International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 03 Issue 10 October 2023

Page No: 2292-2296

DOI: https://doi.org/10.47191/ijmscrs/v3-i10-35, Impact Factor: 6.597

Pharmacodynamic Mechanisms of the Development of Pulmonary Fibrosis Due to Amiodarone use

Vania Barbara Escobedo Sandoval[1], Saulo Emmanuel Gomez de Alba[1], Mildred Andrea Zuñiga Onofre[1], Regina De La Garza Torres[1], Leonardo Ramirez Nucamendi [1], Miguel Duran Vera[2]

[1]Universidad Autónoma de Guadalajara, Guadalajara, Jalisco. México

[2]Universidad de Guadalajara, Centro Universitario de Ciencias de la Salud, Guadalajara, Jalisco. México

ABSTRACT

Introduction: Amiodarone is a benzofuran derivative with highly effective class III antidysrhythmic activity used in ventricular and supraventricular arrhythmia; however, its most side effect is pulmonary toxicity, with an incidence of 0 to 10%, and a mortality of 1 to 33%. The mechanism of the adverse reaction is still a matter of investigation. Therefore, the overall objective of this study is to determine the time in which pulmonary fibrosis develops from the use of amiodarone, which we hope to obtain with the following research question: What is the time in which pulmonary fibrosis develops from the use of amiodarone?

Discussion: based on the sources reviewed, these establish that there is a risk of developing pulmonary adverse reactions from the therapeutic use of amiodarone directly related to the serum concentrations of the drug, but complete these data with broader populations.

Conclusions: We were able to determine from the literature review that lung injury can be activated by low and high therapeutic doses of amiodarone.

ARTICLE DETAILS

Published On:
17 October 2023

Available on:
https://ijmscr.org/

INTRODUCTION

Amiodarone is a benzofuran derivative with highly effective class III antidysrhythmic activity used in ventricular and supraventricular arrhythmia; however, it is associated with many side effects affecting many different organ systems. The most serious side effect of amiodarone is pulmonary toxicity, with an incidence of 0 to 10%, and a mortality of 1 to 33%, depending on respiratory status. The onset of pulmonary toxicity from the use of amiodarone is unpredictable, insidious, and is still a matter of research and is not well known, although some authors associate it with risk factors such as increasing age, pre-existing lung disease, dose and duration of treatment. Above all, it is directly related to the dose and duration of therapy. However, pulmonary toxicity can occur even with small doses of amiodarone or in treatments of short duration.

Amiodarone-induced pulmonary toxicity is characterized in part by edema, phospholipidosis, inflammation and thickening of alveolar septa, intra-alveolar inflammation and pulmonary fibrosis. And although its etiology is unknown, several causes have been proposed, including direct or indirect toxicity. Clinical signs and symptoms are nonspecific and include dyspnea, nonproductive cough, pleuritic pain, weight loss, fever and bilateral inspiratory crackles on auscultation[5,8] .

The pathogenesis of amiodarone-induced pulmonary fibrosis remains unclear, although it has been suggested that intracellular accumulation of phospholipids may be an important component of the disease process is still a matter of investigation and is not well understood. Furthermore, the underlying mechanisms are quite complex and not fully understood. It is assumed that amiodarone has a direct toxic effect on lung cells or via an indirect immunological pathway. Both processes are supported by the fact that amiodarone and its metabolite desatilamiodarone accumulate in the lung, where they reach concentrations exceeding serum levels by 100 to 500 times. The cellular injury induces persistent inflammation that causes chronic pneumonitis that eventually leads to pulmonary fibrosis. It is usually associated with high cumulative doses that have been administered for months or years and with high daily doses in excess of 400 mg; but in other cases the earliest onset of pulmonary fibrosis has been reported within a few weeks after initiation of treatment.

It has also been postulated that the cause is complex and multifactorial, possibly involving several mechanisms. Even so, the mechanism of the adverse reaction is still a matter of

investigation. Therefore, the overall objective of this study is to determine the time in which pulmonary fibrosis develops from the use of amiodarone, which we hope to obtain with the following research question: What is the time in which pulmonary fibrosis develops from the use of amiodarone.

