ORIGINAL ARTICLE

Radioiodine therapy in patients with type II amiodarone-induced thyrotoxicosis

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KEY WORDS

amiodarone, amiodarone-induced thyrotoxicosis, atrial fibrillation, hyperthyroidism, radioiodine therapy

ABSTRACT

INTRODUCTION The treatment of amiodarone-induced thyrotoxicosis (AIT) still remains a clinical challenge, requiring the cooperation of both endocrinologists and cardiologists. Unfortunately, even today AIT is related to significantly increased mortality.

OBJECTIVES The aim of this study was to compare the efficacy of radioidine therapy for type II AIT in 2 groups of patients: with high or normal radioiodine uptake and treated by amiodarone (AM) in the past (AM– group) and with low radioiodine uptake and currently treated with AM (AM+ group).

PATIENTS AND METHODS The AM– group included 57 patients and the AM+ group, 49. All patients received iodine-131 at a dose of 22mCi∼800. Patient data were collected for over 2 years.

RESULTS After radioiodine administration, serum thyroid-stimulating hormone levels in the AM– group and AM+ group were 0.0 ±0.0 and 0.0 ±0.0, respectively, at 1 month; 1.2 ±3.3 and 0.6 ±1.2, respectively, at 12 months; and 4.2 ±3.6 and 1.9 ±0.8, respectively, at 2 years. All differences between the groups were statistically significant (P <0.0001). Free triiodothyronine and thyroxine levels were significantly higher in the AM+ group compared with the AM– group. During follow-up, death occurred in 22 patients in the AM+ group and 6 patients in the AM– group.

CONCLUSIONS Radioiodine treatment is a safe and effective therapeutic modality for patients with type II AIT despite low radioiodine uptake, especially for patients with contraindications to other types of treatment (eg, thyroidectomy). Moreover, since thyrotoxicosis in patients with AIT is a significant risk factor for increased mortality, and since there are no alternative antiarrythmic treatments, radioiodine administration seems to be the only effective therapeutic modality.

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INTRODUCTION Amiodarone (AM) is a iodine-containing class III antiarrhythmic drug, which is widely used in the treatment of ventricular and supraventricular tachyarrhythmias.[1-3] Owing to its relatively low impact on the cardiac output, AM is a drug of choice for patients with congestive heart failure. It has also been shown to be effective in the secondary prevention of sudden cardiac death.[1,4] Its iodine content is very high,[1,2,5] since 1 formulation tablet (200 mg) contains 75 mg of iodine, which, when metabolized, releases from 7 to 21 mg of iodine daily (100-fold more than the required daily uptake).[6] AM and its lipophilic metabolites accumulate in the fat tissue and skeletal and cardiac muscles, contributing to its prolonged elimination.[7] Lately, dronedarone, a drug structurally related to AM, has been introduced for clinical use. It is not iodinated, has lower lipophilicity, reaches therapeutic concentrations over a shorter period of time, and has lower tissue accumulation, but its clinical effectiveness is yet to be confirmed.

The physiology of AM's effect on the thyroid, pituitary-thyroid axis, and thyroid hormone metabolism also involves immunogenic and proinflammatory activity.[2,8] AM, which structurally resembles thyroid hormones, releases large quantities of iodine, contributing to the development of

immune-related pathology of the thyroid. It may cause hypothyroidism in patients with a disrupted Wolff–Chaikoff effect.

The Jod–Basedow phenomenon (also known as iodine-induced thyrotoxicosis) occurs in the areas with iodine deficiency and endemic goiter, or after excess iodine exposure in individuals with nontoxic multinodular goiter in the areas with sufficient environmental iodine content.[9] The pathogenesis of AM-induced thyrotoxicosis (AIT), which often has a sudden onset, is not well understood.[10-12] Based on its physiology, AIT is divided into 2 types. Type I AIT is an aggravation of the present thyroid disease by high iodine content; type II AIT is a result of thyroid damage in patients with normal thyroid function. Mixed or indeterminate forms of AIT encompassing several features of both types I and II AIT have also been observed.[10-14]

Thyroid function disorders occur in 16% to 20% of AM-treated patients. The disorders may develop during the administration of the drug and even up to several months after its withdrawal.[15] Antithyroid drugs are the treatment of choice for AIT.[9,16,17] Other therapeutic options are glucocorticosteroids[14,16,17] and iopanoic acid.[18] Thyroidectomy may be also indicated.[19,20] AIT constitutes a significant clinical challenge. Hyperthyroidism can promote arrhythmia, exacerbation of heart insufficiency, and, consequently, it may lead to increased mortality, especially in elderly patients with left ventricular dysfunction. Additionally, because of AM's long half-life and accumulation in tissues, treatment of AIT is very difficult.[21,22] Radioiodine therapy is an option in patients with AM intolerance, cardiac contraindications to surgery, or poor patient compliance. Due to low radioiodine uptake in patients treated with AM, radioiodine administration is a questionable method of therapy and requires further evaluation in patients with AIT and contraindications to other types of treatment.

The aim of this study was to further investigate the effects of radioiodine therapy in patients with type II AIT. We had previously reported that radioiodine therapy may be a safe and effective treatment even in the case of low radioiodine uptake.[23] In particular, we aimed to investigate whether radioiodine uptake depends on the duration of AM withdrawal, and whether the effectiveness of radioiodine therapy depends on radioiodine uptake.

