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New applications of secretolytics in complex therapy of acute obstructive bronchitis in children of early age

Key words: *children of early age, the acute obstructive bronchitis, herbal drugs, Bronchipret*

Over a billion cases of acute respiratory infections are detected in the world annually,and the prevalence of respiratory diseases in children is 6-fold than in adults [1]. According to official World Health Organization statistics pathology of the respiratory system ranked first in the structure of infant morbidity [2]. The incidence of bronchitis predominates in 1 to 3 ege and ranges from 75 to 250 per 1000 children [1]. Acute bronchitis is an inflammatory lesion of the bronchi, mainly infectious origin, manifested by cough (dry or sputum) and lasts up to 3 weeks. Today acute obstructive bronchitis is the most common disorder of the respiratory system in children [2, 4]. Recurrences of wheezing are observed in almost 30 % of pediatric patients, and more than half of young children during acute bronchitis manifest signs of bronchial obstruction syndrome [5].

The most common cause of bronchial obstruction syndrome in children during the first three years of life are infectious agents and allergy. Among infectious agents respiratory viruses (parainfluenza types 1-3, RS-virus, adenovirus, influenza A and B), measles virus, *Mycoplasma pneumoniae, Chlamydia pneuininiae, Bordetella peitussis, Hemophilus influenza, Streptoccocuspneumonia, Streptococcus pyogenes, Moraxella catairhalis* are encountered [4].

Increasing the viscosity of secretions, its accumulation in the lumen of the bronchi, swelling of the mucous membrane of the bronchial tree and bronchoconstriction are the various underlying mechanisms of pathogenesis of bronchial obstruction syndrome . There is also reducing the refractive power of the lungs on exhalation, decreased mucociliary transport, airway compression. In the case of any adverse effects on the respiratory tract takes place, a violation of bronchial secretion develops, increased production of secretions and increase of its viscosity, the accumulation of viscous secretions in the lumen of the bronchi leads to difficulty in air passing [5, 6]. Hipereksudation is more expressed in children of preschool age. This is the main difference between the flow of obstructive bronchitis in children, unlike adults, for whom the phenomenon of bronchoconstriction is common in this case. That is why the very first clinical symptoms of acute obstructive bronchitis are a cough (as a result of reflex reaction to the irritation of the vagus nerve receptors and manifestation violation mucociliary transport), dyspnea (as a manifestation of bronchoconstriction and lung aeration violation), and intoxication syndrome, which depends on the severity of infection[1, 2].

Treatment of acute bronchitis with obstructive syndrome is a complex clinical task, that have to be carried out without polypharmacy, as in pediatric patients it is the most common cause of antibiotics abuse. The use of antibiotic therapy for acute bronchitis is not recommended either the American College of Physicians (2001) or the American College of Chest Physicians (2006) [3]. According to Centers for Disease Control and Prevention, about half of antibacterial agents prescribed by general practitioners to treat colds, coughs, and other manifestations of viral infections have no effect on pathogens. However, antibiotics, especially macrolides are used in mycoplasma infection and bronchitis of chlamydial etiology, and are the drugs of choice for confirmed pertussis. The National Pediatric Pulmonology Guidelines (Order of the Ministry of Health of Ukraine of 13.01.2005 № 18) antiviral drugs (Remantadin, Arbidol, pensamiksyn, rebetol, interferons and DNA-ase) as the causal treatment of acute bronchitis, and minimizing the use of antibiotics are recommended [3, 6, 7]. According to the recommendations of the

V. K. Tatochenko et al. (2000), included in the treatment protocol of acute bronchitis in children, indications for antibiotics in this condition be:

- children first 6 months of life;
- severe course of bronchitis syndrome;
- burdened premorbid background (birth trauma, malnutrition, prematurity);
- the presence of active (acute) chronic foci of infection (tonsillitis, otitis, etc.);
- suspicion of additional bacterial infection:
- fever with body temperature more than 39°C;
- pronounced intoxication syndrome;
- dyspnea;
- asymmetry wheezing;
- leukocytosis, accelerated erythrocyte sedimentation rate (ESR).

Pathogenetic therapy of acute bronchitis invoves medications that improve the rheological properties of mucus, that helps it to move from the lumen of the bronchial tree [6]. Today they are two groups of such drugs: expectoration stimulators and sekretolytics (mucolytics). The first group of drugs enhance physiological activity of ciliated epithelium and bronchioles peristaltic movement that promotes the excretion of mucus. Besides that, they increase the secretion of bronchial glands and slightly reduce the viscosity of sputum.

