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Review

Pathogenesis of Amiodarone-Related Toxicity

Seval Bulut[1], Enbiya Aksakal[2], Halis Süleyman[1]

[1]Department of Pharmacology, Erzincan Binali Yıldırım University Faculty of Medicine, Erzincan, Türkiye
[2]Department of Pharmacology, Erzincan Binali Yıldırım University Institute of Health Sciences, Erzincan, Türkiye

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ORCID iDs of the authors: S.B. 0000-0003-4992-1241, E.A. 0000-0002-5773-7148, H.S. 0000-0002-9239-4099.

ABSTRACT

Amiodarone is an antiarrhythmic drug widely used to treat atrial and ventricular arrhythmias. On the other hand, amiodarone can cause toxicity in many organs such as the heart, lungs, gastrointestinal tract, liver, eyes, thyroid, and skin during and after treatment. The tendency of amiodarone to accumulate in organs with a high lipid content increases its half-life and causes prolonged therapeutic and toxic effects. Oxidative stress is thought to be the main factor in amiodarone-induced tissue damage. Amiodarone has been shown to cause oxidative damage through an increase in reactive oxygen species (ROS) and a decrease in aioxidants. Amiodarone also disrupts the mitochondrial respiratory chain and decreases adenosine triphosphate (ATP) levels, which are among the causes of toxicity. Amiodarone has also been shown to increase levels of pro-inflammatory cytokines. The increase in these cytokines may further increase ROS levels and exacerbate the damage. On the other hand, the structural feature of amiodarone has been considered another cause of toxicity, and thyroid damage has been attributed to its similarity to thyroxine and iodine content. Considering the widespread use of amiodarone, toxic effects and prevention of toxicity become more important. Given the significant role of oxidative stress and inflammation in amiodarone-related toxic effects, antioxidant and anti-inflammatory therapies are emerging as promising strategies to mitigate these adverse effects. In addition, studies to maintain cellular ATP levels at physiological levels may emerge as an important treatment strategy to prevent amiodarone toxicity.

Keywords: Amiodarone, ATP, inflammation, mitochondrial dysfunction, oxidative stress

INTRODUCTION

Amiodarone, a bi-iodinated benzofuran derivative, is an antiarrhythmic agent widely used in the treatment of atrial and ventricular arrhythmias.[1,2] Amiodarone is considered a class III antiarrhythmic agent according to the Vaughan–Williams classification because it prolongs myocardial repolarization through potassium channel blockade. In addition, amiodarone has a class I effect because it decreases conduction velocity by blocking sodium channels, a class II effect because it acts on α- and β-adrenergic receptors, and a class IV antiarrhythmic effect by blocking calcium channels.[1]

In addition to its therapeutic effects, amiodarone can cause a wide range of side effects affecting various organ systems, some of which can be life-threatening.[2] Ten years after amiodarone was first used in medicine, it was revealed to cause toxicity in several organs, including the heart, lungs, gastrointestinal system, liver, eyes, thyroid, skin, neuromuscular system, and genitourinary system.[1] Even low doses of amiodarone used in humans have been found to cause thyroid, neurological, skin, eye, and bradycardic side effects.[3] Amiodarone tends to accumulate in organs with a high lipid content such as adipose tissue, thyroid, liver, and lungs. This feature increases its half-life and allows both therapeutic and toxic effects to occur even after discontinuation of treatment.[1] It has also been suggested in the literature that amiodarone toxicity increases with increasing dose and duration of use.[4]

Although the mechanism underlying the toxic effects of amiodarone on humans is not fully understood, it is accepted that oxidative stress is the main factor in amiodarone-induced tissue damage.[5,6] Evidence obtained from cell and animal studies also show that amiodarone induces the formation of reactive oxygen species (ROS). In addition, increased release of inflammatory mediators, phospholipase inhibition, membrane destabilization, and

Corresponding author: Halis Süleyman, **E-mail:** halis.suleyman@gmail.com

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mitochondrial dysfunction have also been held responsible for amiodarone toxicity.[4,7] On the other hand, the structural feature of amiodarone has been considered another cause of toxicity, and thyroid damage has been attributed to its similarity to thyroxine and iodine content.[8]

