

## RESEARCH ARTICLE

# The Characteristics of Amiodarone-induced Thyrotoxicosis in a Moderate Iodine Deficit Area

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**Introduction:** Amiodarone (AMI), a class III anti-arrhythmic drug, is associated with a number of side effects, including thyroid dysfunction (both hypo- and hyperthyroidism), which is due to amiodarone's high iodine content and its direct toxic effect on the thyroid.

**Objective:** To evaluate the incidence of Amiodarone induced thyrotoxicosis (AIT) (type, rate of occurrence) and to identify the risk factors involved in its occurrence.

**Material and method:** We examined patients treated with amiodarone, between January 2002 and December 2011, who presented to our Department of Endocrinology Târgu Mureş for thyroid dysfunctions.

**Results:** The retrospective study included 87 patients with thyroid dysfunctions; 58 (66.7%) patients had AIT and 29 (33.3%) had Amiodarone induced hypothyroidism (AIH). In the AIT group: 35 were women (60.3%), 23 were men (39.7%); the average age was  $61.60 \pm 12.39$  years. Risk factors identified for the AIT group were male gender ( $RR = OR = 3.8$ ; Chi-square = 5.7,  $p = 0.004$ ) and pre-existing thyroid abnormalities ( $RR = 2.5$ , Chi-square = 4.1,  $p = 0.005$ ). The thyroid dysfunction occurrence was heterogeneous (0.2–183 months). The patients with previous thyroid abnormalities developed earlier thyroid dysfunction compared to those with an apparently normal thyroid gland ( $22.25 \pm 4.14$  months versus  $32.09 \pm 7.69$  months,  $p = 0.02$ , T test).

**Conclusion:** In the context of the specific iodine geo-climatic intake and the area of origin, amiodarone - induced thyroid dysfunction spectrum is dominated by thyrotoxicosis. Screening and monitoring of thyroid function for patients under chronic amiodarone treatment is necessary.

**Keywords:** amiodarone, hyperthyroidism, risk factors, screening and monitoring

Received: 30 July 2013

## Introduction

Amiodarone (AMI) is a class III antiarrhythmic, currently considered one of the most effective in multiple types of atrial and ventricular arrhythmias [1]. Amiodarone shows remarkable structural resemblance with thyroxine and triiodothyronine [2]. A 200 mg AMI tablet contains 75 mg of iodine, from which 6 mg are released per day, thus causing an overload 50–100 times greater than the WHO daily iodine recommendation (0.15–0.3 mg/day). This amount also disturbs the complex physiology of the thyroid gland and has a direct toxic effect on thyrocytes [3,4,5].

Amiodarone induced thyrotoxicosis (AIT) has an incidence of 2–23%, with a higher frequency in iodine-deficient areas (2–13% in the U.S, 9.6% in Italy) [6,7,8].

The risk of hyperthyroidism is independent of the daily dose and duration of AMI therapy [9,10].

There are three types of thyrotoxicosis associated with amiodarone: differentiation of these forms is important because of different therapeutic approaches [11,12,13]:

- AIT type I is an iodine-induced hyperthyroidism that occurs in patients with thyroid pathology (usually nodular goiter or Graves' disease);
- AIT type II represents a toxic and destructive iodine-induced thyroiditis, which occurs in patients with normal thyroid gland;

- AIT type III is mixed type, showing both type I and type II pathogenic mechanisms.

Screening and monitoring of thyroid function in patients treated with AMI remains a subject of controversy. So far several protocols have been proposed, but one of the most widely accepted is being developed by the North American Society of Pacing and Electrophysiology (NASPE) since 2007. The NASPE guidelines recommend testing of thyroid function (TSH, fT4 and fT3) at the initiation of therapy with AMI, after 3 months of treatment and every 6 months thereafter [5,14].

The objectives of our study were to evaluate the incidence of amiodarone-induced thyrotoxicosis (types, rate of occurrence) and identification of risk factors involved in their occurrence, in a moderate iodine-deficient area. We tried to create an algorithm for screening and monitoring the thyroid function in patients treated with AMI in our area.

## Material and method

We performed a retrospective clinical descriptive study which included patients treated with AMI and diagnosed with amiodarone-induced thyroid dysfunctions. The study took place in the Endocrinology Department Tîrgu Mureş, Romania, between January 2002 and December 2011. Informed consent was obtained from the patients.

