

Quinidine Pharmacodynamics in Patients with Arrhythmia: Effects of Left Ventricular Function

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Objectives. This study was undertaken to determine whether quinidine pharmacodynamics are altered in the presence of left ventricular dysfunction.

Background. Left ventricular function is an independent predictor of antiarrhythmic drug efficacy. However, the effects of left ventricular dysfunction on the pharmacodynamics of antiarrhythmic drugs have not been studied extensively.

Methods. Signal-averaged electrocardiograms were obtained and quinidine plasma concentrations measured during 24-h quinidine washout in 22 patients.

Results. Linear quinidine concentration-effect relations were observed for QRS and QT intervals corrected for heart rate. The slopes of the concentration-effect relation describing changes in the corrected QT (QTc) interval were significantly higher in the group with left ventricular ejection fraction ≥ 0.35 ([mean \pm SD] 29.5 ± 11.2 ms/ μ g per ml) than in the group with a low left ventricular ejection fraction (15.7 ± 9.7 ms/ μ g per ml, $p = 0.001$).

The QRS concentration-effect relations were not different in the two groups. A significant linear correlation was observed between the slopes of the concentration-effect relations describing changes in QTc intervals and left ventricular ejection fraction ($r = 0.7$, $p < 0.001$). Nineteen patients with inducible ventricular tachycardia underwent serial electrophysiologic studies for evaluation of quinidine efficacy. Ventricular tachycardia could not be induced during quinidine therapy in eight patients. The slopes of the quinidine concentration-effect relations for QTc intervals were significantly higher in quinidine responders than in nonresponders ($p < 0.05$).

Conclusions. The effects of quinidine on ventricular repolarization are linearly related to left ventricular ejection fraction. Quinidine concentration-effect relations describing ventricular repolarization are associated with antiarrhythmic efficacy in patients with ventricular tachycardia.

(*J Am Coll Cardiol* 1995;25:989-94)

Left ventricular function has been reported (1-3) to be an independent predictor of antiarrhythmic drug efficacy in patients with ventricular tachycardia and ventricular fibrillation. In the setting of left ventricular dysfunction, the effects of antiarrhythmic drugs may potentially be modified by underlying structural heart disease (3-8), electrolyte abnormalities (9,10), hemodynamic factors (11,12) or neurohumoral mechanisms (13,14) associated with heart failure syndrome. The antiarrhythmic drug quinidine has been used frequently for the management of atrial and ventricular tachyarrhythmias in patients with ventricular dysfunction (15,16). Whether quinidine pharmacodynamics are altered in the presence of left ventricular dysfunction is unknown. Because quinidine prolongs QRS duration and the QT interval on the surface electrocardiogram (ECG), the signal-averaged ECG could be

used to study the pharmacodynamic effects of this antiarrhythmic drug (17,18). Accordingly, the present study sought to 1) evaluate the effects of left ventricular dysfunction on quinidine pharmacodynamics; 2) determine whether the signal-averaged ECG could be used to noninvasively study antiarrhythmic drug pharmacodynamics; and 3) determine whether differences in quinidine pharmacodynamics predict suppression of inducible ventricular tachycardia.

Methods

Study protocol. Patients receiving quinidine for treatment of supraventricular or ventricular tachyarrhythmias were eligible for participation in the study. All patients gave written informed consent to participate in the study, which was approved by the Conjoint Medical Ethics Committee of the University of Calgary. Quinidine therapy was initiated with quinidine bisulfate, and the dose was titrated to achieve a minimal concentration of 10 μ mol/liter or the maximal well tolerated dose (19). The quinidine bisulfate dose ranged from 250 to 750 mg every 8 h. Quinidine was administered at 7 AM on the day of study after quinidine therapy had reached steady state (≥ 5 half-lives). Patients then underwent a 24-h drug washout period. At 0, 1, 2, 4, 6, 8, 10, 12, 14 and 24 h after the last quinidine dose, signal-averaged ECGs were obtained, and

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Manuscript received June 20, 1994; revised manuscript received October 20, 1994, accepted December 5, 1994.

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plasma was collected for quinidine concentration analysis. Rhythm strips were obtained simultaneously for documentation of the RR interval.

