Amiodarone and Thyroid Status in Refractory Arrhythmias

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SUMMARY

Out of 20 subjects selected for refractory arrhythmias, amiodarone therapy (200 mg/day) was efficacious in 85%. No statistically significant variations in electrocardiographic parameters (QTc) were observed; similarly, there was little evidence of side effects 1 year after initiation of treatment. These results were most likely due to the low daily dosage administered. We observed:

1) a significant increase in rT_3 levels;
2) a decrease in TT_3;
3) a uniform homeostasis of free fraction (FT_3; FT_4)

These effects are all characteristic patterns of a " Low T_3 Syndrome ". The dosage of circulating amiodarone in 6 patients with borderline hormonal status (3 hyper- and 3 hypothyroidism) was not found to be an efficacious test for therapeutic monitoring. Identification of a statistically significant linear regression relationship between cumulative dose of amiodarone and rT_3 levels may be a useful test in clinical practise for establishing more appropriate therapeutic dosages. Furthermore, it provides a guideline for threshold levels (maximum rT_3=100–110 ng/dl) which are in close association with several side effects.

Additional Indexing Words:
Amiodarone Arrhythmias Thyroid status Side effects

OVER the last few years, amiodarone has been selectively administered as a therapeutically effective treatment for various types of " refractory " arrhythmias. However, due to the side effects on thyroid metabolism, prolonged administration of amiodarone has been carefully controlled.

The pharmacokinetics and the electrophysiological features of this drug

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have been established.[1)-4)] However, a number of metabolic features relating to its bioavailability must be clarified in order to determine more effective therapeutic schedules with a reduction of side effects. Since 1981[5)] the most accurate test for monitoring the interaction of prolonged amiodarone therapy and thyroid status has been the measurement of sequential reverse T_3 (rT_3) levels.[1)]

In this prospective study, the thyroid hormone status of 20 selected outpatients treated with amiodarone was evaluated, using several cardiological parameters to monitor therapeutic efficacy. This study lasted 6 months, and followed a schedule of blood tests, and clinical and instrumental checks. The findings show a typical picture of the thyroid hormone levels:

1) a statistically significant dose and time dependent increase in reverse T_3 (rT_3),

2) parallel oscillations of the total fractions (TT_3 and TT_4) and of the free fractions (FT_3 and FT_4) of thyroid hormones.

These biochemical patterns are similar to those of the "Low T_3 Syndrome".[6)]

Materials and Methods

Patients:

The group under investigation consisted of 20 outpatients, 10 men and 10 women (mean age respectively 54 and 58 years, with a cumulative range of 19–77 years). Six patients had a previous myocardial infarction, with aneurysmic evolution in 4 cases. Clinical examinations and laboratory tests suggested that no alteration in the thyroid status had occurred in any of the patients. The patients displayed different types of arrhythmias refractory to conventional antiarrhythmic agents (Table I), including 10 cases of paroxysmal supraventricular tachycardia (PSVT), 2 cases of paroxysmal tachycardia associated with the Wolff-Parkinson-White syndrome (WPW), 4 cases of

Table I. Effect of Amiodarone Therapy on Various Types of Cardiac Arrhythmias

	Efficacy rate
Paroxysmal supraventricular tachycardia	8/10
PSVT in Wolff-Parkinson-White syndrome	1/2
Paroxysmal atrial fibrillation	1/1
Atrial arrhythmic disease	1/1
Paroxysmal ventricular tachycardia	4/4
Ventricular extrasystoles	2/2
Total	17/20

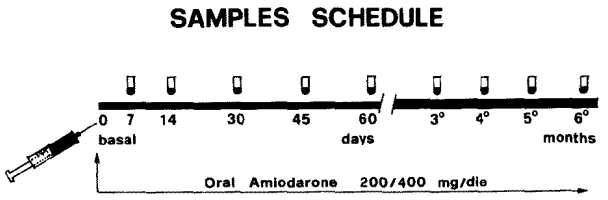

Fig. 1. Scheme of sequential sampling for thyroid hormone determinations.