PATIENTS AND METHODS

Patients We analyzed the medical records of all patients who were diagnosed with type II AIT in a single institution, the Department of Endocrinology, Metabolism and Internal Medicine in Poznań, Poland, between 2005 and 2010. Patients were classified into 2 groups. The first group (AM–) included patients with normal or high radioiodine uptake with a past history of AM treatment, which was discontinued for various reasons from 6 months to 2 years before admission to our department. The second group (AM+) included patients who continued AM treatment.

AIT was defined on the basis of the following criteria: a history of AM treatment for at least 1 month; signs and symptoms of hyperthyroidism confirmed by increased free thyroxine (FT_4), free thriiodothyronine (FT_3) and reduced thyroid-stimulating hormone (TSH) levels observed during therapy or within 2 years after AM withdrawal; a negative titer of circulating thyroid autoantibodies (antithyroglobulin [Tg-Abs], antithyroid peroxidase [TPO-Abs], anti-TSH receptor [TSHR-Abs] autoantibodies)[10,17,18]; and a thyroid of normal or slightly increased volume without relevant nodules (>1 cm) on conventional ultrasonography. Patients were differentiated according to type I and II AIT. Type II AIT was diagnosed on the basis of the lack of hot lesions in thyroid scintigraphy and lack of TSHR-Abs.[10,24,25] Only patients who survived a 2-year follow-up were included into the analysis of hormonal changes.

Methods The hormonal assessment was performed using a Hitachi Cobas e601 chemiluminescent analyzer (Roche Diagnostics, Basel, Switzerland). Autoantibody concentrations were assessed by the radioimmunological method with the use of commercially available BRAMHS anti-TPO, anti-Tg, and TRAK RIA kits and a scintillation gamma counter (LKB Wallac CliniGamma 1272, LKB-Wallac, Finland). The serum TSH concentration was measured with a third-generation assay (sensitivity, 0.005 μIU/ml). The refernce ranges for serum hormone concentrations in our laboratory were as follows: FT_4, 11.5 – 21.5 pmol/l; FT_3, 3.9–6.8 pmol/l; TSH, 0.27–4.2 μIU/ml; TSHR-Abs, <2 IU/l; Tg-Abs, <35 IU/ml; and TPO-Abs, <115 IU/ml.

Sonography, radioiodine uptake, and scintigraphy The Aloka SSD-500 (Aloka, Tokyo, Japan) with a 7.5-MHz linear transducer was used to perform thyroid ultrasonography. Ultrasonography was also used to measure thyroid volume and the ellipsoid model (width × length × thickness × 0.52 for each lobe) was used for calculation.[26] Color-flow Doppler ultrasonography was performed in the entire group. In the case of patients with thyroid nodules, ^{99m}Tc at an intravenous dose of 150 MBq was administered, and 30 minutes later, thyroid scintigraphy was performed (Nucline™ Gamma Camera Family, Mediso, Budapest, Hungary).

Radioiodine treatment and amiodarone Patients with symptomatic paroxysmal atrial fibrillation, in whom the treatment with an antiarrhythmic drug and electrical cardioversion was ineffective, were referred for radioiodine (22mCi~800 MBq) and subsequent AM treatments. The AM– group included patients with a history of AM therapy (lasting at least 1 month), who were diagnosed with AIT up to 2 years after the discontinuation of treatment. The AM+ group included patients

