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The Electrophysiological Actions of the Combination of Quinindine and Propranolol on the Dog Atrium[1] (40200)

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In 1966, Stern reported that the simultaneous use of quinidine and propranolol was more effective in the treatment of resistant atrial tachyarrhythmias than either drug alone (1). These findings were subsequently confirmed and extended to both supraventricular and ventricular tachyarrhythmias (2–6). Recently, Madan and Pendse reported that the combination of quinidine and propranolol was significantly more effective than the individual drugs in canine experimental atrial arrhythmias (7). In addition, Lawson and Wojciechowski have reported an enhancement by propranolol of the antifibrillatory action of quinidine in the dog (8).

We have studied the quinidine-propranolol combination in an attempt to elucidate electrophysiological alterations of the heart induced by the combination which could account for its enhanced antiarrhythmic activity. Previously we reported that the combination of quinidine and propranolol was especially effective in prolonging the ventricular refractory period in the dog (9). We also determined that the combination selectively depressed atrial automaticity while it was no more effective than propranolol alone in depressing ventricular automaticity (10). This paper reports the extension of our studies to include the effect of the combination of quinidine and propranolol on the electrophysiology of the atrium.

Methods. Twenty-five mongrel dogs, weighing 8.6–15.0 kg, were anesthetized with pentobarbital sodium (30 mg/kg iv). The right femoral vein was cannulated for drug injections. The animals were ventilated with room air through a tracheal cannula using a Harvard respiration pump. A heating pad was used to stabilize the animals' temperatures at 36.8 ± 0.3° (mean ± SEM) for the duration of the experiment. Common carotid arterial pressure was determined with a Statham transducer (Model P23AC) and electronically damped to record mean arterial pressure (MAP). Heart rate was obtained from the Lead II electrocardiogram. After exposure of the heart by midline sternotomy, bilateral vagotomy and stellate ganglionectomy were performed to permit atrial pacing at 150 beats/min. The heart was supported in a pericardial cradle and three pairs of sterling silver bipolar electrodes were sewn onto the surface of the right atrial appendage. The first pair of electrodes was used to administer the drive and test stimuli, while the second and third pairs, placed 20 mm apart, were recording electrodes. An additional pair of recording electrodes was affixed to the right ventricle.

Measurements of conduction time (CT), excitability (EXCIT) and effective refractory period (ERP) were determined as previously described for the ventricle (9). Briefly, the Tektronix 160 series waveform and pulse generators allowed delivery of a test stimulus at any time within the 400 msec interval following the tenth drive stimulus. The current strengths of the test and drive stimuli were assessed by displaying (on a Tektronix 502A oscilloscope) the voltage drop across a 1000 ohm resistor placed in a circuit between the stimulators and atrial electrodes. Diastolic threshold was defined as the minimum current strength necessary to drive the atrium at 150 beats/min with a stimulus duration of 5 msec. CT was considered to be the time necessary for the drive impulse to travel between the two recording electrodes placed 20 mm

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apart on the atrium. EXCIT was obtained from strength-duration curves for stimulus durations ranging from 8 to 0.05 msec delivered 300 msec after every tenth drive stimulus. ERP was obtained from strength-interval curves. The interval between test and drive stimuli was progressively decreased and the minimum stimulus strength of 5 msec duration necessary to depolarize the atrium was recorded. An upper limit of 1 mA was set as the maximum current strength used to define ERP. Atrioventricular transmission time (AVTT) and the atrioventricular functional refractory period (AVFRP) were determined as reported by Kniffen *et al.* (11). AVTT was derived from the interval between the appearance of a drive stimulus in simultaneous atrial and ventricular recordings. AVFRP was defined as the minimum interval between ventricular responses obtained for progressively decreasing intervals between the drive and test stimuli administered to the atrium and propagated through the AV node.

The dogs were randomly assigned to five equal groups. Baseline measurements were obtained after a 30 min postsurgical stabilization period. Following the baseline measurements, the appropriate drug regimen was given. Each group received either 0.1 mg/kg or 0.2 mg/kg propranolol hydrochloride (Ayerst), 2.5 mg/kg or 5 mg/kg quinidine sulfate (USP) or the combination of 0.1 mg/kg propranolol hydrochloride plus 2.5 mg/kg quinidine sulfate. All dosages were based on weight of the salt. Propranolol hydrochloride, dissolved in 6 ml of isotonic saline, was given over a 3 min period followed by a 10 min distribution period before experimental measurements were made. Quinidine sulfate, dissolved in 20 ml of isotonic saline, was given over a 10 min period followed by a 15 min distribution period. The animals receiving the combination were given quinidine sulfate first, administered over a 10 min period followed 2 min later by propranolol hydrochloride given over a 3 min period. Ten min after the propranolol hydrochloride infusion was completed the experimental measurements were made. Thus the drugs in the combination were administered in the same time sequence as when administered singly.

