Amiodarone treatment and thyroid autoimmunity markers

Abstract

Autoimmune diseases of the thyroid gland (ADTG), which include, Graves' disease, Hashimoto thyroiditis, primary hypothyroidism with atrophic thyroiditis, postpartum thyroiditis and 'silent' thyroiditis, are characterized by the presence of serum thyroid autoantibodies (TAB). Thyroid autoantibodies are not rare even in the general population of all ages, and their presence in women is 5 times more than in men. *The aim* of our study was to define the prevalence of TAB in patients on chronic treatment with amiodarone (AMD), an antiarrhythmic drug rich in iodine, with a potential cytotoxic effect. *We have used a section study* during a period of two years. Ninety six consecutive patients under AMD treatment were studied, 55 men and 41 women (mean age 62.2 years, range 26-82 years) who referred to us to study their thyroid function. *Our results* showed that antithyroid antibodies in patients under AMD treatment, with or without thyroid dysfunction, were in similar concentrations as in the general population. A statistically significant greater frequency of increased thyroid peroxidase antibodies (TPOAb) was present in female patients under AMD treatment as compared to men under AMD. In addition, when AMD treatment lasted for longer than 2 years, positive TPOAb were statistically of greater frequency than when treatment lasted for less than 2 years.

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Introduction

Autoimmune diseases of the thyroid gland (ADTG) - Graves' disease, Hashimoto thyroiditis, primary hypothyroidism with atrophic thyroiditis, postpartum thyroiditis and "silent" thyroiditis are characterized by the presence of thyroid autoantibodies (TAB) in the serum of these patients. TAB are polyclonal antibodies of different subclasses of IgG, targeted against the antigen of thyroid peroxidase ("microsomic antigen") or against thyroglobulin (Tg) or against the receptor for thyroid stimulating hormone (TSH). Thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) indicate a secondary response to thyroid injury and do not themselves cause autoimmune disease. They represent a marker of autoimmune thyroid damage. Antibodies targeted against the TSH receptor (TRAb) have mainly an agonistic receptor effect. They act as thyrostimulants causing autoimmune hyperthyroidism as in Graves' disease [1, 2].

In ADTG, thyroid gland itself is a place of TAB secreted by the B lymphocytes, infiltrating the gland and other extra thyroid tissues [2]. The level of TPOAb and TgAb correlates with the extent of lymphocyte infiltration of the gland and with the level of thyroidal damage. TAB are more often found in patients with non-ADTG such as in sporadic goiter, in multinodular and single nodular goiter and in thyroid cancer, than in the general population, and may be associated to thyroiditis often found in these cases [1]. A low titer of TAB can be transient during subacute thyroiditis [1]. In the general population, TAB are five times more often in women than in men [1].

The presence of TAB in healthy relatives of patients with ADTG is a significant risk for acquiring themselves ADTG and indicates that there may be a hereditary factor implemented in the production of TAB. Table 1 shows the prevalence of detectable TAB in the general population, in pregnant women, in ADTG patients' relatives, in ADTG and in insulin dependant diabetes mellitus [1].

Table 1. *TAB prevalence in the general population, ADTG, patients' relatives, in IDDM patients and in pregnant women [1].*

Prevalence	TRAb %	TgAb %	TPOAb %
General population	0	5-20	8-27
Graves' disease	80-95	50-70	50-80
Autoimmune thyroiditis	10-20	80-90	90-100
Patients' cousins	0	40-50	40-50
Patients with IDDM	0	40	40
Pregnant women	0	14	14

TAB: thyroid antibodies, TRAb: TSH receptor's antibodies, TgAb: thyroglobulin antibodies, TPOAb: thyroid peroxidase antibodies, IDDM: insulin dependent diabetes mellitus

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Amiodarone (AMD) is a derivative of benzofuran containing two atoms of iodine per molecule, i.e. 37.2% of its molecular weight. In a 200 mg capsule of AMD, there are approximately 75 mg of organic bound iodine. Between 8% and 17% of iodine from AMD is released in the circulation as inorganic iodine, which means that 3 mg of inorganic iodine are released from 100 mg of AMD [3].

AMD is an antiarrythmic drug known as a potential cause of thyroid dysfunction in patients on chronic treatment – AMD induced thyrotoxicosis (AIT) type 1 and type 2, AMD induced hypothyroidism (AIH) and subclinical hypothyroidism and hyperthyroidism. Its role in ADTG is controversial, mainly because of the retrospective nature of many published studies [3-18]. According to many studies, AMD itself does not induce thyroid autoimmunity de novo [19-21], although both AMD and iodine could contribute to the progress of ADTG because they have a direct cytotoxic effect on the gland, leading to greater release of thyroid antigens. Since the effect of AMD on thyroid autoimmunity is a matter of disagreement, as to whether it induces thyroid autoimmunity at all, or the duration of AMD treatment is associated with the appearance in the serum of TAB [4-22].

