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Mini Review

The Role of Carbocysteines in Outpatient Pediatric Practice

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Abstract

The article presents data about modern mucoactive therapy with carbocysteines for acute and chronic bronchopulmonary diseases, operation of these medications, data about experimental and clinical studies and role of carbocysteines in outpatient pediatric practice.

Keywords: *Children; Acute and Chronic Diseases of the Respiratory System; Mucoactive Therapy; Mucoregulators; Carbocysteines, Fluditec*

Introduction

Disturbed process of mucus secretion in respiratory tract takes an important part in pathogenesis of both acute and chronic bronchopulmonary diseases, occasioning typical clinical manifestations [1-3]. Recent studies showed that inflammation and oxidative stress are leading triggers of hypoproduction and secretion of mucus in airways which correlates closely with outcomes of respiratory diseases. Many medical societies of the world officially acknowledge the fact that mucus hypersecretion in respiratory tract plays an important role in respiratory diseases [4].

That is why mucolytics therapy is an integral part of treatment of acute and chronic respiratory diseases in children [1]. Traditional and plant-based medicines as well as remedies of synthetic origin have been widely used in pediatric practice [2]. Carbocisteine and its derivatives are considered an advanced class of mucoactive medicines of indirect action which have microregulatory and mucolytic effect at the same time [1, 2]. Recently we have already drawn attention of pediatricians to this perspective group of medicines [1,5-9].

Carbocisteine was synthesized in 1930 and since 1960 has been used for respiratory diseases as a mucoregulator. Mucoregulatory effect of carbocisteines is preconditioned by normalization of secretory function of glandulocytes. Carbocisteine influences activity of enzymes of goblet cells in bronchial mucous membrane: sialic transferase, which regulates balance between sialomucins and fucomucins. During experimental studies on animal models it was shown that carbocistein increases transportation of chlorides in airway epithe-

lium, which is one of its microregulatory effects [10]. It was found that carbocisteine inhibits TNF-alpha induced growth of viscosity and sialyl-Lewis x-epitopes on fused protein MUC5AC. The obtained data evidence ability of carbocisteine to normalize mucus viscosity due to normalization of fucosa and sialic acid in airways mucin [11]. Besides, carbocisteines makes effect on gel phase of mucus by destroying disulfide bonds of glucoprotein resulting in diffluence of pathologically viscous secretion and contributes to better respiratory epithelial clearance and restoration of respiratory epithelial structure [1,12]. Carbocisteine induces regeneration of mucous membrane, reduction of number of goblet cells especially in terminal bronchus and, as a result, lower secretion of mucus and activation of ciliated epithelium, faster mucociliary clearance which results in faster resolution of inflammation [13]. The latter is achieved by the fact that carbocisteine has anti-inflammatory action: both direct (cinin-inhibiting action of cialomucines) and indirect (improved capillary perfusion, microcirculation). Analysis of modern clinical and experimental studies evidences significant anti-inflammatory antioxidative activity of carbocisteine [12,14]. Carbocisteine medicines facilitate reduced migration of anti-inflammatory cells into airways, restoration of affected endothelium and associated with it coughing sensitivity [15]. Results of the experimental study proved that carbocisteine medicines have protective effect during oxidative stress, decreasing activity of inflammation caused by active oxygen forms. Comparative analysis of different methods of expectorant therapy in patients with bronchial asthma proved that after the course of carbocisteine, the level of coughing threshold assessed by the functional test with capsaicin was significantly higher than that after treatment with Ambroxol or placebo [15]. Carbocisteine inhibits adhesion of pathogenic bacteria to airway epithelium thus facilitates decrease of bacterial contamination in respiratory tract [16]. Carbocistein changes surface structure of Streptococcus pneumoniae which results in its decreased adhesion on cells of respiratory epithelium [17]. It was found as a result of the study that carbocisteine makes for decrease of adhesive characteristics of upper airway epithelium, i.e. for lower number of cells captured by *Haemophilus influenzae*, which by our opinion may contribute to lower frequency of respiratory infections [18]. Clinical experience proves that carbocisteine is very well combined with inhaled glucocorticosteroids and bronchodilators and enhances efficiency of antibacterial therapy [5]. It was proved that simultaneous use of carbocisteine and amoxicillin for exacerbation of chronic bronchitis the content of the antibiotics in bronchial secretion increases significantly which provides synergetic effect and better eradication of pathogenic microorganisms [16].

There exist experimental data evidencing ability of carbocisteine to reduce expression of receptors to human influenza virus in epithelial cells of upper airways by suppression of NF-kappaB factor and increase of pH level in cellular endosomes [19]. Results of the experimental study show that carbocisteine decreases inflammatory processes in lungs and hyperproduction of mucus under effect of conditional stimulus (tobacco smoke) after contamination with influenza virus vis activation of NF-E2-bound factor [20]. According to Japanese scientists carbocisteine inhibits development of rhinovirus infection in epithelial cells of human airways [21]. Carbocisteine inhibits development of rhinovirus infection in epithelial cells of human trachea. It makes effect on inflammatory process in the respiratory tract during viral infection by lowering production of interleukin-6 (IL), IL-8, soluble ICAM-1. There exist data about steady growth of secretory immunoglobulin A level persisting long time after end of treatment with carbocisteine [5,16,22].

