Original Article

Thyroid Dysfunction and Cardiological Management in Patients Receiving Amiodarone

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Objective

To determine the prevalence of thyroid dysfunction in patients receiving amiodarone, and the possible associated factors. The study also aimed at assessing the effect of amiodarone on thyroid function through the application of a questionnaire to cardiologists.

Method

Fifty-six patients chronically (> 3 months) receiving amiodarone were assessed by measurement of their serum levels of TSH, free T4, total T3, and anti-TPO antibodies. Patients with changes in TSH levels were defined as having thyroid dysfunction (TD).

Results

The prevalence of thyroid dysfunction was 33.9%. No difference was observed between this group and that of patients with no dysfunction, except for the greater prevalence of anti-TPO positivity in patients with TD (P=0.02). Subclinical hypothyroidism was diagnosed in 10 (17.9%) patients and clinical hypothyroidism in 6 (10.7%). The prevalence of subclinical hyperthyroidism was 3.6% and that of clinical hyperthyroidism was 1.8%. Anti-TPO antibodies were positive in 5 (8%) patients (of whom, 4 had thyroid dysfunction). When compared with patients negative for anti-TPO antibodies, that group had a greater prevalence of dysfunction (80% vs 29.4%; P=0.04). Only 49.2% of the cardiologists routinely treated their patients' thyroid function, and the prevalence of the referred dysfunction for most of them ranged from 1 to 10%.

Conclusion

The prevalence of thyroid dysfunction in our population was high, showing the need for implementing a laboratory routine. The cardiologists disagreed greatly in regard to the type of follow-up required for patients using amiodarone.

Key words

amiodarone, thyroid dysfunction, hypothyroidism

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Amiodarone has a chemical structure similar to that of thyroid hormones [1]. At usual doses (200-600 mg/day), amiodarone releases 6 to 12 mg/day of iodide, which is much higher than the level recommended by the World Health Organization (0.15 to 0.3 mg/day) [2]. In addition to iodine overload, amiodarone may also cause thyroid dysfunction by other mechanisms, such as inhibition of the peripheral conversion of T4 into T3, which is an antagonistic activity to the action of T3 in its receptor [2], autoimmune reaction [3], and direct toxic action of desthylamiodarone (DEA), which is the major active metabolite of amiodarone [4]. The most common laboratory changes are the increase in the total and free T4 and reverse T3 levels, and the reduction in the total and free T3 levels. The TSH levels may be slightly increased initially, tending towards normality with chronic use (> 3 months) of the drug [5] (tab. I).

The incidence of thyroid dysfunction ranges from 2 to 24% and may occur from the beginning of the treatment up to 3 years after suspending the drug. The development of hypothyroidism is greater in the areas where iodine ingestion is not deficient, while, in the areas of iodine deficiency, thyrotoxicosis prevails [6-9]. Some factors, such as familial history of thyroid disease, presence of antithyroid antibodies, and elevated baseline TSH levels may be associated with clinical thyroid dysfunction [10].

Even knowing the effects of amiodarone on thyroid function, many physicians do not perform appropriate monitoring. A recent study[11] with 39 cardiologists showed that only 37% of those who prescribed amiodarone requested hormone measurements prior to the prescription, and only 10% sought for a marker of autoimmunity.

The major objective of this study was to determine the unknown prevalence of thyroid dysfunction in patients receiving amiodarone. We also analyzed the possible factors associated with the development of thyroid dysfunction.

Method

A prospective study was carried out to assess patients chronically (> 3 months) receiving amiodarone, independent of the dose used. The parameters studied were as follows: age; sex; goiter on palpation; presence of previous thyroid disease (thyroiditis, nodule, hypothyroidism or hyperthyroidism); and autoimmune disease (previous or present). In addition to the daily dose, the total dose of amiodarone since the beginning of the treatment was calculated. The following serum measurements were taken: anti-TPO antibodies (RV: < 35 IU); free T4 (RV: 0.8 - 1.9 ng/dL); total T3 (RV: 82 - 179 ng/dL); and TSH (RV: 0.4 - 4.0 μUI/mL). The project was approved by the committee on ethics in research of the Clementino Fraga Filho Hospital of the medical school of the Federal University of Rio de Janeiro (UFRJ).