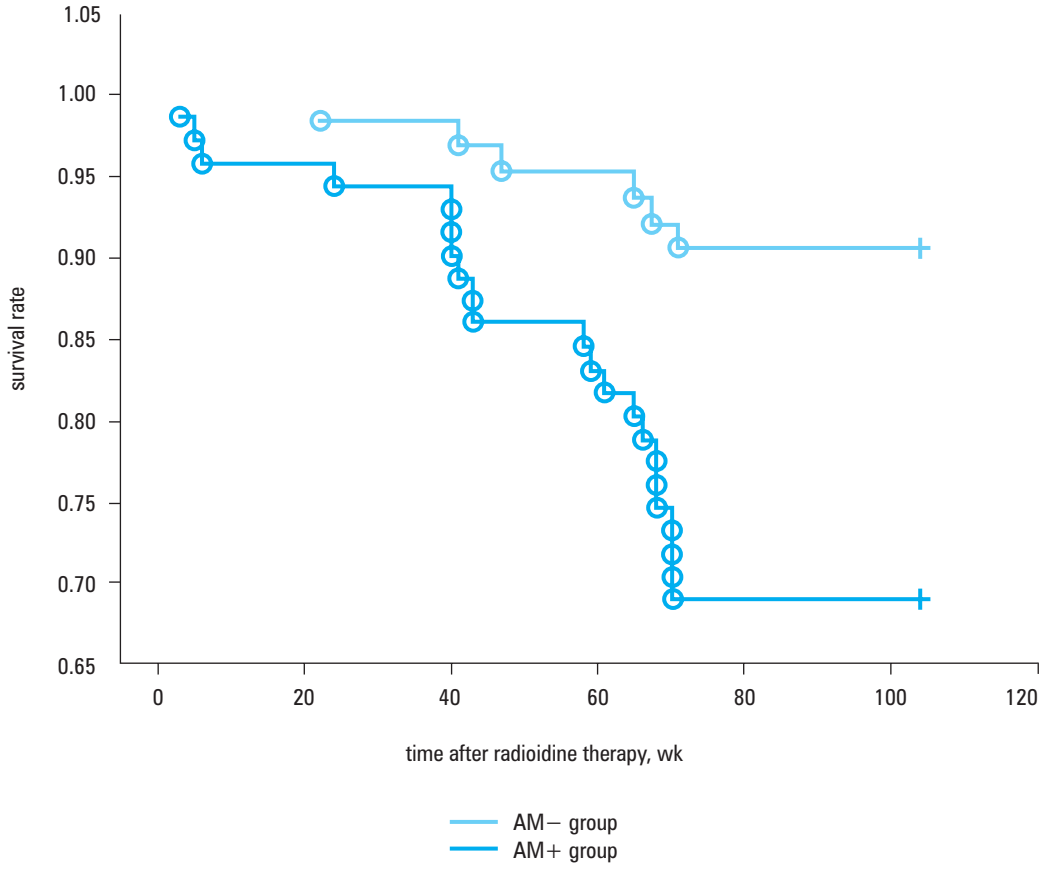

FIGURE 1 Survival curve for all 134 patients at baseline and during 2-year follow-up; time zero set at diagnosis of amiodarone-induced thyrotoxicosis
Abbreviations: AM– group – high radioiodine uptake and past amiodarone treatment, AM+ group – low radioiodine uptake and current amiodarone treatment

who were permanently taking AM as a life-saving drug of choice.

The study was approved by the ethics committee at the Poznan University of Medical Sciences, and patients were informed about the aim of the study and recommended therapeutic treatment and gave their written consent to participate.

Statistical analysis A 2-sample *t* test and χ^2 test were used for group comparisons. Owing to the lack of normal distribution of either thyroid hormones or TSH in the AM– group and because the samples were related (because patients were evaluated several times), the Friedman test was used. Owing to the noncompliance of thyroid hormones and TSH with the normal distribution, the Mann–Whitney test was used to compare the AM+ and AM– groups. For FT_4, because distributions were consistent with the normal distribution and it lacked the equality of variances, we used the test of the Cochran–Cox test only in a 6-month follow-up. The Kaplan–Meier curve censored for death was used to show the cumulative incidence of heart failure by thyroid status. At diagnosis of thyrotoxicosis, AM treatment had been discontinued and the cumulative AM dose was calculated as the total dose of AM. The calculations were performed using the Statistica 10 software (StatSoft, Tulsa, Oklahoma, United States). The results were expressed as mean ± standard deviation, median, and minimum and maximum. A *P* value of less than 0.05 was considered statistically significant.

RESULTS A total of 134 patients with AIT treated in our department between 2005 and 2010 were included (the number of patients at baseline was 63 in the AM+ group, and 71 in the AM– group). The mean age of patients was significantly higher in the AM+ group because it included patients with more severe cardiac conditions, often elderly ones, in whom AM could not be withdrawn. Six deaths occurred in the AM– group and 22 in the AM+ group (FIGURE 1). Significant predictors of death were severe left ventricular dysfunction, old age, and other severe diseases; sex, FT_4, FT_3, and the cumulative AM dose were not risk factors.

Two-year follow-up data were obtained from 106 patients; their baseline characteristics are shown in TABLES 1 and 2. The mean age of the patients was 66 years, and the female-to-male ratio was 1:4.2. In 4 patients (7.0%) in the AM+ group, and in 14 patients (28.5%) in the AM– group, AM was administered initially as an intravenous bolus of 150 mg; the average dose of intravenous and oral AM was from 150 to 900 mg daily. In the AM– group, AM therapy was continued on an outpatient basis (200 mg daily).

At the time of admission to our hospital for radioiodine therapy, all patients received antithyroid drugs: thionamide derivatives of thiouracil (propylthiouracil and methimazole). Although thyroid autoantibodies (Tg-Abs, TPO-Abs, and TSHR-Abs) were negative, 12 patients presented with a family history of hyperthyroidism.

In the AM– group, the mean thyroid volume was approximately 21 ml, and the mean iodine-131 (^{131}I) uptake (radioiodine uptake) was 12.0%

TABLE 1 Demographic characteristics and baseline clinical and biochemical characteristics of patients with high radioiodine uptake and a history of past amiodarone treatment (AM– group) and low radioiodine uptake and current amiodarone treatment (AM+ group)

		AM– group (n = 57)	AM+ group (n = 49)	*P* value
age, y		59 (42–87)	76 (38–87)	0.02
sex, female/male		9/48	6/43	0.05
thyroid status	family history of hyperthyroidism	32 (56.1)	13 (26.5)	0.003
	duration of hyperthyroidism in the past	19 (12–112)	48(4–74)	0.002
previous treatment for hyperthyroidism before radioiodine therapy	ATDs	57 (100)	49 (100)	0.92
	MMI	52 (91.2)	40 (81.6)	0.15
	PTU	8 (14.0)	9 (18.4)	0.54
	oral GCS	38 (66.7)	34 (69.4)	0.76
	subtotal thyroidectomy	2 (3.5)	0 (0)	0.38
	radioiodine therapy	1 (1.7)	0 (0)	0.63
FT_4, pmol/l		24.2 (5.6)	30.6 (5.2)	0.001
FT_3, pmol/l		8.3 (2.5)	10.0 (2.7)	0.001
FT_4/FT_3 ratio		3.1 (0.8)	3.3 (1.0)	0.55
TSH, mU/l		0.03 (0.05)	0.03 (0.09)	0.76
TPO-Abs, IU/l		30.7 (15.5)	25.7 (17.8)	0.55
Tg-Abs, IU/l		61.3 (46.7)	38.9 (32.6)	0.58
TSHR-Abs, IU/l		1.0 (0.5)	0.8 (0.4)	0.17
thyroid volume, cm^3		21.0 (3.4)	24.9 (5.7)	0.03
color-flow Doppler ultrasonography		0	0	1.0
dose of radioiodine, MBq (mCi)[a]		800 (0.0) 22 (0.0)	800 (0.0) 22 (0.0)	
radioiodine uptake, %	after 5 h	12.0 (2.1)	2.1 (1.4)	0.001
	after 24 h	14.1 (3.5)	1.3 (0.9)	0.001

