The Effects of Propranolol on the Electrophysiology of the Heart

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SUMMARY

The effects of propranolol on the electrical behavior of ventricular muscle fibers were investigated in the anesthetized dog by simultaneously recording surface and intracellular electrograms. After administration of propranolol during sinus rhythm, the RR, PQ and QT intervals were significantly prolonged, while the QRS duration remained unchanged. During electrically driven rhythm, propranolol caused a slight but insignificant prolongation of the QT interval. There were no changes in the QRS duration. Significant delay of the interatrial and atrioventricular conduction times was observed. There were no significant changes in the intraventricular conduction time. Propranolol principally affects the sinoatrial node, the atrioventricular node and the conduction time of the atria. Effects of propranolol on the intracellular electrograms from the ventricle were as follows. The duration of the membrane action potential was significantly prolonged. No changes were observed in the amplitudes of the membrane action potential, membrane resting potential and overshoot. The maximum upstroke velocity of the membrane action potential did not change. Propranolol has a quinidine-like action as well as a beta adrenergic blocking action. Both actions contribute to the effectiveness of the drug in the treatment of cardiac arrhythmias.

Additional Indexing Words: Sinus rhythm Electrically driven rhythm Membrane action potential Membrane resting potential Beta adrenergic in situ Antiarrhythmic

PROPRANOLOL is a beta adrenergic blocking agent that interferes with the beta receptors of the adrenergic nervous system. In recent years this drug has been used for the treatment of cardiac arrhythmias,1-3 angina pectoris,4,5 and digitalis intoxication.6,7 The mechanism of the action of propranolol and its electrophysiological effects on the heart have been well...
described in the literature. The influence of propranolol on the intracellular electrical potentials of the heart has been reported, but has been confined to isolated cardiac muscle. Comparatively few investigations of the effects of the drug on the intracellular potentials of the intact, beating heart have been reported.

The present study was carried out by recording the intracellular potentials of the in situ canine heart before and after the administration of propranolol. Intracellular electrograms were recorded simultaneously with surface electrograms and the standard lead II electrocardiograms. It was hoped to gain an understanding of the fundamental electrophysiological changes responsible for the clinical effects of propranolol. In addition, the action of this drug was compared with the antiarrhythmic action of quinidine reported previously from this laboratory. Such a comparison is of special interest in view of the possibility that propranolol has a dual antiarrhythmic action, consisting of a beta adrenergic blocking effect as well as a quinidine-like effect.

**Method**

Fifty-three mongrel dogs weighing 12 to 22 Kg. were used in the experiments. Five of the dogs were used in preliminary control experiments performed under the same conditions as the other experiments but without the administration of propranolol. Thirty dogs were used in the studies of the effects of propranolol on the intracellular and surface electrograms. Eighteen were used in studies of the effects of propranolol on the interatrial, atrioventricular and intraventricular conduction times.

Each dog was anesthetized with an intravenous injection of urethane (400 mg./Kg.) plus chloralose (80 mg./Kg.). Ventilation of the lungs was maintained by artificial respiration. The chest was opened and the heart exposed by the method previously described.

Simultaneous surface electrograms and standard lead II electrocardiograms were recorded during sinus rhythm. During electrically driven rhythm, intracellular electrograms, surface electrograms and standard lead II electrocardiograms were simultaneously recorded. Electrical stimulation was applied near the sinoatrial node at a frequency about 10% above the sinus rate.

Electrically driven rhythm was used to exclude any electrographic changes resulting from the effect of propranolol on the cardiac rate. Seven experiments were performed during sinus rhythm. Twenty-three experiments were performed during electrically driven rhythm. In these experiments, a square wave pulse of 2 msec. duration and from 6 to 8 V. amplitude from a stimulator (Grass S4B) was applied through an electrode situated near the sinoatrial node.

The procedure for simultaneous recording of unipolar surface and intracellular electrograms is illustrated in Fig. 1. Two concentric steel rings covered with polyethylene tubing were placed on the anterior wall of the left ventricle. Arms extending from the rings were firmly affixed to holders on the operating table. Myocardial
movement was minimized by suturing the outer ring to the ventricular surface through the epicardium. The inner ring was unsutured.

