Pharmacokinetic Significance of Serum Reverse T₃ Levels During Amiodarone Treatment: A Potential Method for Monitoring Chronic Drug Therapy

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SUMMARY We studied the antiarrhythmic effects of amiodarone, 600–1400 mg/day, in 18 patients with refractory arrhythmias, and related the drug efficacy and side effects to serum levels of T₄, reverse T₃ (rT₃) and the QTc interval. In the 11 patients with ventricular arrhythmias, premature complexes were reduced by 90–98%, and complex ectopy and runs of ventricular tachycardia were abolished; in the seven patients with paroxysmal atrial flutter, there were no recurrences on stable drug therapy. The QTc lengthened by 11.6% (p < 0.01), T₄ increased by 31.6–63.3% (p < 0.001) and rT₃ increased by 82.9–176.8% (p < 0.001) as a function of dose and duration of amiodarone therapy. A close correlation was found between rT₃ (normal up to 50 ng/dl) and drug efficacy and some of the drug side effects: arrhythmia suppression occurred at levels of 55–100 ng/dl, and some of the known side effects at levels of 100–110 ng/dl. When amiodarone was stopped in nine patients, the changes in QTc, T₄ and rT₃ regressed toward normal and arrhythmia recurred in eight 2–20 weeks (mean 7.4 weeks) and when rT₃ levels fell below 55 ng/dl; arrhythmia resuppression was achieved 3–28 days (mean 11 days) after resumption of amiodarone therapy. The indirect therapeutic half-life of amiodarone in seven patients, computed from the semilogarithmic plots of plasma rT₃ after cessation of amiodarone therapy, ranged from 25 to 55 days (mean 35 days). The data suggest that rT₃ levels may be useful in monitoring the efficacy and certain side effects of amiodarone.

ALTHOUGH the unique electrophysiologic actions of amiodarone on heart muscle were delineated 10 years ago,1,2 only recently has the drug’s extraordinary efficacy in controlling a wide spectrum of recalcitrant ventricular and supraventricular arrhythmias been recognized.3–5 After oral administration, the onset of its action is delayed;6,7 when it is discontinued after chronic therapy, its therapeutic effect may persist.5 However, without knowledge of the drug’s bioavailability, metabolism and disposition in man, the initial loading and subsequent maintenance dose schedules of the drug in clinical use have been nonsystematic and somewhat variable. It has therefore not been possible to standardize dosage regimens to minimize side effects.

Amiodarone is an iodinated compound. During systematic investigation of its effects on thyroid function, dose-dependent increases in serum T₄ and reverse T₃ (rT₃) were found;8 such increases were not accompanied by an altered thyroid state. However, in preliminary observations, an extremely close correlation between serum levels of rT₃ (and, to a lesser extent, of T₄) and the antiarrhythmic efficacy and toxicity of amiodarone during chronic oral therapy was found. This relationship was therefore determined in 18 patients given amiodarone for refractory recurrent atrial and ventricular tachyarrhythmias.

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Supported by grants from the Medical Research Service of the Veterans Administration, the NHLBI (HL-23970-03), and the American Heart Association, Greater Los Angeles Affiliate.

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Received June 2, 1981; revision accepted October 27, 1981.


Methods

Patient Selection

The study included 18 male patients who had recurrent tachyarrhythmias refractory to conventional antiarrhythmic medications. Eleven had symptomatic ventricular arrhythmias and seven had recurrent disabling episodes of atrial flutter. The mean age of the patients was 58 years (range 37–82 years). All but one had organic heart disease, 10 coronary artery disease, five cardiomyopathy and two surgically repaired atrial septal defect. None had recent myocardial infarction.

All patients had troublesome symptoms from the arrhythmia and did not respond to two or more conventional antiarrhythmic compounds (quinidine, procainamide, disopyramide, propranolol and digoxin) given alone or in combination. The mean duration of symptoms was 3.2 years (range 4 months to 14 years) in the group with ventricular arrhythmias and 3.5 years (range 1–5 years) in the group with recurrent atrial flutter. All patients with ventricular arrhythmias had documented episodes of complex ventricular ectopic activity and runs of ventricular tachycardia, but none had a history of cardiac arrest. Before amiodarone therapy was initiated, at least three 24-hour Holter recordings and ECG documentation of the arrhythmia were obtained. Every patient showed a close correlation between symptoms and episodes of the arrhythmia.

Design of the Protocol

For all 18 patients, the baseline data, including three or more 24-hour Holter recordings, 12-lead ECG, serum levels of T₄ and T₃, were initially obtained while the patients were not on specific antiarrhythmic medications. Amiodarone hydrochloride (obtained under a physician-based IND No. 16, 291 and purchased commercially from LABAZ) was initially administered at a
dose of 600–1400 mg/day. The subsequent dosage was increased or decreased in relation to the response of the arrhythmia or the development of side effects. The response to therapy in the case of ventricular arrhythmias was based on the analysis of Holter recordings. The high initial daily doses were based on our preliminary experience, which indicated that these doses were necessary for rapid control of the arrhythmia. During amiodarone therapy, no other antiarrhythmic compound was given.

All patients were admitted into hospital into a special diagnostic treatment unit (SDTU) for at least 2–3 weeks at the beginning of amiodarone therapy. During this period, a 12-lead ECG and blood samples were obtained almost daily. After discharge from hospital, the patients regularly attended the Wadsworth Medical Center Arrhythmia Clinic; during each visit, the patient’s symptoms were reviewed, an ECG was recorded and blood was withdrawn for serum levels of $T_4$ and $T_3$. Twenty-four-hour Holter recordings were also obtained at each change of dose and routinely every 2–3 months.