Reactive oxygen species, which has been implicated in amiodarone toxicity, are normally produced as by-products of oxygen metabolism and are involved in various physiological activities. However, various reasons, such as drug use, lead to a significant increase in ROS production.[9,10] Cells use various antioxidant defense systems to protect themselves from ROS-induced damage. The imbalance between the production and accumulation of ROS in cells and tissues and the ability of biological systems to detoxify these reactive products leads to oxidative stress, which can cause tissue damage.[9] Increased ROS in a state of oxidative stress causes damage by attacking macromolecules, including proteins, membrane lipids, and DNA.[11] A study on the cytotoxic effect of amiodarone in cell culture reported that oxidative stress triggered the molecular mechanism of amiodarone-induced cell death. The results of the study showed an increase in lipid peroxidation and heat shock proteins, indicating oxidative attack, and showed that amiodarone caused a marked decrease in cell viability.[12] In another study on the pneumotoxic effect of amiodarone, it was shown that amiodarone metabolism generates aryl radicals at the cellular level, which in turn generate additional ROS. It was reported that disruption of the redox balance caused endothelial damage, followed by edema, inflammation, and severe lung damage.[13] The results of the study by Vereckeı et al.[14] also support the involvement of oxidative processes in the molecular mechanism of amiodarone toxicity. In this study, the authors pointed out that antioxidant treatment reduced the damage in hepatotoxicity associated with amiodarone use in rats. Similarly, the finding of a significant preventive effect of antioxidant treatment at the level of damage in amiodarone-induced toxicity in various organs and tissues supports the hypothesis that oxidative stress is involved in the pathogenesis of amiodarone-induced toxicity.[5,6,12] Mitochondria, one of the most important organelles in protecting the redox balance, is the main source of ROS as well as adenosine triphosphate (ATP) production, and therefore mitochondria are susceptible to oxidative damage.[5,11] It has been reported in the literature that amiodarone inhibits complexes I, II, and III in the respiratory chain and decreases mitochondrial membrane potential.[15] As a result, disruption of mitochondrial homeostasis leads to disruption of electron transport and a decrease in ATP biosynthesis.[5] Adenosine triphosphate is a nucleoside triphosphate composed of adenine, ribose, and 3 phosphate groups. Adenosine triphosphate is known to be an energy source for the synthesis of low molecular weight antioxidants that scavenge ROS.[10] In a study in human lung fibroblasts, amiodarone was shown to inhibit complex I activity and ATP biosynthesis. It was also reported that amiodarone caused oxidative damage to lipids and proteins and decreased nitric oxide levels, superoxide dismutase (SOD), and catalase (CAT) activities.[5] It has been reported in the literature that amiodarone causes a dramatic decrease in cellular ATP levels and cell viability, even at low concentrations.[16] The results of a recent experimental study showed that amiodarone caused oxidative toxicity by increasing levels of the oxidant malondialdehyde and decreasing enzymatic and non-enzymatic endogenous antioxidants, including total glutathione, SOD, and CAT, in ocular tissue in a dose-dependent manner. In addition, exogenous ATP treatment given with amiodarone was found to be effective in maintaining redox balance and reducing optical damage.[10]

In addition to oxidative stress, proinflammatory cytokine release has also been implicated in amiodarone toxicity.[4] It has been shown that an oxidative environment leads to the activation of nuclear factor kappa B and increased production of cytokines, including tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-12.[17] On the other hand, it has also been reported in the literature that this increase in the synthesis of proinflammatory cytokines exacerbates the damage by further increasing the amount of ROS.[18] Previous studies have reported that amiodarone caused an increase in TNF-α, IL-1β, and IL-6 in rat kidney tissue.[19] Amiodarone was also found to experimentally increase serum levels of IL-1α, IL-1β, IL-4, IL-6, and IL-10.[20] Studies have shown that animals with increased levels of proinflammatory cytokines due to amiodarone also developed histopathological damage.[19,20] Paradoxically, there are also studies in the literature pointing to the antioxidant and anti-inflammatory properties of amiodarone.[21] For example, Polat et al.[22] reported that amiodarone treatment reduced sepsis-induced elevated levels of IL-1β, IL-6, and TNF-α in rats. On the other hand, the protective effect of amiodarone on oxidative ovarian damage was investigated in an experimental study and it was concluded that amiodarone could not prevent oxidative stress and inflammation.[23]

MAIN POINTS

- Oxidative stress is involved in the pathogenesis of amiodarone toxicity.
- Amiodarone triggers inflammation.
- Amiodarone causes mitochondrial dysfunction and consequently intracellular ATP depletion.
- Maintaining intracellular ATP levels may be effective in preventing amiodarone toxicity.

Amiodarone is a drug widely used as a antiarrhythmic agent. However, amiodarone may cause various toxic effects even at low doses. The pathogenesis of amiodarone-induced toxic effects is characterized by oxidative stress, decreased cellular ATP levels, and increased expression of proinflammatory cytokines. Therefore, antioxidant and anti-inflammatory therapies are important to prevent or alleviate amiodarone-induced toxicity. Future studies focused on maintaining cellular ATP levels and exploring combination therapies targeting both oxidative stress and inflammation are essential to develop effective strategies to prevent or mitigate amiodarone-induced toxicity.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

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