Data are expressed as median (minimum–maximum) or number (percentage).

a all euthyroid patients received the same dose of 800MBq (22 mCi) at baseline

Reference values in our laboratory are as follows: FT_4, 11.5–21.5 pmol/l; FT_3, 3.9–6.8 pmol/l; TSH, 0.27–4.2 μU/ml; TSHR-Abs, <2 IU/l; TPO-Abs, 0–34 IU/ml; and Tg-Abs, 10–115 IU/ml. All patients had undetectable serum Tg-Ab, TPO-Ab, and TSHR-Abs levels. Thyroid volume was measured by ultrasonography (reference values range up to 19 ml for women and up to 25 ml for men). The reference range for thyroid radioiodine uptake is from 5% to 15% at 5 hours and from 10% to 30% at 24 hours.

Abbreviations: AAD – antiarrhythmic drugs, ATDs – antithyroid drugs, FT_3 – free thriiodothyronine, FT_4 – free thyroxine, GCS – glucocorticoid, MMI – methimazole, PTU – propulthiouracil, Tg-Abs – thyreoglobulin antibodies, TPO-Abs – thyroperoxidase antibodies, TSH – thyroid-stimulating hormone, TSHR-Abs – TSH receptor autoantibodies

at 5 hours and 14.1% at 24 hours. In the AM+ group, the mean thyroid volume was 24.9 ml, and the mean radioiodine uptake significantly decreased to less than 2.1% at 5 hours and 1.3% at 24 hours. Before treatment, all patients received propylthiouracil or methimazole. Glucocorticosteroids were administered in 72 patients (30 mg daily or more). At the end of the follow-up, thyroid volume was normal or slightly decreased in most cases in both groups. In individual patients in both groups, focal lesions were observed. Those patients received intravenous ^{99m}Tc at a dose of 150 MBq, and 30 minutes later, thyroid scintigraphy was performed, which revealed no focally increased isotope accumulation.

In the majority of the patients, we observed episodes of atrial fibrillation with tachyarrhythmia (67% of the patients in the AM+ group and 56% of the patients in the AM– group), premature ventricular contractions (67%, the AM+ group; 56%, the AM– group), or other arrhythmias with hyperactivity. One case of Eisenmenger syndrome in the AM+ group was diagnosed.

Each patient received ^{131}I at an ablative dose of 800 MBq (22 mCi). At baseline and during follow-up, no side effects of the therapy and no signs of drug intolerance were observed. In the AM– group, subclinical hyperthyroidism occurred in 2 patients (11.8%) after 6 months of radioiodine treatment and 5 weeks of AM administration. In those cases, radioiodine therapy was administered again. Additionally, 5 patients (3 [17.6%] after 12 months and 2 [11.8%] after 18 months) required the administration of an additional dose

TABLE 2 Cardiac status of patients with high radioiodine uptake and a history of past amiodarone treatment (AM– group) and low radioiodine uptake and current amiodarone treatment (AM+ group)

Cardiac status		AM– group (n = 57)	AM+ group (n = 49)	*P* value
hypertension		36 (63.2)	17 (34.7)	0.001
history of myocardial infarction		15 (26.3)	27 (55.1)	0.05
dilated cardiomyopathy		3 (5.3)	11 (22.4)	0.001
hypertrophic cardiomyopathy		12 (21.0)	6 (12.2)	0.05
valvular heart disease		7 (12.3)	8 (16.3)	0.59
ventricular septal defect with Eisenmenger syndrome		0 (0.0)	1 (2.0)	0.45
arrhytmogenic right ventricular cardiomyopathy		1 (1.7)	0 (0.0)	1.0
atrial fibrillation		20 (35.1)	18 (36.7)	1.0
ventricular arrhythmia		37 (64.9)	31 (63.3)	1.0
history of AAD use	class I a: procainamide	1 (1.7)	0 (0.0)	1.0
	class I b: lidocaine	2 (3.5)	1 (2.0)	1.0
	class I c: propafenone	7 (12.3)	3 (6.1)	0.05
	class II: metoprolol	35 (61.4)	14 (28.6)	0.001
	class II: bisoprolol	10 (17.5)	7 (14.3)	0.79
	class II: carvedilol	10 (17.5)	18 (36.7)	0.05
	class II: propranolol	16 (28.1)	7 (14.3)	0.001
	class III: amiodarone	57 (100.0)	49 (100.0)	1.0
	class III: sotalol	5 (8.8)	7 (14.3)	0.54
	class III: digoxin	2 (3.5)	6 (12.2)	0.001
history of direct cardiac cardioversion		14 (24.6)	10 (20.4)	0.65

Data are expressed as number (percentage).

Abbreviations: see TABLE 1

of ^{131}I because of AIT. In the AM+ group, hyperthyroidism occurred in 6 patients (11.8%) after 2 months of radioiodine treatment and 5 weeks of AM administration. In those cases, radioiodine therapy was was administered again. Six patients (4 [17.6%] after 6 months and 2 [11.8%] after 8 months) required the administration of an additional dose of ^{131}I because of AIT. At the end of a 2-year follow-up, 85 patients (86%) were successfully treated (hypothyroid or euthyroid), and 36 (14%) remained hyperthyroid.

