

# A Case Report on Amiodarone-Induced Toxicity Involving the Liver and Thyroid

Athul H<sup>1</sup>, Dr. George Varghese<sup>2</sup>, Dr. Joshua Kuruvilla Mathew<sup>3</sup>, Dr. Vipitha Thomas<sup>4</sup>,  
Dr. Mohan Varghese<sup>5</sup>

<sup>1</sup>Pharm D Intern, Nazareth College of Pharmacy, Othara, Thiruvalla

<sup>2</sup>Junior Resident, Department of General Medicine, Believers Church Medical College Hospital, Thiruvalla, Kerala, India

<sup>3</sup>Clinical pharmacist, Department of General Medicine, Believers Church Medical College Hospital, Thiruvalla, Kerala, India

<sup>4</sup>Clinical pharmacist, Department of General Medicine, Believers Church Medical College Hospital, Thiruvalla, Kerala, India

<sup>5</sup>Consultant Physician and Professor, Department of General Medicine, Believers Church Medical College Hospital, Thiruvalla, Kerala, India

**Abstract:** *Amiodarone is a highly effective class III antiarrhythmic drug. This drug is an iodine containing compound that tends to accumulate in several organs. With the increasing use of amiodarone, there have been reports of a variety of adverse events to various organs, including the lungs, liver, thyroid gland, eyes, skin, and the nervous system (2). We report a case of Systemic Toxicity of amiodarone involving liver and thyroid.*

**Keywords:** Amiodarone, thyrotoxicosis, Steatohepatitis, drug toxicity, cardiac sarcoidosis

## 1. Introduction

Amiodarone is a potent class III antiarrhythmic agent. It is an iodine-containing benzofuran derivative that is commonly used to treat supraventricular and ventricular arrhythmias. (1).

Approximately, amiodarone contains 37% iodine by weight. Each 200-mg tablet is estimated to contain about 75 mg of organic iodide, 8-17% of which is released as free iodide. Standard maintenance therapy with 200-mg amiodarone can supply more than 100 times the daily iodine requirement. It is mainly concentrated in the adipose tissue, muscle, liver, lung, and thyroid gland due to its high lipid solubility.

Long term Amiodarone therapy is associated with severe toxicity to various organs, including the lungs, liver, thyroid gland, eyes, skin, and the nervous system (2). The frequency of adverse reactions can vary widely, ranging from 30% to 90%, with severe effects occurring in between 10% and 26% of patients (1). Although the incidence of this complication has decreased with the use of lower doses of amiodarone, it can occur with any dose. Because amiodarone is widely used, all clinicians should be vigilant of this possibility.

About 24% of patients taking amiodarone showed asymptomatic elevations of serum aminotransferase levels (7). Less than 1% of patients in various studies reported developing significant drug-induced liver injury ranging from symptomatic hepatitis and micronodular liver cirrhosis to hepatic failure requiring liver transplantation.(3)

Abnormalities of thyroid gland have been noted in up to 14-18% of patients receiving long-term amiodarone therapy. However, a meta-analysis suggested that with the

lower doses of amiodarone (150-330mg) incidence of thyroid dysfunction is 3.7%. The effects range from abnormal thyroid function test findings to overt thyroid dysfunction, which may either be amiodarone-induced thyrotoxicosis (AIT) or amiodarone-induced hypothyroidism (AIH).(4).

Pulmonary toxicity is one of the fatal adverse effects of amiodarone, with mortality estimated between 1 and 33% and incidence of approximately 10% shown in previous studies (5).

The most typical symptom of amiodarone-induced ocular toxicity is corneal microdeposits, 98% of which are found after 2 months of treatment. Asymptomatic corneal changes are observed in 50–60% of patients, and visual disturbance is rarely reported (6).

Here, we present a case of multi-system amiodarone toxicity, involving the liver and thyroidgland.