Sekretolytics are divided into two groups: reflexive and resorptive agents. Oral reflexive agents cause moderate irritation of receptors in the gastric mucosa, which stimulates the vomiting center of the medulla oblongata, resulting in amplified secretion of the salivary glands and mucous glands of the bronchi. Resorptive agents, after absobtion in the gastrointestinal tract, are secreted with mucosa of the respiratory tract, stimulating bronchial glands, causing liquefaction of sputum. Mucolytis cause dilution of mucus by means of complex mucin cleavage, which reduces its viscosity and facilitate evacuation. There are three groups of mucolitics: proteolytic enzymes, SH-group amino acids and mucoregulators. Proteolytic enzymes are limited in pediatric patients because of their ability to trigger bronchoconstriction and allergic reactions [4, 7].

The safety of drug therapy is very important in the treatment of bronchitis in children, therefore herbal agents are widely used. It should be noted that the drug of herbal origin does not mean its complete safety for your child, especially young. Thus, drugs Ipecacuanha, Thermopsidis enhance the gag and cough reflexes, therefore should not be used they in infants with central nervous system (CNS) damage, because they can cause aspiration, asphyxia, atelectasis formation and enhance vomiting associated with cough [1, 3]. Anise, licorice, marjoram are not midely used in infants because of their pronounced laxative effect. A major drawback of herbal medicines is likely environmental pollution (pesticides, salts of heavy metals), and often unpredictable clinical effect due to the complexity of the standardization of growth conditions , imperfect methods of obtaining extracts, which leads, finally, to the low therapeutic efficacy of such treatment [4].

Such flaws are missing in extracts developed according to the concept of phytoneering. Their clinical effects is not inferior than that of synthetic agents, and sometimes with a wider range of options. Phytoneering (*phyto* – plant, *engineering* – development, technology) is a new area of herbal medicine that uses modern methods for standardized extracts of plants with innovative technology to develop and produce safe formulations.

Phytoneering concept includes a number of principles:

high quality raw material, which is grown on plantations in strict compliance with the principles of selection and careful selection of seed;

standardized and certified technology of pharmaceutical production – from raw materials to finished formulation;

process of obtaining the finished product without the "thermal stress" – low-temperature vacuum extraction in a closed loop, thus avoiding oxidation and prevent the qualitative and quantitative changes of active substances;

adherence to the principles of essential evidence of efficacy and safety, clinical trials with an appropriate number of patients provides a statistically valid comparison of their pharmacological value.

With the help of phytoneering as innovative phytopharmacological technology herbs with proven clinical efficacy not inferior to synthetic drugs, but often having advantages are known in our days [6, 9].

Recent studies highlight the possibility of extensively use of Bronhypret (Bionorica) as an effective agent of pathogenetic therapy of bronchitis in children. Bronhypret comes in three different formulations – syrup and drops of liquid extract from thyme (BNO 1561) and liquid extract of ivy (BNO 1511), as well as tablets containing dry extract of thyme (BNO 1018) and dry primrose root extract (BNO 1535). It has sekretolytic, bronchospasmolytic, anti-inflammatory, antibacterial, and antiviral activity.

The main active components of the herb thyme are essential oils and especially thymol, which has a local effect on the bronchopulmonary system, as it is excreted from the body through the respiratory tract, disinfecting them, reducing bronchoconstriction and showing expressed mucolytic activity. Bioactive thymol components are capable of binding to lungs adrenoceptors accompanied by the formation of cAMP and, as a result, reduction of the amount of calcium in the cell, which causes relaxation of smooth muscles of the bronchi. Thymol and another active ingredient – falkarinol – have also moderate anti-inflammatory and antibacterial activity. Another equally important components are saponins that increase bronchial secretion through gastric-pulmonary reflex and dilution of mucus through direct interaction with the bronchial mucosa. Herbal components of Bronhypret, improve the expectoration by stimulating the activity of the ciliated bronchial epithelium. In addition, the components of the medication exhibit anti-inflammatory activity, reducing inflammation and moderate immunomodulating effect as well [7, 9].

Results of multicenter, placebo-controlled studies (according to international GCP-standard) showed high efficiency of Bronhypret in simple bronchitis. It was not inferior to synthetic sekretolytics based on ambroxol in terms of eficacy, but had better safety profile.

The aim of the study was to determine the efficacy and safety of Bronhypret for treatment of acute obstructive bronchitis in infants.

Materials and methods

In this study 60 children aged 1 to 3 years with acute obstructive bronchitis were comprehensively examined. Of those aged 1 to 2 years was 45 (75%) children 2 to 3 years – 15 (25%). The mean age of patients was 1,5 ± 0,7 years. There was equal number of girls and boys in the study – 30 patients. In all children acute obstructive bronchitis developed on the background of acute respiratory viral infections, manifested with hyperthermia syndrome, cough, rhinorrhoea, congestion of the mucous membrane of the tonsils and posterior pharyngeal wall. Manifestations of obstructive symptoms in the form of expiratory or mixed dyspnea were observed in all children. Children were hospitalized in the early stages of the disease – 1st to3rd day. Chronic foci of infection such as chronic tonsillitis, and I to III stages adenoid vegetations were found in 34 (56.7%) patients.

