Effects of Beta-Receptor Blockade and Glucagon on the Atrioventricular Transmission System in the Dog

By Leighton S. Whitsitt, Ph.D., and Benedict R. Lucchesi, Ph.D., M.D.

With the Technical Assistance of Barbara Laidlaw

ABSTRACT

The effects of dL-propranolol, d-propranolol, and ICI 46037, a quaternary analog of propranolol, on the functional refractory period and conduction time of the atrioventricular transmission system were studied in anesthetized dogs. dL-Propranolol, 0.5 mg/kg, prolonged the functional refractory period, increased the conduction time, and reduced the maximum frequency of A-V transmission. Larger doses (5 mg/kg) produced only a small additional depression of A-V transmission. In contrast, neither d-propranolol nor ICI 46037, 0.5 mg/kg, depressed A-V transmission. Larger doses of both drugs prolonged both the functional refractory period and the conduction time, the magnitude of the response being quantitatively similar to that produced by increasing the dose of dL-propranolol from 0.5 mg/kg to 5 mg/kg.

The intravenous administration of glucagon, 2 μg/kg, promptly restored normal A-V conduction in animals that had received dL- or d-propranolol, but was ineffective in those which had received ICI 46037. It was concluded that propranolol depresses A-V transmission by both specific (beta-receptor blockade) and nonspecific mechanisms, the former being the more important. In addition, it appears that glucagon is capable of reversing the cardiodepressant action of propranolol on A-V transmission, a finding which may have considerable clinical importance.

ADDITIONAL KEY WORDS propranolol A-V node d-propranolol conduction time ICI 46037 functional refractory period

- Adrenergic stimulation of the heart decreases the functional refractory period of the atrioventricular transmission system both in laboratory animals (1-5) and in human subjects (6). These reports are consistent with the observation that the effective refractory period of the A-V conducting system in conscious human subjects is controlled to a large extent by the activity of the sympathetic nervous system (6). As anticipated, sympathetic denervation (4, 7, 8), norepinephrine depletion by reserpine (4), and beta-receptor blockade by pronethalol and propranolol (3, 5, 8, 9) have been shown to prolong the refractory period of the A-V transmission system.

The clinical effectiveness of propranolol in slowing the ventricular rate in atrial fibrilla-
tion and other supraventricular tachyarrhythmias has been demonstrated in a number of studies recently reviewed by Epstein and Braunwald (10). The ability of propranolol to reduce the ventricular rate during rapid atrial rhythms may be attributed to specific beta-receptor inhibition and thereby to the removal of the influence of background sympathetic tone on A-V transmission. Alternatively, the effects of propranolol may be due, at least in part, to the nonspecific antiarrhythmic properties of the drug described by Lucchesi et al. (11) and by Parmley and Braunwald (12). Rouse (5) has suggested that large doses of propranolol may have a direct nonspecific depressant effect on the A-V conduction system. The present study was conducted in an attempt to determine the specific and nonspecific effects of propranolol on A-V transmission. For this purpose, dl-propranolol was compared with d-, propranolol and ICI 46037, a quaternary analog of propranolol. The latter two compounds have been shown to be lacking in beta-receptor-blocking activity (13, 14).

A number of investigators (15-17) have demonstrated that glucagon possesses cardiac actions which resemble beta-receptor stimulation by norepinephrine and other catecholamines (e.g., positive inotropic and chronotropic effects). However, recent studies (16, 17) have shown that the cardioinhibitory effects of glucagon differ from those of catecholamines in that its effects are more prolonged and are not antagonized by the beta-receptor-blocking drug, propranolol. Furthermore, it was demonstrated (17) that glucagon is capable of reversing the depressant effects of propranolol on both heart rate and myocardial contractility. Since the cardioinhibitory effects of glucagon apparently are not mediated through the excitation of cardiac beta-receptors (16, 17), the present experiments were conducted to determine whether glucagon might similarly reverse the depressant effects of propranolol on A-V conduction.

