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ORIGINAL PAPERS: CLINICAL OR BASIC RESEARCH

Thyroid dysfunctions induced by Amiodarone

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ABSTRACT

Objectives: *The aim of this study is to evaluate the incidence and types of thyroid dysfunctions induced by amiodarone (AMD) therapy. In the same time we tried to perform some considerations regarding the concrete treatment of AMD-induced abnormalities and the follow up of cases.*

Material and methods*: The study group comprised 85 patients, treated with AMD, issued from an iodine-replete area. The patients with thyroid dysfunctions were evaluated clinically, by means of conventional thyroid sonography, color flow Doppler sonography – CFDS (in selected cases), determinations of plasma levels of TSH, thyroid hormones and antithyroid auto antibodies (AT Abs)*

Results: *60.9 % of patients remained euthyroid during AMD treatment, hypothyroidism occurred in 15.6% of cases and thyrotoxicosis was diagnosed in 23.5% of subjects*

Conclusions*: AMD may induce different thyroid dysfunctions, with various severities (sub clinical or clinical forms). Among euthyroid patients, there are some with thyroid morphological and immunological abnormalities, considered "risk cases" for possible future thyroid dysfunctions.*

All AMD-treated cases should be screened for thyroid dysfunctions before the drug introduction and carefully monitored during the treatment.

Keywords: amiodarone, hypothyroidism, thyrotoxicosis

INTRODUCTION

Amiodarone (AMD) is a complex antiarrhythmic agent, widely used in the treatment of cardiac tachyarrhythmias. The drug is an iodinated benzofuranic derivative, with a structural formula similar to that of thyroxine (1).

It contains 37% iodine by weight, equivalent to 75 mg iodine per a tablet of 200 mg. During metabolization, 10% of the molecule is daily deiodinated. The daily maintenance dose is 200-400mg, so that approximately 7-21 mg iodide is available each day, a dose that exceeds the recommendations (2).

In peripheral tissues, AMD inhibits type I 5'-deiodinase activity, which removes an atom of iodine from the outer ring of T_4 to generate T_3 and one from the outer ring of rT3 to produce 3, 3'-diiodothyronine. This inhibition may persist for several months after AMD withdrawal.

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Long-term therapy with AMD may alter the thyroid function tests (3).

AMD affects thyroid hormones metabolism by inhibiting cellular uptake of thyroxine (T_4), hence lowering the availability of intracellular T_4 substrate (this will contribute to the diminishing of T_3 synthesis).

Serum T_4 concentrations are often at the upper limit or above normal range, but serum T_3 levels frequently remain within the low normal range (4).

The changes in serum TSH concentration during AMD administration are related to several mechanisms.

The normal thyroid gland has intrinsic auto regulatory mechanisms, able to handle an iodine overload. Autoregulation results in the maintenance of a normal thyroid secretion, despite wide variations in iodine intake (3,5).

Most of the patients remain euthyroid during AMD treatment, but 15-24% may develop thyroid dysfunctions (hypothyroidism or hyperthyroidism).

The prevalence of AMD-induced thyrotoxicosis (AIT) is higher in patients issued from iodine deficient areas, versus those from iodine-replete areas (14 % vs. 2%) (12,13,25).

AMD-induced hypothyroidism (AIH) occurs more frequently in iodine-sufficient areas: 13-15 % (1, 25), comparative to regions with a low iodine intake: 6% (2,3).

The reported data are more or less concordant, related to the percentage of studied cases, used criteria for AMD-induced dysfunctions and other factors.

The aim of this study is to evaluate of the incidence and types of thyroid dysfunctions induced by AMD therapy. In the same time we tried to accomplish an algorithm for the follow up of treated subjects and to perform some considerations regarding the treatment of AMD-induced abnormalities. ❑

MATERIAL AND METHODS

The study group included 85 patients (44 females and 41 males), issued from an iodine-replete area (median urinary iodine excretion >100ìg/24 h), treated with AMD for different ventricular or supraventricular arrhythmias. The age of the subjects ranged from 43 to 79 years; the mean age for the entire group (mean ± SD) was 63.16± 10.92 years.

