

Radioactive Iodine in the Treatment of Type-2 Amiodarone-Induced Thyrotoxicosis

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Objective: Amiodarone-induced thyrotoxicosis (AIT) is usually classified into two types: type 1, in which a high iodine content triggers the autonomous production of thyroid hormone; and type 2, in which destructive thyroiditis causes the release of preformed thyroid hormone. AIT is a difficult management problem that sometimes requires ablative thyroid therapy. The use of radioactive iodine (RAI) therapy in patients with type-1 AIT who had a 24-hour radioactive iodine uptake (RAIU) value of >10% has been previously reported. Despite its documented efficacy at usual doses (10–30 mCi) in patients with type-1 AIT, the efficacy of RAI in those with type-2 AIT has never been questioned, because type-2 patients usually have low RAIU. We thought that high adjusted-dose RAI might be an attractive alternative to thyroid gland ablation in patients with type-2 AIT.

Patients and Methods: Four patients with type-2 AIT who required thyroid ablation were included in the study. These individuals were either poor candidates for surgery or had refused surgery. The size of the thyroid gland in all subjects was within normal limits, and each thyroid was characterized by a homogenous echotexture on ultrasonography, the absence of vascularity on Doppler sonography, a low (<4%) 24-hour RAIU value and the absence of thyroid autoantibodies—all of which are characteristic of type-2 AIT.

Results: The patients were initially treated with thionamides and glucocorticoids. All patients except one achieved euthyroidism before RAI therapy. All four patients received one dose of RAI (range 29–80 mCi) and followed up for 12 months. No exacerbation of thyrotoxicosis was noted after RAI therapy. Hypothyroidism (in three patients) or euthyroidism (in one patient) was achieved in first six months.

Conclusions: In patients with type-2 AIT, RAI treatment may be the therapy of choice for thyroid gland ablation.

Key words: drugs ■ thyroid ■ treatment

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INTRODUCTION

Amiodarone is a heavily iodinated and very effective antiarrhythmic medication that is frequently used to treat cardiac arrhythmias ranging from paroxysmal atrial fibrillation to life-threatening ventricular tachyarrhythmia.¹ However, amiodarone can cause severe adverse effects, including thyroid dysfunction associated with high iodine content.^{1,2} Patients treated with that agent may present with clinically significant amiodarone-induced hypothyroidism or amiodarone-induced thyrotoxicosis (AIT). Amiodarone-induced hypothyroidism, which is the result of inability of the thyroid to escape from the Wolff-Chaikoff effect, is readily managed by either the discontinuation of amiodarone therapy or treatment with thyroid hormone replacement.³ However, AIT represents a management dilemma for endocrinologists and cardiologists, because the patient's response to the treatment of that disorder is not always predictable, recovery takes time, and patients treated with amiodarone invariably have underlying heart disease that can be exacerbated by ongoing thyrotoxicosis.² AIT may be caused by the excessive iodine-induced synthesis and release of thyroid hormone in individuals who have underlying thyroid disease (type-1 AIT) or by drug-induced destructive thyroiditis and the release of preformed thyroid hormones in individuals with no underlying thyroid disease (type-2 AIT).⁴ Mixed forms of AIT also exist.⁴ The simultaneous administration of thionamides and potassium perchlorate is the treatment of choice for patients with type-1 AIT, and glucocorticoids are the most useful therapeutic option for individuals with type-2 AIT.^{4,8} Patients with a mixed form of AIT are best treated with a combination of thionamides, potassium perchlorate and glucocorticoids.^{7,8}

Ablative thyroid therapy in patients with AIT is reserved as an option for those who cannot tolerate the discontinuation of amiodarone therapy, individuals whose AIT is refractory to conventional medical treatment for thyrotoxicosis and those who require prompt resolution of thyrotoxicosis-related cardiac decompensation.² Research has shown that most such patients are managed success-

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fully by near-total or total thyroidectomy despite a slightly increased surgical risk.⁹⁻¹² There are also a few reports describing ablative therapy with radioactive iodine (RAI) in patients with type-1 AIT who had a normal-to-high level of RAI uptake (RAIU).^{13,14} Because of the low RAIU in patients with type-2 AIT, RAI treatment is not recommended for those individuals.^{15,16} However, we thought that treatment with adjusted high-dose RAI (i.e., an adjustment made according to the patient's 24-hour RAIU and thyroid weight) might be an appropriate alternative to thyroid ablation in patients with type-2 AIT.