Signal-averaged ECG intervals. Bipolar X, Y and Z ECG leads were recorded and analyzed with the Predictor System (Corazonix Corp.). The ECG signal was digitized at a frequency of 1,000 Hz, and samples were acquired to a noise end point of $\leq 0.6 \mu\text{V}$. The unfiltered QRS and QT intervals recorded at each sampling time were manually measured by one of the investigators (M.M.) who had no knowledge of the identity of the patient and the time of ECG recording. The QRS duration was measured from the onset of the initial high frequency deflection of the QRS complex to the final return of the signal to baseline. The terminal component of the QT interval was measured as the point where a tangent drawn from the T wave intersected the isoelectric line (20). The QT interval was corrected for heart rate using the Bazett formula (21). The QRS and QT intervals were remeasured by the same investigator in 10 patients on separate days, and intraobserver variability was assessed by linear regression analysis.

Quinidine antiarrhythmic efficacy. Patients with inducible sustained ventricular tachycardia during a baseline electrophysiologic study underwent a second electrophysiologic study for assessment of quinidine antiarrhythmic drug efficacy. The stimulation protocol has been described elsewhere (8). Antiarrhythmic efficacy was defined as the failure to induce >15 repetitive ventricular responses with the entire ventricular pacing protocol. The electrophysiologic study was performed 5 to 6 h after the last quinidine dose in all but one patient in whom the study was performed 2 h after the last quinidine dose. The quinidine washout study was performed in these patients on the day after their electrophysiologic study.

Data analysis. Patients were stratified into two groups on the basis of left ventricular ejection fraction, which was measured by a gated radionuclide angiographic technique: left ventricular ejection fraction <0.35 and ≥ 0.35 . Quinidine and metabolite plasma concentrations were determined using a high performance liquid chromatographic assay (22,23). The trapezoidal rule was used to calculate the area under the plasma drug concentration-time curve. Concentrations of quinidine, the contaminant dihydroquinidine and the metabolite 3-hydroxyquinidine, as well as QRS durations and corrected QT (QTc) intervals, were compared over time between the two groups. Quinidine concentration-effect relations were determined by linear regression analyses (24,25). Multiple linear regression analysis was applied to determine the relative effects of quinidine on QRS duration and the QTc interval (26). The slopes of the concentration-effect relations were compared between the two groups and in patients with inducible sustained ventricular tachycardia who responded to quinidine therapy versus those who did not.

Statistical analysis. Data are presented as mean value ± 1 SD. Comparisons between groups were made using the non-paired *t* test or Fisher exact test, as appropriate.

Table 1. Clinical Characteristics of 22 Study Patients

	LVEF <0.35 (n = 11)	LVEF ≥ 0.35 (n = 11)
Age (yr)	64 \pm 4	62 \pm 12
Men/women	11/0	7/4
Cardiac diagnosis		
Coronary artery disease	9	4
Cardiomyopathy	1	2
Valvular heart disease	1	1
Primary electrical	0	4
Presenting arrhythmias		
Ventricular tachycardia	8	8
Ventricular fibrillation	3	1
Supraventricular tachycardia	0	2
IVCD	7	1*
NYHA functional class		
I-II	10	2†
III-IV	0	0
LVEF	26 \pm 7	52 \pm 4†
Daily quinidine dose (mg)	1,959 \pm 528	1,639 \pm 636

**p* < 0.05 . †*p* < 0.01 . Data presented are mean value ± 1 SD or number of patients. IVCD = intraventricular conduction delay on 12-lead electrocardiogram; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Results

Study patients. The clinical characteristics of the 22 study patients are shown in Table 1. Patients with a depressed left ventricular ejection fraction more frequently had an intraventricular conduction delay on the 12 lead ECG (*p* < 0.05) and more frequently had symptoms of congestive heart failure (*p* < 0.01) than those with a preserved left ventricular ejection fraction.

Quinidine and metabolite concentrations. Mean quinidine, 3-hydroxyquinidine and dihydroquinidine plasma levels for the low and high left ventricular ejection fraction groups are shown in Figure 1. Quinidine and metabolite concentrations measured over time and the area under the concentra-

Figure 1. Quinidine, 3-hydroxyquinidine (3-HO-quinidine) and dihydroquinidine (DH-quinidine) concentrations over time in the low (solid symbols, n = 11) and high (open symbols, n = 11) ejection fraction groups. Data are mean value ± 1 SD.