The indications for AMD therapy were represented by: supraventricular tachycardias (59 patients, 69.4%), ventricular tachyarrhythmias (10 patients, 11.7%) and other cardiac disorders (16 cases, 18.9%).

The drug was orally administered for different periods of time (4 up to 60 months). Before the treatment the patients were clinically, hormonally and sonographically evaluated for a possible thyroidal involvement.

During treatment, TSH was determined at 1, 3 months and thereafter at 6 months. Depending on clinical picture and TSH levels, the patients were selectively investigated, by determination of peripheral thyroid hormones, CFDS, antithyroid auto antibodies (AT Abs): anti peroxidase antibodies- (TPO-Abs) and anti thyroglobulin antibodies (Tg -Abs). Serum TSH, free T_3, free T_4 was measured using chemiluminescence assay and AT Abs were determined by ELISA technique.

The study group was divided into three major subgroups, depending on the thyroid function during AMD therapy.

The diagnosis of thyrotoxicosis was established on clinical futures and hormonal picture. For the classification of AIT type we used clinical examination (anamnesis, signs) thyroid sonography, CFDS, the concentrations of TPO Abs.

The diagnosis of hypothyroidism was confirmed by clinical examination, hormonal picture, thyroid sonography, and AT Abs titers.

The statistical analyses were performed using Student's t-test. All values were expressed using mean± standard deviation (SD) or median. p values =0.05 were considered statistically significant. ❑

RESULTS

The parameters of the studied groups are presented in Table 1.

Most of the patients remained euthyroid during AMD treatment: 52 (60.9%). Thirty three subjects (39.1%) developed thyroid dysfunctions: 13 hypothyroidism -15.6%, (9 sub clinical and 4 clinical) and 20 thyrotoxicosis -23.5% (2 subclinical and 18 clinical) (Figure 1).

Parameter	A. Patients with euthyroidism	B. Patients with AIH	C. Patients with AIT	p value		
				AvB	BvC	AvC
Female/male ratio	24/28	11/2	8/12			
Age (mean± SD) (years)	63.16 ±10.92	64.84 ±5.63	57.40 ±6.61	0.59	0.02	0.03
Duration of AMD therapy (months) (median values)	19	18	24	0.26	0.20	0.50
Cumulative dose (g) (median values)	132	126	141	0.60	0.40	0.45

