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Interrelationships between serum levels of amiodarone, desethylamiodarone, reverse T₃ and the QT interval during long-term amiodarone treatment

The interrelationships between serum levels of amiodarone, desethylamiodarone, and reverse T₃, and changes in the corrected QT interval (ΔQT_c) were examined in 22 patients during long-term treatment with amiodarone. At 1, 3, and 6 months of follow-up, the correlation coefficient between serum levels of amiodarone or desethylamiodarone and reverse T₃ ranged from 0.01 to -0.2 ($p > 0.4$). At the same time intervals, the correlation coefficient between both amiodarone and desethylamiodarone levels and ΔQT_c ranged from 0.1 to -0.1 ($p > 0.6$), and the correlation coefficient between reverse T₃ and ΔQT_c also ranged between 0.1 to -0.1 ($p > 0.5$). Substituting percent ΔQT_c for ΔQT_c also did not reveal a significant correlation. These data demonstrate that serum levels of reverse T₃ cannot be used as a substitute for serum levels of amiodarone in monitoring patients being treated with amiodarone. The absence of a correlation between serum reverse T₃ levels and ΔQT_c suggests that the delay in repolarization which occurs during amiodarone therapy is not secondary to an amiodarone-induced abnormality in thyroid hormone metabolism. (*AM HEART J* **111**:644, 1986.)

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Amiodarone blocks the peripheral conversion of thyroxine (T₄) to tri-iodothyronine (T₃),¹ resulting in increased production of reverse T₃. Some investigators^{2,3} have reported that the increase in the serum reverse T₃ level which occurs during chronic amiodarone therapy correlates with amiodarone's antiar-

rhythmic action. These investigators have suggested that the serum level of reverse T₃ may be helpful in monitoring long-term amiodarone therapy.

Other investigators have demonstrated that amiodarone's antiarrhythmic effect correlates with the serum amiodarone level.⁴⁻⁶ Therefore, as is the case with serum levels of reverse T₃, serum levels of amiodarone have also been reported as being useful in monitoring amiodarone's efficacy and toxicity. However, the relationship between serum levels of reverse T₃ and serum levels of amiodarone, or its principal metabolite, desethylamiodarone, has not been reported upon to date.

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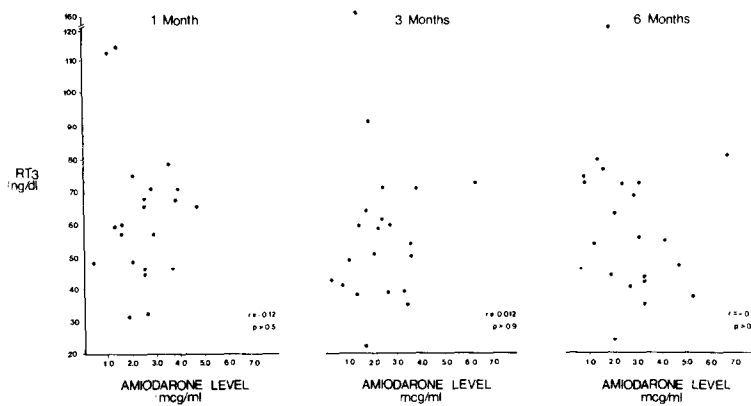


Fig. 1. Relationship between serum amiodarone levels and reverse T₃ (RT₃) levels at 1, 3, and 6 months of treatment. Correlation coefficients and p values are as shown.

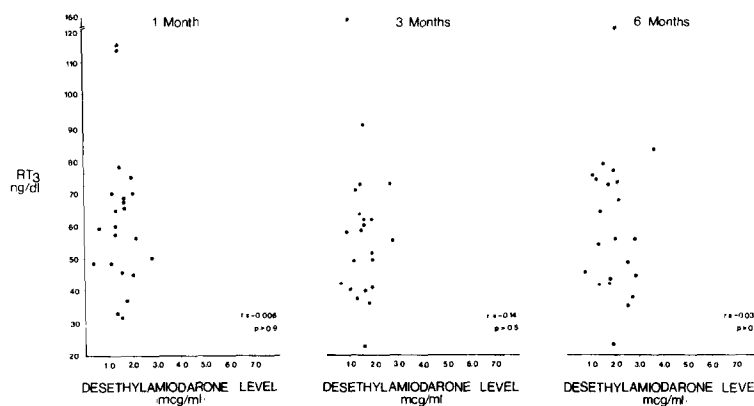


Fig. 2. Relationship between serum desethylamiodarone levels and reverse T₃ (RT₃) levels at 1, 3, and 6 months of treatment. Correlation coefficients and p values are as shown.

