ACUTE PULMONARY INFLAMMATION IN HAMSTERS FOLLOWING INTRATRACHEAL ADMINISTRATION OF AMIODARONE

TERRI L. BLAKE and MARK J. REASOR

Department of Pharmacology and Toxicology
Robert C. Byrd Health Sciences Center of West Virginia University
P.O. Box 9223, Morgantown, West Virginia 26506-9223

Abstract—The use of the antiarrythmic drug amiodarone (AD) has been limited by the propensity of the drug to cause severe lung damage. AD has been shown to produce a transient pulmonary fibrosis in hamsters after intratracheal instillation. The goal of this study was to characterize the early inflammatory events associated with the administration of AD. Male Syrian hamsters that were instilled intratracheally with AD or saline vehicle underwent bronchoalveolar lavage (BAL). Total cells, macrophages, and eosinophils obtained by BAL were elevated by AD treatment at day 3. At both days 1 and 3 after instillation, AD-treated animals had significant elevations in neutrophil number. BAL fluid albumin was significantly elevated at day 1 in treated animals. Chemiluminescence (CL) performed on cells obtained by BAL showed an increase in CL of AD-treated samples compared to controls in phorbol myristate acetate (PMA) stimulated CL. PMA-induced increases in responsiveness were diminished by superoxide dismutase and catalase. These results indicate that oxidants such as superoxide and hydrogen peroxide may be involved in this inflammatory process. The results of this study show that intratracheal instillation of AD results in an inflammatory response that can be assessed by cellular, biochemical, and functional means.

INTRODUCTION

Amiodarone is an iodinated benzofuran derivative that was introduced in the United States as an investigational antiarrythmic drug in 1978 (1). Shortly thereafter, reports of AD-induced pneumonitis and pulmonary fibrosis began to appear in the literature (2). Pathological findings relative to this condition include interstitial and alveolar fibrosis and inflammation. Serious pulmonary toxicities occur in roughly 5–15% of patients receiving AD chronically. Pulmonary toxicity is more likely to occur in patients with underlying respiratory problems (3). High daily doses of AD may increase the frequency and speed of onset of pneumonitis (1).
The process whereby AD induces pulmonary disease has not been elucidated. There is evidence that multiple mechanisms may be involved, including phospholipidosis, hypersensitivity, and direct toxicity (4).

Despite its potentially fatal toxicities, AD was approved in the United States for the treatment of life-threatening arrhythmias. It remains an important pharmacologic tool in cardiology because it is effective against some arrhythmias that do not respond to other drugs. Better understanding of the mechanisms involved in the development of AD-induced lung damage is necessary for elucidation of the etiology of the pulmonary fibrosis. Such knowledge could lead to the development of an antiarrhythmic agent as effective as AD but less damaging to the lung. Therefore, the continued study of AD pulmonary toxicity is important (3).

A model of AD-induced pulmonary fibrosis has been developed in hamsters. Cantor et al. (5) reported that the intratracheal instillation of AD in Syrian hamsters results in an initial, nonspecific alveolitis followed by an AD-specific inflammatory response that includes thickening of the interstitium and cellular influx, as observed by histopathology. At day 21 after administration, the treated animals have significantly elevated lung collagen levels as assessed by trichrome staining. At day 28 the responses have diminished and thereafter are not significant.

A later study by Daniels et al. (6) examined the fibrogenicity of AD and desethylAD, a metabolite, after intratracheal instillation to hamsters. Lung hydroxyproline, an index of fibrosis, was determined and histopathology was performed. Their results matched those of Cantor et al. (5): both AD and desethylAD elevate lung hydroxyproline and cause significant morphological changes consistent with pulmonary fibrosis. These toxicities are greatest 21 days after instillation and decrease by day 28.

Neither of these studies examined the cellular processes associated with the inflammatory reaction and how they might influence the fibrotic response. The study of bronchoalveolar lavage (BAL) fluid from hamsters that received intratracheal AD should provide important insight into the toxic processes, especially the cellular changes, that lead to fibrosis. BAL is widely employed in the study of lung disease and injury. Properly performed, analyzed, and interpreted, this technique is a powerful tool in the detection and description of biochemical and cellular factors of pulmonary inflammation (7). BAL has been successfully used to monitor the development of AD-induced lung changes in humans (8) and rats (9). Such characterization of BAL fluid from hamsters treated with intratracheal AD should help us better understand how AD causes lung injury.

Measurement of chemiluminescence (CL), or light production, is useful in monitoring activated cells. CL has been most frequently used to assess the activity of inflammatory cells, especially neutrophils and macrophages. CL was utilized in this study as a functional assessment of inflammation, or activation