Inclusion criteria were: age over 18 years, treatment with amiodarone p.o./i.v. and euthyroid status prior to amiodar-

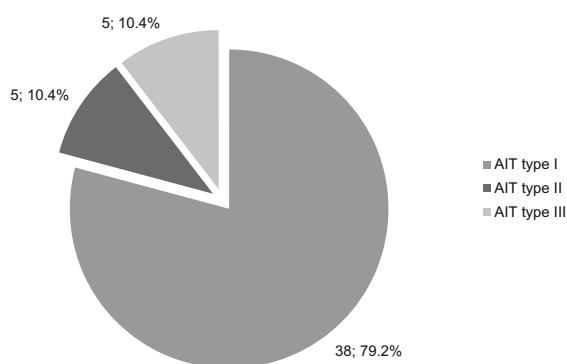


Fig. 1. Types of AIT

one therapy; exclusion criteria were: thyroid replacement therapy or use of antithyroid drugs prior to amiodarone therapy and recent history of administration of iodine contrast substances or other sources of iodine overload.

Clinical diagnosis of AIT was based on clinical exam (symptoms and signs of thyrotoxicosis) and laboratory tests: low serum TSH values (0.44–3.45 mUI/L) associated with increased total T<sub>3</sub> values and/or total T<sub>4</sub> and/or fT<sub>3</sub> and/or fT<sub>4</sub>. The diagnosis of subclinical AIT was based on low serum TSH values (0.44 mUI/L), with normal levels of thyroid hormones.

Type I AIT diagnosis was based on the following criteria: goiter (clinical exam or conventional ultrasonography), hypervascularity on Doppler-flow ultrasonography, positive antithyroid antibodies (TRAb, TPO-Ab) and/or Graves' ophthalmopathy.

Type II AIT diagnosis was based on the following criteria: absence of goiter or small diffuse goiter (clinical exam, conventional ultrasonography), absence of hypervascularity on Doppler-flow ultrasonography, absence of antithyroid circulating antibodies (TRAb, TPO-Ab) and low or undetectable amounts of radioiodine uptake (<20–40% at 2 or 24 hours). We diagnosed type III AIT if thyrotoxicosis presented characteristics of both type I and II AIT.

Statistical analysis: data were analyzed using SPSS version 11 for Windows (SPSS Inc., Chicago, IL, United States of America) and GraphPad Prism 5. The normal distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test or histograms. Distributed continuous variables were expressed as mean ± SD, while those without a normal distribution as the median values.

Student's test was applied in order to compare the values of continuous Gaussian distribution, while the Mann Whitney U-test was used for the retained normal values. A p-value under 0.05 was considered statistically significant. ANOVA test was used to compare multiple values. To estimate the cumulative incidence of an event the test has been applied to binary Log Rank Mantel Cox and resulted a Kaplan Meier Survival (95% confidence interval).

## Results

The study included 87 consecutive patients with thyroid

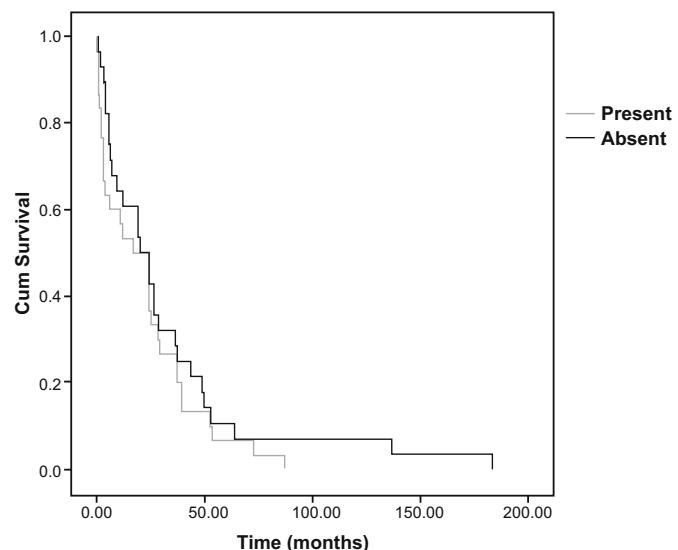


Fig. 2. Kaplan-Meier curve of cumulative risk of occurrence and time to occurrence in relation to pre-existing thyroid abnormalities

dysfunctions: 58 (66.7%) with AIT and 29 (33.3%) with amiodarone-induced hypothyroidism (AIH).

