18,95±0,89#
Urea, mM/l	4,57±0,39	3,83±0,17	2,9±0,48*	4,35±0,5	3,6±0,45	4,63±0,25
Creatinine, mM/l	90,3±7,34	78,45±5,63	92,9±5,29	88,75±1,86	97,58±1,27#	85,05±6,63

Note. * — $p \leq 0,001$, compared to control; # — $p \leq 0,001$, compared to group A

Table 4. **Indicators of enzymatic markers of hepatocyte functions in the blood of animals under the condition of FA-induced inflammation and the action of Nimesulide and the compound Les-6490, n = 10, M±m**

Indicators	Groups of experimental animals					
	1	2	3	4	5	6
	K	N	L	A	AL	AN
ALT, U/l	72,6±3,2	31,15±5,8	52,9±8,7	57,9±7,2	35,55±5,8	35,59±4,1
AST, U/l	237±24,3	192,55±25,5	217,1±24,1	180,1±33,5	142,5±35,8	110,1±4,6
AST/ALT	3,26	6,18	4,1	3,1	4	3,09
ALP (alkaline phosphatase), U/l	263±30,6	233,8±45,5	169,85±12,8	235,05±22,3	250±13,51	312±35,8*

Note. * — $p < 0,001$, compared to control

ses [22]. However, in our studies, both the independent administration of Nimesulide and its use against the background of A unexpectedly reduced the activity of AST and ALT in blood serum, the mechanisms of which require more in-depth studies. An increase in the de Ritis ratio up to 6,18 under the conditions of self administration of Nimesulide is most likely associated with a more significant decrease in ALT activity, so it cannot be interpreted as a cardiotoxic effect. The introduction of Nimesulide under the conditions of modeling the inflammatory process led to an increase in the activity of alkaline phosphatase, which may be a consequence of the cholestatic syndrome, but may also be a consequence of changes in bone tissue metabolism (indicators of phosphorus-calcium metabolism will be discussed below). A study of the effect of the compound Les-6490 on enzymatic markers of liver diseases in comparison with the action of Nimesulide did not reveal the hepatotoxic effect of the substance, however, a decrease in the activity of transaminases was also recorded, which was the most pronounced when using Les-6490 against the background of FA.

Analyzing the effect of drugs on the indicators of lipid metabolism, it should be noted that there was a significant decrease in the level of total cholesterol and triglycerides, caused by the action of both Nimesulide and the drug Les-6490, as well as the introduction of AF in comparison with markers of lipid metabolism in animals of the intact group. For Nimesulide and other selective COX-2 inhibitors, hypolipidemic effects have been demonstrated previously [14, 23], while for the compound Les-6490 such an effect has been shown for the first time.

At the same time, the introduction of Nimesulide and the compound Les-6490 caused an even more pronounced decrease in the content of cholesterol in the serum of rats in groups 5 and 6, that is, in the animals with induced inflammatory process. Thus, in the animals of the specified group, the total cholesterol index was 1,42±0,19, in the animals of group 5 (due to the action of the drug

Table 5. **Indicators of lipid metabolism in animals under the condition of FA-induced inflammation and the effect of Nimesulide and the compound Les-6490, n = 10, M±m**

Indicators	Groups of experimental animals					
	1	2	3	4	5	6
	K	N	L	A	AL	AN
Total cholesterol, mM/l	2,16±0,22	1,35±0,15	1,64±0,35	1,42±0,12	1,29±0,11*	1,23±0,18
Triglycerides, mM/l	1,6±0,37	0,79±0,18*	1,02±0,21	0,73±0,06	0,61±0,06	1,2±0,2

Note. * — P < 0,001, compared to group A

Les-6490 against the background of the inflammatory process) — 1,29±0,11 mmol/l, and in group 6 (due to the action of Nimesulide) — 1,23±0,18 mmol/l. The effect of the drug Les-6490 on the quantitative indicator of triglycerides, which decreased to the level of 0,61±0,06 mmol/l, i.e. by 16,4 % compared to the group 4 animals with FA-induced inflammatory process, is particularly pronounced. While the effect of Nimesulide, on the contrary, was accompanied by an increase in the amount of triglycerides by 64 % (P < 0,001).

