ORIGINAL ARTICLE

Efficacy of carbocisteine in the treatment of chronic obstructive pulmonary disease and impact on the quality of life

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ABSTRACT

Aim To investigate the effects of carbocisteine treatment in the reduction of frequency of productive cough episodes, preventing disease progression and improving the quality of life as well as the tolerability of the administered treatment and patient compliance during the study.

Methods This observational, non-interventional, multicenter, cohort study included 501 patients with chronic obstructive pulmonary disease (COPD) who were administrated carbocisteine capsules 375 mg and followed up during the next 15 days. The patients were observed at 3 points, baseline and two additional assessments. General clinical condition of patients, along with the spirometry testing at all three points were examined. Thr quality of life was assessed on the 1st and 3rd observation with Leicester Cough Questionnaire. Tolerability and patient compliance were measured throughout the study.

Results There was a significant change of forced expiratory volume in 1 second (FEV1) status between the second and third observation (p=0.002). Examination of general symptoms showed a statistically significant reduction in cough by 74.9%, in sputum production by 48.5%, in dyspnea by 29% and in fatigue by 50%. After the administration of carbocisteine the median value of overall quality of life was 3.79 (3.63 – 3.89).

Conclusion 375mg carbocisteine capsules were found to be effective and well-tolerated in the treatment of COPD, with a small percentage of reported mild adverse reactions and with a significant improvement of quality of life.

Keywords: lung disease, cough, expectorants

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and morbidity both in developed and developing countries that is mainly characterized by progressive and not fully reversible airflow limitation (1). There are wide variations in the prevalence of COPD across countries (2). The COPD is common in older population and is highly prevalent in those aged over 75 years. The Burden of Obstructive Lung Disease (BOLD) study from 12 sites involving 9425 subjects, who had completed post bronchodilator spirometry testing, found that the overall prevalence of COPD of GOLD stage II or higher was 10.1 per cent and the prevalence was 11.8 per cent for men and 8.5 per cent for women (2).

According to the Health institute of the Federation of Bosnia and Herzegovina, a leading cause of morbidity of patients in the Federation of Bosnia and Herzegovina are the diseases of the respiratory system with 30% of share. They are also the largest burden for the primary care units in the Federation of Bosnia and Herzegovina. In the structure of morbidity, the most common respiratory system diseases are acute respiratory infections (70.7%) and COPD (6.4%). For most patients, the diagnosis of COPD is made in the mid – fifties. 45-65% of COPD patients are not diagnosed because dyspnea and fatigue are commonly associated with normal process of aging, and the smoker's cough is considered normal (3).

COPD is characterized by a decline in lung function over time and accompanied by respiratory symptoms, primarily dyspnea, cough, and sputum production (4).Active smoking remains the main risk factor, but other factors are becoming better known, such as occupational factors, infections and the role of air pollution (5).Current data suggest that COPD mortality is increasing, and by 2020, COPD is predicted to be the third-leading cause of death worldwide (4).

Guidelines from the Czech Republic, England and Wales, France, Germany, Poland, Portugal, Russia and Sweden stratified patients on the basis of the degree of airflow limitation into the four stages set forth in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy, as follows. Stage 1 (mild): FEV1 (forced expiratory volume) ≥80% predicted; stage 2 (moderate): FEV1 50–79% predicted; stage 3 (severe): FEV1 30–49% predicted; and stage 4 (very severe): FEV1 <30% predicted (6).

Health-related quality of life (HRQOL) is a multi-dimensional concept that includes domains related to physical, mental, emotional and social functioning (8). The Leicester Cough Questionnaire (LCQ) is a 19-item questionnaire that assesses cough-related QOL and takes 5 to 10 minutes to complete. Scores in three domains (physical, psychological and social) are calculated as a mean for each domain (range 1 to 7). A total score (range 3 to 21) is also calculated by adding the domain scores together. Higher scores indicate better quality of life (8). In this study, the LCQ used was in the Bosnian language. Because the LCQ is a measure originally developed in the English language, it should be translated to the target language, in our case Bosnian, and adapted to the social and cultural circumstances of the target country (8).

