The Effect of Rate on Prolongation of Ventricular Refractoriness by Quinidine in Humans

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ROSENHECK, S., ET AL.: The Effect of Rate on Prolongation of Ventricular Refractoriness by Quinidine in Humans. *In this study, the rate dependent effect of quinidine on the ventricular effective refractory period (VERP) was evaluated in 30 patients undergoing electropharmacological testing with quinidine. The VERPs were measured in the baseline state and after at least 2 days of treatment with 1,458–2,044 mg/day of quinidine gluconate (mean plasma quinidine concentration 2.2 ± 0.7 mcg/mL). In 20 patients, the VERP was measured using conventional basic drive trains of 8 beats and basic drive cycle lengths of 600, 500, 400, and 350 msec. In another 10 patients, the VERP was measured after 3 minutes of continuous ventricular pacing at cycle lengths of 600 and 400 msec, and compared to the VERPs measured at the same basic drive cycle lengths using basic drive train durations of 2 and 8 beats. In the baseline state and after treatment with quinidine, the VERP shortened progressively as the basic drive train cycle length decreased and as the drive train duration increased to 3 minutes ($P < 0.001$). Quinidine consistently prolonged the VERP by 9%–11% ($P < 0.001$), regardless of the basic drive train cycle length. Quinidine's effect was also not affected by the basic drive train duration. In conclusion, the effect of quinidine on VERP in humans is independent of the rate of the basic drive train, both when measured using conventional 8-beat basic drive trains and when a three minute drive train duration is used in order to attain the maximum effect of the basic drive train cycle length on the VERP. Therefore, in contrast to quinidine's known rate dependent effect on conduction, it's effect on ventricular refractoriness at doses and basic drive train cycle lengths which are used clinically are not rate dependent. (PACE, Vol. 13, November, Part I 1990)*

quinidine, ventricular refractoriness, rate dependent effect

Introduction

Many antiarrhythmic drugs, including quinidine, have been demonstrated in experimental and clinical studies to block sodium channels and to slow conduction in the heart in a use dependent fashion.[1–15] Whereas experimental studies have demonstrated that quinidine's effect on the ventricular effective refractory period (VERP) is also use dependent,[13,16–19] this effect has not been investigated in humans. Therefore, the purpose of this study was to determine whether the prolongation in ventricular refractoriness which occurs in patients treated with quinidine is rate dependent.

Methods

Thirty patients who had inducible, sustained, monomorphic ventricular tachycardia during a baseline electrophysiology test and who were appropriate candidates for electropharmacological testing with quinidine were the subjects of this study. Patients in whom ventricular tachycardia was induced by programmed ventricular stimulation with one extrastimulus and patients with

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atrial fibrillation were excluded from the study. Patients also were excluded if they did not tolerate ventricular pacing at a cycle length of 400 msec for 3 minutes.

There were 26 men and four women and their mean age was 60 ± 14 years (mean ± standard deviation). Twenty-four patients had coronary artery disease, one patient had undergone surgical correction of pulmonic stenosis, one patient had a hypertrophic cardiomyopathy and four patients did not have structural heart disease. The mean left ventricular ejection fraction was 0.39 ± 0.15.

Electrophysiology Study Protocol

Electrophysiology tests were performed in the fasting, unsedated state after informed consent was obtained. Each patient had a baseline test at least five half-lives after all antiarrhythmic treatment was discontinued. Two or three quadripolar electrode catheters (1-cm interelectrode distance) were positioned in the right atrium, right ventricular apex, and across the tricuspid valve for recording the His-bundle depolarization. Bipolar pacing was performed using a programmable stimulator (Bloom Associates Ltd. Narbeth, PA, USA) with stimuli 2 msec in duration at a current strength twice the diastolic threshold. Leads V_1, I, III, and the intracardiac electrograms were recorded on a Mingograf 7 recorder (Siemens-Elema, Solna, Sweden) at a paper speed of 25–100 mm/sec.

Measurement of the VERP

The study protocol was approved by the Human Research Committee at the University of Michigan Medical Center, and was performed before, or upon completion of, the clinically indicated portion of the electrophysiology test. In 20 patients, the VERP was measured using basic drive train cycle lengths of 600, 500, 400, and 350 msec. The basic drive train duration was 8 beats and the intertrain pause was 3 seconds. An extrastimulus was introduced at a coupling interval shorter than the expected VERP, and the coupling interval was lengthened by increments of 2 msec until a ventricular depolarization was evoked. This incremental method of measuring the VERP was used because a previous study demonstrated that it yields a more accurate determination of the VERP than the decremental method.[20] The longest coupling interval that did not evoke a ventricular response was defined as the VERP.

