

Neltenexine Versus Carbocysteine in the Treatment of Exacerbations of Mild Chronic Obstructive Pulmonary Disease: A Randomized, Controlled, Open-Label Study

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ABSTRACT

Background: Despite the positive results of several long-term, randomized, controlled studies of mucoactive drugs for chronic obstructive pulmonary disease (COPD), the European Respiratory Society and American Thoracic Society guidelines do not recommend the prescription of these drugs in COPD. New efficacy data on mucoactive drugs may help calculate the sample size for future large studies evaluating COPD exacerbation frequency, changes in quality of life, and pharmacoeconomic factors.

Objective: The aim of this randomized, open-label, controlled study was to compare the efficacy and tolerability of neltenexine versus carbocysteine in patients with COPD exacerbations treated concurrently with antibiotics.

Methods: Patients with COPD exacerbation were treated with standard antibiotic therapy (ampicillin 1 g IM BID for 6 days) and randomly assigned to receive 1 of 2 treatments: neltenexine oral powder 1 sachet TID for 12 days or carbocysteine 5% syrup, 50 mg TID for 12 days. Treatment with aminophylline in standard doses was also allowed. The efficacy variables were sputum characteristics and volume, cough, difficulty in expectorating, dyspnea, pulmonary auscultation findings, vital capacity (VC), peak expiratory flow, and forced expiratory volume in 1 second (FEV₁).

Results: A total of 30 patients were enrolled, with 15 patients randomized to each group. All patients completed the study. The differences between neltenexine and carbocysteine in terms of cough reduction and improvement in sputum characteristics was significantly different ($P < 0.05$). The time to improvement in difficulty expectorating, cough, and sputum characteristics was significantly shorter for patients in the neltenexine group ($P < 0.05$, $P < 0.02$, and $P < 0.02$, respectively, at day 4). No statistically significant changes versus baseline were observed in VC, FEV₁, or peak expiratory flow. Only 1 patient, in the neltenexine group, experienced an adverse event (heartburn).

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Conclusions: These results confirm the efficacy and tolerability of neltenexine in patients with exacerbations of COPD. Neltenexine may be a good therapeutic alternative to carbocysteine during exacerbations of COPD treated with antibiotics.

Key words: chronic obstructive pulmonary disease, neltenexine, carbocysteine, antibiotics. (*Curr Ther Res Clin Exp.* 2001;62:851-861)

INTRODUCTION

The natural history of chronic obstructive pulmonary disease (COPD) is characterized by frequent exacerbations, with increased cough, purulent sputum, and dyspnea. These episodes usually are caused by a secondary infection.¹ International guidelines^{1,2} recommend treating exacerbations with a course of broad-spectrum antibiotics. Amoxicillin, tetracycline derivatives, amoxicillin/clavulanic acid, and the newer cephalosporins, macrolides, and fluoroquinolones are the most frequently administered antibiotics for COPD exacerbations.^{2,3} Anthonisen et al⁴ classified COPD exacerbations into 3 types, depending on the number of symptoms present. The presence of increased dyspnea, sputum volume, and purulence was indicative of a type 1 exacerbation. In type 2 exacerbations, increases in 2 of the 3 symptoms occur, and in type 3 exacerbations, increases in 1 of the 3 symptoms occur along with at least 1 additional minor respiratory sign. Using this classification as a prognostic element, Anthonisen et al⁴ showed that antibiotic therapy is associated with a high success rate (>62%) in type 1 exacerbations and apparently confers no benefit in type 3 exacerbations.

The use of mucoactive drugs for the treatment of chronic mucus hypersecretion is controversial. Mucolytic drugs, widely prescribed in general practice, have been shown in long-term, randomized, controlled studies^{5,6} to be effective in reducing the frequency and duration of COPD exacerbations. However, the European Respiratory Society¹ and American Thoracic Society⁷ have deemed these benefits insufficient and do not recommend mucoactive drugs in their guidelines for the treatment of COPD. Recently, new physiopathologic considerations have provided support for therapy with mucoactive drugs in COPD. Chronic mucus hypersecretion has been found to be a significant risk factor for death in patients with impaired ventilatory function⁸⁻¹⁰; in addition, a low forced expiratory volume per second (FEV₁) has been identified as an important predictor of COPD-related mortality.¹¹ Given that chronic mucus hypersecretion is related to accelerated deterioration of FEV₁,¹² the role and efficacy of mucoactive drugs in COPD management¹³ should be reevaluated. The rationale for this therapy is the qualitative and quantitative alteration of bronchial secretions with stasis of mucus, alteration of the defense system of the respiratory tree, and facilitation of bacterial adhesion.¹⁴ Among COPD patients, treat-

ment with mucoregulatory drugs has been shown to significantly reduce hyperviscosity compared with no treatment.¹⁵

