

POTENTIAL USAGE OF NEW ANTITUSSIVE MEDICATIONS «BRONCHOTUS FORTE – ELIXIR» AND «AMBRORITE – TABLETS» DURING THE NATURAL HISTORY OF COVID-19

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Abstract:

Cough is the most frequent symptom of the infection of the 21st century – COVID-19. Cough occurs in 70-80% of patients, being the second most frequent symptom caused by SARS – CoV-2. In this regard, interest arose in the development of new combinations of medications that have antitussive, mucolytic and expectorant properties, such as «Bronchotus forte - elixir» and «Ambrorite - tablets». The purpose of the study is to determine the pharmacological effects of new antitussives «Bronchotus forte - elixir» and «Ambrorite - tablets». The investigation of the efficacy of the medications were conducted, using known drugs, that are close in composition and accredited in the Republic of Uzbekistan according to the common methods of investigations. The experiments were conducted at Testing laboratory (ISO 17025) at «METPHARM» LLC. The experiment was conducted on healthy sexually mature white rats and guinea pigs of both sexes which were quarantined for 14 days after their adaptation period in the vivarium, physical conditions of which were monitored for 4-5 days. To investigate the antitussive effect, guinea pig cough model was used; citric acid-induced coughing was modelled. Mucolytic and expectorant effects were determined by the amount of excreted sputum by white rats, influenced by the studied medications. Statistical processing of the obtained data was carried out with the help of software package

Microsoft Excel 2007 (for Windows 7), the reliability of which was evaluated by the Student's t-test. The results showed that the investigated medication «Bronchotus forte - elixir» has a pronounced antitussive effect and is not inferior to the known medication «Codelac® Broncho with thyme - elixir» in terms of the abovementioned property, besides it has a pronounced mucolytic effect.

The medication «Ambrorite – tablets» possesses pronounced expectorant effect and is not inferior to the brand-name medication «Ambroxol», produced by «MERRYMED FARM» LLC, Uzbekistan, in terms of efficacy. Obtained data allows the medications to be recommended for the clinical practice as a treatment of cough during the natural history of COVID-19.

Keywords: cough, COVID-19, antitussives, mucolytic effect, expectorant effect, antitussive effect.

Introduction

Cough is the most frequent symptom of the infection of the 21st century – COVID-19. Cough occurs in 70-80% of patients, being the second most frequent symptom caused by SARS – CoV-2. Besides, one of the frequent residual symptoms after the disease is post COVID-19 persistent cough. The cough that occurs during the natural history of the virus SARS –CoV-2 is the result of the damage of epitheliocytes in lungs. However, during natural history of mild COVID-19, there are no symptoms, such as inflammatory exudate observed [1].

The study of cough pathogenesis during the natural history of COVID-19 shows its similarity to that of interstitial lung diseases. For instance, during the natural history of the disease such as idiopathic pulmonary fibrosis, cough of a similar nature develops. Treatment of cough during the natural history of COVID-19 consists of pathogenetic and symptomatic therapy.

SARS – CoV-2 is a viral infection that affects the epithelium of the respiratory tract. Since epithelial cells are damaged, large amounts of autacoids are produced, as well as growth factors and cytokines. One of the properties of cytokines is to affect the receptors and ion channels which are located at the sensory nerve endings, which in turn are located in the respiratory tract. Afterwards, an action potential occurs and leads to the excitation of these nerves, thus increasing their sensitivity to the influence of the stimuli. After the irritation of sensory endings of the vagus nerve, which is the core of the regulation of the cough reflex, dry cough occurs.

Dry cough can develop into productive cough in cases, when the disease is severe and there is coinfection. In such cases the respiratory tract is severely affected, which leads to the increased production of bronchial mucus [2].

During the natural history of bacterial infections, acute respiratory infection and other severe bronchial diseases, the epithelium changes its normal structure. This can take a form of an increase in goblet cells, and, in addition, alteration of the physical and chemical structure of mucus. As a result, the viscosity of the mucus increases and

impairs the drainage function of the bronchi, therefore, cough develops to improve the drainage function. The main normal function of the cough is to help the sanitation of the respiratory tract.

There is a mechanism called mucociliary clearance and bronchiole peristalsis used to drain the bronchi from mucus. In cases when there is an excess of bronchial mucus, not only is the bronchial ability to self-cleanse impaired, but there is also an impairment of immune system that can be noticed.

Considering the literature data on the known mechanisms of cough pathogenesis, we have developed two antitussive medications.

In this article we outline the results of the research on the investigation of pharmacological properties of new combination drugs «Bronchotus forte - elixir» and «Ambrorite - tablets».

Purpose of the study is to investigate the efficacy of new antitussives «Bronchotus forte - elixir» and «Ambrorite - tablets».