It should be noted that none of the patients presented with the clinical symptoms of hyperthyroidism. This was probably due to the antiadrenergic action of AM.

Mean TSH levels were significantly reduced in both groups at the beginning of the follow-up. At baseline and at 6 months, there were no significant intergroup differences (Mann–Whitney test; TABLES 1 and 2).

Serum TSH levels in the AM– and AM+ groups were 0.0 ±0.0 and 0.0 ±0.0, respectively, at 1 month; 1.2 ±3.3 and 0.6 ±1.2, respectively, at 12 months; and 4.2 ±3.6 and 1.9 ±0.8, respectively, at 2 years (P <0.0001; Mann–Whitney test; TABLE 3, FIGURE 2).

FT_4 levels were significantly higher in the AM+ group compared with the AM– group at baseline (30.6 ±5.2 pmol/l and 24.2 ±5.6 pmol/l, respectively, Mann–Whitney test, P <0.001) and during follow-up (at 1 month: 32.2 ±9.3 and 21.5 ±1.9, respectively; at 6 months: 23.4 ±5.9 and 17.6 ±4.4, respectively; at 12 months: 23.1 ±6.0 and 16.5 ±3.2, respectively; at 24 months: 21.0 ±5.0 and 14.9 ±3.1, respectively; FIGURE 3).

Similarly, FT_3 levels were significantly higher in the AM+ group compared with the AM– group at baseline (10.0 ±2.7 pmol/l and 8.3 ±2.5 pmol/l, respectively; Mann–Whitney test, P <0.001) and during follow-up (at 1 month: 12.0 ±4.6 pmol/l and 7.6 ±2.3 pmol/l, respectively; at 6 months: 10.2 ±2.7 pmol/l and 6.3 ±2.0 pmol/l, respectively; at 12 months: 8±2.8 pmol/l and 5.4±1.3, respectively; and at 24 months: 7.7±3.0 pmol/l and 4.5±0.7 pmol/l, respectively; FIGURE 4).

In the AM+ group, the time of normalization of FT_3 and FT_4 levels was significantly longer than in the AM– group.

At all time points and in all cases, negative levels of TSHR-Abs were observed. Similarly, the serum concentrations of Tg-Abs and TPO-Abs were normal or slightly elevated without any considerable clinical significance. Throughout the follow-up, there were no cases of Graves disease induced by AM. In addition, patients had undetectable TSHR levels, which confirms no incidence of this disease in our study.

DISCUSSION Based on its physiology, AIT is typically divided into 2 types as described above. The current study focused on type II AIT because only patients without an underlying thyroid disease, with no hot lesions on thyroid scintigraphy and TR-Ab autoantibodies, were included. However, the etiologic and pathogenic differences between the 2 types of AIT depend on many factors which are not fully understood; it cannot be excluded that the mixed type of AIT occurred in some patients, especially those with prolonged hyperthyroidism.

The most important condition affecting the epidemiology of types I and II AIT appears to be the supply of iodine in the diet. Type I AIT is likely to develop in patients with nodular goiter or autoimmune thyroid damage, while type II AIT, in subjects with normal thyroid function. In the areas rich in iodine, the destructive, inflammatory form of AIT is more common.[15]

According to numerous studies,[10-14] differentiation between the 2 types of AIT, assesed with radioaiodine uptake and sestaMIBI, is important in therapeutic decision making.[27] are important in planning the treatment. However, some authors, such as O'Sullivan et al.,[28] reported that it is better not to differentiate between the 2 types of the disease according to the etiology, but rather according to the duration of AM exposure. In clinical practice, it is difficult to distinguish between both types of AIT, so the most frequently used forms of therapy are combinations of antithyroid drugs, oral glucocorticoids, potassium perchlorate, and iopanoid acid. In addition, thyroid ablation may be considered: either total

TABLE 3 Thyroid hormones, thyroid-stimulating hormone, thyroid autoantibodies, and thyroid volume in patients with high radioiodine uptake and a history of past amiodarone treatment (AM– group) and low radioiodine uptake and current amiodarone treatment (AM+ group) during a 2-year follow-up

