N-Dimethylisopropyl Propranolol
Effects on Myocardial Oxygen Demands

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SUMMARY N-Dimethylisopropyl propranolol (DMP) is a quaternary derivative which lacks significant beta-adrenergic blocking and local anesthetic effects. It has been reported, nonetheless, to be effective in treating experimental arrhythmias and in limiting the extent of ST-segment elevations following experimental coronary occlusion. The present study examined the effects of DMP on the hemodynamics and myocardial oxygen demands of anesthetized dogs.

After a single dose of 3 mg/kg, heart rate fell from 146 ± 8 to 124 ± 6 beats/min (P < 0.0025), and aortic systolic pressure fell from 151 ± 11 to 141 ± 9 mm Hg (0.05 < P < 0.10), resulting in a 16.8% reduction in the tension-time index. Stroke volume was reduced by 10% despite a 54% increase in left ventricular end-diastolic pressure, suggesting a negative inotropic effect. This was supported by a decrease in maximum extrapolated contractile element velocity from 9.10 ± 1.05 to 6.61 ± 65 units/sec (P < 0.0025). Myocardial oxygen consumption was reduced from 12.0 ± 1.4 to 9.9 ± 1.5 ml/min/100 g tissue (P < 0.05). Myocardial oxygen extraction was unchanged, indicating that the decrease in oxygen consumption resulted from a reduction in myocardial oxygen demand.

When heart rate and systolic pressure were artificially restored to control levels, after the administration of DMP, myocardial oxygen consumption remained significantly below the control level. DMP, therefore, appeared to reduce myocardial oxygen demands primarily by its negative inotropic effect. This drug may have application in the treatment of ischemic heart disease.

THE ANTIARRHYTHMIC AND ANTIANGINAL actions of propranolol have been attributed to two properties, beta-adrenergic blockade and membrane stabilization. The first property is manifested by specific, competitive inhibition of beta-receptor agonists.1 The second property has been related to the local anesthetic effect of the drug and to its effect on the rate of rise and degree of overshoot of the cardiac action potential.2 These quinidine-like effects have been shown to be distinct from membrane effects of beta-adrenergic stimulation or blockade.3 They may, however, contribute to the nonspecific myocardial depression produced by high doses of propranolol.4

The combination of beta-adrenergic antagonism and nonspecific effects seems responsible for the side effects of propranolol, as well as for its therapeutic actions, and has stimulated the search for agents with more discrete actions.5

N-Dimethylisopropyl propranolol is a quaternary compound derived from propranolol. The terminal amino group has been dimethylated, abolishing any significant affinity for the beta receptor site (fig. 1). Schuster et al. have shown that dimethyl propranolol has no significant beta-blocking properties and lacks demonstrable local anesthetic properties in the isolated frog sciatic nerve-trunk preparation.6 Surprisingly, in this study, the drug was effective against experimental arrhythmias induced by ouabain or myocardial ischemia.

A recent study has also indicated that dimethyl propranolol is effective in limiting the extent of ST-segment elevations following an experimental coronary occlusion.7 This suggested that, like propranolol, this new derivative might reduce myocardial oxygen demands. The present study was designed to test this hypothesis, and to evaluate the factors responsible for any changes in myocardial oxygen consumption.

Methods

A. Dose-Response Study

The response to increasing doses of dimethyl propranolol was studied in eight mongrel dogs anesthetized with pentobarbital, 30 mg/kg, intravenously. Catheters were placed in the ascending aorta and the coronary sinus. Pressures were measured via fluid-filled tubing connected to Statham P23Db transducers, and were recorded together with lead II of the electrocardiogram on an Electronics for Medicine DR-8 recorder. Oxygen contents of aortic and coronary sinus blood samples were measured utilizing a Lexington Instruments Corporation Lex O2 Con. Left ventricular coronary blood flow was measured by 133Xenon washout curves (see below), and cardiac output was measured by indocyanine green dye dilution, utilizing a Beckmann Densitometer.

Dimethyl propranolol,* as the chloride salt, was prepared in normal saline as a 5 mg/ml solution, and was infused intravenously at 5 mg/min.