It was confirmed that the body weight and circulating triglycerides were reduced in rats with AF-induced inflammation compared to the control. There is also an increase in the quantitative level of total cholesterol and triglycerides.

The factors that enhance osteogenesis (calcitonin, androgens, estrogens, alkalosis) reduce calciumemia, whereas the factors that enhance osteolysis (increased levels of PTH or parathyroid hormone-binding protein PTHrP, prostaglandins, excess thyroid hormones, hypervitaminosis A, acidosis) lead to an increase in calcium in the blood, which is not only the main component of bones, but also is necessary for the proper blood clotting, the spread of excitement in the nervous system, and the contraction of striated muscles. It is also the main element of the signaling and regulatory systems of the cell, especially in the field of activity of many enzymes [24–26]. It was confirmed that the action of Nimesulide is accompanied by a decrease in the amount of phosphorus by 43 % and calcium in the serum by 23 % (p < 0,001), while the drug Les-6490 does not show such an effect. However, against the background of the FA-inflammatory process, both investigated substances show rather a «normalizing» effect. Moreover, an increase in the level of calcium in the serum is to a greater extent characteristic of the drug Les-6490. (Fig. 4).

Thus, we compared the effects of selective COX-2 inhibitor Nimesulide and derivative Les-6490 on the indicators of lipid and phosphorus-calcium metabolism and determined markers of hepatotoxicity both when the drugs are administered independently and when they are used against the background of FA.

Conclusions

1. The studied 4-thiazolidinone derivative Les-6490 is not inferior to the level of anti-inflammatory activity of the NSAID Nimesu-

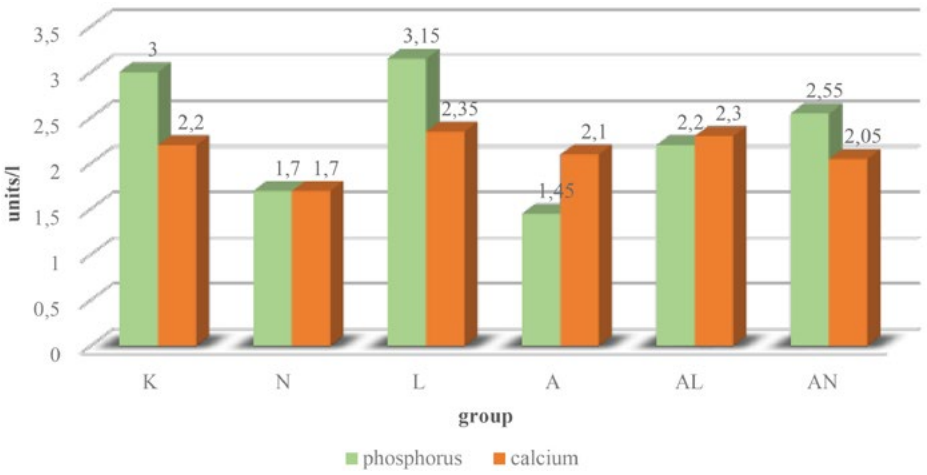

Fig. 4. Indicators of phosphorus and calcium in blood serum of rats (units/l).

lide in terms of markers of the inflammatory process (total number of leukocytes and ESR).

2. The compound Les-6490 slows down the development of the inflammatory process in the AF inflammation model.

3. The study of the effect of the compound Les-6490 on markers of liver function in comparison with the effect of Nimesulide did not reveal a significant hepatotoxic effect of the substance; however, a decrease in the activity of transaminases, which was most pronounced when using Les-6490 against the background of FA, was observed.

4. The compound Les-6490 showed a hypolipidemic effect both under the conditions of self-administration and when modeling the inflammatory process, which was similar to the effects of Nimesulide.