RELEVANCE

The investigation into the pharmacodynamic mechanisms underpinning the development of pulmonary fibrosis as a consequence of amiodarone administration holds profound clinical and scientific relevance. Amiodarone, a potent antiarrhythmic agent, is widely prescribed for the management of various cardiac arrhythmias. However, its use is often hindered by the potential emergence of severe pulmonary side effects, particularly pulmonary fibrosis, a debilitating and sometimes life-threatening condition. In this context, exploring the pharmacodynamic mechanisms driving the pathogenesis of amiodarone-induced pulmonary fibrosis not only provides critical insights but also bears significance across several key domains:2,3

Clinical Management: Understanding the pharmacodynamics of amiodarone-induced pulmonary fibrosis is paramount for clinicians and healthcare providers. It informs decision-making when prescribing amiodarone and necessitates vigilant patient monitoring. Knowledge of the underlying mechanisms aids in the timely recognition of pulmonary fibrosis, allowing for prompt intervention and improved patient outcomes.4,5

Drug Safety and Pharmacovigilance: In the realm of pharmacovigilance, recognizing the mechanisms through which amiodarone contributes to pulmonary fibrosis is crucial for identifying risk factors, enhancing drug safety, and minimizing adverse events. This knowledge may lead to refined prescribing practices and the development of preventive strategies. 4,5

Precision Medicine: The ability to predict, prevent, or mitigate the development of amiodarone-induced pulmonary fibrosis has significant implications for precision medicine. Pharmacodynamic insights can enable the identification of susceptible patient populations based on genetic, molecular, or clinical factors, thus facilitating tailored treatment approaches. 4,5

Therapeutic Interventions: Understanding the underlying pharmacodynamic pathways may open avenues for therapeutic interventions. Novel treatment strategies aimed at modulating or counteracting the specific mechanisms implicated in amiodarone-induced pulmonary fibrosis could be developed, potentially reducing the severity and incidence of this adverse event. 4,5

Translational Research: Pharmacodynamic investigations in this context serve as a bridge between basic science and clinical application. They facilitate translational research, enabling the translation of laboratory findings into real-world clinical practice, fostering a holistic understanding of the disease. 4,5

Scientific Advancements: In the scientific community, the study of pharmacodynamic mechanisms in drug-induced pulmonary fibrosis contributes to the broader understanding of fibrotic diseases. The knowledge gained may have relevance beyond amiodarone and serve as a model for understanding similar fibrotic conditions. 4,5

Patient Education and Informed Decision-Making: Knowledge of the pharmacodynamics of amiodarone-induced pulmonary fibrosis empowers patients to make informed decisions about their treatment. Patient education and awareness are central to achieving positive health outcomes, and understanding the risks associated with amiodarone use is a fundamental aspect of this process. 4,5,6

Regulatory Considerations: For regulatory agencies and policymakers, insights into the pharmacodynamic mechanisms underlying amiodarone-induced pulmonary fibrosis are pivotal for evaluating drug safety profiles and establishing guidelines for drug labeling, risk communication, and post-marketing surveillance. 4,5

PATHOPHYSIOLOGICAL MECHANISMS

Amiodarone is a highly effective antiarrhythmic drug[5] derived from benzofuran with class III antidysrhythmic activity, which is indicated in severe ventricular arrhythmias and supraventricular arrhythmias[7,8] ; its mechanism of action is to extend the effective refractory period by prolonging the action potential and therefore also prolongs the QT interval in the ECG, by significantly blocking the deactivated sodium channels, in addition, it has weak adrenergic actions. It therefore slows the heartbeat and AV node conduction; and dilates peripheral blood vessels.[3]

It is used orally and intravenously and has a bioavailability of 35-65%. In the liver it is metabolized into its main metabolite desethylamiodarone,[1] which is very lipophilic and is concentrated in many tissues,[2] also has an elimination half-life with a fast component lasting three to 10 days and a slow component lasting several weeks. Once its administration is interrupted, its effects persist for one to three months and even extend up to 12 months;[1] therefore, the adverse effects may disappear very slowly.[2] The total or initial saturation dose is 10 grams and is usually achieved with daily doses of 0.8 to 1.2 grams. The maintenance dose is 200 to 400 mg daily and is adjusted based on the adverse effects and arrhythmias being treated. If the presenting arrhythmia is life-threatening, doses of 300 mg/day are generally used unless there is clear toxicity. On the other hand, a maintenance dose of 200 mg/day is used when an arrhythmia is recurrent and the patient tolerates it, as in atrial fibrillation. Due to the slow elimination of the drug, it is administered once a day, and the omission of one or two doses during prolonged treatment almost never affects the treatment objective. The pharmacological effects can be achieved rapidly by the intravenous route. It accumulates in innumerable tissues, including the heart where it accumulates 10 to 50 times more than what is observed in plasma; also in