The purpose of this study was to determine whether any relationship exists between serum levels of reverse T₃ and amiodarone or desethylamiodarone during chronic amiodarone therapy. Because either serum reverse T₃ or serum amiodarone levels may be more conveniently obtained in a particular hospital or community, it would be useful to know if these serum levels can be used interchangeably in following patients being treated with amiodarone. Also examined was the relationship between serum levels of reverse T₃, amiodarone, and desethylamiodarone, and an index of amiodarone's cardiac tissue effect, namely prolongation of the QT interval.

METHODS

This study was conducted in 22 patients who were treated with amiodarone for a period of at least 6 months. All patients had normal baseline thyroid function and no clinical evidence of renal or hepatic dysfunction. There were 18 men and 4 women, and their mean age was 53 ± 17 years (mean ± standard deviation). Coronary

artery disease was present in 11 patients, valvular heart disease was found in three, and idiopathic dilated cardiomyopathy was seen in one, whereas four patients had no identifiable structural heart disease. The indication for amiodarone therapy in these patients was ventricular tachycardia refractory to conventional antiarrhythmic drugs in 18 patients, and atrial fibrillation or flutter in four patients.

Before the initiation of therapy with amiodarone, an ECG was obtained at least four half-lives after discontinuation of all antiarrhythmic drugs, as were baseline blood samples for determination of the serum levels of reverse T₃, amiodarone, and desethylamiodarone. Amiodarone therapy was initiated at a dose of 1200 mg/day for 1 week, followed by 800 mg/day for 1 month, then 600 mg/day for 1 month; the chronic maintenance dose was 200 to 400 mg/day. An ECG and blood samples for determination of the serum levels of amiodarone, desethylamiodarone, and reverse T₃ were obtained after 1, 3, and 6 months of treatment.

The QT interval was measured from the ECG lead in which termination of the T wave was best defined. The

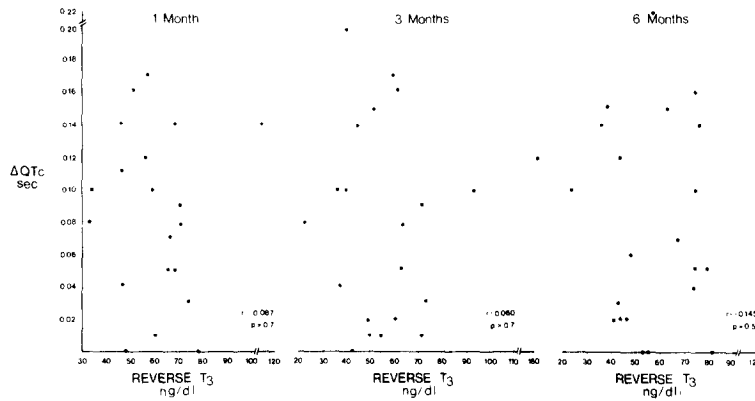


Fig. 3. Relationship between serum reverse T_3 levels and ΔQT_c at 1, 3, and 6 months of treatment. Correlation coefficients and p values are as shown.