Variable	At baseline		At 1 month		At 6 months		At 12 months		At 24 months	
	AM– group	AM+ group	AM– group	AM+ group	AM– group	AM+ group	AM– group	AM+ group	AM– group	AM+ group
FT_4, pmol/l	24.2 ±5.6 (20.8; 15.7–36.2)	30.6 ±5.2[a] (29.5; 21.5–43.0)	21.5 ±1.9 (20.8; 11.6–38.9)	32.2 ±9.3[a] (29.4; 20.1–65.0)	17.6 ±4.4 (17.6; 3.9–29.6)	23.4 ±5.9[a] (23.2; 13.2–37.4)	16.5 ±3.2 (16.9; 6.8–21.6)	23.1 ±6.0[a] (22.1; 11.2–36.4)	14.9 ±3.1 (15.6; 7.4–20.4)	21.0 ±5.0[a] (19.8; 11.2–37.8)
FT_3, pmol/l	8.3 ±2.5[b] (8.2; 4.5–14.6)	10.0 ±2.7[b] (9.3; 5.1–15.4)	7.6 ±2.3 (7.6; 4.0–13.2)	12.0 ±4.6[a] (12.3; 4.3–26.0)	6.3 ±2.0 (5.9; 3.4–14.3)	10.2 ±2.7[a] (9.9; 4.3–16.2)	5.4 ±1.3 (5.4; 3.2–9.2)	8.0 ±2.8[a] (6.9; 3.9–15.4)	4.5 ±0.7 (4.3; 3.2–6.2)	7.7 ±3.0[a] (6.3; 3.9–17.6)
TSH, mU/l	0.03 ±0.05 (0.01; 0.0–0.25)	0.03 ±0.09 (0.01; 0.0–0.25)	0.0 ±0.06 (0.01; 0.0–0.5)	0.02 ±0.04[a] (0.01; 0.0–0.3)	1.2 ±3.3 (0.1; 0.0–21.8)	0.6 ±1.2 (0.3; 0.0–6.8)	1.2 ±3.3 (0.1; 0.0–21.8)	0.8 ±1.5[b] (0.3; 0.0–6.9)	4.2 ±2.3 (3.6; 0.2–10.3)	1.9 ±2.3[a] (0.8; 0.0–8.6)
TPO-Abs, IU/ml	30.7 ±15.5 (29.5; 21.5–43.0)	25.7 ±17.8 (23.9; 10.5–33.5)	57.3 ±33.4 (32.0; 24.0–46.5)	32.9 ±19.6[a] (31.0; 18.5–76.0)	47.3 ±31.2 (37.0; 34.0–46.5)	34.8 ±12.6[b] (34.7; 21.5–64.4)	43.9 ±16.9 (26.3; 19.4–49.0)	35.7 ±15.7[b] (29.2; 15.8–43.5)	34.8 ±19.4 (32.6; 18.9–56.4)	34.9 ±21.8 (39.0; 16.7–55.2)
Tg-Abs, IU/ml	61.3 ±46.7 (43.0; 23.5–143.0)	38.9 ±32.6[b] (29.0; 19.5–73.0)	99.0 ±78.5 (62.0; 39.9–173.2)	103.4 ±84.5 (73.0; 39.9–156.2)	87.8 ±49.0 (48.0; 28.4–133.0)	48.9 ±36.0[a] (32.0; 10.2–98.0)	97.2 ±51.4 (48.0; 32.7–117.3)	56.4 ±37.0[a] (42.0; 14–121.3)	57.8 ±49.0 (48.0; 32.8–154.2)	51.8 ±37.4 (37.4; 19.3–198.0)
TSHR-Abs, IU/l	1.0 ±0.5 (0.9; 0.5–1.3)	0.8 ±0.4[b] (0.9; 0.5–1.3)	2.1 ±0.6 (0.8; 0.4–2.6)	1.2 ±0.3[a] (0.6; 0.2–1.3)	1.5 ±0.8 (0.7; 0.2–1.9)	1.2 ±0.3[b] (0.9; 0.2–1.7)	1.0 ±0.4 (0.6; 0.4–1.4)	0.9 ±0.6 (0.4; 0.3–1.0)	1.0 ±0.4 (0.2; 0.2–1.4)	0.9 ±0.7 (0.3; 0.5–1.3)
thyroid volume, cm^3/m^2	21.0 ±3.4 (19.0; 17.8–25.4)	24.9 ±5.7[a] (21.8; 20.8–25.4)	19.0 ±2.4 (17.2; 15.8–21.4)	21.6 ±3.6[a] (18.8; 17.7–25.2)	17.5 ±2.7 (16.9; 15.1–22.3)	20.9 ±4.8[a] (17.6; 16.5–24.3)	15.6 ±2.9 (15.7; 14.1–20.4)	18.9 ±3.6[a] (16.5; 13.4–20.3)	13.2 ±3.1 (13.2; 10.4–16.4)	12.7 ±1.6 (11.8; 11.2–14.3)
radioiodine dose, 800 MBq	–	–	–	800 (0.0) 22 (0.0)	–	–	800 (0.0) 22 (0.0)	800 (0.0) 22 (0.0)	–	–

Data are presented as means ± standard error of the mean (median; minimum and maximum); **a** $P < 0.001$, **b** $P < 0.05$. Abbreviations: see **TABLE 1**

thyroidectomy or radioiodine uptake. Owing to low radioiodine uptake in patients with type II AIT, especially those on current AM treatment, radioiodine administration seems to be a questionable therapeutic option.

According to our results, radioiodine uptake was higher in the AM– group, which discontinued AM. Reduced or normal radioiodine uptake in this group depended on the time of therapy and on time from the withdrawal of AM (in most cases 6 to 24 months). Despite differences in radioiodine uptake between the groups, the use of radioiodine proved effective.

The clinical course of AIT may cause difficulties in clinical diagnosis. Typical symptoms may be nonspecific, mainly due to the antiadrenergic action of the drug and inhibition of peripheral conversion of FT_4 to FT_3. In the majority of our patients, episodes of atrial fibrillation occurred with tachyarrhythmia, premature ventricular contractions, or other arrhythmias with hyperactivity. One case of Eisenmenger syndrome in the AM+ group was diagnosed. The symptoms of coronary artery disease were also present in most cases. According to Ladeson et al.,[29] the sensitivity of the cardiovascular system predisposes to the development of arrhythmias and cardiac failure in thyrotoxicosis, particularly in patients receiving permanent AM treatment. In our study, mortality was observed in patients with low left ventricular ejection fraction (<40%). A left ventricular ejection fraction of less than 40% is a powerful predictor of mortality. Therefore, it is not surprising that mortality is high when thyrotoxicosis and a proarrhythmic condition develop.[29]

The decision to use of such a radical treatment as radioiodine therapy resulted primarily from a high level of experience because this form of therapy has been used in Poland since 1956 (it was in our department that radioiodine was used for the first time in Poland). Secondly, in addition to the ablative treatment, in most cases, oral glucocorticoids were used. In over 70% of the cases, antithyroid drugs were used before radioiodine therapy alone or with $KClO_4$. In over 20% of the cases, antithyroid drugs, potassium perchlorate, or lithium could not be used because of leukopenia.