Material and methods:

The efficacy of the medication is determined by the active components they are composed of. The composition of «Bronchotus forte - elixir» includes ambroxol hydrochloride, licorice root and coltsfoot. The composition of «Ambrorite – tablets» includes ambroxol hydrochloride, erythromycin, povidone.

The experiment was conducted on healthy sexually mature white rats and guinea pigs of both sexes which were quarantined for 14 days after their adaptation period in the vivarium, physical conditions of which were monitored for 4-5 days. All experimental studies were conducted in accordance with the Geneva Conventions (Geneva, 1990), with the requirements of The Declaration of Helsinki of 2000 and modern requirements for preclinical studies [5] followed. The animals were kept in the vivarium conditions and provided with standard diet, temperature rate, light, and free access to water and food. All the manipulations with animals were carried out at the same time in the morning, taking into account the chronobiological dependence of most physiological processes in the organism.

Since the investigated medications «Bronchotus forte - elixir» and «Ambrorite - tablets» are original, decision was made to conduct studies with known medications that are close in composition and accredited in the Republic of Uzbekistan, to determine their efficacy.

Determination of antitussive effect

To investigate the antitussive effect of the medication «Bronchotus forte - elixir», the medication «Codellac® Broncho with thyme – elixir», 100 ml, was used for comparison. To investigate the antitussive effect the guinea pig cough model was used; citric acid-induced coughing was modelled [5].

After the administration of the compared drugs, each guinea pig was being sprayed with 15% citric acid during 5 minutes. After being exposed to the citric acid, the guinea pigs were monitored for 30 minutes. Simultaneously, the number of coughing fits was registered. The obtained results were expressed as a percentage relative to untreated control. Control made up 100%.

Determination of mucolytic effect

The experiment was conducted on 18 white rats which were divided into three groups: one control group and two experimental groups. The rats of the experimental groups were intragastrically administered the compared drugs once a day for three days respectively. In three days the rats were narcotized by nembutal anesthesia, and after the rib cage dissection their trachea was extracted. The pre-made gauze wick drains were stretched through the rats' trachea and kept in place for 15 minutes. The amount of excreted sputum was determined through the differences between the weight of dry gauze wick drains and gauze wick drains with sputum. The obtained results were expressed as a percentage relative to untreated control. Control made up 100%.

Determination of expectorant effect

To determine the efficacy of the medication «Ambrorite - tablets», the drug «Ambroxol», produced by «MERRYMED FARM» LLC, Uzbekistan, was taken for comparison. The experiment was conducted on 18 sexually mature white rats of both sexes. The white rats were divided into three groups: one control group and two experimental groups. The rats were narcotized by urethane, and cannula was inserted into the white rats' trachea. Afterwards, the white rats were placed so that their heads were hanging down at the angle of 45°. The sputum in cannula was collected with the use of syringes within 2 hours after the administration of the compared drugs [5]. The amount of the collected sputum from each group of rats was expressed as a percentage relative to untreated control.

Discussion:

In the guinea pig cough model, with citric acid-induced coughing modelling, it was identified that the number of coughing fits of the control group of guinea pigs made up $37,5 \pm 1,0$ on observation day 1 and $37 \pm 0,8$ on observation day 2. While investigating the antitussive effect of the medication «Bronchotus forte - elixir» it was found that the guinea pigs that were administered the drug saw a decrease in the number of coughing fits by 67% in comparison with the observation day 1, i.e. the number of coughing fits (before drug administration) made up $37,8 \pm 1,4$, and on observation day 2 of the experiment (after drug administration) the number of coughing fits made up $12,5 \pm 1,0$.

The number of coughing fits from the 3rd group of guinea pigs, that were administered the drug «Codelac® Broncho with thyme – elixir», 100 ml, made up $23,5 \pm 1,1$ on observation day 2. This number is by 36,7% less in comparison with the observation

day one of the experiment, i.e., before drug administration. However, if the data collected from the 2nd and the 3rd groups are compared, it is clear that there is a difference between the values, i.e. the number of coughing fits of the guinea pigs that were administered the drug «Bronchotus forte - elixir» made up by 57% less than of the guinea pigs, that were administered the drug «Codelac Broncho with thyme - elixir». Thus, the obtained results from the research showed that the investigated medication «Bronchotus forte - elixir», that was developed at the Tashkent Pharmaceutical Institute, Uzbekistan, has a more pronounced antitussive effect compared to the medication «Codelac® Broncho with thyme - elixir», 100 ml, and its efficacy is superior to the latter.

This is explained by the fact that the composition of the investigated medication «Bronchotus forte - elixir» includes licorice root, which can be used as dry cough treatment due to its pharmacological properties.