PATIENTS AND METHODS

The Baskent University Ethics Committee for Human Studies approved the protocol for this study. All participants provided informed consent. The study consisted of four patients with type-2 AIT who required ablative thyroid therapy. All patients except one (who refused surgery) were poor candidates for thyroidectomy. Thyrotoxicosis was confirmed in all patients by the presence of decreased levels of serum thyrotropin (TSH) and an increase in free-T₃ and free-T₄ levels. The diagnosis of type-2 AIT required the fulfillment of the following criteria in all patients: no history of thyroid disease; a thyroid gland within normal limits for size and with a homogeneous echotexture on ultrasonography; the absence of thyroidal vascularization on color flow Doppler sonography; low (<4%) 24-hour RAIU; and the absence of circulating antithyroglobulin (TgAb), antithyroperoxidase (TPOAb) and anti-TSH receptor (TRAb) antibodies.

Commercially available kits were used to determine the serum concentrations of free T₄, free T₃, TSH, anti-TPO, anti-Tg (DPC kits, Diagnostic Products Corp., Los Angeles, CA) and TRAb (TRAK-Assay, Brahms Diagnostica GmbH, Berlin, Germany).

Thyroid ultrasonography was performed by the same endocrinologist, who used a 10-MHz linear probe (Logiq 5 Pro, GE Medical Systems, Wisconsin). The length, width and depth measurements of the thyroid glands were noted, and the volume of each thyroid gland was calculated according to the ellipsoid formula below:

$$\text{Volume (mL): } \frac{\text{width} \times \text{depth} \times \text{length} \times \pi}{6}$$

Estimates of thyroid weight were based on the volume obtained by means of ultrasonography. The density of the thyroid gland was assumed to be 1 g/mL. The administered RAI dose was based on thyroid volume and the RAIU value. The measurement of each patient's 24-hour RAIU was performed with 100 μ Ci I-131, the neck activity was counted at 25 cm with a standard NaI thyroid uptake detector (Atomlab 950, Biodex Medical, New York). The administered radioiodine dose was calculated according to the following formula:

$$\text{RAI dose (mCi): } \frac{\text{thyroid weight (g)} \times 80 \mu\text{Ci/g of thyroid tissue}}{24\text{-hour RAIU (\%)}}$$

The delivered activity of 80–200 μ Ci/g of thyroid tissue is generally recommended.¹⁷ To prevent I-131-induced exacerbation of thyrotoxicosis in our high-risk population, our goal was to deliver 80 μ Ci/g of thyroid tissue. In all cases, the calculated dose to be administered exceeded the maximum dose allowed as treatment in outpatient settings in Turkey. Therefore, the treatment was administered in a lead-lined room.

The patients underwent thyroid function evaluation on the day after discharge from the lead-lined room and at follow-up examinations at one, three, six, nine and 12 months after the treatment was administered.

RESULTS

The patients' demographic and clinical characteristics are presented in Table 1. All patients except one were euthyroid before RAI therapy. Amiodarone treatment was continued in all but one patient. All patients received one dose of RAI therapy (range 29–80 mCi). Thyrotoxicosis resolved in all patients after RAI therapy. At subsequent follow-up examinations, three of the patients were hypothyroid and one was euthyroid. No patient experienced adverse effects related to RAI therapy, and all patients were hemodynamically stable throughout the follow-up period.

