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Carbocysteine in the Management of Stable COPD: Are Its Antioxidant and Anti-Inflammatory Properties Clinically Relevant?

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Abstract

BACKGROUND: The recent epidemiological and experimental evidence suggest possible antioxidant effect of carbocysteine in patients with chronic obstructive pulmonary disease (COPD).

AIM: To assess efficacy and tolerability of carbocysteine in the management of stable COPD.

METHODS: We performed an observational, non-randomized, open study (a real life study) including 87 patients with stable COPD (group B and D by combined COPD assessment) divided in two groups, examined group (EG) and control group (CG). All participants were treated with the regular treatment of the stable disease, but in the participants of the EG carbocysteine 1,500 mg daily was added to their regular treatment during the period of two months. The study protocol included completion of the COPD Assessment Test (CAT) and spirometric measurements at initial visit and at the end of the mentioned period.

RESULTS: We found significantly lower mean value of the overall CAT score in the EG at the end of the study as compared to its mean value registered at initial visit (26.9 vs. 24.3; P = 0.007). In regard to certain CAT items, we found significantly lower values of the mean scores related to cough phlegm and sleep disturbances as compared to their mean scores at initial visit. In addition, the mean values of the overall CAT scores at initial visit and at the end of the study in controls were similar. In EG we found significantly higher mean value of the MEF 25-75 at the end of the study as compared to its mean value registered at initial visit (59.3% vs. 67.2%; P = 0.003). There was no significant difference in the mean values of other spirometric parameters at the end of the study as compared to their mean values at initial visit. In controls we registered similar values of all measured spirometric parameters at the end of the study as compared to their values registered at initial visit. Mild gastrointestinal manifestations were registered in 13.3% of the participants of the EG during the examined period.

CONCLUSION: Our findings indicate positive effects of carbocysteine regarding the symptoms and lung function, as well as its good tolerability in the patients with stable COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) represents one of the principal demands of the public health at global level due to high morbidity, early mortality, high date rates and significant costs to health systems. The projection of the Global Burden of Disease Study indicates that COPD in 2020 will be the third leading cause of death worldwide (from sixth in 1990) and fifth leading cause of years lost (disability-adjusted life years - DALYs) through early mortality or handicap (12th in 1990) [1]. The health costs related to COPD are significant. Namely, in the European Union, the total direct costs of respiratory disease is estimated to be about 6% of the total health care budget, with COPD accounting for more than a half of this cost (38.6 billion Euros) [2].

The management of COPD, including management of stable disease and management of exacerbations, is a matter of growing interest and importance, and not a little controversy. According to the actual recommendations of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) the management of a stable disease is based on the

classification of the COPD patients in four groups (A, B, C and D) based on the combined assessment of the disease. The COPD patients from the groups A and C are characterized by fewer symptoms than patients from the groups B and D. In addition, the COPD patients from the groups A and B are characterized by mild or moderate airflow limitation and low risk of exacerbations, whereas the patients from the groups C and D are characterized by severe or very severe airflow limitation and high risk of exacerbations. Personalized pharmacological treatment based on combined assessment of the disease is considered as an optimal treatment of stable COPD [3, 4].

Carbocysteine, i.e. S-Carboxymethyl-L-cysteine, is a mucolytic that reduces the viscosity of sputum allowing its easily bringing up. As a mucolytic it is used for a period of time in respiratory diseases characterized by hypersecretion of viscose mucus, such as acute bronchitis and exacerbations of chronic bronchitis, COPD and bronchiectasis [5]. Due to the antioxidant properties of carbocysteine and other mucolitics (i.e. free radicals scavenging and anti-inflammatory effects), several studies investigated the possibility for their use in the management of stable COPD [6, 7, 8].

The aim of the present study was to assess efficacy and safety of carbocysteine in the management of stable disease in Group B and Group D COPD patients.

Methods

Study design and setting

An observational, non-randomized, open study (i.e. real life study) was performed at the Institute for Occupational Health of R. Macedonia, Skopje - WHO Collaborating Center and GA^{2}LEN Collaborating Center in the period March – November 2015. The efficacy and tolerability of two months treatment with carbocysteine was assessed in the groups B and D of patients with stable COPD by assessment of their symptoms (i.e. the impact of the disease on their health status) and lung function at initial visit and at the end of the study.

Study subjects

The study population included 87 subjects divided in two groups: examined group (EG) and control group (CG).

