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SUBSTANTIATION OF THE COMPOSITION OF A RECTAL DOSAGE FORM CONTAINING KETOPROFEN AND GLUCOSAMINE SULFATE FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT — In the course of this study, it was found that currently more than 30 million people are forced to take non-steroidal anti-inflammatory drugs (NSAIDs) daily. It is reliably known that nonsteroidal anti-inflammatory drugs with prolonged use cause a number of side effects, the main of which are erosive and ulcerative changes in the mucous membrane of the gastrointestinal tract. Special attention is paid to the classification and comparative evaluation of various NSAIDs and possible complications in the case of their use. As a result of the performed analysis, it was found that rectal forms have been developed for most NSAIDs, which is convenient for use in pediatric practice, in patients with gastropathies, nausea, vomiting, swallowing disorders, in an unconscious state. The common sides of their pharmacological action are anti-inflammatory, antipyretic, analgesic effects due to inhibition of cyclooxygenase I, II activity and leading to disruption of arachidonic acid metabolism with suppression of prostaglandin synthesis in the focus of inflammation. Data analysis showed that NSAID suppositories are prescribed for: articular syndrome; pain in the spine, neuralgia, myalgia, traumatic inflammation of soft tissues and musculoskeletal system; rheumatism, diffuse connective tissue diseases; dysmenorrhea.

KEYWORDS — rectal dosage form, non-steroidal anti-inflammatory drugs (NSAIDs), ketoprofen, rheumatoid arthritis, a combination of dexketoprofen and glucosamine hydrochloride.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology characterized by symmetrical erosive arthritis (synovitis) and a wide range of extra–articular (systemic) manifestations. Rheumatoid arthritis is an extremely common disease affecting approximately 1% of the world's population. The cardinal signs of rheumatoid arthritis include steadily progressive joint damage (chronic pain, deformity, dysfunction), leading to disability and even a decrease in the life expectancy of patients. 4 groups of medicines are used for the treatment of rheumatoid arthritis: 1) nonsteroidal anti-inflammatory drugs (NSAIDs); 2) "basic" drugs; 3) glucocorticosteroids (GCS); 4) "biological" agents.

Nevertheless, NSAIDs induce damage to the gastrointestinal tract throughout its entire length from the esophagus to the rectum.

A more effective dosage form is rectal suppositories with NSAIDs, which is convenient for use in pediatric practice, in patients with gastropathies, nausea, vomiting, swallowing disorders, in an unconscious state.

Purpose of study

There is a justification of the composition, technology of a new rectal dosage form containing ketoprofen and glucosamine sulfate, which will reduce the ulcerogenic effect of ketoprofen due to joint use with glucosamine.

MATERIALS AND METHODS

The article presents an overview of the results of scientific research on the treatment of rheumatoid arthritis with various nonsteroidal anti-inflammatory drugs. The object of the study were preparations of nonsteroidal anti-inflammatory drugs (ketoprofen, ibuprofen, diclofenac, indomethacin, etc.). The search was carried out in electronic databases: PubMed, Cyberleninka, Elibrary Scopus. The search queries were performed in Russian and English.

RESULTS

Autoimmune rheumatoid arthritis is a progressive disease that affects the joints, leading to chronic pain, deformity, and dysfunction. Ultimately, the disease leads to disability (Fig. 1).

The development and progression of rheumatoid arthritis is determined by a complex combination of genetically determined and acquired defects ("imbal-

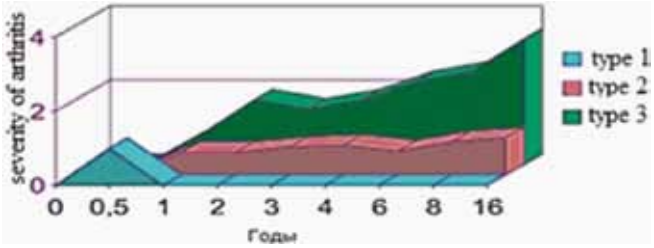

Fig. 1. *Development and progression of rheumatoid arthritis*
Type 1 — Not progressive 5–20%
Type 2 — Moderately progressive5–20%
Type 3 — Progressive 60–90%

ance") of normal (immuno) regulatory mechanisms that limit the pathological activation of the immune system in response to potentially pathogenic, and often physiological stimuli. This leads to a rapid transformation of the physiological (protective) acute inflammatory reaction into chronic progressive inflammation, which is an integral feature of RA.

Nonsteroidal anti-inflammatory drugs prescribed for rheumatoid arthritis, with prolonged use, cause a number of side effects, the main of which are erosive and ulcerative changes in the mucous membrane of the gastrointestinal tract.

Against the background of course admission, acute, usually multiple, gastroduodenal erosions and ulcers occur with predominant localization in the antrum of the stomach.

The danger of gastroduodenal erosions and ulcers, the development of which is caused by taking NSAIDs, is that they are often multiple in nature and are often accompanied by sudden gastrointestinal bleeding. The mechanism of the negative effect of NSAIDs on the gastric mucosa is mainly associated with inhibition of the synthesis of prostaglandins, which have a cytoprotective effect, as well as with a decrease in the production of gastric mucus and a change in its qualitative composition, violation of capillary circulation in the gastric mucosa, epithelial cell regeneration processes, accumulation of free radicals (Table 1).

Medications used in the treatment of arthritis are divided into two groups: fast-acting and slow-acting symptom-modifying. The drugs of the first group are aimed at suppressing pain and normalizing the function of the affected joints. These include nonsteroidal anti-inflammatory drugs and glucocorticoids. The appointment of NSAIDs to patients with arthritis is justified by the persistence of the inflammatory process in the joints and periarticular soft tissues. However, these drugs actively affect the metabolism of cartilage, mainly reducing the synthesis of proteoglycans, type II collagen and hyaluronic acid, and thus contribute to the progression of structural changes. In addition, NSAIDs increase the risk of developing gastropathies and cardiovascular catastrophes, even in people without concomitant pathology.

Table 1. *Relative risk of gastrointestinal complications when using different NSAIDs*

NSAIDS	Relative risk
ibuprofen	1.84
naproxen	4.10
diclofenac	3.34
indomethacin	4.14
ketoprofen	3.92
ketorolac	11.5
meloxicam	3.47
piroxicam	7.43
rofecoxib	2.32
nimesulide	3.83

Among the drugs of the second group – symptom-modifying drugs of delayed action, the primary role belongs to the natural component of the cartilaginous intercellular substance glucosamine, which is the most studied among the drugs of this group. The drugs of the second group have not only a symptom-modifying effect, but are able to control the course of the disease, slow down the rate of its progression, stabilize structural changes in hyaline cartilage and prevent the development of inflammatory conditions in intact joints. In this regard, they are considered as pathogenetic (basic, chondromodulating) drugs in the treatment of arthritis.

Preparations containing glucosamine are characterized by a slower development of symptom-modifying action, pronounced aftereffect, when after discontinuation of treatment the effect persists for another 4 to 8 weeks.

CONCLUSION

Therefore, it can be concluded that the presence of side effects, which are inherent in most NSAIDs, necessitate the search for new methods of their use, in which the toxic effect on the body is removed or reduced, and the use of a combination of ketoprofen + glucosamine in rectal dosage form makes it possible to avoid such a negative effect, while having a potential structural-modifying effect.

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