Effect of Timolol versus Propranolol on Hypertension and Hemodynamics

WILBERT S. ARONOW, M.D., JACK FERLINZ, M.D., MICHAEL DEL VICARIO, M.D., KRISHNA MOORTHY, M.D., JOHN KING, M.D., AND JOHN CASSIDY, M.D.

SUMMARY The effect of timolol versus propranolol on hypertension, hemodynamics, and plasma renin activity was evaluated in 20 men. After two weeks of placebo, 11 men received timolol 30 to 60 mg daily, and nine men received propranolol, 240 to 480 mg daily, for five weeks in a double-blind randomized study. The 20 men then received placebo again for two weeks. Right heart catheterization was performed in all 20 patients after two weeks of the first placebo and after five weeks of timolol or propranolol. Equipotent doses of timolol and propranolol were equally effective in significantly lowering supine and upright systolic and diastolic blood pressure and heart rate recorded on an outpatient basis. Equipotent doses of timolol and propranolol caused similar hemodynamic effects including similar significant depression of cardiac index. Equipotent doses of timolol and propranolol caused similar marked depression of plasma renin activity. The hypotensive action of timolol and of propranolol was unrelated to their effect on plasma renin activity.

The mean age of the 11 men randomly assigned to timolol who completed this study was 53.0 ± 9.6 years; the mean age of the nine men randomly assigned to propranolol who completed this study was 50.0 ± 6.7 years. Four of these 11 men on timolol and two of these nine men on propranolol were black; the other 14 men were Caucasian. Three of these 11 men on timolol and three of these nine men on propranolol had electrocardiographic evidence of left ventricular hypertrophy. No other clinical differences between the two groups of patients were present.

The blood urea nitrogen, serum creatinine, serum potassium, and liver function tests were normal in all patients. The cardiothoracic ratio measured from the PA chest roentgenogram ranged from 0.46 to 0.54 in the 20 patients and was 0.52 or less in 19 of the 20 patients.

If the patients were receiving antihypertensive medication (15 of the 20 patients), this medication was stopped for at least two weeks before the onset of the control period. In the control period, the supine diastolic blood pressure ranged from 96 to 124 mm Hg and exceeded 100 mm Hg in 19 of the 20 patients. The patients remained on a normal salt diet during this study. None of the patients took any medication other than the placebos and timolol or propranolol during the study.

Supine and upright blood pressures and heart rates were recorded on an outpatient basis in all patients and the results of two blood pressures averaged in the control period, on the seventh and 13th days of the first placebo, on the seventh, 14th, 21st, 28th, and 34th days of timolol or propranolol treatment, and on the seventh and 14th days of the second placebo. The blood pressures were recorded with a Roche Arteriosonde 1216 automatic blood pressure monitor. The supine blood pressures and heart rates were recorded after 5 min of rest in that position; the upright blood pressures and heart rates were measured 2 min after standing.

The patients received two placebo capsules three times daily for the first two weeks. Then the patients received in a double-blind randomized study two 5 mg timolol capsules or two 40 mg propranolol capsules three times daily for the first week of the five weeks on timolol or propranolol therapy. The dosage of either timolol or propranolol was titrated at weekly increments or decrements of 15 mg daily of timolol and of 120 mg daily of propranolol taking into consideration the blood pressure, resting heart rate, and presence of any adverse effects. During the fifth week of timolol treatment,

PROPRANOLOL has been found to be effective as an antihypertensive agent as a single drug and especially in combination with other drugs such as diuretics or vaso-dilators. Timolol is a new beta-adrenergic blocking drug with no membrane stabilizing effect and with no intrinsic sympathomimetic activity which has also been found effective as an antihypertensive agent. Franciosa and associates reported that equipotent doses of propranolol and timolol which caused a similar degree of inhibition of amyl nitrite induced tachycardia had similar effects on lowering blood pressure and heart rate. However, after five weeks of treatment, the mean cardiac output rose slightly in six patients receiving timolol, whereas the mean cardiac output decreased significantly in 11 patients receiving propranolol. Franciosa and Freis also reported in another study that timolol administered for five weeks to 11 patients caused a significant decrease in mean supine systolic and diastolic blood pressure, a significant decrease in mean heart rate, and no significant change in cardiac output.