TABLE 1. Parameters of the study subgroups

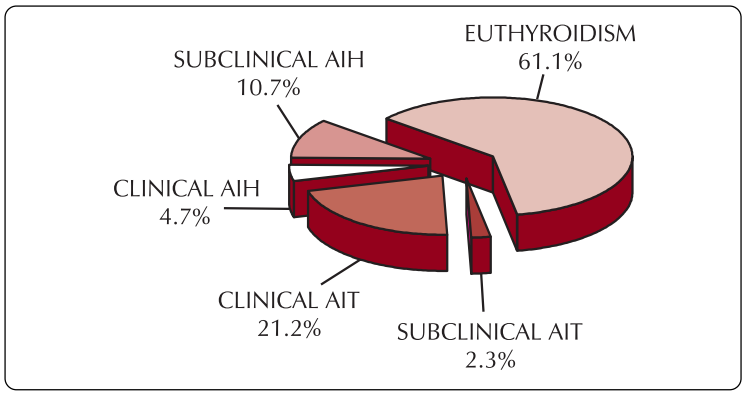

FIGURE 1. Thyroid dysfunctions induced by AMD in the study group

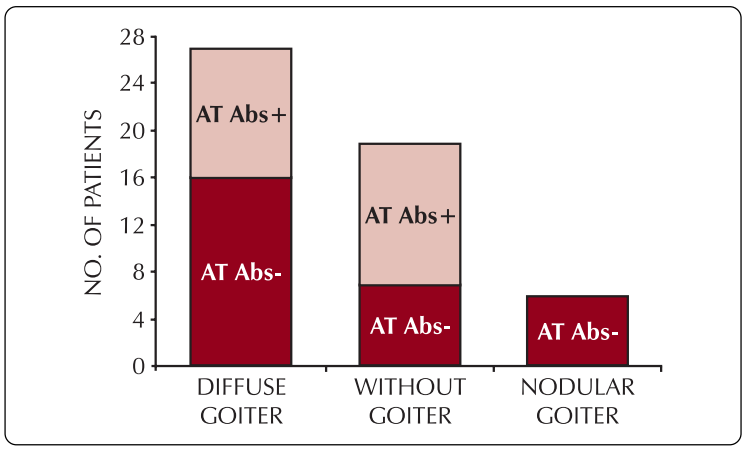

FIGURE 2. Thyroid parameters in euthyroid patients

In the euthyroid group, 19 patients had normal thyroid volumes, 27 patients presented diffuse goiters, and 6 nodular goiters.

Among the patients with diffuse goiters (27 subjects), 20 had significantly increased titers of AT Abs (especially TPO-Abs). 12/19 patients with normal thyroid volumes, showed increased titers of AT Abs.

The goiter (diffuse or nodular) and/or the presence of AT Abs were considered risk factors for future thyroid dysfunction (Figure 2).

For certainty of a normal thyroid function in AMD-treated cases, a complete evaluation of thyroid functional parameters is necessary (see Table 2).

Serum T_3 levels seem not to be a reliable parameter, because T_3 could decrease even in euthyroid patients (10,11).

The statistical analysis of the studied groups is presented in Table 1.

The median values of cumulative dose did not differ significantly between patients' subgroups. Thyrotoxicosis developed later comparative to hypothyroidism (after approximately 24 months).

The peculiarities of our cases with AIT are presented in Table 3.

Parameter	Untreated subjects	Euthyroid subjects AMD- treated
FT_4 (pmol/l)	11-20	12-24.7
TT_3 (nmol/l)	1.3-3	1-2.3
FT_3 (pmol/l)	3.5-6	2.5-5.1
TSH (mU/l)	0.35-4.3	0.35-4.3

TABLE 2. Reference values for serum thyroid hormones and TSH in euthyroid untreated subjects and in euthyroid patients receiving long-term AMD-therapy (Martino et al, 2001)

Parameter	Type I AIT (patients)	Type II AIT (patients)	Mixed forms (patients)
I. Clinical and laboratory data			
1. Nodular goiter	2	–	–
2. Hypoechoic diffuse goiter			
With AT Abs	5	–	–
Without AT Abs	–	–	2
3. Hypoechoic normal volume thyroid			
With AT Abs	1	1	2
Without AT Abs	–	2	3
4. CDFS (performed in 14 patients)	8 had marked hypervascularity	3 showed absent vascularity	3 had mild hypervascularity
II. Response to therapy			
1. Antithyroid drugs	8	–	3
2. Antithyroid drugs+ corticotherapy	–	3	4
Final classification	**8**	**3**	**7**

TABLE 3. Classification of clinical forms of AIT

Sixteen of these patients with clinical AIT presented new recurrences of supraventricular arrhythmias (atrial fibrillation, atrial flutter) with weight loss, sweating and tremor, while two had only mild tachycardia, weight loss and tremor.

Among the patients with type I AIT, ultrasonographic examination of the thyroid showed nodular goiter in 2 cases, hypoechoic goiter in 7 cases and one case with thyroid normal volume, but with positive AT Abs (TPO-Abs), suggestive for Graves' disease.

In all thyrotoxic patients, AMD was replaced with other antiarrhytmic drugs; after remission of thyrotoxic state, AMD was not re-introduced.

The treatment of AIT is complex and difficult, depending on the type of AIT. The main therapeutic strategies include: thionamides, potassium perclorate in type I, steroids in type II and combined therapies in mixed forms (20, 21,22,23).

Some authors consider that a differentiation between the two types of AIT does not influence the management or outcome (24). ❑

DISCUSSIONS

AIT may develop during AMD-therapy or even several years after AMD withdrawal. There are no parameters for predicting the occurrence of AIT. The pathogenesis is complex and not completely understood (14).