A number of mucoactive drugs have been used during the last 20 years to relieve chronic and pathologic mucus hypersecretion. However, only a few of these drugs (eg, ambroxol, carbocysteine, neltexine, and bromhexine) directly affect the production or composition of airway secretions by acting on the biomolecular structure of mucin, regulating mucus production and modifying its adhesiveness. Neltexine,* an amide derivative of ambroxol and thiophene carboxylic acid recently developed in Italy, has been shown *in vitro* to stimulate motility of the cilia and production of alveolar surfactant¹⁶; thus, it affects mucociliary clearance. Neltexine appears to be able to improve experimental bronchitis and has *in vitro* antielastase activity.¹⁷ Neltexine is absorbed from the intestinal tract, and is thus partially metabolized in the liver, lung, and kidney into its active metabolite ambroxol.¹⁸ Neltexine reaches peak plasma concentrations 2 to 3 hours after administration, whereas the time to peak plasma level of ambroxol is longer. The half-lives of neltexine and ambroxol are 4.05 and 8 hours, respectively. Recent clinical trials comparing neltexine with placebo^{18,19} and with other mucolytic drugs^{20,21} have shown that neltexine is effective treatment for patients with COPD exacerbations.

The purpose of the present, randomized, open-label, controlled study was to compare the efficacy and tolerability of neltexine versus carbocysteine, a cysteine derivative with a blocked thiol group,²²⁻²⁴ in the treatment of patients with COPD exacerbations. The study was designed to be as similar as possible to clinical practice in a respiratory diseases department of a hospital.

PATIENTS AND METHODS

This was a randomized, single-center (Segni Hospital, Ozieri, Sassari, Italy), open-label, active-controlled, 12-day study. The study enrolled adult patients of the hospital's internal medicine department who had a preexisting diagnosis of COPD documented in their medical records. The diagnosis had to have been made based on international guidelines^{1,2} at least 2 years before study entry. Patients were included only if FEV₁ was $\geq 75\%$ of the predicted value and a COPD exacerbation was present at baseline. Exacerbation was defined as the presence of increased dyspnea, sputum volume, and purulence (type 1 exacerbation) and was treated with concomitant standard antibiotic therapy (ampicillin 1 g IM BID for 6 days).

The exclusion criteria were pregnancy or breast-feeding, hypersensitivity to any of the study drugs, cystic fibrosis, bronchiectasis, tuberculosis, lung cancer, evidence of asthma, and community-acquired pneumonia (CAP) or other diseases likely to require antibiotic therapy. Patients with completely reversible airway obstruction without features of chronic bronchitis or emphysema

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were considered to have asthma and were excluded, as were patients who had features of chronic bronchitis without airway obstruction. The diagnosis of a COPD-related exacerbation was verified based on medical history (patients enrolled were known by department staff), chest radiography (to exclude CAP), and results of previous bronchodilator reversibility testing (to exclude asthma). Computed tomography was not performed.

The use of inhaled anticholinergic bronchodilators, expectorants, other mucolytic agents, corticosteroids, antitussive drugs, and beta₂-agonists was specifically prohibited during the study. At baseline, patients were instructed as to which drugs to avoid. As required by international guidelines,¹ use of aminophylline at the standard dosage (400 mg BID orally) was allowed.

The study was conducted in accordance with the Declaration of Helsinki. Each patient gave written informed consent.

Patients were randomly assigned to 1 of 2 treatment groups, using a computer-generated list. Patients received either neltenexine oral powder (1 sachet 3 times daily for 12 days) or carbocysteine 5% syrup (50 mg TID for 12 days).