Therefore, we performed a double-blind randomized study to evaluate the effect of timolol versus propranolol on blood pressure, heart rate, stroke index, cardiac index, systemic vascular resistance, and other hemodynamic variables. This paper presents the data in the 20 patients who completed this study.

Materials and Methods

Twenty patients with diastolic hypertension were to complete this study. Twenty-three men received either timolol or propranolol. The mean age of the 20 men who completed this study was 52.7 ± 10.8 years. None of the patients had coronary heart disease, valvular heart disease, a history of cerebrovascular disease, a history of congestive heart failure, poor myocardial contractility, sinus bradycardia, bundle branch block, atrioventricular block, chronic obstructive lung disease, a history of bronchial asthma, allergic rhinitis, or peripheral vascular disease. Informed consent was obtained from all participants.

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Table 1. Supine and Upright Mean Blood Pressure and Heart Rate = 1 Standard Deviation during the Control Period, on the First Placebo, on Timolol, and on the Second Placebo (11 patients)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>First placebo</th>
<th>Timolol</th>
<th>Second placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 1</td>
<td>Week 2</td>
<td>Week 1</td>
<td>Week 2</td>
</tr>
<tr>
<td>Supine SBP (mm Hg)</td>
<td>171.1</td>
<td>166.4</td>
<td>165.6</td>
<td>161.7</td>
</tr>
<tr>
<td>Upright SBP (mm Hg)</td>
<td>171.6</td>
<td>168.2</td>
<td>167.1</td>
<td>162.2</td>
</tr>
<tr>
<td>Supine DBP (mm Hg)</td>
<td>109.1</td>
<td>109.1</td>
<td>103.6</td>
<td>98.1</td>
</tr>
<tr>
<td>Upright DBP (mm Hg)</td>
<td>110.9</td>
<td>111.1</td>
<td>105.6</td>
<td>102.9</td>
</tr>
<tr>
<td>Supine HR (beats/min)</td>
<td>83.1</td>
<td>81.3</td>
<td>80.7</td>
<td>64.7</td>
</tr>
<tr>
<td>Upright HR (beats/min)</td>
<td>87.8</td>
<td>85.8</td>
<td>84.2</td>
<td>65.8</td>
</tr>
</tbody>
</table>

*P < 0.001.
†P < 0.01.
‡P < 0.02.
§P < 0.05.

Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

Six patients received 30 mg daily, one patient received 45 mg daily, and four patients received 60 mg daily. During the fifth week of propranolol treatment, two patients received 240 mg daily, two patients received 360 mg daily, and five patients received 480 mg daily. The patients received during the second two weeks of placebo therapy the same number of capsules of placebo three times daily as they did during the fifth week of timolol or propranolol treatment.

On the 13th day of the first placebo and on the 34th day of either timolol or propranolol treatment, patients had their plasma renin activity measured by radioimmunoassay by Bioscience Laboratories after four hours of standing and on a normal salt intake. PA and lateral chest roentgenograms, an electrocardiogram, a complete blood count, a urinalysis, and serum sodium, potassium, chloride, calcium, blood urea nitrogen, serum creatinine, fasting blood sugar, serum alkaline phosphatase, serum bilirubin, serum albumin and total protein, and serum glutamic oxaloacetic transaminase measurements were obtained.

On the 14th day of the first placebo and on the 35th day of timolol or propranolol treatment, the patients were brought to the cardiac catheterization laboratory in the post-absorptive state without any premedication. All gave informed consent and underwent complete right heart hemodynamic evaluation, intra-arterial pressure recordings, and cardiac output determinations with the green dye indicator-dilution technique. For this purpose, an intra-arterial line was placed percutaneously in the brachial artery. Right-sided pressures and the pulmonary capillary wedge pressure were obtained with a no. 7 Courand catheter. All pressures were measured with Statham model P23Db strain gauges and recorded with an Electronics for Medicine DR-12 Simultrace recorder. Cardiac output was determined by the Lyons green dye indicator-dilution computer.

Green dye was injected into the pulmonary artery and sampled from the brachial artery. Four serial cardiac output determinations were performed and the results averaged. Heart rate was recorded at the same time, and stroke volume (stroke volume = cardiac output/heart rate) calculated. The hemodynamic measurements were made approximately 90 min after the patients had taken their morning dose of medication.

