

**Effect of N-acetylcysteine Administration
on the clinical outcome
of Chronic Obstructive Pulmonary Disease Patients**

A Thesis

Submitted for Fulfillment of Master Degree in
Pharmaceutical Science
(*Clinical Pharmacy*)

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالُوا سُبْحَنَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم
سورة البقرة - الآية ٣٢

Acknowledgment

*First and foremost I feel always indebted to **Allah**, the most kind and the most merciful.*

*I would like to express my deepest gratitude to **Professor Dr. Abd El Raheem Mourad**, Professor of Clinical Pharmacy, Faculty of Pharmacy, Misr University for Science and Technology, for his continuous help, support and encouragement.*

*I would like also to extend my special thanks to **Dr. Ahmed Abd El Hafeez**, Assistant Professor of Chest Diseases Faculty of Medicine, Cairo University, who enriched this work with his knowledge and offered me much of his time, effort and help.*

*I would like to express my sincere thanks and extreme gratitude to **Dr. Lamia M. El Wakeel**, lecturer of Clinical Pharmacy, Faculty of pharmacy, Ain Shams University, for her great effort and continuous guidance during this work. Every step, and every detail in this thesis has been kindly assisted by her untiring effort and her sincere care.*

I am very grateful to all the staff of the clinical pharmacy department, Ain shams university and National Institute for Researches of Chest diseases and Allergy Imbaba, Giza, Egypt.

Contents	Page
List of tables	i
List of figures	iii
List of abbreviations	iv
Abstract	vii
Introduction	١
Review of literature	٤
I- Chronic Obstructive Pulmonary Disease (COPD)	٤
II- Acute Exacerbation of COPD	٣٣
III- Oxidative Stress	٤٨
IV- Role of N-acetylcysteine in the management of COPD	٦٠
V- Role of clinical pharmacist in COPD	٦٨
Aim of the Work	٧١
Patients and methods	٧٢
Results	٩٠
Discussion	١١٤
Summary	١٢٣
References	١٢٦
Appendix	١٥٦
Arabic Summary	

List of tables

Number	Table	Page
Table (١)	Spirometric classification of COPD severity based on post-bronchodilator FEV ₁	٨
Table (٢)	Pathological changes in COPD	١٥
Table (٣)	Proteases and anti-proteases involved in COPD	١٩
Table (٤)	Inflammatory mediators involved in COPD	٢٤
Table (٥)	Management of COPD stages	٣٠
Table (٦)	The known causes of exacerbations of COPD	٣٤
Table (٧)	Pathological alterations in acute exacerbation of COPD	٣٥
Table (٨)	Physiologic pulmonary alterations in COPD exacerbations.	٣٦
Table (٩)	Assessment of COPD exacerbations	٣٧
Table (١٠)	Indications for hospitalization of patients with a COPD exacerbation.	٤٠
Table (١١)	Indications for intensive care unit or special care unit admission.	٤١
Table (١٢)	Management of severe but not life-threatening exacerbations of COPD in the emergency department or the hospital	٤٢
Table (١٣)	Indications and relative contraindications for NIV	٤٥
Table (١٤)	Indications for invasive mechanical ventilation	٤٦
Table (١٥)	Stratification of patients with COPD exacerbation for antibiotic treatment and potential microorganisms involved in each group	٧٥
Table (١٦)	Antibiotic treatment in COPD exacerbations	٧٦
Table (١٧)	Patients' Demographics	٩١
Table (١٨)	Patients' parameters on admission	٩٣

Number	Table	Page
Table (١٩)	Spirometry Data Assessment after Treatment in the ٣ Groups	٩٦
Table (٢٠)	Laboratory Data Assessment after Treatment in the ٣ Groups	٩٧
Table (٢١)	Significant correlation between study parameters	١١٠

List of figures

Number	Figure	Page
Figure (١)	Mechanisms underlying airflow limitation in COPD	٥
Figure (٢)	Pathogenesis of COPD	١٧
Figure (٣)	Relationship between oxidative stress and inflammation in COPD	١٨
Figure (٤)	Possible points of action of NAC	٦٣
Figure (٥)	Patients flow chart	٧٢
Figure (٦)	Standard curve for IL- Λ assay	٨٥
Figure (٧)	Standard curve for colorimetric assay for MDA	٨٧
Figure (٨)	FEV _١ values in the ٣ groups before & after treatment	٩٨
Figure (٩)	FVC values in the ٣ groups before & after treatment	٩٩
Figure (١٠)	FEV _١ /FVC values in the ٣ groups before & after treatment	١٠٠
Figure (١١)	Spirometry parameters in the ٣ groups before & after treatment	١٠١
Figure (١٢)	PaO _٢ levels in the ٣ groups before & after treatment	١٠٢
Figure (١٣)	MDA levels in the ٣ groups before & after treatment	١٠٣
Figure (١٤)	IL Λ levels in the ٣ groups before & after treatment	١٠٤
Figure (١٥)	Spirometry evaluation between low & high dose groups after ١٠ days of treatment	١٠٦
Figure (١٦)	ABGs levels in low & high dose groups after ١٠ days treatment	١٠٧
Figure (١٧)	PaO _٢ levels in low & high dose groups on admission & after ١٠ days of treatment	١٠٨
Figure (١٨)	IL Λ levels in low & high dose groups on admission & after ١٠ days treatment	١٠٩
Figure (١٩)	Correlation between PaO _٢ & FVC values after treatment.	١١١
Figure (٢٠)	Correlation between IL Λ & FEV _١ values after treatment.	١١٢

