



Results of preventive radioiodine therapy in euthyroid patients with history of hyperthyroidism prior to administration of amiodarone with permanent atrial fibrillation — a preliminary study

Wyniki profilaktycznej terapii radiojodem u chorych w stanie eutyreozy z nadczynnością tarczycy w wywiadzie przed podaniem amiodaronu z utrwalonym migotaniem przedsionków — badanie wstępne

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Abstract

Introduction: Radioiodine (RAI) therapy is a standard procedure in the treatment of hyperthyroidism. However, the use of RAI in euthyroid patients requiring chronic administration of amiodarone (AM) where other antiarrhythmic drugs may lack efficacy is still controversial.

Objective: The aim of this study was to assess the safety and efficacy of an AM therapy prior to treatment with radioiodine therapy in euthyroid patients with permanent atrial fibrillation (PAF), who had been treated for hyperthyroidism in the past.

Material and methods: This was a retrospective observational study. Patients were assessed at baseline and two, six, eight, and 12 months after RAI therapy. 17 euthyroid patients with PAF were qualified to the RAI (female/male 3/14; age range 65 to 87, median 71). The patients required chronic administration of AM as a prophylaxis against sudden death.

Results: Each patient received an ablative dose of 800 MBq (22 mCi) of ¹³¹I. At baseline and during follow-up, no side effects of the therapy and no signs of drug intolerance were observed. Subclinical hyperthyroidism occurred in two (11.8%) cases after two months of RAI and five weeks of AM administration. In this situation, RAI therapy was repeated. Three patients (17.6%) after six months, and another two (11.8%) after eight months, required an additional dose of ¹³¹I due to amiodarone-induced thyrotoxicosis (AIT). Twelve patients (70.6%) returned to spontaneous sinus rhythm within two months. Fourteen patients (82.4%) had sinus rhythm during follow-up after six and 12 months of treatment.

Conclusions: Preventive RAI in euthyroid (but previously hyperthyroid) patients with PAF before administration of AM may be the method of choice. This is particularly important for patients who will require permanent AM administration as a life-saving drug. (Endokrynol Pol 2014; 65 (4): 269–274)

Key words: amiodarone-induced thyrotoxicosis; radioiodine therapy; permanent atrial fibrillation

Streszczenie

Wstęp: Terapia radiojodem (RAI) jest standardowym postępowaniem w leczeniu nadczynności tarczycy. Jednakże stosowanie RAI w stanie eutyreozy u pacjentów wymagających przewlekłego podawania amiodaronu (AM), w przypadku braku skuteczności innych leków przeciwarytmicznych, jest kontrowersyjne. Celem pracy była ocena bezpieczeństwa i skuteczności profilaktycznego zastosowania RAI, przed podaniem AM, u pacjentów w eutyreozy z utrwalonym migotaniem przedsionków (PAF), w przeszłości leczonych z powodu nadczynności tarczycy.

Materiał i metody: przeprowadzono analizę retrospektywną. Chorych oceniano na początku badania oraz 2, 6, 8 i 12 miesięcy po zastosowaniu RAI. 17 pacjentów z eutyreozą z towarzyszącym PAF zostało zakwalifikowanych do RAI (kobiety/ mężczyźni 3/14; wiek: 65–87, mediana 71 lat). Pacjenci wymagali przewlekłego stosowania AM jako profilaktyki nagłego zgonu sercowego.

Wyniki: Każdy pacjent otrzymał dawkę ablacyjną ¹³¹I {800 MBq (22 mCi)}. Po podaniu RAI, jak również w okresie obserwacji nie zaobserwowano powikłań. Subkliniczna nadczynność tarczycy wystąpiła w 2 przypadkach (11,8%) po 2 miesiącach od podania RAI i 5 tygodniach od włączenia AM. W tej sytuacji leczenie RAI przeprowadzono ponownie. Trzech pacjentów (17,6%) po 6 miesiącach oraz 2 (11,8%) po 8 miesiącach wymagało podania dodatkowej dawki ¹³¹I z powodu nadczynności tarczycy indukowanej AM. Dwunastu pacjentów (70,6%), powróciło do spontanicznego rytmu zatokowego w ciągu dwóch miesięcy. Po 6 i 12 miesiącach leczenia 14 pacjentów (82,4%) wykazało rytm zatokowy w badaniu kontrolnym.