The effect of carbocisteine manifests at all levels of the respiratory tract: at the level of mucous membrane of bronchial tree, nasopharynx, maxillary sinuses and the middle ear [1,3,23,24]. Cough with viscous hard expectoration is a direct indication for the use of Carbocisteine [5,23]. At the same time Carbocistein is quite ineffective when used as aerosol inhalation.

Positive quality of carbocisteines is their "after-effect". Their negative qualities, such as poor solubility in water, acid pH and unsatisfactory organoleptic characteristics demanded for the development of adapted medicinal forms [1,5,6,25,26].

Fluditec® in particular is a very well buffered solution of carbocisteine which is sold as 5% (for adults) and 2% (for children) tasty syrup. According to Balyasinskaya GL., *et al.* treatment with Fluditec® (in comparison with Ambroxol) in 4 to 5 month old children significantly decreased mean period of broncho-obstructive syndrome and cough as well as duration of hospital stay [27]. Studying children of 2 to 12 years old with acute respiratory infection of lower airways taking carbocisteine (Fluditec®) (treatment group) and acetylcysteine (control group) Solovyova NA., *et al.* reported higher clinical efficiency of therapy, proved safety and good tolerance of mucoactive therapy in the treatment group [24].

A comparative evaluation of the clinical efficacy of carbocisteine (Fluditec ®) and soothing herbal preparations revealed that carbocysteine is highly effective and safe in children of 2 - 17 years old with recurrent respiratory infections of lower airways. It was noted that administration of carbocysteine in the first days of disease significantly reduced its duration and hospital stay period as well as duration of cough and moist rale in the lungs, enhanced local immunity (sIgA) in contrast with the comparison group patients taking plant-based expectorant drugs [5,25].

Comparative study in children from 3 to 8 years old with upper airways diseases (rhinitis, adenoiditis) taking carbocystein showed its clinical efficiency manifesting as effective nasal discharge and reduction of nasal secretion, reduced swelling of the nasal mucosa, normalization of nasal breathing and data of exfoliative cytogram of nasal secretion compared to patients of the control group [28]. Similar data were obtained by the authors studying effect of Fluditec® in combination with antibacterial therapy (penicillin-type antibiotics, 3rd generation cephalosporins and macrolides) and decongestants in children with acute rhinosinusitis, acute exudative medium otitis, acute rhinopharyngitis [29].

It should be noted that there are numerous publications about high therapeutic efficacy of carbocysteine in adult patients with chronic obstructive pulmonary disease (lower frequency of exacerbations and improved patients' life quality). In the course of a clinical study of patients with chronic bronchitis it was established that as a result of therapy including carbocysteine, sputum viscosity reduced by 3.5 times, mucociliary transport was restored on the 4th day from the beginning of treatment, persistent "after-effect" lasted during 8 days after end of therapy [32]. This after-effect of carbocysteines allows us to recommend them as courses of treatment for chronic lung diseases requiring long-term muco-regulatory therapy. Data from numerous clinical studies evidence that use of carbocysteines have no risk of excessive sputum liquefaction [1,3,5-9,25,27,32].

According to the data of clinical studies, carbocysteines have high safety profile [31]. Systematic Cochrane review of 34 studies involving 2,064 children over the age of two, with the objective to evaluate efficacy and safety profile of mucolytics for acute respiratory infection came to conclusion that carbocysteine was safe for children older two years of age [33].

We should note that selection of mucoregulators is especially important in the therapy of lower respiratory diseases in children of early and preschool age, since vulnerability to exudation and swelling of bronchi mucosa, pronounced hyperproduction of mucus, increased mucus viscosity and narrow airways are the main pathogenic factors.

Analysis of modern literature, data of our own clinical studies let us offer the following indications as additional indications for administration of carbocysteines: 1) acute, especially repeated, recurrent and protracted respiratory infections of the lower respiratory tract, associated with diffuse wet wheezing in the lungs and hyperproduction of sputum; 2) acute bronchoobstructive syndrome during ARI (in combination with bronchodilators), accompanied by viscous, difficult to discharge sputum, its worsening evacuation; 3) chronic bronchitis.

Positive mucoactive effect is achieved with a comprehensive treatment, including treatment and protection regime, sufficient hydration, rational diet, etiotropic therapy (antiviral drugs, antibiotics according to indications). To improve the drainage function of the lower respiratory tract, kinesitherapy and respiratory gymnastics are used.

Conclusion

In general, carbocysteines are the most advanced mucoactive drugs with muco-regulating effect, which makes them stand among the most sought-after drugs for treatment of both acute and chronic, recurrent bronchopulmonary pathology in children.

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