Effects of Coenzyme Q10 on Amiodarone-Induced Lung Toxicity in Adult and Senile Male albino Rats

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تأثير مساعد الانزيم Q10 علي تسمم الرئة الناتج عن الأميوداورون في ذكور الجرذان البيضاء البالغة والمسنة

رسالة مقدمة من

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lList of Abbreviations

AD	Alzheimer's Disease
AEC	Alveolar Epithelial Cell
AIPT	Amiodarone Induced Pulmonary Toxicity
ANOVA	Analysis Of Variance
ARDS	Acute Respiratory Distress Syndrome
ATP	Adenosine Triphosphate
CD	Cardioverter-Defibrillator
COPD	Chronic Obstructive Pulmonary Disease
DCs	Dendritic Cells
DEA	Desethylamiodarone
DNA	Deoxyribonucleic Acid
DS	Down´s syndrome
ECM	Extracellular Matrix
Fig.	Figure
FM	Fibromyalgia
HD	Huntington's Disease
HMG-CoA	3-Hydroxy-3-Methylglutaryl Coenzyme A
HPF	High-Power Field
H&E	Hematoxylin And Eosin
LDL	Low-Density Lipoprotein

MUC genes	Mucin Genes
NEB	Neuroepithelial Bodies
NEC	Neuroendocrine Cells
Oct	Octamer-Binding Transcription Factor
PBS	Phosphate Buffered Saline
PD	Parkinson's Disease
PG	Prostaglandin
RER	Rough Endoplasmic Reticulum
RNI	Reactive Nitrogen Intermediates
ROS	Reactive Oxygen Species
SPSS	Statistical Package For Social Studies
TNFα	Tumor Necrosis Factor-Alpha
Vd	Volume Of Drug Distribution
VEGF	Vascular Endothelial Growth Factor

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Introduction

Amiodarone is an antiarrhythmic agent commonly used to treat supraventricular and ventricular arrhythmias. This drug is an iodine-containing compound that tends to accumulate in several organs, including the lungs. It has been associated with a variety of adverse effects, the most serious of which, is amiodarone induced pulmonary toxicity (AIPT). It is usually manifested as acute or subacute pneumonitis, typically with diffuse infiltrates on chest x-ray and high-resolution computed tomography. More localized forms of pulmonary toxicity may occur including pleural disease, migratory infiltrates and single or multiple nodules ***(Wolkove and Baltzan, 2009).***

Microscopic examination of the lungs of patients with AIPT typically shows diffuse interstitial pneumonitis, hyperplasia of alveolar epithelial cell (AEC) II and widening of alveolar septa with a cellular inflammatory infiltrate together with varying degrees of interstitial fibrosis ***(Malhotra et al., 2003)***.

Two major hypotheses of amiodarone-induced pulmonary injury include direct cytotoxicity and a hypersensitivity reaction ***(Schwaiblmair et al., 2010).*** Multiple mechanisms may be responsible for cytotoxic pulmonary injury due to drugs, including reactive oxygen species (ROS) ***(Kim et al., 2009)***,

reduction in deactivation of metabolites of the lung, impairment of alveolar repair mechanisms ***(Takano et al., 2004)*** and release of various cytokines ***(Suzuki et al.,2003)***. The toxic mechanism of amiodarone leads to disruption of the lysosomal membranes of the molecules through protein C activation with the subsequent release of ROS, which may induce activation of caspase pathways and lead to apoptosis of lung epithelial cells ***(Baritussio et al., 2001)***.

Amiodarone and its metabolites can also produce lung damage indirectly by an immunological reaction ***(Camus et al., 2004)***. This was supported by finding cytotoxic T cells in bronchoalveolar lavage fluid from patients diagnosed with AIPT ***(Sunderj et al, 2000)***.