Over the years evidence has accumulated that mucus hypersecretion is an important manifestation of chronic obstructive pulmonary disease (COPD). In the classical phenotype of chronic bronchitis, mucus hypersecretion is the key presenting symptom that appears independent of airflow obstruction (9). A large number of studies have been performed on the use of mucolytic drugs in the treatment of chronic bronchitis and COPD (9). These studies clearly demonstrate that treatment with mucoactive drugs reduces exacerbations in patients with COPD with virtually no side-effects, though the mechanisms by which these effects might be observed are still unclear (9).

The aim of this study was to examine the effects of carbocisteine treatment in the reduction of the frequency of productive cough episodes, preventing disease progression and improving the quality of life as well as the tolerability of the administered treatment and patient compliance during the study.

PATIENTS AND METHODS

Patients and study design

An observational, non-interventional, multicenter, cohort study in 15 medical centers from major cities of Bosnia and Herzegovina including Sarajevo, Tuzla, Zenica, Žepče, Gradačac, Ljubače, Bukinje, Devetak, Kalesija, Tešanj, Hadžići and

Ilijaš was conducted. The study included a total of 501 patients with COPD, who were admitted to a family medicine practice at the primary healthcare level in the period from February 2016 to April 2016. The patients were administered carbocisteine capsules 375 mg manufactured by Bosnalijek Sarajevo and followed up 15 days after the start of carbocisteine administration. Criteria for inclusion in the study included patients with stage I COPD (FEV1/FVC <70 %; FEV >80%), patients with stage II COPD (FEV1/FVC < 70%; 50% < FEV1< 80%) and patients with productive cough for a period longer than three months a year. The clasification is based on the GOLD Classification of severity of airflow obstruction (6).

Patients who showed hypersensitivity to carbocisteine or had an active peptic ulcer were not included in the study, and the patients who showed deterioration of the underlying disease, development of serious adverse events that require discontinuation of the therapy or developed a disease that affected the flow of research were excluded from the study.

Methods

Patients were observed at 3 time points, e.g. the first baseline and two additional control assessments. For assessments of HRQOL on COPD the cough-specific quality-of-life questionnaire, Leicester cough questionnaire (LCQ) was used (8), since the questionnaire addresses some of the main symptoms of COPD.

The FEV1 in the first second obtained by spirometry, before and after the treatment with carbocisteine capsules 375 mg, was measured. For result comparison general guidelines were used as the criteria for defining airflow obstruction in the diagnosis of COPD. Blood examination including C - reactive protein (CRP), leukocytes (LKC) and sedimentation (SE) as well as the patient's general symptoms were examined.

First observation (day 0) included spirometry and an assessment of whether the inclusion criteria were met. Patients were further divided into two groups based on the spirometry: Group A - patients with stage I COPD and Group B – patients with stage II COPD. The first observation also includes an assessment of the quality of life based on the validated LCQ. The second observation was performed on the 5th day and included only an assessment of the general clinical condition of the patient along with spirometry. Third observation was performed on the 15th day (from the start of the study) and included a final assessment of the effectiveness of the treatment based on the improvement of the patient's general condition, spirometry as well as the assessment of the quality of life based on the LCQ. After 15 days, effectiveness, tolerability and patient compliance were also recorded. The measurements of the study outcomes was independent from the study investigators.

The drug effectiveness was assessed on the basis of physician's examination of the patients. The safety of the product administration was observed by monitoring the incidence of adverse reactions of drugs with the assessment of the relation between drug administration and adverse reaction occurrence (certain, probable, possible, not probable, unclassified relation and non-classifiable).

Statistical analysis

The study results were presented as the mean value (X) and standard deviation (SD) for variables that followed a normal distribution, or as a median and interquartile range for variables that did not follow a normal distribution and as absolute and relative numbers. Evaluation of categorical variables was performed by the $\chi 2$- test for independent variables or by the McNemar's test for dependent categorical data. Fridman test was used for dependent variables that are ordinal. The accepted statistical significance was set at the level $p<0.05$.

