The Effects of a Cardioselective (Metoprolol) and a Nonselective (Propranolol) Beta-adrenergic Blocker on the Response to Dynamic Exercise in Normal Men

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SUMMARY We compared the effects of a cardioselective β-adrenergic blocking drug, metoprolol, with a nonselective β-adrenergic blocker, propranolol, on the response of 10 normal men to dynamic treadmill exercise. The volunteers underwent a standard graded exercise test to exhaustion while receiving placebo; propranolol, 40 mg every 6 hours; propranolol, 80 mg every 6 hours; metoprolol, 50 mg every 6 hours; or metoprolol, 100 mg every 6 hours. The drugs were given in a double-blind fashion for 48 hours before exercise. Five days were allowed between successive drug administrations and the order of drug administration was randomized. Heart rate, arterial pressure, oxygen consumption, minute ventilation and CO₂ production were monitored. Plasma drug concentrations were measured at the time of exercise. Judged by plasma levels, propranolol was about three times more potent than metoprolol in attenuating heart rate. Both drugs produced a wide variation in plasma levels after a given oral dose, and both drugs attenuated the systolic blood pressure response to exercise. Neither drug affected diastolic blood pressure or maximum oxygen consumption, maximum minute ventilation or the anaerobic threshold. We conclude that there is no evidence that the cardioselective drug metoprolol is superior to propranolol in terms of the ability to perform or respond to short-term maximal exercise. In addition, the fact that maximal oxygen consumption and the anaerobic threshold were unaffected implies that fatigue during exercise while on β-adrenergic blocking drugs is not due to an effect of these drugs in limiting blood flow to the exercising extremities.

THE β-ADRENERGIC blocking drugs propranolol and metoprolol are used widely in the treatment of patients with hypertension, ischemic heart disease and a variety of other conditions. Metoprolol is cardioselective, presumably avoiding the unnecessary and undesirable effects of β-adrenergic blockade in the lung and peripheral vasculature. Patients with reactive airway disease may thus tolerate metoprolol therapy better than propranolol.

However, it is not clear whether there is any advantage of cardioselective, β₁-adrenergic blockade in preserving the ability to perform or respond to exercise. β₂-Adrenergic blockade produced by propranolol, circulating epinephrine can produce unopposed, α-adrenergically mediated vasoconstriction in skeletal muscle. This
effect of propranolol might reduce exercise tolerance and provide an advantage for a cardioselective β₁-adrenergic blocking drug. Indeed, McSorley and Warren reported better preservation of blood flow to exercising skeletal muscles after metoprolol than after propranolol.9

Both drugs are being prescribed for more patients who are being encouraged to undergo exercise rehabilitation programs. Thus, effects of these two β-adrenergic blockers on exercise tolerance and the response to exercise could have therapeutic implications. Therefore, we directly compared the effects at steady state of clinically used, presumably equipotent doses of metoprolol and propranolol in maximally exercising normal men. The dose ratio of 5:4 metoprolol tartrate to propranolol hydrochloride was chosen as equipotent on the basis of several animal and human studies.8, 10, 11

Subjects and Methods

Ten healthy, active, male volunteers participated after giving informed consent. No one was taking any medication, suffered from any cardiorespiratory illness, or was a highly trained athlete. Each subject was screened with a history and physical examination, ECG, chest x-ray, complete blood count, serum electrolytes and blood urea nitrogen. The subjects ranged in age from 25–32 years (mean 27 years) and had a mean weight of 77 ± 5 kg (± SD).

After orientation to the apparatus, the subjects underwent maximal graded exercise testing using the Bruce protocol.12 At 1-minute intervals, blood pressure, heart rate, respiratory rate and volume, ECG and expired gas content were monitored. Expired gases were analyzed using a Beckman LBI CO₂ analyzer, a fuel cell O₂ analyzer and a hot-wire anemometer that fed into a dedicated Data General Micro Nova computer with hard-copy printout. From these data, the minute ventilation (V:E), oxygen consumption (VO₂), CO₂ production and anaerobic threshold were determined. The anaerobic threshold was determined by examining graphically the relationship V:E/VO₂ during exercise vs time at 30-second intervals. Two blinded observers independently identified the anaerobic threshold as the first major inflection point where V:E/VO₂ began to rise.