List of abbreviations

ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate transaminase
ATS	American thoracic society
BALF	Broncho alveolar lavage fluid
b.i.d	Twice daily
BLVR	Bronchoscopic lung volume reduction
BODE	Body mass index, airflow obstruction, dyspnea and exercise capacity
BRONCUS	Bronchitis Randomized on NAC Cost-Utility Study
BUN	blood urea nitrogen
CBC	Complete blood count
cc	cubic centimeter
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
DNA	Deoxyribonucleic acid
EBC	Exhaled breath condensate
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immune-sorbent assay
ERS	European respiratory society
FEV₁	Forced expiratory volume in first second
FiO₂	Fraction of inspired oxygen
FR_s	Free radicals
FVC	Forced vital capacity
GM-CSF	Granulocyte-Macrophage - colony-stimulating factor
GOLD	Global initiative for chronic obstructive lung disease
GPx	Glutathione peroxidase
GSH	Reduced glutathione
GST	Glutathione s-transferase
H₂O₂	Hydrogen peroxide
HCO₃⁻	bicarbonate
HIV	Human immunodeficiency virus
HO-1	Heme oxygenase-1
HOCL	Hypochlorous acid
HRP	Horse radish peroxidase

HRQOL	Health related quality of life
ICAM-1	Intercellular adhesion molecule-1 expression
ICU	Intensive care unit
i.d.	Internal diameter
IL	Interleukin
IPF	Idiopathic pulmonary fibrosis
LTB₄	Leukotriene B ₄
MDA	Malondialdehyde
MMPS	Matrix metallo proteinases
NAC	N-acetylcysteine
NF-κB	Nuclear factor-κB
NHLBI	The national heart, lung, and blood institute
NICD	National Institute of Chest and allergic Diseases
NICE	The national institute for clinical excellence
NIV	Noninvasive mechanical ventilation
NO[•]	Nitric oxide radical
NOSs	Nitric oxide synthases
O₂^{•-}	Superoxide anion
O₃	Ozone
OH[•]	Hydroxyl radical
ONOO⁻	Peroxynitrite anion
PaCO₂	Partial pressure of carbon dioxide
PaO₂	Partial pressure of oxygen
PE	Pulmonary embolism
P/F	Partial pressure of oxygen/fraction of inspired oxygen
PH	Blood acidity
PMNs	Polymorphonuclear leukocytes
PUFAs	Poly-unsaturated fatty acids
R[•]	Carbon centered radical
RBCs	Red blood cells
RNS	Reactive nitrogen species
RO[•] or LO[•]	Alkoxy radical
ROO[•] or LOO[•]	Peroxyl radical
ROOH	Lipid hydroperoxide
ROS	Reactive oxygen species
rpm	Revolutions per minute
SaO₂	Oxygen saturation
S. Cr.	Creatinine

List of abbreviations

SOD	Superoxide dismutase
SPSS	Statistical Package for Social Sciences
TBA	Thiobarbituric acid
TCA	Trichloroacetic acid
TGF-β	Transforming growth factor- β
TID	Three times daily
TIMP $1-3$	Tissue inhibitors of MMP $1-3$
TLC	Total leukocytes count
TMB	Tetramethyl benzidine
TNF-α	Tumor Necrosis Factor α
VA/Q	Ventilation-perfusion
WHO	World health organization

Abstract

Introduction. COPD is a progressive disease characterized by airflow limitation that interferes with normal breathing and is not fully reversible. COPD exacerbations contribute to the overall severity of COPD patients. Oxidative stress and increased production of IL- α and TNF- α , represent pathogenic mechanisms leading to the development and progression of COPD. Ameliorating oxidative stress would be expected to attenuate the progression of COPD.

Aim of the study. To compare the effects of high dose NAC versus low dose on inflammatory response, oxidative stress, pulmonary functions and clinical outcome in patients with COPD acute exacerbations.

