Procedia of Engineering and Medical Sciences
Volume: 06 | 2023

Antiflogenic Action of Non-Steroid Anti-Inflammatory Drugs

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Anti-inflammatory drugs are a group of drugs that are used to treat a variety of diseases accompanied by an inflammatory process. In recent years, the study of inflammation has been enriched with numerous new data. Advances in molecular biology, biochemistry, immunology, cytology, physiology, pharmacology and other biomedical disciplines have led to the discovery of fundamentally new facts about the nature of inflammation and the mechanisms involved in its development. Despite the fact that the modern arsenal of anti-inflammatory drugs includes a large number of drugs, the problem of finding new highly effective anti-inflammatory drugs remains very relevant. This is due to the fact that known anti-inflammatory drugs do not meet high requirements for effectiveness and safety.

Large teams of chemists and pharmacologists from a number of institutions are involved in the development of new drugs in this group. Over the past 25 years, employees of the Department of Pharmacology of the Urgench branch of the Tashkent Medical Academy, together with other scientific teams, have been conducting comprehensive research on the synthesis, search, study and introduction into practical medicine of new highly effective anti-inflammatory antiarrhythmic and anti-atherosclerotic drugs among some classes of synthetic drugs (pyrazole, triazole, thiocarbamate, thiourea, etc.) and natural (glycyrrhetic acid) compounds, and some progress has been achieved in this regard. This work is part of this comprehensive study, which examined the anti-inflammatory and several other pharmacological properties, as well as the toxicity of a new silicon-containing pyrazole derivative of parachlorobenzoic acid.

It is known that the course of the inflammatory process is conditionally divided into three phases: alternative, exudative and proliferative. Under experimental conditions, the last two stages of inflammation are relatively clearly manifested. In this regard, we studied the effect of the drug K-72 separately on the exudative and proliferative phases of inflammation. At the same time, for comparison, in addition to butadione, indomethacin and voltaren were taken in some series of experiments, as the most active non-steroidal anti-inflammatory drugs used in the clinic.

In experiments conducted on rats, it was revealed that when administered orally, K-72 has a significant inhibitory effect on the exudative phase of aseptic inflammation caused by phlogogenic agents of various origins - formalin, dextran, histamine, serotonin and carrageenan. At the same time, in the formalin model of inflammation K-72 has an antiphlogistic effect that is 1.5 times superior to butadione and slightly stronger than indomethacin and voltaren. Against the background of carrageenan and dextran inflammation, K-72 is 1.5 times more active than butadione and is approximately equivalent to indomethacin and voltaren.

The effect of the drug K-72 on the exudative phase of inflammation was studied in a model of peritonitis caused by the introduction of a silver nitrate solution into the abdominal cavity, where

the main criterion for the severity of the inflammatory process is the amount of exudate formed in the abdominal cavity. In this indicator, K-72 is 1.5 times superior to butadione and is noticeably stronger than indomethocin and voltaren.

To simultaneously study the effect of the drug on exudative and proliferative processes, the Selye method (1953) was used. Under the influence of K-72, a significant decrease in the mass and dry granuloma sac and a decrease in the protein content in the exudate are observed. According to these indicators, K-72 is approximately 1.5 times superior to butadione and is slightly stronger than indomethacin and voltaren.

The effect of drugs on the proliferative phase itself was studied using the method of subcutaneous implantation of cotton swabs ("Cotton pellet"). As the results of experiments have shown, under the influence of K-72, the weight gain of both wet and dry granulomas is significantly reduced and the drug is approximately 1.5 times more active than butadione.

Thus, based on the results of the last two series of experiments, under the influence of K-72, the weight gain of both wet and dry granulomas is significantly reduced and the drug is approximately 1.5 times more active than butadione.

Thus, based on the results of the last two series of experiments, it can be concluded that K-72 has a pronounced inhibitory effect on the proliferative phase of inflammation.

