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ABSTRACT

Amiodarone, used in the treatment of cardiac arrhythmias, is associated with thyroid dysfunction. No reports exist on its frequency in southern Brazil, nor studies evaluating the usefulness of clinical scores to diagnose thyroid abnormalities in these patients. This study aimed at determining the prevalence of amiodarone-induced thyroid dysfunction in a representative sample from a tertiary center, to study the conditions associated to this dysfunction and to evaluate the reliability of clinical scores of hypo and hyperthyroidism. One hundred ninety-five amiodarone users were submitted to a clinical and laboratory evaluation. Of these, 2.1% were hyperthyroid, 25.1% hypothyroid and 9.2% had only a high T₄. Considering thyroid dysfunction variables researched, thyroid autoimmunity was positively associated (OR 4.8; p= 0.02), and male gender had a trend to a positive association (OR 1.86; p= 0.06). Clinical scores were highly sensitive for hyperthyroidism (100%), but not for hypothyroidism (8%). The low prevalence of amiodarone-induced hypothyroidism suggests that this specific region is iodine-sufficient. All patients receiving chronic amiodarone therapy should be checked for clinical scores for hyperthyroidism and laboratory evaluation should be performed, as a screening for thyroid dysfunction, especially if they are male or have positive microsomal antibodies. (**Arq Bras Endocrinol Metab 2005;49/6:916-922**)

Keywords: Amiodarone; Hyperthyroidism; Hypothyroidism; Thyroid dysfunction; Risk factors

RESUMO

Disfunção Tiroideana Induzida por Amiodarona em Um Centro Terciário do Sul do Brasil.

A amiodarona, usada no tratamento de arritmias cardíacas, está associada com disfunção tiroideana. Não existem relatos sobre sua frequência no sudeste do Brasil e nem estudos avaliando a utilidade de scores clínicos para o diagnóstico de anormalidades tiroideanas nesses pacientes. Este estudo visou determinar a prevalência de disfunções tiroideanas induzidas pela amiodarona numa amostra representativa de um centro terciário, para estudar as condições associadas a esta disfunção e para avaliar a confiabilidade de scores clínicos para hipo e hipertiroidismo. Avaliação clínica e laboratorial foi realizada em 195 pacientes em uso de amiodarona; desses, 2,1% tinha hipertiroidismo, 25,1% hipotiroidismo e 9,2% tinha apenas um T₄ elevado. Considerando as variáveis pesquisadas de disfunção tiroideana, a autoimunidade tiroideana estava associada positivamente (OR 4,8; p= 0,02), e o sexo masculino teve uma tendência para associação positiva (OR 1,86; p= 0,06). Os scores clínicos mostraram-se altamente sensíveis para o hipertiroidismo (100%), mas não para o hipotiroidismo (8%). A baixa prevalência de hipotiroidismo induzido pela amiodarona sugere que esta região geográfica específica seja suficiente em iodo. Todo paciente recebendo terapia crônica com amiodarona deve ser investigado pelos scores clínicos para hipertiroidismo e avaliado laboratorialmente com um *screening* para disfunção tiroideana, especialmente se for do sexo masculino ou tiver anticorpos

anti-microsossomais positivos. (**Arq Bras Endocrinol Metab 2005;49/6:916-922**)

Descritores: Amiodarona; Hipertireoidismo; Hipotireoidismo; Disfunção tireoideana; Fatores de risco

AMIODARONE IS AN IODINE-RICH drug that has been tested in many clinical trials to control cardiac arrhythmias and is now widely used (1). In usual doses, it may generate 6mg iodine a day, much higher than the optimal iodine intake recommended by the World Health Organization, which is 0.15 to 0.3mg/day. These pharmacological doses of iodine may affect thyroid hormone production and secretion (2). Common abnormalities, usually asymptomatic, are increases in serum thyroxine (T_4) and reverse triiodothyronine (rT_3) levels, accompanied by a decrease in serum triiodothyronine (T_3), determined by amiodarone inhibition of type 1 deiodinase (3). Amiodarone-induced thyrotoxicosis (AIT) occurs in 1.4 (4) to 21% (5) of the users. Some patients present a slight transient increase in serum thyrotropin (TSH) in the first months of therapy, and 1.9 (6) to 27% (7) will develop permanent hypothyroidism. This wide range of hypo and hyperthyroidism rates could be related to the variability in the hyper and hypothyroidism criteria, or to the iodine intake of the population studied.

