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Amiodarone-Induced Thyrotoxicosis

Clinical Course and Predictors of Outcome

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Objectives This study sought to determine the clinical course and predictors of long-term outcome in patients with documented amiodarone-induced thyrotoxicosis (AIT).

Background Amiodarone-induced thyrotoxicosis is a condition that is difficult to manage, in particular because of the long half-life of amiodarone. Data on optimal treatment for AIT are scarce.

Methods We performed a retrospective review among patients with documented AIT at a tertiary care center. Baseline characteristics, treatment received, laboratory parameters, and events during follow-up were evaluated. The predefined composite end point consisted of the following AIT-associated complications: death, heart transplantation, hospitalization for heart failure, myocardial infarction, stroke, hospitalization for arrhythmia management, or hospitalization for treatment complications.

Results Eighty-four patients were included in the present analysis; 27 patients received prednisone for AIT. There was no difference in time to normalization of free thyroxine between those receiving and those not receiving prednisone. Long-term follow-up showed high morbidity and mortality; 47 patients (56%) reached the primary end point. Patients receiving prednisone had a worse outcome than those not receiving prednisone ($p = 0.003$). Although patients received prednisone for 84 ± 65 days, curves started to separate only 12 months after the initial diagnosis.

Conclusions Patients with AIT have a high event rate during follow-up. Prednisone had no effect on time to normalization of thyroxine levels and was associated with an increased event rate. Importantly, AIT-related problems must be expected late, at a time when thyroid function is under control. (J Am Coll Cardiol 2007;49:2350–5) © 2007 by the American College of Cardiology Foundation

Amiodarone is the most effective drug in maintaining sinus rhythm in patients with atrial fibrillation (1) and in reducing shock delivery in recipients of an implantable defibrillator (2). Unlike class I and III antiarrhythmic drugs, amiodarone does not carry the risk of increased mortality caused by a proarrhythmic effect (3,4), including in patients with heart failure (5).

Although very effective, the use of amiodarone can be associated with significant side effects. Among these, thyroid dysfunction is a common manifestation. The exact prevalence and pathogenesis of amiodarone-induced thyrotoxicosis (AIT) or hypothyroidism, respectively, are unknown. The risk of thyroid dysfunction is lower when lower doses of amiodarone are used (6).

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Because of the long half-life of amiodarone, AIT may take a prolonged course (7). Type 1 AIT occurs in patients with pre-existing or "latent" thyroid disease. Type 2 AIT is a form of destructive thyroiditis that develops in patients with normal thyroid function at baseline (8) (Table 1). However, mixed forms manifesting features of both type 1 and type 2 disease commonly are found (9). Although prospective data are scarce (10), type 1 disease is usually treated with antithyroid drugs and type 2 disease is usually treated with additional prednisone therapy and/or iopanoic acid (11). Some refractory cases even need thyroidectomy (12).

Short-term follow-up showed (13) that AIT is associated with a higher mortality than thyrotoxicosis because of Graves' disease. However, no data about the long-term outcome in patients with AIT are available. Because in these patients amiodarone with its very long half-life must be stopped most of the time, significant arrhythmia problems may occur during long-term follow-up, even after thyroid hormone levels have returned to normal.

The goal of this study was to examine the clinical long-term outcome in patients with AIT. Furthermore, different treatment regimens for AIT were compared with regard to the duration of hyperthyroidism and long-term outcome.

Methods

Patients. A retrospective analysis was performed. Eighty-four patients with a documented diagnosis of AIT between 1996 and 2005 were included. Patient charts in the Departments of Cardiology and Endocrinology at the University Hospital Basel, Switzerland, were screened for cases with a previous diagnosis of AIT. We defined AIT as a combination of suppressed thyroid-stimulating hormone (TSH) levels (below lower reference value) and elevated levels of free thyroxine (fT4) and/or triiodothyronine (T3), and newly manifesting while the patient was taking amiodarone.