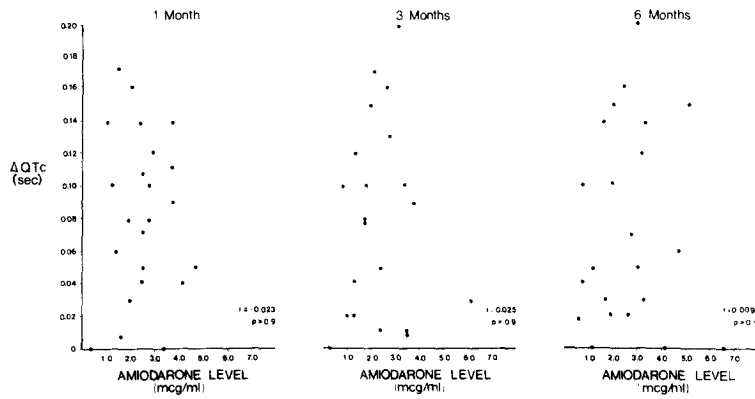


Fig. 4. Relationship between serum amiodarone levels and ΔQT_c at the regular follow-up intervals. Correlation coefficients and p values are as shown.

same ECG level was used for all QT measurements in each patient. The QT intervals were measured independently by two observers blinded to the serum levels of reverse T_3 and amiodarone. If the QT measurement differed by more than 0.02 second, differences were resolved by common agreement. The corrected QT interval (QT_c) was calculated with Bazett's formula.⁷

Serum levels of reverse T_3 were determined by radioimmunoassay. Serum levels of amiodarone and desethylamiodarone were determined with the extraction technique of Storey et al.,⁸ and the chromatographic conditions of Flanagan et al.⁹

Correlation coefficients were determined with a linear regression model. p values of < 0.05 were considered significant.

RESULTS

There was not a significant correlation between serum levels of amiodarone or desethylamiodarone and reverse T_3 after either 1, 3, or 6 months of

treatment with amiodarone (Figs. 1 and 2). There was not a significant correlation between serum levels of reverse T_3 and ΔQT_c after either 1, 3, or 6 months of treatment with amiodarone (Fig. 3). Also, there was not a significant correlation between serum levels of amiodarone or desethylamiodarone and ΔQT_c at any of the follow-up intervals (Figs. 4 and 5). Expressing ΔQT_c in terms of percent change resulted in no improvement in the above correlations.

DISCUSSION

The results of this study demonstrate that neither serum levels of amiodarone nor desethylamiodarone correlate with the serum level of reverse T_3 during long-term amiodarone therapy. Therefore, serum levels of reverse T_3 cannot be used as a substitute for serum levels of amiodarone in monitoring patients being treated with amiodarone (Fig. 6).

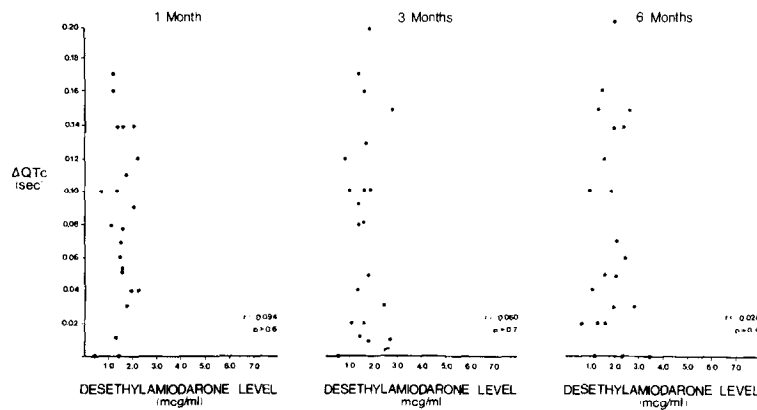


Fig. 5. Relationship between serum desethylamiodarone levels and ΔQT_c at the regular follow-up intervals. Correlation coefficients and *p* values are as shown.