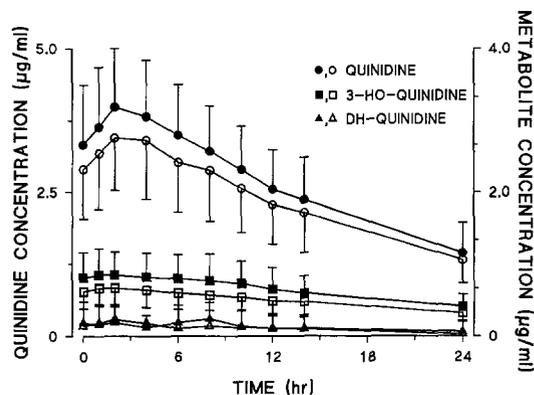


Table 2. Quinidine Pharmacokinetics and Pharmacodynamics

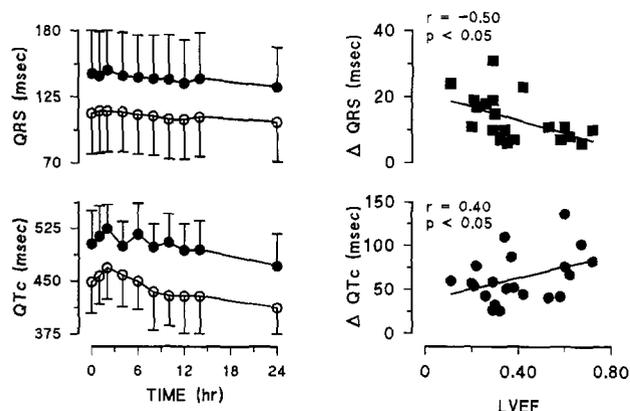
	LVEF <0.35 (n = 11)	LVEF ≥0.35 (n = 11)
AUC quinidine (μg/ml·h)	64.7 ± 18.1	55.4 ± 17.8
AUC 3-HQ (μg/ml·h)	16.0 ± 6.8	12.1 ± 4.2
AUC DHQ (μg/ml·h)	3.1 ± 3.2	2.7 ± 3.3
K _{el} quinidine (h ⁻¹)	0.0511 ± 0.0113	0.0554 ± 0.0116
t _{1/2} quinidine (h)	14.3 ± 3.4	13.0 ± 2.8
Slope QRS (ms/μg per ml)	4.51 ± 2.32 (2.10-10.9)	4.64 ± 2.74 (1.07-11.8)
r value	0.83 ± 0.08 (0.68-0.94)	0.74 ± 0.11 (0.59-0.91)
Slope QTc (ms/μg per ml)	15.7 ± 9.7 (3.81-22.8)	29.5 ± 11.2* (9.9-43.2)
r value	0.68 ± 0.22 (0.38-0.90)	0.76 ± 0.08 (0.62-0.85)

*p = 0.001. Data presented are mean value ± 1 SD (range). AUC = area under concentration-time curve; DHQ = dihydroquinidine; 3-HQ = 3-hydroxyquinidine; K_{el} = elimination rate constant; LVEF = left ventricular ejection fraction; QTc = corrected QT interval; Slope = slope of linear regression analysis; t_{1/2} = elimination half-life.

tion-time curves were similar in both groups (Table 2), as was the elimination half-life of quinidine.

Quinidine pharmacodynamics. Intraobserver variability of QRS and QT measurements was minimal. The correlation coefficient for repeat QRS measurements on a different day was 0.87, the slope 1.03 and intercept -5 ms. The correlation coefficient for repeat QT measurements was 0.95, the slope 1.08 and intercept 9 ms. Mean QRS durations and QTc intervals over the 24-h washout period are shown in Figure 2. The QRS durations and the QTc intervals were greater in the low than in the high left ventricular ejection fraction group throughout the washout period (p < 0.05). The RR intervals were similar during the 24-h quinidine washout in both groups

Figure 2. Left, QRS durations and corrected QT intervals (QTc) during 24-h quinidine washout period for the low (solid circles, n = 11) and high (open circles, n = 11) left ventricular ejection fraction (LVEF) groups. Data are mean value ± 1 SD. Right, Relations between left ventricular ejection fraction and maximal change (Δ) in QRS duration and corrected QT interval (QTc) measured during the study.



and did not change significantly over time (data not shown). The maximal change (from peak to trough effect) in QTc intervals observed during the washout phase correlated linearly, whereas that for QRS durations correlated inversely, with left ventricular ejection fraction (p < 0.05) (Fig. 2).