Table 2. Supine and Upright Mean Blood Pressure and Heart Rate = 1 Standard Deviation during the Control Period, on the First Placebo, on Propranolol, and on the Second Placebo (9 patients)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>First placebo</th>
<th>Propranolol</th>
<th>Second placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 1</td>
<td>Week 2</td>
<td>Week 1</td>
<td>Week 2</td>
</tr>
<tr>
<td>Supine SBP (mm Hg)</td>
<td>170.0</td>
<td>168.2</td>
<td>162.9</td>
<td>155.8</td>
</tr>
<tr>
<td>Upright SBP (mm Hg)</td>
<td>170.9</td>
<td>170.9</td>
<td>163.6</td>
<td>156.4</td>
</tr>
<tr>
<td>Supine DBP (mm Hg)</td>
<td>110.2</td>
<td>108.0</td>
<td>103.5</td>
<td>101.6</td>
</tr>
<tr>
<td>Upright DBP (mm Hg)</td>
<td>110.9</td>
<td>109.8</td>
<td>107.8</td>
<td>103.7</td>
</tr>
<tr>
<td>Supine HR (beats/min)</td>
<td>83.3</td>
<td>83.8</td>
<td>83.6</td>
<td>65.8</td>
</tr>
<tr>
<td>Upright HR (beats/min)</td>
<td>86.0</td>
<td>88.0</td>
<td>88.4</td>
<td>68.4</td>
</tr>
</tbody>
</table>

*P < 0.001.
†P < 0.01.
‡P < 0.02.
§P < 0.05.

For abbreviations see table 1.
The systemic vascular resistance and pulmonary vascular resistance were calculated by the following equations:

\[
SVR = \frac{80 \times (MAP - RAP)}{CO}
\]

\[
PVR = \frac{80 \times (MPAP - PCWP)}{CO}
\]

where \(SVR\) = systemic vascular resistance (in dynes sec cm\(^{-5}\)/m\(^2\)); \(PVR\) = pulmonary vascular resistance (in dynes sec cm\(^{-5}\)/m\(^2\)); \(PCWP\) = pulmonary capillary wedge pressure; \(MAP\) = mean arterial pressure; \(RAP\) = right atrial pressure; \(CO\) = cardiac output (liters/min); \(MPAP\) = mean pulmonary artery pressure; \(PCWP\) = pulmonary capillary wedge pressure.

The data were analyzed by our biostatistician using the \(t\)-test for correlated means in analyzing the data on timolol and on propranolol versus the placebo and the control period. The \(t\)-test for uncorrelated means was performed in analyzing the differences between timolol and propranolol. Computations were performed on the Sigma 7 computer at the University of California, Irvine.

**Results**

Twenty of 23 patients completed this study. One patient was removed from the study because he developed a transient right hemiparesis on the 33rd day of propranolol therapy. This patient's supine diastolic blood pressure was 100 mm Hg at the time of his hemiparesis. One patient was not included in this study because the cardiac output could not be obtained during the first right heart catheterization. One patient dropped out of the study after three weeks of propranolol treatment because of nausea, fatigue, and depression. The 20 patients who completed this study did not have any adverse side effects from their medication.

Table 1 indicates the supine and upright mean systolic and diastolic blood pressure and heart rate data for 11 patients on timolol. Table 2 shows the supine and upright mean systolic and diastolic blood pressure and heart rate data for nine patients on propranolol.

No significant differences in supine or upright systolic blood pressure, diastolic blood pressure, or heart rate were found between the timolol and propranolol-treated patients during any of the treatment periods.

The doses of timolol and of propranolol used in our study markedly suppressed plasma renin activity in all 20 patients. In comparison to the second week on the first placebo, five of our 11 patients on timolol (45%) and three of our nine patients on propranolol (33%) had a reduction in supine diastolic blood pressure of 10 mm Hg or greater after five weeks of drug treatment. In comparison to the second week on the second placebo, seven of our 11 patients on timolol (64%) and three of our nine patients on propranolol (33%) had a reduction in supine diastolic blood pressure of 10 mm Hg or greater after five weeks of treatment. No correlation was found between the antihypertensive action of propranolol or of timolol and the lowering of plasma renin activity. In fact, two of the three patients with the lowest plasma renin activity level on the first placebo had a 10 mm Hg or greater reduction in supine diastolic blood pressure on timolol or propranolol compared to placebo therapy.