**Methods**

Mongrel dogs (6.8 to 14 kg) of both sexes were anesthetized with pentobarbital sodium, 30 mg/kg iv. The vagus nerves were severed bilaterally at midcervical levels. Positive pressure respiration was maintained through an endotracheal tube by a Harvard respirator pump. After exposure of the heart through a right thoracotomy, small clip electrodes were attached to the apex of the right ventricle for recording local ventricular electrograms. Systemic blood pressure was measured from a cannulated femoral artery by means of a Statham P 23 AA transducer and was recorded simultaneously with lead II electrocardiograms and right ventricular electrograms on a Grass Model 7 polygraph. The right ventricular electrograms were displayed on a Tektronix dual beam oscilloscope, the sweep of which was triggered by the driving or test stimulus.

The functional refractory period of the atrioventricular transmission system was studied by two techniques, both of which have been described by Krayer et al. (1) and by Morrow et al. (4). The first method consisted of driving the atrium electrically at a constant basic rate slightly greater than the spontaneous sinus rate, and delivering occasional single premature systoles at specific time intervals following the basic driving stimulus. In most experiments, the basic pacing rate required was about 180 beats/min. For this reason, all studies were conducted at this constant rate. Driving stimuli of three times threshold intensity and 1 msec duration were applied through the clip electrodes (A1) attached to the right atrial appendage. By triggering the sweep of the oscilloscope with the basic drive stimulus, the position of the ventricular electrogram (V1) gives the atrioventricular conduction time (AV1), or the time required by an impulse to travel from the atrial stimulating electrodes to the ventricular recording electrode via the A-V node. A second electronic stimulator was coupled to the first in such a way as to permit the application of an occasional test shock (A2) to the right atrium at any desired time interval (delay, or A1-A2 interval) after the last driving stimulus. The test stimulus consisted of a 1 msec square-wave shock at three times threshold intensity. Both basic pacing and test stimuli were

\[ ^{1}(3\text{-diethylmethylammonium-3-hydroxy-n-propoxy}) \text{napthalene iodide.} \]

\[ ^{2}\text{American Electronics Laboratory 104A.} \]
TABLE I
Effects of d/-Propranolol, d-Propranolol, and ICI 46037 on the A-V Functional Refractory Period and Conduction Time Studied by the Atrial Premature Systole Technique

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Functional refractory period*</th>
<th>Conduction time</th>
<th>% Change</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>msec ± SE</td>
<td>msec ± SE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dl-Propranolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n = 5)</td>
<td>197.6 ± 5.7</td>
<td>112.0 ± 4.7</td>
<td>+16.5%</td>
<td>(P &lt; .005)</td>
</tr>
<tr>
<td>0.5 mg/kg</td>
<td>230.2 ± 6.1</td>
<td>137.2 ± 2.5</td>
<td>+22.5%</td>
<td>(P &lt; .005)</td>
</tr>
<tr>
<td>5.0 mg/kg</td>
<td>256.2 ± 9.1</td>
<td>166.0 ± 9.3</td>
<td>+29.7%</td>
<td>(P &lt; .005)</td>
</tr>
<tr>
<td>d-Propranolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n = 5)</td>
<td>224.4 ± 6.5</td>
<td>103.0 ± 4.6</td>
<td>+3.8%</td>
<td>(P &gt; .05)</td>
</tr>
<tr>
<td>0.5 mg/kg</td>
<td>233.0 ± 1.4</td>
<td>106.2 ± 4.6</td>
<td>+3.1%</td>
<td>(P &gt; .05)</td>
</tr>
<tr>
<td>5.0 mg/kg</td>
<td>254.4 ± 13.6</td>
<td>128.4 ± 6.8</td>
<td>+24.7%</td>
<td>(P &lt; .05)</td>
</tr>
<tr>
<td>ICI 46037</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n = 5)</td>
<td>204.8 ± 6.6</td>
<td>113.4 ± 6.2</td>
<td>+4.0%</td>
<td>(P &gt; .05)</td>
</tr>
<tr>
<td>0.5 mg/kg</td>
<td>213.0 ± 1.8</td>
<td>118.2 ± 7.2</td>
<td>+4.2%</td>
<td>(P &lt; .05)</td>
</tr>
<tr>
<td>5.0 mg/kg</td>
<td>226.2 ± 14.7</td>
<td>147.2 ± 7.8</td>
<td>+59.6%</td>
<td>(P &lt; .001)</td>
</tr>
</tbody>
</table>

Values were determined at a constant heart rate of 150 beats/min.

