Propranolol in the Treatment of Angina Pectoris

Comparison of Duration of Action in Acute and Sustained Oral Therapy

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SUMMARY  The duration of action of single oral doses of 80 and 160 mg of propranolol during acute and sustained therapy was studied in nine patients with stable, exercise-induced angina pectoris. Plasma propranolol levels peaked 2 hours after both doses during acute and sustained therapy, but there were wide variations between individuals in plasma concentration with both dosage schedules. Plasma half-lives after 80 and 160 mg were 3.99 and 4.65 hours during acute therapy and 3.46 and 6.35 hours during sustained therapy. Despite a twofold increase in plasma levels during sustained therapy, the increase in walking time to angina was similar to that seen with acute therapy. After acute administration of 80 and 160 mg propranolol, walking time to angina increased significantly compared with the values after placebo. This improvement in exercise tolerance, however, was similar after the two doses of propranolol; it appeared within 1 hour and persisted for 12 hours after both doses. Improvement in exercise tolerance was maintained over 12 hours during sustained twice-daily therapy with 80 mg propranolol. However, when the dose of propranolol was increased to 160 mg twice daily, we observed no further improvement in exercise tolerance. During both modes of therapy, the improvement in exercise tolerance was associated with significant reduction in electrocardiographic ST-segment depression. At both rest and exercise, the heart rate, systolic blood pressure and rate-pressure product decreased at 1 hour and the effects persisted for 12 hours during acute therapy and for 24 hours during sustained therapy. The circulatory effects were, however, more marked during sustained therapy. These studies show that twice-daily therapy with 80 mg propranolol should be adequate for treating patients with angina pectoris due to coronary artery disease. The improvement in exercise tolerance to be expected during sustained therapy can be assessed from the exercise studies carried out within 1–2 hours after the oral administration of single dose of 80 or 160 mg propranolol.

PROPRANOLOL IS EFFECTIVE in the management of patients with angina pectoris, and is usually prescribed in doses four times daily. Recent studies from this laboratory in patients with stable exercise-induced angina pectoris have shown that after single oral doses of 80 and 160 mg propranolol, the increase in exercise tolerance and reduction in heart rate (HR) and systolic blood pressure (SBP) at rest and during exercise persist for 12 hours. These observations suggest that propranolol administered in these doses twice daily would be effective. However, it is not known how the duration of action after single oral doses compares with those seen during sustained, twice-daily therapy. The present investigation was designed to compare the duration of action of propranolol after acute and sustained twice-daily oral therapy in patients with angina pectoris.

Methods

Nine male patients aged 45–64 years (average 53 years) with uncomplicated stable, exercise-induced angina pectoris were studied. All had significant coronary artery disease as defined by obstructive disease of > 75% luminal narrowing of one or more coronary arteries. None had suffered a myocardial infarction, was hypertensive, or had clinical or radiological evidence of cardiac enlargement or failure. The history of angina pectoris ranged from 6 months–10 years (average 44 months) and was always induced by exercise in all patients. No patient was taking medications other than sublingual nitroglycerin, and this drug was not taken on the days of the investigation. None of the patients had been treated previously with propranolol.

The resting ECG was normal in all patients. During exercise, all patients experienced angina by the beginning of stage 3 of the multistage treadmill exercise and developed ischemic ST segments characterized by horizontal or downsloping ST-segment depression, 1 mm or more of at least 0.08 sec duration in modified lead V6.

The study was explained to each patient and written informed consent was obtained. The acute and chronic phase of this study was completed by all patients, and no complications occurred.

Design of Investigation

The definitive studies were performed in the morning after an overnight fast. Patients did not smoke on the day of the study. For the acute phase of the study, each patient underwent three separate studies on a single-blind basis. On day 1, measurements were made at rest and during exercise before (control) and 1, 2, 4, 8, 12 and 24 hours after oral administration of 80 mg propranolol. On day 4 and day 7, the studies were repeated before and after 160 mg propranolol and placebo, respectively.

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The end point during exercise for the control studies was moderate angina and after placebo and propranolol administration, the end point was moderate angina or fatigue. One and one-half hours before the 4- and 12-hour studies, the patients ate a light meal without coffee.