EG included 45 patients with stable COPD of both genders, aged 44 to 74 years classified by the combined COPD assessment into Group B and Group D. The exclusion criteria were: patients classified as Group A and Group C COPD patients, patients with another respiratory disease (e.g. bronchial asthma, bronchiectasis, pneumonia, cystic fibrosis, etc); exacerbations occurred during the study period, known hypersensitivity to carbocysteine, patients who did not retain sufficient capacity for normal conduction of the study, and serious adverse effects during the treatment with carbocysteine.

The study subjects from EG besides the regular treatment of stable disease were treated with carbocysteine 1,500 mg daily (2 capsules carbocysteine 375 mg twice daily) in the period of two months. In addition, 42 Group B and Group D COPD patients matched to the patients from EG by sex and age were studied as controls. During the study period the controls were treated with their regular treatment of stable COPD.

All participants were informed about the study and their written consent was obtained.

Study protocol

The study protocol included collection of demographic characteristics, completion of the COPD Assessment Test (CAT) and lung function measurements.

Demographics of the study subjects were collected by questionnaire at initial visit. All study subjects completed the COPD Assessment Test (CAT) at initial visit and at the end of the study. Furthermore, spirometric measurements including measuring of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC ratio and maximal expiratory flow at 25 to 75% of the vital capacity (MEF_{25-75}), were performed in all study subjects at initial visit and at the and of the study.

Completion of the questionnaire for demographic characteristics

Demographics of the study subjects, including sex, age, smoking status, body mass index (BMI), previous or current occupational exposure to noxious particles and gases, and comorbidities were collected by questionnaire at initial visit.

Classification of smoking status of the study subjects was done by World Health Organization (WHO) recommendations [9]. Passive smoking or exposure to environmentl tobacco smoke was defined as an exposure to tobacco combustion products from smoking by others (at home, workplace, etc.), i.e. as a presence of at least one smoker in the household and/or in the workplace [10, 11].

Completion of the CAT

All study subjects completed the CAT at initial visit and at the end of the study.

The questionnaire consisted of 8 original CAT questions translated in Macedonian:

- Q1 *I never cough / I cough all the time;*
- Q2 *I have no phlegm (mucus) in my chest at all / My chest is completely full of phlegm (mucus*);
- Q3 *My chest does not feel tight at all / My chest feel very tight;*
- Q4 *When I walk up a hill or one flight of stairs I am not breathless / When I walk up a hill or one flight of stairs I am very breathless;*
- Q5 *I am not limited doing activities at home / I am very limited doing activities at home;*
- Q6 *I am confident leaving my home despite my lung condition / I am not at all confident leaving my home because of my lung condition;*
- Q7 *I sleep soundly / I don't sleep soundly because of my lung condition;*
- Q8 *I have lots of energy / I have no energy at all.*

Each question had score ranging from 0 to 5 points (0 = no impairment). An overall CAT score was derived as a sum of the scores for each response. It may range from 0 to 40 providing a measure of the impact of the disease on a patient's health status. The overall CAT scores more than 30 and more than 20 indicate very high and high impact of COPD on patient's health status, respectively. The overall CAT score ranging from 10 to 20 indicates medium impact, the overall CAT score less than 10 indicates low impact of the disease on the patient's health status, whereas the overall CAT score of 5 represents the upper limit of normal in healthy non-smokers [12].

Spirometry

Spirometric measurements were performed in all study subjects at initial visit and at the end of the study by spirometer Ganshorn SanoScope LF8 (Ganshorn Medizin Electronic GmbH, Germany) with recording the best result from three measurements the values of FEV_1 of which were within 5% of each other. The results of spirometry were expressed as percentages of the predicted values. Interpretation of the results was based on the actual recommendations of European Repsiratory Society (ERS) and American Thoracic Society (ATS) [13, 14].

Statistical analysis

The quantitative variables were expressed as mean values with standard deviation (SD), whereas the qualitative variables as absolute frequencies and percentages. The comparison of the mean scores of the particular CAT questions, as well as the mean overall CAT scores was done by Student's t-test. The comparison of the mean values of measured spirometric parameters was also done by Student's t-test. A *P*-value less than 0.05 was considered as statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 11.0 for Windows.

Results

Study subjects from both groups have similar demographic characteristics (Table 1).