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Wnioski: Prewencyjne zastosowanie RAI przed włączeniem AM u pacjentów w eutyreozie (w wywiadzie: nadczynność tarczycy) z PAF, gdy terapia innymi lekami antyarytmicznymi okazuje się nieskuteczna, może być rozważana jako metoda z wyboru. Jest to szczególnie ważne w przypadku pacjentów wymagających stałego podawania AM jako leku ratującego życie. (*Endokrynol Pol* 2014; 65 (4): 270–274)

Słowa kluczowe: nadczynność tarczycy indukowana amiodaronem; leczenie jodem radioaktywnym; utrwalone migotanie przedsionków

Introduction

Amiodarone (AM) belongs to the 3rd class of antiarrhythmic drugs (AAD) according to Vaughan-Williams [1, 2]. However, it has some of the properties of classes I and II through inhibition of the inward sodium currents [1]. In addition, it has been used in atrial and ventricular tachyarrhythmias. AM treatment may be regarded as prophylaxis against sudden cardiac death [3]. To date, it is considered to be the best and the most widely used AAD [1, 4]. AM is particularly applicable in pharmacological control of AF, especially the maintenance of primary prevention of AF or conversion of AF to sinus rhythm [5]. Its use is not without a number of side effects such as severe toxicity of lung, liver, nerves, skin, and thyroid [6–9]. The mechanism of AM's influence on the thyroid is not entirely known [10, 11]. While amiodarone-induced hypothyroidism is not a clinical problem, hyperthyroidism (AIT, amiodarone-induced thyrotoxicosis) still presents a difficult challenge even for a skilled endocrinologist [12, 13]. Due to the long half-life and accumulation in tissues [14, 15] hyperthyroidism may develop over time of use, or many months after its withdrawal [10, 11]. AIT may lead to increased mortality, particularly in the elderly with left ventricular dysfunction [16]. Also, AIT is very explosive and very difficult to treat and other pharmacological agents should possibly be used concomitantly with therapy [17].

Treatment options of AIT include: antithyroid drugs (ATD) [12, 18, 19], glucocorticoids [12, 19, 20], iopanoic acid [21], thyroidectomy [22, 23] or radioiodine (RAI) therapy [24–27]. There is a need for the evaluation of a possible role of RAI in euthyroid patients with persistent atrial fibrillation (PAF) requiring AM as a drug of choice to control symptomatic ventricular arrhythmias, primarily to prevent recurrence of ventricular tachycardia (VT) and ventricular fibrillation (VF).

The aim of this study was to assess the safety and efficacy of an AM therapy prior to treatment with radioiodine therapy in euthyroid patients with PAF, who had been treated for hyperthyroidism in the past.

Material and methods

Patient characteristics

We retrospectively analysed medical records of 17 euthyroid patients (female/male 3/14; age range from 65 to 87, median 71 years) with PAF and history of hyperthyroidism, monitored at the Outpatients Department

of Endocrinology, Metabolism and Internal Medicine in Poznan. All patients were subjected to RAI and evaluated retrospectively in a one-year follow-up after inclusion of AM. The following data were recorded: age, gender, time of occurrence of PAF, aetiology of heart disease, previous antiarrhythmic therapy, family history of hyperthyroidism, and type and duration of therapy for hyperthyroidism in the past.