Table II. Effect of Amiodarone on Electrocardiographic Parameters*

	Sinus frequency (bpm)	PQ interval (sec)	QRS interval (sec)	QTc interval (sec)
Baseline	81±11	0.16±0.02	0.10±0.03	0.45±0.04
1st week	73±11	0.17±0.02	0.11±0.03	0.45±0.06
2nd week	76±10	0.15±0.01	0.10±0.03	0.46±0.06
1st month	69±13	0.12±0.03	0.12±0.03	0.46±0.04
3rd month	77± 9	0.11±0.03	0.11±0.03	0.45±0.02
6th month	78±15	0.10±0.02	0.10±0.03	0.45±0.03

* Values expressed as mean±standard deviation.

paroxysmal ventricular tachycardia (PVT), 2 cases of ventricular extrasystoles, 1 case of paroxysmal atrial fibrillation and 1 case of atrial arrhythmia.

Therapeutic regimen:

Amiodarone was administered, as in other studies,[7] according to the following dosage regimen (Fig. 1): 600 mg/day, for the first 3 days or until the antiarrhythmic effect was obtained; 400 mg/day for 6 subsequent days and 200 mg/day for 1 month. The maintenance dose for the subsequent month was set at 200 mg/day for 5 days per week.

Cardiological checks:

Electrocardiographic parameters (sinus frequency, PQ interval, QTc and QRS duration) were measured before and after treatment, at the end of the first, second and fourth week, and at the end of the third and sixth month (Table II). The corrected QT ratio (QTc) was obtained according to the formula:

$$QTc = (QT/R) - R$$

Thyroid hormones and circulating amiodarone levels assay methods:

Venous blood samples for circulating thyroid hormones and circulating amiodarone measurements were taken before the beginning of treatment and

after the first, second, fourth, sixth and eighth weeks and subsequently at the end of the third, fourth, fifth and sixth months of therapy (Fig. 1). The sequential assessment of thyroid hormone status included RIA of total (TT_3 and TT_4) and free (FT_3 and FT_4) fraction, TSH and rT_3. The amiodarone plasma levels were measured on a limited number of patients (6 cases; Table V) with chromatographic analyses, according to a previous protocol.[2] For the measurements of TT_3, TT_4, FT_3, FT_4, TSH, RIA Kits from Lepetit S.p.A. (Milan) were used; for rT_3 RIA Kits from Biodata S.p.A. (Milan) were used all with adequate internal controls. The possible interference of amiodarone in RIA dosages of T_4 through cross-reactions at different drug dilutions was ruled out.

Statistical analysis:

The experimental results were treated with the following statistical approach:

Calculation of distribution parameters (mean, standard deviation, standard error, skewness, kurtosis) (Table III).

Two way analysis of variance of thyroid hormone concentrations assayed in the course of the experimental schedule to evaluate significant changes during time.

Least square linear regession for the determination of significant correlations among hormone courses.

Spearman test for the evaluation of statistical differences of hormonal status between patients over and below the age of 60 years.

Least square linear regression between cumulative amiodarone dosages and thyroid hormone concentrations.

Table III. Basic Statistics of Thyroid Hormones during 6 Month Amiodarone Therapy (20 Patients)

	TT_3	TT_4	FT_3	FT_4	TSH	rT_3
n	158	158	153	152	100	157
Mean	0.93	10.48	4.17	13.90	3.44	0.53
Standard deviation	0.32	2.39	1.06	4.21	3.84	0.37
Standard error	0.02	0.19	0.08	0.34	0.38	0.03
Coeff. of skewness	1.31	0.22	1.55	2.37	2.20	1.45
Coeff. of kurtosis	5.10	−0.57	5.26	9.12	4.35	1.59
Median	0.90	10.20	4.20	12.90	2.05	0.40
25 quantile	0.75	8.70	3.40	11.50	1.10	0.27
75 quantile	1.10	12.30	4.60	15.55	3.65	0.68

Results

The results of this study show that chronic amiodarone therapy in low doses is effective against refractory cardiac arrhythmias and that unwanted thyroid side effects are produced at an extremely low rate (1 patient out of 20).