To establish unequivocally that the relationship between arrhythmia suppression and amiodarone therapy was causal, nine of the 18 patients in the study were readmitted to hospital into the SDTU for a controlled withdrawal of amiodarone. The second objective of the drug withdrawal protocol was to determine, in a controlled fashion, the time that elapsed before the recurrence of the arrhythmia after cessation of therapy in relation to alterations in the QTc interval of the ECG and serum levels of $T_4$ and $rT_3$. In this part of the study, five patients had ventricular arrhythmias and four recurrent atrial flutter. None of these nine patients had a history of arrhythmic cardiac arrest, and the historical features suggested that withdrawal of amiodarone did not pose a life-threatening risk, especially because the arrhythmia in each case had been completely resistant to previous conventional therapy. After the withdrawal of the drug in this group, ECGs and blood samples (for the estimation of serum $T_4$ and $rT_3$) were again taken almost daily for about 2–3 weeks in hospital, every week thereafter during outpatient clinic visits to the arrhythmia clinic. During these visits, 24-hour Holter recordings were also obtained. In the case of ventricular arrhythmias, when the first 24-hour Holter recording showed the recurrence of complex ectopic activity or runs of ventricular tachycardia, amiodarone therapy was re instituted. In the case of atrial flutter, the drug was restarted after the recurrence of the arrhythmia was documented electrocardiographically, irrespective of the ventricular response, flutter rate or severity of symptoms.

In five patients with ventricular arrhythmias, the long-term regimen was varied to permit the administration of the total weekly maintenance dose of amiodarone in two to seven equally divided doses per week. This dose schedule was only instituted after the therapeutic range for $rT_3$ levels was identified. The follow-up measurements in this group as in the others included serial determinations of serum $T_4$ and $rT_3$, QTc interval on the ECG, heart rate and 24-hour Holter recordings in addition to the clinical symptoms.

The protocol was approved by the Committee for the Protection of Human Subjects at the Wadsworth Veterans Administration Medical Center. Each patient gave informed consent.

**Specific Measurements**

The total $T_4$ levels in the serum were measured by radioimmunoassay (RIA). Three antiserum to $T_4$ were used to rule out spurious recognition of amiodarone by a specific $T_4$ antibody. To exclude cross-reaction of amiodarone in the $T_4$ RIA, serial dilutions of the drug were made in euthyroid and hypothyroid control sera, and no cross-reaction was found.

Reverse $T_3$ was measured by double-antibody equilibrium RIA using a modification of the method of Chopra, allowing the assay of unextracted serum by using 8-anilino-1-naphthalene sulfonic acid as a blocker of protein binding. The $T_4$-free and $T_3$-free serum was used to prepare $rT_3$ standards. Fifty percent displacement (B/BO) was achieved at 50 ng/dl. The mean $rT_3$ value in 28 normal euthyroid patients was 33 ± 8.5 ng/dl (mean ± sd). The lower limit of sensitivity was 0.71 ng/dl. The thyroid hormone measurements were made by persons who did not have access to the clinical data of the study patients. The ECG was analyzed for alterations in the PR, QRS, QT and RR intervals. The QT interval was measured from records taken at a paper speed of 50 mm/sec and QTc was calculated as QT/VR-R. The 24-hour Holter recordings were analyzed for mean heart rate, number of premature ventricular complexes (PVCs) per hour, and number of complex ventricular ectopic beats per hour. The analysis was obtained by the Pathfinder Computer (Reynolds Medical) using a semiautomated technique. This system has proved accurate for us in detecting and counting 96–98% of PVCs when analysis at 60 times real time was compared with the results of the beat-by-beat analysis in real time.

A two-tailed $t$ test for paired data was used to assess the significance of changes in pairs of observations within each patient. A $p$ value of $\leq 0.05$ was considered significant.

**Results**

**Antiarrhythmic Efficacy vs QTc, Serum $T_4$ and $rT_3$**

Amiodarone, 600–1400 mg/day, was uniformly effective in controlling the arrhythmia. In the 11 patients with ventricular arrhythmias, it suppressed 90–98% of the total PVCs per 24 hours and abolished all complex ventricular ectopic activity, including the runs of ventricular tachycardia. In the seven patients with recurrent atrial flutter, during what appeared to be the steady-state conditions of amiodarone administration, the arrhythmia did not recur in any of the seven, and the effect was sustained over a mean follow-up of 8 months (range 2–12 months). The mean follow-up for the entire series of 18 patients is 11 months (range 5–18 months). Except during the period that the drug was withdrawn, the patients have been on amiodarone con-
TABLE 1. Effects of Amiodarone on Heart Rate, QTc Interval and Serum Levels of T₄ and Reverse T₃ in 18 Patients with Atrial and Ventricular Arrhythmias