Cardiac status

In all patients, heart failure was diagnosed, NYHA class II in five and class III in 12 cases. The aetiology of PAF included: ischaemic heart disease (four patients), dilated cardiomyopathy (four patients), myocardial infarction (four patients), haemodynamically insignificant left-side valve disease (excluding mitral valve stenosis; two patients) and idiopathic PAF (three patients). Eight patients were implanted with a cardioverter-defibrillator. The mean duration of PAF was 232.3 ± 128.4 days. The admitted patients with PAF were treated unsuccessfully with other AADs such as procainamide (class Ia), propafenone (class Ic), atenolol (class II), propranolol (class II), sotalol (class III), etc. Therefore in the whole group, AM was used as the treatment of choice because of the escalating and life-threatening tachyarrhythmias. Additionally, in the whole studied group, hs-CRP (high sensitivity C-reactive protein) levels were measured as a sensitive marker associated with an increased rate of cardiovascular disease and mortality [28, 29]. The hs-CRP level (reference range < 3 mg/L) was determined with a highly sensitive latex-based immunoassay (Dade Behring; sensitivity 0.05 mg/L) [30]. Clinical characteristics of the analysed population are presented in Table I.

Thyroid status

According to medical records reviewed before RAI therapy, all patients had been treated by antithyroid drugs (ATDs) — thionamide derivatives of thiouracyl {PTU, propylthiouracil (Thyrosan [Sun-Farm]) and imidazole [MMI, thiamazole, Metizol (INC Polfa-Rzeszów)], in one case RAI with glucocorticoids was used (Table I). Furthermore, in one patient, subtotal thyroidectomy was performed before the occurrence of hyperthyroidism. Twelve patients had a family history of hyperthyroidism. Current hormonal profile was characterised by lower limit of normal serum thyrotropin (TSH) and proper range of free thyroxine (fT_4) and free triiodothyronine (fT_3) concentrations as well as negative thyroid

Table I. Clinical and biochemical features of patients included in the study at baseline**Tabela I. Charakterystyka kliniczna i biochemiczna badanej grupy podczas rocznej obserwacji**

Age [year; median (range)]*	71 (65–87)
Sex (F/M)	3/14
Cardiac state	
Mean duration of PAF [days, mean (sd)]	232.3 (128.4)
Aetiology (n, %):	
ischaemic heart disease	4 (23.5)
cardioverter-defibrillator	8 (47.0)
history of myocardial infarction	2 (11.7)
idiopathic AF	2 (11.7)
insignificant left-sided valve disease	1 (5.8)
Heart failure; NYHA class (n, %):	
II	5 (29.4)
III	12 (70.6)
Previous treatment for cardiac disease (n, %):	
AAD:	
Class I a: procainamide	2 (11.8)
Class I b: lidocaine	2 (11.8)
Class I c: propanolone	9 (52.9)
Class II: metoprolol	10 (58.8)
Bisoprolol	6 (35.3)
Atenolol	3 (17.6)
Propranolol	5 (29.4)
Class III: sotalol	12 (70.6)
DCC:	14 (82.3)
Hs-CRP [mg/dL]	5.2 (2.9)
Thyroid state	
Family history of hyperthyroidism (%)	12 (70.6)
Duration of hyperthyroidism in past [months; median (range)]	17 (8–112)
Previous treatment for hyperthyroidism (n, %)	
ATDs:	
MMI	15 (88.2)
PTU	2 (11.8)
oGCS	1 (5.8)
Subtotal thyroidectomy	2 (11.8)
RAI therapy	1 (5.8)
fT ₄ [pmol/L; mean (sd)]	18.3 (1.8)
fT ₃ [pmol/L; mean (sd)]	5.4 (0.9)
TSH [mIU/L; mean (sd)]	0.3 (0.1)
TPO-Abs [IU/mL; mean (sd)]	48.8 (25.1)
Tg-Abs [IU/mL; mean (sd)]	33.8 (11.3)
TSHR-Abs [IU/L; mean (sd)]	0.7 (0.2)
Thyroid volume [mL/m ²]	13.4
CFDS	0
Dose of radioiodine [MBq; mean (sd)]	800 (0.0)
RAIU [mean (sd)] %	
After 5 h	12.0 (2.1)
After 24 h	14.1 (3.5)