Procedures. All patients alive at follow-up were contacted for a detailed interview. Medical history was assessed using a structured questionnaire. Additionally, the treating general practitioners, cardiologists, and endocrinologists were contacted for further information. Data about the date of onset of AIT, duration of and reason for amiodarone therapy, comorbidities, left ventricular function at the time of AIT diagnosis, and previous thyroid disease were collected. Type and duration of therapy for AIT was assessed.

Predefined events occurring during follow-up were identified using the same data sources. Laboratory parameters were retrieved from patient charts and from the archive of the laboratory of the University Hospital Basel, Switzerland. Baseline and at least 1 follow-up value for TSH and fT4 were available for all patients. Baseline and follow-up T3 were available for 53 patients (63%). The present analysis was approved by the local ethics committee. All contacted patients provided informed oral consent.

Statistical analysis. Continuous variables are expressed as median (interquartile range [IQR]) unless stated otherwise. Qualitative parameters are given as proportions (percentage). Between-group differences for categorical variables were compared using the chi-square test or the Fisher exact test if at least 1 cell had an expected cell count below 5. Normality of distribution of continuous variables was assessed using skewness (<1), kurtosis (<1), and visual inspection of the histograms. No variable used for statistical tests had a normal distribution. Thus, comparisons were made using the Mann-Whitney *U* test.

Abbreviations and Acronyms

AIT = amiodarone-induced thyrotoxicosis
fT4 = free thyroxine
IQR = interquartile range
T3 = triiodothyronine
TSH = thyroid-stimulating hormone

Two different outcome categories were analyzed. First, we analyzed the time to normalization of TSH, fT4, and T3. We compared patients receiving and not receiving prednisone for AIT with regard to the time to normalization of TSH, fT4, and T3. Second, a composite primary end point was defined before the data were analyzed. The AIT-related complications, namely death, heart transplantation, hospitalization for congestive heart failure, stroke, myocardial infarction, arrhythmia-related hospitalization (atrial fibrillation, sustained ventricular arrhythmia, implantation of pacemaker or defibrillator), and hospitalization for AIT-related treatment complication, were included in the primary end point (time to first event analysis).

Kaplan-Meier curves were constructed, and the outcome in patients receiving and not receiving prednisone for AIT was compared using the log-rank test. Because only 6 patients received iopanoic acid during follow-up, no analyses were performed for this subgroup. Patients with normal left ventricular function, defined as ≥50% by echocardiography, were compared with those with impaired left ventricular function.

Finally, we entered the variables age, gender, history of coronary artery disease, left ventricular function (normal vs. abnormal), therapy with prednisone, and fT4 levels at the time of AIT diagnosis into a multivariable Cox regression model using a backward elimination approach to define independent predictors of outcome. Initially, all variables were included in the model, and the least significant variable was removed until all remaining variables in the model had a value of $p < 0.1$. A 2-tailed p value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed with SPSS version 13.0 (SPSS Inc., Chicago, Illinois).

Results

In total, 84 patients with AIT were identified. Baseline characteristics and indication for amiodarone therapy are

Table 1 Differential Diagnosis of AIT

	Type 1 AIT	Type 2 AIT
Pre-existing thyroid disease	Yes	No
Ultrasound	Diffuse or nodular goiter	Heterogeneous pattern
Doppler sonography	Normal or increased flow	Decreased flow
24-h radioiodine uptake	Normal or elevated (typically >5%/24 h)	Very low (typically <2%/24 h)
Thyroid autoantibodies	May be present	Usually absent
Response to steroids	No	Usually yes

AIT = amiodarone-induced thyrotoxicosis.

