

The QT interval: a predictor of the plasma and myocardial concentrations of amiodarone

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SUMMARY A study was performed to assess whether plasma and myocardial concentrations of amiodarone correlated with changes on the surface electrocardiogram. Nine patients—seven with angina and two with paroxysmal ventricular tachycardia—were treated with oral amiodarone (200–400 mg daily) for at least nine months before undergoing cardiac surgery. QT intervals were measured from lead II of the surface electrocardiograms recorded before amiodarone treatment and immediately before surgery. Patients with prominent U waves after taking amiodarone were excluded from the study. Plasma and myocardial samples were collected at the beginning of the surgical procedure for estimating plasma and myocardial concentrations using the high performance liquid chromatographic technique. Amiodarone caused a significant lengthening of the QTc interval. There was a good correlation between plasma and myocardial concentrations, and both correlated well with the percentage increase in the QTc interval. Although there was a strong correlation between the dosage given (mg/kg/day) and both plasma and myocardial concentrations, the correlation with the percentage increase in the QTc interval was weaker but still highly significant. Despite previous reports to the contrary, the findings indicate that the plasma concentration of amiodarone does correlate well with the myocardial concentration. The degree of lengthening of the QTc interval may be used clinically to estimate the myocardial concentration of amiodarone.

Amiodarone was first introduced as an antianginal drug.^{1,2} Its electrophysiological effect of prolonging the action potential was discovered later,^{3,4} and amiodarone is now recognised as a Vaughan Williams class III antiarrhythmic agent.⁵ The drug is widely used for the treatment of both angina and arrhythmias.⁶

The pharmacokinetics of amiodarone received scant attention, however, until the introduction of a high performance liquid chromatographic technique allowed the fast and accurate assay of the drug in plasma.^{7,8} Amiodarone is highly tissue bound,⁹ and it was thought that blood concentrations of the drug were of only limited clinical use¹⁰ and did not correlate with its efficacy. Recently, this widely held belief has been challenged by reports of a correlation between plasma concentrations and efficacy.¹¹ It has also been reported that amiodarone induced lengthening of the QTc interval may be an indicator

of clinical effect.⁸ The purpose of this study was to investigate the relation between plasma concentration, myocardial concentration, drug dosage, and electrocardiographic changes induced by amiodarone.

Patients and methods

PATIENTS

The study group consisted of nine patients (six men) aged from 43 to 76 (mean 57) years. All patients had documented ischaemic heart disease; seven complained of angina pectoris and two of palpitations due to paroxysmal ventricular tachycardia associated with a left ventricular aneurysm. All patients were due to undergo coronary artery bypass grafting with or without aneurysmectomy. The patients were treated with amiodarone as an antianginal or antiarrhythmic agent before surgery. A regimen of 200 mg amiodarone a day for five days out of seven was used in five patients and that of 400 mg a day for five days out of seven in the remaining four. (This regimen resulted in dosages ranging from 2.50 to 6.15 mg/kg/day.) Treatment was started at least 12 months before surgery in all

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patients except one who received the drug for nine months.

A large series of 30 patients has been studied to determine the relation between myocardial and plasma concentrations of amiodarone.¹² Of these 30 patients, nine met all the specific criteria for the present study: (a) no treatment with other drugs known to affect the QT interval; (b) no bundle branch block, pre-excitation, or other form of abnormal QRS complex; (c) no prominent U waves on the electrocardiogram before treatment with amiodarone; and (d) availability of good quality preoperative and post-operative electrocardiograms. All routine haematological and biochemical investigations were normal. Written informed consent was obtained from each patient before entry to the study.

ELECTROCARDIOGRAMS

Twelve lead electrocardiograms were recorded before the start of amiodarone treatment and again just before surgery. The QT intervals were measured directly from standard lead II using a digitising system on line to a computer. The sensitivity of the measuring system (at a recording speed of 25 mm/s) was 2 ms. The measurements were made double blind (as far as the electrocardiographic changes induced by amiodarone on the electrocardiogram would allow) by two different operators. Interobserver error was small, and the mean of both values was used for calculating the QTc interval. The QT interval was measured from the beginning of the QRS complex to the end of the T wave, including the reduplication of the T wave that often appears with long term amiodarone treatment (Fig. 1). The measured QT intervals were corrected according to heart rate using Bazett's hyperbolic formula.¹³ The percentage increase in the corrected QT intervals after amiodarone treatment was calculated.

PLASMA AND MYOCARDIAL SAMPLES

Twenty millilitres of arterial blood were collected during general anaesthesia before the chest was opened. The blood was stored in heparinised tubes

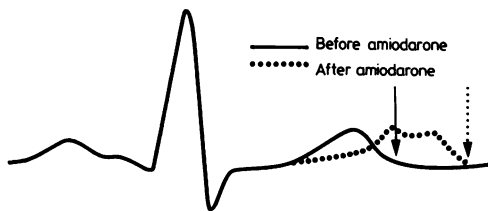


Fig. 1 Diagram showing electrocardiographic features before and after treatment with amiodarone. The arrows indicate the points at which the QT intervals were measured.

and centrifuged. Plasma was frozen and stored in the dark at -30°C . Five patients had received their last dose of amiodarone 24 hours before surgery and four their last dose 12 hours before surgery.