The study area was kept moist and warm by continuous irrigation with Ringer’s solution at a thermostatically controlled temperature of 37°C. A surface electrode and an intracellular electrode were applied to the approximate center of the inner ring. For intracellular potentials, a flexible glass capillary electrode described by Woodbury and Brady11) with an electrical resistance of 10 to 20 megohms was used. Extrinsic factors in recording the intracellular electrograms were minimized by positioning the indifferent electrode for the intracellular electrogram as close as possible to the intracellular electrode. Wilson’s central terminal was used as the indifferent electrode for recording the unipolar surface electrograms. The surface electrode was made of tungsten wire about 0.1 mm. in diameter.

Interatrial, atrioventricular and intraventricular conduction times were determined while the heart was driven by electrical stimulation. Contiguous bipolar electrodes were placed on the endocardium of the left atrial appendage, on the epicardium of the left ventricular base, and on the endocardium of the apex of the heart (Fig. 2). Electrograms from these 3 sites were simultaneously recorded with the standard lead II electrocardiogram. The bipolar electrodes used for measuring conduction, as well as the stimulating electrode, were made of copper wire about 0.1 mm. in diameter, and were adjusted to maintain an interpolar distance of 1 mm.

Procedures for measuring the conduction times were as follows. The interatrial conduction time was the time interval between the onset of the stimulus artifact induced by electrical stimulation near the sinoatrial node and the peak of the main deflection in the bipolar electrogram recorded from the left atrial appendage. The atrioventricular conduction time was the time interval between the onset of the stimulus artifact and the peak of the main deflection in the bipolar electrogram recorded from the endocardium of the apex of the heart. The intraventricular conduction time was
Fig. 2. Schema for measuring the interatrial, atrioventricular and intra-ventricular conduction times. Bipolar electrograms were simultaneously recorded from the endocardium of the left atrial appendage, from the epicardium at the base of the left ventricle and from the endocardium at the apex of the heart.

the time interval between the peak of the main deflection in the bipolar electrogram recorded simultaneously from the endocardium of the apex and the epicardium at the base of the left ventricle.

Clinically, propranolol hydrochloride is preferably administered orally. In animal experiments, the drug is usually given intravenously. In the present experiments, 0.5 mg./Kg. propranolol hydrochloride (Inderal through the courtesy of Dr. A. Sahagian-Edwards, Ayerst Laboratories, New York) was diluted to 5 ml. with Ringer's solution and injected intravenously over a period of about 60 sec. Electrograms were recorded for 20 min. or more after beginning the administration of propranolol.

Cardiac potentials were amplified by direct-coupled preamplifiers (Grass P6). The output voltage from each preamplifier was introduced into an oscilloscope (Tektronix 502) and into a direct-writing electrocardiograph (Sanborn 150). For accurate study of the upstroke velocity of the membrane action potential and of conduction time, oscillographic sweep rates of 1 msec./cm. and 50 to 100 msec./cm., respectively, were used. Tracings were photographed at selected intervals with a kymograph recording camera (Grass C4H). Analysis of the membrane action potentials and of the conduction times were made from enlarged copies of these photographs. Surface electrograms were used for measuring PR and QT intervals and the duration of the QRS. The standard lead II electrocardiogram was used for measurements of the PQ interval.

RESULTS

The Effects of Propranolol during Sinus Rhythm

Five dogs were used for preliminary control experiments. Seven dogs were given injections of propranolol. As illustrated in Fig. 3, propranolol caused significant increases of the RR, PQ and QT intervals within the first 5 to 10 min. after its administration. The QRS duration was not altered.
Fig. 3. Changes, percentage of the initial values, in the RR, PQ and QT intervals and QRS duration after the administration of propranolol during sinus rhythm. Dotted lines are control values (N=5). Solid lines show changes induced by propranolol (N=7). Mean values and ±1 standard deviations are shown by vertical brackets.