Table 2 Baseline Characteristics of 84 Patients With Amiodarone-Induced Thyrotoxicosis at the Time of Clinical Presentation

Age (yrs)	60 ± 16
Men (%)	62 (74)
Indication for amiodarone (%)	
Atrial fibrillation	48 (57)
Atrial flutter	5 (6)
Left atrial tachycardia	1 (1)
Ventricular tachycardia	27 (32)
Ventricular extrasystole	3 (4)
Duration of amiodarone therapy (months)	31 (19–38)
Coronary heart disease (%)	25 (30)
Previous myocardial infarction	12 (14)
Previous myocarditis	6 (7)
Congenital heart disease	3 (4)
Left ventricular ejection fraction*	
<50% (%)	26 (31)
≥50% (%)	57 (69)
Previous thyroid disease	9†
TSH at diagnosis	0.006 (0.005–0.03)
fT4 at diagnosis	44 (31–76)
T3 at diagnosis‡	2.7 (1.6–3.3)

Data are mean ± SD, n (%), or median (interquartile range). *Measured by echocardiography; available for 83 patients only. †Eight patients with euthyroid goiter, 1 patient with Graves' disease treated with radioiodine therapy 7 years before the diagnosis of amiodarone-induced thyrotoxicosis. ‡T3 levels were available for 53 patients.
fT4 = free thyroxine; T3 = triiodothyronine; TSH = thyroid-stimulating hormone.

shown in Table 2. Mean (± SD) age was 60 ± 16 years, and most of the patients were male. Before AIT was diagnosed, patients received amiodarone for a median of 935 days (IQR 479 to 1,146 days). Left ventricular function was normal in 69% of the patients based on echocardiography. For 1 patient, no information about left ventricular function was found, and for 7 patients, no quantitative measurements were available. Symptoms at the time of diagnosis included unexplained weight loss in 50%, heavy sweating in 42%, palpitations in 37%, hyperkinesia in 29%, muscle weakness in 27%, heat intolerance in 24%, overall weakness in 20%, diarrhea in 12%, and hair loss in 7%. Baseline thyroid values are shown in Table 2.

Therapy received for AIT is shown in Table 3. The majority of patients received antithyroid therapy (83%), mostly carbimazole. Five patients received carbimazole first and propylthiouracil thereafter, all of them because of severe side effects of carbimazole, namely agranulocytosis in 4 patients and hepatic side effects in 1 patient. No combination therapy was used.

In total, 27 patients (32%) received prednisone at a mean dose of 30 ± 8 mg/day. Mean duration of prednisone therapy was 84 ± 65 days. The only significant difference in baseline characteristics between patients with and without prednisone therapy was that fT4 levels were higher (60 pmol/l [IQR 44 to 85 pmol/l] vs. 37 pmol/l [IQR 29 to 63 pmol/l], p = 0.004) in patients receiving prednisone therapy. There was a trend toward lower TSH levels in patients with prednisone therapy (0.005 U/l [IQR 0.005 to 0.02 U/l] vs. 0.008 U/l [IQR 0.005 to 0.08 U/l], p = 0.092). In those with available T3 levels, there was no difference between these 2 groups (2.6 vs. 3.0 ng/ml; p = 0.288). Six patients were treated with iopanoic acid.

The time course of changes of thyroid hormone levels is shown in Table 4. Median duration from diagnosis of AIT to normalization of TSH was longer than normalization of fT4. The shortest time to normalization was found for T3, although only 53 patients could be included in this analysis. Patients with shorter follow-up periods received prednisone more frequently than those with longer follow-up (data not shown).

There was no difference in time to normalization of circulating thyroid hormone values between patients receiving and not receiving prednisone. The results did not change after exclusion of 15 patients with possible type 1 AIT (8 with a history of thyroid nodules and 7 with Graves' disease or detectable thyroid receptor antibodies). In patients with available T3 levels, there was a trend toward a shorter time to normalized T3 level in those treated with prednisone (Table 4).

Thyroidectomy was performed in 8 patients after 112 days (IQR 82 to 276 days), 5 patients having total and 3 patients having subtotal thyroidectomy. Before the intervention, all individuals received antithyroid therapy, 2 received prednisone, and 1 received iopanoic acid. Median fT4 level at the time of AIT diagnosis was 71.3 pmol/l (IQR 27.4 to 83.5 pmol/l) compared with 42.0 pmol/l (IQR 31.4 to 65.7 pmol/l) in those without thyroidectomy (p = 0.58). Five of these 8 patients (63%) had an adverse event, all occurring before thyroidectomy (2 hospitalizations for heart failure, 2 hospitalizations for atrial fibrillation, and 1 hospitalization for agranulocytosis and fever).