RESULTS

The study included a total of 501 patients with COPD, who met the inclusion criteria. Out of the total of 501 patients, 273 (54%) were males and 228 (46%) were females with no significant difference in gender distribution. The average age of the patients was 52±17.3 years. Out of the total of 501 patients, 222 (44%) were smokers and 279 (56%) were non-smokers. The patients were given carbocisteine during 15 days. Primary dosage was two capsules of carbocisteine 375 mg three times a day for the first five days. Maintenance dosage was one capsule of carbocisteine 375 mg four times a day for the next ten days.

The FEV1 in the first second did not show a significant change in the status of patients between the first and second observation (p=0.092). There

was a significant change of FEV1 status between the second and third observation (p=0.002) (Table 1). During the first observation 2.5% of patients had FEV1 < 30%. During the second observation 2.27% of patients had FEV1 < 30% and during the third observation a significant change was noticed, 0.62% patients had FEV1 < 30%. During the first observation 23.29% patients had FEV1 between 30-50%, during the second observation the percentage of patients with FEV1 between 30-50% was 19.32% and during the third observation it was 18.63%. During the first observation 62.33% of patients had FEV1 between 50-80% from expected. During the second observation the percentage of patients with FEV1 between 50-80% increased to 65.91% and during the third observation the percentage of patients was lowered to 52.18%. During the first observation 12.33% of patients had FEV1>80 % than expected. During the second observation the percentage of patients was 12.5% and during the third observation the percentage of patients with FEV1>80% was 28.5%.

Table 1. Results of forced expiratory volume (FEV) 1spirometry measurements in patients with chronic obstructive pulmonary disease (COPD) before and after the administration of carbocisteine

	FEV1 (%)				FEV1 (%)		
Obstruction level (%)	Observation I	Observation II	Change from observation I to II (%)	p	Observation III	Change from observation II to III (%)	p
<30.00	2.05	2.27	0.22	0.092	0.62	-1.65	0.002
30.01 – 50.00	23.29	19.32	-3.97	0.092	18.63	-0.69	0.002
50.01 – 80.00	62.33	65.91	3.58	0.092	52.17	-13.74	0.002
80.01 +	12.33	12.50	0.17	0.092	28.57	16.07	0.002

Examining general symptoms in patients with COPD before and after the treatment with carbocisteine, a significant reduction in the number of patients with cough, sputum production, dyspnea and fatigue was found (Table 2). There was also a significant reduction of CRP, LKC and SE before and after the treatment with carbocisteine. Blood examination showed a significant improvement after the treatment with carbocisteine in the number of patients involved in the study. The median value of CRP before the treatment was 5.75 (2.08 - 9.85) and after the treatment the median value was 4.0 (2.0 – 5.5). The median value for leukocytes before the treatment was 9.10 (7.10 – 11.19) and the median value after the administration of carbocisteine was 7.88 (6.30 – 9.10). Also, the median value for sedimentation before the treatment was 16.00 (10.00 – 24.00) and the median value after the treatment was 11.00 (7.50 – 17.00). These results show a significant reduction in all three points of blood examination (p=0.001).

Table 2. Presence of general symptoms in patients with chronic obstructive pulmonary disease (COPD) before and after the administration of carbocisteine

General symptoms	Observation I (%)	Observation II (%)	Observation III (%)	Change from observation I to III (%)	p
Cough	485 (96.9)	346 (69.1)	110 (22)	-74.9	0.0001
Sputum production	396 (79)	326 (65)	153 (30.5)	-48.5	0.0001
Dyspnea	194 (39)	131 (26)	48 (10)	-29	0.0001
Fatigue	323 (65)	167 (33)	77 (15)	-50	0.0001

Patients' quality of life (Leicester Cough Questionnaire)

The median value for physical domain was 3.63 (3.25 – 4.0) before the treatment. After the administration of carbocisteine the median value for physical domain was 3.88 (3.64 – 4.0). These results showed a significant improvement of physical domain (p=0.0001).

The median value for psychological domain before the treatment with carbocisteine was 4.14 (3.71 – 4.4) and the median value after the treatment was 3.57 (3.43 – 3.86), which shows a significant deterioration of psychological domain (p=0.0001).

When it comes to social domain there was no significant improvement (p=0.722). Before the treatment, the median value for social domain was 3.75 (3.5 – 4.25). After the treatment, the median value for social domain was 4.0 (3.5 – 4.0) (Figure 1).