Inclusion criteria: the diagnosis of acute obstructive bronchitis and at least 5 points of Bronchitis Severity Score (BSS) patients were included in the study. The diagnosis was based on patients history, clinical manifestation, laboratory tests. In doubtful cases x-ray of the chest was performed . Availability of informed parents consent.

Exclusion criteria: hereditary and congenital pathology of the respiratory system, clinically significant congenital malformations of internal organs, III stage respiratory failure , allergic reactions to individual components of the medication, the use of systemic corticosteroids in the treatment of respiratory diseases and the refusal of parents to participate in the program.

Combined therapy of patients was carried out according to the Ministry of Health of Ukraine Guidline № 18 (13.01.2005) and included antibiotics, antihistamines, bronchodilators, sekretolytics, and biological agents. Antibiotic therapy (7–10 days), antihistamines and biological agents were administered in the mean age dose depending on the clinical situation. Severe manifestations of obstructive syndrome required the use of emergency treatment – -2 short-acting-agonists (Ventolin via nebulizer 3 to 4 days).

Depending on the kind of sekretolytic administered in the treatment of acute obstructive bronchitis, patients were divided into two groups: the main group – 30 children who received Bronhypret; comparison group – 30 children treated with Ambroxol.

Bronhypret in the main group was administered in mean age doses – 1 drop per kg of body weight plus 10 drops of syrup three times a day. Because the study involved infants, Bronhypret was used only in the form of syrup, which allowed for the use from 1 year old age. Syrup Ambroxol in the comparison group was administered in mean age doses: children under 2 years – 7.5 mg 2 times daily, 2 to 3 years – 7.5 mg three times daily. Duration of treatment was determined by the dynamics of clinical and paraclinical parameters and made 10 to14 days.

Te main endpoints were the severity and duration of the intoxication syndrome, the nature of the temperature curve, the character on the frequency of coughing day and night attacks and sputum – according to BSS (American College of Chest Physicians, 2007), severity of dyspnea, percussion and auscultation data, results of laboratory studies (blood tests), the presence of C-reactive peptide and IgE in serum.

Safety and tolerability were assessed by the presence / absence of side effects.

Observation of patients was performed within 10-14 days of hospitalization. On the 3rd, 5th and 10th day after admission control of the clinical condition of patients have been performed . On the 5th and 10th day of disease laboratory parameters control was held.

Results and discussion

In the first two days of the disease patients in both groups experienced expressed signs of intoxication syndrome in the form of hyperthermia, drowsiness, lethargy, loss of appetite. Hyperthermia above 38,5 ° C was in 43 (71.7%) of children, drowsiness, lethargy and loss of appetite were observed in all patients. Expiratory dyspnea was observed in 57 (95%) of children, 3 (5%) had symptoms of mixed dyspnea. Frequent dry unproductive cough was observed in all patients. Percussion of the lungs determined box shade lung sound, auscultation – wet and dry sibilant rales on the background of hard breathing. BSS index was 12 ± 1,5 points, indicating moderate severity of bronchitis.

At the onset of the disease in the hemogram of 46 (76.7 %) children showed moderate leukocytosis, eosinophilia, in 36 (60 %) of children increased ESR in the range of 15 to 28 mm / h was registered. In biochemical analysis of blood serum content of C-reactive peptide was 5,6 ± 0,06 mg / l (normal up to 4 mg / L) in immunological study of serum IgE content was 118 ± 6,9 IU / ml (normal 86,4 ± 2,6 IU / ml).

Considering the efficacy of combined therapy in children and the secretolytics pathogenic therapy, dynamics of clinical symptoms was analyzed by BSS on the 3rd, 5th and 10th day of treatment. In the study group on the background Bronhypret use after 3 days of treatment wet cough and phlegm mucus discharge enhancement in 28 (93.3%) of patients was observed. After 5 days of treatment (which is 2 to 3 days earlier than in the comparison group) the number of sputum decreased, indicating a decrease of inflammation with signs of exudation (overproduction of mucus) in the bronchi.The the intensity of cough (day and night attacks) also decreased in 26 (86.7%) of children. The greater was the severity of clinical manifestations – the higher the efficiency of the treatment was.

On day 10 of therapy cough was completely eliminated in 26 (86.7%) of children of the main group, 4 (13.3%) of children had cough of minimum intensity with a small amount of mucous sputum.