The interaction of the individual drug effects when administered in combination was determined using a modification of the procedure reported by Alfonso *et al.* (12). The combination dosage consisted of one-half of the 0.2 mg/kg dose of propranolol hydrochloride and one-half of the 5.0 mg/kg dose of quinidine sulfate. If the combination produced a change from baseline statistically greater ($P \leq 0.05$) than that produced by 0.2 mg/kg propranolol hydrochloride or 5.0 mg/kg quinidine sulfate as determined with the Newman-Keuls Test (13), it was considered potentiation. Randomness of the samples was confirmed for the various baseline measurements by analysis of variance and changes from baseline for a particular drug regimen were analyzed using the paired t test (13).

Results. Baseline values. Animals were randomly assigned to one of five groups. Comparison of baseline values for each group by analysis of variance ($P \leq 0.05$) indicated no significant variation attributable to assignment of the animals. The baseline electrophysiological values for the 25 dogs used in this study are given in Table I.

Excitability. The changes in atrial excitability produced by the various drug regimens are given in Table II. Since stimuli of short duration are a more sensitive index of drug-induced alterations in excitability than stimuli of longer duration (14), the effects of the drug regimens were compared at the shortest test stimulus duration, 0.05 msec. Propranolol, in doses utilized, did not significantly increase the stimulus strength required to depolarize the atrium. Quinidine sulfate, 5 mg/kg, produced a significant increase in strength of test stimulus required to depolarize the atrium, indicating a marked depression of excitability. The combination of quinidine and propranolol also required a significant increase in strength of the depolarizing stimulus. However, this increase was no dif-

TABLE I. BASELINE ELECTROPHYSIOLOGICAL VALUES.[a]

Atrial excitability (mA) – EXCIT	1.00 ± 0.05
Atrioventricular transmission time (msec) – AVTT	133.4 ± 3.8
Atrioventricular functional refractory period (msec) – AVFRP	254.4 ± 6.1
Atrial conduction time (msec) – CT	30.0 ± 0.1
Atrial effective refractory period (msec) – ERP	123.0 ± 2.8

[a] Mean ± SEM for 25 dogs.

TABLE II. CHANGE IN ATRIAL ELECTROPHYSIOLOGICAL MEASUREMENTS PRODUCED BY QUINIDINE, PROPRANOLOL OR THEIR COMBINATION.[a]

Regimen	*n*	EXCIT (mA)	ERP (msec)	CT (msec)	AVTT (msec)	AVFRP (msec)
Quinidine (2.5 mg/kg)	5	0.03	5.0	1.0	4.0	8.0
		±0.03	±4.2	±1.0	±2.5	±6.4
Quinidine (5.0 mg/kg)	5	0.17[b]	21.0[b]	2.0	16.0[b]	15.0[b]
		±0.04	±4.3	±1.2	±3.7	±5.0
Propranolol (0.1 mg/kg)	5	0.01	4.0[b]	1.0	2.0	10.0[b]
		±0.01	±1.0	±1.0	±3.4	±3.2
Propranolol (0.2 mg/kg)	5	0.03	5.0	1.5	11.0	12.0
		±0.02	±2.2	±1.0	±3.7	±6.2
Quinidine (2.5 mg/kg) + Propranolol (0.1 mg/kg)	5	0.25[b]	24.0[b]	6.0[b,c]	17.0[b]	16.0[b]
		±0.06	±1.9	±1.0	±1.2	±5.5

[a] Values represent the changes from the respective group baseline given as mean ± SEM. See text for definition of abbreviations.

[b] Significantly different ($P \leq 0.05$) from baseline, paired *t* test.

[c] Significantly greater ($P \leq 0.05$) than change from baseline produced by quinidine, 5 mg/kg or propranolol, 0.2 mg/kg, Newman-Keuls test.

ferent than that produced by 5 mg/kg quinidine sulfate; consequently a potentiation by propranolol of the quinidine action to depress atrial excitability was not demonstrated.

Effective refractory period. ERP was defined as the interval obtained from the strength-interval curves for a stimulus strength of 1.0 mA. The effect of the various drug regimens on ERP of the atrium are given in Table II. Quinidine sulfate, 5 mg/kg, produced a significant increase in ERP. Propranolol hydrochloride, 0.1 mg/kg, produced a significant increase although 0.2 mg/kg did not. This was attributed to the larger variation observed with the higher dosage. The combination of quinidine and propranolol also produced an increase in ERP. However, this increase in ERP was not significantly greater than the increase produced by 5 mg/kg quinidine sulfate alone. Therefore, the increase in ERP produced by quinidine was not potentiated by coadministration of propranolol. However, the combination apparently produces a more consistent response as indicated by the smaller SE of the mean.

Conduction time. Neither quinidine sulfate nor propranolol hydrochloride in the doses used produced a significant increase in CT of the atrium; however, when the combination of quinidine and propranolol was tested a significant increase in CT was observed (Table II). Moreover, this increase in CT produced by the combination was greater than that produced by twice the dose of either quinidine or propranolol present in the combination. Thus, potentiation was observed.