Table I - Effects of amiodarone on euthyroid patients

Test	Treatment lenght < 3 months	Treatment lenght > 3 months
T4	Transitory elevation	The level may be in the upper limit of normality or slightly above the reference value
T3	Reduced	The level may be in the lower limit of normality or below the reference value
TSH	Elevated	Normal
rT3	Elevated	Elevated

The following patients were excluded from the study: patients receiving supra-physiological doses of lithium or glycocorticoids; patients with chronic renal failure; and individuals who had already been diagnosed with hypo- or hyperthyroidism, but lacked reliable information whether the dysfunction appeared before or after starting amiodarone.

All patients with TSH levels out of the reference range values (0.4 - 4.0 µIU/mL), accompanied or not by alterations in the T3, free T4, or anti-TPO levels, or both, and by clinical manifestations were defined as having thyroid dysfunction. Patients with the following characteristics were analyzed separately: subclinical hypothyroidism (TSH > 4.0 and normal free T4); hypothyroidism (TSH > 4.0 and free T4 < 0.8); subclinical hyperthyroidism (TSH < 0.4 and normal free T4); and hyperthyroidism (TSH < 0.4 and free T4 > 1.9).

To assess the role played by amiodarone in thyroid dysfunction, a questionnaire was given to 63 cardiologists, and was immediately collected after completion without identifying the interviewee. The cardiologists were randomly chosen among those present in the service of the university-affiliated Clementino Fraga Filho Hospital (UFRJ) and the Hospital de Cardiologia de Laranjeiras, in the city of Rio de Janeiro, at the moment the researcher delivered the questionnaire.

The statistical analysis was performed using the EPI-INFO (version 6.04) program. Means, standard deviations, and medians were calculated for the continuous variables, and proportions with 95% confidence interval (95% CI) were calculated for the categorical variables. The chi-square test was used for comparing the proportions; the *t* test was used for comparing 2 means, when the variances were homogeneous according to the Bartlett test; and the Kruskal-Wallis test was used for comparing 2 means, when the variances were not homogeneous. The significance level of $P < 0.05$ was adopted.

Results

The study comprised 56 patients [31 (55.4%) females and 25 (44.6%) males] with a mean age of 58.0 ± 14.3 years. On clinical examination, 4 (6%) patients had goiter as follows: 1 patient had hyperthyroidism, 2 had subclinical hypothyroidism, and the other had normal readings for all hormone measurements.

Positivity for anti-TPO antibodies was found in 5 (7.5%) patients as follows: 2 had hypothyroidism, 1 had subclinical hypothyroidism, 1 had subclinical hyperthyroidism, and the other had euthyroidism (tab. II). The frequency of thyroid dysfunction in these patients was greater than that found in patients whose anti-TPO antibody levels were negative (80% vs 29.4%; P=0.04).

Nineteen (33.9%) patients had thyroid dysfunction (TD). No significant difference was found between this group and that of patients without thyroid dysfunction, except for the greater prevalence of anti-TPO antibody positivity in patients with thyroid dysfunction (P = 0.02) (tab. III).

Clinical hypothyroidism was diagnosed in 6 (10.7%) patients, 4 females and 2 males. The number of patients positive for anti-TPO antibodies was also greater in this group than in the euthyroid group (33.3% vs 2.7%; P=0.006). No difference between the 2 groups was observed in regard to age, daily and cumulative dose, and duration of the use of amiodarone.

Ten (17.9%) patients had subclinical hypothyroidism. No statistical difference was observed between these patients and euthyroid patients with regards to sex, age, daily and cumulative dose, length of treatment, and prevalence of positivity for anti-TPO antibodies. Clinical hyperthyroidism was diagnosed in 1 (1.8%) patient, and subclinical hyperthyroidism was diagnosed in 2 (3.6%) patients.