Biopsy specimens of atrial myocardium were taken from the tip of the right atrial appendage at the time of cannulation of the caval veins before extracorporeal circulation was established. Myocardial biopsy specimens were immediately stored in dried tubes away from the light and frozen to -30°C .

Amiodarone concentrations were measured by a high performance liquid chromatography technique, adapted for tissue biopsy specimens.¹² The sensitivity of this method was proved to be 8.3 ng of amiodarone.¹²

STATISTICAL ANALYSIS

Where a correlation between two variables was sought, least squares linear regression analysis was used, and the probability (p) deduced from the regression coefficient (r). Data were compared using Student's t test for paired data. Results were considered to be statistically significant when $p < 0.05$.

Results

The mean QTc interval before amiodarone treatment was 454 ± 34 ms and during amiodarone treatment 533 ± 61 ms. The increase of 79 ms was significant at the 1% level.

The percentage increase in the QTc interval ranged from 6.8% to 35.8% with a mean increase of 18.5%. The linear regression between the oral dose (mg/kg/day) and the percentage increase in the QTc interval showed that the higher the dosage the greater the increase in QTc. The correlation coefficient (r) was 0.88, and the intercept 0.96 mg/kg/day (Fig. 2).

Plasma concentrations ranged from 0.13 mg/l to 0.76 mg/l (mean 0.37 mg/l) and myocardial concentrations from 3.46 mg/kg to 11.16 mg/kg (mean 7.11 mg/kg). Linear correlations between amiodarone concentrations and dosage (correlation

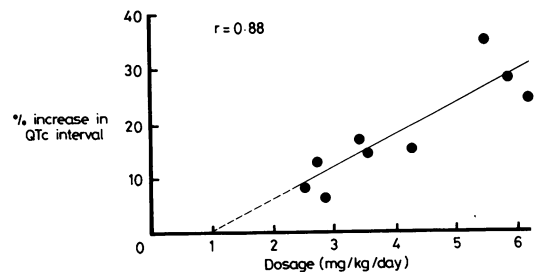


Fig. 2 Correlation between the percentage increase in the QTc interval and the dosage of amiodarone given.

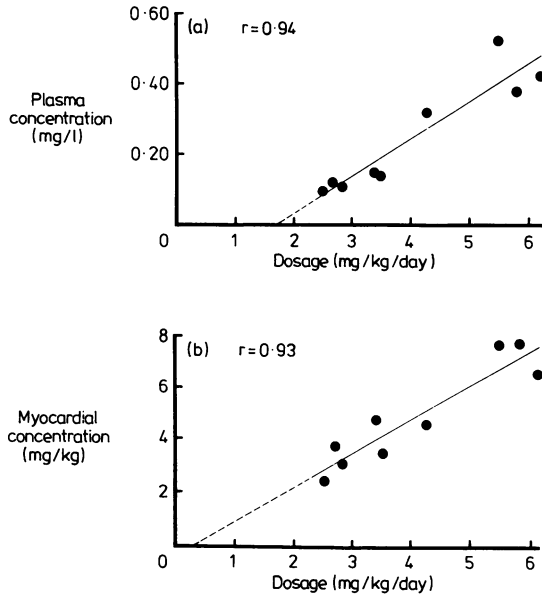


Fig. 3 Correlation (a) between the plasma concentration of amiodarone and the dosage given and (b) between the myocardial concentration of amiodarone and the dosage given.

coefficients $r=0.94$ for plasma and $r=0.93$ for myocardium) were obtained. For the plasma concentrations the intercept was 1.71 mg/kg/day and for the myocardial concentrations the intercept was 0.27 mg/kg/day (Fig. 3). There was a strong correlation between plasma and myocardial concentrations with an r value of 0.92 and an intercept of -0.27 mg/l (Fig. 4).

Linear regression showed a good correlation between percentage increase in the QTc interval and plasma concentration of amiodarone with an r value of 0.92 and an intercept of -0.13 mg/l. Similarly, the correlation between myocardial concentration of the drug and percentage increase in the QTc interval was extremely good with an r value of 0.96 and an intercept of 1.40 mg/kg (Fig. 5).

These results are summarised in the Table.

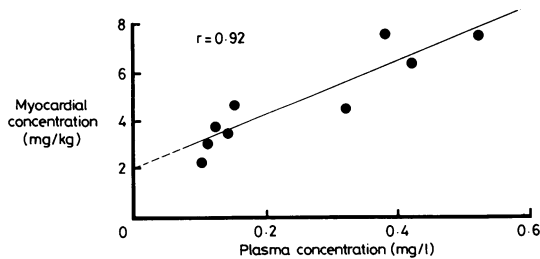


Fig. 4 Correlation between the myocardial concentration and the plasma concentration of amiodarone.