Case 1

A 46-year-old male patient with type-2 diabetes mellitus had atrial fibrillation and dilated cardiomyopathy secondary to rheumatic mitral valve disease. The patient's

Table 1. Demographic and clinical characteristics of the study subjects

Patient Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age/sex	46/male	70/male	74/female	83/male
Duration of amiodarone therapy (mo)	36	24	14	26
Thyroid radioiodine uptake 24 hours after treatment with thionamides and glucocorticoids (%)	2.1	3.7	2.5	2.9
Thyroid weight (g)	21	23	9	13
I-131 dose (mCi)	80	50	29	35
Discontinuation of amiodarone	No	No	No	Yes
Restoration of euthyroidism (mo)	3	3	6	6

atrial fibrillation was controlled and had converted to a normal sinus rhythm as a result of 36 months of treatment with amiodarone after therapy with numerous other antiarrhythmic agents had failed. This patient presented with the signs and symptoms of thyrotoxicosis. The results of thyroid function tests, ultrasonography and RAIU evaluation were consistent with the diagnosis of type-2 AIT. Treatment with propylthiouracil and steroids was continued for five months but failed to restore euthyroidism. Our cardiology department staff insisted on this patient's continuing amiodarone therapy, and the patient was considered at high risk for thyroidectomy. Three months after he had received 80 mCi of RAI, euthyroidism developed. He was lost to follow-up for a brief period but returned for evaluation six months after treatment, at which time euthyroidism had persisted without further therapy.

Case 2

A 70-year-old man with ischemic dilated cardiomyopathy had been treated with amiodarone for 24 months after the implantation of an implantable cardioverter-defibrillator to correct recurrent ventricular tachycardia. Hyperthyroidism was diagnosed when a routine evaluation showed that his TSH levels were low and his free-T4 level had increased. Further investigation of the cause of his thyrotoxicosis resulted in the diagnosis of type-2 AIT. This patient was successfully treated with propylthiouracil and prednisone in addition to his ongoing amiodarone therapy. Recurrent symptomatic type-2 AIT developed three months after prednisone therapy. His cardiologist stated that treatment with amiodarone could not be terminated. The patient was unable to tolerate thyroidectomy and was referred for treatment with 50 mCi of RAI. Three months after having undergone that treatment, he was hypothyroid, and L-thyroxine replacement therapy was initiated.

Case 3

A 74-year-old woman with type-2 diabetes, hypertension and right hemiplegia caused by an embolic stroke had been treated with amiodarone to control atrial fibrillation after coronary bypass surgery. Asymptomatic thyrotoxicosis developed after 14 months of amiodarone treatment. As treatment with amiodarone was stepped down, therapy with methimazole was initiated without etiologic consideration of the patient's thyrotoxicosis. Liver function abnormalities developed as a result of treatment with methimazole, which was discontinued. At that time, this patient was euthyroid. She presented with atrial fibrillation and a high ventricular rate that was refractory to conventional antiarrhythmic treatment, and amiodarone therapy was again required. Symptomatic thyrotoxicosis consistent with type-2 AIT was diagnosed three months after amiodarone therapy had been resumed. A brief course of treatment with propylthiouracil and prednisone restored her euthyroidism, after which she received RAI therapy (29 mCi). Six months after that treatment, she was hypothyroid.

Case 4

An 83-year-old man had been treated with amiodarone to control ventricular tachycardia. Symptomatic hyperthyroidism developed after 26 months of that therapy. He had been initially treated with propylthiouracil and prednisone at another medical center. Thyroid function tests performed after his admission to our hospital revealed unresolved thyrotoxicosis, and further testing resulted in a diagnosis of type-2 AIT. Amiodarone therapy was discontinued, but his cardiologist stated that reintroduction of treatment with that agent would soon be required, although the patient could little tolerate a recurrence of thyrotoxicosis. He refused thyroidectomy, and RAI therapy (35 mCi) was administered. Six months later, hypothyroidism developed and therapy with L-thyroxine was initiated.