It is known that the mechanism of the antiphlogogenic action of non-steroidal anti-inflammatory drugs has not yet been fully established. It is assumed that they exhibit antagonism towards inflammatory mediators, inhibit the activity of hyaluronidase and the migration of leukocytes, reduce vascular permeability, lysosomal membranes, immune reactions, and also affect the pituitary-adrenal system and a number of other factors [8, 10]

The results of studies to elucidate the possible mechanism of the anti-inflammatory effect of K-72 showed that the drug in adrenalectomized animals exhibits less pronounced anti-inflammatory activity than in intact animals. This differs from butadione, whose anti-inflammatory activity does not manifest itself in adrenalectomized rats.

Thus, the above data show that the adrenal cortex plays a certain role in the anti-inflammatory effect of K-72.

One of the phlogogenic factors contributing to the formation of the inflammatory process in the early stage of its development is an increase in vascular permeability [3], and anti-inflammatory drugs reduce it to a certain extent [6, 7, 9].

As the results of our studies (on rabbits) showed, K-72 clearly reduces capillary permeability and in this indicator it turned out to be stronger than butadione.

At the same time, data from another series of experiments showed that K-72 significantly reduces the effect of kinin on vascular permeability (in rabbits). These data and the fact that K-72, as noted above, strongly suppresses inflammation caused by histamine and serotonin, suggest that the test compound exhibits pronounced antagonism towards "inflammatory mediators".

In addition, in a separate series of experiments (on rabbits) it was found that K-72 inhibits the activity of the enzyme hyaluronidase and in this effect it is also superior to butadione.

Thus, the above data indicate that the mechanism of the anti-inflammatory effect of the drug K-72 is to a certain extent due to its antagonism to inflammatory mediators, inhibition of the activity of the blood kinin system and the enzyme hyaluronidase, a decrease in vascular permeability and is to some extent associated with the adrenal cortex. The results of the above experiments allowed us to conclude that K-72 has a complex mechanism of anti-inflammatory action.

It is known that anti-inflammatory drugs, as a rule, cause antipyretic and analgesic effects and these properties are of certain importance for practical medicine.

Testing K-72 in this direction (experiments on white rats) showed that it also has analgesic and antipyretic effects. However, they are less pronounced than the anti-inflammatory properties of the drug.

It is known from the literature that many anti-inflammatory drugs during treatment in patients cause various side effects and serious complications [5, 10, 11, 12, 13], which significantly limits their successful use in the clinic. The most dangerous complications of non-steroidal anti-inflammatory drugs include, in particular, ulcerative lesions of the digestive tract mucosa, exacerbation and sometimes perforation of gastric and duodenal ulcers and inhibition of the function of hematopoietic organs (for example, agranulocytosis) and others [1,9].

In this regard, in a special series of experiments, the effect of K-72 (in doses that caused an anti-inflammatory effect) on the course of gastric ulcers in rats was studied. It has been shown that oral administration of K-72 not only does not worsen the course of neuro-reflex gastric ulcers (caused by immobilization in combination with fasting), but also has a pronounced anti-ulcer effect, which should be considered as an advantage of this drug over many known anti-inflammatory drugs.

It should be noted that the drug K-72 has low toxicity. That the drug K-72 has low toxicity. Its LD50 when administered orally in white mice is 2000 (1910.5±2100.2) mg/kg with p=0.05. According to literature data [50], LD5 0 of butadione is equal to 430 (344 ± 538). Comparing these data, it can be noted that K-72 is 4.5 times less toxic than butadione.

Taking into account the variations (indicator) of acute toxicity of the studied compound, according to the classification of K.K. Sidorov [5], it can be classified as a low-toxic drug, since the average lethal dose of K-72 is beyond 500 mg/kg.

Long-term (for 6 months) administration of K-72 to animals did not have a negative effect on growth dynamics, morphology of internal organs and different parts of the brain. The drug does not have a local irritant property and does not cause ulceration of the mucous membrane of the gastrointestinal tract.

The above gives grounds to consider K-72 a low-toxic and highly active anti-inflammatory substance. In terms of the breadth of its anti-inflammatory action, it is significantly superior to butadione, indomethacin and voltaren and is of practical interest as a potential anti-inflammatory drug.

At the same time, the results obtained indicate the prospects of targeted research and study of new, more advanced anti-inflammatory drugs in the series of silicon-containing pyrazole derivatives, parachlorobenzoic acids and related compounds.

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