Previous thyroid disease, as well as low iodine intake, predisposes amiodarone users to AIT (8), while positive thyroid antibodies may be predictive of amiodarone-induced hypothyroidism (AIH) (9). Nevertheless, some authors described an increasing incidence of AIT in Japan, where iodine intake is sufficient (10), and others did not find specific risk factors for adverse thyroid effects due to amiodarone (11). Indeed, it was recently shown that amiodarone itself might induce apoptosis in thyroid cells, exerting direct cytotoxicity independent of its iodine content (12).

Recently the importance of symptoms and signs of both hyperthyroidism and hypothyroidism in the diagnosis of thyroid dysfunction has been questioned, since they are non-specific and can be mimicked by other conditions. The development of TSH assays with improved sensitivity has been changing the diagnosis of thyroid dysfunction: subclinical hypo and hyperthyroidism are being diagnosed by the presence of high and low TSH, respectively, associated with normal free thyroid hormone values in asymptomatic individuals (13). None of the studies on amiodarone-associated thyroid dysfunction had evaluated the relationship between clinical and laboratory diagnosis, i.e., whether clinical scores are useful or not to diagnose the usual thyroid abnormalities seen in this patient setting.

The aim of the present study was, therefore, to evaluate thyroid function in patients using amiodarone with several cardiac diseases on an outpatient basis. Furthermore, we studied possible associated variables, which could be predictive of thyroid dysfunction among amiodarone users and the reliability of clinical scores of hypo and hyperthyroidism to reflect laboratory abnormalities in this patient setting.

METHODS

The Institute of Cardiology of Rio Grande do Sul is a tertiary center to which patients are referred from all over the state of Rio Grande do Sul. This state is the southernmost of Brazil bordering on Argentina and Uruguay. Since there is no information concerning the prevalence of thyroid dysfunction in this region, it was assumed as 5% among the population at large and 15% among amiodarone users. Considering that approximately 8% of the patients with an appointment in the outpatient department were amiodarone users, as identified by a pilot study, 160 patients were the number needed for a representative sample of amiodarone users in the outpatient clinic (beta error of 80%).

Patients were selected from the outpatient appointments and asked whether amiodarone was part of their treatment. All patients identified as amiodarone users were included. A questionnaire was given and a clinical examination performed by medical students previously trained by the principal investigator, an endocrinologist. There were no exclusion criteria. Patients were asked about duration of therapy and amiodarone dose, symptoms of hyperthyroidism (exertional dyspnea, palpitations, tiredness, preference for cold, excessive sweating, nervousness, increased appetite and weight lost), and hypothyroidism (diminished sweating, hoarseness, paraesthesia, dry skin, constipation, hearing impairment, weight gain). Thyroid glands were inspected by palpation. Heart rate, blood pressure, weight, height, presence or absence of fine finger tremor, hyperkinetic or slow movements, hot and/or moist hands, coarse skin, cold skin, periorbital puffiness were assessed. These symptoms and signs were used to calculate indices of hyperthyroidism (14) and hypothyroidism (15) as suggested in literature. Blood samples were collected for thyroid function tests (T_3 , T_4 , TSH and microsomal antibodies).

Thyroid hormones (T_3 and T_4) and TSH by a sensitive assay (sTSH) were measured by polarized fluorescence using commercial kits (Abbott, Park, IL, USA). Reference values for T_3 are 47–135ng/dL, for

T₄ 4.5–12.5ng/dL and for sTSH 0.32–5mU/L. The coefficients of variation for each sample were less than 9.8% for T₃, 8.6% for T₄ and 8% for TSH. Microsomal antibodies (McAb) were measured by hemagglutination, using commercial kits (Abbott-Murex, Park, IL, USA). Significant antibody titers were thought to be present at a dilution greater than 1:100.

The prevalence of thyroid dysfunction was based exclusively on hormone determinations. Patients with sTSH equal or lower than 0.1mU/l were considered to have hyperthyroidism, subclinical if T₃ and T₄ were normal and clinical if T₃ and/or T₄ were high. Patients with sTSH equal or higher than 5mU/l were considered to have hypothyroidism, subclinical if T₃ and T₄ were normal and clinical if T₃ and/or T₄ were low. The criterion used to diagnose hyperthyroidism was based on the guidelines of the American Thyroid Association (2000), suggesting that virtually all types of hyperthyroidism encountered in clinical practice are accompanied by a serum sTSH concentration lower than 0.1mIU/L and not with sTSH just below the normal range (16). On the other hand, high sTSH, even though just above the upper limit of the normal range, is implicated in depression and higher cholesterol levels, which are representative of tissue hypothyroidism (15). High thyroxine levels, associated with a normal sTSH in patients using amiodarone, were considered an adverse drug effect.