The functional refractory period of the atrioventricular transmission system; i.e., the minimum interval between two ventricular impulses both propagated from the atrium.

Applied through the same pair of electrodes. The ventricular electrograms resulting from the atrial premature systole were monitored on an oscilloscope, the sweep of which was triggered by the test stimulus. This permitted the direct measurement of the A-V conduction time for the interpolated beat (the A2V2 interval). The interval between the last driving stimulus and the test shock (A1A2 interval) was varied by 5 to 10-msec steps and the intervals between the corresponding ventricular responses (V1V2 intervals) were recorded. The atrial intervals (A1A2) were plotted against the ventricular intervals (V1V2). The functional refractory period of the atrioventricular transmission system was determined as the minimum interval between two ventricular responses both propagated from the atrium, as determined by Rosenblueth et al. (18).

In another series of experiments, the functional refractory period was studied by a second technique, which consisted of stimulating the right atrium at increasing frequencies through the clip electrodes attached to the right atrium, using 1-msec square-wave stimuli at three times threshold voltage. The maximum frequency of atrial stimulation at which each atrial impulse was conducted through to the ventricle (maximum frequency of A-V transmission) was determined.

The time interval (in milliseconds) between these successive stimuli was regarded as the functional refractory period, as determined by this technique (1).

Determinations of the functional refractory period by both methods, as well as the A-V conduction times, were made in the control state and at 20-minute intervals after the intravenous administration of increasing doses of dl-propranolol, d-propranolol, or ICI 46037. All drugs were administered through a cannulated jugular vein. The data were analyzed according to the method described by HiI for paired comparisons (19).

Results

Effects of Beta-Receptor Blockade by dl-Propranolol on the A-V Transmission System

The intravenous administration of dl-propranolol, 0.5 mg/kg, to five vagotomised dogs resulted in a significant prolongation of the functional refractory period of the A-V transmission system, as determined by the atrial premature systole technique described by Krayer et al. (1). This dose of dl-propranolol was previously shown to produce relatively...
Effect of dl-propranolol on the functional refractory period of the A-V node. The solid 45° line represents the situation that would exist if the $V_1V_2$ intervals were the same as the $A_1A_2$ interval at each point. Note the delay in A-V conduction at short interatrial intervals. The example given compares the relationships between the $A_2A_3$ and $V_1V_2$ intervals after dl-propranolol with those under control conditions.

complete beta-receptor inhibition in the anesthetized dog (14). As shown in Table 1, the functional refractory period increased by 16.5%. Increasing the dose of dl-propranolol to 5 mg/kg further prolonged this period to a total increase of 29.7% over the control value. The results obtained in a sample experiment are illustrated in Figure 1, which shows the prolongation of the refractory period by dl-propranolol. The functional refractory period has been defined as the minimum interval between two ventricular impulses (minimum $V_1V_2$ interval), both propagated from the atrium. In addition, Figure 1 shows that the more premature an atrial extrasystole the greater is the delay in propagation of the impulse into the ventricles. This is seen as a progressive shifting of the curve away from the 45-degree axis as the interatrial interval ($A_1A_2$ interval) is shortened.

