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### Research Article

The purpose of this study was to test the hypothesis that oral administration of a low dose of practolol in man produces selective beta-1 receptor blockade, whereas oral administration of a high dose blocks both beta-1 and beta-2 receptors. Normal men were studied 2-4 h after a single oral dose of practolol (1.5 or 12 mg/kg) and after placebo. Effects on beta-1 receptors were studied by measuring heart rate responses to exercise. Effects on beta-2 receptors were tested by measuring forearm vascular responses to brachial arterial infusions of isoproterenol. Neither dose of practolol altered base-line heart rate, forearm vascular resistance, and arterial pressure. Both low and high doses significantly attenuated heart rate responses to exercise. Forearm vasodilator responses to isoproterenol were attenuated by the high dose, but not the low dose, of practolol. Serum concentrations of practolol 2 h after administration of the drug and at the time of the studies of forearm vascular responses averaged  $0.5 \pm 0.1$  (SE) and  $5.9 \pm 1.0$   $\mu\text{g/ml}$  for low and high doses of practolol, respectively. The results indicate that the phenomenon of selective beta-1 receptor blockade in man is related to the dose and serum concentration of practolol selectively block beta-1 receptors; a high dose and serum concentrations block both beta-1 and beta-2 receptors.

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# Selective Beta-1 Receptor Blockade with Oral Practolol in Man

## A DOSE-RELATED PHENOMENON

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**ABSTRACT** The purpose of this study was to test the hypothesis that oral administration of a low dose of practolol in man produces selective beta-1 receptor blockade, whereas oral administration of a high dose blocks both beta-1 and beta-2 receptors. Normal men were studied 2-4 h after a single oral dose of practolol (1.5 or 12 mg/kg) and after placebo. Effects on beta-1 receptors were studied by measuring heart rate responses to exercise. Effects on beta-2 receptors were tested by measuring forearm vascular responses to brachial arterial infusions of isoproterenol. Neither dose of practolol altered base-line heart rate, forearm vascular resistance, and arterial pressure. Both low and high doses significantly attenuated heart rate responses to exercise. Forearm vasodilator responses to isoproterenol were attenuated by the high dose, but not the low dose, of practolol. Serum concentrations of practolol 2 h after administration of the drug and at the time of the studies of forearm vascular responses averaged  $0.5 \pm 0.1$  (SE) and  $5.9 \pm 1.0$   $\mu\text{g/ml}$  for low and high doses of practolol, respectively. The results indicate that the phenomenon of selective beta-1 receptor blockade in man is related to the dose and serum concentration of practolol. A low dose and serum concentration of practolol selectively block beta-1 receptors;

a high dose and serum concentration block both beta-1 and beta-2 receptors.

## INTRODUCTION

Since Ahlquist introduced the concept of alpha and beta adrenergic receptors in 1948 (1), other investigators have reported that there are subtypes of beta adrenergic receptors (2). Propranolol, the standard beta receptor antagonist, blocks both beta-1 and beta-2 receptors (3). Practolol, another beta receptor antagonist, has been reported to selectively block beta-1 receptors when administered intravenously or intra-arterially to animals and man (4-6), but recently two groups of investigators have suggested that the property of selective beta receptor blockade is not present when practolol is administered orally to man (7-8). For example, Bodem, Bramwell, Weil, and Chidsey (7) stated that practolol administered orally has equivalent blocking effects on vascular (beta-2) and cardiac (beta-1) receptors in man. In addition, Schneck, Aoki, Kroetz, and Wilson (8) observed that oral administration of practolol attenuates the fall in diastolic arterial pressure produced by isoproterenol and suggested, therefore, that it blocks vascular (beta-2) receptors.

In this study we evaluated the possibility that the property of selective beta-1 receptor blockade with oral practolol in man is related to the dose and blood level. If the affinity of practolol for beta-1 receptors is greater than affinity for beta-2 receptors, low doses and serum levels might block beta-1 receptors selectively, whereas high doses and serum levels might block both beta-1 and beta-2 receptors (9). Thus, the purpose of

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this study was to test the hypothesis that oral administration of a low dose of practolol (1.5 mg/kg) produces selective beta-1 receptor blockade, whereas oral administration of a high dose (12 mg/kg) blocks both beta-1 and beta-2 receptors in man.

## METHODS

10 normal men participated in the studies. They ranged in age from 20 to 28 yr and in body weight from 53 to 97 kg. Informed written consent was obtained from each subject. The study was approved by the University of Iowa Committees on Research Involving Human Beings and on Clinical Pharmacology and conformed to the principles of the Declaration of Helsinki.