In summary, the present study was a retrospective analysis showing the undervalued role of radioiodine in the therapy of type II AIT. It is particularly useful when other forms of treatment cannot be applied (in particular, thyroidectomy). The results of the present study support the use of radioiodine therapy as a method of choice, even in patients with type II AIT, permanently taking AM and with low radioiodine uptake. In conclusion, radioiodine can be used even in the case of extremely reduced radioiodine uptake, but it requires great patience both from the physician and the patient. Thyrotoxicosis in patients permanently treated with AM has been reported to be associated with increased mortality. Therefore, the withdrawal of AM in the case of AIT should

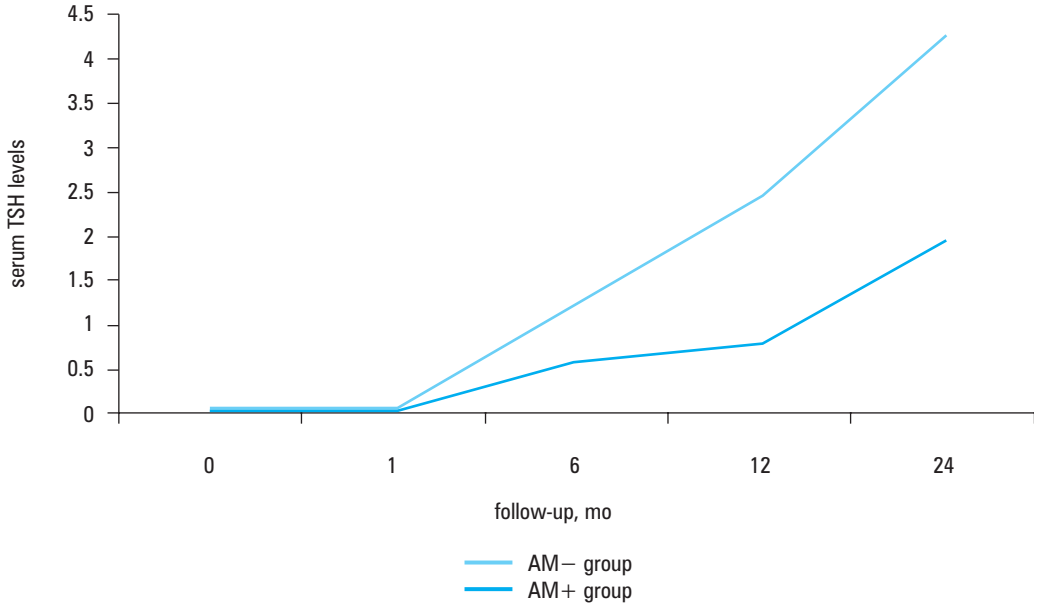

FIGURE 2 Serum thyroid-stimulating hormone (TSH) levels in patients with high radioiodine uptake and a history of past amiodarone treatment (AM– group) and low radioiodine uptake and current amiodarone treatment (AM+ group) during a 2-year follow-up (reference values, 0.27–4.2 μU/ml)

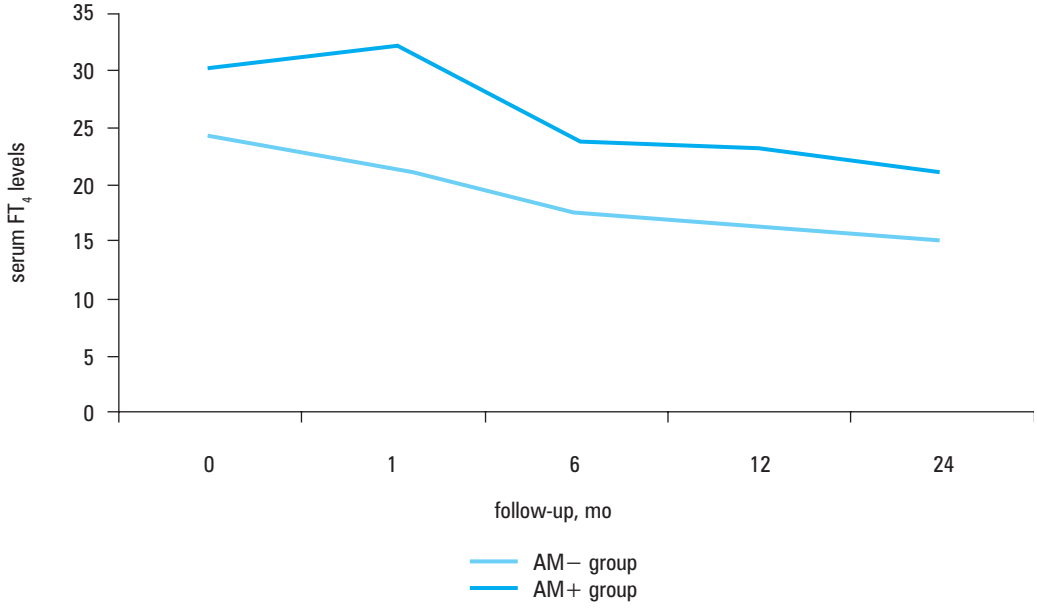

FIGURE 3 Serum free thyroxine (FT_4) levels in patients with high radioiodine uptake and a history of past amiodarone treatment (AM– group) and low radioiodine uptake and current amiodarone treatment (AM+ group) during a 2-year follow-up (reference values, 11.5–21.5 pmol/l)