In ten other patients, the VERP was measured using drive train durations of 2 beats, 8 beats, and 3 minutes at cycle lengths of 600 and 400 msec. These various basic drive train durations were used to determine whether there is an interaction between the effect of quinidine on the VERP and the duration of pacing. Prior studies have demonstrated that up to 3 minutes may be required for the VERP to fully adapt to an increase in rate, and therefore, a maximum drive train duration of 3 minutes was used in this study.[21] After 3 minutes of continuous ventricular pacing at cycle lengths of 600 or 400 msec, an extrastimulus was inserted after every eighth beat at an initial coupling interval shorter than the VERP, without any interruption in the basic drive train. The VERP was determined by increasing the coupling interval in steps of 2 msec until a ventricular response was elicited. In previous studies, using the same method of VERP determination, reproducibility was demonstrated to be within 4 msec.[22]

After the baseline test, each of the 30 subjects was treated with quinidine gluconate, 1,458–2,044 mg/day, for at least 48 hours. An electrophysiology test identical to the baseline test then was performed. The mean plasma quinidine concentration was 2.2 ± 0.7 mg/mL at the time of the second study.

Statistical Analysis

A repeated measures analysis of variance was used to compare the VERPs. Pearson's correlation coefficient was used to evaluate the correlation between the change in VERP and quinidine plasma concentration. A P value < 0.05 was considered significant.

Results

The Effect of Quinidine on VERP at Basic Drive Train Cycle Lengths of 600–350 msec (Table I)

The sinus cycle length was 826 ± 120 msec baseline and 859 ± 172 msec after quinidine (P

Table I.

Effect of Quinidine on the Ventricular Effective Refractory Period at Basic Drive Train Cycle Lengths of 600–350 msec

	Basic Drive Train Cycle Length (msec)			
	600	**500**	**400**	**350**
Baseline	264 ± 21*	254 ± 20	243 ± 21	235 ± 21
Quinidine	287 ± 18**	277 ± 18**	267 ± 18**	258 ± 17**
ΔQ-B (msec)	23 ± 23	23 ± 21	25 ± 23	24 ± 20
ΔQ-B (%)	9 ± 9	10 ± 9	11 ± 11	11 ± 9

* The ventricular effective refractory periods (VERP) are expressed in msec as mean ± one standard deviation. **P < 0.001 compared to baseline. The progressive shortening of the VERP with the decrease in the basic drive train cycle length was significant (P < 0.001). There were no significant differences in ΔQ-B among the different basic drive train cycle lengths. B = baseline; Q = quinidine.

= NS). The VERP shortened progressively as the basic drive train cycle length decreased from 600–350 msec, both in the baseline state and during treatment with quinidine (P < 0.001). Quinidine prolonged the VERP by 9%–11% (P < 0.001), and there were no differences in the magnitude of quinidine's effects among the various basic drive train cycle lengths. There was linear correlation between the VERP prolongation, and the serum quinidine concentration at all four cycle lengths (P < 0.05). The difference between the prolongation of VERP caused by quinidine at different cycle lengths ranged between 0.1 ± 5 and 1.7 ± 8 msec (P = NS) and the correlation with the plasma quinidine concentration was not significant.

Interaction Between Rate and Duration of Pacing (Table II)

The sinus cycle length was 736 ± 137 msec baseline and 775 ± 130 msec after quinidine (P = NS). The VERP shortened as the basic drive train duration increased from 2 beats to 3 minutes (P < 0.001), and the basic drive train cycle length decreased from 600–400 msec, both in the baseline state and during treatment with quinidine (P < 0.001). Quinidine prolonged the VERP by 12%–14% regardless of the basic drive train duration, at a basic drive train cycle length of both 600 and 400 msec. Therefore, there was no interaction between the effects of rate and the duration of

Table II.

Interaction Between Effects of Rate and Duration of Pacing on the Ventricular Effective Refractory Period

BDTCL	**600 msec**			**400 msec**		
BDTD	**2 beats**	**8 beats**	**3 min**	**2 beats**	**8 beats**	**3 min**
Baseline	257 ± 20*	252 ± 19	240 ± 20	249 ± 17	240 ± 17	214 ± 15
Quinidine	294 ± 34**	287 ± 25**	269 ± 21**	284 ± 17**	271 ± 19**	244 ± 42**
ΔQ-B (msec)	37 ± 23	35 ± 19	29 ± 18	34 ± 15	31 ± 15	29 ± 33
ΔQ-B (%)	14 ± 9	14 ± 8	12 ± 9	14 ± 7	13 ± 7	13 ± 13

* The ventricular effective refractory periods (VERP) are expressed in milliseconds as mean ± one standard deviation. **P < 0.001 compared to baseline. The shortening of the VERP with the decrease in the basic drive train cycle length was significant (P < 0.001). There were no significant differences in ΔQ-B among the different basic drive train durations or between the two basic drive train cycle lengths. B = baseline; Q = quinidine; BDTCL = basic drive train cycle length; BDTD = basic drive train duration.

pacing on the VERP, either in the baseline state or after treatment with quinidine.