Table 3 indicates that no significant differences between the two groups were found in the 17 variables measured.

Table 4 indicates the mean supine and upright arterial pressures for the five patients who ultimately received more than 30 mg of timolol daily. Table 4 shows similar data for the seven patients on propranolol who received more than 240 mg daily. The dose of timolol or of propranolol used did not correlate with the presence or absence of left ventricular hypertrophy or the duration of known hypertension.

**Discussion**

Our data show that 30 to 60 mg of timolol and 240 to 480 mg of propranolol were equally effective in significantly lowering systolic and diastolic blood pressure and heart rate

<table>
<thead>
<tr>
<th>Variable</th>
<th>11 patients on timolol</th>
<th>9 patients on propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 2 on first placebo</td>
<td>Week 5 on first placebo</td>
</tr>
<tr>
<td></td>
<td>Week 2 on timolol</td>
<td>Week 5 on propranolol</td>
</tr>
<tr>
<td>Syst intra-art press (mm Hg)</td>
<td>174.7 ± 17.2</td>
<td>177.1 ± 17.0</td>
</tr>
<tr>
<td>Diast intra-art press (mm Hg)</td>
<td>98.4 ± 9.8</td>
<td>93.3 ± 13.8</td>
</tr>
<tr>
<td>Mean intra-art press (mm Hg)</td>
<td>123.9 ± 13.9</td>
<td>125.7 ± 13.9</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>84.9 ± 13.3</td>
<td>63.0 ± 4.6</td>
</tr>
<tr>
<td>SI (ml/beat/m²)</td>
<td>42.6 ± 46.0</td>
<td>47.8 ± 6.6</td>
</tr>
<tr>
<td>CI (liters/min/m²)</td>
<td>3.62 ± 0.55</td>
<td>3.91 ± 0.77</td>
</tr>
<tr>
<td>SVR (cm Hg)</td>
<td>1506.4 ± 244.7</td>
<td>1709.0 ± 383.9</td>
</tr>
<tr>
<td>PVR (cm Hg)</td>
<td>114.9 ± 45.7</td>
<td>171.3 ± 38.8</td>
</tr>
<tr>
<td>PCW (mm Hg)</td>
<td>7.2 ± 3.7</td>
<td>9.7 ± 1.6</td>
</tr>
<tr>
<td>PA syst (mm Hg)</td>
<td>23.1 ± 3.1</td>
<td>22.8 ± 6.9</td>
</tr>
<tr>
<td>PA diast (mm Hg)</td>
<td>10.9 ± 3.1</td>
<td>11.8 ± 6.9</td>
</tr>
<tr>
<td>PA mean (mm Hg)</td>
<td>15.8 ± 3.9</td>
<td>18.1 ± 3.2</td>
</tr>
<tr>
<td>RV syst (mm Hg)</td>
<td>24.7 ± 4.6</td>
<td>28.1 ± 6.5</td>
</tr>
<tr>
<td>RV diast (mm Hg)</td>
<td>5.5 ± 3.4</td>
<td>5.6 ± 6.3</td>
</tr>
<tr>
<td>RA (mm Hg)</td>
<td>4.2 ± 3.5</td>
<td>3.2 ± 3.2</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>2.47 ± 0.50</td>
<td>2.06 ± 0.53</td>
</tr>
<tr>
<td>CTR</td>
<td>0.492 ± 0.018</td>
<td>0.511 ± 0.018</td>
</tr>
</tbody>
</table>

*P* values derived from \(t\)-tests comparing placebo vs drug treated periods.

**Table 3. Effect of Timolol versus First Placebo and of Propranolol versus First Placebo on Hemodynamic Parameters, Plasma Renin Activity, and Cardiothoracic Ratio**

**Discussion**

Our data show that 30 to 60 mg of timolol and 240 to 480 mg of propranolol were equally effective in significantly lowering systolic and diastolic blood pressure and heart rate
on an outpatient basis. The higher the dose, the better the antihypertensive activity of timolol or propranolol.

Although some investigators have suggested a close correlation between hyporeninemic and hypotensive action, our data support the investigators who have found that suppression of plasma renin activity by beta-adrenergic blockade is not the primary focus of the antihypertensive action. In a preliminary report, Hollifield and associates proposed a dual mechanism of action for propranolol in lowering blood pressure. A low dose effect (160 mg daily of propranolol) was associated with reduction of plasma renin activity. A high dose effect was unrelated to plasma renin activity. The conflict between our findings and those reported by Uhler and associates may be due to the fact that 1) our patients were not categorized according to plasma renin activity, whereas Uhler and associates deliberately included patients with low renin essential hypertension, and 2) the doses of propranolol used in the present study were much greater.