All euthyroid patients with PAF (who had had hyperthyroidism in past) received at baseline the same dose of 800MBq (22 mCi) ¹³¹I. Data is expressed as mean(sd). Normal values in our laboratory were as follows: free T₄: 11.5–21.5 pmol/L; free T₃: 3.9–6.8 pmol/L; TSH: 0.27–4.2 μIU/mL; TSHR-Abs: < 2 IU/L, TPO-Abs: 0–34 IU/mL and Tg-Abs: 10–115 IU/mL and: CRP ≤ 5.0 mg/dL. All patients had undetectable serum Tg-Ab, TPO-Ab, TSHR-Abs. Thyroid volume was measured by ultrasonography (normal values range to 19 for F and to 25 ml for M). Abbreviations: F — female; M — male; PAF — permanent atrial fibrillation; AAD — antiarrhythmic drugs; HY — hyperthyroid, EU — euthyroid typical for AIT (with normal range of fT₃); TSH — thyroid stimulating hormone; fT₄ — free tetraiodothyroxine; fT₃ — free triiodothyronine; TPO-Abs — thyroperoxidase antibodies; TSHR-Abs — autoantibodies to the thyrotropin receptor; HsCRP — High sensitivity C-reactive protein; CFDS — colour flow Doppler sonography; ATDs — antithyroid drugs; MMI — methimazole; PTU — propylthiouracyl; oGCS — oral glucocorticoids; RAI — radioiodine therapy; DCC — direct cardiac cardioversion; SR — sinus rhythm

autoantibodies (Tg-Abs: thyroglobulin autoantibodies, TPO-Abs: thyroperoxidase autoantibodies, TSHR-Abs: autoantibodies to the thyrotropin receptor). The normal ranges for serum hormone concentrations in our laboratory were as follows: TSH: 0.27–4.2 μIU/mL, fT₄: 11.5–21.5 pmol/L, fT₃: 3.9–6.8 pmol/L, Tg-Ab: 10–115 IU/mL, TPO-Ab: 0–34 IU/mL and TSHR-Abs: < 2 IU/L. Free T₄, free T₃, as well as TSH, were measured by the electrochemiluminescent method (Roche). Serum TSH concentration was measured with a third-generation sensitivity ≤ 0.005 IU/mL. Serum Tg-Abs, TPO-Abs and TSHR-Abs were measured by RIA (Brahms).

Sonography, radioiodine uptake and scintigraphy

Thyroid ultrasonography was performed using an Aloka SSD-500 (Aloka, Tokyo, Japan) with a 7.5-MHz linear transducer. Thyroid volume was measured by ultrasonography and calculated using the ellipsoid model (width × length × thickness × 0.52 for each lobe) [31, 32]. In the whole group, CFDS (colour-flow Doppler sonography) was performed [33]. The thyroid scintiscan 30 min. after an i.v. administration of 150 MBq of ^{99m}Tc [Nucline gamma camera (Mediso, Hungary)] was performed in cases where thyroid nodules occurred. Thyroidal radioiodine uptake (RAIU) values were measured 5 and 24 h after the administration of a diagnostic dose (ca. 2MBq) of ¹³¹I. The thyroid scintiscan showed lack of accumulation of isotope.

Treatment

Radioiodine

All patients received an identical therapeutic ablative dose of ¹³¹I [22mCi = 800 MBq] before initiation of AM treatment.

Amiodarone

In the whole studied group, AM was used in recurrent, symptomatic PAF after ineffective treatment with AAD and electrical cardioversion. Oral AM administration in all patients was started at about the same time, 3–6 weeks after RAI therapy. In two (11.76%) cases, AM was administered initially as an intravenous 150 mg bolus. The average dose of AM was from 150 to 900 mg daily. The therapy was continued on an outpatient basis.