The development of amiodarone-induced lung complications appears to be associated with the duration of treatment, cumulative dosage, pre-existing lung disease, co-existing respiratory infections as well as old age ***(Papiris et al., 2010).***

Aging was found to be associated with physiological and morphological changes in the lung ***(Janssens et al., 1999).*** The documented physiological changes in the pulmonary function that occur with advancing years are a result of loss of elastic recoil in both alveoli and airways. Histopathological changes associated with aging include, increased collagen accumulation and

progressive pulmonary fibrosis ***(Calabresi et al., 2007)***. In humans, there is an increase in the size of air spaces, dilatation of alveoli, decrease in the gas-exchange surface area and decreased supporting tissue for small airways ***(Susan et al., 2009).***

It has been recorded in what is called ‘‘molecular gerontology’’ that oxygen free radicals play a role in degenerative senescence. Oxidants may be released endogenously from inflammatory cells, pulmonary alveolar macrophages, neutrophils and eosinophils. However, exogenous oxidants from oxygen or ozone in the air, cigarette smoke and other inhalants or ingestants were also encountered ***(Kenneth and Bruce, 1998).***

Coenzyme Q10 is a naturally occurring potent lipophilic antioxidant that is capable of recycling and regenerating other antioxidants such as tocopherol and ascorbate. It has a fundamental role in cellular bioenergetics as a cofactor in the mitochondrial electron transport chain (respiratory chain) ***(Hemmi and Raj, 2006).***

Regarding the beneficial effects of coenzyme Q10 on parenchymatous organs, experimental studies have shown that it protects the rat liver against acute acetaminophen hepatotoxicity, most probably through its antioxidant, anti-inflammatory and antiapoptotic effects ***(Fouad and Jresat, 2012).*** It was also found

to be effective in the treatment of the rat liver ischemia-reperfusion damage ***(Portakal and Inal-Erden, 2000).*** In addition, coenzyme Q10 represents a potential therapeutic option to protect the testicular tissue from the harmful effects of arsenic intoxication ***(Fouad and Jresat, 2012).*** Regarding the effects of coenzyme Q10 on the lung, ***Lim et al. (2010)*** stated that, it reduced the increase in tumor necrosis factor-alpha (TNFα).

Yet, up to our knowledge, few studies focused on the possible beneficial effects of coenzyme Q10 on the drug induced pulmonary toxicity and its comparison in both adult and senile rat lungs. Being anti-oxidant, anti-apoptotic and anti-inflammatory, coenzyme Q10 may play a protective role against Amiodarone induced lung toxicity in adult and senile rats.

Aim of the Work

Amiodarone induced pulmonary toxicity is predominantly an air space inflammatory and fibrosing active disease affecting mainly bronchioles, terminal bronchioles, alveolar ducts and acinar spaces ***(Papiris et al., 2010)***. Thus, it became the aim of this study to demonstrate the effects of coenzyme Q10 on AIPT mainly on the bronchiolar tree and alveoli in both adult and senile rats.

Objectives:

- Compare the histological structure of the lung in both adult and senile rats.
- Compare the effects of amiodarone on the lung of both adult and senile rats.
- Detect the possible protective effects of coenzyme Q10 on the lung in both adult and senile rats treated with amiodarone in concomitants with coenzyme Q10.
- The above objectives were fulfilled using light and electron microscopes, morphometrical and immunohistochemical studies.

Anatomy and Histology of Human Lung

Lungs are the essential organs of respiration. They are situated on either side of the heart and other mediastinal contents. Each lung is free in its pleural cavity, except for its attachment to the heart and trachea at the hilum and pulmonary ligament ***(Ayed, 2004).***

The right lung consists of three lobes and the left of two lobes. Fissures separate the lobes from each other. These are lined by visceral pleura ***(Standring, 2008).***

➢ *The Airways:*

The airways start with the trachea. Trachea divides into two **primary bronchi** that enter each lung at the hilum, along with arteries, veins and lymphatic vessels. The angle of the first bifurcation is 20–30° for the right and 45° for the left main bronchus. After entering the lungs, the primary bronchi course downward and outward, giving rise to three **secondary (lobar) bronchi** in the right lung and two in the left lung, each of which supplies a pulmonary lobe. These lobar bronchi again divide forming **tertiary (segmental) bronchi** ***(Mescher, 2016)***