<table>
<thead>
<tr>
<th></th>
<th>After 2-4 weeks of treatment</th>
<th>Maximal effects (after 2-5 months of treatment)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>with amiodarone*</td>
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<tr>
<td></td>
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</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>69.0 ± 14.8</td>
<td>60.9 ± 9.6 (p &lt; 0.01)</td>
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<td></td>
<td></td>
<td>58.0 ± 9.6 (p &lt; 0.005)</td>
</tr>
<tr>
<td>QTc (sec)</td>
<td>0.43 ± 0.05</td>
<td>0.48 ± 0.048 (p &lt; 0.001)</td>
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<td></td>
<td></td>
<td>0.49 ± 0.038 (p &lt; 0.001)</td>
</tr>
<tr>
<td>T₄ (μg/dl)</td>
<td>7.9 ± 2.2</td>
<td>10.4 ± 2.7 (p &lt; 0.001)</td>
</tr>
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<td></td>
<td></td>
<td>12.9 ± 3.4 (p &lt; 0.001)</td>
</tr>
<tr>
<td>rT₃ (ng/dl)</td>
<td>36.2 ± 6.2</td>
<td>66.2 ± 15.5 (p &lt; 0.001)</td>
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<td>100.2 ± 19.6 (p &lt; 0.001)</td>
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</tbody>
</table>

The data are mean ± sd from 18 patients.

*The dose of amiodarone for these 18 patients varied from 600-1400 mg/day (600 mg in four, 800 in four, and 1000-1400 mg in 10). The tests of significance relate to the differences from the baseline values.

tinuously. The onset of action as judged by a change in symptoms and by the results of Holter recordings was clearly apparent within 2-3 weeks. For patients with atrial flutter, the onset of action of the drug was taken arbitrarily when there was a 50% or greater reduction in the number of episodes compared with that under control conditions. For those with ventricular tachyarrhythmias, a reduction in the total ectopic beats by 90% compared with that during the control Holter recording was considered to be indicative of the earliest drug effect. In individual patients, the maximal effect — total suppression of episodes of atrial flutter and elimination of complex ectopic activity, including runs of ventricular tachycardia — was not achieved until after 2-5 months of continuous therapy. The mean data for the corresponding changes in heart rate and in the QTc interval obtained under identical conditions from conventional 12-lead ECG tracings, as well as in the serum levels of T₄ and rT₃, are presented in table 1.

Although the dose range of the drug was 600-1400 mg/day, for clarity of presentation, the data are pooled for each period of analysis of drug effect. After 2-3 weeks of therapy, amiodarone reduced the heart rate by 10.4% (p < 0.01) and lengthened the QTc by 11.6% (p < 0.001), but there was no further increment thereafter despite a progressive increase in the therapeutic effect. The T₄ level increased by 31.6% (p < 0.001) after 2-4 weeks and by 63.3% (p < 0.001) after 2-5 months of continuous amiodarone therapy. Of all the measurements, the most consistent and a virtually linear increase was in the values for T₄ (mean increase 82.9%) (p < 0.001) at 2-3 weeks and 176.8% (p < 0.001) by 2-5 months of therapy. Figure 1 shows the individual values for the serum rT₃ levels at different schedules for all 18 patients under control conditions, after 2-4 weeks and after 2-5 months of continuous administration of amiodarone. The drug induced a reasonably linear increase in serum rT₃, and levels continued to increase without a change in dose for 2-5 months. Even allowing for the somewhat varying times for the sampling of blood for serum rT₃ levels, a wide variation in the levels of rT₃ in different patients for a given dose of amiodarone is evident. After 2-4 weeks of treatment, a clear relationship between dose and rT₃ levels was lacking. However, after the longer duration of treatment, the highest rT₃ levels were found in patients on the larger dose schedules, although this was not always so. For example, two patients on 600 mg/day of amiodarone developed rT₃ levels greater than 100 ng/dl after 5 months of drug treatment. This variability in the serum rT₃ levels for similar dose schedules in different patients is further illustrated in figures 1 and 2, which show time course of change in the levels of rT₃ obtained from eight patients during the early stages of amiodarone therapy at a constant dose. Although the increases in rT₃ levels tended to be the most rapid at the highest doses, this was not always so. In some patients, the rate of increase in rT₃ levels was similar despite a marked difference in their drug dose schedules.

The upper limit of normal for rT₃ in our laboratory

![Figure 1](http://circ.ahajournals.org/content/vol66/issue1/Figure1)

**Figure 1.** Effect of dose and duration of amiodarone administration in serum levels of reverse T₃ (rT₃) in 18 patients with refractory cardiac arrhythmias. The levels increase as a function of the duration of therapy, with wide interindividual variation in levels in all three dose schedules. The data suggest widely varying rT₃ elimination half-lives, accounting for the correspondingly variable rates of attainment of steady-state serum levels. The range of 55-100 ng/dl, indicated by the dotted lines, represents the rT₃ levels over which arrhythmia control was attained. Each symbol represents data from one patient. The statistical significance refers to the differences of the mean ± so from control.
(mean ± 2 sd) is 50 ng/dl. In all 18 patients, the goals of antiarrhythmic therapy (complete suppression of recurrent episodes of atrial flutter, elimination of complex ectopic activity and of runs of ventricular tachycardia) were achieved with 55–100 ng/dl (figs. 1 and 2). This level was not always achieved after 4 weeks of therapy, even at doses of 1000–1400 mg/day. Except for occasional instances of nausea and gastrointestinal discomfort during the initial high-dose therapy, drug side effects did not appear until after 3–4 months of continuous therapy. Such side effects were invariably associated with serum rT3 levels greater than 100 ng/ml, which increased as a function of time after the initiation of therapy. The side effects included halo vision in two patients, proximal muscle weakness in two, skin photosensitivity in three and elevations in the serum levels of hepatic enzymes in four. All the adverse effects regressed as the drug dose was reduced and when rT3 level fell below 100 ng/dl. Patients who exhibited photosensitivity were also advised to avoid prolonged exposure to sunlight.