## 2. Case Report

A 77-year-old man presented to ER with the complaints of decreased food intake and progressive fatigue since 2 weeks. He is a known case of Refractory Cardiac Sarcoidosis – is on Once weekly Methotrexate 10mg and Prednisolone 5 mg twice daily along with Inj. Adalimumab 40 milligrams every alternate week, Recurrent Ventricular Tachycardia (s/p single chamber AICD) – On Tab. Amiodarone for more than 10 years, Currently on 200 milligrams twice daily, Coronary artery Disease, Carcinoma Prostate s/p radiotherapy (2017), Type 2 Diabetes Mellitus and Systemic Hypertension.

He was admitted and evaluated under the General Medicine Department. His routine blood investigations showed

elevated CRP levels and mild hyponatremia. Blood counts and renal functions were within normal range. LFT showed mild direct hyperbilirubinemia (Total bilirubin – 1.63mg/dl, direct – 0.70mg/dl) with evidence of transaminitis (AST 157U/L, ALT – 277U/L). Urine routine showed albuminuria, pyuria, microscopic hematuria with bacteriuria. However, the patient had no lower urinary symptoms and was afebrile. Urine culture showed no growth after 48hrs of incubation. His Troponin I levels were minimally elevated at the time of admission; Repeat ECG and 2D ECHO showed only old changes with fair LV systolic function.

He was managed conservatively with broad spectrum antibiotics and supportive care. Hyponatremia was corrected with saline infusions. Despite inflammatory markers showed improving trend, patient had persistent tiredness in background of anorexia, weight loss and tremors. Considering high clinical suspicion of possible drug induced hyperthyroidism? amiodarone, detailed evaluation with TFT was done which revealed suppressed TSH and high freeT4 levels. USG thyroid showed few spongiform nodules in the left lobe, largest measuring 0.9 x 0.3cm – TIRADS-1. However, Anti TPO levels were within physiological limits and hence autoimmune thyroiditis was ruled out. Amiodarone was stopped and switched to Tab. Mexiletine 50milligrams twice daily in view of possible Amiodarone induced Thyrotoxicosis. Further evaluation with CECT abdomen was done which reported diffuse hyper attenuation of both lobes of liver, which could be attributed to possible amiodarone induced steatohepatitis.

HRCT Thorax was done which showed no evidence of any pulmonary toxicity like chronic interstitial pneumonitis/ intrapulmonary nodules.

### 3. Discussion

Amiodarone is a widely prescribed drug for treating arrhythmias which acts through multiple mechanisms, such as depressing the sinus and atrioventricular nodes and prolonging the repolarization and refractoriness in the myocardium.

Amiodarone is a lipophilic drug, which mainly accumulates in the adipose tissue and organs with high blood perfusion rate, such as the liver, lungs, and skin. Its long-term use can lead to various adverse reactions like photosensitivity, hypothyroidism, hyperthyroidism, hepatic dysfunction, bone marrow suppression, corneal microdeposits, and neuromotor defects (2). The elimination half-life of amiodarone is highly variable, ranging from 50-100 days; total body iodine stores remain increased for up to 9 months even after discontinuation of the drug. (1)

Due to the structural similarity between amiodarone and thyroid hormones, amiodarone causes thyroid dysfunction due to excessive iodine overload or due to its direct cytotoxicity to the thyroid gland (8). Amiodarone can induce both hypothyroidism and hyperthyroidism. The incidence of amiodarone-induced thyrotoxicosis (AIT) is 2 to 10%, and it more commonly develops in areas of the world where iodine deficiency is common (7).

There are two different forms of AIT, and differential diagnosis between the two forms is important, since treatments are different. However, it is often not possible to clearly distinguish AIT1 and AIT2.