Observations were made in the control state. They were repeated 20 minutes after administration of dimethyl propranolol, 1 mg/kg, then 20 minutes after an additional 1 mg/kg, and then 20 minutes after a final 1 mg/kg. A last set of observations was made five minutes after intravenous administration of atropine, 0.5 mg. The antiarrhythmic effects of dimethyl propranolol have been shown to persist for two hours.6

B. Factors Influencing Myocardial Oxygen Demands

An additional 11 dogs were anesthetized with Dial-Urethane (allobarbitol, 60 mg/kg; urethane, 240 mg/kg; and monoethylurea, 240 mg/kg) to achieve physiologic heart rates and blood pressures. The lead II electro-

*Kindly supplied as SC-27761 by Searle Laboratories.
cardiogram, aortic pressure, oxygen contents of blood samples from the aorta and coronary sinus, left ventricular coronary blood flow, and cardiac output were recorded.

In addition, provisions were made for the estimation of myocardial contractility and for the control of heart rate and blood pressure. An electrode pacemaker catheter was placed in the right atrium. A double lumen, stainless steel cannula was passed from the left carotid artery into the left ventricle. One lumen was connected through a side hole to an inflatable balloon positioned in the ascending aorta, above the sinuses of Valsalva. The balloon could be inflated to increase the pressure faced by the left ventricle. The other lumen terminated in a short rubber tip, with side holes, positioned in the left ventricle. A Statham P23Db transducer was attached directly to this lumen, allowing high fidelity left ventricular pressure measurements. The natural frequency of this system has previously been determined to be 140 cycles per second.* The left ventricular pressure tracings were recorded on magnetic tape, and later used to calculate $V_{\text{max}}$, the maximum extrapolated contractile element velocity (see below).

Observations were made in the control state and 20 minutes after administration of dimethyl propranolol, 3 mg/kg. This dose had produced significant changes in all parameters measured in protocol (A).

C. Controlled Heart Rate and Blood Pressure

Dimethyl propranolol reduced heart rates and blood pressures in most of the eleven dogs studied in protocol (B). After observations were made in the control and drug states, heart rates were restored to control levels by atrial pacing. Systolic aortic pressures were restored toward control by aortic balloon inflation. Systolic pressure could be adjusted to within 5 mm Hg of the control measurement in seven dogs. These animals were studied to isolate the factors primarily responsible for the changes in myocardial oxygen consumption.

Left ventricular and aortic pressures, cardiac output, coronary flow, aortic and coronary sinus oxygen contents, and $V_{\text{max}}$ had been measured at rest and after dimethyl propranolol. In these seven dogs, all measurements were repeated five minutes after heart rate and blood pressure had been returned to control levels.

Analysis of Data

The tension-time index (mm Hg · min) was calculated as the product of the heart rate, the systolic ejection period, and the mean systolic pressure, all of which were determined from pressure tracings.

To estimate left ventricular coronary flow, $^{133}$Xenon (1 to 2 mCi dissolved in normal saline) was injected into the left anterior descending artery. Count rates were recorded by a scintillation counter using a 1 inch by 1 inch collimated sodium iodide crystal placed over the apex of the heart. A semi-logarithmic plot of the exponential clearance curve was constructed and the steepest slope was chosen. From this slope, myocardial blood flow was calculated using the formula, $F = 100 (k) (\lambda)/p$, where $F$ is the myocardial blood flow in ml/min/100 g tissue, $\lambda$ is the partition coefficient for $^{133}$Xenon (assumed 0.72), $p$ is the specific gravity of the myocardium (assume 1.05), and $k$ is the slope of the exponential washout curve.9

Myocardial oxygen consumption (ml/min/100 g tissue) was calculated as the product of myocardial blood flow and the aortic-coronary sinus oxygen content difference.

The high fidelity left ventricular pressure recordings were analyzed by a Varian digital computer after analog to digital conversion. Contractile element velocities were calculated from developed pressures during isometric systole, using the formula, $CEV = (\Delta P/\Delta T)/(32P)$, where $CEV$ is the contractile element velocity in units/second, and $\Delta P/\Delta T$ is the slope of the pressure tracing at any developed pressure, $P$. The plot of contractile element velocities versus developed pressures was extrapolated to zero load using a least squares fit to an exponential curve. This provided an estimate of the maximum unloaded contractile element velocity, $V_{\text{max}}$10,11

Comparisons to control measurements were made utilizing the $t$-test for paired data.