Table 1: Demographic of the study subjects

Characteristic	EG (n = 45)	CG (n = 42)
M/F ratio	1.4	1.4
Mean age (years)	58.3 ± 7.6	57.4 ± 8.4
Mean BMI	25.6 ± 3.1	25.8 ± 2.7
Smoking status		
Active smokers	14 (31.1%)	11 (26.2%)
Ex-smokers	8 (17.7%)	8 (19.1%)
Passive smokers	9 (20.0%)	10 23.,8%)
Occupational exposure to dusts or gases (current or former)	21 (46.7%)	18 (42.8%)
Mean duration of the disease (years)	10.7 ± 3.3	9.2 ± 3.8
Combined assessment of the disease		
Group B	23 (51.1%)	23 (54.7%)
Group D	22 (48.9%)	20 (45.3%)
Management of the stable disease		
Monotherapy with LA bronchodilator	23 (51.1%)	23 (54.7%)
LA β_2-agonist	9 (20.0%)	8 (19.1%)
LA anticholinergic	14 (31.1%)	15 (35.7%)
Combined therapy	22 (48.9%)	20 (45.3%)
Combination LA β_2-agonist + ICS	12 (26.6%)	10 (23.8%)
Combination LA β_2-agonist + LA anticholinergic + ICS	10 (22.2%)	10 (23.8%)
Comorbidities	29 (64.4%)	25 (59.5%)
Arterial hypertension	12 (26.7%)	12 (28.6%)
Osteo-muscular disorders	10 (23.2%)	12 (28.6%)
Diabetes type 2	7 (15.5%)	5 (11.9%)
Ishaemic heart disease	4 (8.9%)	5 (11.9%)

Data are presented as n, mean ± SD, or n (%). M: male; F: female; BMI: body mass index; LA: long-acting; ICS: inhaled corticosteroid.

The mean scores for each CAT question at initial visit in EG varied from 3.0 for *Q3* to 3.8 for *Q2*, whereas the mean scores for each CAT question at the end of the study varied from 2.8 for *Q3* to 3.3 for *Q2*. Statistically significant reduction in the mean scores at the end of the study as compared to the mean scores at initial visit was registered for *Q1*, *Q2* and *Q7*.

Table 2: Mean scores for each CAT question and overall CAT mean score registered in EG at initial visit and at the end of the study

Mean score	At initial visit	At the end of the study	*P* - value
Q1	3.6 ± 0.5	3.1 ± 0.4	0.000
Q2	3.8 ± 0.4	3.3 ± 0.3	0.000
Q3	3.0 ± 0.6	2.8 ± 0.4	0.066
Q4	3.1 ± 0.4	2.9 ± 0.6	0.062
Q5	3.2 ± 0.3	3.1 ± 0.4	0.183
Q6	3.3 ± 0.5	3.2 ± 0.7	0.437
Q7	3.5 ± 0.4	3.0 ± 0.5	0.000
Q8	3.4 ± 0.3	3.2 ± 0.7	0.082
Overall CAT score	26.9 ± 4.2	24.3 ± 4.6	0.006

Data are presented as mean ± SD. CAT: COPD Assessment Test.

The mean scores registered at the end of the study for *Q3*, *Q4* and *Q8* were lower than then their values registered at initial visit, but the difference was not statistically significant, whereas the values of mean scores registered for *Q5* and *Q6* at the end of the study were similar to their values registered at initial visit. In addition, the overall CAT mean score registered at the end of the study was significantly lower than its value registered at initial visit (Table 2).

Significant improvement of the overall CAT mean scores in EG was registered in both Group B and Group D COPD patients (18.3 *vs.* 13.2; *P* = 0.017 and 32.7 *vs.* 29.1; *P* = 0.023, respectively) (Figure 1).

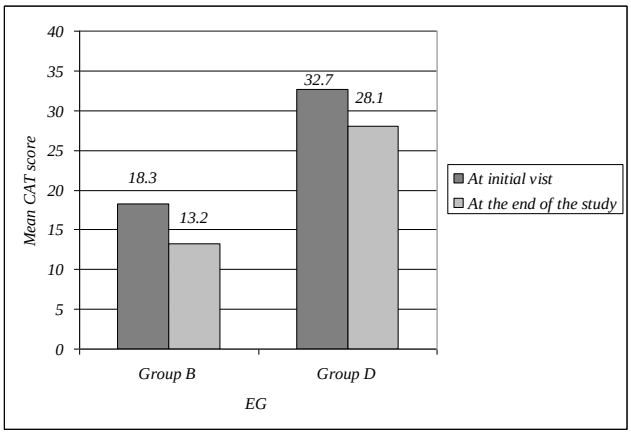

Figure 1: Overall CAT mean scores registered in Group B and Group C COPD patients

The mean scores for each CAT question, as well as the overall CAT score, registered in controls at initial visit were similar to their values registered at the end of the study (Table 3).