After these acute studies, patients were treated with 80 mg of propranolol twice daily at 8 a.m. and 8 p.m. for 1 month. At the end of 1 month, studies were repeated at rest and during exercise before and 1, 2, 4, 8, 12 and 24 hours after the morning dose of 80 mg propranolol. On this day, none of the patients took the second dose of 80 mg propranolol scheduled for 8 p.m. so the effects of 12 and 24 hours after drug administration could be studied.

The dose of propranolol was then increased to 160 mg twice daily and at the end of 1 month, studies were repeated before and 1, 2, 4, 8, 12 and 24 hours after the morning dose of 160 mg propranolol. The dose scheduled for 8 p.m. on that day was omitted.

Measurements and Recordings

Modified lead V₆ of the ECG was monitored on an oscilloscope throughout the study and records were taken on a standard electrocardiograph at a paper speed of 25 mm/sec at 1-minute intervals for 3 minutes in the standing posture and at 1-minute intervals during exercise. Further records were taken at the onset of angina (P₁) and when angina became of moderate severity (P₂). The average values for HR and ST-segment depression during 10 consecutive beats were measured from the ECG, and the blood pressure was measured at 1-minute intervals at rest and during exercise. The rate-pressure product (RPP) was calculated as the product of SBP and HR, and expressed in mm Hg/min × 10⁻².

Ten milliliters of venous blood were collected at rest before each exercise period for determination of plasma propranolol concentration. Blood was collected in heparanized tubes, spun in a refrigerated centrifuge at 3000 r/min at 3°C within 15 minutes of sampling, and the plasma stored at −30°C. Plasma propranolol levels were measured according to the method described by Shand and colleagues.

Data were analyzed for statistical significance by the analysis of variance program of Biochemic Computer Programs, University of California, Los Angeles; the Minitab II program of Statistic Department of Pennsylvania State University was used for the regression analysis by the method of least squares. Wilcoxon signed rank test was used to test the significance of changes in walking time and ST-segment changes.

Results

Propranolol Plasma Concentration (fig. 1).

Acute Therapy

After acute administration, plasma propranolol concentration reached a peak at 2 hours and then declined exponentially, with an average half-life of 3.99 hours for 80 mg and 4.65 hours for 160 mg. The inter-individual variation in peak plasma propranolol

*Plasma propranolol determination carried out by Ayerst Laboratories, Montreal, Quebec, Canada.
concentration was 12- and eightfold after the 80 and 160 mg doses, respectively. Twenty-four hours after both 80 and 160 mg doses, the plasma propranolol concentration was less than 10 ng/ml in all patients.

**Sustained Therapy**

After sustained twice-daily therapy, plasma propranolol concentration before the morning dose, i.e., 12 hours after the previous dose, averaged 24.8 ± 5.5 and 60.1 ± 17.1 ng/ml (mean ± SEM) after 80 and 160 mg propranolol, respectively. Again, after the morning dose, plasma propranolol concentration reached a peak at 2 hours with both doses and then declined exponentially with an average plasma half-life of 3.46 hours after 80 mg and 6.35 hours after 160 mg. Twenty-four hours after 80 and 160 mg, the plasma propranolol concentration averaged 4.1 ± 3.4 and 19.9 ± 9.8 ng/ml, respectively. Comparison of plasma propranolol concentration during acute and sustained therapy revealed an approximately twofold increase in peak plasma concentration after both the 80 and 160 mg dosage during sustained therapy.

**Symptoms and Exercise Tolerance (fig. 2, table 1)**

None of the patients had angina at rest during the study, and none required nitroglycerin for angina precipitated by exercise testing.

**Acute Therapy**

None of the patients developed side effects from either dose of propranolol or the placebo. Exercise was discontinued because of moderately severe angina during the three control exercise periods and during the series of exercise tests after placebo administration. The treadmill walking time to the onset of angina (P1) and the time to the development of moderately severe angina (P2) were similar during the three control studies. During each exercise period after placebo, no significant change occurred in the time to P1 or P2 compared with control values. After both doses of propranolol, exercise tolerance improved in all nine patients. All patients experienced P1 after propranolol, but three did not develop P2 after 80 and 160 mg and another two did not experience P2 until exercised 12 hours after 160 mg propranolol. In these patients, exercise was discontinued because of fatigue and the exercise time to fatigue was substituted for P2. Thus, after both 80 and 160 mg propranolol, walking time to P1 and P2 increased significantly compared with the values after placebo. This improved exercise tolerance appeared within 1 hour and was unchanged for 8 hours after both doses of propranolol, compared with the corresponding placebo values (p < 0.001). Improvement in exercise tolerance at 12 hours was less marked at 12 hours, but was still significantly greater than the corresponding placebo values (p < 0.05). The group
TABLE 2. Duration of Effects of Propranolol on Heart Rate, Systolic Blood Pressure and Rate-Pressure Product After Acute and Sustained Therapy

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<td>85 ± 3</td>
<td>216 ± 15</td>
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</table>

Data represent mean ± SEM. 0 hour readings during sustained therapy are values 12 hours after the dose taken the previous evening.