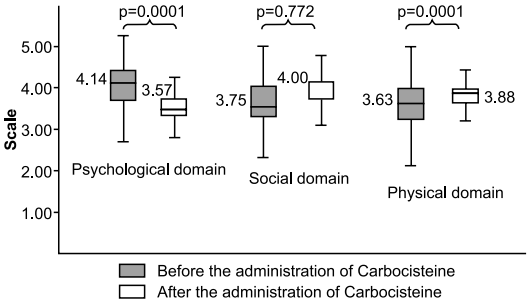

Figure 1. Quality of life in all three domains before and after the administration of carbocisteine

Examining the results of overall assessment of quality of life obtained by the LCQ before and after the treatment, we found no significant improvement of the quality of life in patients involved in the study (p=0.065).

The median value of overall quality of life before the treatment was 3.84 (3.53 – 4.16). After the administration of carbocisteine the median value of overall quality of life was 3.79 (3.63 – 3.89).

DISCUSSION

This study was conducted to show the effectiveness of carbocisteine in patients with COPD that was measured as an improvement in the general clinical features as well as the quality of life conditions. Examination of general symptoms in patients before and after the treatment with carbocisteine showed a statistically significant reduction in cough by 74.9%, in sputum production by 48.5%, in dyspnea by 29% and in fatigue by 50%. The overall results of spirometry testing showed a reduction in airflow obstruction in patients with all stages of COPD (I, II, III and IV).

S-Carboxymethylcysteine (carbocysteine or SCMC) is a mucoactive drug with antioxidant and anti-inflammatory properties, and is commonly used for the treatment of COPD. Pre-clinical and clinical studies on the pharmacological properties of SCMC have demonstrated that this cysteine derivative has the ability to increase the synthesis of sialomucins, important structural components of mucus. In effect, SCMC resets the balance between sialomucins and fucomucins, possibly by intracellular stimulation of sialyl transferase activity, restoring the viscoelastic properties of mucus (10).

Carbocisteine is available as an oral preparation both as SCMC and its lysine salt (SCMC-Lys). The structure and mechanism of action of carbocisteine differs from other commonly available mucolytic drugs such as N-acetylcysteine (NAC) and erdosteine that bear free sulfhydryl (thiol) groups via which they split glycoprotein bonds in mucus (11). Carbocisteine is well absorbed when taken orally. Peak serum concentrations are achieved at 1 to 1.7 hours and the plasma half-life is 1.33 hours. It achieves good penetration into lung tissue and bronchial secretions. Approximately 30% to 60% of the drug is excreted unchanged in urine (11). Thanks to its unique pharmacological properties, it has an excellent safety profile and is suitable for special groups of patients such as children, adults and people with impaired liver and/or kidney function.

This study shows that COPD exacerbation may have important effects on health status and is a useful outcome measure in clinical studies of the disease. Reduction of exacerbation frequency would be expected to improve well-being, though this has not been formally tested in an interventional study. Health status measures show a strong relationship with exacerbation frequency and thus may be useful in determining which patients are at risk of exacerbation and associated disability (12).

A study conducted in 1998 has shown the impact of chronic cough on the quality of life. First, chronic cough was significantly associated with meaningful adverse psychological and physical effects on the quality of life. Compared with individuals with no health-related dysfunction, baseline Sickness Impact Profile (SIP) scores revealed that cough was associated with dysfunction in patients' usual daily activities, particularly in the categories of ambulation, social interaction, sleep and rest, work, home management and recreation and pastimes. Secondly, successful treatment of chronic cough was associated with the resolution of patients' deterioration in the quality of life (13).

Carbocisteine reduces intercellular adhesion molecule-1 expression and blocks entry of rhinovirus ribonucleic acid into the endosomes. Therefore, carbocisteine may be useful in the prevention of common colds and exacerbations in COPD patients (7). The preventive effects of carbocisteine on acute exacerbations of COPD were investigated in a multicenter (n523), parallel-group, randomized study (7). The study showed a significant reduction in the number of common colds and exacerbations in the study group than in the control group.

St George's Respiratory Questionnaire (SGRQ) total score and components (impacts, symptoms, and activities) total score decreased in the study group but not in the control group, indicating that carbocisteine improved patients' quality of life (QOL). In addition, all three component scores decreased in the study group, suggesting that carbocisteine administration improved both physical and mental aspects of QOL (7).