The following possible associated variables were explored: sex, age, race, thyroid autoimmunity, duration of therapy, and amiodarone dose. The amiodarone dose was coded as a categorical variable with low (< 200mg/d), medium (200mg/d) and high (> 200mg/d) levels.

The protocol was approved by the Research Unit Ethics Committee and informed consent was obtained from each patient.

STATISTICAL ANALYSIS

All data are expressed as mean ± SD. The level of significance was 0.05 for all analyses. Differences between mean values of variables were tested by one-way ANOVA when more than 2 groups were compared. Risk factors were determined using univariate analysis. Categorical variables were analyzed using chi-square analysis. Continuous variables were analyzed using the unpaired Student *t* test. The association of different variables (gender, age, race, amiodarone dose, duration of therapy and presence of thyroid autoimmunity) and thyroid dysfunction (dependent variable) was

analysed by a multivariate regression logistic model and expressed as odds ratio, with 95 percent confidence intervals using thyroid dysfunction as a dependent variable. A non-parametric regression model (Spearman) was used to assess the relationship between clinical scores and hormone measurements. Sensitivity and specificity of the clinical scores were calculated considering hormone measurements as the gold standard.

RESULTS

All 3,552 patients 18 years old or more, attending the outpatient department of IC-FUC during 6 weeks between November 2000 and May 2001, were asked whether they used amiodarone. Of these, 214 (6%) were using the drug, but 19 did not want to participate in the study, and thus the 195 remaining patients were evaluated. The underlying cardiac diseases included coronary artery disease (28.7%), cardiomyopathy of any etiology (20.5%), valvular heart disease (19%), heart failure (9.2%) and systemic hypertension (41.1%).

A total of 195 patients were studied, 89.2% Caucasian, 102 male (52.3%), with ages ranging from 18 to 97 years (59.3 ± 14.8 years). Among the 195 patients evaluated, 142 were euthyroid, 49 (25.1%) were hypothyroid and 4 (2.1%) were hyperthyroid. Eighteen (9.2%) euthyroid patients had only high T₄ levels. Goiter was present in 14.9% of the whole population studied. The clinical characteristics of these individuals are shown in table 1.

Except for the presence of microsomal antibodies, none of the factors evaluated were significantly different in patients who developed amiodarone-induced hypothyroidism compared with those who did not. These data are shown in table 2. Thirty-four patients (17.4%) were using a low dose of amiodarone (< 200mg/d), 150 (76.9%) were on a medium dose (200mg/d) and 9 (4.6%) were on a high dose (> 200mg/d). These data revealed that the population studied usually had been prescribed 200mg/d of amiodarone. The association between amiodarone dose and thyroid dysfunction was not assessed because of the small number of patients using high and low doses. Variables associated with amiodarone-hyperthyroidism were not assessed because of the small number of patients with this diagnosis.

There was no relationship between age, race and duration of therapy and the development of thyroid dysfunction. However, the odds ratio of thyroid autoimmunity, expressed as positive McAb, was 4.8 (95% CI,

Table 1. Clinical data of the patients studied.

	All patients	Euthyroid	Hypothyroid	Hyperthyroid
Number of cases (n and %)	195	142 (72.8)	49 (25.1)	4 (2.1)
Age (years)	59.3 ± 15	59.3 ± 14	58.7 ± 11	66.7 ± 12
% of men	52.3	48.6	61.2	75
BMI (kg/m ²)	26.4 ± 4	26.8 ± 4	25.6 ± 4	25.4 ± 5
Caucasian (%)	89.2	89.4	91.8	50
Heart rate (bpm)	71.7 ± 12	71.5 ± 12	72.3 ± 14	72.7 ± 10
Systolic Blood Pressure (mmHg)	128.5 ± 22	130.2 ± 23	123.7 ± 20	130.0 ± 36
Diastolic Blood Pressure (mmHg)	78.5 ± 14	78.9 ± 14	77.9 ± 13	66.7 ± 6
Duration of treatment (months)	35.7 ± 21	36.0 ± 22	34.1 ± 19	48.5 ± 31
T ₃ (ng/dL)	74.9 ± 18	74.3 ± 15	75.8 ± 24	84.2 ± 33
T ₄ (ng/dL)	9.1 ± 3	9.9 ± 2	6.7 ± 3**	14.1 ± 4*
TSH (mU/l)	6.3 ± 13	1.8 ± 1	19.9 ± 21**	0.06 ± 0.02#
McAb + (%)	5.1	2.8	12.2**	0