Table 1. Effect of Propranolol on Surface Electrograms during Sinus Rhythm

<table>
<thead>
<tr>
<th></th>
<th>Control Experiments (N=5)</th>
<th>Propranolol Experiments (N=7)</th>
<th>( p ) Value **</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial Value (msec.)</td>
<td>Change after 5 Min. (% of the Initial Value)</td>
<td>Initial Value (msec.)</td>
</tr>
<tr>
<td>RR Interval</td>
<td>358.6±28.2</td>
<td>-1.0±1.9</td>
<td>355.6±47.0</td>
</tr>
<tr>
<td>PQ Interval</td>
<td>90.0±7.1</td>
<td>-0.2±1.7</td>
<td>90.7±9.7</td>
</tr>
<tr>
<td>QRS Duration</td>
<td>40.4±7.6</td>
<td>+1.0±4.0</td>
<td>37.8±4.0</td>
</tr>
<tr>
<td>QT Interval</td>
<td>199.6±14.7</td>
<td>+0.4±1.3</td>
<td>200.4±10.8</td>
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</table>

Values represent the initial values and the changes (percentage of the initial values) at the first 5 min. without and with the administration of propranolol. The RR, PQ and QT intervals were highly significantly prolonged with propranolol. The widening or shortening of the QRS duration was not significant without and with propranolol. Values represent mean ± 1 standard deviation. N = number of experiments. N.S. = Not significant. *The PQ interval was measured from a standard lead II electrocardiogram. **The \( p \) values were calculated using Student's T test.
The electrographic changes, as expressed in percentages of the initial values, in the propranolol-injected dogs 5 min. after administration of the drug were compared with those in control dogs (Table I). In the propranolol-injected dogs, the prolongations of the RR, PQ and QT intervals averaged 35.9±15.1 (mean±1 standard deviation)%, 34.6±10.4%, and 18.3±9.2%, respectively.

The differences between the percentage changes of the RR, PQ and QT intervals in the control dogs and in the propranolol-injected dogs during sinus rhythm are apparent (p<0.01).

**Effects of Propranolol during Electrical Stimulation**

Propranolol was administered to a series of 23 dogs during electrically driven rhythm. Surface and intracellular electrograms were recorded from the anterior surface of the left ventricle before and after the injection of the drug. The electrograms of 15 of the 23 animals were analyzed.

In these experiments with electrically induced rhythm, values for the RR and PQ intervals are not presented. A slight but not significant increase in the QT interval was observed in the surface electrogram after propranolol.

<table>
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<tr>
<th>Table II. Effect of Propranolol on Surface Electrograms and Conduction Times during Electrically driven Stimulation</th>
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<tbody>
<tr>
<td>Control Experiments (N=5)</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Initial Value (msec.)</td>
</tr>
<tr>
<td>QRS Duration</td>
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<tr>
<td>QT Interval</td>
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<tr>
<td>Interatrial Conduction Time</td>
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<tr>
<td>Atrioventricular Conduction Time</td>
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<tr>
<td>Intraventricular Conduction Time</td>
</tr>
</tbody>
</table>

Values represent the initial values and the changes (percentage of the initial values) at the first 5 min. without and with the administration of propranolol. The interatrial and atrioventricular conduction times were significantly prolonged with propranolol. There were no significant changes in intraventricular conduction time and the QRS duration without and with propranolol. The QT interval was insignificantly prolonged. Values represent the mean±1 standard deviation. N=number of experiments. N.S.=Not significant. *The p values were calculated using Student’s T test.
Fig. 4. Surface electrograms (upper tracings) and intracellular electrograms (lower tracings) recorded simultaneously from contiguous sites on the anterior epicardial surface of the left ventricle during electrical stimulation. Tracings in A were recorded before the administration of propranolol. Tracings in B were recorded after propranolol. The QT interval and the duration of the MAP became significantly prolonged after administration of the drug. There were no significant drug-induced changes in the QRS duration or in the amplitude of the MAP, MRP and overshoot.

Table III. Effect of Propranolol on the Intracellular Electrogram in the Ventricle during Electrically driven Stimulation

<table>
<thead>
<tr>
<th></th>
<th>Initial Value</th>
<th>After Propranolol</th>
<th>P Value</th>
<th>Change (% of initial value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude of MAP (mV.)</td>
<td>104.6±6.15 (N=44)</td>
<td>104.0±4.86 (N=44)</td>
<td>N.S.</td>
<td>—</td>
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<tr>
<td>Amplitude of MRP (mV.)</td>
<td>81.6±4.09 (N=44)</td>
<td>81.3±3.21 (N=44)</td>
<td>N.S.</td>
<td>—</td>
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<tr>
<td>Overshoot (mV.)</td>
<td>23.0±3.79 (N=44)</td>
<td>22.7±4.66 (N=44)</td>
<td>N.S.</td>
<td>—</td>
</tr>
<tr>
<td>Duration of MAP (msec.)</td>
<td>151.5±4.60 (N=35)</td>
<td>164.0±7.11 (N=35)</td>
<td>&lt;0.01</td>
<td>+8.3%</td>
</tr>
<tr>
<td>Maximal Upstroke Velocity of MAP (V/sec.)</td>
<td>130.7±32.09 (N=30)</td>
<td>123.0±30.39 (N=30)</td>
<td>N.S.</td>
<td>—</td>
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</tbody>
</table>