Most recently, PEACE study supported previous findings that long-term use of carbocisteine re-

duced the rate of exacerbations of COPD. The advantage of carbocisteine over placebo in prevention of exacerbations was note-worthy even after the adjustment for COPD severity and concomitant therapy (14). In addition to preventing COPD exacerbations, carbocisteine was shown to improve the patients' quality of life (14).This finding differed from our study in which significant improvement of the quality of life by carbocisteine was shown, which may indicate that only long-term studies may evaluate the effect of carbocisteine on exacerbation rate.

Future randomized controlled trials should examine the value of mucolytic drugs in patients who have repeated, prolonged or severe exacerbations or who are repeatedly admitted to hospital with exacerbations of chronic obstructive pulmonary disease. The use of mucolytic in acute exacerbations of chronic obstructive pulmonary disease should also be studied. All of these studies should include a measure of the use of healthcare resources (15).

While a great deal is known about the diagnosis and treatment of cough, there are methodological challenges that need to be solved in order to achieve further advances in our understanding of how to best manage patients with this common symptom. One of the most basic challenges is the development of a valid and reliable method by which to assess the impact of cough on the health-related quality of life of patients. Such a method would provide an important measure of the efficacy of cough therapies (16).

The other part of our study was focused on examining the quality of life in patients with COPD. The examination of physical domain showed a significant improvement.

The main limitation of this study is the short duration as well as the limited follow up with the patients in the study. However, this study is the first in our region that has been conducted to show the importance of measurement of the quality of life in patients with COPD. Also, it is the first application of the Leicester Cough Questionnaire in monitoring the quality of life in patients with COPD in Bosnia and Herzegovina.

Available medical evidence supports the conclusion that mucolytic drugs containing carbocisteine in the dose of 375 mg xx daily in the treatment of chronic obstructive pulmonary disease contribute to the improvement of the general condition of the patient and reduce cough, decrease sputum production, reduce dyspnea and fatigue. In addition, the therapy with carbocisteine affects the reduction of C – reactive protein, leukocytosis and sedimentation, which confirms carbocisteine anti-inflammatory properties. The results of our study show that cabocisteine has good effectiveness and tolerability.

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DECLARATION OF INTEREST

Competing interests: None to declare.

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Efikasnost karbocistina u tretmanu hronične opstruktivne plućne bolesti i njegov utjecaj na kvalitet života

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SAŽETAK

Cilj Ispitati efekte terapije s karbocisteinom u smanjenju učestalosti epizoda produktivnog kašlja, sprečavanju progresije bolesti i poboljšanju kvalitete života, te podnošljivost primijenjene terapije i suradljivost ispitanika tokom istraživanja.

Metode Ova opservacijska, neintervencijska, multicentrična, kohortna studija uključivala je 501 pacijenta s hroničnom opstruktivnom plućnom bolesti (HOPB), kojima su ordinirane kapsule karbocisteina od 375 mg, te su praćeni narednih 15 dana. Pacijenti su se pratili kroz tri mjerenja: nulto i dva kontrolna. Opće kliničko stanje i spirometrija su praćeni tokom sva tri mjerenja. Kvalitet života je procjenjivan na prvom i trećem mjerenju, koristeći *Leicester Cough Questionnaire*. Podnošljivost terapije i suradljivost ispitanika su praćeni tokom čitave studije.

Rezultati Postojala je značajna promjena FEV1 statusa između drugog i trećeg mjerenja (p=0.002). Ispitivanje općih simptoma pokazalo je statistički značajno smanjenje kašlja za 74.9%, iskašljaja za 48.5%, dispneje za 29% i zamora za 50%. Nakon terapije karbocisteinom srednja vrijednost kvalitete života iznosila je 3.79 (3.63 – 3.89).

Zaključak Primjena karbocistein kapsula od 375 mg pokazala se efikasnom, i dobro podnošljivom u tretmanu HOPB-a, sa rijetkim neželjenim efektima te značajnim poboljšanjem kvalitete života pacijenata.

Ključne riječi: plućne bolesti, kašalj, ekspektoranti