In the above series of experiments, dl-propranolol produced a marked prolongation of the atrioventricular conduction time, as determined from the $A_1V_1$ intervals. These data are also summarized in Table 1. It can be seen that a dose of 0.5 mg/kg prolonged the conduction time by 22.5%. The dose of 5.0 mg/kg further prolonged the conduction time to 48.8% above the control value. These values were determined at a constant heart rate of 180 beats/min. Figure 2, A, shows a photographic record from a typical experiment. The sweep of the oscilloscope was triggered by the pacing stimulus so that the A-V conduction time could be directly ob-

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The ability of dl-propranolol to significantly diminish the maximum frequency at which the A-V nodal system is capable of conducting all atrial impulses to the ventricles was demonstrated in a second series of five vagotomized dogs. These data are summarized in Table 2, which show that dl-propranolol, 0.5 mg/kg, reduced the maximum frequency of A-V transmission from a control value of 351.6 impulses/min to 268.8 impulses/min. Simultaneously, the spontaneous heart rate was reduced from a control of 164.8 beats/min to 118.8 beats/min. Increasing the dose of dl-propranolol to 2.5 and 5 mg/kg produced little additional change.
in either spontaneous ventricular or maximum A-V transmission rates. If it can be assumed that the maximum frequency of A-V transmission is limited by the functional refractory period of the A-V transmission system, then the refractory period can be calculated from these values. When determined by this method the control functional refractory period was significantly smaller than that obtained by the atrial premature systole method. dl-Propranolol, 0.5, 2.5, and 5.0 mg/kg, prolonged the refractory period by 39.9%, 39.7%, and 48.2%, respectively. Comparable results were obtained in a third series of dogs without prior bilateral vagotomy.

Effects of dl-Propranolol on the A-V Transmission System.—In contrast to cW-propranolol, the intravenous administration of dl-propranolol, 0.5 mg/kg, to five vagotomized dogs did not produce a statistically significant prolongation of the functional refractory period of the A-V transmission system, as determined by the atrial premature systole technique (Table 1) or when calculated from the maximum frequency of A-V transmission (Table 2). Table 1 shows that dl-propranolol, 0.5 mg/kg, prolonged the refractory period by only 3.8%. Increasing the dose to 5 mg/kg further prolonged the refractory period to 13.4% above the control value. The difference in the effects of the two doses was quantitatively similar to the difference in the effects of the same doses of dl-propranolol. These effects on the functional refractory period seen with large doses are presumably due to a nonspecific action of the drug since dl-propranolol does not block cardiac beta-receptors (14).

Table 1 shows that dl-propranolol, 0.5 mg/kg, also failed to alter the A-V conduction time determined at a constant heart rate of 180 beats/min. The dose of 5.0 mg/kg prolonged the conduction time by 24.7% above the control level. A sample experiment is illustrated in Figure 2, B. As with the data on refractory period, the difference in the effects of the two doses was quantitatively similar to the difference in the effects of the same two doses of dl-propranolol. The right side of Figure 3 illustrates a typical experiment in which dl-propranolol, 5 mg/kg, prolonged the conduction time at each constant pacing rate studied, the effect being much greater at the higher heart rates, an effect also observed with dl-propranolol (left side of Figure 3).

Similarly, Table 2 shows that dl-propranolol failed to alter significantly the maximum frequency at which the A-V transmission system conducts impulses to the ventricles. Thus, in four vagotomized dogs, 5 mg/kg reduced the maximum frequency of A-V transmission from a control level of 337.8 impulses/min to 306 impulses/min, a 9.4% reduction. The subsequent administration of dl-propranolol, 0.5 mg/kg, produced an immediate decrease to 239.8 impulses/min, a reduction of 29.1% from control. The functional refractory period as determined from the maximum frequency of A-V transmission increased by 10% following the administration of dl-propranolol, 0.5, 2.5, and 5.0 mg/kg. dl-Propranolol, 0.5 mg/kg, promptly increased the refractory period to 39.2% above the control value. These data are summarized in Table 2.