Type 1 AIT usually occurs in an abnormal thyroid gland (latent Graves' disease, multinodular gland) and is the consequence of increased thyroid hormone biosynthesis due to iodine excess in patients with a preexisting thyroid disorder (Amiodarone contains 37% iodine by weight). Type 1 AIT is more common in iodine deficient regions. Type 2 AIT is a destructive process of the thyroid gland leading to the release of pre-formed hormone. This thyroiditis is an intrinsic toxic effect of amiodarone. Type 2 AIT usually persists for one to three months until thyroid hormone stores are depleted. In most countries Type 2 AIT is more common than Type 1 AIT. Differences between Type 1 and Type 2 AIT are described in table 1. Differentiating between AIT Type 1 and 2 is often very difficult. (9)

**Table 1:** Differences between Type 1 and 2 Amiodarone Induced Thyrotoxicosis

	Type 1	Type 2
Underlying thyroid disease	Yes (Multinodular goiter, Grave's)	No
Time after starting amiodarone	Short (median 3 months)	Long (median 30 months)
24-hour iodine uptake	Low-Normal (may rarely be high in iodine deficient regions)	Low to Suppressed
Thyroid Ultrasound	Diffuse or Nodular Goiter may be present	Normal or small gland
Vascularity on Echo color Doppler ultrasound	Increased	Absent
T4/T3 ratio	Usually <4	Usually >4

AIT Type 1 should be treated with high doses of methimazole (20-60 mg/day) or PTU (400-600 mg/day) to prevent the synthesis of thyroid hormones. (10)

AIT Type 2 can be treated with prednisone, starting with an initial dose of 0.5-0.7 mg/kg body weight per day and the treatment is usually continued for three months. If worsening of the condition occurs during the taper, the dose of prednisone should be increased. Methimazole and propylthiouracil are generally not useful in Type 2 AIT. (10)

Distinguishing between the two states is important as both have different therapeutic approaches. Mixed or indefinite AIT (AIT type3) is used when the classification is unclear or when both types of AIT occur at once. Because the distinction between AIT Type 1 and 2 is difficult and not always clear, and because some patients have mixed forms of AIT, these therapies for AIT Type 1 and 2 are often combined.

Hepatotoxicity is a relatively uncommon adverse reaction to amiodarone. Amiodarone induces histological findings similar to alcohol-induced steatohepatitis, so differential

diagnosis from alcoholic liver disease should be considered. Pathologic findings include macro- and microvesicular steatosis, Mallory bodies, polymorphonuclear leukocyte infiltration, ballooning degeneration of hepatocytes and phospholipidosis (3). The possible reason for hepatotoxicity is amiodarone, as its principal metabolite, desethylamiodarone induces production of reactive oxygen species and leads to hepatic triglyceride accumulation and microvesicular steatosis in hepatocytes (11).

In this case report, we observed amiodarone toxicity involving the liver and thyroid gland. The main mechanism of amiodarone-induced toxicity is known as direct cytotoxicity and immunologic reaction.

The long duration and high dosage of amiodarone were combined with treatment that may interact pharmacologically with amiodarone metabolism. He had been taking a atorvastatin concurrently with amiodarone. Many studies have reported an interaction between statins and amiodarone as the potential cause of hepatotoxicity due to inhibition of the mitochondrial enzyme CYP3A4, which metabolizes statins, by amiodarone (12,13).

In conclusion, this case indicates systemic amiodarone organ toxicity is a cause of concern in high-risk patients. Amiodarone toxicity should be considered in patients receiving amiodarone with any new symptoms, because this may involve various organs. A multisystem approach to amiodarone toxicity is important, because adverse events may occur in various organs simultaneously. Guidelines for monitoring adverse events in patients taking amiodarone for a long time must be established. Once diagnosis is determined, amiodarone must be discontinued promptly, and the use of systemic steroids needs to be assessed.

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#### Conflict of Interests

The authors declare that the case report was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

#### Abbreviations:

**AIT:** Amiodarone Induced Thyrotoxicosis.

**PTU:** Propylthiouracil

**AIH:** Amiodarone Induced Hypothyroidism

**AICD:** Automated Implantable Cardioverter defibrillator

**HRCT:** High Resolution Computed Tomography

**TFT:** Thyroid function test

**CECT:** Contrast Enhanced Computed Tomography

**TIRADS:** Thyroid Imaging Reporting And Data System

**TPO Ab:** Thyroid Peroxidase Antibody

**TgAb:** Thyroglobulin Antibody

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