**Amiodarone Withdrawal After Chronic Therapy**

The changes in the levels of rT3 and T4 relative to those in the heart rate and the QTc interval of the ECG and to the reappearance of the arrhythmia are shown in table 1 and figure 3. The drug was stopped abruptly once the arrhythmia was under control, after a mean of 5.7 months (range 2–12 months) of continuous therapy. The dose of amiodarone for this group varied from 600–1200 mg/day. The mean alterations in rT3, T4, heart rate and the QTc for the nine patients were

**Figure 2.** The effect of amiodarone dose schedule on rate of increase in serum reverse T3 (rT3) levels in eight patients. The therapeutic range is indicated by the hatched panel. The rT3 levels rise as a function of time, with the fastest increase at the highest doses, but with wide variability. The data suggest that 'therapeutic' levels may be attained rapidly by large initial loading doses.

**Figure 3.** Effects of amiodarone therapy on serum T4, reverse T3 (rT3), QTc interval and heart rate in patients with resistant cardiac arrhythmias. The data are mean ± sd; in the drug withdrawal phase, the data are from eight patients. The most consistent relationship between arrhythmia suppression or the development of side effects was found in the case of changes in the levels of rT3. Arrhythmia suppression occurred at rT3 levels of 55–100 ng/dl; the side effects of amiodarone developed when rT3 levels were above 100–110 ng/dl (a two- or threefold rise above baseline).
similar to those for the entire group (table 1). Arrhythmia was suppressed in all nine after 2–5 months of amiodarone therapy; in the case of ventricular arrhythmias, PVCs were reduced by 90–98%, with the complex PVCs and runs of ventricular tachycardia eliminated. In the case of patients with atrial flutter, recurrences of episodes of arrhythmia were prevented completely after 2–5 months of therapy. When the drug was discontinued, all values gradually returned toward normal (fig. 4). Coincident with the falls in rT3, the ventricular arrhythmia recurred at 3–20 weeks (table 2) after withdrawal of amiodarone; the episodes of atrial flutter also recurred in three of the four patients 2–18 weeks after the drug was stopped. The remaining patient continues free of atrial flutter despite the regression of the values for rT3 (48–56 ng/dl), T4, heart rate and the QTc interval almost to the range for the baseline values. In the eight patients in whom the drug was resumed on the initial appearance of the arrhythmia (complex PVCs or runs of ventricular tachycardia or a documented episode of atrial flutter), the mean duration for the suppression of the arrhythmia comparable to that attained initially was 11 days (range 3–28 days). This period was considerably shorter than that (2–5 months) required for the initial suppression of the arrhythmia despite a small difference in the mean dose (844 mg/day vs 920 mg/day).

In general, the increases in serum T4 and the QTc interval and the reduction in heart rate correlated reasonably well with the antiarrhythmic efficacy of the drug, but there were many exceptions. In the case of the QTc interval, the maximal change occurred early during amiodarone therapy, but an increasing suppression of arrhythmia continued to occur without a significant further increment in the QTc interval. Similarly, there were often few or no alterations in heart rate (e.g., patients 2 and 9) or in serum T4 (e.g., patients 1 and 9) despite pronounced antiarrhythmic effects. In contrast, the correlation between the changes in the levels of rT3 and antiarrhythmic effects were uniformly consistent. However, the suppression of the arrhythmia in individual patients occurred at different serum levels of rT3; the range of serum rT3 levels for this was 63–100 ng/dl and side effects only occurred when levels clearly and consistently exceeded 100–110 ng/dl (table 2).

In seven patients, enough serial values for rT3, during the withdrawal period of amiodarone permitted the calculation of the elimination half-life of rT3 from the semilogarithmic plot of rT3 vs time. The mean value

<table>
<thead>
<tr>
<th>Pt</th>
<th>Amiodarone dose (mg/day)</th>
<th>Type and frequency of arrhythmia (duration)</th>
<th>Baseline measurements</th>
<th>After 2–3 weeks</th>
<th>At maximal effect of drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>rT3, T4, QTc, HR</td>
<td>rT3, T4, QTc, HR</td>
<td>rT3, T4, QTc, HR</td>
</tr>
<tr>
<td>1</td>
<td>600</td>
<td>PVCs, 122/hr (2 yrs)</td>
<td>30, 6.2, 0.45, 85</td>
<td>65, 8.2, 0.48, 56</td>
<td>70, 9.5, 0.49, 53</td>
</tr>
<tr>
<td>2</td>
<td>600</td>
<td>PVCs, 420/hr (3 yrs)</td>
<td>41, 9.1, 0.40, 54</td>
<td>82, 11.7, 0.48, 58</td>
<td>110, 17.6, 0.48, 60</td>
</tr>
<tr>
<td>3</td>
<td>1000</td>
<td>PVCs, 550/hr (1 yr)</td>
<td>44, 7.9, 0.43, 67</td>
<td>80, 8.9, 0.49, 52</td>
<td>105, 12.0, 0.50, 50</td>
</tr>
<tr>
<td>4</td>
<td>1000</td>
<td>PVCs, 2900/hr (10 yrs)</td>
<td>39, 10.1, 0.48, 85</td>
<td>74, 10.6, 0.54, 70</td>
<td>120, 17.4, 0.56, 67</td>
</tr>
<tr>
<td>5</td>
<td>800</td>
<td>PVCs, 720/hr (3 yrs)</td>
<td>27, 9.1, 0.47, 77</td>
<td>40, 8.7, 0.51, 54</td>
<td>73, 13.2, 0.51, 56</td>
</tr>
<tr>
<td>6</td>
<td>800</td>
<td>Atrial flutter, (3–4 episodes/wk) (2 yrs)</td>
<td>46, 8.8, 0.46, 80</td>
<td>66, 14.7, 0.49, 65</td>
<td>90, 14.8, 0.50, 60</td>
</tr>
<tr>
<td>7</td>
<td>600</td>
<td>Atrial flutter requiring cardioversion, 1/mo (1 yr)</td>
<td>31, 4.3, 0.34, 55</td>
<td>53, 7.6, 0.40, 48</td>
<td>96, 12.6, 0.45, 44</td>
</tr>
<tr>
<td>8</td>
<td>1000</td>
<td>Atrial flutter, 4 × wk (1 yr)</td>
<td>30, 4.5, 0.37, 81</td>
<td>55, 6.2, 0.46, 71</td>
<td>102, 8.2, 0.45, 75</td>
</tr>
<tr>
<td>9</td>
<td>1200</td>
<td>Atrial flutter, 2 × wk (2–3 yrs)</td>
<td>30, 8.1, 0.43, 62</td>
<td>55, 11.9, 0.42, 60</td>
<td>102, 10.6, 0.46, 60</td>
</tr>
</tbody>
</table>