Study protocol

In all patients, serum TSH, fT₄, fT₃ and autoantibodies (Abs) concentrations were measured at baseline and two, six, eight and 12 months afterwards. Hypothyroidism was defined when serum TSH concentration increased above the normal range (with a concomitant decrease in serum free thyroid hormone concentrations). The diagnosis of AIT was based on the following criteria: history of AM medication for at least one

month, signs and symptoms of hyperthyroidism confirmed by increased fT₄ and suppressed TSH levels that occurred during therapy, a negative titre of circulating thyroid Abs (Tg-Abs, TPO-Abs, TSHR-Abs), thyroid of normal or slightly increased volume without relevant nodules (≥ 1 cm) at conventional ultrasonography. Signs associated with thyroid ophthalmopathy (Dalrymple's sign, Kocher's sign, von Graefe's sign and Mobius sign) were negative in our group of patients.

The study protocol was approved by the Ethics Committee at the University of Medical Sciences in Poznan. After informing patients about the aim of the study and proposed treatment, written permission was obtained from each patient.

Statistical analysis

The calculations were performed using Statistica v. 10 from StatSoft. A *P* value under 0.05 was considered statistically significant. Statistical significance of changes in laboratory parameters were calculated using variance analysis test for dependent variables (if there was a normal distribution of variable) or Friedman test (in cases of a lack of normal distribution). If a result was statistically significant, Tukey's test was used to identify results which differed significantly from each other.

Results

Patient characteristics

The study group comprised 17 consecutive patients (female/male 3/14; aged from 65 to 87, median 71 years) with PAF, in whom AM was used to prevent life-threatening tachyarrhythmias. All patients in the past had been treated due to recurrences of hyperthyroidism. The clinical and biochemical examination at baseline and during one-year follow-up are presented in Table I and Table II.

Results of thyroid status and serology

Each patient received an ablative dose of 800 MBq (22 mCi) of ¹³¹I. At baseline and during follow-up, no side effects of the therapy and no signs of drug intolerance were observed. Subclinical hyperthyroidism occurred in two (11.8%) cases after two months of RAI and five weeks of AM administration. In this situation, RAI therapy was performed again. Additionally, three patients (17.6%) after six months, and two (11.8%) patients after eight months, required the administration of an additional dose of ¹³¹I due to AIT. It should be noted that in none of the patients clinical symptoms of hyperthyroidism were observed. This was due to the antiadrenergic action of AM on the thyroid gland. The mean results of RAIU (before

RAI therapy) after 5 and 24 hours were 12.0% and 14.1%, respectively.

At baseline and two, six, eight and 12 months after RAI, the changes in levels of fT₄ and fT₃ were not significant. The mean (\pm SD) serum fT₄ and fT₃ levels were: 18.3 \pm 1.8 and 5.4 \pm 0.9 pmol/L (before RAI), 18.5 \pm 2.0 pmol/L and 5.6 \pm 1.0 pmol/L (after two months), 18.2 \pm 4.9 pmol/L and 6.1 \pm 2.1 pmol/L (six months), 16.3 \pm 5.6 pmol/L and 5.3 \pm 1.1 pmol/L (eight months), and 14.6 \pm 4.1 pmol/L and 4.6 \pm 1.1 pmol/L (12 months), respectively. The values of serum TSH were: 0.3 \pm 0.1 at baseline, 0.6 \pm 0.6 after two months, 1.4 \pm 1.1 (six months), 1.4 \pm 2.8 (eight months), and 4.2 \pm 3.0 IU/mL (12 months). These changes were significant (*P* < 0.0001). Furthermore, TSH level after 12 months was significantly higher than those at baseline and after two and eight months. The TPO-Abs, Tg-Abs, and TSHR-Abs were within normal limits and did not change significantly during the period of observation (Table I and II). During 12-month follow-up, in seven (40.9%) patients, hypothyroidism was diagnosed and in all these cases L-thyroxine was administered; in another two (11.8%) patients, subclinical hypothyroidism was noted.