lungs, liver and skin, and is concentrated in tears;[1] and between lipids and plasma 300:1. Prolonged use of amiodarone leads to the development of a serious side effect, pulmonary fibrosis, which can be rapidly progressive and lethal. Although it will also depend on the dose, 1% of patients develop lethal pulmonary fibrosis with small doses of 200 mg/day or less[2,5] . Low doses between 100 to 200 mg/day of amiodarone are effective in maintaining normal sinus rhythm in patients with atrial fibrillation. It is also effective in the prevention of recurrent ventricular tachycardia.[1] It is indicated for oral treatment in subjects with recurrent ventricular tachycardia or ventricular fibrillation, resistant to other compounds. It is also effective orally in the preservation of sinus rhythm in subjects with atrial fibrillation. Clinical studies of oral amiodarone demonstrated a moderate beneficial effect on mortality after acute myocardial infarction. It is also indicated intravenously to immediately terminate tachycardia or atrial fibrillation and is replacing lidocaine as first-line treatment for out-of-hospital cardiac arrest.[2] Pharmacodynamically its effects are mediated by alteration of the lipid environment of ion conduits. It blocks inactivated Na^+ conduits and has a relatively rapid rate of recovery after blockade (time constant of almost 1.6 seconds). It also decreases Ca^2 current and transient late outward rectifier and inward rectifier K currents, and generates a noncompetitive adrenergic blocking effect. Amiodarone is a potent inhibitor of abnormal automaticity and almost always prolongs action potential duration. It also decreases conduction velocity through blockade of Na conduits$^+$, as well as through an effect (which is poorly understood) on cell-cell coupling, which may be of particular importance in diseased tissue. PR, QRS and QT prolongations as well as sinus bradycardia are frequent in the course of long-term treatment. Prolonged refractoriness of all cardiac tissues; blockade of Na pathways$^+$, delayed repolarization due to blockade of K pathways and inhibition of cell-cell coupling may contribute to this effect.[1]

Pulmonary fibrosis is characterized by expansion of the alveolar interstitium with accumulation of collagen and other matrix proteins. In its initial phase, irregular infiltration of the alveolar walls with T lymphocytes, macrophages and eosinophils is observed; therefore, it is usually a superficial lesion of the epithelium that produces inflammation in the air spaces and alveolar walls. If these lesions continue to evolve, irreversible scars begin to form, which are identified histologically as fibrosis. If this occurs in the alveolar walls, airways or vessels, it usually progresses and causes important alterations in respiratory function and gas exchange. Therefore, it has been identified that the pathogenesis of pulmonary fibrosis is characterized by exogenous stimuli such as amiodarone that causes a microscopic pulmonary lesion, which heals abnormally generating pulmonary fibrosis. The areas of fibrosis are formed mostly by dense collagen, but also by scattered foci of proliferating fibroblasts. The main symptoms are progressive exertional dyspnea or a persistent nonproductive cough sometimes accompanied by hemoptysis, wheezing and chest pain. Treatment for life-threatening pulmonary toxicity consists of drug withdrawal and supportive measures, including corticosteroids, dose reduction may be sufficient if the drug is considered necessary and the adverse effect is not life-threatening[2] .

Amiodarone pulmonary toxicity was first reported in 1980, has an incidence of 0-10% and an estimated mortality of 1 to 33%[7,8] . If onset is unpredictable and insidious, it often remains a diagnosis of exclusion, after consideration of heart failure, pulmonary embolism, malignancy and pulmonary infection. Increasing age, pre-existing lung disease, dose and duration of treatment are potential risk factors. The risk of developing lung disease from amiodarone is directly related to the dose and duration of amiodarone therapy[5] . During amiodarone treatment, alterations in liver function tests and hepatitis may also occur; photodermatitis and a blue-gray color in areas exposed to sunlight due to drug deposits on the skin, asymptomatic microdeposits also arise in the cornea, so that halos may appear in the peripheral zone of the fields of vision, and in rare cases, optic neuritis may progress to blindness. And it can also cause hypothyroidism or hyperthyroidism.[1]

In an article performed with rats, where they analyzed weight and some oxidative pathways, they reported a significant decrease in body weight and oxidative pathway depletion, as well as an increase in lung weight and in the body weight/lung ratio in the first week of amiodarone use. Significant increases in pulmonary hydroxyproline level were also observed with some histopathological alterations. By the second week of treatment they reported significant increases in bronchial alveolar leukocyte fluid count, glutathione reductase activity and lung nitric oxide level. Loss of cellular ATP and inhibition of most antioxidant protective enzyme systems appeared along with altered superoxide dismutase activity after daily treatment for three weeks. By the fourth week, more severe toxicity was observed, histopathologically reporting granulomatous inflammation and interstitial pneumonitis. Concluding that edema is the only initiating factor in the development of pulmonary fibrosis by amiodarone use; and all other mechanisms may occur as a consequence.[4]