The aim of our study was to define the prevalence of TAB in patients under chronic treatment with AMD.

Patients and methods

Using a section study, 96 consecutive patients receiving sufficient iodine supply from iodinated salt [23], were studied retrospectively for two years (2004-2005). There were 55 men and 41 women, referred to us for thyroid dysfunction screening, because of AMD treatment. Table 2A), and B) shows the characteristics of the investigated patients according to age, sex, the average AMD treatment duration, and their thyroid status related to the duration of AMD treatment. The average age of these patients was 62.2 years (range 26-82 years). The average duration of AMD treatment was 31.88 months (range 15 days to 180 months). Patients' history and clinical examination data were studied. Clinical examination included measuring pulse rate and body weight, identifying dry or moist skin, hands tremor, and the presence of goiter. Laboratory tests studied were: ultra sensitive serum TSH, free thyroid hormone, thyroxine (FT_4) and triiodothyronine (FT_3), serum TgAb, TPOAb and TRAb. FT_4 was tested by luminoimmunoassay (LIA, FT4 Brahms Diagnostica, GMBH, Germany) and FT_3 by DELFIA (DELFIA FT3, Wallac Oy, Turku, Finland). The range of normal values for FT_4 was 10-25 pmol/L and 4.6 -7.8 pmol/L for FT3. TSH was measured by ultra sensitive immunoluminometric assay (ILMA, Brahms Diagnostica, GMBH Germany) (range of 0.3-4 mIU/L). Subclinical hypothyroidism was defined as the presence of serum TSH higher than 4 mIU/L and normal values of the free fractions of thyroid hormones. Subclinical hyperthyroidism was defined as the state of normal free fractions of thyroid hormones and suppressed TSH, of less than 0.1 mIU/l. TgAb and TPOAb were measured by luminoimmuno assay (LIA) by

Table 2. *Description of the patients according to A) age and AMD treatment duration related to sex, and B) AMD treatment duration related to thyroid status.*

A.

Patients	M	Fem	All
	55	41	96
Age (y)	M	Fem	all
Average	62.96	61.17	62.2
Min	26	34	26
Max	82	81	82
SD	10.6	9.9	10.33
Duration of AMD Tr (m)	Males	Females	All
Average	28.82	35.99	31.88
Min	3	0.5	0.5
Max	168	180	180
SD	32.67	42.62	37.2
Median	24	24	24

B.

Duration of AMD Tr (m)	EU	AIH	AIT	Sc Hypo	Sc Hyper
Average	29.27	46.8	16.8	44.35	26.6
Min	1	6	12	0.5	7
Max	180	120	24	180	60
SD	35.89	36.30	6.57	56.28	20.8
Median	24	42	12	23	24

Tr: treatment Fem: female, y: years, m: months, SD: standard deviation, EU: euthyroid, AIT: AMD induced thyrotoxicosis, AIH: AMD induced hypothyroidism, Sc Hyper: subclinical hyperthyroidism, Sc Hypo: subclinical hypothyroidism

Brahms Diagnostica, GMBH, Germany with a normal range of less than 60 IU/mL and TRAb were measured by luminoreceptor assay and by radioreceptor assay (LRA-LIA and RRA-RIA, TRAK human, Brahms Diagnostica, GMBH, Germany) with normal values up to 1 IU/L. Thyroid planar scintiscans were performed 15-20 min after the intravenous administration of 74-111 MBq of $^{99m}TcO_4^-$ using one-headed Siemens Diacam gamma camera, Germany and high resolution parallel hole collimator.

The age of the patients and the duration of AMD treatment are shown in Table 2 as medium value ± SD or median (Me) for values whose variation coefficient was higher by 30%. The difference between Me was analyzed by a Me test. X^2-independence test was used to analyze the significance of difference in the frequency of events, which are of interest among certain groups of patients.

Results

After 3 to 180 months of AMD treatment, 66/96 subjects studied remained euthyroid, 15/96 had clinical thyroid disease and 15/96 had subclinical thyroid hypothyroidism or hyperthyroidism (Fig. 1). The prevalence of increased TAB related to patient's thyroid status and to the duration of AMD treatment, is shown in Table 3.