Mean ± SD
36.9 ± 7.2, 7.6 ± 2.1, 0.43 ± 0.05, 71.7 ± 12, 64.4 ± 13.3, 9.8 ± 2.6, 0.47 ± 0.04, 59 ± 8, 96.4 ± 16.4, 12.9 ± 3.2, 0.49 ± 0.03, 58 ± 9

Abbreviations: rT3 = Reverse T3 in ng/dl; T4 = thyroxine; HR = heart rate (beats/min); PVC = premature ventricular complexes.

*Subsequent levels of rT3 have been 48–56 ng/dl.
*In many cases, the dose of amiodarone had already been decreased to lower dose schedules before complete cessation of therapy.
TABLE 2. (Continued)

<table>
<thead>
<tr>
<th>Outcome and duration of therapy before drug withdrawal†</th>
<th>Measurements at the time of recurrence of arrhythmia</th>
<th>Duration for return of arrhythmias (wks)</th>
<th>Measurements at the time arrhythmia resuppressed</th>
<th>Amiodarone dose and duration needed for arrhythmia resuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 98% suppression of PVCs; 2 mo</td>
<td>rT3 52; T4 8.0; QTc 0.46; HR 67</td>
<td>Duration for return of arrhythmias (wks)</td>
<td>rT3 73; T4 8.3; QTc 0.48; HR 54</td>
<td>Amiodarone dose and duration needed for arrhythmia resuppression</td>
</tr>
<tr>
<td>&gt; 95% suppression of PVCs; 8 mo</td>
<td>rT3 62; T4 11.3; QTc 0.41; HR 56</td>
<td>6</td>
<td>rT3 94; T4 10.7; QTc 0.50; HR 56</td>
<td>600 mg; 6 days</td>
</tr>
<tr>
<td>90% suppression of PVCs; 3 mo</td>
<td>rT3 53; T4 8.8; QTc 0.43; HR 64</td>
<td>3</td>
<td>rT3 100; T4 11.7; QTc 0.48; HR 50</td>
<td>1000 mg; 11 days</td>
</tr>
<tr>
<td>&gt; 98% suppression of PVCs; 6 mo</td>
<td>rT3 51; T4 8.0; QTc 0.47; HR 64</td>
<td>20</td>
<td>rT3 71; T4 9.0; QTc 0.56; HR 62</td>
<td>1400 mg; 3 days</td>
</tr>
<tr>
<td>&gt; 98% suppression of PVCs; 3 mo</td>
<td>rT3 48; T4 8.3; QTc 0.46; HR 74</td>
<td>5</td>
<td>rT3 63; T4 9.2; QTc 0.50; HR 48</td>
<td>1000 mg; 6 days</td>
</tr>
<tr>
<td>No recurrences: 1 yr</td>
<td>rT3 56*; T4 8.9; QTc 0.47; HR 86</td>
<td>*No recurrence of arrhythmia at 5 months after drug withdrawal</td>
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</tr>
<tr>
<td>No recurrences: 8 mo</td>
<td>rT3 28; T4 5.8; QTc 0.36; HR 50</td>
<td>18</td>
<td>rT3 68; T4 6.6; QTc 0.45; HR 50</td>
<td>600 mg; 4 wks</td>
</tr>
<tr>
<td>No recurrences: 4 mo</td>
<td>rT3 43; T4 6.3; QTc 0.42; HR 62</td>
<td>2</td>
<td>rT3 69; T4 9.6; QTc 0.46; HR 69</td>
<td>1000 mg; 2 wks</td>
</tr>
<tr>
<td>No recurrences: 5 mo</td>
<td>rT3 48; T4 9.7; QTc 0.43; HR 64</td>
<td>2</td>
<td>rT3 86; T4 10.9; QTc 0.46; HR 58</td>
<td>1200 mg; 2 wks</td>
</tr>
<tr>
<td>±9.5; ±8.3; ±0.43; ±66</td>
<td>±1.7; ±1.0; ±0.04; ±10</td>
<td>±13.5; ±1.6; ±0.03; ±7</td>
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</tr>
</tbody>
</table>

for this group was 35 days (range 25–55 days). Since an excellent concordance was demonstrated between serum rT₃ levels during amiodarone therapy and the drug's antiarrhythmic effects, the assumption was made that the pharmacologic or therapeutic half-life of the compound may be monitored by that of serum rT₃ during chronic therapy. This small series showed a wide range of elimination half-lives for rT₃. The complete sequence of changes in serum rT₃ and the QTc interval relative to the suppression of the arrhythmia on therapy, its recurrence after drug withdrawal and its subsequent resuppression on the resumption of amio-