5. Despite the fact that the compound Les-6490 is characterized by an increase in the level of calcium in the serum (compared to the action of Nimesulide), which does not promote osteogenesis, the studied derivative may be considered promising for in-depth studies as a potental anti-inflammatory agent.

Prospects for further research. It is planned to study the effect of the researched compound Les-6490 on the composition of the intestinal microbiota of rats in a model of rheumatic inflammation.

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Ethics approval

The permission to conduct experiments on animals, and isolate/work with cultures of microorganisms was approved by protocol No. 6 on June 25, 2018, and No. 10 on December 20–2021 of the commission on ethics of scientific research, experimental development, and scientific works of Danylo Halytsky LNMU, Ukraine.

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Вплив похідного 4-тіазолідинону Les-6490 на запальний процес у щурів порівняно з німесулідом

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Вступ. Нестероїдні протизапальні препарати (НПЗП), що використовують в лікуванні численних хвороб, можуть спричинювати низку побічних ефектів. Тому розробка нових молекул з протизапальними та антимікробними властивостями є важливим завданням сучасної медицини та ветеринарії. Перспективною групою препаратів вище описаної дії, є численні похідні 4-тіазолідинонів. Тіазолідинонове кільце є частиною багатьох існуючих потенційних антимікробних і протизапальних засобів і в поєднанні з фармакофорним піразольним фрагментом в одній структурі може призвести по посилення ефекту у лікуванні. **Мета.** Оцінити вплив похідного 4-тіазолідинону Les-6490 та традиційного протизапального засобу німесуліду на гематологічні та біохімічні показники у щурів у контексті індукованого запального процесу з використанням повного ад'юванта Фрейнда (АФ). **Методи.** Запальний процес у тварин моделювали повним ад'ювантом Фрейнда. Оцінку змін з боку організму тварин проводили за біохімічними показниками сироватки крові: активність трансаміназ та лужної фосфатази, показники вміст загального білка та альбуміну, рівень креатиніну та сечовини, показники ліпідного обміну (загальний вміст холестеролу та тригліцеридів), кількісний рівень фосфору та кальцію як маркери мінерального обміну. **Результати.** Встановлено: сполука Les-6490 сповільнює розвиток запального процесу на моделі запалення АФ; розвиток індукованого запального процесу не супроводжувався суттєвими змінами концентрації загального білка та альбуміну. Німесулід спричинив достовірне на 22,7 % ($p < 0,001$) зниження концентрації альбуміну, змін з боку сполуки Les-6490 на тлі запалення не зареєстровано. Самостійна дія сполука Les-6490 супроводжувалася достовірним зниженням сечовини в порівнянні з контролем. Введення Les-6490 на тлі запального процесу зумовлювало підвищення на 9,9 % ($P < 0,001$) рівень креатиніну в крові та зниження активності трансаміназ. Встановлено, що дія німесуліду супроводжується зниженням кількості фосфору та кальцію в сироватці крові, у той час, як сполука Les-6490 такого ефекту не виявляє. **Висновки.** досліджувана сполука Les-6490 за маркерами запального процесу не поступається рівнем протизапальної активності німесуліду; дослідження впливу сполуки Les-6490 на маркери захворювань печінки в порівнянні з дією німесуліду не виявило суттєвої гепатотоксичної дії речовини; сполука Les-6490 проявляла гіполіпідемічний вплив як за умов самостійного введення, так і при моделюванні запального процесу, що був схожий до ефектів німесуліду; досліджену сполуку можна вважати перспективною для подальших досліджень як речовини з протизапальною дією. Сполука Les-6490 сповільнює розвиток запального процесу на моделі запалення АФ.

Ключові слова: НПЗП, 4-тіазолідинони, німесулід, ад'ювант Фрейнда, запальний процес, білок, альбумін, креатинін, лейкоцити, ліпідний обмін, тригліцериди.

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