TgAb were measured in 65 patients and were increased in 6/65 patients, 4 women and 2 men. Four of these 6 patients

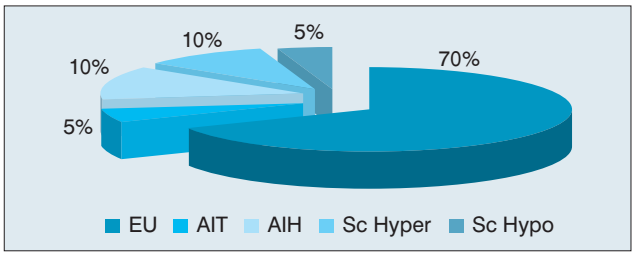

Figure 1. Functional thyroid status in AMD treated patients at the time of investigation

were euthyroid and 2 had AIH. Eighteen patients, out of the 59/65 with a normal level of TgAb, had AMD induced thyroid dysfunction: 4 with AIH, 4 with AIT, 2 with subclinical hyperthyroidism and 8 with subclinical hypothyroidism. All patients with subclinical dysfunctions and AIH were asymptomatic, while patients with AIT were oligosymptomatic, with mild tachycardia or worsening of arrhythmia as the only symptoms. There was not any statistically significant difference in the frequency of the increased level of TgAb in patients under AMD treatment regarding thyroid status, sex and the duration of AMD treatment as shown in Table 4.

TPOAb were measured in 48/96 patients. In 7/48, 6 women and 1 man, they were increased. Four patients, out of these 7, all women, had: asymptomatic AIH (3) or subclinical hypothyroidism (1). Thirty patients out of the 41 with normal levels of TPOAb, were euthyroid (73%) and the rest 11 (27%) had thyroid dysfunction: 4 AIH, 1 AIT, 3 subclinical hyperthyroidism and 3 subclinical hypothyroidism. There was not any statistically significant difference in the frequency of the increased level of TPOAb in regard to thyroid status in patients under AMD treatment. Serum levels or TPOAb were significantly higher in women after AMD. In addition AMD treatment for longer than 24 months, induced a smaller increase of TPOAb (Table 5).

TRAb were measured in 78/96 patients, 53 euthyroid and 25 with thyroid dysfunction. Only 5 men had AIT type 2, i.e. a type of destructive thyroiditis with thyrotoxicosis similar to that of subacute thyroiditis, except lack of neck pain. In all patients 78/96, TRAb was normal, except one. This one patient had mildly increased TRAb (2.5 IU/ml), was euthyroid and was treated with AMD for 6 months.

Out of 25 patients who were tested for both TgAb and TPOAb, only one woman had both antibodies increased and had AIH, while another woman had AIH and only TPOAb increased. Two euthyroid patients, a man and a woman had only TgAb increased.

Discussion

It has been reported that correction of iodopenia in areas with a low iodine diet was linked with increased incidence of A-DTG. On the other hand, increased iodine intake in healthy individuals living in non-iodopenic areas, rarely causes thyroid dysfunction [9]. Iodination of Tg has been known to increase its immunopathogenicity in experimental animals presumably through the formation of iodine-containing neoantigenic determinants that can elicit an autoimmune response [18, 24-26].

Our patients who lived in an area of sufficient iodine supply, during chronic AMD treatment had an incidence of 5% of AIT, 10% of AIH and 15% of transient subclinical hyper or hypothyroidism, while 70% remained euthyroid.

It was reported that patients with increased serum TPOAb before starting AMD treatment who during treatment with AMD developed hypothyroidism, had further increase in TPOAb [4]. We did not measure basal serum TPOAb or TgAb, before starting AMD treatment. Another study showed that after 30 days of AMD treatment, 55% of the patients de-

Table 3. *Prevalence of increased level of TAB among patients according to their thyroid status, during AMD treatment.*

Thyroid status	EU	AIT	AIH	Sc TD
AMD Tr (m) average	27.2	15.6	41.1	38.4
AMD Tr (m) median	21	12	36	24
TgAb +	9%	0%	25%	0%
TPOAb +	9%	0%	30%	14%
TRAb +	2%	0%	0%	0%

EU: eythyroid status, AIT: AMD induced thyrotoxicosis AIH: AMD induced hypothyroidism, Sc TD: subclinical thyroid dysfunction; Tr: treatment; m: months.

Table 4. *Statistical differences in frequency of increased TgAb according to thyroid status, sex and the duration of AMD treatment.*

TgAb	C_2	Statistical difference	P
Thyroid status	0.1	NS	0.01
Sex	1.34	NS	0.01
Duration of AMD Th	1.51	NS	0.01

Tr: treatment, NS: statistically not significant, P: level of relevance.

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Sex	1.34	NS	0.01
Duration of AMD Th	1.51	NS	0.01

Tr: treatment, NS: statistically not significant, P: level of relevance.