Table 3: Mean scores for each CAT question and overall CAT mean score registered in controls at initial visit and at the end of the study

Mean score	At initial visit	At the end of the study	*P* - value
Q1	3.7 ± 0.6	3.6 ± 0.5	0.409
Q2	3.8 ± 0.3	3.7 ± 0.6	0.337
Q3	2.9 ± 0.4	3.0 ± 0.4	0.255
Q4	3.0 ± 0.3	3.1 ± 0.5	0.269
Q5	3.2 ± 0.4	3.1 ± 0.3	0.198
Q6	3.2 ± 0.4	3.2 ± 0.6	1.000
Q7	3.3 ± 0.3	3.2 ± 0.4	0.198
Q8	3.3 ± 0.4	3.2 ± 0.5	0.315
Overall CAT score	26.4 ± 3.1	26.2 ± 3.8	0.792

Data are presented as mean ± SD. CAT: COPD Assessment Test.

The mean values of FVC, FEV_1 and FEV_1/FVC registered in EG at initial visit were lower than their values registered at the end of the study, but the difference is not statistically significant. The mean value of MEF_{25-75} registered at initial visit was significantly lower than its mean value registered at the end of the study (Table 4).

Table 4: Mean values of spirometric parameters in EG registered at initial visit and at the end of the study

Spirometric parameter	At initial visit	At the end of the study	*P* - value
FVC	72.2 ± 7.8	73.8 ± 6.7	0.300
FEV_1	47.6 ± 8.9	49.7 ± 6.3	0.200
FEV_1/FVC	0.61 ± 0.04	0.62 ± 0.02	0.137
MEF_{25-75}	59.3 ± 9.6	67.2 ± 10.1	0.003

Data are presented as mean ± SD. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; MEF_{25-75}: maximal expiratory flow at 25 to 75% of the vital capacity.

The mean values of FVC, FEV_1, FEV_1/FVC and MEF_{25-75} registered in controls at initial visit were similar to their mean values registered at the end of the study (Table 5).

Table 5: Mean values of spirometric parameters in controls registered at initial visit and at the end of the study

Spirometric parameter	At initial visit	At the end of the study	*P* - value
FVC	70.9 ± 9.4	70.1 ± 11.3	0.725
FEV_1	46.3 ± 8.1	47.4 ± 9.4	0.567
FEV_1/FVC	0.60 ± 0.06	0.61 ± 0.04	0.371
MEF_{25-75}	60.2 ± 12.7	61.7 ± 11.2	0.567

Data are presented as mean ± SD. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; MEF_{25-75}: maximal expiratory flow at 25 to 75% of the vital capacity.

The frequency of adverse effects in the EG during the study period was 13.3%. Mild gastrointestinal manifestations (nausea, vomiting, and epigastric pain) which did not require discontinuation of the treatment were registered in six patients.

Discussion

Oxidative stress and chronic inflammation are key features in the COPD pathogenesis. Oxidative stress plays an important role in several elements of the lung physiology and the development of COPD, such as oxidative inactivation of antiproteases and surfactants, mucus hypersecretion, membrane lipid peroxidation, alveolar epithelial injury, and remodeling of extracellular matrix. Therefore, targeting oxidative stress with antioxidants may be effective in the treatment of stable COPD [15-21].

The aim of the present study was to assess efficacy and tolerability of carbocysteine in patients with stable COPD. According to the actual GOLD recommendations, pharmacological treatment of stable COPD is classified as recommended first choice, alternative choice and other possible treatments. Carbocysteine is recommended as other possible treatment for Group D COPD patients [3]. In addition, according to the actual recommendations of Leicestershire Medicines Strategy Group (LMSG), carbocysteine is recommended in the treatment of stable COPD in the patients with expressed chronic cough and sputum production (i.e. COPD patients

classified in groups B and D) [22].