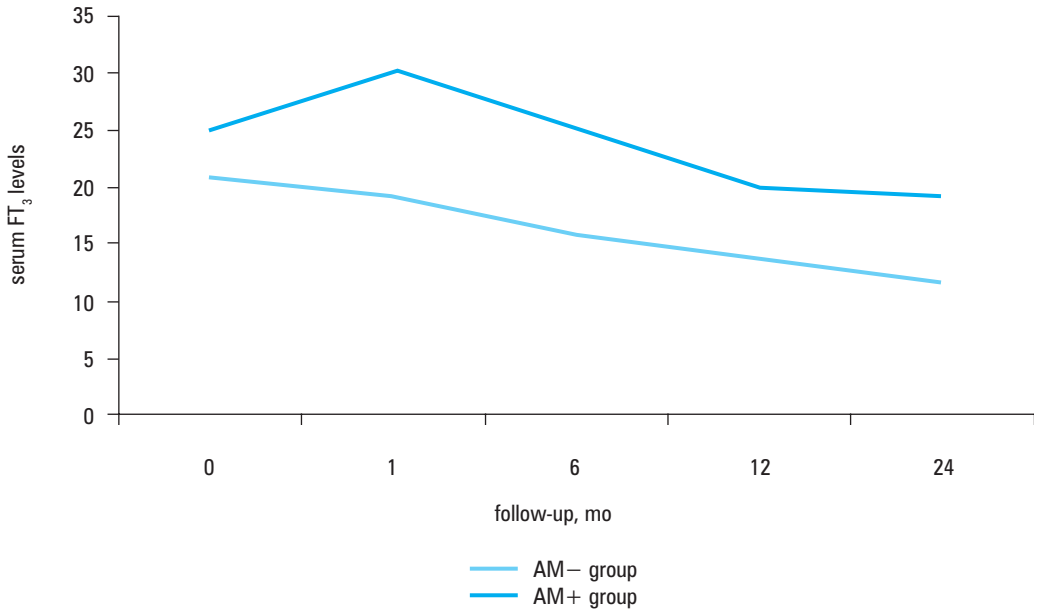

FIGURE 4 Serum free thriiodothyronine (FT_3) levels in patients with high radioiodine uptake and a history of past amiodarone treatment (AM– group) and low radioiodine uptake and current amiodarone treatment (AM+ group) during a 2-year follow-up (reference values, 3.9–6.8 pmol/l)

be considered. However, even if it is not possible, radioiodine therapy can be used effectively.

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Contribution statement AC and IW-S conceived the idea for the study and contributed to the design of the research. AC, IW-S, KW, AS, JW-S, AM, and MR were involved in data collection. AC and IM analyzed the data. All authors were involved in writing the manuscript, and edited and approved the final version.

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Terapia radiojodem u chorych z typem II nadczynności tarczycy indukowanej amiodaronem

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SŁOWA KLUCZOWE

amiodaron, migotanie przedsionków, nadczynność tarczycy, nadczynność tarczycy indukowana amiodaronem, terapia radiojodem

STRESZCZENIE

WPROWADZENIE Terapia nadczynności tarczycy wywołanej amiodaronem (*amiodarone-induced thyrotoxicosis* – AIT) stanowi istotne wyzwanie kliniczne, wymagające ścisłej współpracy specjalistów endokrynologii i kardiologii. Niestety, również w dzisiejszych czasach AIT wiąże się z istotnie zwiększoną śmiertelnością.

CELE Celem niniejszej pracy było porównanie skuteczności leczenia radiojodem AIT typu II w dwóch grupach pacjentów: z wysoką lub prawidłową jodochwytnością, nie przyjmujących aktualnie amiodaronu (AM; grupa AM–), oraz u chorych z niską jodochwytnością pobierających AM (grupa AM+).

PACJENCI I METODY Grupa AM– liczyła 57 chorych, a grupa AM+ 49 chorych. Pacjentom podano jod-131 w dawce 22 mCi~800 MBq. Dane dotyczące pacjentów zbierano przez 2 lata.

WYNIKI Po podaniu radiojodu, stężenie tyreotropiny w surowicy w grupie AM– oraz w grupie AM+ wynosiło odpowiednio 0,0 ±0,0 i 0,0 ±0,0 po 1 miesiącu; 1,2 ±3,3 i 0,6 ±1,2 po 12 miesiącach oraz 4,2 ±3,6 1,9 ±0,8 po 2 latach. Wszystkie różnice pomiędzy analizowanymi grupami pacjentów były istotne statystycznie ($p < 0{,}0001$). Ponadto, stężenia wolnej trójjodotyroniny i wolnej tyroksyny były istotnie wyższe w grupie AM+ w porównaniu z grupą AM–. W trakcie obserwacji zmarło 22 chorych w grupie AM+ oraz 6 w grupie AM–.

WNIOSKI Terapia radiojodem stanowi bezpieczne i skuteczne narzędzie terapeutyczne u chorych z typem II AIT, mimo niskiej jodochwytności. Dotyczy to zwłaszcza chorych, u których stwierdzono przeciwwskazania do innych form leczenia (np. tyreoidektomii). Ponadto, jako że tyreotoksykoza u chorych na AIT stanowi istotny czynnik zwieszonej śmiertelności, oraz wobec braku alternatywnego leczenia antyarytmicznego, terapia radjojodem wydaje się być jedyną skuteczną metodą terapii.

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