Thyroid status:

The most evident deviation from the baseline values (intended as the hormonal levels before the first drug administration) of the thyroid hormones, during the observation period, was observed for rT3 and total fractions (TT_3 and TT_4, Fig. 2). Reverse T_3 increased progressively from a mean baseline concentration of 35 ng/ml to 75 ng/ml (114% increase) at the sixth month. By contrast, the total fractions oscillated about their baseline levels, with no significant variation up to the 22nd week, beyond this period levels of the two hormones decreased markedly (i.e., from 1.08 ng/ml to 0.85 ng/ml for TT_3 at the 27th week). Free fractions (Fig. 3) through the observation period, showed no significant variation from the baseline percentage values. The two way analysis of variance was used to identify the significance of the deviations from the baseline values of hormonal concentrations during the study. A least square linear regression was applied to evaluate correlations between hormone

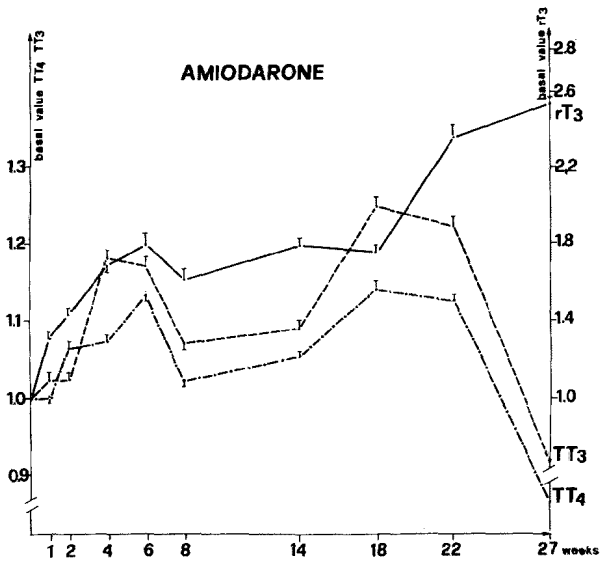

Fig. 2. Sequential TT_3, TT_4, rT_3 values expressed as percentage shift from basal value.

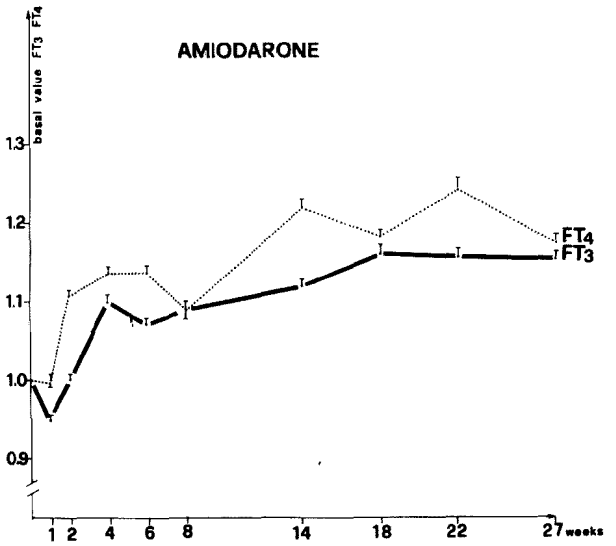

Fig. 3. Sequential FT_3 and FT_4 values expressed as percentage shift from basal value.

