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

A Thesis

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By

Hend M. Kamel M. El Hady

B. Pharm. Sci.

Head of pharmacy department

National Institute of Chest and Allergic Diseases - Giza

Ministry of Health

.

Supervised by:

Prof. Dr. Abd El Raheem M. Mourad, Ph.D.

Professor of Clinical Pharmacy

Faculty of Pharmacy

Misr University for Science and Technology

Dr. Ahmed Mahmoud Abd El Hafeez, M.D.

Assistant Professor of Chest Disease

Faculty of Medicine

Cairo University

Dr. Lamia M. El-Wakeel, Ph.D.

Lecturer of Clinical Pharmacy

Faculty of Pharmacy

Ain Shams University

Faculty of Pharmacy

Ain Shams University

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

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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
FEV_1	Forced expiratory volume in first second
FiO_2	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
H_2O_2	Hydrogen peroxide
HCO_3^-	bicarbonate
HIV	Human immunodeficiency virus
HO-1	Heme oxygenase-1
HOCL	Hypochlorous acid
HRP	Horse radish peroxidase

HRQOL	Health related quality of life
ICAM-١	Intercellular adhesion molecule-١ expression
ICU	Intensive care unit
i.d.	Internal diameter
IL	Interleukin
IPF	Idiopathic pulmonary fibrosis
$LTB_٤$	Leukotriene $B_٤$
MDA	Malondialdehyde
MMPS	Matrix metalo protienases
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
$NO^{\bullet}$	Nitric oxide radical
NOSs	Nitric oxide synthases
$O_٢^{\bullet-}$	Superoxide anion
$O_٣$	Ozone
$OH^{\bullet}$	Hydroxyl radical
$ONOO^{-}$	Peroxynitrite anion
$PaCO_٢$	Partial pressure of carbon dioxide
$PaO_٢$	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
$R^{\bullet}$	Carbon centered radical
RBC_S	Red blood cells
RNS	Reactive nitrogen species
$RO^{\bullet}$ or $LO^{\bullet}$	Alkoxy radical
$ROO^{\bullet}$ or $LOO^{\bullet}$	Peroxyl radical
ROOH	Lipid hydroperoxide
ROS	Reactive oxygen species
rpm	Revolutions per minute
$SaO_٢$	Oxygen saturation
S. Cr.	Creatinine

SOD	Superoxide dismutase
SPSS	Statistical Package for Social Sciences
TBA	Thiobarbituric acid
TCA	Tricholoroacetic acid
TGF-β١	Transforming growth factor-β١
TID	Three times daily
TIMP١-٤	Tissue inhibitors of MMP ١-٤
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-٨ and TNF-a , 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 ٤٥ 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 ٢٠٠ mg sachets TID, high dose group received NAC ٤٠٠mg sachets TID for ١٠ days. IL٨, malondialdehyde (MDA), arterial blood gases and spirometric parameters were evaluated at baseline and after treatment.

Results. IL٨ levels significantly decreased (p<٠,٠٠١) in high dose group (٣,٤٧±٠,٨١), versus low dose group (٥,٥٧±١,٦٦) and control group

(٨.٣٣±١,٦٩). MDA levels significantly decreased (p<٠,٠٠١) in high dose group and low dose group over time. Pulmonary functions (FEV١, FVC and FEV١/FVC) and Partial pressure of oxygen $PaO_٢$ significantly improved (p<٠,٠٠١) in high dose group versus low dose group and control group over time. The P/F ratio significantly improved (p<٠,٠٠١) 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-٨, 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., ٢٠٠١)***.

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, ٢٠٠٧; Rabe et al., ٢٠٠٧).*** 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, ٢٠٠٧).***

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, ٢٠٠٨)***.

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, ٢٠٠٥a)***.

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, ٢٠٠٨).***

Moreover, chronic mucus hypersecretion is significantly and consistently associated with an increased risk of hospitalization for COPD patients ***(McDonald et al., ٢٠١٢).***

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., ١٩٩٧).***

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., ١٩٩٤)*** 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 ٦-month treatment with NAC (٤٠٠-٦٠٠ 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, ١٩٩٩ ; Sadowska et al., ٢٠٠٧)***.

Up till now, the most common dosage of NAC in clinical practice and in clinical studies is ٦٠٠ mg/day. Currently, a once daily formulation of NAC of ٦٠٠ mg is available which is more convenient for the patient.

A higher dose of NAC ١,٢ g once daily reduced the concentration of $H_٢O_٢$ in exhaled breath condensate (EBC) within ٣٠ days, suggesting that there is a dose-dependent effect on this marker of oxidative stress ***(De Benedetto et al., ٢٠٠٥).*** 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., ٢٠٠٥).*** To date, NAC is still used in a dose of ٦٠٠ mg per day for COPD patients, while the higher doses still need further evaluation.