Effects of ICI 46037 on the A-V Transmission System.—ICI 46037, which lacks significant beta-receptor-blocking properties (13), was almost identical to dl-propranolol in its effects on the A-V transmission system. Reference to Tables 1 and 2 shows that ICI 46037, 0.5 mg/kg, did not significantly prolong the refractory period as determined by either method, and failed to alter either the A-V conduction time or the maximum frequency of atrial stimulation which the ventricles would follow. The effects of 5 mg/kg on these measurements were quantitatively similar to the effects of the same dose of dl-propranolol. The differences between the two drugs were not statistically significant. As with dl-propranolol, the differences in the effects of 0.5 and 5 mg/kg of ICI 46037 were quantitatively similar to the differences in the effects of the same doses of dl-propranolol.

Figure 2, C, is a photographic record illustrating the effects of ICI 46037 on the
A-V conduction time. The dose of 0.5 mg/kg failed to increase the conduction time, whereas 5 mg/kg prolonged it. Figure 4 shows the effects of ICI 46037 on A-V conduction times at different paced heart rates. A dose of 0.5 mg/kg did not alter the conduction time, whereas 5 mg/kg increased it at each paced rate, the effect being more marked at the higher rates. Table 2 shows the minimal effects of ICI 46037 on the maximum frequency of A-V transmission and on the functional refractory period calculated from these values. The intravenous administration of dl-propranolol, 0.5 mg/kg, after ICI 46037 promptly decreased the maximum frequency of A-V transmission and prolonged the refractory period to levels comparable to those obtained with dl-propranolol alone.

Effects of Glucagon on the Depressed A-V Transmission System.—Glucagon, 2 µg/kg, was administered by rapid intravenous injection to each animal at the point of peak depression of A-V conduction by 5 mg/kg of dl-propranolol, d-propranolol, and ICI 46037. These results are summarized graphically in Figure 5. It can be seen that the values for the A-V conduction times (A-V intervals), depressed by dl-propranolol and d-propranolol, were restored to near control levels by glucagon. This effect of glucagon on the A-V conduction time was observed within 30 seconds of injection. In contrast, glucagon failed to restore the A-V conduction time to control levels when administered to the animals that had received ICI 46037. There was a slight reduction in the conduction time, but this effect required 2 to 5 minutes to develop and was incomplete. Photographic records of sample experiments from each series are given in Figure 2.

The functional refractory period of the A-V transmission system was not determined after the administration of glucagon, 2 µg/kg, because in some experiments the spontaneous heart rate rose after glucagon to exceed the paced rate. However, the shortening of the conduction time always attained its peak level before the spontaneous rhythm became
dominant, thereby making it possible to record the $A_V$ intervals (conduction time) following glucagon. In each experiment it was noted that the maximum frequency of atrial stimulation at which the ventricles follow the atria, markedly depressed by $dL$-propranolol and $dL$-propranolol, was immediately restored to control values by glucagon. These results suggest that glucagon is capable of reversing the depressant effects of $dL$-propranolol and $dL$-propranolol (but not ICI 46037) on the functional refractory period and conduction time through the A-V transmission system.

Discussion
The studies of Hoffman and Cranefield (20) have demonstrated that the normal delay in A-V transmission occurs within a narrow region at the atrial margin of the A-V node, through which conduction is decremental. Intracellular recordings (20) from the atrial margin of the A-V node reveal transmembrane action potentials characterized by a low resting membrane potential, a slow rate of rise, notches or slurs on the upstroke, and low amplitude, features believed to be responsible for diminished or decremental conduction. In addition, the A-V node has been found to have a longer effective refractory period than either atrial or ventricular muscle (21). A relatively long refractory period would be expected to enhance decremental conduction of atrial impulses passing through the A-V node. It would be anticipated that any intervention, physiologic or pharmacologic, which increases the resting membrane potential and thereby the rate of rise and amplitude of the action potential and abbreviates the functional refractory period of the A-V node, would diminish decrement and lessen the A-V conduction delay. Matsuda et al. (22) have demonstrated that epinephrine exerts such actions on A-V nodal fibers. These findings are in agreement with reports that intravenous catecholamines and stellate ganglion stimulation enhance A-V conduction (1-6) and shorten the functional refractory period in experimental animals (1-5) and in human subjects (6). Furthermore, Wallace and associates (2, 3, 8) have shown that cardiac adrenergic stimulation shortens the A-V conduction time by as much as 50%, without a concomitant alteration of either the velocity of the spread of excitation through the peripheral Purkinje system or the sequence of epicardial activation of the ventricles. Ventricular excitation time was similarly unaffected.