Results

A. Dose-Response Study

Dimethyl propranolol, 1 mg/kg, decreased stroke volume from $11.4 \pm 1.5$ (mean ± se) to $9.7 \pm 1.3$ ml, $P < 0.005$; cardiac output from 2.2 ± .2 to 1.6 ± .2 L/min, $P < 0.005$; and heart rate from 193 ± 8 to 169 ± 7, $P < 0.0025$ (table 1). After a cumulative dose of 3 mg/kg, the mean stroke volume was reduced by 40%, cardiac output by 53% and heart rate by 19.2% of control. Stroke volume and cardiac output were significantly reduced by each consecutive dose
of dimethyl propranolol. Mean systolic aortic pressure was significantly reduced from control only at the 1 mg/kg and 3 mg/kg but not the 2 mg/kg dose levels.

Myocardial oxygen consumption was significantly reduced from control at 2 mg/kg (17.8 ± 1.5 to 14.0 ± 1.8 ml/min/100 g, P < 0.05) and at 3 mg/kg (13.6 ± 1.6, P < 0.0025). Myocardial blood flow was reduced from control at all dose levels. The aortic-coronary sinus oxygen content difference and the percent myocardial oxygen extraction were slightly increased at all dose levels, but were not significantly different from control at the 3 mg/kg dose level.

None of the changes produced by dimethyl propranolol were totally reversed by atropine, 0.5 mg (table 1). Although heart rate was increased significantly (156 ± 12 to 163 ± 11 beats/min, P < 0.01), it remained well below control.

B. Parameters Affecting Myocardial Oxygen Demands

In the 11 dogs anesthetized with Dial-Urethane, the control heart rates and blood pressures were lower than in the dogs prepared with pentobarbital (table 2). In this setting, dimethyl propranolol produced a reduction in mean systolic arterial pressure of only 10 mm Hg (151 ± 11 to 141 ± 9 mm Hg, 0.05 < P < 0.10). The mean heart rate was reduced from 146 ± 8 to 124 ± 6 beats/min, P < 0.0025. Mean stroke volume was reduced by 10% (11.4 ± 1.1 to 10.2 ± 1.1 ml, P < 0.01), despite a 54% increase in left ventricular end-diastolic pressure (6.7 ± 1.1 to 10.3 ± 1.4, P < 0.0025). The decrease in stroke volume with an increase in preload suggested a negative inotropic action, which was supported by the change in the extrapolated maximum contractile element velocity: \( V_{\text{max}} \) fell from 9.10 ± 1.05 to 6.61 ± 0.65 units/sec, P < 0.0025.

These changes were accompanied by a fall in myocardial oxygen consumption from 12.0 ± 1.4 to 9.9 ± 1.5 ml/min/100 g, P < 0.05, and a fall in coronary flow from 118 ± 24 to 91 ± 16 ml/min/100 g, P < 0.01. The myocardial arteriovenous oxygen difference did not change significantly.

C. Controlled Heart Rate and Blood Pressure

Heart rate and blood pressure were restored to control levels after dimethyl propranolol administration in seven animals. The data from these studies were analyzed to isolate the factors primarily responsible for the decrease in myocardial oxygen consumption produced by the drug. The changes in hemodynamic and mechanical parameters produced by dimethyl propranolol alone in this subgroup were identical to those noted for the total group of eleven dogs.

In these seven animals, heart rate fell from 149 ± 8 to 124 ± 7 beats/min (P < 0.0025) after dimethyl propranolol. Systolic blood pressure fell from 164 ± 13 to 148 ± 12 mm Hg, P < 0.025. Stroke volume fell from 13.1 ± 1.2 to 11.4 ± 1.5 ml, P < 0.01, while left ventricular end-diastolic pressure rose from 7.9 ± 1.5 to 12.2 ± 1.6 mm Hg, P < 0.005. \( V_{\text{max}} \) fell from 7.90 ± 1.08 to 5.59 ± 0.68 units/second, P < 0.005 (table 3).

Atrial pacing increased the mean heart rate to 150 ± 8 beats/min, which was within 1 beat/min of the mean control rate. Balloon inflation increased the mean systolic pressure to 167 ± 13 mm Hg, which was within 3 mm Hg of the control pressure. Thus, the tension-time index was increased to 66.9 ± 8.8 mm Hg × min, which was almost identical to the control of 66.2 ± 9.3 (fig. 2).

After dimethyl propranolol, left ventricular end-diastolic pressure had increased. With restoration of control heart rate and blood pressure, it increased further from 12.2 ± 1.6 to 20.1 ± 4.8 mm Hg, P < 0.05. Stroke volume had been reduced by drug treatment. It was further reduced by pacing and balloon inflation from 11.4 ± 1.5 to 7.6 ± 1.4 ml, P < 0.0025 (fig. 3). Cardiac output was also further reduced from 1.5 ± 0.3 to 1.2 ± 0.3 L/min, P < 0.025.