Five days later, each subject received one of the following preparations as unidentifiable capsules distributed in randomized, double-blind fashion: placebo; metoprolol, 50 mg (M50); metoprolol, 100 mg (M100); propranolol, 40 mg (P40); or propranolol, 80 mg (P80). The preparations were taken orally at 6-hour intervals for 48-hours. Four hours after the last dose, each subject underwent graded exercise testing, monitored as before. Blood was drawn immediately before exercise to determine the plasma concentrations of metoprolol and propranolol.

Five days later, each subject began another of the preparations, took it for 48 hours and exercised again. The sequence was continued at weekly intervals until each subject had been evaluated under the influence of each of the five preparations.

The plasma samples were analyzed for concentra-

Results

The group of 10 men had a mean supine blood pressure at rest of 121 ± 13/71 ± 6 mm Hg, and standing blood pressure at rest of 123 ± 9/77 ± 9 mm Hg. Resting heart rate was 64 ± 11 beats/min supine and 82 ± 15 beats/min standing.

The relationship between the dose of β-adrenergic blocking drug and the resulting plasma concentration obtained four hours after the last dose of a 48-hour course of medication is shown in figure 1. Both drugs showed a large scatter of the plasma concentration achieved at each dose. The mean plasma concentration at the different doses was: P40, 41.3 ± 16.9 ng/ml; P80, 111.3 ± 54.9 ng/ml; M50, 72.7 ± 56.3 ng/ml; M100, 213.2 ± 118.6 ng/ml. There was a weak correlation (r = 0.53, p < 0.05) between the plasma levels achieved on propranolol and those achieved on metoprolol at comparable doses, indicating that in general, subjects who achieve a high propranolol concentration also achieve a high metoprolol concentration.

The effect of the β-adrenergic blocking drugs on the measured responses to exercise are shown in figures 2–5 and table 1. Because only four of the subjects completed stage 5 exercise and all completed stage 4, only data from the first four stages are shown. The heart rate was decreased by both drugs at rest and during each stage of exercise (fig. 2), but there was no statistically significant difference between the two drugs at either dose. However, there was a significant (p < 0.01) relationship between the plasma concentration of the two drugs and the reduction of the tachycardia produced by maximum exercise (fig. 3). The curves for propranolol and metoprolol relating the reduction in maximum exercise tachycardia and plasma concentration were parallel, but metoprolol was significantly (p < 0.05) less potent, requiring about three times the plasma concentration to produce effects equivalent to propranolol. There was no significant correlation between the dose of propranolol and the reduction of maximum exercise tachycardia (r = 0.22) and a very weak correlation between the dose of metoprolol and reduction of maximum exercise tachycardia (r = 0.53, p < 0.05).

Both doses of both drugs reduced systolic blood pressure at rest and at all stages of exercise compared with placebo (p < 0.05) (fig. 4). The higher doses of both drugs were more effective than the lower during
stage IV exercise ($p < 0.05$), but not at rest or a lesser amount of exercise. The corresponding doses of metoprolol and propranolol had similar effects on systolic blood pressure response. Neither drug had any effect on diastolic blood pressure at rest or with exercise compared with placebo.

Neither drug consistently reduced oxygen consumption at any level of exercise (fig. 5). Exercise duration was slightly reduced by propranolol, 320 mg/day (table 1). The onset of the anaerobic threshold was unchanged by any regimen (table 1). The anaerobic threshold is the point at which oxygen consumption ceases to rise in proportion to minute ventilation. During placebo, the onset of the anaerobic threshold was $8.6 \pm 1.6$ minutes of the exercise protocol, corresponding to $59.0 \pm 13.3\%$ of maximum oxygen consumption during exercise. These values are within the normal range for healthy adults.14

Discussion
This study directly compared the effects on exercise of the cardioselective $\beta$-adrenergic blocking drug metoprolol with the nonselective drug propranolol. The ratio of doses selected (40 mg of propranolol vs 50 mg of metoprolol) produced equivalent effects on exercise tachycardia. However, when plasma concentrations of the drugs were compared, propranolol was about three times as potent as metoprolol in reducing exercise tachycardia. This was not reflected in a twofold difference in dose required because there was a very wide scatter of plasma concentrations resulting from a given dose for both drugs, and metoprolol produced plasma levels that were nearly twice those pro-

FIGURE 1. The plasma concentrations produced by propranolol (circles) and metoprolol (triangles). Standard deviations are shown.