Clinical assessments were performed at baseline, on day 4 (examination 1), on day 8 (examination 2), and at the end of therapy (day 12). At each examination, difficulty in expectorating, cough, dyspnea, and pulmonary auscultation findings were assessed using a 5-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe; and 4 = very severe). Cough and difficulty expectorating were subjective symptoms reported directly by the patients at each visit. Dyspnea and pulmonary auscultation findings were evaluated during the study period by the same investigator to reduce the possibility of bias. A complete physical examination (including measurement of body temperature, heart rate, and blood pressure) was performed at each visit.

Sputum was collected and the volume (mL/24 h) measured at each visit. At each visit, sputum was characterized by an independent reader (a medical doctor specializing in microbiology who was blinded to the study treatment) using a 5-point scale: 1 = serous; 2 = seromucous; 3 = mucous; 4 = mucopurulent; 5 = purulent.

Vital capacity (VC), FEV₁, and peak expiratory flow (PEF) were measured at baseline and at the end of treatment.

At the end of the trial, overall clinical responses were classified by the investigator as excellent, good, moderate, or unsatisfactory.

To verify compliance at each visit, patients were instructed to return any unused study drug and to report all concomitant drugs taken.

All adverse events, whether reported by the patient or observed by the investigator, were recorded at the time of the examination and classified according to their severity, duration, and possible relation to the study drug.

Blood tests, blood chemistry (hepatic aminotransferases, bilirubin, alkaline phosphatase, blood urea nitrogen, and sedimentation rate), and urinalysis were performed at baseline and at the final examination.

Statistical Analysis

Statistical analyses were carried out using Systat 1989 version for Macintosh (Systat Inc, Evanston, Illinois). Data were presented as means of the usual descriptive statistics: mean, SD, standard error of the mean (SEM), median, minimum and maximum, and absolute and relative frequencies. Two-tailed tests were used for the parameters analyzed, and statistical significance was set at the 5% level. Parametric data were analyzed using analysis of variance (ANOVA) or Student *t* tests, as appropriate, whereas the nonparametric data were analyzed by means of the Mann-Whitney, Friedman, and Wilcoxon tests. Comparisons were made both within groups and between groups. Sources of variation for the ANOVA for independent groups were treatment, time, and treatment-by-time interaction.

RESULTS

The demographic and clinical characteristics of the study population are listed in Table I. No statistically significant differences were found between groups at baseline. A total of 30 patients were randomized, 15 to each group. All patients completed the study.

At the final examination, patients in the neltenexine group had a significantly greater improvement versus baseline in cough ($P < 0.05$) and sputum characteristics ($P < 0.05$) compared with the carbocysteine group (Table II).

The time to improvement in expectoration ($P < 0.05$ at day 4), cough ($P < 0.02$ at day 4), and sputum characteristics ($P < 0.02$ at day 4) was significantly shorter in the neltenexine group.

Table I. Characteristics of the patients at the baseline visit.

	Neltenexine (n = 15)	Carbocysteine (n = 15)	All Patients (N = 30)
Sex			
Female	5	10	15
Male	10	5	15
Age, y			
Mean \pm SD	69.27 \pm 10.70	61.60 \pm 18.23	65.43 \pm 15.19
Range	40–82	23–88	23–88
Smoking status			
Nonsmoker	1	1	2
Smoker	8	7	15
Ex-smoker	6	7	13
No. pack-years* of smoking, mean \pm SD	28.33 \pm 11.29	27.67 \pm 16.28	28.00 \pm 13.77
No. exacerbations/y, mean \pm SD	1.27 \pm 0.60	1.20 \pm 0.41	1.23 \pm 0.50

*Total pack-years = number of cigarettes smoked per day/20 \times number of years of smoking.

Table II. Difficulty expectorating, cough, dyspnea, pulmonary auscultation findings, sputum characteristics, and body temperature in the neltenexine and carbocysteine treatment groups (mean \pm SD).