*Experimental design.* Each subject participated in four experimental sessions at 1-wk intervals. In two sessions heart rate responses to exercise were measured after either placebo or a single dose of practolol. In two other sessions forearm vasodilator responses to isoproterenol were measured after either placebo or a single oral dose of practolol. The order of sessions was randomized, and the study was "single-blind".

Four subjects received practolol, 1.5 mg/kg orally as a single dose, and six subjects received practolol, 12 mg/kg orally as a single dose. The subjects were assigned to 1.5 mg/kg or 12 mg/kg in random order. Initially, both groups consisted of six subjects, but two subjects who were assigned to the low dose did not complete the study, and the drug was withdrawn from clinical investigation before other subjects were recruited to replace these two subjects. One of the two subjects did not complete the study because of concurrent contact dermatitis ("poison ivy") after a placebo session; the other subject completed the studies of heart rate responses, but did not complete the studies of forearm vascular responses because we were unable to cannulate his brachial arteries. The studies were performed 2-4 h after practolol and placebo because previous studies (8) in our laboratories had demonstrated that serum concentrations of practolol plateau by 2 h and remain stable until 4 h after a single oral dose.

*Heart rate responses to exercise.* Chronotropic responses to leg exercise on a bicycle ergometer were studied 2 h after placebo or practolol. The work load ranged from 240 to 420 kg/min; the work load for each subject was determined from a preliminary session and was arbitrarily selected as that load which approximately doubled the base-line heart rate. This load was then used for placebo and practolol sessions. Exercise was performed for 4 min. Heart rate was calculated during the last minute from the average R-R interval of six consecutive complexes of lead II of the electrocardiogram. Blood samples for determination of serum practolol concentration were obtained before and 2 h after practolol and placebo.

*Forearm vascular responses to isoproterenol.* Subjects were studied in the supine position in a warm room (26-27°C). Forearm blood flow was measured by venous occlusion plethysmography with a Whitney mercury-in-silastic strain gauge plethysmograph (10). A small cannula (PE 90) was inserted into a brachial artery for measurement of arterial pressure and for intra-arterial administration of drugs (11). Forearm vascular resistance was calculated by dividing mean arterial pressure (mm Hg) by forearm blood flow (ml/min  $\times$  100 ml forearm volume).

Forearm vascular responses to brachial arterial infusions of isoproterenol and nitroglycerin were obtained 2-4 h after

placebo or practolol. One forearm was studied in the placebo session, and the contralateral forearm was studied in the practolol session to avoid cannulating the same artery twice within a short period of time. Variability of responses to isoproterenol and nitroglycerin between extremities is minimal in man (11). Isoproterenol was infused into the brachial artery in doses ranging from 6.25 to 50 ng/min. Nitroglycerin, used as an internal dilator control, was infused in doses ranging from 0.625 to 5  $\mu$ g/min. Four doses of each drug were given to each subject. The doses were given sequentially with each dose administered for 4 min. The order of administering isoproterenol and nitroglycerin was randomized. 20 min separated administration of the two drugs to allow return to base-line values. All doses of both drugs were given into the brachial artery in 5% dextrose and water at 0.6 ml/min; previous studies in our laboratory have demonstrated that this rate of infusion of dextrose and water alone does not alter forearm blood flow (12). Nitroglycerin was dissolved in 5% dextrose and water, pH was adjusted to 7.40, and the solution passed through a millipore filter. Observations were obtained during the last minute of each dose. In each subject, responses to three of the four doses of isoproterenol and nitroglycerin given after placebo were contrasted with responses to equivalent doses given after practolol. The three doses of isoproterenol and nitroglycerin which produced graded and approximately equivalent responses were selected for analysis. The three doses are referred to as "low, middle, and high" in the results; the low dose of isoproterenol was 6.25 or 12.5 ng/min; the low dose of nitroglycerin was 0.625 or 1.25  $\mu$ g/min. The middle dose was twice the low dose, and the high dose was twice the middle dose. Venous blood samples for serum practolol levels were obtained before practolol and placebo and also 2 and 4 h after treatment (before and after the experimental procedures, respectively).

*Measurement of serum practolol.* The spectrophotometric procedure described by Fitzgerald and Scales (13) was used. Blanks were prepared with serum samples obtained before practolol and placebo for each individual.

*Statistical analysis.* Student's *t* test for paired data and analysis of variance were used to establish the effects of treatments (14). A value of "*P*" less than 0.05 was selected as the level of statistical significance.