Table IV. Least Square Linear Regression Correlation among Thyroid Hormones during 6 Month Amiodarone Therapy (20 Patients)

	TT_3	FT_3	FT_4	rT_3	TSH
TT_4	r=0.274	r=0.047	r=0.449	r=0.281	r=−0.271
	p<0.001	ns	p<0.001	p<0.001	p<0.01
FT_3	r=0.329	—	—	—	—
	p<0.001	—	—	—	—
FT_4	r=0.162	r=0.312	—	—	—
	p<0.05	p<0.001	—	—	—
rT_3	r=0.090	r=0.023	r=0.037	—	—
	ns	ns	ns	—	—
TSH	r=−0.026	r=−0.329	r=−0.388	r=−0.082	—
	ns	p<0.001	p<0.001	ns	—

levels so that it was possible to prepare a correlation matrix (Table IV) that shows significant relationships between TT_4 and rT_3 ($p<0.001$), TT_4 and FT_4 ($p<0.001$), TT_3 and FT_3 ($p<0.001$), TT_4 and TT_3 ($p<0.001$), FT_4 and FT_3 ($p<0.001$).

These statistical findings emphasize the effects of amiodarone on thyroid hormone levels. First, the free hormone fraction (FT_3 and FT_4) homeostasis was unaffected. Second, the enzymatic peripheral monodeiodation of thyroxin was compromised as indicated by a high increase in rT_3. No significant correlation was found between hormone thyroid status, during the observation

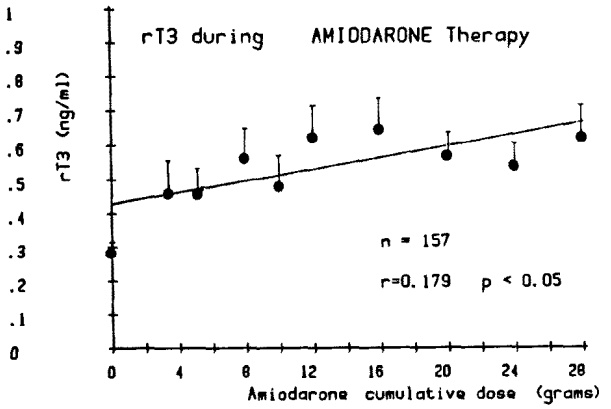

Fig. 4. Correlation between rT_3 concentration and amiodarone therapy.

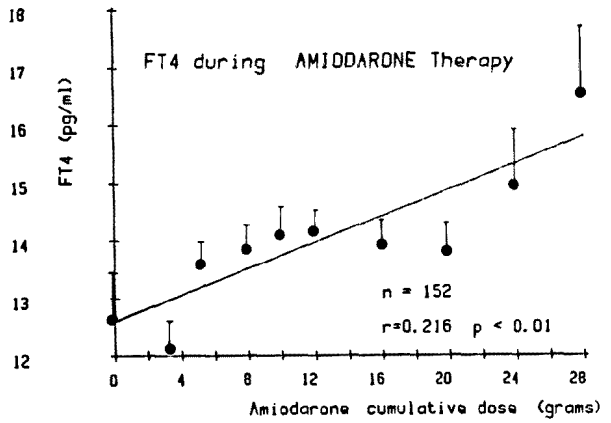

Fig. 5. Correlation between FT_4 concentration and amiodarone therapy.

period, in patients below and over the age of 60 years.

Least square linear regression analysis revealed a significant relationship between cumulative doses of amiodarone and rT_3 (Fig. 4), FT_4 (Fig. 5) levels.

Circulating amiodarone levels:

The circulating amiodarone assay was carried out on 6 patients, 3 with a tendency towards hypothyroidism (cases 1, 2, 3) and 3 with hyperthyroidism (cases 4, 5, 6). Table V shows the circulating amiodarone values from the 1st, 2nd, 3rd and 4th months of therapy. A slight increase in amiodarone levels was found during chronic therapy in this limited sample.

Table V. Serum Levels of Amiodarone (ng/ml) in Patients with Hyper-, Hypo-, or Normal Thyroid Function

Patient	Baseline	1st month	2nd month	3rd month	4th month
1*	nm	0.44	1.64	1.07	1.02
2*	0.30	0.54	0.27	0.42	0.36
3*	0.51	0.17	0.33	nm	0.10
4†	0.19	0.42	0.25	0.43	0.38
5†	0.20	0.41	0.59	0.63	0.99
6†	0.15	0.22	0.61	0.85	0.57

nm=not measurable.
* patients with normal or borderline hypothyroid function.
† patients with hyper- or borderline hyperthyroid function.