FIGURE 4. The rates of decline in the elevated levels of serum reverse T₃ (rT₃) on cessation of amiodarone therapy in seven patients. A markedly variable decline in rT₃ levels in different patients is indicated; the overall picture is a mirror image of the levels noted during the initial administration phase of drug therapy. In one patient, rT₃ increased abruptly to levels above 200 ng/dl during an intercurrent episode of pneumonia; despite these high levels, side effects attributable to amiodarone were not encountered and rT₃ levels fell rapidly when pneumonia resolved. The decline, reflecting the true elimination phase of rT₃ levels, was rapid. The subsequent decline, reflecting the true elimination phase of rT₃ (on amiodarone), was much slower. The half-lives calculated on the basis of the decline of rT₃ in seven patients gave a mean therapeutic half-life of amiodarone of 35 days. The therapeutic range for rT₃ is indicated by the hatched panel.
Figure 5. The relationship between changes in reverse T₃ (rT₃), QTc interval and arrhythmia suppression in a patient with recurrent ventricular tachyarrhythmias. For complete suppression, the initial dose of the drug that produced rT₃ levels in the therapeutic range had to be administered for longer than 40 days; on withdrawal, the levels rose abruptly due to the coincidental development of pneumonia, but they fell equally promptly on recovery. The subsequent rate of decline of rT₃ was slower, reflecting an extremely long elimination half-life in this patient. Serious arrhythmias did not recur until 110–135 days after stopping amiodarone, at a time when QTc interval had returned to baseline and rT₃ levels were less than 60 ng/dl. The resumption of amiodarone at a high dose led to a prompt increase in rT₃ and lengthening of QTc, with a complete resuppression of the ventricular arrhythmia. The data illustrate the close correlation with antiarrhythmic efficacy and serum rT₃ level. PVC = premature ventricular complex; VT = ventricular tachycardia.

Figure 6. Control of ventricular arrhythmia by amiodarone relative to alterations in serum reverse T₃ (rT₃) and QTc interval. The data are very similar to those in figure 5, but the therapeutic half-life of amiodarone as judged by the elimination half-life of rT₃ is much shorter in this patient. The wider therapeutic range for rT₃ in contrast to that for QTc enhances its clinical value. PVC = premature ventricular complex; VT = ventricular tachycardia.

darone in two patients with widely varying rT₃ elimination half-life (as an index of drug half-life) are illustrated in figures 5 and 6. An excellent concordance between antiarrhythmic effect and serum rT₃ levels is shown, in addition to a marked difference in the duration for the reappearance of the arrhythmia on cessation of amiodarone therapy.

In five patients with ventricular arrhythmias, the level of rT₃ has been correlated with varying and lower doses of amiodarone and with the antiarrhythmic effects, once the arrhythmia was satisfactorily controlled by an initial higher dose (table 3). After a mean follow-up of 4 months (range 3–5 months) on the lower and less frequent dose schedule, arrhythmias have not recurred and reverse rT₃ levels have remained in the therapeutic range (55–100 ng/dl). No side effects have been noted during the period of observation.

Discussion

Our results confirm the extraordinary efficacy of orally administered amiodarone in suppressing symptomatic ventricular and atrial arrhythmias resistant to two or more conventional antiarrhythmic agents, and suggest a reliable method for monitoring the efficacy and toxicity of amiodarone. All the patients had stable patterns of arrhythmia; therefore, elimination of the arrhythmia by amiodarone could not reasonably be attributed to spontaneous variations of the arrhythmia. When the drug was withdrawn after the initial stabilization of therapy, the arrhythmia recurred in eight of the nine patients in whom controlled withdrawal was undertaken. The subsequent resuppression of the arrhythmia in all eight provided further evidence for the predictable antiarrhythmic efficacy of amiodarone in refractory arrhythmias. In the remaining patient, the failure of the recurrence of the atrial arrhythmia despite the lapse of 5 months after drug withdrawal raises the possibility of the spontaneous variation in the severity of the arrhythmia.

Our results are particularly important in relation to
the role of rT3 in monitoring the efficacy and toxicity of amiodarone. The onset of action of the drug may be delayed for days.4,5,11 Furthermore, the electrophysio-
logic effects of the intravenously administered drug is different from those after chronic oral therapy.6 For example, the lengthening of the QTc interval of the ECG, an almost invariable accompaniment of antiar-
rhythm action, occurs only after chronic therapy and not after the acute i.v. administration.1,14 It is therefore
unlikely that the drug’s observed antiarrhythmic effect on chronic treatment is due to the activity of the parent
molecule. For these reasons, we have systematically examined other measurable effects noted during chronic
therapy as potential indexes for monitoring drug
efficacy and toxicity. Although the heart rate fell, the
QTc interval lengthened and the serum T3 became elevated in all patients given amiodarone, the range of
change in these measurements was narrow. Moreover,
an inconsistent dose-response relationship with respect
to duration of therapy and to drug efficacy and toxicity
precluded their routine use in monitoring amiodarone
therapy.