## RESULTS

*Effects of oral practolol on heart rate.* Practolol did not alter resting heart rate (Table I). Both low and high doses of practolol significantly attenuated the chronotropic responses to exercise (Fig. 1). The extent of blockade of tachycardia with the high dose was not significantly greater than that obtained with the low dose.

*Effects of oral practolol on forearm vessels.* Neither dose of practolol altered base line mean arterial pressure, forearm blood flow, or forearm vascular resistance (Table I).

The low dose of practolol did not alter forearm vasodilator responses to isoproterenol (Fig. 2). Responses to nitroglycerin tended to be less after the low dose of practolol, but were not significantly different from those after placebo.

TABLE I  
Effects of Practolol on Resting Values

	Group 1*		Group 2†	
	Placebo	Practolol (1.5 mg/kg)	Placebo	Practolol (12 mg/kg)
Heart rate, beats/min	75±3	81±3	74±3	70±3
Mean systemic arterial pressure, mm Hg	87.5±0.9	91.5±5.1	89.6±3.2	87.6±4.8
Forearm blood flow, ml/min per 100 ml	6.7±0.9	6.3±1.3	5.7±0.5	5.4±0.5
Forearm vascular resistance, U	14.1±2.2	16.1±2.7	16.9±1.3	17.2±1.6

\* n = 4.

† n = 6.

Entries are mean ± SE.

Values after practolol did not differ significantly from values after placebo.

The high dose of practolol attenuated forearm vasodilator responses to isoproterenol, but did not alter forearm vascular responses to nitroglycerin (Fig. 3).

*Effects of practolol in relation to serum concentration.* At the time of the studies of heart rate responses to exercise (2 h after practolol), serum practolol concentration averaged 0.9±0.1 (SE) and 5.9±1.2 µg/ml after the low and high doses, respectively.

At the study of forearm vascular responses, serum practolol concentration was measured 2 and 4 h after

practolol; these measurements bracketed the period during which forearm vascular responses were obtained. The serum levels after the low dose were 0.5±1.0 at 2 h and 0.6±0.1 µg/ml at 4 h. The serum levels after the high dose were 5.9±1.0 at 2 h and 5.6±0.4 µg/ml at 4 h. Values at 2 and 4 h did not differ significantly. In addition, these levels did not differ significantly from those observed in the studies of heart rate responses to exercise.

The relationships between serum practolol levels and the effects of practolol on cardiac (chronotropic) and vascular responses are shown in Fig. 4. Low serum concentrations of practolol produced 40% blockade of the heart rate response to exercise, but did not alter forearm vasodilator responses to isoproterenol. In contrast, high concentrations of serum practolol were associated with equivalent blockade of cardiac and vas-

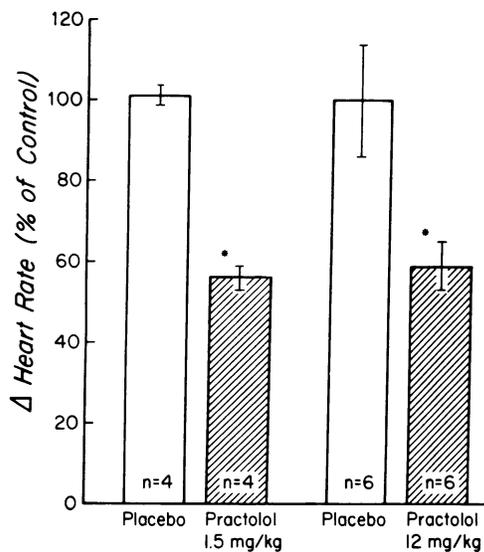


FIGURE 1 Effects of low dose (1.5 mg/kg) and high dose (12 mg/kg) of practolol on heart rate responses to leg exercise. Entries are mean ± SE for changes in heart rate during exercise expressed as percent of resting values. As indicated in Table I, resting values were not significantly different after placebo and practolol. Asterisks indicate that both low and high doses of practolol significantly attenuated ( $P < 0.05$ ) heart rate responses to exercise.

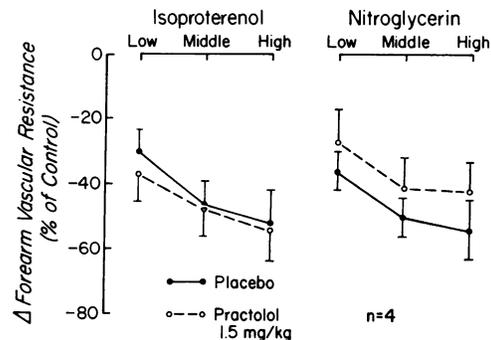


FIGURE 2 Effects of low dose (1.5 mg/kg) of practolol on forearm vasodilator responses to isoproterenol and nitroglycerin. Entries are mean ± SE for changes in forearm vascular resistance expressed as percent of resting values. As indicated in Table I, resting values were not significantly different after placebo and practolol. Analysis of variance indicated no significant difference ( $P > 0.05$ ) between responses after placebo and after practolol.