We did not confirm the observation reported by Franciosa and associates that in contrast to propranolol, timolol administered for five weeks does not decrease cardiac output. We found that timolol and propranolol caused a similar decrease in cardiac index (20% decrease for each drug). The reduction in cardiac index is a major factor contributing to the antihypertensive action of propranolol and timolol.

The significant decrease in cardiac index in both groups of patients reflected the significant decrease in heart rate as neither timolol nor propranolol caused a significant change in stroke index. One would normally expect an increase in stroke index to compensate for the decrease in heart rate. Therefore, one must implicate some depression of myocardial contractility in our patients receiving timolol 30 to 60 mg daily or propranolol 240 to 480 mg daily.

Systemic vascular resistance was significantly increased after five weeks of propranolol therapy (P < 0.05). This measure did not change significantly in the group on timolol. However, there was no significant difference in systemic vascular resistance between the two treatment groups.

The increasing evidence that part of the antihypertensive action of propranolol may be due to an action on the central nervous system may explain why higher dosage regimens are required to lower blood pressure than are needed to achieve effective beta-blockade. Although a significant antihypertensive effect for both timolol and propranolol was demonstrated in our patients when their blood pressures were recorded on an outpatient basis, under the stress of a second catheterization neither timolol nor propranolol effected a significant antihypertensive response. Perhaps the stress of the invasive procedure in our unmedicated patients overcame the central nervous system effect of timolol and of propranolol but not the chronotropic effect of timolol and of propranolol. This would suggest that these drugs may be ineffective in some patients with marked responses to very stressful stimuli.

In conclusion, our data show that the doses given, timolol and propranolol are equally effective in lowering systolic and diastolic blood pressure. Our data also show that equipotent doses of timolol and of propranolol cause similar hemodynamic effects including similar depression of cardiac index. Both timolol and propranolol caused marked depression of plasma renin activity. The antihypertensive action of both drugs was unrelated to their effect on plasma renin activity.

### Acknowledgment

The authors wish to express their appreciation to Jack Vangrow, M.D., Nordy Spivack, M.D., Max Warren, M.D., Wayne Laverty, M.D., and Michael Vawter, M.D., for their assistance in performing this study, to Clifford Risk, Ph.D., for biostatistical analysis of the data, and to the Clinical Research Department of Merck Sharp and Dohme Research Laboratories for supplying the placebos, timolol, and propranolol.

### References

A Study of Comparative Blood Pressure Measures in Predicting Risk of Coronary Heart Disease

RAY H. ROSENMAN, M.D., ROBERT I. SHOLTZ, M.S., AND RICHARD J. BRAND, PH.D.

SUMMARY The Western Collaborative Group Study is a prospective study of 3,154 employed men, aged 39–59 years. Coronary heart disease (CHD) occurred in 257 subjects during 8.5 years of follow-up. The multiple logistic risk model was used to assess the comparative strength of systolic, diastolic, mean arterial and pulse pressure for the prediction of CHD in two age decades after adjusting for age, serum cholesterol, cigarette smoking, behavior pattern and weight.

The risk of CHD was more strongly associated with the systolic than the diastolic pressure. The general practice of assessing the importance of blood pressure based only on the diastolic component should be reassessed.

Methods and Materials

The Western Collaborative Group Study (WCGS) is a prospective epidemiological study of 3,154 initially well men, aged 39 to 59 years at intake in 1960–61 and employed in ten California companies. Data collection was terminated with the annual re-examination in 1969, resulting in 8.5 years of follow-up. Detailed descriptions of the study population and methodology are provided in earlier reports, and only those features which are particularly relevant to the present report are again described.

The risk factors studied in the present analysis are systolic and diastolic blood pressures, serum cholesterol, cigarette smoking, age and behavior pattern since these variables were found by multivariate analysis to be significantly associated with the incidence of CHD in the WCGS population. One analysis also considered the possible effects of three measures of weight: the reported weight gain from age 25 to intake, body mass index (kg/m²), and an estimate of...
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