* p < 0.05 vs. euthyroid and hypothyroid individuals; ** p < 0.05 vs. euthyroid and hyperthyroid individuals; # p < 0.05 vs. hypothyroid individuals

Table 2. Association between amiodarone-induced hypothyroidism and different variables (means ± SD and %).

	Hypothyroidism	No hypothyroidism	P
Male/Female (%)	61.2/38.8	49.3/50.7	0.14
Age (years)	58.7 ± 10.9	59.5 ± 15.9	0.75
Caucasians/Blacks (%)	91.8/8.2	88.4/11.6	0.49
Duration of therapy (months)	34.1 ± 18.9	36.3 ± 22.1	0.53
McAb + (%)	12.2	2.8	0.009

1.28–18.6, p = 0.02). Although not statistically significant, the odds ratio of the male gender for thyroid dysfunction was 1.86 (95% CI, 0.95–3.63, p = 0.06), showing a tendency for men to develop amiodarone-induced thyroid dysfunction. The data are shown in table 3.

Of the patients classified as hypothyroid based only on laboratory tests (n = 49), 8.1% were considered hypothyroid based only on clinical grounds. Of the patients classified as hyperthyroid based only on laboratory tests (n = 4), 100% were designated as hyperthyroid based only on clinical grounds. Taking laboratory tests as the gold standard for thyroid dysfunction diagnosis, these data confer 8% sensitivity and 99% specificity for the hypothyroidism score and 100% sensitivity and 14% specificity for the hyperthyroidism score. However, there was no correlation between the clinical scores as suggested for evaluation and TSH measurements (r = 0.04, p = 0.60 for hypothyroidism and r = -0.01, p = 0.88 for hyperthyroidism). Subclinical hypothyroidism was present in 35 out of 49 cases, but no cases of subclinical hyperthyroidism were detected.

DISCUSSION

There is a high prevalence of amiodarone-associated thyroid dysfunction (27.1%) in this sample of adults with any kind of cardiac disease, especially hypothy-

roidism (25.1%). Thyroid autoimmunity is significantly associated with the development of thyroid dysfunction and hypothyroidism. Male gender, although not statistically significant, was also positively associated with thyroid dysfunction.

Our study is the first in Latin America that evaluated amiodarone users with all kinds of cardiac diseases, in a number sufficient to identify differences between the observed prevalence in the sample studied and the expected prevalence in the whole population. Besides our own study, we know only of two others carried out in Latin America dealing with the prevalence of thyroid dysfunction among amiodarone users: one was also performed in Brazil, but studied only chagasic patients (7) and one performed in Argentina, part of a multicentric study, which also included European and Canadian centers. Since the results were published together, it was not possible to detect regional differences in amiodarone-induced abnormalities, which are well known to occur (4). It is possible that a number of patients evaluated in our study already have thyroid dysfunction, which could not be attributed to amiodarone use, because it was a cross-sectional study. Since the prevalence of thyroid dysfunction in the general population is low (16–20), the differences between our findings and the real ones should also be low.

Table 3. Association between different variables and amiodarone-induced thyroid dysfunction (logistic regression model).

Risk factors	Beta	OR	CI (95%)	P
Gender (male)	0.62	1.86	0.95-3.63	0.06
Age (years)	0.0036	1.0	0.97-1.02	0.77
Race (Caucasian)	0.62	0.73	0.25-2.08	0.56
Duration of therapy(months)	-0.0048	0.89	0.97-1.01	0.57
McAb +	1.56	4.8	1.28-18.6	0.02

Transient abnormalities in thyroid hormone metabolism are usually observed during the first months of therapy with amiodarone (21). We could not attribute the high prevalence of hypothyroidism in our sample to these transient abnormalities, since all hypothyroid patients we detected had been treated with amiodarone for more than 3 months.