DISCUSSION

AIT occurs in 2–12% of patients who receive long-term amiodarone treatment, depending on the dietary iodine content of the geographic area in which they live.^{18,19} In some of those patients, discontinuation of amiodarone is not feasible because they are subject to recurrent arrhythmia that is refractory to other antiarrhythmic agents. Even if amiodarone treatment were discontinued in those individuals, their thyrotoxicosis might not improve.² Because these patients also exhibit significant comorbid cardiac conditions and often do not tolerate a state of hyperthyroidism, their thyrotoxicosis requires prompt resolution. AIT differs from other forms of thyrotoxicosis in that severe left ventricular dysfunction is associated with increased mortality.²⁰

The medical management of AIT includes, if possible, the discontinuation of amiodarone therapy and treatment with an antithyroid drug, steroids, a cholecystographic agent and potassium perchlorate.^{2,5-8} In some patients, the discontinuation of amiodarone alone sometimes results in complete remission of thyrotoxicosis, which (because of the long half-life of that drug) can take several weeks to months to occur. Recurrence of thyrotoxicosis after initial successful medical treatment is not uncommon.² Patients whose thyrotoxicosis is refractory to conventional drug therapy (even if treatment with amiodarone has been discontinued) and those who require prompt resolution of thyrotoxicosis-related cardiac decompensation may be treated with other therapies, including lithium, plasmapheresis or ablative therapy (either thyroidectomy or RAI).^{13,14,21,22} Many series have reported the successful surgical management of AIT.⁹⁻¹² However, thyroidectomy is not feasible in some patients, such as the elderly or those with a significant cardiac condition that precludes surgery. Furthermore, thyrotoxicosis places the patients at higher risk for perioperative morbidity and mortality.²

RAIU is usually considered an important factor in the outcome of RAI therapy. High RAIU levels are generally accepted as a prerequisite for a successful outcome,²³ and very low RAIU in patients with AIT is suggested by some

authors to be a contraindication to RAI therapy.¹⁵ AIT is thought to be caused by the large iodine burden that results from the high iodine content of amiodarone. However, data on the association between RAIU and the response to RAI therapy remain controversial. In some studies, a significant association between a low 24-hour RAIU and a successful response to RAI therapy has been reported.²⁴⁻²⁶ Recently, in both a case report and study on a group of 15 patients with type-1 AIT, RAI therapy was used successfully to ablate the thyroid gland in subjects with a sufficiently high fractional uptake of iodine (>10%).^{3,4} In a case report by Iskandar and colleagues, a 79-year-old patient with type-1 AIT who had a 24-hour RAIU of 54% was successfully treated by therapy with 30 mCi of RAI.¹⁴ Hermida and colleagues retrospectively evaluated the effects of RAI therapy in preventing the recurrence of type-1 AIT in 15 euthyroid patients who required the reintroduction of amiodarone treatment.¹³ Those patients had an RAIU value of >10%, and a standard dose ranging from 10–20 mCi of RAI was administered. The authors claimed that RAI therapy appeared to be an effective and safe method for the treatment of type-1 AIT and the prevention of recurrent AIT, and suggested that RAI therapy could facilitate the reintroduction of amiodarone treatment.

Although RAIU is usually undetectable or very low in patients with type-2 AIT, we theorized that adjusted high-dose RAI therapy would benefit those individuals. In our study, four patients with type-2 AIT that required ablative thyroid therapy were included. All patients who had a 24-hour RAIU of <4% were successfully treated with one dose of RAI therapy (range 29–80 mCi). Three out of four patients developed hypothyroidism being on amiodarone treatment. However, we keep in mind the possibility that these patients developed iodine-induced hypothyroidism or hypothyroidism as a late consequence of the inflammatory process of the thyroid gland.²⁷

RAI therapy can cause radiation thyroiditis via the release of stored thyroid hormone into the circulation, which results in the occasional worsening of hyperthyroidism and (rarely) the precipitation of thyroid storm. Accordingly, elderly patients and individuals with significant pre-existing heart disease, severe systemic illness or any form of debility are particularly prone to that devastating complication.²⁶ In the treatment of thyrotoxicosis in our study, the delivered activity of RAI per gram of thyroid tissue was kept to a minimum (80 mCi) to prevent the development of radiation thyroiditis. No patient experienced adverse effects related to RAI therapy. We concluded that RAI therapy may be an effective alternative to surgery in patients with type-2 AIT.

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