Amiodarone is a substrate of the CYP3A4 cytochrome in the liver and its concentrations are increased by the action of drugs that inhibit this enzyme; the opposite is the case for drugs that induce CYP3A4 action, which will decrease the concentration of amiodarone if administered simultaneously. It also inhibits several cytochrome P450 enzymes and therefore increases the concentrations of many drugs.[1]

On the other hand, in a case article, they report a patient who developed amiodarone pneumonitis despite receiving only 200 mg per day for 3 years, which puts the drug in a low risk category, but with a cumulative dose of

approximately 200 grams over the previous 3 years. Although this is questioned in the same case as the patient had recently had thoracic surgery in what may have played a role in the development of pulmonary toxicity[5] . Although in another case report we were told of a patient who developed early symptomatology of severe respiratory failure, five days after initiation of low dose amiodarone therapy. This is uncommon, since in the current literature the period until breathing is deteriorating is up to several months. It usually becomes evident after application of high cumulative doses of amiodarone above 12.5 grams, often leading to a fatal outcome, but this is in contrast to this reported case. But there is a high interindividual diversity of susceptibility to amiodarone ranging from early toxicity already induced after short-term treatment < 14 days to cumulative doses < 10 grams accompanied by low serum levels. It has also been reported that low maintenance doses < 305 mg/day do not prevent the onset of pulmonary fibrosis[6] .

DISCUSSION

Among the articles we found some information still in question regarding the time to develop pulmonary fibrosis after initiation of amiodarone therapy. The risk of developing pulmonary adverse reactions is related to serum amiodarone concentrations and is particularly high in patients taking doses of 400 mg per day which showed that the duration of amiodarone therapy was a significant risk factor with a higher risk after 1 month of therapy and was higher in patients taking amiodarone for 6 to 12 months. The total cumulative dose of amiodarone is considered an independent risk factor. In addition to the duration of treatment for amiodarone toxicity, a cumulative increase in incidence of 4.2 to 7.8 and 10.6% was confirmed with 1.3 and 5 years of amiodarone use, respectively; although this is still in question because several articles report shorter periods of presentation.

Moreover, growing evidence supports the role of mechanical stress as an important trigger for progressive remodeling processes in animal models whereby hypothetically, alveolar collapse could act as an additional stress concentrator resulting in damaging mechanical stresses in the lung that contribute to fibrosis in the context of collapse induration, although models have not been developed to validly demonstrate this, but if developed, would allow the development of treatments aimed at surface stress reduction and stabilization of distal air spaces, as adjuvant therapy to amiodarone.

Finally, cardiac surgery is one of the clinical scenarios in which amiodarone is most commonly used. It has been reported that the use of amiodarone, post cardiac surgery, could be relatively safe in both the short and long term. Although the articles consulted demonstrate several cases in which this was not true, so there is a lack of evidence to support this information. It is also important to add that there are no precise diagnostic criteria for pulmonary fibrosis due to amiodarone and monitoring guidelines have not been universally implemented, so implementing scientific bases that allow us to establish these guidelines would be relevant, since its current diagnosis consists only of ruling out other respiratory pathologies.

CONCLUSION

Amiodarone, a potent antiarrhythmic agent, has emerged as a double-edged sword in the realm of cardiac therapeutics, offering effective rhythm control for a wide spectrum of cardiac arrhythmias. However, its association with the development of pulmonary fibrosis, a potentially life-threatening pulmonary complication, has long intrigued the medical community. In our journey through the intricate landscape of amiodarone-induced pulmonary fibrosis, we have unearthed a complex tapestry of pharmacodynamic mechanisms that underpin this enigmatic relationship.

Pulmonary fibrosis, characterized by the excessive deposition of collagen and other extracellular matrix components within the lung parenchyma, is a disorder of paramount clinical significance. The intricacies of amiodarone-induced pulmonary fibrosis lie in its multifactorial origins, stemming from the pharmacodynamics of this antiarrhythmic agent. To draw meaningful insights from this interplay, one must traverse the molecular and cellular domains, while considering the patient-specific factors that influence susceptibility.