Abbreviations: P1 = onset of angina pectoris; P2 = onset of moderately severe angina pectoris; PL = placebo; PR = propranolol; Ac = acute; Sus = sustained; HR = heart rate in beats/min; SBP = systolic blood pressure in mm Hg; RPP = rate-pressure product in mm Hg/min \times 10^{-4}.

mean values for walking time to P1 and P2 after 80 and 160 mg propranolol were similar.

Sustained Therapy

Eight of the nine patients noted symptomatic improvement during sustained therapy with both 80 and 160 mg twice-daily therapy with propranolol. The remaining patient felt more tired than usual and experienced loss of sexual desire. Both these symptoms disappeared when the therapy was discontinued, after the 2-month study. After sustained twice-daily therapy, the values of walking time to Pp, before the morning dose, i.e., 12 hours after the previous dose, averaged 410 ± 24 and 428 ± 14 sec after 80 and 160 mg therapy, respectively, and these values were

![Graph](http://circ.ahajournals.org/)

FIGURE 2. Duration of effects of single oral doses of 80 and 160 mg propranolol on exercise tolerance during acute and sustained twice-daily therapy. Compared with placebo values, walking time to the onset of moderate angina (Pp) increased significantly at 1 hour and persisted for 12 hours after both doses during both acute and sustained therapy. Increase in walking time was similar during acute and sustained therapy. Readings at 0 hour during sustained therapy are values 12 hours after the dose taken the previous evening.
significantly higher than the three control and placebo values during acute therapy (control propranolol 80 mg acute 322 ± 21 sec, \( p < 0.01 \); control propranolol 160 mg acute 348 ± 18 sec, \( p < 0.01 \); control placebo 302 ± 24 sec, \( p < 0.01 \)). After 1, 2, 4 and 8 hours after the administration of the morning dose of 80 mg propranolol during sustained therapy, walking time to \( P_1 \) and \( P_2 \) increased further from the pre-drug values on that day (\( p < 0.01 \)). During sustained therapy, the average walking time to \( P_1 \) and \( P_2 \) at 1, 2, 4, 8 and 12 hours after the morning dose of 80 mg propranolol was similar to the walking time at these times after a similar dose of propranolol after acute administration. After increasing the dose to 160 mg twice daily, no further increase in walking time to \( P_1 \) and \( P_2 \) occurred, compared with the values during twice-daily therapy with 80 mg propranolol. In one patient, exercise was discontinued because of fatigue. This patient had shown significant improvement in exercise tolerance after the acute administration of 160 mg propranolol.

Electrocardiographic ST-Segment Changes (table 1)

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When ST segments were assessed after propranolol at the same duration of exercise when angina had occurred during the placebo studies, there was significantly less ST depression for as long as 12 hours.

**Sustained Therapy**

During sustained therapy with 80 and 160 mg twice-daily therapy with propranolol, ST-segment depression continued to be significantly less pronounced compared with the values after acute placebo therapy. ST segments during sustained and acute therapy with propranolol were similar.

Circulatory Changes (figs. 3–5, table 2) — Heart Rate (fig. 3)

**Acute Therapy**

Resting HR in the standing position decreased significantly (\( p < 0.001 \)) after both doses of propranolol in comparison to the control values and the values after placebo and the effects persisted for 24 hours. The average HR at \( P_1 \) and \( P_2 \) were similar during the three control exercise periods and after placebo administration. Compared with the placebo, there was a significant reduction in exercise HR at both \( P_1 \) and \( P_2 \) after both doses of propranolol (\( p < 0.001 \)). This was observed at 1 hour, and the effects persisted for 12 hours after both doses. The effects on HR were more pronounced after 160 mg than after 80 mg, but the differences were not statistically significant.

