Impact of Olmesartan Medoxomil on Amiodarone-Induced Pulmonary Toxicity in Rats: Focus on Transforming Growth Factor-ß1

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Abstract: Amiodarone (AD) is one of the most frequently prescribed anti-arrhythmic agents worldwide, but its effectiveness is limited due to the development of pulmonary toxicity. Several lines of evidence have suggested that AT1 receptor antagonists can attenuate pulmonary fibrosis in different animal models. This study was performed to evaluate the effect of olmesartan medoxomil (OM) on lung injury induced in rats by AD which was assessed biochemically (hydroxyproline content, MDA level and SOD activity), histologically (Ashcroft criteria and Mason’s trichrome stain) and immunohistochemically (TGF-ß1 expression in lung tissue). The expression levels of TGF-ß1 and type I collagen mRNA were also determined by quantitative real-time polymerase chain reaction. Forty-eight adult male rats were randomized into six equal groups: control group, OM control groups, AD group received 40 mg/kg/day, p.o. for 4 weeks to induce pulmonary injury in rats and OM-treated groups received 0.6 and 6 mg/kg/day, p.o. concomitantly with AD for the same period. The results indicated that OM significantly decreased collagen deposition and hydroxyproline content, ameliorated pathological score and decreased the elevation in type I collagen and TGF-ß1 mRNA expression in lung tissue. Furthermore, it attenuated the AD-induced increase in the MDA level and increased SOD activity in lung tissue. It can be concluded that OM exerts a protective effect against AD-induced lung damage in rats which is attributed to modulation of pro-fibrogenic cytokine (TGF-ß1) and antioxidant effect.

Many medications used for different therapeutic goals have been associated with pulmonary complications of various types, including bronchospasm, pulmonary oedema, pleural effusion, interstitial inflammation and fibrosis [1]. Amiodarone (AD), a benzofuran derivative, is a potent agent frequently used in the treatment of cardiac arrhythmias [2]. Despite its high efficacy when compared to other anti-arrhythmics but also AD, it has a wide range of adverse effects [3]. Moreover, AD has several pharmacological properties that contribute to its toxicities, including the presence of two iodine atoms that result in the release of 7 mg iodine per 200 mg AD, its lipophilic nature, large distribution volume, long half-life and high affinity for tissue accumulation [2]. Consequently, AD accumulates in fatty tissue, the lungs and liver in chronic users, which leads to direct organ toxicities.

The adverse effect of greatest concern is pulmonary toxicity, which is characterized initially by alveolitis and interstitial inflammation and subsequently by pulmonary fibrosis [4]. These changes are caused by N-desethylamiodarone, AD’s major metabolite, which has a greater toxic potency than AD and may act synergistically with AD to cause lung toxicity [5]. The mechanisms involved in AD-induced pulmonary injury are incompletely understood but several mechanisms have been implicated, including alterations of cell membrane properties, generation of oxidants, inflammatory reactions, immunological reactions, phospholipidosis and apoptosis [5,6]. There are several known risk factors for AD-induced pulmonary toxicity, including duration of AD therapy, pre-existing lung disease, high oxygen therapy and old age [7].

Besides the systemic renin-angiotensin system (RAS), many peripheral tissues are capable of generating RAS components which are so-called tissue RAS [8]. Angiotensin II (Ang II), the main peptide of the RAS, regulates cell growth, inflammation, fibrosis and contributes to the progression of injury of various organs through angiotensin type 1 (AT1) receptors [9]. It has been demonstrated that Ang II has a number of profibrotic effects on lung parenchymal cells and contributes to pulmonary fibrosis progression [10]. Locally produced Ang II is thought to exert its effect by directly inducing NADPH oxidase activity, stimulating the release of inflammatory cytokines, generating reactive oxygen species, stimulating transforming growth factor-ß1 (TGF-ß1) production and triggering fibroblast proliferation and differentiation into collagen-secreting myofibroblasts [11,12].

Treatment with AT1 receptor antagonists can attenuate experimentally induced pulmonary fibrosis [13]. Olmesartan medoxomil (OM) is a highly selective non-peptide AT1 receptor antagonist and is effective and well tolerated in the treatment of arterial hypertension. It is a pro-drug which is rapidly and completely de-esterified to the active form of OM after oral administration [14]. Previous studies have reported the