

EFFECTIVENESS OF NATURAL MEDICINES ORIGINS IN EXPERIMENTAL MODELS INFLAMMATION OF THE UPPER RESPIRATORY TRACT

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Summary: Despite the wide range of immunomodulatory agents used in the clinic, the search for new ischnoregulators of both synthetic and natural origin is actively underway.

Keywords: medicinal herbs, rhinosinusitis , antibacterial, antiviral

The relevance of research ARVI is a heterogeneous group of diseases, whose etiological agents are respiratory viruses, predominantly affecting the epithelium of the upper respiratory tract(1,22,24). The most common disease of this group is acute rhinosinusitis, its contribution to the structure of ARVI is up to 80% (5,7,11,23). According to the European guidelines for rhinosinusitis (2,9,14,17,18, 20), acute rhinosinusitis - acute inflammation of the mucous membrane of the cavity nose and paranasal sinuses (appearing suddenly and lasting no more than 12 weeks), characterized by nasal congestion and/or discharge from the nose or along the back of the throat. The concept of “acute rhinosinusitis” covers a wide range of different nosological conditions, ranging from a banal acute respiratory viral infection to those complicated by acute bacterial rhinosinusitis, for which in 30% of cases antibacterial drugs are prescribed (3,8,10,15,19), for severe bacterial infection. About 5% ARVI 2006). Acute tonsillitis, along with acute rhinosinusitis, is also a widespread disease. Acute tonsillitis is an acute inflammation of predominantly the palatine tonsils, accompanied by their swelling, hyperemia, the presence of exudate, as well as an increase in body temperature and the reaction of peripheral lymph nodes (4,13,16,21). It has now been established that the

cause of acute tonsillitis in most cases is a viral rather than a bacterial infection (6,12,18, 20), while systemic antibacterial therapy against viral tonsillitis is not effective (1, 14).

Today, the most widely used drugs for the treatment of upper respiratory tract diseases are antibacterial drugs and nonsteroidal anti-inflammatory drugs (NSAIDs). Effective treatment with antibacterial drugs requires additional research, which often takes time, and the use of NSAIDs entails the development of side effects. Therefore, today the search for new effective and safe drugs for the treatment of inflammatory diseases of the upper respiratory tract remains relevant. The literature widely describes experimental models of allergic and bacterial rhinitis, but there is no description of experimental models of aseptic rhinosinusitis and acute tonsillitis, which makes it urgent to search for new experimental methods for assessing the effectiveness of drugs used in the treatment of diseases of the upper respiratory tract (5,8, 12).

Degree of development of the research topic:

The drugs Freshnos and KLS-04 proposed for study are new drugs and products. Plants, extracts of which were used to create the drug freshnos, have been widely studied and presented in the literature. However, the combination of extracts of sage, yarrow herb, St. John's wort herb and wild rosemary shoots in the form of nasal drops has not yet been studied. These plants are widely known for their anti-inflammatory, antibacterial, antiviral and endothelium-protective properties. In addition, the drug contains mint essential oil, which is widely used in preparations intended for the treatment of inflammatory diseases of the upper respiratory tract (9,11, 13) and thymol, which is often used in complex drugs as an antiseptic (4,8,12,14). Thus, the main active ingredients of the drug under study are the volatile components of essential oils and flavonoids, which provide a wide range of pharmacological effects of this drug (5,10).

Goals and objectives of the study:

The purpose of this study was to evaluate the effectiveness of new drugs of natural origin, freshnos and KLS-04, using developed and validated models of aseptic acute rhinosinusitis and acute cervical lymphadenitis.

Research objectives:

1. To develop and validate a new experimental model of aseptic acute cervical lymphadenitis, taking into account biochemical, hematological, pathophysiological and pathomorphological parameters.

2. To develop and validate a new experimental model of aseptic acute rhinosinusitis based on pathophysiological and pathomorphological parameters.

3. To evaluate the effectiveness of the new domestic drug freshnos in the form of nasal drops on an experimental model of acute rhinosinusitis in comparison with vibrocil and aquamaris.

Scientific novelty:

For the first time, experimental methods for assessing the effectiveness of drugs on models of aseptic inflammation of the upper respiratory tract have been developed and validated. It has been shown that for the induction of acute cervical lymphadenitis as a pro-inflammatory agent, it is most appropriate to use lipopolysaccharide of the cell wall of E. coli bacteria (LPS) at a dose of 0.1 mg/kg and carrageenan at a dose of 0.8 mg/kg, and for the development of acute rhinosinusitis - formalin at a dose of 12 mg/kg. It has been proven that during the formation of acute cervical lymphadenitis, it is pathogenetically significant to determine the concentration of the pro-inflammatory cytokine in the blood of experimental animals TYR-a - 4 hours after the induction of pathology and the level of C-reactive protein (CRP) 72 hours after the induction of pathology. At the same time, during the formation of acute rhinosinusitis, the degree of increase in the number of goblet cells and the severity of cellular infiltration of the nasal passages are pathogenetically significant. For the first time, the effectiveness of using different doses of the new anti-inflammatory drug Yu1S-04 in the form of a spray to relieve pathological processes accompanying the development of aseptic lymphadenitis was tested, while the advantages of using KLS-04 were proven in comparison with Tantum Verde, diclofenac and dexamethasone. Also, for the first time, the anti-inflammatory effectiveness of the new complex drug Freshnos was assessed in a wide

range of doses on a model of aseptic acute rhinosinusitis in comparison with Vibrocil and Aquamaris, which made it possible to establish a range of effective doses of the drug for subsequent clinical testing.

