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 rT₃ levels;
2) a decrease in TT₃;
3) a uniform homeostasis of free fraction (FT₃; FT₄)

These effects are all characteristic patterns of a "Low T₃ 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 rT₃ levels may be a useful test in clinical practise for establishing more appropriate therapeutic dosages. Furthermore, it provides a guideline for threshold levels (maximum rT₃=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...
have been established.\textsuperscript{1}-\textsuperscript{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\textsuperscript{5} the most accurate test for monitoring the interaction of prolonged amiodarone therapy and thyroid status has been the measurement of sequential reverse T\textsubscript{3} (rT\textsubscript{3}) levels.\textsuperscript{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\textsubscript{3} (rT\textsubscript{3}),

2) parallel oscillations of the total fractions (TT\textsubscript{3} and TT\textsubscript{4}) and of the free fractions (FT\textsubscript{3} and FT\textsubscript{4}) of thyroid hormones.

These biochemical patterns are similar to those of the “Low T\textsubscript{3} Syndrome”.\textsuperscript{6}

\textbf{Materials and Methods}

\textit{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

\begin{table}[h]
\centering
\caption{Effect of Amiodarone Therapy on Various Types of Cardiac Arrhythmias}
\begin{tabular}{l|c}
\hline
Condition & Efficacy rate \\
\hline
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 \\
\hline
Total & 17/20 \\
\end{tabular}
\end{table}
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, 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:

$$QTc = \frac{QT}{R} - R$$

**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 Biocat 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 regression 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 | 4.55 | 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 (TT3 and TT4, Fig. 2). Reverse T3 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 TT3 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
levels so that it was possible to prepare a correlation matrix (Table IV) that shows significant relationships between TT4 and rT3 (p<0.001), TT4 and FT4 (p<0.001), TT3 and FT3 (p<0.001), TT4 and TT3 (p<0.001), FT4 and FT3 (p<0.001).

These statistical findings emphasize the effects of amiodarone on thyroid hormone levels. First, the free hormone fraction (FT3 and FT4) homeostasis was unaffected. Second, the enzymatic peripheral monodeiodation of thyroxin was compromised as indicated by a high increase in rT3. No significant correlation was found between hormone thyroid status, during the observation
Least square linear regression analysis revealed a significant relationship between cumulative doses of amiodarone and rT₃ (Fig. 4), FT₄ (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

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

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 rT₃ and a decrease in TT₃ with normal homeostasis of the free hormone fractions (FT₃, FT₄). Many authors have attributed these effects to the amio-
Amiodarone interference on the de-iodinization of $T_4$, leading to a biochemical pathognomonic picture of "Low T₃ 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\(^{9),14),17}\) and other side effects.\(^{18)-23}\) It has long been noted that rT₃ 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 rT₃ 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\(^{31),27}\) 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 rT₃ 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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