Values represent the initial values and the values of the maximum changes during the 3 to 7 min. period following administration of propranolol. There are highly significant changes in the duration of the MAP. There are no significant changes in the amplitudes of the MAP, MRP and overshoot nor in the maximum upstroke velocity of the MAP. Values represent the mean±1 standard deviation. N=number of observations. N.S.=Not significant.
Fig. 5. Changes, percentage of the initial values, of QRS duration, QT interval and conduction times after the administration of propranolol during electrical stimulation. Dotted lines are control values (N=5). Solid lines show changes caused by propranolol (N=15). Mean values and ±1 standard deviations are shown by vertical brackets.

(Table II, Figs. 4, 5-B). There were no significant changes in the QRS duration (Fig. 5-A).

Values in various parameters of the intracellular electrograms are shown in Table III. During approximately the first 3 to 7 min. after administration of propranolol, there were no significant changes in the amplitudes of the membrane action potential (MAP), membrane resting potential (MRP) or overshoot. However, the duration of the MAP increased 8.3% (p<0.01) (Table III, Fig. 4).

To study the effects of propranolol on the maximum upstroke velocity of the MAP, 30 observations were made in 11 of the 23 dogs (Fig. 6). No significant changes were observed in the maximum upstroke velocity of the MAP (Table III).
Fig. 6. Tracing of the upstroke of the MAP. Tracing 1 represents the upstroke of the MAP before the administration of propranolol. Tracing 2 represents the upstroke of the MAP after propranolol. The maximal upstroke velocity did not change significantly.

Effects of Propranolol on the Conduction Times

The effects of propranolol on interatrial, atrioventricular and intraventricular conduction times were observed in 18 experiments. In the 15 valid experiments of the original 18, the interatrial conduction time increased by an average of 11.7% during the first 5 min. after administration of propranolol, while the atrioventricular conduction time increased 32.9% (Table II, Figs. 5-C, 5-E). These changes reached almost maximum values between 5 to 10 min. after injection of the drug. The differences between the changes of interatrial and atrioventricular conduction times in the control dogs and in the propranolol-injected dogs are apparent (p<0.05 and p<0.01, respectively). There were no significant drug-induced changes in the intraventricular conduction time (Fig. 5-D).

In the 5 preliminary control experiments, there were no significant changes in these conduction times during 20 min. of electrically driven stimulation.

Discussion

There is much in the literature on the mechanism of propranolol as an agent for the treatment of cardiac arrhythmias. Katz suggested that the antiarrhythmic action of the drug on cyclopropane-catecholamine-induced arrhythmias consists of specific beta adrenergic blockade. Benfey and Varma
reported that propranolol and pronethalol (a beta adrenergic blocking agent pharmacologically similar to propranolol but with adverse side-effects) possess an antifibrillatory property which is not directly related to their beta receptor blocking activity. Somani and Bachand studied the antiarrhythmic action of propranolol in the heart-lung preparation of dogs. They found that doses of 0.5 mg./Kg. effectively blocked the epinephrine-induced arrhythmia, whereas an average of 9.5 mg./Kg. was needed to suppress ouabain-induced arrhythmias. They suggested that the mechanisms of suppression of epinephrine-induced arrhythmias are different from those of ouabain-induced arrhythmias. Vaughan Williams studied the effects of quinidine, pronethalol and propranolol on intracellular potentials in isolated cardiac muscle. He found that all 3 drugs caused (a) no change in MRP, (b) little or no change in duration of the MAP, and (c) marked decrease in the rate of rise and in the amplitude of the MAP. Epinephrine, in contrast, caused an increase in rate of rise and in amplitude of the MAP. Vaughan Williams concluded that the antiarrhythmic drugs do not delay repolarization or prolong the refractory period of myocardial cells but rather interfere in some way with the process which leads to the sudden increase in sodium conductivity on excitation. He further suggested that the supposed superiority of propranolol to quinidine as an antiarrhythmic agent may be due to 2 types of effects: 1) a specific beta adrenergic blocking action, occurring at low doses, which prevents epinephrine from speeding up activation of myocardial cells, and 2) a quinidine-like effect, at higher doses, which reduces the rate of activation to subnormal levels.