Patients and Methods. This randomized controlled study included 40 COPD acute exacerbation patients. All patients received standard COPD exacerbation treatment and were randomly assigned to either; control group with no add on therapy, low dose group received NAC 300 mg sachets TID, high dose group received NAC 600 mg sachets TID for 10 days. IL α , malondialdehyde (MDA), arterial blood gases and spirometric parameters were evaluated at baseline and after treatment.

Results. IL α levels significantly decreased ($p < 0.001$) in high dose group (3.47 ± 0.81), versus low dose group (6.07 ± 1.66) and control group

(8.33 ± 1.69). MDA levels significantly decreased ($p < 0.001$) in high dose group and low dose group over time. Pulmonary functions (FEV₁, FVC and FEV₁/FVC) and Partial pressure of oxygen PaO₂ significantly improved ($p < 0.001$) in high dose group versus low dose group and control group over time. The P/F ratio significantly improved ($p < 0.001$) in high dose group versus control group. No side effects were reported with NAC administration.

Conclusion. High dose NAC improves clinical outcome of COPD exacerbations patients by ameliorating oxidative stress and inflammatory response, hence improving lung spirometry and pulmonary oxygenation.

Key words. COPD, exacerbations, NAC, IL-6, oxidative stress.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease characterized by the progressive development of airflow limitation that is not fully reversible. COPD is caused by an abnormal inflammatory response of the lungs to noxious particles or gases in particular cigarette smoking. The clinical course of COPD is one of gradual progressive pulmonary impairment, which may eventually lead to respiratory failure (*Pauwels et al., 2001*).

An acute exacerbation of COPD is defined as a sustained worsening of a patient's condition that is acute in onset and necessitates a change in regular medications (*Celli and Barnes, 2000; Rabe et al., 2000*). The frequency of these exacerbations increases with the severity of COPD. Early identification of patients at particular risk for exacerbations may reduce morbidity and mortality from complications associated with COPD exacerbations. Reduction of exacerbation rates is one of the main treatment goals in COPD management since exacerbations bear heavily on the patient's quality of life and prognosis as well as on COPD related costs (*Wedzicha and Seemungal, 2000*).

There is considerable evidence that an increased oxidative burden occurs in the lungs of patients with COPD and this results in an imbalance between oxidants/antioxidants or oxidative stress, which may play a role in many of the processes involved in the pathogenesis of COPD. These include enhanced enzymatic proteolytic activity, mucus hyper-secretion and the enhanced inflammatory response in the lungs to inhaling tobacco smoke (*Rahman, 2004*).

COPD is recognized to have multiple systemic consequences, such as weight loss and skeletal muscle dysfunction. It is thought that oxidative stress may extend beyond the lungs and is involved in these systemic effects (*MacNee, 2002a*).

Antioxidant therapy therefore would seem to be a logical therapeutic approach in COPD. The need for more potent antioxidant therapies to ameliorate the deleterious oxidative stress burden in COPD is still required as a therapeutic strategy for the prevention and treatment of COPD (*Rahman, 2004*).

Moreover, chronic mucus hypersecretion is significantly and consistently associated with an increased risk of hospitalization for COPD patients (*McDonald et al., 2002*).

N-acetylcysteine (NAC), a mucolytic agent with potent antioxidant properties, has an extensive and sometimes controversial history of use in the treatment of COPD (*Repine et al., 1997*).

A study with NAC suggests that an improvement in the antioxidant profile of the lung of patients with COPD may reduce the number of exacerbations (*Hansen et al., 1994*) and perhaps attenuate the accelerated worsening of the lung function.

Controlled clinical trials on a wide number of patients suffering from chronic bronchitis with or without airway obstruction showed that a 6-month treatment with NAC (2000-6000 mg/day p.o.) significantly improved respiratory symptoms and reduced rate and duration of exacerbations as well as the number of sick days (*Pela et al, 1999* ; *Sadowska et al., 2002*).

Up till now, the most common dosage of NAC in clinical practice and in clinical studies is 600 mg/day. Currently, a once daily formulation of NAC of 600 mg is available which is more convenient for the patient.

A higher dose of NAC 1,2 g once daily reduced the concentration of H_2O_2 in exhaled breath condensate (EBC) within 30 days, suggesting that there is a dose-dependent effect on this marker of oxidative stress (*De Benedetto et al.*, 2009). Moreover data suggest that NAC in a higher dose may be more effective as evidence by a study in patients with idiopathic pulmonary fibrosis (IPF) (*Demedts et al.*, 2009). To date, NAC is still used in a dose of 600 mg per day for COPD patients, while the higher doses still need further evaluation.