Amiodarone-induced hypothyroidism prevails in areas with a high iodine intake, therefore our data simply confirm that Rio Grande do Sul is an iodine-sufficient area (22), similar to results obtained in Massachusetts (8) and in São Paulo (7). Accordingly, the low prevalence of goiter in the whole studied population, of 14.9%, compared to 60% observed in iodine-deficient areas (23), supports the idea of an adequate supply of iodine in our region.

Other mechanisms could also be operating to determine the hypothyroidism, since some iodine-sufficient areas do not have so many cases of AIH (11). Hypothyroidism associated with chronic amiodarone administration can result from the disclosure of previous thyroid autoimmune disease. Thyroid autoimmunity can be triggered by high iodine intake, which inhibits thyroid hormone synthesis (9). In our sample, individuals who developed AIH had positive McAb more frequently as compared to those who did not develop AIH. However, only 13% of those individuals had positive McAb. Other authors described a prevalence of 33 to 40% of thyroid autoimmunity in these patients, much higher than ours (8). It must be emphasized that these data were obtained employing similar assays in terms of sensitivity as we did.

In the absence of thyroid antibodies it is speculated that AIH is caused by a subtle defect in thyroid hormone synthesis. These patients could be more susceptible to the inhibitory effect of iodide on hormone synthesis (Wolff-Chaikoff effect) and fail to escape this effect (8), temporarily or permanently. In vitro studies showed inhibitory effects on amiodarone-treated thyroid cells at lower iodide concentrations than those seen in iodide-treated cells. Because of that, hypothyroidism could have been induced by the drug as a

result of the combined effects of the constant iodide release associated with a specific drug toxicity (24).

In agreement with the statement that AIH prevails in iodine-sufficient areas and AIT in iodine-deficient areas, and considering our state an iodine-sufficient area, we observed a very low prevalence of hyperthyroidism in our sample. The few (four) cases of hyperthyroidism, together with the 49 cases of hypothyroidism, present results similar to those obtained in developed countries, which are typically iodine-sufficient (25). However, since the study of Harjai et al. was a retrospective analysis of cases that were referred to a main center because of suspected thyroid dysfunction, it was not as reliable as ours in determining the prevalence of thyroid dysfunction in a specific population. The only other study showing a low prevalence of thyrotoxicosis among amiodarone users (1.4%), similar to ours, was presented recently at the 22nd Annual Scientific Sessions of the North American Society of Pacing and Electrophysiology (4). However, as previously mentioned, this study analyzed data from different countries together, which does not permit the observation of regional differences of thyroid dysfunction prevalence. It is possible that high prevalences of hyperthyroidism, usually observed in European countries (8,21), analyzed together with the low prevalences observed in the United States (25) produced biased final results.

The unusually high prevalence of AIT in the studies by Thorne et al., performed in an intermediate region concerning iodine sufficiency, and by Sato et al., who studied referred patients suspected of having amiodarone-induced thyroid dysfunction to a tertiary center, calls attention to other factors in the pathogenesis of this disorder. Some of these factors have been proposed by others: 1) An iodine-induced thyroid auto-regulation disorder, precipitating Graves' disease (26); 2) A possible cytotoxic effect of amiodarone itself on thyroid follicles (12); or 3) A susceptibility of the individual patient, since certain HLA genes have been associated with AIT (27) can contribute to the development of thyrotoxicosis.

Concerning the variables studied in search of those with a possible causal relation to thyroid dysfunction, our study shows that there is an association between amiodarone-induced thyroid dysfunction, especially AIH, and positive thyroid antibodies. Similar results have already been described by other authors (21,28). It is possible that amiodarone precipitated the onset of preexisting autoimmune disease in these patients. However, the increased association between amiodarone-induced thyroid dysfunction and male gender was not previously reported. Indeed, other risk factors described before are female gender (5,21), presence of cyanotic heart disease (5), cumulative dose (29), body mass index and geographic location (4). The increased risk of amiodarone-associated thyroid dysfunction in women may be a reflection of their greater propensity to autoimmune thyroid disease. This fact could explain why female gender was not associated with thyroid dysfunction in our study, since the prevalence of thyroid autoimmunity in our sample was very low (5.1%). The finding of Crystal et al. that residence in Europe predisposes to AIT and residence in North America predisposes to AIH simply reflects the different iodine supply of the two regions, as already discussed. It is still unclear why cyanotic patients and those with low (increased risk for AIT) or high body mass index (increased risk for AIH), besides being male are at increased risk of amiodarone-induced thyroid dysfunction.