<table>
<thead>
<tr>
<th>TABLE 1. The Effects of Cumulative Doses of Dimethyl Propranolol</th>
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<tbody>
<tr>
<td><strong>Control</strong></td>
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<tr>
<td>------------</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
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<tr>
<td>Cardiac output (L/min)</td>
</tr>
<tr>
<td>Stroke volume (ml/beat)</td>
</tr>
<tr>
<td>Cor flow (ml/min/100 g)</td>
</tr>
<tr>
<td>AV O₂ diff. (ml/100 ml)</td>
</tr>
<tr>
<td>O₂ Extraction (%)</td>
</tr>
<tr>
<td>MV O₂ (ml/min/100 g)</td>
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</tbody>
</table>

*Statistically significant change from control, by paired t-test, N = 8.

**TABLE 2. The Effects of Dimethyl Propranolon on Myocardial Oxygen Demands**

<table>
<thead>
<tr>
<th>Dimethyl propranolol 3 mg/kg</th>
<th><strong>P</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>146 ± 8</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>151 ± 11</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>1.72 ± 0.21</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>11.4 ± 1.1</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>6.7 ± 1.1</td>
</tr>
<tr>
<td>( V_{\text{max}} ) (units/sec)</td>
<td>9.10 ± 1.05</td>
</tr>
<tr>
<td>TTI (mm Hg × min)</td>
<td>60.6 ± 6.1</td>
</tr>
<tr>
<td>Cor flow (ml/min/100 g)</td>
<td>118 ± 24</td>
</tr>
<tr>
<td>AV O₂ diff (ml/100 ml)</td>
<td>11.2 ± 1.0</td>
</tr>
<tr>
<td>O₂ extraction (%)</td>
<td>57.8 ± 5.8</td>
</tr>
<tr>
<td>MV O₂ (ml/min/100 g)</td>
<td>12.0 ± 1.4</td>
</tr>
</tbody>
</table>

*Statistically significant by paired t-test, N = 11.

**Abbreviations:** LVEDP = left ventricular end-diastolic pressure; \( V_{\text{max}} \) = maximum extrapolated contractile element velocity; TTI = tension-time index; MV O₂ = myocardial oxygen consumption; Cor flow = coronary flow; AV O₂ diff = aortic-coronary sinus oxygen content difference; O₂ extraction = % myocardial oxygen extraction (\( A-V \) O₂/100).
Table 3. Comparison of the Effects Produced by Dimethyl Propranolol Before and After Restoration of Heart Rate and Aortic Systolic Pressure to Control Levels

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Dimethyl propranolol 3 mg/kg</th>
<th>Dimethyl propranolol 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>heart *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>149 ± 8</td>
<td>124 ± 7</td>
<td>150 ± 8</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>164 ± 13</td>
<td>148 ± 12</td>
<td>167 ± 13</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>2.04 ± 26</td>
<td>1.50 ± 0.28</td>
<td>1.21 ± 0.28</td>
</tr>
<tr>
<td>Stroke volume (ml/beat)</td>
<td>13.1 ± 1.2</td>
<td>&lt;0.005</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>7.9 ± 1.5</td>
<td>&lt;0.005</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>TTI (min mm Hg × min)</td>
<td>66.2 ± 9.3</td>
<td>&lt;0.005</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Cor flow (ml/min/100 g)</td>
<td>137 ± 38</td>
<td>&lt;0.025</td>
<td>NS</td>
</tr>
<tr>
<td>AVO2 diff (ml/100 ml)</td>
<td>11.4 ± 1.4</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MVO2 (ml/min/100 g)</td>
<td>13.4 ± 1.8</td>
<td>&lt;0.05</td>
<td>10.6 ± 1.9</td>
</tr>
</tbody>
</table>

*Statistical significance of change from control by paired t-test, N = 7.
†Data expressed as mean ± standard error.

Vmax had fallen after drug treatment, and then it rose slightly with increasing heart rate, blood pressure, and end-diastolic pressure, from 5.59 ± 6.8 to 6.16 ± 6.8 units/second, P < 0.05. However, it remained significantly below the control level of 7.90 ± 1.08, P < 0.05 (fig. 3).

Myocardial oxygen consumption had fallen after drug treatment to 10.6 ± 1.9 ml/min/100 g. It was not affected by restoration of control heart rate, blood pressure, and tension-time index. Myocardial oxygen consumption remained at 10.4 ± 1.5, substantially below the control level of 13.4 ± 1.8 ml/min/100 g, P < 0.0125. Myocardial blood flow and arteriovenous oxygen content difference were not changed significantly by atrial pacing and balloon inflation (fig. 4).