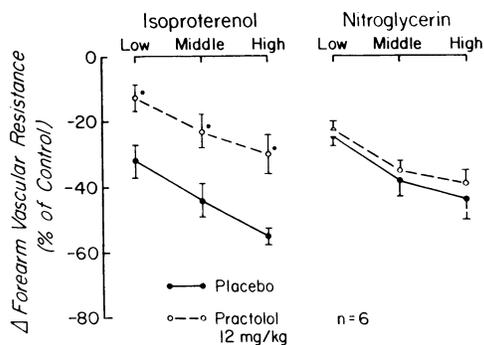


FIGURE 3 Effects of high dose (12 mg/kg) of practolol on forearm vasodilator responses to isoproterenol and nitroglycerin. Entries are mean  $\pm$  SE. As indicated by asterisks, analysis of variance indicated that responses to isoproterenol were significantly less ( $P < 0.05$ ) after practolol than after placebo. Responses to nitroglycerin after placebo and practolol did not differ significantly ( $P > 0.05$ ).

cular responses. The degree of blockade of the exercise-induced tachycardia with the high serum concentration was not greater than the blockade obtained with the low serum concentration (Fig. 4).

## DISCUSSION

The major finding in this study is that the phenomenon of selective blockade of beta-1 receptors by practolol in man is related to dose and serum concentration of the drug. A low dose and serum concentration of practolol selectively block beta-1 receptors; a high dose and serum concentration block both beta-1 and beta-2 receptors.

Effectiveness of blockade of heart rate responses (beta-1) responses to exercise with the high dose (serum level  $5.9 \pm 1.2 \mu\text{g/ml}$ ) was not significantly greater than effectiveness of blockade with the low dose (serum level  $0.9 \pm 0.1 \mu\text{g/ml}$ ). In several previous studies (7, 8, 15) increments in serum practolol level from approximately 0.6 to 2.5  $\mu\text{g/ml}$  have been associated with slight increases in effectiveness of blockade of heart rate responses to exercise. The point we would emphasize from this and the previous studies is that serum levels of 0.6–1.0  $\mu\text{g/ml}$  associated with the low dose produce maximal or at least nearly maximal blockade of beta-1 responses (7, 8, 15). Consequently, the increment of beta-1 receptor blockade, which results from increasing the serum level above 1.0  $\mu\text{g/ml}$ , is small compared to the increment derived from increasing the serum level from zero to 1.0  $\mu\text{g/ml}$ .

Forearm vasodilator responses to isoproterenol were not altered by the low dose of practolol (Fig. 2), but vasodilator responses to nitroglycerin tended to be less after the low dose of practolol than after placebo (Fig. 2). It should be noted that this tendency was weighted

by results in one subject. We doubt that the tendency for decreased responses to nitroglycerin is related to a pharmacological effect of practolol since it was not consistent and was not seen with the high dose of practolol (Fig. 3). More importantly the observation does not detract from the conclusion that the low dose of practolol does not block beta-2 receptors in blood vessels, because if anything the low dose of practolol was associated with an increase, not a decrease, in responses to isoproterenol when compared to nitroglycerin.

The high dose of practolol significantly attenuated forearm vasodilator responses to isoproterenol, but did not decrease vasodilator responses to nitroglycerin. These results indicate specific blockade of vascular beta receptors (beta-2) by the high dose of practolol.

Thus, the data suggest that oral administration of a low dose of practolol (1.5 mg/kg) produces selective beta-1 receptor blockade, whereas administration of a