Table 5. *Statistical differences in frequency of increased TPOAb according to thyroid status, sex and the duration of AMD treatment.*

TPOAb	C_2	Statistical difference	P
Thyroid status	1.07	NS	0.01
Sex	7.3	SS	<0.01
Duration of AMD	4.51	SS	<0.05

Tr: treatment, NS: statistically not significant, SS: statistically significant, P: level of relevance.

veloped TPOAb, while none in the placebo group did. Six months after AMD withdrawal these antibodies returned to normal [7]. Others found transiently positive TRAb with no thyroid hormone releasing activity in cultured human thyroid follicles in patient who have developed thyrotoxicosis of subacute onset after 48 months of AMD treatment [8]. In another study, there was no statistical increase of TAB after a short-term or a chronic AMD treatment as compared to the control group [9].

Most of other studies indicate that thyroid antibodies are not likely to appear in patients under AMD treatment if not present before [10-11, 18-22]. In some susceptible individuals, AMD can contribute to or can aggravate previously existing organ specific autoimmunity [24]. This result especially important in AIH where most of the patients have circulating autoantibodies before treatment with AMD [12, 25-28]. We do not know the levels of TAB in our patients before starting AMD treatment. This may be important because in patients with asymptomatic underlying thyroid autoimmunity we could predict the risk of AIH since the excess iodine from AMD could precipitate existing iodine organification defect and lead to hypothyroidism. However, we have noticed that the prevalence of TgAb and TPOAb during AMD treatment was similar to that reported for the general population, between 9% and 15%. This indicates that AMD itself does not de novo induce TAB.

As we mentioned earlier, 2/6 and 3/7 of our patients with AIH had increased TgAb and increased TPOAb, respectively. We could assume that in these patients TAB were already present developing hypothyroidism during AMD treatment, as was reported by others [25-28].

We found that women on AMD treatment had a higher frequency of increased TPOAb, which is in accordance with the known higher frequency of autoimmune thyroid disorders in women [23]. We have also noticed that treatment with AMD for longer than 2 years contributes to a greater probability of having positive TPOAb (Table 5). Although the numbers of our patients are few, it seems that TROAb is more often increased than TgAb, suggesting a greater specificity of TROAb than TgAb.

In addition to the in vitro tests, especially the radioreceptor assay for TRAb, thyroid scintiscans are important for the differential diagnosis between AIT type 1 and 2. We have found preserved activity or increased thyroid uptake of pertechnetate in a female patient with AIT type 1, with underlying autoimmunity of Grave's disease and in a male patient with AIT type 1 with underlying single autonomous nodular goiter, (Fig. 2A and 3) [29-30]. It was shown that, despite iodine overload caused by AMD treatment, in this two cases of AIT type 1, autonomously stimulated thyroid gland, the thyroid can accumulate ^{99m}Tc-pertechetate. Contrary, in AIT type 2, as shown in Figure 2B, the thyroid is blocked (no accumulation of pertechnetate) due to destructive thyroiditis caused by cytotoxicity of AMD itself and excess iodine. According to these findings, in an area of sufficient iodine supply, thyroid scintiscan, as an in vivo method, could support diagnosis between AIT type 1 and AIT type 2.

Figure 2. ^{99m}Tc-pertechnetate scintiscans in two patients with AIT. A. Female patient with AMD induced Graves' disease (AIT type 1) and B. Male patient with AIT type 2 and "blocked" thyroid.

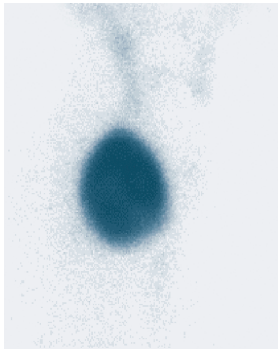

Figure 3. Single nodular toxic goiter in a 61 year old male patient presenting with thyrotoxic symptoms and sings one year after beginning of AMD treatment, with elevated free fractions of thyroid hormones and suppressed TSH (FT4=32.7 pmol/L, FT3=11.5 pmol/L, TSH=0.01 m IU/L), successfully treated with radioiodine after withdrawal of AMD treatment.

In conclusion, the prevalence of TAB in patients with sufficient iodine intake under AMD treatment was similar to that of the general population. Among AMD treated patients, women and those with treatment longer than 2 years had greater frequency of positive TPOAb, which could present greater risk of developing thyroid dysfunction during AMD treatment.

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CT scans may cause electronic medical devices to malfunction

FDA warns in a public health notification (free)

The agency says it has received a "small number of reports" involving interference with devices such as pacemakers, defibrillators, neurostimulators, and implantable and external infusion pumps. Adverse events include accidental stimuli from neurostimulators, malfunctions of insulin infusion pumps, and temporary changes in pacemaker pulse rates. No patient deaths have been reported.

The agency notes that the increase in reported events may be due to greater use of CT scans, higher radiation doses emitted by newer CT machines, more patients wearing medical devices, or improved reporting systems.