The methods for studying propranolol in the present paper are similar to those used in this laboratory for studying the action of quinidine. A comparison of the results of these 2 studies is especially relevant to Vaughan Williams’ hypothesis. In the earlier study, it was found that quinidine significantly prolonged the RR, PQ and QT intervals and the QRS duration in surface electrograms from the in situ canine heart during sinus rhythm. The PQ interval and the QRS duration were even more markedly prolonged by quinidine, when the effect of the drug on the cardiac rate was excluded by driving the heart with applied electrical stimulation. Associated with the quinidine-induced prolongation of the QT interval in the surface electrograms, was a significant prolongation in duration of the MAP in simultaneously recorded intracellular electrograms. The quinidine-induced prolongation of the QRS duration in the surface tracings was associated with the decrease in upstroke velocity of the MAP in the intracellular tracings. These electrographic changes are similar to those observed in the present experiments. However, there are 2 apparent differences. Propranolol did not prolong the QRS duration and did not decrease the upstroke velocity of the MAP during
electrical stimulation. An additional difference between the effects of the two drugs at the dosage used is that propranolol caused a smaller increase in the QT interval and in the duration of the MAP than did quinidine.

The absence of apparent changes in the upstroke velocity of the MAP following administration of propranolol was consistent with the results of the intraventricular conduction time. It has been established that the upstroke velocity of the MAP is related to the conduction velocity. In the present experiments, propranolol (1.5 mg./Kg.) significantly prolonged the interatrial conduction time, highly significantly prolonged the atrioventricular conduction time, but did not significantly affect the intraventricular conduction time. In view of a study by Singer, et al., it may be that delays in intraventricular conduction time would be produced by propranolol if sufficiently toxic doses of the drug were used. Singer, et al., reported that low dosages (2 to 5 mg./Kg.) of pronethalol in the intact animal principally affected the atria, increasing refactororiness, slowing conduction and depressing excitability. In doses of 5 to 10 mg./Kg., pronethalol caused sinus slowing, arrhythmia and atrioventricular conduction delays. Finally, toxic dosages of 10 to 25 mg./Kg. resulted in marked delay of intraventricular conduction.

The intracellular effects of quinidine and propranolol observed in this laboratory differ from the effects reported by Vaughan Williams in the following 3 respects: 1) The duration of the MAP was found to increase significantly after administration of quinidine. On the basis of this result, the antiarrhythmic effect of quinidine was attributed partly to a prolongation of the effective refractory period. Vaughan Williams, in contrast, observed little or no change in duration of the MAP and accordingly concluded that the repolarization process was not affected by antiarrhythmic drugs. 2) Whereas Vaughan Williams observed a decrease in amplitude of the MAP after administration of antiarrhythmic drugs, no such change was observed in this laboratory with either quinidine or propranolol. 3) Vaughan Williams observed a decrease in rate of rise of the MAP following administration of all antiarrhythmic agents studied. In this laboratory, quinidine but not propranolol decreased the rate of the rise of the MAP. These discrepancies may be attributed to the fact that Vaughan Williams’ work was done in isolated muscle whereas the work in our laboratory was performed on the in situ heart. The failure of propranolol to affect significantly the rate of the rise of the MAP in the present study, like the failure of the drug to delay intraventricular conduction, is probably a consequence of the relatively low dosage employed. On the other hand, work now completed has demonstrated that the 0.2 mg./Kg. dose of propranolol used in this new study blocks the effects of epinephrine on the intracellular potentials. Thus, it appears that this lower dose is suffi-
cient to produce a beta adrenergic blocking effect but not a quinidine-like effect on the rate of the rise of the MAP. These findings are consistent with the conclusion of Somani and Bachand\textsuperscript{15} and of Vaughan Williams\textsuperscript{8} that the beta adrenergic blocking effect of propranolol occurs with lower dosages than does the quinidine-like effect and probably involves a different mechanism at the intracellular level.

**ACKNOWLEDGEMENTS**

The authors thank Professor K. Yamada (Research Institute of Environmental Medicine, Nagoya University, Japan) for advice and suggestions; and Mr. F. Smith for technical services.

**REFERENCES**