In the AIT group (58 patients) there were 35 women (60.3%) and 23 men (39.7%). The average age was 61.60 ± 12.39 years with abnormal distribution according to the Shapiro-Wilk test ( $p = 0.0024$ ).

According to the diagnostic criteria, our group is shown in Figure 1.

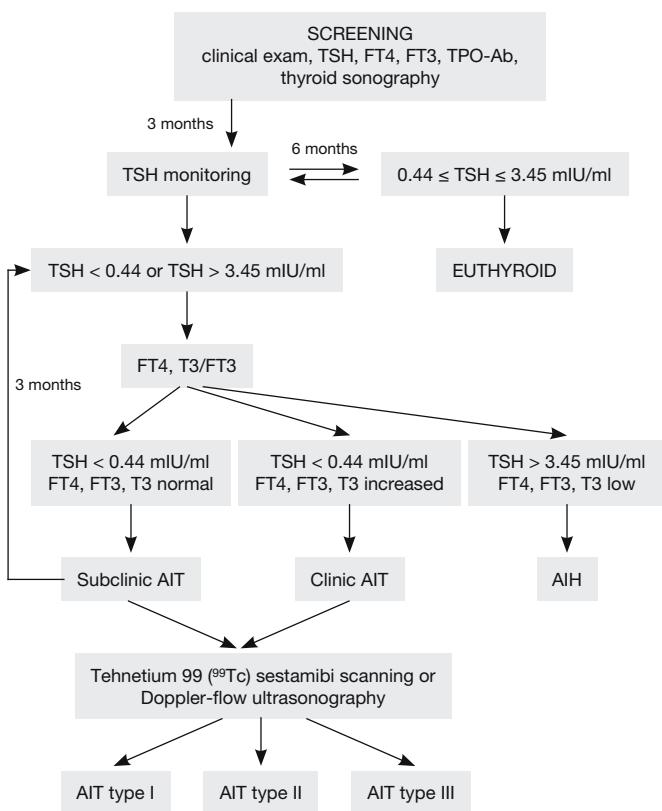
Risk factors identified in the AIT group were: male gender (RR = OR = 3.8; Chi-square = 5.7;  $p = 0.004$ ) and pre-existing thyroid abnormalities (RR = 2.5; Chi-square = 4.1;  $p = 0.005$ ).

Pre-existing thyroid abnormalities in our group were significant: 29 (76.31%) patients with type I AIT had a previous history of thyroid pathology like diffuse goiter in 2 cases (6.9%), nodular goiter in 26 cases (89.7%) and Graves-Basedow disease in 1 case (3.4%). None of the patients with type II AIT presented pre-existing pathology and in the type III AIT group only one patient had Graves-Basedow disease.

The development of dysfunction was heterogeneous: 0.2–183 months, and the average time of occurrence of amiodarone-induced dysfunctions in the study was 24.2 months. The Log Rank Mantel-Cox test ( $p = 0.016$ ) proved that the rate of diagnosis differed significantly in the type I AIT group (25% of cases at 37.5 months, 50% of cases at 24.2 months, 75% of cases at 4 months), compared to the type II AIT group (25% of cases at 12 months, 50% of cases at 9 months, 75% of cases at 4 months).

Patients with pre-existing thyroid abnormalities developed AIT sooner than those without previous thyroid disorders:  $22.25 \pm 4.146$  months (median 12 months) vs.  $32.09 \pm 7.69$  months (median 24 months),  $p = 0.02$  (Figure 2).

In the study group the screening rate was 21.88% and the monitoring rate was 28.13%.



**Fig. 3.** Algorithm for screening and monitoring of patients treated with AMI in a iodine-deficient area

## Discussion

The incidence of AIT reported in the literature varies between 2–30% [6–8,15,16] of treated cases, depending upon the individual's underlying thyroid status and dietary iodine intake.

In our study we found a higher incidence of AIT compared to AIH, which indicates that our region is still a iodine deficient area [6,7]. In areas with normal iodine intake (e.g. USA) AIH predominates [6–8,15,16].