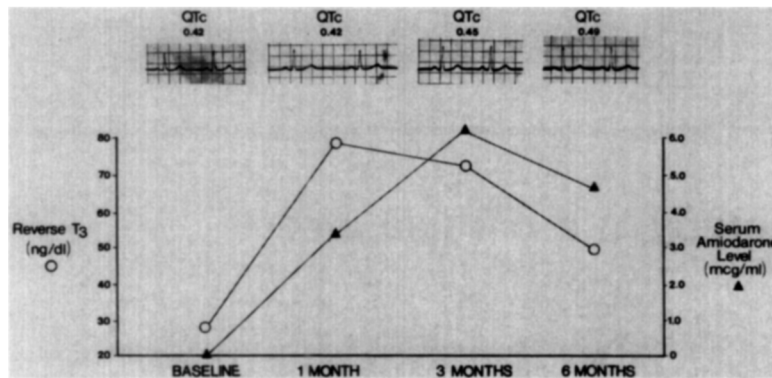


Fig. 6. QT_c , together with serum levels of reverse T_3 and amiodarone, are demonstrated for an individual patient on long-term amiodarone therapy for ventricular tachycardia. Note the discordant trends in all three variables.

Also of note is the finding that the serum level of reverse T_3 did not correlate with the degree of amiodarone-induced delay in repolarization, as measured by prolongation of the QT interval. Some investigators have suggested that amiodarone's mechanism of action may involve the induction of a local hypothyroid state in cardiac muscle.^{2,3} However, the lack of correlation between changes in the QT interval and reverse T_3 during treatment with amiodarone suggests that the delay in repolarization which occurs with amiodarone is not secondary to an abnormality in thyroid hormone metabolism. Of note is that iopanoic acid, which has effects on thyroid hormone metabolism similar to amiodarone, has been shown to be without antiarrhythmic effects.¹⁰

Serum amiodarone or desethylamiodarone levels also did not correlate with changes in the QT interval during long-term treatment with amioda-

rone. It is unknown whether tissue levels of amiodarone or its metabolite might correlate to a better degree with changes in the QT interval.

This study has several limitations. Firstly, blood samples were drawn at the time of outpatient visits at a variable number of hours after the last dose of amiodarone. However, it is unlikely that this factor significantly affected the results of this study, because Haffajee et al.⁴ reported that there are only minor fluctuations in the serum amiodarone level in the 24-hour dosing interval during maintenance amiodarone therapy. Second, because myocardial tissue levels of amiodarone or desethylamiodarone were not measured, it is unknown whether tissue levels of amiodarone or its metabolite correlate with changes in the QT interval. Third, we were unable to correlate serum drug or reverse T_3 levels with amiodarone's antiarrhythmic efficacy; the majority of patients in this study had infrequent and sporadic

arrhythmias, and antiarrhythmic efficacy could not be adequately assessed over a 6-month follow-up period.

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Lorcainide therapy in a cardiac arrest population

Thirty-eight patients with a prior history of cardiac arrest underwent programmed electrical stimulation (PES) studies and serial drug testing. Lorcainide was tested acutely in all 38 patients and prevented ventricular tachycardia (VT) or ventricular fibrillation (VF) induction in 14 patients and failed in 24 (efficacy rate 37%). Procainamide had failed clinically (cardiac arrest or breakthrough VT) in 16 patients, seven patients had previously severe adverse side effects, and thus only 15 were tested on procainamide at PES testing with seven protected. Following initial studies, 14 patients were started on lorcainide oral therapy and 24 on other therapy determined effective at PES testing (N-acetylprocainamide-two, flecainide-nine, bethanidine-three, slow-release procainamide hydrochloride-three, quinidine-two, cibenzoline-one, amiodarone-four). After 29 ± 7 months follow-up, three are alive on lorcainide therapy, five discontinued therapy due to side effects; six died—three sudden deaths (33%) and two cardiac deaths (both myocardial infarctions). Twenty out of 24 patients are alive who were started on PES predicted effective therapy other than lorcainide; four died—three sudden deaths (13%) and one cardiac nonsudden death. Antiarrhythmic therapy guided by PES studies gives overall encouraging results in a cardiac arrest group of patients. Lorcainide, however, is not tolerated well and affords less protection against a sudden death recurrence than is noted in a population on other antiarrhythmic therapy predicted effective at PES testing. (*AM HEART J* 111:648, 1986.)

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Patients with a prior history of a cardiac arrest are among the most electrically unstable, with a high incidence of recurrence. They have identified themselves as being at risk for life-threatening arrhythmias. Studies by Cobb et al.¹⁻³ have indicated that