Atrioventricular transmission time. Only 5 mg/kg quinidine sulfate and the combination produced significant increases in the AVTT (Table II). However, the response observed with the combination was no larger than that of 5 mg/kg quinidine sulfate, consequently, potentiation did not occur.

Atrioventricular functional refractory period. Both 5 mg/kg quinidine sulfate and 0.1 mg/kg propranolol hydrochloride produced significant increases in AVFRP (Table II). The higher dose of propranolol hydrochloride (0.2 mg/kg) produced a more variable response than the low dose which was not statistically significant. The combination of quinidine and propranolol also increased AVFRP but no greater than 5 mg/kg quinidine sulfate. Therefore, potentiation was not observed.

Blood pressure. Baseline mean arterial pressure for the 25 dogs was 116.0 ± 2.9 mmHg (mean ± SEM). Comparison of baseline mean arterial pressure values for each group by analysis of variance ($P \leq 0.05$) indicated no significant variation in MAP attributable to the assignment of the animals to different groups. Quinidine dosing caused a fall in blood pressure which was attenuated by administration over a 10-min period. Average MAP decrease with quinidine sulfate at 2.5 mg/kg was 14.0 mmHg, and at 5.0 mg/kg was 24.0 mmHg. Propranolol administration produced only slight changes in MAP. Coad-

ministration of quinidine withpropranolol attenuated the decrease in MAP with the average decrease being only 5.0 mmHg.

Discussion. Combined quinidine and propranolol therapy has been shown to produce long term conversion of resistant atrial tachyarrhythmias (1–6). The effects of quinidine and propranolol and their combination were investigated in order to determine whether the conversion of resistant tachyarrhythmias observed clinically could be explained by an enhanced effect of the combination on atrial electrophysiology. This study shows that combining quinidine and propranolol produces no significant enhancement of the individual drugs' actions to increase the atrial effective refractory period, atrioventricular transmission time and atrioventricular functional refractory period or to depress atrial excitability. However, the combination had a most pronounced effect on atrial conduction. The combination of 0.1 mg/kg propranolol and 2.5 mg/kg quinidine produced a 400% greater increase in conduction time than that produced by twice the propranolol dosage (0.2 mg/kg) present in the combination and a 300% greater increase in conduction time than that produced by twice the quinidine dosage (5.0 mg/kg) present in the combination. Atrial conduction appears to be especially sensitive to the action of quinidine and propranolol when they are administered in combination and thus may account in part for the ability of the combination to convert resistant atrial tachyarrhythmias.

Recently, the results of intracellular studies utilizing the quinidine–propranolol combination in isolated canine atria have been reported (15). In this prepration the combination of quinidine and propranolol produced a highly significant (24-fold) increase in activation time in isolated canine atria. An increase in activation time is equivalent to an increase in conduction time. These studies support our conclusions and emphasize the sensitivity of atrial conduction to depression by the quinidine–propranolol combination.

The interpretation of results from studies of drug interactions is difficult, especially if one or both of the compounds possess direct and indirect activity. To reduce problems of interpretation, these studies on the atrial electrophysiology of the quinidine-propranolol combination were done in healthy, open-chested, pentobarbital–anesthetized dogs subjected to bilateral vagotomy and stellate ganglionectomy. This was the same model employed for our studies of the effect of the combination on ventricular electrophysiology (9). In addition, the dosage regimen used in the atrial studies was equivalent to the lower dosage regimen in the ventricular studies. A comparison of these two studies indicates a difference in tissue electrophysiological responses to the combination. Our studies indicate that while conduction was most sensitive to coadministration of quinidine and propranolol in the atrium, the most sensitive ventricular index was the refractory period (9). This tissue difference in response to the combination was also observed in our automaticity studies which showed that atrial but not ventricular automaticity was sensitive to combined quinidine and propranolol treatment (10). The different observations obtained for the atrial and ventricular studies indicate a tissue-dependent response to the combination of quinidine and propranolol.

Summary. The combination of quinidine and propranolol has been reported to be effective in conversion of atrial tachyarrhythmias resistant to standard conversion techniques. The electrophysiology of the quinidine–propranolol combination was studied in pentobarbital anesthetized dogs which had undergone bilateral vagotomy and stellate ganglionectomy. The purpose of these studies was to determine a possible mechanism for the enhanced antiarrhythmic activity of the combination. Coadministration of quinidine and propranolol was shown to potentiate the slowing of atrial conduction time produced by the individual drugs. The quinidine–propranolol combination did not potentiate the individual drug actions to depress atrial excitability or to increase the atrial effective refractory period, atrioventricular functional refractory period and atrioventricular transmission time. Thus, these studies demonstrate that the combination of quinidine and propranolol is especially effective in slowing atrial conduction, which could account in part for the enhanced antiarrhythmic activity of the combination against resistant atrial tachyarrhythmias.

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