Long-term follow-up showed high morbidity and mortality in all patients (Table 5). Although patients with reduced left ventricular function had a worse outcome compared with those who had normal left ventricular function (p = 0.04), the event rate in the latter was still very high (49%). Kaplan-Meier curves up to 60 months (few events occurred thereafter) showed early separation of the curves, although the log-rank test failed to show statistical significance (Fig. 1A).

Table 3 Therapy Received for Hyperthyroidism (n = 84)

Antithyroid therapy (%)	70 (83)
Carbimazole	64
Propiothiouracil	11
Both	5
Prednisone (%)	27 (32)
Mean prednisone dose (mg)	30 ± 8
Iopanoic acid (%)	6 (7)
Mean dose of iopanoic acid (mg)	1,000 ± 100
Thyroidectomy (%)	8 (10)
Median time to thyroidectomy (days)	112 (82–276)

Data are mean ± SD, n (%), or median (interquartile range).

Table 4 Time to Normalization of Thyroid Hormone Values

	All (n = 84)	Prednisone (n = 27)	No Prednisone (n = 57)
Time to normal TSH (days)	138 (92–234)	138 (94–220)	141 (90–252)*
Time to normal fT4 (days)	103 (63–177)	98 (53–177)	108 (64–189)†
Time to normal T3 (days)‡	68 (34–172)	31 (17–73)	56 (26–84)§

Data are median (interquartile range). *p = 0.94 compared with patients treated with prednisone. †p = 0.46 compared with patients treated with prednisone. ‡Follow-up T3 values available in 53 patients only. §p = 0.14 compared with patients treated with prednisone.
fT4 = free thyroxine; T3 = triiodothyronine; TSH = thyroid-stimulating hormone.

In Figure 1B, the event-free survival is shown for patients receiving prednisone compared with those not receiving prednisone. In patients receiving prednisone for AIT therapy, the outcome was significantly worse than in patients not receiving prednisone (p = 0.003). Although patients received prednisone for 84 ± 65 days, the curves did not start to separate before 12 months of follow-up, well after TSH normalization (median 4.6 months). More detailed analysis of the events showed that mainly the end point hospitalization for arrhythmia management was different between the 2 groups (11 events [41%] in patients receiving prednisone therapy and 12 events [21%] in patients without prednisone). In the prednisone and no-prednisone groups, respectively, 2 and 4 patients had recurrence of ventricular tachycardia, 2 and 2 patients had ventricular fibrillation (2 needed resuscitation and 2 had appropriate implantable cardioverter-defibrillator shocks), 4 and 3 had hospitalization for atrial fibrillation, 1 and 2 needed implantable cardioverter-defibrillator implantation because amiodarone had to be stopped, and 2 and 1 needed pacemaker implantation.

Finally, multivariate Cox regression analysis showed that the use of prednisone remained a predictor of the primary end point after adjusting for confounding variables (hazard ratio 1.96; 95% confidence interval 1.03 to 3.72).

Discussion

The present analysis confirms that medical therapy for AIT is challenging. It may take several months before euthyroidism can be restored. Furthermore, this is the first analysis that shows considerable long-term morbidity and mortality in affected patients. More than one-half of the patients reached the primary end point, and nearly 1 in 5 patients died. These numbers are substantial considering the relatively young age, the low number of comorbidities, and the normal left ventricular function in the majority of patients. Because the retrospective design of this analysis does not allow us to prove any cause-and-effect relationship, further studies are required to analyze whether AIT engenders adverse long-term effects in affected patients.

Acute therapy for AIT. Some data from the literature, expert opinions, and personal experience suggest a benefit of prednisone in a subgroup of patients with type 2 AIT (14). Patients treated with prednisone did not have a faster recovery of fT4 or TSH levels than patients without prednisone therapy. Unfortunately, data on T3 levels are not available in a sufficient number of patients. Excluding patients with probable type 1 AIT did not change these results. Higher baseline levels of fT4 suggest that patients with more severe disease were treated with prednisone.