Hs-CRP levels were slightly elevated and were not significantly different during follow-up. At the baseline the ultrasound of the thyroid gland showed deeply decreased and irregular echogenicity and slightly decreased gland size during one-year follow-up. The CFDS indicated completely reduced vascularisation.

Results of cardiac status

Twelve patients (70.6%) returned to spontaneous SR within two months. Fourteen patients (82.4%) had SR during control examination after six and 12 months of treatment (Table II). Repeated DCC (direct cardiac cardioversion) was performed in four (23.5%) patients: three (17.6%) after six months and one (5.8%) after eight months of follow-up. No complications were observed.

Additionally, in two patients after eight months of follow-up who developed hyperthyroidism, beta-blocker (atenolol; mean dose 36.2 \pm 13.4 mg/day) was administered. Therefore, all of these patients required an additional dose of ¹³¹I again. In none of the cases was sudden cardiac death observed. During the 12 months of follow-up, no side-effects of AM were observed (Table II). Hyperthyroidism that occurred during the observation did not deteriorate the patients' clinical cardiac status.

Discussion

Among all available antiarrhythmic drugs (AADs), AM is the most effective and is used for short-term inpatient and outpatient therapy. Particularly it is necessary to

Table II. Clinical characteristics of the study group during one-year follow-up

Tabela II. Charakterystyka kliniczna grupy badanej podczas rocznej obserwacji

Time of observation during AM therapy (months)	2	6	8	12
Thyroid state (n, %)				
EU	15 (88.2)	14 (82.3)	12 (70.6)	8 (47.0)
HYP0	–	–	3 (17.6)	9 (52.9)
HYP0 (= AIT)	2 (11.8)	3 (17.6)	2 (11.8)	–
fT4 [pmol/L; mean (sd)]	18.5 (1.9)	18.2 (4.9)	16.3 (5.6)	14.6 (4.1)
fT3 [pmol/L; mean (sd)]	5.6 (1.0)	6.1 (2.1)	5.3 (1.1)	4.6 (1.1)
TSH [mU/L; mean (sd)]	0.6 (0.6)	1.2 (1.0)	1.4 (2.8)	4.2 (3.0)
TPO-Abs [IU/mL; mean (sd)]	67.5 (35.6)	37.9 (24.5)	39.3 (22.8)	33.6 (23.1)
Tg-Abs [IU/mL; mean (sd)]	43.2 (23.5)	59.2 (22.4)	33.9 (21.3)	49.9 (21.8)
TSHR-Abs [IU/L; mean (sd)]	1.2 (0.3)	1.0 (0.5)	0.8 (0.4)	0.9 (0.7)
Hs-CRP [mg/dL; mean (sd)]	5.1 (2.7)	6.3 (2.1)	5.9 (2.5)	5.4 (2.8)
Thyroid volume [mL/m ²]	13.4	12.1	10.3	9.2
Dose of radioiodine [800 MBq (22mCi); mean (sd)]	800 (0.0) 22 (0.0)	800 (0.0) 22 (0.0)	800 (0.0) 22 (0.0)	–
Return SR (n, %)	12 (70.59)	14 (82.35)	13 (76.47)	14 (82.35)
DCC	–	3 (17.6%)	1 (5.8%)	–

Abbreviations: AM — amiodarone; EU — euthyroidism; HYP0 — hypothyroidism; HYP0 — hyperthyroidism; AIT — amiodarone-induced thyrotoxicosis; fT4 — free tetraiodothyroxine; fT3 — free triiodothyronine; TSH — thyroid stimulating hormone; TPO-Abs — thyroperoxidase antibodies; Tg-Abs — thyroglobulin antibodies; TSHR-Abs — autoantibodies to the thyrotropin receptor; Hs-CRP — High sensitivity-C-reactive protein; SR — sinus rhythm; CI — coincidence interval; DCC — direct cardiac cardioversion

achieve sinus rhythm (SR) during defibrillation testing in patients with PAF undergoing implantation of a cardioverter–defibrillator (ICD) [34, 35]. According to Lelakowski et al. [35], AF may adversely influence the inappropriately on ICD as VF and/or ventricular tachycardia, may occur damaging the ventricular defibrillation programme.