Men presented a 5.7 times higher risk than women for the development of AIT in our study. Similarly, Sidhu et al. [17], compared the incidence of AIT in 216 UK men and women and demonstrated a significant difference between sexes, with males being more frequently affected than females and at increased risk for cardiovascular diseases.

In our study patients with pre-existing thyroid disease had a 4.1 times higher risk than those with normal thyroid status. Pre-existing thyroid abnormalities have been reported in 76.31% of patients diagnosed with AIT type I, but subjects with type II AIT did not have a significant history of thyroid diseases. According to the diagnostic criteria of AIT, pre-existing thyroid diseases represent a risk factor for the future development of type I AIT; the presence of goiter is a risk factor for the development of type I and type III AIT in 80% of patients and it is not a risk factor for type II AIT [18–21].

Patients with pre-existing thyroid abnormalities developed AIT earlier than those with normal thyroid function

(50% of cases at 16 months vs 50% of cases at 22 months). So pre-existing thyroid disease was a prognostic factor in relation to the occurrence of AIT.

The prevalence of AIT types in our study was: 79.2% for AIT type I, 10.4% for AIT type II and 10.4% for AIT type III. Bogazzi's study included 215 patients with AIT with a mean follow-up of 27 years. He showed that AIT type I was the most common form (60%) in the early years, and the average annual number of patients decreased from 3.6 to 2.5 in the last years of the study. The average number of patients with AIT type II grew progressively from 2.2 to 12.5. The incidence of AIT type II has increased significantly ( $p < 0.0001$ ) reaching 89% of cases, while that of AIT type I remained constant. This increase could be explained by the effective monitoring programme, decrease of AMI dose or withdrawal of the drug, especially in those with previous thyroid disorders [22].

In our study, the average time of occurrence of amiodarone-induced dysfunctions was 24.2 months, compared with an average time of 36 months published in the literature [23]. We believe that the shorter average time is due to moderate iodine deficiency in the area. In our study, the time and rate of occurrence were heterogeneous (0.2–183 months) and similar in both thype of dysfunctions (AIT and AIH).

There were significant differences between the types of AIT, especially between AIT type I and AIT type II with respect to time and rate of occurrence. AIT type II had a shorter onset time and an incidence of almost 50% at 9 months. In comparison, the incidence of AIT type I was 50% at 24.2 months. This difference in occurrence is due to the mechanism of pathogenesis: in AIT type II there is a direct toxic effect of amiodarone on thyroid follicular epithelial cells.

Various studies reported that screening rates vary between 37% and 65.8% [24] and the rate of monitoring between 2.9% and 72.7% [25]. Our study revealed modest screening and monitoring rates. In order to increase the rate of screening and monitoring, an interdisciplinary collaboration is required to establish an effective protocol for patients treated with amiodarone.

The NASPE Recommendations belong to a cardiology guide and they are designed considering an area of normal intake of iodine, where the prevalence of hypothyroidism is 2–4 times higher than that of thyrotoxicosis. Given the increased risk for the development of AIT in endemic iodine-deficient areas and the persistence of a mild deficiency iodate endemic in Romania [26–28], we recommend to perform a thyroid ultrasound to identify patients with thyroid nodular goiter who are at risk for developing thyroid dysfunctions, especially if they come from areas with deficient iodine intake.

## Conclusions

Our study came to the following conclusions:

- In the context of the specific iodine geoclimatic intake

and the origin area of the subjects, the amiodarone-induced thyroid dysfunction spectrum is dominated by thyrotoxicosis;

- The predominant pathogenic form of AIT in our study was type I;
- Male gender presents a 5.7 times higher risk than female gender for the development of AIT and patients with preexisting thyroid disease present a 4.1 times higher risk than those with normal thyroid status.
- The average time of occurrence was heterogeneous but significantly decreased, with a significantly higher rate of occurrence of AIT in patients with pre-existing thyroid abnormalities.
- Application of the screening protocol, monitoring of thyroid dysfunction induced by amiodarone in our geographic area, as specifically proposed within this paper, will enable endocrinologists and cardiologists to establish an early diagnosis of thyroid dysfunction induced by amiodarone, in a subclinical stage, with the reduction of morbidity and mortality.

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