We could not identify enough patients treated with iopanoic acid to make valid conclusions. Thyroidectomy was performed relatively late. Higher fT4 levels suggest that patients with the most severe disease underwent surgery. Considering the increased event rate, early thyroidectomy may be worthwhile in selected cases because definite cure of AIT can be achieved rapidly and long-term amiodarone therapy can be continued safely. Surgery is an option

Table 5 Duration of Follow-Up and Incidence of the Primary Composite End Point in All Patients and in Patients Stratified According to Left Ventricular Function at the Time of AIT Diagnosis

	All Patients (n = 84)	Normal EF (n = 57)	Impaired EF (n = 26)	p Value
Duration of follow-up (months)	50 (17–78)	50 (19–78)	44 (16–78)	0.54*
Primary composite end point (%)	47 (56)	28 (49)	19 (73)	0.04†
Death (%)	16 (19)	8 (14)	8 (31)	0.07†
Heart transplantation (%)	3 (4)	1 (2)	2 (8)	0.23‡
Hospitalization for heart failure (%)	13 (16)	8 (14)	5 (19)	0.55‡
Stroke (%)	5 (6)	2 (4)	3 (12)	0.18‡
Acute myocardial infarction (%)	3 (4)	2 (4)	1 (4)	1.00‡
Hospitalization for arrhythmia management (%)	23 (27)	11 (19)	12 (46)	0.01†
Atrial fibrillation	7 (8)	5 (9)	2 (8)	
Ventricular fibrillation/tachycardia	10 (12)	2 (4)	8 (31)	
Implantation of defibrillator device	7 (8)	1 (2)	6 (23)	
Pacemaker implantation	7 (8)	4 (7)	3 (12)	
Hospitalization for treatment complication	3 (4)	3 (5)	0	0.53‡

Data are numbers (percentage) or median (interquartile range). *p value is based on a Mann-Whitney *U* test. †p value is based on a chi-square test. ‡p value is based on a Fisher exact test.