Of the questionnaires analyzed, 39.7% of the physicians prescribed amiodarone frequently (once a week or more), 39.7% of the physicians prescribed amiodarone occasionally (once or twice a month), and 20.6% of the physicians prescribed the drug rarely. The routine laboratory assessment of thyroid function prior to prescribing the antiarrhythmic drug was very heterogeneous among the cardiologists (tab. IV). The most required hormone measurements were TSH (100%), free T4 (74%), and T3 (52%) levels. Only 1 (2%) physician required anti-TPO antibody levels. In addition to hormone measurements, 68% regularly conducted a targeted anamnesis in search for previous thyroid disease, 24% conducted it occasionally, and 8% never asked about it.

After beginning the treatment with amiodarone, 49.2% of the interviewees always monitored their patients' thyroid function, 28.6% monitored it occasionally (some patients), and 20.6% mo-

Table II - Patients positive for anti-TPO

Anti-TPO	TSH	Free T4	Sex	Diagnosis
52,5	0,35	1,7	F	Subclinical hyperthyroidism
35,2	6,81	1,2	M	Subclinical hypothyroidism
37,9	3,34	1,6	F	Euthyroid
39,7	29,3	0,7	F	Clinical hypothyroidism
38,8	26,3	0,4	M	Clinical hypothyroidism

RV - Anti-TPO (< 35 IU); TSH (0.4-4.0 µIU/mL); free T4 (0.8-1.9 ng/dL)

Table III - Characteristics of the patients with and without disfunction (TD)

	(TD) With TD	(TD) Without TD	P value
N	19	37	
Age (years)	57.2 ± 16.4	58.9 ± 13.6	0.18
Sex (F/M)	8/11	23/14	0.25
Anti-TPO*	4 (21.1%)	1 (2.7%)	0.02
Dose (mg/day)	268.2 ± 112.2	225.8 ± 107.7	0.17
Length (months)	30 (4-120)	24 (4-183)	0.66
Total dose (g)	186 (26-960)	141 (30-1.248)	0.57

* Anti-TPO positive = n (%)

nitored thyroid function only in patients with clinical signs of thyroid dysfunction. During follow-up, the most required measurements were TSH (98.4%), free T4 (74.6%), and T3 (41.3%) levels. The anti-TPO antibody measurement was required by 6.3% of the physicians.

Another question analyzed was the management adopted by cardiologists in face of the different cases of thyroid dysfunction. In hypothyroidism, 85.7% of the physicians suspended the medication, and, in hyperthyroidism, 82.4% did. In subclinical dysfunctions, this percentage was 54% and 52.4% in hypothyroidism and hyperthyroidism, respectively.

Most (42.9%) cardiologists interviewed reported that clinical or laboratory thyroid dysfunction, or both, was present in 1 to 10% of the patients using amiodarone (tab. V).

Replacement of the drug by another antiarrhythmic agent was always a problem for 36.5% of the cardiologists, and was a problem only in some cases for 46% of the cardiologists interviewed.

Discussion

Amiodarone is a widely used antiarrhythmic drug, and, despite its well-known side effects, the number of patients chronically using that drug and not investigated for possible complications is high, particularly regarding thyroid status. In medical practice, the frequency of thyroid dysfunction, the diagnostic methods used, and the managements adopted are extremely varied.

Among our patients, the prevalence of laboratory thyroid dysfunction was elevated. It is worth emphasizing that those diagnosed with hypo- or hyperthyroidism were excluded, and, therefore, the prevalence of actual thyroid dysfunction in that population was greater than 33.9%. It was difficult to compare this value with that in the literature, because no definition exists for thyroid dysfunction in patients using amiodarone, which is common in published studies, resulting in a varied prevalence (2 to 24%) [7,12-19]. The fact that our prevalence was similar to that found in some studies assessing patients before and during the use of the drug allows us to believe that a causal association exists between the development of thyroid dysfunction and the use of amiodarone. In addition, our prevalence was much greater than that of the general population, which ranges from 7 to 10%, when only an alteration in the TSH levels is used for diagnosis [20,21]. A study carried out with the staff of the Federal University of Rio de Janeiro found that 7.3% of the sample had an alteration in TSH levels (Reis, 2001).