Variable	Group	Baseline	Day 4	Day 8	Final Visit
Difficulty expectorating*	Neltenexine	2.33 \pm 0.82	1.33 \pm 0.49 [†]	0.73 \pm 0.46 [†]	0.33 \pm 0.49
	Carbocysteine	2.60 \pm 0.83	2.13 \pm 0.52	1.80 \pm 0.56	1.27 \pm 0.59
Cough*	Neltenexine	2.53 \pm 0.64	1.53 \pm 0.52 [‡]	1.13 \pm 0.35	0.40 \pm 0.63 [†]
	Carbocysteine	2.47 \pm 0.52	2.13 \pm 0.52	1.67 \pm 0.49	1.13 \pm 0.52
Dyspnea*	Neltenexine	2.60 \pm 1.06	1.60 \pm 0.51	1.07 \pm 0.59	0.60 \pm 0.51
	Carbocysteine	2.07 \pm 0.70	1.60 \pm 0.83	1.33 \pm 0.98	0.87 \pm 0.64
Pulmonary auscultation*	Neltenexine	2.20 \pm 0.68	1.20 \pm 0.41	0.93 \pm 0.26	0.53 \pm 0.52
	Carbocysteine	1.93 \pm 0.27	1.43 \pm 0.65	1.07 \pm 0.47	0.79 \pm 0.43
Sputum characteristics [§]	Neltenexine	2.53 \pm 1.25	1.80 \pm 0.77 [‡]	1.67 \pm 0.62 [‡]	1.40 \pm 0.51 [†]
	Carbocysteine	1.80 \pm 1.61	2.53 \pm 1.06	2.60 \pm 0.83	2.13 \pm 0.64
Body temperature, °C	Neltenexine	37.60 \pm 0.74	37.25 \pm 0.47	37.10 \pm 0.39	37.03 \pm 0.30
	Carbocysteine	37.43 \pm 0.57	37.13 \pm 0.28	37.00 \pm 0.00	37.00 \pm 0.00

*Scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe.

[†] $P < 0.05$ between groups.[‡] $P < 0.02$ between groups.[§]Scale: 1 = serous; 2 = seromucous; 3 = mucous; 4 = mucopurulent; 5 = purulent.

Table III. Vital capacity (VC), forced expiratory volume in 1 second (FEV₁), peak expiratory flow (PEF), and erythrocyte sedimentation rate (ESR) in the neltенexine and carbocysteine treatment groups (mean \pm SD).

Parameter	Neltенexine		Carbocysteine	
	Baseline	Final Visit	Baseline	Final Visit
VC, L	2.46 \pm 0.69	2.79 \pm 0.85	2.46 \pm 0.52	2.59 \pm 0.49
FEV ₁ , L	1.87 \pm 0.54	2.09 \pm 0.57	1.90 \pm 0.51	1.98 \pm 0.49
PEF, L	3.74 \pm 1.30	3.99 \pm 1.32	3.95 \pm 1.45	4.15 \pm 1.41
ESR	30.20 \pm 32.42	23.13 \pm 27.19	32.15 \pm 18.38	23.92 \pm 14.55

In the neltенexine group, mean \pm SD values for sputum volume (mL/24 h) were 4.33 \pm 3.20 (at baseline), 12.00 \pm 11.62 (after 4 days), 15.33 \pm 10.60 (after 8 days), and 7.00 \pm 3.00 (at the final examination). In the carbocysteine group, the mean values were 3.33 \pm 5.23 (at baseline), 6.67 \pm 4.50 (after 4 days), 10.33 \pm 11.25 (after 8 days), and 9.33 \pm 8.84 (at the final examination). The differences between groups were not statistically significant at any assessment point (Figure).

No statistically significant changes versus baseline in VC, FEV₁, or PEF values were observed in either group at the final examination.

At the final examination, changes in body temperature (Table II) and erythrocyte sedimentation rate (Table III) did not differ significantly between the 2 groups. However, within-group comparisons indicated a statistically signifi-

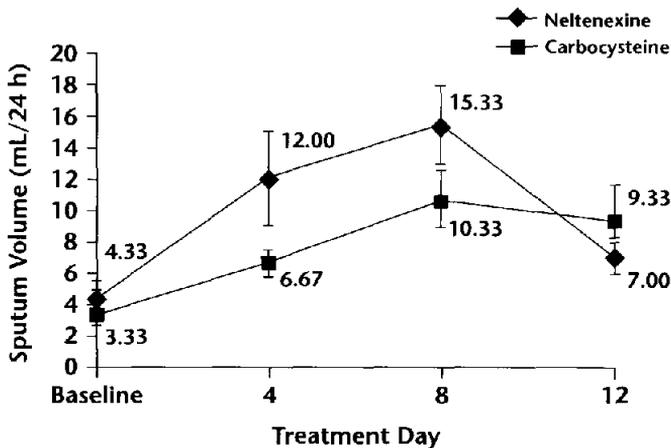


Figure. Mean sputum volume (\pm SE) in the neltенexine and carbocysteine groups at baseline, after 4 and 8 days of treatment, and at the final examination.

cant reduction versus baseline in body temperature and sedimentation rate ($P < 0.01$) in both groups.