In contrast, a close correlation between the levels of
rT3 and the salutary antiarrhythmic effects of the com-
pound, both during the initial stabilization phase of
therapy and after a temporary withdrawal and subse-
quently resumed drug treatment, permitted the
definition of a range of serum rT3 values over which suppression of arrhythmia in this series invariably
occurred. In our laboratory, this range was 55–100 ng/dl
and the side effects occurred only when serum rT3
levels exceeded 100–110 ng/dl; they disappeared as
the dose of amiodarone was reduced and rT3 levels fell
into the therapeutic range. Similarly, the arrhythmia
recurred when the serum rT3 dropped to less than 55–
60 ng/dl. The rate of decline of serum rT3 levels after
withdrawal of amiodarone was variable in different
patients, but was almost a mirror image of the rate of
increase in levels at the initiation of therapy. Since a
close correlation was demonstrated between the time
course of reappearance of the arrhythmia after drug
withdrawal and the time taken for the serum rT3 levels
to return to control, chronic therapy may be inferred
from the elimination half-life of rT3 in the serum. By
this method, the therapeutic half-life of amiodarone
was 25–55 days. On this basis, if the elimination kinetics
of amiodarone is linear and if therapy is to be
initiated at maintenance dose schedules (200–600 mg/
day) without a loading dose, 5 months or longer (i.e., 5
elimination half-lives) may be necessary in some patients
for steady-state drug effects to be obtained.

If these inferences are confirmed, our findings may
not only account for the observation that side effects
of amiodarone appear only after many months of therapy,
but also for the somewhat variable antiarrhythmic efficacy
reported by different investigators,5,10–12 since dosage schedules cannot be standardized. At least in
some instances, therapy with the drug may have been
abandoned prematurely when the anticipated benefit,
on maintenance doses, was not apparent within a few
weeks of drug treatment. The variable elimination
half-life of amiodarone in different patients requires
individualized and initially large loading doses for a
rapid control of arrhythmias.13 Our data suggest that
such an individualized approach is feasible by serial
measurements of rT3, the serum levels of which may
provide an accurate and reliable index of drug efficacy
and also of the side effects.

The elevation of rT3 during amiodarone therapy has
been reported,15,16 but its dose dependence, its time
course of change and interpatient variability during chronic therapy, and its relationship to the antiarrhyth-
mic efficacy of the drug have not. The in vivo deiodina-
tion of amiodarone results in the release of iodine,17
which may cause hypothyroidism or hyperthyroidism
in about 2–4% of patients on chronic amiodarone ther-
apy.13 The exact incidence is unknown because no
uniform criteria for the diagnosis of altered thyroid
state during amiodarone treatment have been estab-
lished. In our series, there were no cases of hypothy-

<table>
<thead>
<tr>
<th>Pt</th>
<th>Initial amiodarone dose and duration of treatment (mg/day)</th>
<th>Baseline rT3 (ng/dl)</th>
<th>rT3 (ng/dl) under steady-state conditions of amiodarone</th>
<th>rT3 (ng/dl) on maintenance dose and duration of follow-up</th>
<th>Maintenance dose regimen of amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1000 (5 mo)</td>
<td>40</td>
<td>113</td>
<td>98 (3½ mo)</td>
<td>600 mg, 3 x/wk</td>
</tr>
<tr>
<td>2</td>
<td>800 (2 mo)</td>
<td>27</td>
<td>73</td>
<td>60 (3 mo)</td>
<td>800 mg, 2 x/wk</td>
</tr>
<tr>
<td>3</td>
<td>1000 (2 mo)</td>
<td>33</td>
<td>105</td>
<td>99 (5 mo)</td>
<td>200 mg daily</td>
</tr>
<tr>
<td>4</td>
<td>600 (2 mo)</td>
<td>30</td>
<td>65</td>
<td>57 (3 mo)</td>
<td>800 mg, 2 x/wk</td>
</tr>
<tr>
<td>5</td>
<td>1000</td>
<td>44</td>
<td>112</td>
<td>64 (5 mo)</td>
<td>600 mg, 3 x/wk</td>
</tr>
</tbody>
</table>

*All five patients had ventricular arrhythmias resistant to conventional antiarrhythmic therapy.
†Goal of arrhythmia suppression satisfied.
oidism or hyperthyroidism; thus, no correlation between rT₃ levels and the development of clinically significant change in thyroid function could be made.

Hypothyroidism or hyperthyroidism during amiodarone therapy appears specific for iodine rather than for amiodarone. For example, Lugol's iodine in amounts equivalent to that in clinical doses of amiodarone has no electrophysiologic effects on heart muscle in animals, nor does it produce elevations in serum rT₃ or T₃ levels in patients. In contrast, amiodarone increases total and free T₄ and rT₃, with concomitant minor decreases in total T₃ associated with no significant changes in thyroglobulin binding protein. These effects of amiodarone on thyroid function are consistent with the knowledge that thyroid function is not clinically depressed in most patients taking amiodarone. The drug-induced changes are not found in euthyroid patients without T₄ replacement. Thus, the data have been interpreted as indicative of the inhibition by amiodarone of the peripheral conversion of T₄ to T₃, which may account for the observed increases in T₃ and rT₃ on amiodarone. Also, elevation of serum T₄ levels during chronic amiodarone therapy may be due to diminished clearance. The sustained T₃ elevation cannot be attributed to the transient increases in thyroid-stimulating hormone found during the early stages of amiodarone therapy. The order of change in this variable is less marked compared with that in rT₃. We found it less useful for monitoring toxicity on efficacy of amiodarone. However, elevated T₃ levels may confuse the interpretation of thyroid function tests in the instances of iodine-induced hyperthyroidism or hypothyroidism, which complicate amiodarone treatment; in these apparently rare cases, the measurement of thyroid-stimulating hormone and thyrotropin-releasing hormone stimulation tests are necessary to confirm the clinical suspicion of an altered thyroid state.