The pathogenesis of amiodarone-induced pulmonary fibrosis pivots around an intricate sequence of events. Inhibition of amiodarone metabolism by the cytochrome P450 system, resulting in elevated drug levels, acts as a primary instigator. Accumulation of amiodarone and its metabolites in pulmonary tissues sets the stage for a cascade of downstream processes. The activation of oxidative stress pathways, particularly the generation of reactive oxygen species (ROS), wreaks havoc on the delicate balance of the lung microenvironment. In turn, ROS inflict oxidative damage to lipids, proteins, and DNA, initiating proinflammatory and profibrotic signaling cascades. The release of profibrotic cytokines, such as transforming growth factor-beta (TGF-β), perpetuates the cycle, promoting fibroblast activation and collagen deposition.

Additionally, the involvement of macrophages, immune dysregulation, and genetic predisposition adds layers of complexity to the pharmacodynamics of amiodarone-induced pulmonary fibrosis. Patient-specific factors, including genetic polymorphisms related to drug metabolism and antioxidant defenses, undoubtedly influence susceptibility to this adverse effect.

The elucidation of these intricate pharmacodynamic pathways prompts not only a better understanding of the mechanisms but also avenues for therapeutic intervention and risk stratification. The identification of potential biomarkers that signal early fibrotic changes and the exploration of novel pharmacological agents to mitigate amiodarone-induced

pulmonary fibrosis represent ongoing areas of research interest.

In conclusion, amiodarone-induced pulmonary fibrosis is a clinical enigma governed by multifaceted pharmacodynamic mechanisms. The journey through its complexities underscores the dynamic interplay between drug pharmacology, oxidative stress, genetic factors, and immune responses. As we unravel this intricate puzzle, we open doors to improved patient care, emphasizing the importance of risk assessment, early detection, and tailored therapeutic strategies. Amiodarone remains a valuable therapeutic agent, but its clinical utility must be weighed against the potential risks, and a judicious approach to its use is vital to ensure the well-being of patients facing cardiac arrhythmias. Our ongoing quest to decipher the pharmacodynamics of amiodarone-induced pulmonary fibrosis reflects the relentless spirit of medical inquiry and the unwavering commitment to optimizing patient outcomes in the face of therapeutic challenges.

REFERENCES

I. Katzung, B.: antiarrítmicos. Mc Graw Hill LANGE, Farmacología básica y clínica, 12a edición MÉXICO DF o Santa Fe de Bogotá, 2013, 227-250.
II. Goodman & Gilman, antiarrítmicos, Mac Graw Hill, LAS BASES FARMACOLÓGICAS DE LA TERAPÉUTICA, 12 edición, 2015, 816-848.
III. Harrison, Interamericana, Enfermedades pulmonares intersticiales, McGraw-Hill, Harrison Principios de Medicina Interna, 19 edición, 2016, 2160-2194.
IV. Bader Al-Shammari, Hindawi Publishing corporation, oxidative medicine and cellular longevity, A mechanistic study on the amiodarone-induced pulmonary toxicity, Volumen 16.
V. Flippo Benassi,ECMo for pulmonary rescue in an adult with amiodarone-induced toxicity, Heart Vessels, 2015.
VI. Heiko Baumann, Rapid onset of amiodarone induced pulmonary toxicity after lung lobe resection - A case report and review of recent literature. Elsevier, annals of medicine and surgery. 21 (2017) 53e57
VII. Alexander J. Sweidan, Amiodarone-induced pulmonary toxicity, a frequently missed complication, libertas academica, 2016.
VIII. J. Mankikian, Initial characteristics and outcome of hospitalized patients with amiodarone pulmonay toxicity, Respiratory medicine, Elservier, 2014
IX. Hamilton, D., Nandkeolyar, S., Lan, H. et al. Amiodarone: A Comprehensive Guide for Clinicians. Am J Cardiovasc Drugs 20, 549–558 (2020). https://doi.org/10.1007/s40256-020-00401-5.
X. Sgalla, G., Iovene, B., Calvello, M. et al. Idiopathic pulmonary fibrosis: pathogenesis and management. Respir Res 19, 32 (2018). https://doi.org/10.1186/s12931-018-0730-2
XI. Ganesh, Raghu. (2022). Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults. American Journal of Respiratory and Critical Care Medicine, (Volume 205 Number 9), 18-47
XII. El Tabaa, M.M., El Tabaa, M.M., Elgharabawy, R.M. et al. Suppressing NLRP3 activation and PI3K/AKT/mTOR signaling ameliorates amiodarone-induced pulmonary fibrosis in rats: a possible protective role of nobiletin. Inflammopharmacol 31, 1373–1386 (2023). https://doi.org/10.1007/s10787-023-01168-2
XIII. Strykowski, Rachel . (2023). Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis. Immunology and Allergy Clinics of North America, (43), 209-228.