FIGURE 2. The mean heart rate (+ SEM) at rest and at different stages of exercise during the treatment regimens: placebo; propranolol, 40 mg every 6 hours; propranolol, 80 mg every 6 hours; metoprolol, 50 mg every 6 hours; and metoprolol, 100 mg every 6 hours. Asterisk indicates a significant difference ($p < 0.05$) from placebo.
Reduced by propranolol when the drugs were given in a 5:4 ratio of metoprolol:propranolol. The pharmacokinetic variability producing the wide range of plasma concentrations is consistent with the literature for both drugs.\textsuperscript{15, 16}

The relationship between the plasma propranolol concentrations and the reduction of exercise tachycardia is similar to that described by Pine et al.\textsuperscript{17} They found that a propranolol concentration of 100 ng/ml produced an average 30% reduction in exercise tachycardia. We found that a propranolol concentration of 100 ng/ml produced an average 28% reduction in exercise tachycardia, but for metoprolol, 350 ng/ml was required to produce an equivalent effect. Like propranolol, metoprolol produced a considerable effect on exercise tachycardia even at low plasma concentrations. Thus, one-half of the effect produced by 100 ng/ml propranolol would be predicted to require only 12 ng/ml, and one-half the effect produced by 350 ng/ml metoprolol required concentrations of only 35 ng/ml. This flat dose-response relationship for these two drugs allows the duration of \( \beta \)-adrenergic blockade to persist much longer than the half-life of the drugs.

Both drugs produced equivalent dose-related effects on the systolic blood pressure response to dynamic exercise, indicating that cardioselectivity does not confer an advantage in this circumstance despite the known increase in circulating epinephrine concentrations during exercise. These findings disprove the hypothesis that unopposed \( \alpha \)-adrenergic stimulation in the face of blockade of peripheral vascular \( \beta \)-adrenergic receptors might lead to higher blood pressures during propranolol than during metoprolol. Equivalent effects of the two drugs on the blood pressure response to dynamic exercise have also been reported by Leenen et al.\textsuperscript{17} and Clausen et al.\textsuperscript{18}

The anaerobic threshold is a reflection of the adequacy of perfusion to exercising muscles. It is the point at which oxygen demand of the muscles outstrips the oxygen supply. At this point, anaerobic glycolysis occurs with the production of lactic acid. Conditions of low cardiac output and peripheral blood flow cause the anaerobic threshold to occur earlier; conditions that improve blood flow, such as aerobic conditioning, delay the onset of the anaerobic threshold.\textsuperscript{18} Since both metoprolol and propranolol reduce cardiac output at rest and with exercise,\textsuperscript{6} both drugs might be expected to hasten the onset of the anaerobic threshold. Propranolol might also be expected to result in peripheral vasoconstriction, further hastening the onset of the anaerobic threshold; but this was not observed. The anaerobic threshold was unaffected by either drug, suggesting that blood flow to the exercising muscles was preserved. Presumably, local autoregulation and increases in oxygen extrac-
tion by the muscles overcame both the relative decrease in overall cardiac output as well as propranolol-induced peripheral β-adrenergic blockade. These same mechanisms may explain the minimal effect of these drugs on maximal exercise ability and maximum oxygen consumption. These latter findings agree with some reports in the literature.6,7 However, other reports indicate that β-adrenergic blockade may decrease both exercise tolerance and maximal oxygen consumption.1,8 Differences may be due to different effects of single-dose vs multiple-dose β-adrenergic blockade or to the use of hypertensive subjects instead of normal subjects. Our subjects clearly were at maximal exercise during placebo, as indicated by the mean maximum heart rate of 190.7 ± 13.2 beats/min and VO2 max of 4.54 ± 0.84 l/min. The lack of effect of these drugs on the anaerobic threshold and maximal oxygen consumption implies that the common symptom of fatigue produced by β-adrenergic blocking drugs may not be related to hemodynamic changes that result in an inability to perform short-term dynamic exercise, but must be due to other mechanisms.

One might argue that no major differences were seen between metoprolol and propranolol because the cardioselectivity of metoprolol is largely lost, even at our lower dose of 50 mg every 6 hours, and that an advantage might have been seen at a still lower dose. However, neither drug adversely affected any measured response to exercise; it seems unlikely that lower doses would have caused the drug to show an adverse or beneficial effect.

In summary, a direct comparison of metoprolol and propranolol in normal subjects showed that propranolol was about three times as potent as metoprolol with regard to heart rate attenuation, judged by plasma levels, but the dose ratio of propranolol/metoprolol of 4:5 produced equivalent effects; both drugs showed a wide variation in plasma levels after a given oral dose, and neither drug affected maximum oxygen consumption or the anaerobic threshold. At the high dose, propranolol slightly decreased exercise duration.