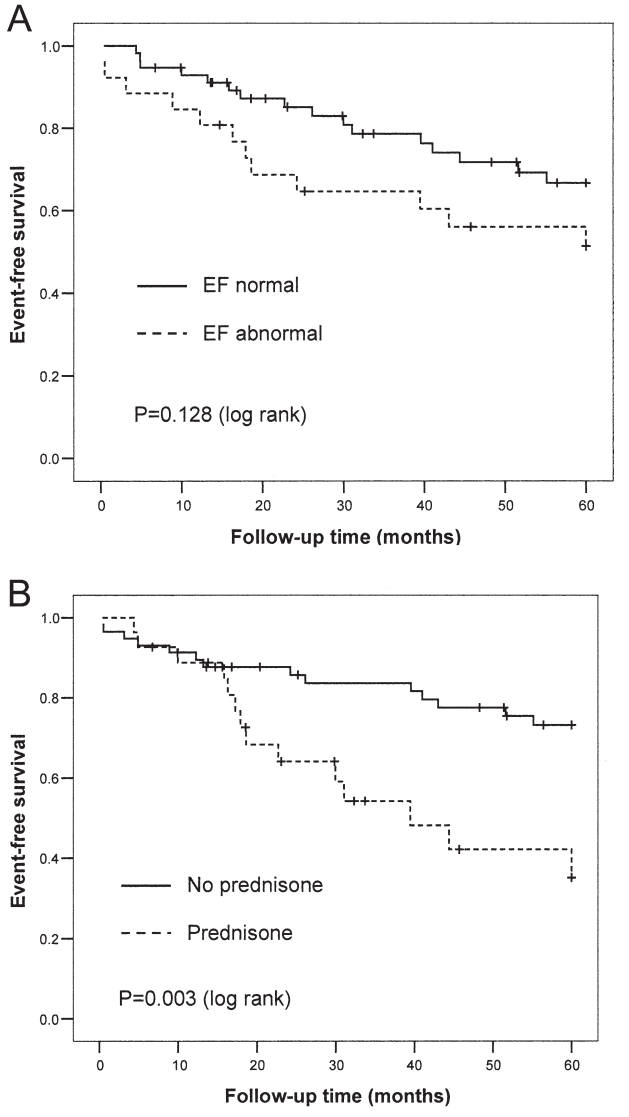

Figure 1 **Event-Free Survival**

Kaplan-Meier event-free survival for patients with normal versus abnormal left ventricular function **(A)** and for patients treated with versus without prednisone **(B)**. Normal ejection fraction (EF) was defined as EF ≥50% by echocardiography (or described as normal in 7 patients). For patients with long follow-up, follow-up time is censored at 60 months.

especially for patients who are too sick to wait for medical therapy to work. In our patients, surgery was performed relatively late (after a median of 112 days). Earlier surgery might have been more beneficial, and some of the frequent adverse events in these patients might have been avoided. On the other hand, complications associated with surgical therapy in patients with hyperthyroidism also must be considered (12).

Long-term follow-up. We found that patients with abnormal left ventricular function (defined as ejection fraction <50% by echocardiography) had more adverse events during follow-up. These results confirm the prognostic importance of reduced left ventricular function (15). However, the presence of left ventricular dysfunction failed to be an independent predictor of the primary end point in the multivariate analysis. This may be related to reduced statistical power because of the low number of patients in the group with reduced left ventricular function. Alternatively, after AIT patients may remain at high long-term risk, reducing the influence of left ventricular function on outcome. This especially may be true when amiodarone as the most effective antiarrhythmic drug must be discontinued permanently.

Therefore, with regard to the high incidence of arrhythmia-related events during long-term follow-up, continuation of amiodarone despite the occurrence of AIT may be considered as a therapeutic option. Some uncontrolled analyses suggest that amiodarone may be continued safely during and after AIT (16,17). However, prospective controlled data about continued amiodarone therapy in patients with AIT are needed.

Clinical implications. In patients with AIT, the high event rate suggests the need for close monitoring. The acute therapy should be carefully selected. Clinical examination, thyroid ultrasound and Doppler sonography (18), assessment of radioiodine uptake (19), and certain biomarkers such as interleukin-6 (20) may be helpful in selecting those AIT patients who may benefit from prednisone therapy. Early favorable response to a short course of prednisone might be another criterion for finding those patients who benefit from continuation of steroid therapy until restoration of euthyroidism. Patients with severe disease and a poor response to medical therapy are candidates for early thyroidectomy.

Because the findings from this analysis suggest that patients with AIT are at risk for complications during a long period of time, prolonged follow-up visits after normalization of thyroid function should be recommended. In particular, clinicians should look for overt or silent arrhythmia recurrence, the most common complication during long-term follow-up.

Study limitations. First, a retrospective nonrandomized analysis was performed. Although we adjusted for confounding factors, residual confounding cannot be excluded. Second, the study design precludes the establishment of a causal relationship. Third, we included a predominantly Caucasian population without iodine deficiency, and the results may not be generalizable to other populations. Fourth, although this is one of the largest cohorts of patients with AIT in the literature, some subgroups examined were small. Fifth, T3 levels were not available for all patients. Finally, no systematic approach has been used to distinguish patients with type 1 and type 2 AIT. Thus, the prescribing pattern and patient selection for prednisone therapy may have changed over time. Prednisone may have been used as a second-line therapy in some patients. Both could have contributed to the finding that prednisone was

not associated with a more rapid recovery of thyroid hormone levels.

Conclusions

Patients with AIT have high morbidity and mortality during long-term follow-up. Importantly, AIT-related adverse events must be expected late during follow-up, at a time when thyroid function is under control. Furthermore, prednisone was not associated with a shorter time to normalization of fT4 levels in this retrospective analysis. Further studies should evaluate which patients may be safely treated with prednisone during the acute phase, and in which patients amiodarone may be continued without the risk of recurrent AIT.

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