No difference was observed between patients with and without thyroid dysfunction in regard to sex, age, duration of use and dose of amiodarone, similarly to that which is found in the literature [7,15-17,18,22,23]. Some authors have shown that being female is a risk factor for the development of thyroid dysfunction associated with the use of amiodarone, probably due to the fact that females have a greater risk of developing autoimmune thyroid diseases, such as Hashimoto's thyroiditis and Graves' disease [14,16].

The prevalence of clinical hypothyroidism was 10.7%. Studies on follow-up of patients before and during the use of amiodarone reported an incidence of hypothyroidism ranging from 3.6 to 19.2%. Some authors considered as having amiodarone-induced hypothyroidism patients with only laboratory alterations [14,18,24-26], while others used the association with clinical manifestations of thyroid hypofunction as a diagnostic criterion [7,13,16,27-28]. The prevalence of hypothyroidism in the general population ranged from 0.5 to 2% [29-32].

Only 1 (1.8%) patient was diagnosed with clinical hyperthyroidism. This percentage was similar to that in the literature, and considering other studies with patients using amiodarone carried out in an area with no iodine deficiency, it was lower than the prevalence of clinical hypothyroidism [18,22,27,33]. It is worth emphasizing that the clinical manifestation of these patients may be only the recurrence of an arrhythmia that had already been previously controlled with amiodarone [17].

Subclinical hypothyroidism and hyperthyroidism were diagnosed in 21.5% of the sample. As expected in iodine-sufficient areas, hypothyroidism was more prevalent than hyperthyroidism (17.9% vs 3.6%). The prevalence of subclinical hypothyroidism in the general population as reported in a recent study using diagnostic criteria and reference values equal to those used in our study was 10.8% [34]. Tunbridge et al [35] carried out one of the most important studies on thyroid disorders in the healthy population and defined as having mild hypothyroidism patients with TSH levels above 6.0 IU/mL, finding a prevalence of 5%. Comparing this value with that found in our study using the same cut point (TSH > 6 IU/mL), a significant difference was observed (5% vs 17.9%; P = 0.000073). We concluded that in the population using amiodarone, the prevalence of hypothyroidism may be 3 to 4 times greater.

Some patients with subclinical disease may reverse the scenario spontaneously or with the suspension of amiodarone [25,36-38]. Nevertheless, some patients require treatment for relieving the clinical manifestations or reducing some associated risk factors, such as osteoporosis and atrial fibrillation in the case of hyperthyroidism, or dyslipidemia, myocardial or muscle dysfunction, or both, in patients with subclinical hypothyroidism [29,39-41]. For these reasons, identifying patients with subclinical disease using amiodarone is extremely important.

The prevalence of positivity for anti-TPO antibodies was similar to that in studies assessing the development of antithyroid antibodies in patients using amiodarone [42,43]. The high prevalence of thyroid dysfunction in anti-TPO-positive patients found in our case series (80%) suggests that patients with autoimmune thyroid disease are at a greater risk of developing hypothyroidism [44].

The information on the management adopted by cardiologists regarding the follow-up of thyroid function in patients chronically

Table IV - Assessment of thyroid function prior to amiodarone

	n	%
Always	11	17.5
Only in cases with clinical signs of thyroid dysfunction	39	61.9
Never	13	20.6

Table V - Frequency of thyroid dysfunction according to the physicians

	n	%
1 to 5%	27	42.9
5 to 10%	22	34.9
10 to 20%	9	14.3
20 to 40%	2	3.2
Did not respond	3	4.8

using amiodarone is scarce. We found only 1 study assessing these specialists in regard to the amiodarone versus thyroid function binomial [11], showing the need for implementing a clinical and laboratory routine so that patients with alterations in thyroid function can always be diagnosed and managed in the most appropriate manner.