On the basis of the foregoing considerations, cardiac sympathetic inhibition would be expected to have the opposite effects; i.e., a prolongation of both the refractory period and the conduction time. Thus sympathetic denervation (4, 7, 8), depletion of cardiac norepinephrine stores by reserpine (4), beta-receptor blockade by pronethalol and propranolol (3, 5, 8, 9) have been shown to increase the refractory period and slow A-V conduction. These effects are presumably due to removal of the influence of background sympathetic nervous tone and circulating catecholamines on A-V transmission, since Wallace (3, 8) has shown that they are not observed in well-trained awake dogs, in which sympathetic nervous tone is low or nonexistent. In addition, pronethalol and propranolol antagonize the effects of injected catecholamines on A-V transmission (3, 5, 8, 9). These results suggest that the effects of cardioactive catecholamines on A-V transmission are mediated through the stimulation of cardiac beta-receptors.

The results of the present investigation are consistent with the studies of previous investigators (3, 5, 8, 9). $dL$-Propranolol, in a dose (0.5 mg/kg) previously shown to produce relatively complete beta-receptor blockade of ordinary doses of isoproterenol and of cardiac sympathetic nerve stimulation (14), significantly prolonged the functional refractory period and the conduction time. In addition, the maximum frequency of A-V transmission was markedly reduced. In contrast, both $dL$-propranolol and ICI 46037, which do not block beta-receptors (11, 13), failed to alter any of these measurements at the same dose level. These results indicate...
that the effects of \( dl \)-propranolol, 0.5 mg/kg, on A-V transmission are almost entirely due to cardiac beta-receptor blockade. Large doses (5 mg/kg) of all three drugs produced an additional depressant effect on A-V transmission. The quantitative differences in the effects of the 0.5 and 5 mg/kg doses were the same for each of the three drugs. Thus it appears that these drugs have a nonspecific depressant effect on the A-V transmission system, consistent with earlier observations which have demonstrated nonspecific anti-arrhythmic and negative inotropic and chronotropic actions for \( dl \)- and \( d \)-propranolol (11, 12, 14, 23) and ICI 46037 (13). The precise nature of this “nonspecific” action is unclear, but is most likely associated with a general depression of excitable membranes, or with a membrane-stabilizing property of the drugs in which there is interference with the entry of depolarizing current during excitation (13, 24, 25).

It should be noted that the control refractory period was significantly different when determined by the two methods; that calculated from the maximum frequency of A-V transmission (Table 2) was considerably lower than that determined by the atrial premature systole technique (Table 1). This difference may be attributed to the level of cardiac sympathetic nervous tone in the two methods. When the maximum frequency of A-V transmission is determined (and the refractory period calculated), the high paced rates cause a large reduction in systemic blood pressure which reflexly augments sympathetic nervous tone and thereby shortens the functional refractory period. On the other hand, determination of the refractory period by the atrial premature systole method does not involve any such circulatory embarrassment. Consequently, sympathetic nervous tone is not elevated and the refractory period is correspondingly greater. This explanation draws support from the observation that the effect of \( dl \)-propranolol, 0.5 mg/kg, was much greater in the former series, consistent with an elevated sympathetic nervous tone. In addition, there is no significant difference between the levels of the refractory period after beta-receptor blockade in the two series of experiments. These results suggest that the atrial premature systole technique gives a more accurate assessment of the absolute functional refractory period. Although the second method does not provide a true measure of the refractory period, it does provide an assessment of the effects of drugs on the ability of the A-V node to transmit impulses during rapid atrial arrhythmias.