Table Summary of the correlations between the plasma and myocardial concentrations of amiodarone, the dosage given, and the percentage increase in the QTc interval

	% Increase in QTc interval	Plasma concentration (mg/l)	Myocardial concentration (mg/kg)
Plasma concentration (mg/l)	$r=0.92$ $p<0.001$		
Myocardial concentration (mg/kg)	$r=0.96$ $p<0.001$	$r=0.92$ $p<0.001$	
Dose of amiodarone (mg/kg/day)	$r=0.88$ $p<0.005$	$r=0.94$ $p<0.001$	$r=0.93$ $p<0.001$

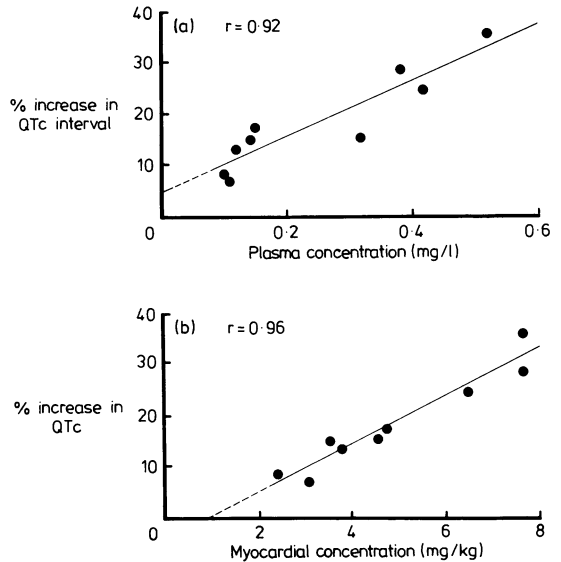


Fig. 5 Correlation between the percentage increase in the QTc interval and (a) the plasma concentration and (b) the myocardial concentration of amiodarone.

Discussion

The antiarrhythmic efficacy of amiodarone is now well proved, and it is widely used for a variety of atrial, junctional, and ventricular arrhythmias.¹⁴ Amiodarone treatment is, however, difficult to monitor because of the tissue, and particularly myocardial, affinity for the drug. The long half life of the drug and the variable time before therapeutic efficacy is achieved¹⁵ also increase the difficulty. The myocardial concentration of the drug is obviously the most relevant index by which to monitor treatment,¹⁶ but it is impossible to measure on a routine clinical basis.

Plasma concentrations of the drug have been said to be of no value in the long term follow up of patients taking amiodarone.¹⁰ In this study, the plasma concentration and the myocardial concentration of the

drug both correlated well with the dose given and with each other. The relation between plasma concentration and dosage (Fig. 3) suggests that there is a dose threshold that must be exceeded before the drug appears in the plasma. This has also been shown in a larger study of 30 patients.¹² This phenomenon suggests that the drug is avidly taken up by tissues—including the myocardium—with plasma concentrations not measurable until the tissues have removed a considerable amount of the drug from the circulation. This is in part confirmed by the relation between myocardial concentrations and drug dosage in which—in contrast to plasma—no threshold phenomenon is seen. Nevertheless, the myocardial drug concentration can be inferred from concentrations of drug in the plasma. Thus in contradiction of widely accepted dogmas, this study shows that long term amiodarone treatment can be monitored using trough plasma concentration estimates. This new conclusion probably relates to the improved accuracy of the present method (8.3 ng of amiodarone), because concentrations in plasma are 10 times lower than those in the myocardium.

In this group of patients, atrial myocardial biopsy specimens were examined to determine the relation between an increase in the QT interval and the myocardial amiodarone concentration. A previous study¹² had already shown that there is no statistical difference between amiodarone concentrations in atrial and ventricular myocardium. Even allowing for the long half life of amiodarone,¹⁷ steady state myocardial concentration will have been achieved in this group of patients treated for at least nine months. The measurement of the QT interval (from lead II of the surface electrocardiogram) was made to the end of the T (double T or fused T/U) wave. Patients with discrete U waves (after the end of the T wave) were excluded from the analysis. There were highly significant relations between the increase in this measurement and amiodarone dosage and between plasma and myocardial concentrations. The higher the dosage, the longer the QTc intervals. A threshold dosage of 0.96 mg/kg/day was necessary to produce a measurable increase in the QTc interval. It has been previously suggested that the increase in the QTc interval is directly related to the efficacy of the drug,⁸ and this is supported by the results of the present study in view of the strong correlation found between the QTc interval and the myocardial concentration of amiodarone. Measurements of electrocardiographic repolarisation changes allow the myocardial concentrations to be estimated clinically.

Many side effects of amiodarone are well known,^{15 18–21} and others have been reported recently,^{22–24} which are perhaps due to higher dosage regimens. Most of the side effects are dose related,

and the vast majority disappear when the drug is stopped. The increase in the QTc interval may be used as a clinical test to estimate myocardial concentration and may thus allow doses in individual patients to be reduced.

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