Most cardiologists interviewed (80%) prescribed amiodarone at least once or twice a month, suggesting that they had theoretical and practical knowledge about the antiarrhythmic drug. Despite this, only 17.5% asked for a laboratory thyroid evaluation before prescribing the drug. This number was lower than that found by Binz et al [11], who showed that 37% of the cardiologists of a private hospital and 100% of those in a university-affiliated hospital required that evaluation. In our study, we did not find this division, because most of the interviewees belonged to both public (university-affiliated hospital) and private services concomitantly. The evaluation of hormones and antibodies before starting the treatment may identify the patients who should be monitored more frequently or may contraindicate the use of the drug, even transitorily (until treating the thyroid disease) in those with dysfunction. Although we did not ask about the indications for using amiodarone, we know that atrial fibrillation is one of them and may be one of the major manifestations of hyperthyroidism, justifying, therefore, the measurement of TSH levels in these patients [45].

Few cardiologists asked their patients whether they had any thyroid disease before starting amiodarone as compared with those found by Binz [11]: 65% vs 95%. Patients with autoimmune thyroid diseases or altered TSH levels are known to be at a greater risk of developing thyrotoxicosis or hypothyroidism induced by amiodarone. In our opinion, all patients should be asked about that fact, because this is a simple, easy, and costless manner to identify a risk factor for a possible complication of the drug.

Most cardiologists reported that in cases of hyper- or hypothyroidism they do not prescribe amiodarone. Hyperthyroidism is an actual contraindication to the use of that drug, which is not the case of hypothyroid patients being properly medicated with thyroid hormones [11]. Based on the questionnaire, we cannot know whether these physicians use another antiarrhythmic agent, or whether they treat the thyroid dysfunction first and introduce amiodarone later.

The number of physicians who reported routinely monitoring thyroid function (49.2%) was lower than that expected. The literature shows that all patients using a drug should be assessed periodically in regard to their thyroid function. The interval recommended between the measurements may range from 3 to 12 months [2,8,10-11,28,36,38,46].

The most cited serum measurements in our questionnaire were TSH (98.4%), free T4 (74.6%), and T3 (41.3%). The search for anti-TPO antibodies was reported by 6.5% of the specialists. There is no consensus in the literature in regard to the laboratory tests for the follow-up of these patients. The measurement of TSH levels seems to be the best test for screening, while the measurement of free T4 and T3 should be reserved for patients with altered TSH levels [47]. The measurement of anti-TPO antibody level helps in the etiological diagnosis of the dysfunction and in the differentiation between type I and type II thyrotoxicosis [48]. Some authors recommend that, in cases of hyperthyroidism (even subclinical), amiodarone should be suspended, and, in cases of hypothyroidism, the patient should continue to use it if they are adequately medicated with levothyroxine [11,26,46].

One of the most interesting questions in the questionnaire was that about the percentage of patients who developed clinical or laboratory thyroid dysfunction according to the individual experience of the physician. Forty-nine cardiologists (77.8%) reported values ranging from 1 to 10%. This frequency was similar to the result obtained by Binz et al [11] (72 to 95% of the cardiologists). The frequency estimated by the specialists, approximately 3 times smaller than that found in our case series (33.9%), was due to their lack of investigation. One factor reinforcing this hypothesis is that only half the interviewees reported performing a routine assessment of thyroid function.

In this study, a high prevalence of unknown thyroid dysfunction was observed in patients using amiodarone. Although these data are already known in the medical literature, many patients have not been investigated for this possible complication. No clinical, laboratory, or epidemiological variables have been found in association with thyroid dysfunction, except for anti-TPO antibody positivity, which reinforces the fact that all individuals using amiodarone should be monitored. A great disagreement was found among cardiologists regarding the best type of follow-up for patients using amiodarone, showing the need for implementing a laboratory routine.

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