Table 1 shows that \( dl \)-propranolol, \( d \)-propranolol, and ICI 46037 produced a much greater prolongation of the conduction time than of the refractory period. This difference may be related to the nature of the measurements. The A-V transmission system is a heterogeneous system involving atria, A-V node, His bundle and its branches, the peripheral Purkinje system, and the ventricular myocardium. The measurement of the functional refractory period of the composite system reflects only that part of the system which has the longest functional refractory period. For the A-V transmission system, this is the A-V node (1, 5). Therefore, a drug such as propranolol which prolongs the functional refractory period may prolong it for all components of the A-V transmission system, but only its prolongation in the A-V node contributes to the measurement of the refractory period of the system. Conversely, the conduction time, as measured in these experiments, represents the sum of the conduction times from atrium to A-V node, across the A-V node and His bundle, and through the ventricle to the recording electrode. Thus, the prolongation of atrial, ventricular, or both conduction times, as well as the conduction time through the A-V node, by a drug would contribute to the prolongation of the conduction time for the A-V transmission system. This might explain the greater prolongation of the conduction time than of the functional refractory period by the three drugs used in this study. Wallace (3, 8) and Rouse (5) have demonstrated that small doses of propranolol do not alter atrial or ventricular conduction velocities. Thus, the effect of \( dl \)-
propranolol, 0.5 mg/kg, on conduction time is probably due to a slowing of conduction through the A-V node. However, earlier studies in this laboratory (11) demonstrated that large doses of dl- and d-propranolol do slow ventricular conduction. These results suggest that the large effects on conduction time of large doses of the three drugs used in this study are due at least in part to their effects on conduction in atria and ventricles. In this respect, the nonspecific actions of large doses of these drugs resemble the actions of quinidine (28).

The present study clearly demonstrated that glucagon is capable of rapidly reversing the depression of the A-V transmission system induced by dl- and d-propranolol, a finding consistent with an earlier report (16) that glucagon is capable of reversing the cardiodepressant (negative isotropic and chronotropic) effects of propranolol. Lucchesi (16) has demonstrated that reversal by glucagon apparently is not mediated through beta-receptor activation. Thus small doses of glucagon were found to reverse the cardiodepressant effects of doses of propranolol that completely antagonize relatively large doses of isoproterenol. Recent studies (16, 17) have suggested that glucagon and cardioactive catecholamines may exert their cardiostimulatory actions through a common metabolic pathway; i.e., the activation of adenyl cyclase and the consequent formation of cyclic 3',5'-AMP. They differ in that the effects of glucagon are not antagonized by propranolol. The potential clinical significance of these findings is obvious. The most serious reported clinical drawbacks to the use of propranolol include the intensification of heart failure and of A-V block (27). It would appear that glucagon might be a valuable means of reversing these detrimental effects of beta-receptor blockade. The inability of glucagon to reverse the cardiodepressant effects of ICI 46037 cannot be explained on the basis of the present experiments.

It thus appears likely that the clinical effectiveness of propranolol in controlling the ventricular rate in atrial flutter and fibrillation (10) is largely due to its ability to produce beta-receptor blockade and thereby diminish the frequency and velocity of A-V transmission. This is based on the fact that the ventricular rate in rapid atrial arrhythmias is limited by the functional refractory period, and the effect of propranolol in prolonging the refractory period is more pronounced at rapid atrial rates, as shown in the present study. Furthermore, Epstein and Braunwald (28) reported that propranolol reduces the ventricular rate in patients with atrial fibrillation without altering the atrial rate. They also attributed this to the effects of beta-receptor blockade on the refractory period. In these situations, d-propranolol or ICI 46037 would be of limited effectiveness. However, all three drugs are capable of abolishing enhanced ventricular automaticity resulting from digitalis cardiotoxicity (11, 13). Thus d-propranolol and ICI 46037 would seem to offer distinct clinical advantages over dl-propranolol in the management of digitalis cardiotoxicity when beta-receptor blockade might be disadvantageous, i.e., in patients with evidence of incipient cardiac decompensation or varying degrees of A-V block. Rouse (5) has shown that propranolol and digitalis act synergistically on the A-V node to increase the degree of block.

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References


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