In our study, many of the patients had had an ICD aimed at the treatment of PAF when AADs were not effective. However, defibrillation may lead to SR restoration which may be hazardous due to the increased risk of thromboembolic complications [35]. The efficacy of a direct cardioverter-defibrillator in patients with PAF is on average about 75% and varies between 60% and 90%. The final effect depends on the energy and the type of impulse used [36, 37]. AM seems to be the most validated among numerous AADs with documented properties of restoring SR [38, 39]. However, administration of AM in patients who previously developed hyperthyroidism is dangerous. Unfortunately, the side effects in severe AIT can even lead to death.

The RAIU values do not seem to have clinical significance since patients were taking ‘ablative’ doses of RAI. However, its determination is very important in order to assess the efficiency of RAI in patients receiving AM. This medication causes almost complete reduction of RAIU (less than 1%) which is characteristic for Type II AIT. Although the value of RAI in AIT in this situation

remains controversial, our prior studies confirmed the efficacy of RAI therapy in AIT with greatly reduced RAIU [26].

In our study, an ‘ablative’ dose of 800 MBq of ¹³¹I (22 mCi) was used, regardless of the size of the thyroid gland. However, Hermida [40] administered various doses of RAI from 370 to 740 MBq (10–20 mCi) depending on the thyroid volume. Despite the fact that at baseline all patients were euthyroid, in five cases a second dose of RAI was required due to the development of AIT (Table II). In clinical practice, the maximum dose of ¹³¹I should be applied prior to AIT for a protective effect.

We are aware of the limitations of our study: first of all, there was no detailed analysis of cardiac examinations (e.g. echocardiography) during follow-up; secondly, the administration of an ablative dose of ¹³¹I in already euthyroid patients may give rise to much controversy. We realise that the AM contains a large amount of iodide (39% iodine by weight) [13] and is often administered ‘blindly’, mostly in the emergency departments, which can result in severe complications. AIT is a dangerous condition, which is very difficult to treat. First of all it may worsen the underlying cardiac disease, e.g. affect the control of arrhythmias. Secondly, thyrotoxicosis can increase the metabolism of oral anticoagulants, which are essential in patients with PAF. Furthermore, early diagnosis can be very difficult, especially in elderly patients as AIT can show unusual clinical manifestations with atypical symp-

toms limited to depression, reduced appetite, apathy or general weakness.

Therefore, endocrinologists often suggest to cardiologists that they should withdraw AM and replace it by another AAD. However, in these particular cases which are the subjects of our dissertation, while other AADs were already ineffective, AM was a life-saving drug and prevented sudden death.

According to Hermida et al. [40] and also our observation, taking into account the potential risk/benefit ratio of permanent AM administration, RAI prior to AM medication seems to be the only effective and adequate preventative treatment in such difficult clinical situations when AIT may occur. This is particularly important in the following situations: 1) unsuccessful treatment after all other AADs have been used; 2) life-threatening atrial and ventricular tachyarrhythmias; 3) prior documented episode of AIT [40].

It is essential to observe patients carefully before and during AM administration. In our opinion, thorough thyroid gland examination and serum TSH measurement should be performed at least once a month in patients continuously receiving AM. Additionally, we would recommend fT4 and fT3 determinations no less than once every three months.

To summarise, our results demonstrate that preventative RAI therapy before including AM in euthyroid patients (but with a history of hyperthyroidism), with atrial tachyarrhythmias when other AAD drugs are ineffective may be a method of choice.

This is particularly important for patients who will require permanent administration of AM as a life-saving drug. Additionally, it should be noted that the only 'complication' after RAI therapy may be permanent hypothyroidism. However, in this particular clinical situation, hypothyroidism should be considered as a goal rather than the side effect of RAI therapy.

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