In a comparison group of children who taking ambroxol in the treatment of obstructive bronchitis, amplification of wet cough and mucus hyperproduction were recorded on the 3rd day of the disease in 27 (90%) of patients. However, the amount of sputum decreased later – till 7 to 8 day of treatment cough intensity decreased in 25 (83.3%) of children. On 10th day of the therapy cough was completely eliminated in 24 (80%) of children in comparison group, and another 6 (20%) had non-intensive cough with a small amount of mucous sputum (Table 1).

Dynamics of paraclinical parameters showed normalization of the number of lymphocytes, neutrophils and eosinophils in

Table 1

Dynamics of clinical symptoms in children on the background of the complex therapy of acute obstructive bronchitis (%)

Clinical symptom	Main group – Bronhypret (n=30)			Comparison group – Ambroxol (n=30)		
	3rd day	5th day	10th day	3rd day	5th day	10th day
Body temperature above 38°C	80%	36,7%	–	76,7%	40%	–
BSS score	11 ±0,8	8±0,4	4±0,02	12±0,92	7±0,36	4±0,02
Expiratory dyspnea	36,7%	3,3%	–	40%	–	–
Mixed dyspnea	6,7	3,3	–	3,3	3,3	–
Cough: dry wet no cough	 6,7% 93,3% –	 86,7% 13,3%	 13,3% 86,7%	 10% 90% –	 3,3% 96,7% –	 20% 80%
Sputum: no sputum mucous purulent	 83,3% 16,7% –	 3,3% 96,7% –	 86,7% 13,3% –	 90% 10% –	 20% 76,7% 3,3%	 80% 20% –
Breathing: hard weakened	 73,3% 26,7%	 76,7% 13,3%	 26,7%	 76,7% 23,3%	 70% 16,7%	 23,3%
Crepitation: dry wheezing fine moist rales medium moist rales coarse moist rales	 36,7% 26,7% 36,7%	 23,3% 46,7% 30%	 3,3% 3,3%	 33,3% 36,7% 30%	 30% 50% 20%	 6,7%

Table 2

Dynamics of C-reactive peptide and IgE in children from studied groups

Parameter	Main group – Bronhypret (n=30)		Comparison group – Ambroxol (n=30)	
	Disease onset	10th day of treatment	Disease onset	10th day of treatment
C-reactive peptide, mg / l	5,6±0,06	2,1 ±0,02*	5,3±0,04	2,4±0,02*
IgE, IU / ml	118±6,9	84±4,7*	121 ±7,1	81 ±3,9*

Note: * – significant difference with respect to baseline(p<0,05).

2 (6.7%) of children of the main group at the 5th day treatment and in 24 (80%) of children on the 10th day after admission. Children in comparison group had similar dynamics: in 1 (3.3%) child on the 5th day of inpatient treatment and in 26 (86.7%) of children – on the 10th day. Dynamics of C-reactive peptide and IgE in children in both groups are shown in Table 2.

In 24 (80%) of children of the main group after 10 days of treatment had normal values of C-reactive peptide in serum and normalization of IgE in 28 (93.3%) of children was observed. In the comparison group of children 23 (76.7%) of patients after 10 days of treatment had normal values of C-reactive peptide and 29 (96.7%) – reduction of IgE in serum.

Bronhypret was well tolerated, no medication refusals, no adverse effects in the form of allergic reactions or dysfunction of the digestive tract were observed.

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НОВЫЕ ВОЗМОЖНОСТИ ПРИМЕНЕНИЯ СЕКРЕТОЛИТИКОВ В КОМПЛЕКСНОЙ ТЕРАПИИ ОСТРОГО ОБСТРУКТИВНОГО БРОНХИТА У ДЕТЕЙ РАННЕГО ВОЗРАСТА

В. М. Дудник

Резюме. *Проведено обследование и лечение 60 детей раннего возраста с острым обструктивным бронхитом. Применение в комплексной терапии комбинированного фитопрепарата Бронхипрет показало эффективность, не уступающую синтетическим секретолитическим средствам. Высокая эффективность, хорошая переносимость и безопасность препарата Бронхипрет позволяют рекомендовать его применение для лечения острого обструктивного бронхита у детей раннего возраста.*

Ключевые слова: *дети раннего возраста, острый обструктивный бронхит, фитопрепараты, Бронхипрет.*

NEW APPLICATIONS OF SECRETOLYTICS IN COMPLEX THERAPY OF ACUTE OBSTRUCTIVE BRONCHITIS IN CHILDREN OF EARLY AGE

V. M. Dudnik

Summary. *Carried out an examination and treatment of 60 children of early age with acute obstructive bronchitis. Application in complex therapy combined herbal drug Bronchipret showed effectiveness equal to synthetic secretolytic drugs. High efficacy, the tolerability and safety of the Bronchipret allow to recommend it for the treatment of acute bronchitis in children of early age.*

Key words: *children of early age, the acute obstructive bronchitis, herbal drugs, Bronchipret.*