Cardiological findings:

Table I shows the results of the antiarrhythmic therapy with amiodarone. The drug proved completely effective in controlling ventricular extrasystoles and preventing paroxysmal atrial fibrillation crises and paroxysmal ventricular tachycardia crises. For paroxysmal supraventricular tachycardias, amiodarone showed complete efficacy in 8 cases (80%) and no efficacy in 2 cases (20%). In the 2 cases of WPW, one showed no further tachycardia crises, whereas the second patient had less frequent crises. The antiarrhythmic drug efficacy was 85% by the end of the 1st month. In only one patient (case 4, Table V), did the recurrence of arrhythmia (ventricular extrasystoles), associated with sinus tachycardia and the borderline values for hyperthyroidism, result in a temporary suspension of amiodarone therapy.

Table II shows variations in several electrocardiographic parameters during amiodarone therapy. None of the parameters (sinus frequency, QTc, QRS, PQ intervals) showed statistically significant variations during the study. The incidence of thyroid side effects was extremely low, which is probably due to the low drug dosage; in fact in only one case were corneal deposits detected after 6 months of treatment.

Discussion

The clinical and instrumental findings from 20 selected cases confirm the efficacy of prolonged oral amiodarone therapy in low doses (200 mg/day) for treatment of ventricular and supraventricular arrhythmias not responsive to conventional antiarrhythmic agents. This low dose showed a low incidence of side effects on thyroid metabolism. Most patients showed an increase in rT_3 and a decrease in TT_3 with normal homeostasis of the free hormone fractions (FT_3, FT_4). Many authors have attributed these effects to the amio-

darone interference on the de-iodinization of T_4, leading to a biochemical pathognomonic picture of " Low T_3 Syndrome ".[8)-15)]

The low incidence of clinical side effects (1 case of transient hyperthyroidism in 20 patients) may reflect the low therapeutic amiodarone doses rather than the small sample size and limited observation period.[8)] Other studies with higher dosages revealed higher incidence of biochemical and/or clinical dysthyroidism[9),16),17)] and other side effects.[18)-23)] It has long been noted that rT_3 concentrations increase with chronic amiodarone therapy.[5),10),24)] Recently, it has been shown that this increase is linear with both the threshold of the antiarrhythmic effects of circulating amiodarone (55–100 ng/dl) and with the level of occurrence of side effects (100–110 ng/dl).[25),26)] Therefore, one can estimate the total circulating amiodarone concentrations from rT_3 levels to keep therapeutic levels below 100–110 ng/dl, the threshold for increased incidence of side effects.

The mechanisms of action of this drug have not been clarified[3),27)] although its thyroid action, the inhibition of conversion of T_4 to T_3 with resulting modification of the ionic-transmembrane system, seems fundamental.[1),28),29)] Although the circulating levels of amiodarone and its main metabolite (dietil amiodarone) were slightly higher in patients with side effects, they were not correlated with the quantity of drug administered.[8),19),30)] Even in 6 selected cases with a borderline biochemical picture of hyper- or hypothyroidism, circulating amiodarone did not vary significantly over the time course of the study. Therefore, the plasma levels of the drug cannot be considered as a reliable parameter for therapeutic monitoring.

Serial rT_3 values are a more reliable index, and should not exceed 100–110 ng/dl to prevent side effects. No significant difference in the hormone status of the group of patients over (8 cases) and under (12 cases) 60 years of age was found at different times of study. Amiodarone interference with the thyroid metabolism is probably caused by a self-regulating mechanism in the gland. In most patients treated with amiodarone therapy or diagnostic examinations with iodinated contrast media, metabolic homeostasis (with virtually constant values of the free hormone fractions) is maintained. Hyper- or hypothyroidism seems to be a potential side effect only in patients with a latent or disregarded thyroid miopragia.

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