Discussion

Main Findings

The results of this study demonstrate that quinidine's effect on the VERP in humans is independent of rate, at least at basic drive train cycle lengths of 600–350 msec, which is the range of basic drive train cycle lengths commonly used during programmed ventricular stimulation in the clinical electrophysiology laboratory. A rate dependent effect of quinidine on the VERP was present neither when a conventional 8-beat basic drive train duration was used to measure refractoriness, nor when the VERP was measured using a basic drive train duration of three minutes, which allowed for complete adaptation of the VERP to the increase in rate caused by pacing.

Results of Prior Studies

In contrast to the results of the present study, prior experimental studies have concluded that quinidine's effect on ventricular refractoriness is rate dependent. Nattel and Zeng[17] used microelectrode techniques in isolated canine Purkinje fibers and demonstrated a use dependent effect of quinidine on the refractory period. At a quinidine tissue bath concentration of 5.7 mcg/mL, quinidine lengthened refractoriness by less than 15% when the stimulation cycle length was 5000 msec, compared to an increase of 25% when the pacing cycle length was 300 msec. Furthermore, Franz and Costard[19] demonstrated a linear inverse correlation between the stimulation cycle length and the increase in VERP caused by quinidine in the canine heart in situ. A mean serum quinidine concentration of 3.3 ± 0.5 mcg/mL prolonged the VERP by 19–22 msec at stimulation cycle lengths of 400–500 msec, but by 61 ± 21 msec at a cycle length of 220 msec, demonstrating a marked rate dependent effect.

There are several possible reasons for the discrepancy between the results of the prior experimental studies and the results of the present study. The reasons include a species difference in the rate dependent effect of quinidine on the VERP, an effect of general anesthesia in the experimental studies, or the influence of autonomic effects in awake patients. For example, it is possible that sympathetic activation associated with incremental pacing rates might antagonize a rate dependent effect of quinidine on ventricular refractoriness. However, this possibility seems unlikely because a prior study demonstrated that programmed ventricular stimulation using an 8-beat basic drive train duration in patients without inducible ventricular tachycardia does not result in elevation of the plasma epinephrine or norepinephrine concentration.[23] Moreover, a rate dependent effect of other Class I antiarrhythmic drugs on intraventricular conduction has been demonstrated in awake patients subjected to the same pacing rates used in the present study.[24]

It is possible that the rate dependent effect of quinidine on the VERP is dose dependent, and that the mean quinidine plasma concentration of 2.2 ± 0.7 mcg/mL in the present study, which was lower than the quinidine concentrations tested in the experimental studies, was less than the critical concentration necessary for a rate dependent effect to occur. Another possible explanation for the discrepancy between the findings of the present study and those of the experimental studies is that the range of pacing cycle lengths tested in the present study was 600–350 msec, which out of necessity was considerably narrower than the range of 5,000–220 msec used in the experimental studies. It is possible that the demonstration of a rate dependent effect of quinidine on refractoriness may require rapid or slow stimulation rates.

Of note is that the only two other clinical studies that investigated whether the effect of a Class IA antiarrhythmic drug on the VERP is rate dependent had findings similar to ours.[25,26] Nademanee et al,[25] in a recently published study, showed no significant differences in the effect of quinidine on the ventricular effective refractory period at cycle lengths of 350, 400, 500, and 600 msec. As in this study, they found a 9%–12% prolongation in ventricular refractoriness regardless of the basic drive train cycle length. Marchlinski and Shinnar[26] measured the VERPs in 14 patients in the baseline state and after the intravenous administration of procainamide; they used basic drive train cycle lengths of approximately 650–250 msec, and a basic drive train duration of 12 beats. The data were fit to an exponential

function and based on the exponential fit, they predicted that procainamide would lengthen the VERP by 26 msec at a basic drive train cycle length of 800 and 200 msec. Therefore, neither quinidine nor procainamide can be demonstrated to have a rate dependent effect on the VERP in humans.

Conclusions

In conclusion, although quinidine can be demonstrated to have a rate dependent effect on ventricular refractoriness in the experimental setting, in the range of cycle lengths commonly used in the clinical electrophysiology laboratory, and at quinidine plasma concentrations obtained in clinical practice, quinidine's effect on ventricular refractoriness is independent of rate. Therefore, quinidine's effect on the VERP at any basic drive train cycle length between 600–350 msec will accurately reflect quinidine's effect at all basic drive train cycle lengths within this range.

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