Linear concentration-effect relations. Linear quinidine concentration-effect relations for QRS durations were significant (p < 0.05) in all 11 patients with a low left ventricular ejection fraction and in 9 of 11 with a high left ventricular ejection fraction. For QTc intervals, linear concentration-effect relations were significant (p < 0.05) in 9 of 11 patients with a low left ventricular ejection fraction and 10 of 11 with a high left ventricular ejection fraction (Fig. 3). The slopes of the QRS concentration-effect relations were similar in both groups (Table 2); however, slopes describing changes in QTc intervals were significantly lower in the low than in the high left ventricular ejection fraction group (p = 0.001) (Table 2). Similar results were observed when 3-hydroxyquinidine concentration-effect relations were analyzed (data not shown). In addition, a significant linear correlation was observed between the slopes of the quinidine concentration-effect relations describing changes in the QTc interval and left ventricular ejection fraction (p < 0.001) (Fig. 3). Multiple linear regression analysis revealed that quinidine concentration correlated independently with QRS duration in six patients in the low ejection fraction group and in two in the high ejection group, whereas quinidine concentration correlated independently with the QTc interval in one patient in the low ejection fraction group and in four in the high ejection fraction group. In the remaining patients, QRS durations and QTc intervals were not independently associated with quinidine concentration (p = NS).

Antiarrhythmic drug efficacy. During quinidine therapy, ventricular tachycardia could not be induced during a follow-up electrophysiologic study in 2 of 10 patients in the low left ventricular ejection fraction group and in 6 of 9 in the high left ventricular ejection fraction group (p < 0.07). Quinidine concentrations measured at the time of the electrophysiologic study were 2.7 ± 1.3 μg/ml in the quinidine drug responders and 3.5 ± 0.7 μg/ml in the nonresponders (p = NS). The slopes of the quinidine concentration-effect relations describing changes in the QTc interval were significantly higher in the quinidine drug responders (24.9 ± 10.0 ms/μg per ml) than in nonresponders (15.9 ± 7.1 ms/μg per ml, p < 0.05). Differences in the slopes of the quinidine concentration-effect relations describing changes in ventricular conduction time were not observed between drug responders (4.73 ± 2.17 ms/μg per ml) and nonresponders (5.03 ± 3.52 ms/μg per ml, p = NS).

Discussion

Although it is well recognized that left ventricular dysfunction is an independent predictor of antiarrhythmic drug inefficacy (1-3), few studies have evaluated the influence of left ventricular dysfunction on the pharmacodynamics of antiarrhythmic drugs. The major findings of the present study are

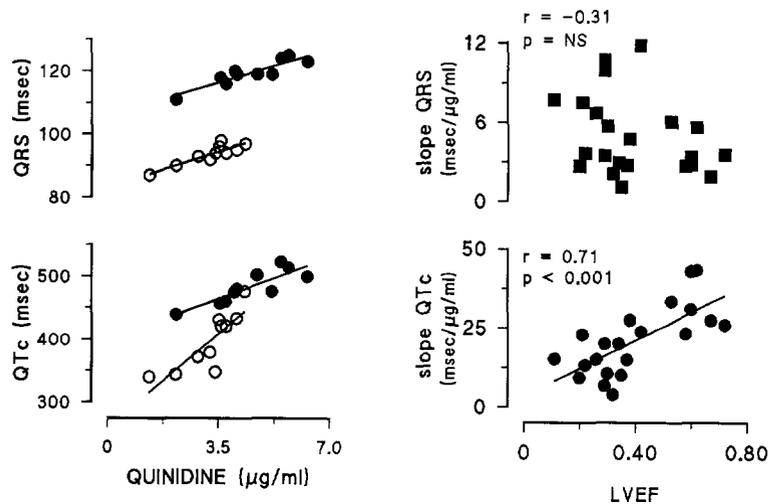


Figure 3. Examples of linear concentration-effect relations. **Top left,** Linear relations between the QRS interval and quinidine concentration for one representative patient in the high (open circles [slope 3.28 ms/µg per ml, $r = 0.89$, $p < 0.001$]) and one in the low (solid circles [slope 3.01 ms/µg per ml, $r = 0.90$, $p < 0.001$]) left ventricular ejection fraction group. **Bottom left,** Linear relations between the corrected QT interval (QTc) and quinidine concentration for both patients (high left ventricular ejection fraction, slope 42.8 ms/µg per ml, $r = 0.84$, $p = 0.003$; low left ventricular ejection fraction, slope 18.9 ms/µg per ml, $r = 0.87$, $p = 0.001$). **Right,** Relations between slopes of the concentration-effect relations and left ventricular ejection fraction.

that quinidine concentration-effect relations are altered in the setting of left ventricular dysfunction and that these altered concentration-effect relations are associated with antiarrhythmic drug inefficacy. The effect of quinidine on ventricular repolarization and conduction time correlated directly and inversely, respectively, with left ventricular ejection fraction.