We could not assess variables related to AIT, since there were so few patients in this group (4). This issue remains controversial, since some authors did not find any risk factors for AIT (11,21) and others did (4). The usual concept is that the development of AIT is unpredictable, occurring suddenly during treatment with amiodarone.

The high sensitivity of the Wayne index for the clinical diagnosis of hyperthyroidism in amiodarone users makes it a useful screening test for AIT. However, this is not true for the hypothyroidism index, whose low sensitivity renders it useless to detect hypothyroidism among amiodarone users. These data probably result from the high incidence of subclinical hypothyroidism (35 from 49 cases) together with the low incidence of subclinical hyperthyroidism (0 out of 4 cases) in the population studied. In fact, the development of TSH assays with improved sensitivity has changed the diagnosis of thyroid dysfunction: subclinical hypo and hyperthyroidism are frequently diagnosed. The pathophysiological importance of these new categories of thyroid dysfunction has been highlighted by new studies, which demonstrated that both

subclinical hypo and hyperthyroidism are characterized by abnormalities that can potentially be reversed by treatment (30,31). Consequently, minor degrees of thyroid dysfunction that appear inconsequential in an endocrinological setting may be important in special groups, such as cardiac patients, who are particularly sensitive to changes in thyroid function.

While AIH does not represent a clinical challenge, the management of AIT is a difficult problem, and therapeutic actions should be promptly undertaken to avoid risks related to excess thyroid hormone in these particularly high risk patients. Fortunately our region has a very low prevalence of AIT, and therefore clinicians should not avoid using amiodarone whenever necessary, while not ignoring the other side effects of the drug involving the skin, liver and lungs. Clinical symptoms of hyperthyroidism should be checked and thyroid function tests monitored in all patients receiving chronic amiodarone therapy, especially if they have positive microsomal antibodies and are thus at increased risk of developing thyroid dysfunction. Larger samples should be studied to evaluate the association between male gender and amiodarone-induced thyroid dysfunction.

REFERENCES

1. Naccarelli GV, Wolbrette DL, Dell'Orfano JT, Patel HM, Luck JC. Amiodarone: What we have learned from clinical trials. **Clin Cardiol** 2000;23:73-82.
2. Wiersinga WM, Trip MD. Amiodarone and thyroid hormone metabolism. **Postgrad Med** 1986;62:909-14.
3. Burger A, Dinichert D, Nicod P, Jenny M, Lemarchand-Béraud T, Vallotton MB. Effect of amiodarone on serum triiodothyronine, reverse triiodothyronine, thyroxine, and thyrotropin. A drug influencing peripheral metabolism of thyroid hormones. **J Clin Invest** 1976;58:255-9.
4. Crystal E, Gent M, Roberts RS, Thorpe KE, Dorian P, Camm AJ, et al. Predictors of amiodarone thyroid toxicity: Rates and risk factors from 5,148 patients enrolled into randomized double-blind placebo-controlled trials. **Pacing Clin Electrophysiol** 2001;24:547. (abstract)
5. Thorne AS, Barnes I, Cullinan P, Somerville J. Amiodarone-associated thyroid dysfunction: Risk factors in adults with congenital heart disease. **Circulation** 1999;100:149-54.
6. Gomez JM, Virgili N, Montaña E, Gausi C, Soler J. Thyroid dysfunction induced by amiodarone in Catalonia. Prevalence and characteristics. **Rev Clin Espanh** 1991;188:127-30.
7. Ward L, Fernandes GD, Guariento ME. Indicadores de função tireoidiana na cardiopatia chagásica com e sem tratamento com amiodarona. **Braz J Clin Ther** 1997;23:201-6.