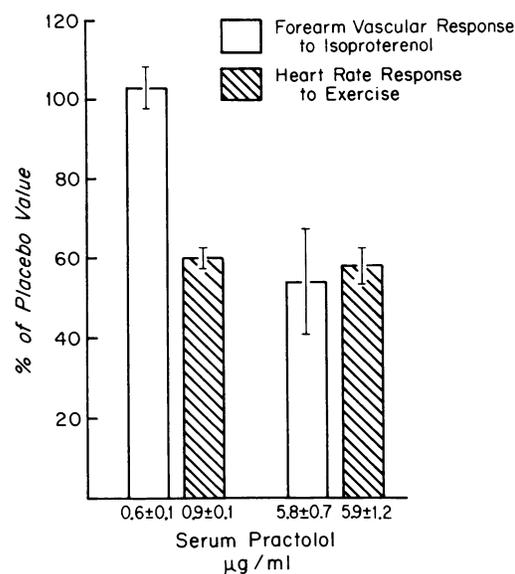


FIGURE 4 Relationship between effects of practolol and serum concentrations. Effects of practolol are shown by expressing responses after practolol as percent of responses after placebo (mean  $\pm$  SE). A value of 100% of placebo value indicates no difference between responses after placebo and practolol. A single value for the forearm vascular response to three doses of isoproterenol was obtained by calculating the area under the dose-response curve. Entries for the low serum concentrations are mean  $\pm$  SE for four subjects, and entries for the high serum concentrations are mean  $\pm$  SE for six subjects. The serum concentrations corresponding to the studies of forearm vascular responses (0.6  $\pm$  0.1  $\mu\text{g/ml}$  and 5.8  $\pm$  0.7  $\mu\text{g/ml}$  for the low and high doses of practolol, respectively) are pooled values of the 2- and 4-h measurements mentioned in the text.

high dose (12 mg/kg) blocks both beta-1 and beta-2 receptors.

In regard to these conclusions, it should be noted that the stimulus which was used to activate beta-1 receptors (exercise) in this study was different from the stimulus which was used to activate beta-2 receptors (brachial arterial infusion of isoproterenol). This raises the possibility that the difference in effects of the low dose of practolol on chronotropic and vasodilator responses might be related to a difference in the agonists and not to a difference in effects of practolol on beta-1 and beta-2 receptors. It should be noted, however, that a recent study (8) in our laboratory demonstrated that the low dose of practolol significantly attenuated chronotropic responses to isoproterenol (the agonist which was used to activate vascular beta receptors in the present study) as well as to exercise. Therefore, it seems unlikely that the difference in effects of the low dose of practolol on chronotropic and vascular responses was related to the agonists. Although the results thus suggest a difference in effects of the low dose and blood level on beta-1 and beta-2 receptors, we cannot from this study derive a quantitative figure for the relative potency of practolol on cardiac and vascular beta receptors.

Bodem et al. (7) compared effects of oral practolol on beta-1 (cardiac) and beta-2 (vascular) receptors in man and concluded that practolol produces equivalent blockade of beta-1 and beta-2 receptors. Although these investigators evaluated effects of graded doses and blood levels of practolol on beta-1 receptors, it appears that the effects on forearm vascular responses to isoproterenol (beta-2 receptors) were evaluated only at the dose which produced maximal blockade of beta-1 receptors and blood levels averaging  $2.5 \pm 0.5 \mu\text{g/ml}$ . We also found that a high oral dose and blood level of practolol produce equivalent blockade of beta-1 and beta-2 receptors, but our study indicates that a low dose and blood level block beta-1 but not beta-2 receptors. These findings demonstrate that the dose-response relationship for blockade of beta-1 receptors with practolol differs from that for beta-2 receptors, but this difference is obscured at high doses and blood levels which produce equivalent blockade of both beta-1 and beta-2 receptors.

It should be noted that conclusions regarding beta-1 receptors derived from studies of heart rate may not be completely applicable to other responses considered to be mediated by beta-1 receptors, such as lipolysis (2). For example, Sirtori, Azarnoff, and Shoeman (16) reported that a dose of oral practolol, which was similar to the low dose in our study produced nearly maximal blockade of epinephrine-induced tachycardia, but produced, little effect on epinephrine-induced lipolysis.

The results of our studies are relevant to clinical use of selective beta-receptor antagonists. For example, the property of selective beta-1 receptor blockade, as opposed to nonselective beta receptor antagonism, may be beneficial in treating patients with angina pectoris. Possible benefits include decreased incidence of bronchospasm in patients with bronchial asthma and obstructive pulmonary disease (17) and avoidance of increased vascular resistance caused by blockade of vascular beta receptors (7). Practolol has been used to treat patients with angina pectoris (18, 19). The doses frequently employed produce serum concentrations which are similar those obtained with the high dose (12 mg/kg) of practolol in our study. The present study indicates that with these high doses and serum concentrations the property of selective beta-1 receptor blockade is lost without deriving significantly greater blockade of chronotropic responses to exercise. These studies of practolol also emphasize the importance of considering effects of different doses when evaluating effects of new so-called selective beta receptor antagonists on beta-1 and beta-2 receptors in man.

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