Determination of mucolytic effect

The investigation of the mucolytic effect of the medication «Bronchotus forte - elixir», compared to the medication «Codelac® Broncho with thyme - elixir», 100 ml, produced by «Pharmstandard - Leksredstva» JSC, Russia, Kursk city, showed the following results. The mass of gauze wick drain with sputum collected from the control group of rats after being installed in rats' trachea made up $32 \pm 1,0$ mg, which is twice as much as the mass of dry gauze wick drain before the investigation.

While measuring the mass of gauze wick drain with sputum collected from the experimental group of rats that were introduced to the medication «Bronchotus forte - elixir», it was revealed that the difference between the masses of dry gauze wick drain and gauze wick drain with sputum constituted $26,8 \pm 2,1$ mg; at the same time, the difference between the masses of dry gauze wick drain and gauze wick drain with sputum collected from the control group of rats constituted $16,5 \pm 1,3$ mg ($P < 0,05$), i.e. there is an increase of 62,4 % in the amount of sputum in comparison with the volume of sputum collected from the control group of rats.

Table Mucolytic effect of the drug «Bronchotus forte – elixir compared to «Codelac® Broncho with thyme– elixir»

№ Of animal	Weight, g	Mass of dry gauze wick drain, mg	Mass of gauze wick drain with sputum, mg	Difference from the mass of dry gauze wick drain	
				mg	%
Control group					
M ± m	219,2 ± 16,2	15,5 ± 0,5	32 ± 1,0	16,5 ± 1,3	100
«Bronchotus forte – elixir»					
M ± m	228,3 ± 20,3	15,8 ± 0,7	42,6 ± 1,7	26,8 ± 2,1	162,4
«Codelac® Broncho with thyme– elixir», «Pharmstandard - Leksredstva» JSC					
M ± m	222,2 ± 13,5	15,8 ± 0,7	42,3 ± 1,6	26,5 ± 1,3	160

While measuring the mass of gauze wick drain with sputum collected from the experimental group of rats that were introduced to the medication «Codelac® Broncho with thyme - elixir», 100 ml, it was identified that the difference between the masses of dry gauze wick drain and gauze wick drain with sputum constituted $26,5 \pm 1,3$ mg, i.e. there was an increase of 60% in the amount of sputum.

The results of the study illustrate that the new combination drug «Bronchotus forte - elixir» possesses pronounced mucolytic effect and is not inferior to the referential medication «Codelac® Broncho with thyme - elixir», 100 ml.

Determination of expectorant effect

The investigation of the expectorant effect of the medication «Ambrorite - tablets», compared to the medication «Ambroxol - tablets», produced by «MERRYMED FARM» LLC, Uzbekistan, showed the following results. The volume of sputum collected from the control group of rats made up $0,11 \pm 0,013$ ml.

The volume of sputum collected from the experimental group of rats, that were introduced to the medication «Ambrorite - tablets», made up $0,2 \pm 0,012$ ml, which is by 81,8% more in comparison with the volume of sputum collected from the control group of rats.

The volume of sputum collected from the experimental group of rats, that were introduced to the medications «Ambroxol - tablets», produced by «MERRYMED FARM» LLC, Uzbekistan, made up $0,18 \pm 0,01$ ml, which is by 63,6% more in comparison with the volume of sputum collected from the control group of rats.

As can be seen from the Table, the medication «Ambrorite - tablets», developed at the Tashkent Pharmaceutical Institute, Uzbekistan, has a more pronounced expectorant effect compared to the medication «Ambroxol», produced by «MERRYMED FARM» LLC, Uzbekistan.

Conclusions:

Nowadays, there is a wide range of synthetic medications available, however, year by year the therapy with the use of herbal remedies preserves its relevance. The use of drug combinations, including comprehensive treatment cases, expands therapeutic possibilities and facilitates better clinical results.

In this regard, interest has arisen in the development of new combinations of medications that possess antitussive, mucolytic and expectorant properties. Taking into account the fact, that cough is the most common symptom, as well as the main symptom of respiratory diseases, including COVID-19, we have developed the medications «Bronchotus forte» and «Ambrorite». The results of the research have shown that the investigated medication «Bronchotus forte - elixir» has a pronounced antitussive effect and is not inferior to the referential medication Codelac® Broncho with thyme - elixir» in terms of the abovementioned property, besides it has a pronounced mucolytic effect.

The medication «Ambrorite – tablets» has pronounced expectorant effect and is not inferior to the brand-name analogy «Ambroxol», produced by «MERRYMED FARM» LLC, Uzbekistan.

Obtained data allows the tablets to be recommended for the clinical practice as a treatment of cough during the natural history of COVID-19.

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