The elevated rT₃ resulting from the inhibition of the peripheral conversion of T₄ to T₃ is unlikely to be of direct pharmacologic significance; it is an incidental accompaniment of an overall complex action of amiodarone. The rT₃ levels may increase during the administration of certain pharmacologic agents and certain iodine-containing radio contrast dyes and during fasting and systemic infections such as pneumonia.

When this occurs, as it did in one of our patients (fig. 5), rT₃ levels rise and fall relative to the time course of the intercurrent illness. The rapidity of change in the rT₃ level in this context will be governed by its normal rate of decline in the blood. Clearly, under these circumstances rT₃ levels will not reliably reflect changes induced by amiodarone. The half-life of rT₃ is normally very short and the greatly prolonged half-life of rT₃ during amiodarone therapy may be due in part to interference with its metabolic clearance. However, the apparent selectivity of the action of amiodarone on heart muscle, especially relative to its extraordinarily potent antiarrhythmic effects, must be explained. The peripheral conversion of T₃ to T₄ may occur to a variable extent in different tissues. Amiodarone may inhibit such a conversion in heart muscle to a much greater extent. Whether such a differential action constitutes the sole basis for the known myocardial actions of the drug is unknown.

Freedberg et al. showed that thyroidectomy in rabbits produced a uniform shortening of atrial repolarization and the converse in hyperthyroidism. Singh and Vaughan Williams showed that chronically administered amiodarone produced an identical effect on repolarization in rabbit atrial and ventricular potentials, an effect that could be prevented by the concomitant administration of T₄. They postulated that the drug had cardiосpecificity, inhibiting thyroxine-dependent metabolic pathways in the heart. Our clinical data are in line with this hypothesis. They indicate a relationship between the genesis of cardiac arrhythmias and the action of thyroid hormones on cardiac muscle, but they do not provide an insight into the ionic mechanisms.

In addition to the inhibition of T₃ to T₄ conversion in cardiac muscle, amiodarone might act by influencing the effects of T₃ on the ionic translocations at the myocardial membrane or by blocking the actions of T₄ on the nuclear receptor. This would account for the known antianginal effects of the drug and for the observed uniform shortening of the cardiac action potential without effect on depolarization. Such an action is markedly different from those of other known classes of antiarrhythmic compounds. The fundamental ionic basis for the strikingly similar homogeneous shortening of the action potential duration noted during hypothyroidism and during amiodarone therapy is not known. However, as shown here, in the case of amiodarone it is clearly associated with an extreme potency for the control of refractory atrial and ventricular tachyarrhythmias resistant to conventional agents. Clinically, this effect was accompanied by an increase in the QTc interval. An increased propensity to arrhythmias occurs in other clinical contexts in which QTc prolongation may predispose to ventricular tachycardia or fibrillation. Therefore, one may infer that amiodarone lengthens the absolute refractory period and normalizes the heterogeneity in cardiac repolarization, reducing electrical instability in the myocardium.

Whatever ionic mechanisms are established for the salutary antiarrhythmic actions of amiodarone and for the alterations in levels of thyroid hormones accompanying the chronic therapy with the drug, two conclusions may be drawn from our data: First, the results confirm the potency of amiodarone for the control of recurrent atrial and ventricular tachyarrhythmias resistant to conventional antiarrhythmic compounds. The design of the protocol in our study was such that the efficacy of amiodarone in controlling arrhythmias could be established clearly by a period of drug withdrawal after the initial suppression had been achieved. The recurrence of the arrhythmia and its subsequent resuppression by the resumption of amiodarone therapy provide further evidence for the drug’s effectiveness in resistant tachyarrhythmias.

Second, the determination of serum rT₃ levels during amiodarone therapy may constitute a simple and
reliable technique for monitoring the drug’s antiar- rhythmic efficacy and toxicity, thereby enhancing its
clinical value. The use of rT\textsubscript{3} levels may be valuable in
developing an appropriate therapeutic regimen with
amiodarone for the control of refractory atrial and ven-
tricular tachyarrhythmias.

Acknowledgment
We are much indebted to Carolyn Williams and Alma Gump for
secretarial assistance in the preparation of this manuscript; to Paul V.
Reicher for the illustrations; and to the nursing staff of the Special
Diagnostic Care Unit for their willing and expert assistance in the care of
the patients admitted for cardiac arrhythmias. The thoughtful comments of Dr. Inder J. Chopra (Department of Endocrinology, UCLA School of
Medicine) are gratefully acknowledged.

Rabbit rT\textsubscript{3} antiserum was generously provided by Dr. Michael
Kaplan, Boston.

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Circulation. 1982;66:202-211
doi: 10.1161/01.CIR.66.1.202

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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