Discussion

In the present study, dimethyl propranolol reduced myocardial oxygen consumption and coronary blood flow. No direct vascular or metabolic effect is indicated, since no change in the aortic-coronary sinus oxygen difference or in the myocardial oxygen extraction occurred. These results suggest that the reduction in coronary flow is a response to reduced myocardial oxygen demands.

The reduction in demands was related to a decrease in heart rate and contractility, resulting in a decrease in cardiac output and tension-time index. The decrease in contractility was demonstrated both by a fall in stroke volume despite an increased left ventricular end-diastolic pressure, and by a reduction in the extrapolated contractile element velocity, Vmax.

The decrease in contractility, alone, was sufficiently pronounced to decrease myocardial oxygen demands. When heart rate and blood pressure were restored to at least control levels by pacing and aortic obstruction, oxygen consumption remained below the control value. In fact, oxygen consumption was not significantly changed by this

Figure 2. Comparison of the heart rate, systolic pressure, and tension-time index before and after dimethyl propranolol administration and then after pacing and balloon inflation. Heart rate (HR) was returned to within 1 beat/min of control, and systolic pressure (Ao Syst) was returned to within 3 mm Hg of control. These interventions increased the tension-time index to within 0.7 mm Hg × min of control. P values have been inserted between the states compared by paired t-test.

Figure 3. Comparison of the effects produced by dimethyl propranolol alone and the effects produced by dimethyl propranolol when heart rate and aortic systolic pressure were restored to control levels. Pacing and balloon inflation caused a further decrease in stroke volume, despite a further increase in left ventricular end-diastolic pressure (LVEDP). Vmax was increased slightly, but remained below the control level. P values have been inserted between the states compared by paired t-test.
manipulation. Thus, the decrease in contractility seemed the predominant factor in the reduction of myocardial oxygen demands produced by dimethyl propranolol.

These results are consistent with the observations of Kniffen et al.\(^7\) comparing the actions of propranolol and dimethyl propranolol. They found that both slowed heart rate and limited the extent of epicardial ST-segment elevation produced by experimental coronary occlusion. Whereas propranolol failed to prevent the ST-segment changes when heart rate was restored to the control value by pacing, dimethyl propranolol reduced the ST-segment changes of coronary occlusion even when heart rate was restored to the control value.

Since doses of 10 mg/kg did not block the cardiac response to isoproterenol in a previous study,\(^8\) the negative inotropic and chronotropic effects of dimethyl propranolol are probably not mediated by the beta-adrenergic system. The current experiments, therefore, indicate that dimethyl propranolol improves the balance between myocardial oxygen supply and demand primarily by a direct effect on myocardial contractility.

This negative inotropic action, together with its previously demonstrated known antagonism of ouabain-induced arrhythmias, suggests that dimethyl propranolol has retained the direct membrane actions of propranolol. However, dimethyl propranolol is unusual in that these two actions are present without demonstrable local anesthetic activity.\(^8\) Propranolol (racemic and dextroisomer) and its derivatives racemic and dextro-pronethalol, and oxprenolol, all possess antiarrhythmic, myocardial depressant, and local anesthetic actions. Compounds lacking local anesthetic actions, such as practolol and sotalol, have been shown to be ineffective against ouabain-induced arrhythmias and to be weak myocardial depressants.\(^4\)

Local anesthetics may not, however, be synonymous with cardiac membrane activity. Morales-Aquilera and Vaughan Williams have found that propranolol is only slightly more active than pronethalol as a local anesthetic.\(^5\) Yet, propranolol is three times as active, by weight, in reducing the rate of rise and degree of overshoot of the cardiac action potential. Although the effects of dimethyl propranol on cardiac cell membrane potentials and ion transport remain to be studied, its spectrum of action suggests that direct membrane activity exists in the absence of demonstrable local anesthetics.

In conclusion, N-dimethyisopropyl propranolol is a quaternary analog without significant beta-blocking or local anesthetic actions. It reduces myocardial oxygen demands, primarily by its negative inotropic effect. It may, therefore, find application in the treatment of ischemic heart disease.

References

N-dimethylisopropyl propranolol. Effects on myocardial oxygen demands.
E G Olson, A V Goodyer, R A Langou, L S Cohen and S Wolfson

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