We conclude that there is no evidence of superiority of the cardioselective drug metoprolol over propranolol in terms of the ability to perform or the response to short-term maximal dynamic exercise in normal persons.

Table 1. The Effects of Metoprolol and Propranolol on Exercise Measurements

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>P40</th>
<th>P80</th>
<th>M50</th>
<th>M100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise duration (min)</td>
<td>14.3 ± 1.3</td>
<td>13.7 ± 1.4</td>
<td>13.2 ± 1.0*</td>
<td>13.9 ± 1.9</td>
<td>13.8 ± 0.8</td>
</tr>
<tr>
<td>Max O2 consumption (l/min)</td>
<td>4.54 ± 0.84</td>
<td>3.93 ± 0.73</td>
<td>4.25 ± 0.48</td>
<td>4.62 ± 1.2</td>
<td>4.16 ± 0.66</td>
</tr>
<tr>
<td>Anaerobic threshold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minutes</td>
<td>8.6 ± 1.6</td>
<td>9.0 ± 1.5</td>
<td>8.7 ± 1.3</td>
<td>9.1 ± 2.0</td>
<td>8.6 ± 1.6</td>
</tr>
<tr>
<td>% VO2 max</td>
<td>59.0 ± 12.6</td>
<td>63.1 ± 11.5</td>
<td>61.9 ± 11.5</td>
<td>59.2 ± 16.0</td>
<td>59.7 ± 13.8</td>
</tr>
<tr>
<td>Max minute-ventilation (l/min)</td>
<td>165.9 ± 22.8</td>
<td>152.6 ± 12.8</td>
<td>154.3 ± 24.6</td>
<td>167.4 ± 27.6</td>
<td>152.9 ± 20.9</td>
</tr>
</tbody>
</table>

*Values are mean ± sd.
*p < 0.05 compared to placebo value.

Abbreviations: P40 and P80 = propranolol, 40 and 80 mg every 6 hours; M50 and M100 = metoprolol, 50 and 100 mg every 6 hours.
GLUCOSE AND LIPID LEVELS IN HYPERTENSION/Ames and Hill

References

Improvement of Glucose Tolerance and Lowering of Glycohemoglobin and Serum Lipid Concentrations After Discontinuation of Antihypertensive Drug Therapy

RICHARD P. AMES, M.D., AND PETER HILL, PH.D.

SUMMARY Diuretic-based antihypertensive drug therapy causes a disturbance in glucose tolerance and in serum lipid and lipoprotein concentrations. To determine the reversibility of the glucose intolerance and to identify mechanisms of the metabolic alterations, we examined a short glucose tolerance test and insulin, glycohemoglobin and lipid concentrations during the supervised withdrawal of long-term drug therapy in 35 patients with primary hypertension. An average of 7 weeks after stopping drugs, glucose tolerance and glycohemoglobin improved, total cholesterol decreased 18 mg/dl, triglyceride decreased 27 mg/dl, and the ratio of total to high-density lipoprotein cholesterol decreased ($p < 0.01$ for all variables vs treatment values). The changes in lipid concentrations from the treated to untreated state correlated with the changes in glycohemoglobin and indexes of glucose metabolism. The findings suggest that insulin resistance develops during drug therapy and disturbs both glucose and lipid metabolism. Attention to these alterations may provide directions for further control of atherosclerotic complications during the treatment of hypertension.

DIURETIC DRUGS cause a modest increase in serum lipid and lipoprotein concentrations.\textsuperscript{1-4} Beta-adrenoceptor blocking agents are reported to increase serum triglyceride and decrease high-density lipoprotein (HDL) cholesterol concentrations.\textsuperscript{7,8} These lipid and lipoprotein alterations increase the risk of myocardial infarction.\textsuperscript{9} When used alone or in combination with methylomega, diuretic drugs also impair glucose tolerance.\textsuperscript{10,11} It seems possible that the glucose and lipid disturbances are related, because there are several links in their metabolic pathways. Elevated serum glucose concentrations can raise the glycohemoglobin content of erythrocytes.\textsuperscript{12} Whether the mild carbohydrate intolerance caused by diuretic drugs is sufficient to affect glycohemoglobin has not been examined. We had an opportunity to investigate these issues during the supervised withdrawal of

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Circulation. 1982;65:894-899
doi: 10.1161/01.CIR.65.5.894
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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