The study population in present study included 87 patients with stable COPD classified by combined assessment of the diseases into groups B and D. The study subjects were divided in two groups regarding the treatment with carbocysteine besides the regular treatment of the disease. In both groups there was a large proportion of active and passive smokers, as well as a low proportion of ex-smokers, that was similar to their prevalence in general population documented in our previous studies [23, 24]. These findings suggest insufficient anti-smoking activities, i.e. they indicate a need of improvement of the control of tobacco use in R. Macedonia. According to the results of studies on smoking status conducted in developed countries, e.g. New Jersey Adult Tobacco Survey and Australian National Health Survey, in the countries with more effective anti-smoking strategies there is a significantly lower prevalence of active and passive smokers and significantly higher prevalence of ex-smokers as compared to their prevalence registered in our studies [25, 26].

We found significant reduction of the impact of COPD on health status in the study subjects from carbocysteine group after a period of two months due to improvement of majority symptoms of the disease assessed by CAT. Significant reduction was registered in mean scores for cough, phlegm and sleep disturbances at the end of the study as compared to their values at initial visit. Values of the mean scores for chest tightness and exercise tolerance at the end of the study obtained at the end of the study were also lower, but the difference was not statistically significant. In addition, in the study subjects from carbocysteine group we found significant reduction of the mean value of MEF_{25-75} (i.e. index of the airflow in the small airways) at the end of the study as compared to its value at initial visit.

The findings from other studies in this domain are somewhat inconsistent depending on their design, study population, daily dose of administered carbocysteine, period of administration, etc. Results from the double blind, placebo-controlled study including 709 patients with severe COPD carried out by Zheng et al. (PEACE Study) indicated significant improvement of quality of life assessed by St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C) and significant reduction of exacerbations after one year administration of carbocysteine 1,500 mg daily [27]. Similar results were obtained in the studies carried out by Tatsumi et al. and Yasuda et al. including COPD patients treated with carbocysteine 1,500 mg daily during one year [28, 29]. In addition, results of the study carried out by Esposito et al. suggested that daily administration of carbocysteine for prolonged period in addition to regular COPD treatment could be considered as a good strategy for reduction of exacerbation frequency [30]. Furthermore, results from several studies indicated that carbocysteine could restore steroid sensitivity in steroid insensitive pulmonary diseases and could improve the targets of regular treatment in patients with severe COPD [31, 32]. On the contrary, results of some studies indicated that administration of carbocysteine in COPD patients was associated with small overall benefits, i.e. that its use could reduce exacerbations with little or no effect on overall quality of life [33, 34]. Results from some studies indicated that treatment of stable COPD with carbocysteine was more effective in COPD patients not receiving inhaled corticosteroids in regard to reducing a frequency of exacerbations [27, 33, 34]. In the present study we did not assess the efficacy of carbocysteine in regard to frequency of exacerbations, but we found significant improvement of symptoms in patients who received and did not receive inhaled corticosteroids as their regular treatment.

In the present study we found a low frequency of adverse effects in carbocysteine group, i.e. mild gastrointestinal manifestations which did not require discontinuation of the treatment. Similar findings were registered in the PEACE study [24].

The findings of this study are subjects of at least three limitations. First, relatively small number of the study subjects could have certain implications on data obtained and its interpretation. Second, the study design could also have certain implications on data obtained and its interpretation. Third, relatively short period of treatment with carbocysteine do not enable to assess its effect on the frequency and severity of COPD exacerbations knowing that they have significant impact on the COPD course and progression. On the other study, the strength of the study is its observational design in regard to assessment of symptoms and lung function in a certain groups of COPD patients by standardized and validated questionnaire and spirometry before and after treatment with carbocysteine.

In conclusion, in an observational, non-randomized, open study aimed at assessment of efficacy and tolerability of carbocysteine in the management of stable COPD we found improvement of the symptoms and spirometric parameters reflecting airflow in the small airways in the group of COPD patients treated with carbocysteine in the period of two months. Our findings also indicate a need of further studies in this domain in order to obtain more effective management of COPD.

Ethical Approval

The Ethical Committee of the Institute of Occupational Health of R. Macedonia, Skopje – WHO Collaborating Center and GA^{2}LEN Collaborating Center gave approval for performing the study and publishing the results obtained (0302-481/01.06.2015).

Authors Participations

JM participated in the study design, data collection, managing the analyses of the study, and writing all versions of the manuscript. JKB and TP participated in the study design, managing the analyses of the study, as well as writing all versions of the manuscript. KV performed the statistical analysis and participated in the managing of the analyses of the study. SS and DM participated in the data collection and in the managing of the analyses of the study. All authors read and approved the final manuscript.

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