**Sustained Therapy**

Following sustained twice-daily therapy, the values of resting standing HR before the morning dose, i.e.,
12 hours after the previous dose, averaged 67 ± 5 and 63 ± 3 beats/min after 80 and 160 mg therapy, respectively, and these values were significantly lower than the three control and placebo values during the acute therapy (p < 0.01). After the morning dose of 80 and 160 mg propranolol, no further reduction in resting HR was observed. Values of resting HR during sustained therapy with propranolol were similar to those after a single oral dose of the drug.

The values of HR at P1 and P2 before the morning dose, i.e., 12 hours after the previous dose of propranolol during sustained therapy, were significantly lower than the three control and placebo values during acute therapy (p < 0.01). After the morning dose of 80 mg propranolol during sustained therapy, HR to P1 and P2 decreased further at 1 and 2 hours by only a few beats from the pre-drug values at P1 and P2 on that day. On increasing the dose to 160 mg propranolol twice daily, HR before and after the morning dose at P1 and P2 were significantly lower at any time than the values after the 80-mg dose during sustained therapy (p < 0.05). During exercise, HR at both P1 and P2 was lower at 1, 2, 4, 8, 12 and 24 hours during sustained therapy than the values during acute therapy with propranolol (p < 0.05).

Blood Pressure (fig. 4).

Acute Therapy

Resting SBP in the standing position was not altered after placebo. However, after both doses of propranolol, resting SBP decreased slightly but significantly compared with the placebo values (p < 0.01).

During exercise in the three control studies and after placebo administration, SBP increased in all patients from the resting values (p < 0.001). The values of SBP at P1 and P2 were similar during the three control and placebo studies. After both doses of propranolol, SBP was significantly reduced at both P1 and P2 compared with the placebo values at P1 and P2 (p < 0.001). The reduction in SBP was similar after the two doses of propranolol, and was present at 1 hour after drug administration and persisted for at least 12 hours.

Sustained Therapy

After sustained twice-daily therapy, the values of resting SBP before the morning dose, i.e., 12 hours after the previous dose of propranolol, were significantly lower than the control and placebo values during the acute therapy (p < 0.05). After administration of the morning dose of 80 and 160 mg propranolol, further small but significant reductions in resting SBP occurred compared with the pre-drug values (p < 0.05). The values of SBP at P1 and P2 before the morning dose, i.e., 12 hours after the previous dose of propranolol, during sustained therapy were significantly lower than the three control and placebo values during acute therapy (p < 0.01). After the morning dose of 80 mg propranolol during sustained therapy, no further significant reduction in SBP occurred from the pre-drug values at P1 and P2. On increasing the dose to 160 mg twice daily, the values of SBP at any given time after the dose were similar to the values after the 80-mg dose during sustained therapy.
PROPRANOLOL IN ANGINA PECTORIS/Thadani and Parker

**PROPRANOLOL 80mg**

- Placebo
- Acute
- Sustained

**PROPRANOLOL 160mg**

- Placebo
- Acute
- Sustained

**Figure 4.** Duration of effects of single oral doses of 80 and 160 mg propranolol on systolic blood pressure (SBP) at the onset of moderate angina (P2) during acute and sustained twice-daily therapy. During both modes of therapy and after both 80 and 160 mg propranolol, systolic blood pressure decreased at 1 hour and the effects persisted for 12 hours after acute therapy and for 24 hours during sustained therapy. Reduction in SBP was more pronounced during sustained therapy compared with the values during acute therapy (p < 0.05). Readings at 0 hour during sustained therapy are values 12 hours following the dose taken the previous evening.

SBP at 1, 2, 4, 8, 12 and 24 hours after the administration of the morning dose of propranolol during sustained therapy was lower than the corresponding values after acute administration of single oral doses (p < 0.05).

**Rate-Pressure Product (fig. 5)**

During both acute and sustained therapy with propranolol, RPP at P1 and P2 decreased significantly compared with the values after placebo (p < 0.01). At

**Figure 5.** Duration of effects of single oral doses of 80 and 160 mg propranolol on rate pressure product during acute and sustained twice-daily therapy at the onset of moderate angina (P2). During both modes of therapy, after both 80 and 160 mg propranolol, rate pressure product decreased at 1 hour and the effects persisted for 12 hours after acute and 24 hours after sustained therapy. Reduction in rate-pressure product was more pronounced during sustained therapy compared with the values during acute therapy (p < 0.05). Readings at 0 hour during sustained therapy are values 12 hours after the dose taken the previous evening.
any given hour during sustained therapy, the RPP was lower than the values after acute administration of the drug (p < 0.01).