Quinidine pharmacodynamics. Pharmacodynamic models are used to describe the equilibrium relation between concentration and effect (24). In the present study, linear quinidine concentration-effect relations were observed for changes in QRS durations and QT intervals. This is not surprising because the concentration range evaluated in the present study was small and well below the concentration at which 50% of maximal effect would be observed, and therefore it fell on the linear portion of the concentration-response relation for quinidine (24,25). The slope of the linear regression analysis describes the relation between concentration and effect and allows comparison of these relations when concentrations vary between subjects (24,25). A significant difference in the quinidine concentration-effect relations describing changes in the QTc interval was observed between patients with a low and those with a high left ventricular ejection fraction. Because the slope of the concentration-effect relation is a derived value, errors in this calculation might explain the stronger correlation observed between slope and left ventricular ejection fraction than that observed between the maximal change in the QTc interval and left ventricular ejection fraction. However, this calculation incorporates differences in plasma quinidine concentrations observed between patients and hence could be a stronger measure of the effects of quinidine than changes in ECG intervals alone.

We previously reported (11) similar relations between the pharmacodynamics of disopyramide and left ventricular ejection fraction. There are four potential explanations for these relations: 1) Diastolic stretch is well known to modulate action potential duration and ventricular refractory periods (27-29). Thus, direct electrophysiologic effects of antiarrhythmic drugs may be partially offset by the indirect consequences of the

effects of the drugs on left ventricular function or by the effects of left ventricular dysfunction on cardiac repolarization. 2) Increased sympathetic activity or increased circulating catecholamines associated with clinical congestive heart failure might attenuate or reverse the effects of antiarrhythmic drugs, including quinidine (30-35). Against this hypothesis, none of our patients with a low left ventricular ejection fraction had functional class III or IV congestive heart failure symptoms. 3) Ion channel function may be altered in the setting of myocardial disease (4,7,36,37). It is possible that outward potassium currents in hypertrophied/failing myocytes may be less responsive to the effects of quinidine. 4) Changes in plasma protein binding associated with significant left ventricular dysfunction might alter the unbound fraction of quinidine and the pharmacodynamics of quinidine (38,39).

We also demonstrated a negative linear correlation between maximal change in QRS duration and left ventricular ejection fraction. These findings might be explained by the presence of an intraventricular conduction abnormality in seven of the patients in the low left ventricular ejection fraction group. Diseased, slowly conducting myocardium might be more vulnerable to conduction slowing or blocking by quinidine and other antiarrhythmic drugs because of altered cellular electrophysiology or abnormalities of cell-to-cell coupling (4,5,7,40,41).

Quinidine antiarrhythmic efficacy. In patients with ventricular tachycardia we observed that quinidine concentration-effect relations describing changes in ventricular repolarization correlated with antiarrhythmic efficacy. We (42) and other investigators (43) previously observed that greater antiarrhythmic drug-induced prolongation of ventricular refractoriness is associated with antiarrhythmic efficacy. Patient responders had a higher left ventricular ejection fraction, and many did not have coronary artery disease. However, future studies will be necessary to determine the mechanism(s) of the altered pharmacodynamics in the setting of left ventricular dysfunction.

Potential limitations. The ECG intervals measured in the present study reflect global ventricular depolarization and

repolarization. Thus, the effects of quinidine on global electrophysiologic variables may not reflect the effects of quinidine on local tissue involved in a reentrant circuit. As well, the non-steady state conditions that existed during the present study may not reflect the concentration-effect relations that exist during the steady state. Measurement of the QT interval may be confounded by the presence of a U wave. In the present study we attempted to minimize this problem by selecting a lead with one discrete waveform (20). Furthermore, all measurements were performed by one observer who was unaware of patient identity and time of ECG recording. The QT interval is most frequently corrected for heart rate using the Bazett formula (21). Nevertheless, there is controversy concerning which formula is appropriate to correct for heart rate (44). The use of Bazett formula may cause a substantial overcorrection, particularly at slow heart rates. However, in the present study heart rates were similar throughout the 24-h washout period in both patient groups, thus minimizing this limitation. Moreover, the use of the Fridericia formula (44) did not change the results (unpublished data).

Summary. We observed altered quinidine pharmacodynamics in patients with significant left ventricular dysfunction. The effects of quinidine on ventricular repolarization directly correlate with left ventricular ejection fraction. Furthermore, these effects are associated with antiarrhythmic efficacy for ventricular tachycardia. However, the mechanism(s) of this altered pharmacodynamic response requires further study.

We thank Linda Ellis, BSc and Heather J. Mathison, BSc for technical assistance and Marilyn Devlin for manuscript preparation.

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