AIT may occur in a gland with preexisting abnormalities (type I AIT) or in a normal thyroid gland (type II). Type I is due to an increased thyroid hormones synthesis, as a consequence of a massive iodine load from the drug (15).

Classical picture of thyrotoxicosis may be absent, due to the antiadrenergic action of AMD, which also diminishes the T_4 conversion to T_3. The diagnosis should be suspected in patients with previous good response to AMD, who present a worsening of the underlying cardiac disorder (tachyarrhythmia or angina).

Suppressed TSH levels and high free T_3 confirm the diagnosis (6, 7, 8).

In type II AIT, the patients have no thyroid abnormalities. AMD induces a destructive thyroiditis with leakage of preformed thyroid hormones from the damaged thyroid follicles. Often the features of type I and II may coexist, leading to mixed forms (14, 16).

The two main types can be distinguished by clinical, laboratory and imaging data, including: thyroid sonography, color flow Doppler sonography (CFDS), serum antithyroid auto antibodies (AT Abs), serum interleukin-6 (IL-6), thyroid radioactive iodine uptake (RAIU) (1,17,18,19) (Table 4).

Despite of these diagnostic criteria, many cases of AIT escape a clear-cut classification.

In our study, type I AIT patients were treated with thionamides to block thyroid hormone synthesis. We applied a step-wise approach in type II and mixed forms, starting with thionamides and adding glucocorticoids for no responders.

In our study, thyroid function in type I AIT patients normalized faster comparing to those

Parameter	Type I AIT		Type II AIT
	Toxic nodular goiter	Graves' disease	
Thyroid before AMD- treatement	Nodular goiter	Latent Graves' disease	Normal
Clinical examination	Nodular goiter	Normal size or diffuse goiter	Normal size or diffuse goiter
Thyroid sonography	Nodule(s)	Diffuse goiter	Diffuse goiter with heterogeneous aspect
CFDS	Normal or increased vascularity	Normal or increased vascularity	Absent vascularity
Antithyroid autoantibodies	Absent	Often present (in high titers)	Usually absent
Serum IL-6	Normal or slightly increased	Normal or slightly increased	Markedly increased
RAIU	Low/normal/ increased	Low/normal/ increased	Suppresed

TABLE 4. Classification of AIT (derived from Martino E. et al, 2001).

with type II and mixed forms. Some authors report a self limiting evolution of type I AIT, considering as an entity with a milder outcome (3,4).

The patients with sub clinical AIT continued AMD-treatment, with close monitoring, without any additional side effects.

The clinical features of AIH patients were subtle, the patients presenting mainly lethargy, cold intolerance, and dry skin.

The mean values of TSH in symptomatic patients were significantly higher comparative to subclinical forms (72.4 ± 12.69 mIU/ml, vs. 11.1±6.45 mIU/ml, $p<0.01$).

Nine patients with hypothyroidism presented high titers of antithyroid antibodies TPO (3 patients with clinical and 6 with subclinical form), before initializing the AMD therapy. This aspect suggests a previous chronic autoimmune thyroiditis (Figure 3).

There were no cases with de novo AT Abs detected during AMD treatment.

AMD treatment was not interrupted in these patients and thyroxine was commenced in clinical AIH. Subclinical hypothyroid cases were monitored every 4 months and no treatment with thyroxine was added.

AIH may develop both in subjects with apparently normal thyroid glands and in those with preexisting thyroid abnormalities. Hypothyroidism develops earlier than hyperthyroidism, generally in the first 12-18 months of therapy (3). The risk factors are represented by the presence of AT Abs, a slight increase of TSH levels before AMD therapy, female sex and elderly age. The risk seems to be independent of the daily or cumulative dose of AMD.

The clinical picture resembles to that of primary hypothyroidism. An elevated serum TSH with low levels of T_4 confirms the diagnosis (2).