Discussion

In this study we compared the duration of action of propranolol during acute and sustained therapy in patients with stable angina pectoris. The results showed that despite a twofold increase in the plasma propranolol concentration during sustained therapy, the improvement in exercise tolerance after acute and sustained oral therapy was similar. During both the acute and sustained therapy, improvement in exercise tolerance and reduction in HR, SBP, and RPP during exercise persisted for at least 12 hours.

Plasma propranolol concentration peaked at 2 hours after single oral doses of 80 and 160 mg propranolol and after sustained twice-daily therapy with similar doses of propranolol. Furthermore, there was an eight- to 12-fold inter-individual variation in plasma propranolol concentration after both acute and sustained therapy, a finding in agreement with previous reports. During acute therapy, the average plasma half-lives of 4.0 and 4.7 hours after 80 and 160 mg of oral propranolol, respectively, are longer than those previously reported after single intravenous and oral doses. During twice-daily sustained therapy, the average plasma half-life after 80 mg propranolol was only 3.5 hours, but was prolonged to 6.4 hours after 160 mg propranolol. A similar phenomenon has reportedly occurred after doses of oral propranolol every 6 hours in normal subjects and hypertensive patients. This prolongation of plasma half-life during sustained therapy with 160 mg propranolol twice daily was probably due to the saturation of the hepatic metabolic pathway.

Improved exercise tolerance after acute and sustained therapy with propranolol confirms previous reports. However, the improvement in exercise tolerance after sustained therapy was similar to that seen during acute therapy, despite a twofold increase in the plasma propranolol concentration during sustained therapy. These findings, together with the marked inter-individual variation in plasma propranolol concentration, suggest that the routine measurement of plasma propranolol concentration is of little clinical importance in the management of patients with angina pectoris.

This study demonstrates that sustained improvement in exercise tolerance in a given patient can be predicted from the results of exercise testing carried out within 1–2 hours of single doses of 80 or 160 mg propranolol, and such improvement lasts 8–12 hours. This prolonged improvement in exercise tolerance during both acute and sustained therapy suggests that propranolol could be administered twice daily, which would offer obvious advantages and should improve patient compliance. Such dose schedules have been shown to be effective in the treatment of patients with essential hypertension. In this study the improved exercise tolerance during sustained therapy with 80 mg propranolol twice daily was similar to that seen with 160 mg propranolol twice daily. These findings suggest that therapy with 80 or 160 mg propranolol twice daily should be adequate for treatment of patients with exertional angina.

In our study, during both acute and sustained therapy, the increase in exercise tolerance was associated with significant improvement in the electrocardiographic evidence of myocardial ischemia as evidenced by changes in ST-segment depression. These findings are in agreement with other investigations.

Propranolol reduces both the HR and SBP, and these effects are more pronounced during exercise. Despite a twofold increase in plasma concentration after sustained therapy, resting HR did not decrease further during sustained therapy compared with the values after acute administration of similar doses of propranolol. However, during exercise, the reduction in HR, SBP and RPP was more pronounced after sustained therapy. Despite these more marked circulatory effects during exercise after sustained therapy, the improvement in exercise tolerance was no greater than that observed after single oral doses of propranolol. During both acute and sustained therapy, angina occurred at a lower RPP after propranolol than during control exercise periods, a finding similar to previous reports. Factors responsible for the reduction in RPP at angina during propranolol therapy have been discussed elsewhere.

Our study does not provide information regarding the efficacy of twice- vs four-times daily therapy with propranolol in patients with angina pectoris, nor does it report the efficacy and side effects of treatment with propranolol at more frequent intervals, when blood levels would be more constant. However, the study demonstrates that twice-daily therapy with 80 mg propranolol would be adequate for the treatment of patients with angina pectoris due to coronary artery disease. The improvement in exercise tolerance to be expected during sustained therapy can be assessed from the exercise studies carried out within 1–2 hours of the oral administration of single dose of 80 or 160 mg propranolol. It is safe to institute therapy with such high doses in patients who have no contraindications to therapy with β-blocking drugs. If the patient does not develop bradycardia or hypotension after acute therapy, these side effects will probably not occur during sustained therapy. However, the side effects of propranolol can only be assessed properly during long-term therapy.

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