8. Martino E, Safran M, Aghini-Lombardi F, Rajatanavin R, Lenziardi M, Fay M, et al. Environmental iodine intake and thyroid dysfunction during chronic amiodarone therapy. **Ann Intern Med** 1984;101:28-34.
9. Martino E, Aghini-Lombardi F, Bartalena L, Grasso L, Loviselli A, Velluzzi F, et al. Enhanced susceptibility to amiodarone-induced hypothyroidism in patients with thyroid autoimmune disease. **Ann Intern Med** 1994;120:272-6.
10. Sato K, Miyakawa M, Eto M, Inaba T, Matsuda N, Shiga T, et al. Clinical characteristics of amiodarone-induced thyrotoxicosis and hypothyroidism in Japan. **Endocr J** 1999;46:443-51.
11. Tisdale JE, Follin SL, Ordelova A, Webb CR. Risk factors for the development of specific noncardiovascular adverse effects associated with amiodarone. **J Clin Pharmacol** 1995;35:351-6.
12. Di Matola T, D'Ascoli F, Fenzi G, Rossi G, Martino E, Bogazzi F, et al. Amiodarone induces cytochrome c release and apoptosis through an iodine-independent mechanism. **J Clin Endocrinol Metab** 2000;85:4323-30.
13. O'Reilly DS. Thyroid function tests - time for reassessment. **BMJ** 2000;320:1332-4.
14. Crooks J, Wayne EJ, Robb RA. A clinical method of assessing the results of therapy in thyrotoxicosis. **Lancet** 1960;20:397-401.
15. Zulewski H, Müller B, Exer P, Miserez AR, Staub JJ. Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls. **J Clin Endocrinol Metab** 1997;82:771-6.
16. Ladenson PW, Singer PA, Ain KB, Bagchi N, Bigos ST, Levy EG, et al. American Thyroid Association guidelines for detection of thyroid dysfunction. **Arch Intern Med** 2000;160:1573-5.
17. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. **Clin Endocrinol** 1991;34:77-83.
18. Barbisan JN, Fuchs FD, D'Agord Schaan B. Prevalence of thyroid dysfunction in patients with acute atrial fibrillation attended at a cardiology emergency room. **São Paulo Med J** 2003;112(4):159-62.
19. Mendonça SCL, Jorge PT. Estudo da função tireoidiana em uma população com mais de 50 anos. **Arq Bras Endocrinol Metab** 2002;46(5):557-65.
20. Bagchi N, Brown TR, Parish RF. Thyroid dysfunction in adults over age 55 years. **Arch Int Med** 1990;150:785-7.
21. Trip MD, Wiersinga W, Plomp TA. Incidence, predictability, and pathogenesis of amiodarone-induced thyrotoxicosis and hypothyroidism. **Am J Med** 1991;91:507-11.
22. Knobel M, Medeiros-Neto G. Moléstias associadas à carência crônica de iodo. **Arq Bras Endocrinol Metab** 2004;48(1):53-61.
23. Aghini-Lombardi F, Antonangeli L, Martino E, Vitti P, Maccherini D, Leoli F, et al. The spectrum of thyroid disorders in an iodine-deficient community: The Pescopagano survey. **J Clin Endocrinol Metab** 1999;84:561-6.
24. Pitsiavas V, Smerdely P, Boyages SC. Amiodarone compared with iodine exhibits a potent and persistent inhibitory effect on TSH-stimulated cAMP production in vitro: A possible mechanism to explain amiodarone-induced hypothyroidism. **Eur J Endocrinol** 1999;140:241-9.
25. Harjai KJ, Licata AA. Amiodarone induced hyperthyroidism: A case series and brief review of literature. **Pacing Clin Electrophysiol** 1996;19:1548-54.
26. Martino E, Bartalena L, Bogazzi F, Braverman LE. The effects of amiodarone on the thyroid. **Endoc Rev** 2001;22:240-54.
27. Erdogan MF, Güleç S, Tutar E, Güldal M, Baskal N, Erdogan G. HLA-B40, HLA-Cw3, and HLA-DR5 - Associated susceptibility to amiodarone-induced thyroid dysfunction. **Thyroid** 2000;10:369-70.
28. Martino E, Aghini-Lombardi F, Mariotti S, Bartalena L, Lenziardi M, Ceccarelli C, et al. Amiodarone iodine-induced hypothyroidism: Risk factors and follow-up in 28 cases. **Clin Endocrinol (Oxf)** 1987;26:227-37.
29. Bouvi ML, Heerdink ER, Hoes AW, Leufkens HG. Amiodarone-induced thyroid dysfunction associated with cumulative dose. **Pharmacoepidemiol Drug Safety** 2002;11:601-6.
30. Biondi B, Fazio S, Palmieri EA, Carella C, Panza N, Cittadini A, et al. Left ventricular diastolic dysfunction in patients with subclinical hypothyroidism. **J Clin Endocrinol Metab** 1999;84:2064-7.
31. Sgarbi JA, Villaça F, Garbeline B, Villar HE, Romaldini JH. The effects of early antithyroid therapy for endogenous subclinical hyperthyroidism in clinical and heart abnormalities. **J Clin Endocrinol Metab** 2003;88(4):1672-7.

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