Chronic autoimmune thyroiditis (CAT) is an important risk factor for the occurrence of AIH. The pathogenic mechanism of AIH is represented by the inability of thyroid gland (damaged by preexisting CAT) to maintain normal thyroid hormone synthesis after an iodine load (9).

Patients taking AMD treatment should be monitored every 6 months for thyroid function (TSH, FT_3, FT_4, and ultrasonography).

An algorithm for monitoring the patients is presented in fig.4 (modified after Martino et al, 2001) (1,16,25,26). ❑

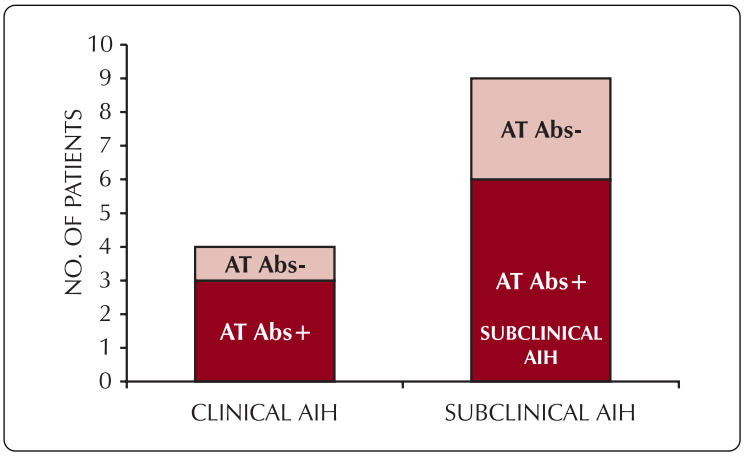

FIGURE 3. Severity and AT Abs incidence in AIH forms

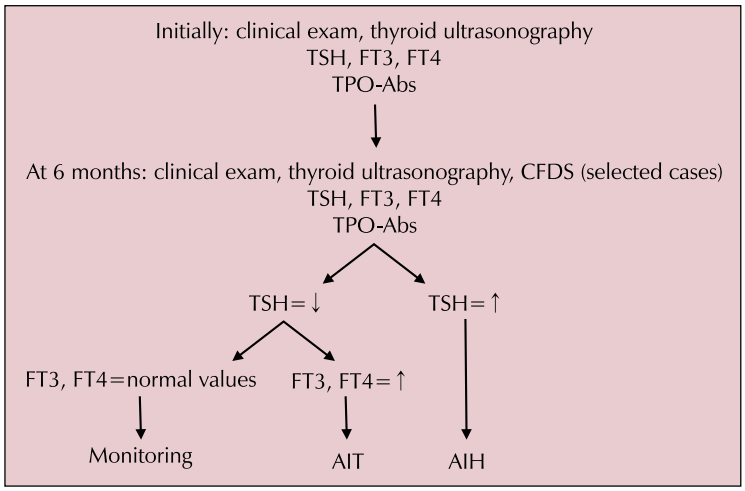

FIGURE 4. Algorithm for monitoring the patients under AMD treatment

CONCLUSION

1. From 85 cases treated with AMD, most of them remained euthyroid: 60.9%. A percent of 30.1% presented clinical and subclinical thyroid dysfunctions: 15.6% of patients developed hypothyroidism and 23.3% thyrotoxicosis. Our results indicate a higher rate of thyroid disturbances in the study group, compared to those published by other authors.
2. The monitoring of thyroid function during AMD-therapy was performed initially at 3 months and thereafter at 6 months and included: clinical examination (endocrinological and cardiological), thyroid sonography and thyroid hormonal parameters.
3. Our cases of AIT were dominated by type I, followed by mixed forms and type. AMD-induced thyrotoxicosis presented as recurrent tachyarrhythmia and seldom with classical clinical picture.
4. Among AIH cases, 9 (69.2%) showed significantly increased titers of AT Abs. There were no patients with de novo AT Abs detected during AMD treatment.
5. Euthyroid subjects presenting morphological and immunological thyroid abnormalities (27 subjects with diffuse goiter and 12 with high titers of AT Abs) were considered "risk cases" for future thyroid dysfunction.

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