The overall assessment of clinical response was good for 11 patients treated with neltenexine and moderate for 4 patients. In the carbocysteine group, the overall assessment was good for 6 patients, moderate for 8 patients, and unsatisfactory for 1 patient.

One adverse event, pyrosis (heartburn), was experienced by 1 patient in the neltenexine group. The pyrosis, which resolved after 5 days and did not lead to discontinuation, was classified as mild; relationship to the study drug was considered doubtful. No adverse events were reported in the carbocysteine group.

No significant changes in laboratory values were observed at the end of the study in either group.

DISCUSSION

In many European countries, physicians prescribe mucoactive drugs for the management of respiratory diseases associated with chronic airflow obstruction, even if these drugs are not recommended by international guidelines on COPD management.^{1,2} The need to meet patients' demand for well-being is in keeping with the idea that the goal of COPD treatment should be "not only to improve lung function, but also to improve patients' symptoms and enhance their quality of life."²⁵ Data from this trial may be useful in calculating the sample size for future large, short-term and long-term studies of COPD exacerbation frequency, changes in quality of life, and pharmacoeconomic factors. The results of this study were consistent with data obtained from previous trials of neltenexine^{18,19,26} for the treatment of COPD. In those studies, neltenexine reduced intraluminal stasis and hypersecretion, processes that facilitate stagnation of the secretions and possible bacterial overlapping, worsening of the stenotic-obstructive pathology, and chronicity of the inflammatory process.

The study design has several limitations. The trial was designed to be as similar as possible to normal clinical practice in a respiratory diseases department of a hospital. This explains the short-term use of mucoactive drugs, the selected population (patients were well known by the department staff), and the mild severity of baseline COPD based on FEV₁.¹

The diagnostic criteria used to include patients with purely COPD-related exacerbations were not optimal—computed tomography would have been a helpful diagnostic tool, but this technology was not available in our department at the time of the study. In addition, the criteria used in this study (medical history and chest radiography) are typically applied in daily medical practice, and an incorrect diagnosis would not have had significant therapeutic consequences for the patients in the study.

The criteria for identifying the onset of COPD exacerbations were subjective. However, these criteria (increased sputum volume, purulence, and dyspnea)

are currently applied in daily medical practice and their validity has been confirmed in international trials.⁴

The ampicillin antibiotic therapy, the dosage, and the duration of the treatment were chosen in accordance with medical practice and international guidelines.

The study was planned with an open-label design. Because we used 2 different types of formulations (neltenexine oral powder vs carbocysteine 5% syrup), a double-blind design would have required a complex double-dummy technique.

Finally, an anomalous factor was observed in the study population: 10 (67%) of the 15 patients in the carbocysteine group were female. Although no statistically significant difference in sex distribution between the 2 groups was evident ($P > 0.05$), this distribution is not reflective of the population generally affected by COPD. No correlation was found between treatment group and other patient characteristics such as smoking status.

Patients in the neltenexine group had significantly greater improvements in cough symptoms and sputum characteristics compared with the carbocysteine group. In addition, although no statistically significant differences in sputum volume were observed between the 2 groups at the different assessment points, sputum volume increased during the first 8 days of neltenexine therapy and returned to normal at the final examination, consistent with clinical improvement.

Decreases in both groups in body temperature and erythrocyte sedimentation rate could indicate general improvement of the underlying COPD; however, these improvements could not be correlated with the mucoactive treatments used.

CONCLUSIONS

In this study, neltenexine improved the signs and symptoms of COPD exacerbations, was well tolerated, and did not interfere with the activity of the antibiotic. Considering that the present study was designed to reflect normal clinical practice in a respiratory diseases department of a hospital, neltenexine may represent a good therapeutic alternative to carbocysteine in the management of COPD exacerbations.

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