Theoretical and practical significance:

The theoretical significance of the work lies in the testing and validation of new experimental models of acute cervical lymphadenitis and acute rhinosinusitis in rats. The results of the experimental study of the drug KLS-04 were included in the dossier for the drug to obtain permission to conduct clinical trials.

Methodology and research methods:

The experiments included the development and validation of new pharmacological models of acute cervical lymphadenitis and acute rhinosinusitis in rats, as well as evaluation of the effectiveness of drugs of various pharmacological groups in these models. The research methodology involved assessing the rates of correction of acute inflammation with drugs of natural origin using pharmacological, biochemical, pathophysiological and histological methods. The study was carried out in compliance with all the rules of evidence-based medicine.

Main points submitted for defense:

1. A new experimental model of acute cervical lymphadenitis has been developed, which is initiated by introducing solutions of LPS at a dose of 0.1 mg/kg or carrageenan at a dose of 0.8 mg/kg under the capsule into the mesenchymal tissue of the cervical lymph nodes of rats. The experimental model of acute cervical lymphadenitis was validated in terms of accuracy (accuracy) and convergence. The model is reproducible regardless of the time of year.

2. Using a developed and validated model of experimental acute cervical lymphadenitis, the anti-inflammatory and anti-edematous effects of the studied anti-inflammatory drug KLS-04 were established.

3. A new experimental model of acute rhinosinusitis has been developed by instilling a formalin solution at a dose of 12 mg/kg into the nasal cavity of rats. The experimental

model of acute rhinosinusitis was validated in terms of convergence. The model is reproducible regardless of the time of year.

4. Using a developed and validated model of experimental acute rhinosinusitis, the anti-inflammatory effect of the new herbal preparation freshnos, due to the flavonoids and terpenes contained in the drug, was established.

CONCLUSION:

The conducted studies made it possible to establish the effectiveness of the use of new drugs of natural origin KLS-04 and Freshnos, which have pronounced anti-inflammatory properties in newly developed and validated experimental models of upper respiratory tract diseases - acute cervical lymphadenitis and acute rhinosinusitis, respectively. The mechanisms for the implementation of pharmacological effects by drugs were identified. So, with acute cervical lymphadenitis, anti-inflammatory effects. Thus, in acute cervical lymphadenitis, an anti-inflammatory cascade of inflammatory reactions occurs, which is reflected in a decrease in the level of pro-inflammatory cytokines, C-reactive protein and leukocytes. Also, in an experimental model of acute cervical lymphadenitis, a pronounced anti-edematous effect of KLS-04 was shown, which was reflected in a decrease in the difference in the weight of the affected and intact lymph nodes, as well as in the percentage of weight loss of the affected lymph node after freeze-drying. Also, in an experimental model of acute cervical lymphadenitis, a pronounced anti-edematous effect of KLS-04 was shown, which was reflected in a decrease in the difference in the weight of the affected and intact lymph nodes, as well as in the percentage of weight loss of the affected lymph node after freeze-drying. Such a pronounced therapeutic effect of KLS-04 is due to the inhibition of the synthesis of prostaglandins and leukotrienes from arachidonic acid, and the initiation of the formation of resolvins, protectins and maresins involved in the resolution of the inflammatory process (8,12, 13). When assessing the effectiveness of the anti-inflammatory effect of the studied drug freshnos based on plant raw materials, a pronounced decrease in the number of goblet cells in the nasal passages of experimental animals and a significant

decrease in the infiltration of the mucous membrane and submucosal layer with leukocytes were shown. This anti-inflammatory effect is due to the flavonoids contained in each component of the drug, which have pronounced antioxidant properties and were confirmed during clinical studies.

CONCLUSIONS

1. When developing an experimental model of aseptic acute rhinosinusitis, based on pathophysiological and pathomorphological parameters, the most suitable test system for this pathology was selected (female Wistar rats), the optimal damaging agent was determined (an aqueous solution of formalin at a dose of 12 mg/kg), and a deadline was set. the most pronounced process of acute rhinosinusitis after the administration of a pro-inflammatory agent (7 days), a list of clinical diagnostic indicators was formulated to evaluate a new experimental model of aseptic acute rhinosinusitis.

2. A new experimental model of aseptic acute rhinosinusitis has been validated in terms of convergence. It was determined that there was no influence of the season on the indicators of aseptic inflammation of the nasal passages under standard conditions of keeping experimental animals.

3. Comparison of the effectiveness of the new domestic anti-inflammatory drug freshnos based on the herb yarrow, sage leaves, St. John's wort herb, wild rosemary shoots, thymol and peppermint oil in comparison with vibrocil and aquamaris in an experimental model of acute rhinosinusitis confirmed the pronounced anti-inflammatory dose-dependent effect of freshnos. The mechanism of action of the drug is associated with the anti-inflammatory, decongestant and antioxidant properties of the components of the drug freshnos. The most pronounced therapeutic effect of the drug freshnos is achieved when it is used at a maximum dose of 30 µl/100 g of body weight.

PRACTICAL RECOMMENDATIONS

Developed and validated models of acute rhinosinusitis and acute cervical lymphadenitis are recommended for implementation in preclinical studies of the anti-inflammatory activity of new drugs for ENT practice.

The results of an experimental study of the new complex anti-inflammatory drug KLS-04 are presented in the form of a dossier for the drug to obtain permission to conduct clinical trials. On this basis, the drug KLS-04 can be recommended for clinical testing as an anti-inflammatory and decongestant agent for the treatment of diseases of the upper respiratory tract, such as acute tonsillitis (tonsillitis), laryngitis, pharyngitis, taking into account the identified effective doses. The established anti-inflammatory activity of the new herbal preparation freshnos allows us to recommend it for use in ENT practice for the treatment of acute and chronic rhinitis and rhinosinusitis.

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