Pharmacodynamic Studies of Beta Adrenergic Antagonism Induced in Man by Propranolol and Practolol

GUNTER BODEM, H. L. BRAMMELL, JOHN V. WEIL, and CHARLES A. CHIDSEY

From the Departments of Medicine and Pharmacology, University of Colorado
Medical Center, Denver, Colorado 80220

A B S T R A C T The pharmacodynamic activities of two beta adrenergic antagonists, propranolol and practolol, were compared in eight hypertensive patients. The activity of each antagonist was established in relation to its blood concentration at maximal and submaximal adrenergic blockade defined by inhibition of exercise tachycardia. Maximal inhibition of exercise tachycardia was comparable with both drugs and averaged 74±7% of the control value during drug treatment. This inhibition was achieved with a blood concentration of 2.5±0.4 µg/ml practolol and 0.10±0.08 µg/ml propranolol. The antagonist activities of these drugs against adrenergic stimulation with isoproterenol infusion indicated a much greater relative potency of propranolol against this stimulus, and in vivo estimates of PA_2 values differed by more than 600-fold. Relative antagonist activity of practolol during isoproterenol stimulation was equivalent both at cardiac (inotropic and chronotropic) and at vascular adrenergic receptors, whereas greater antagonist activity of propranolol was observed at vascular receptors than at cardiac receptors. Thus, the activity of practolol was not limited to cardiac receptors as previously suggested. Practolol did not reduce cardiac output at any dose level and the effect on resting blood pressure was small. Both practolol and propranolol had much greater hypotensive activity during exercise. These studies have defined the differing pharmacodynamic activities on the cardiovascular system of two effective beta adrenergic receptor antagonists and have established the blood levels of these antagonists necessary to achieve effective adrenergic blockade.

INTRODUCTION

As the therapeutic indications for pharmacologic blockade of beta adrenergic receptors are broadened, it becomes increasingly important to define the specific pharmacodynamic activity of beta adrenergic antagonists in man. This is especially the case in the hypertensive patient where beta blockade with propranolol has been shown to effectively lower blood pressure (1, 2). Such a response could be mediated by the adrenergic blocking activity of this drug or by its nonspecific cardiodepressant activity (3) which may be present when large amounts of the drug are administered (1).

Although the extent of pharmacologic blockade of beta adrenergic receptors always should be defined in patients receiving propranolol, this is often difficult to establish in the usual clinical study. Estimation of blockade involves an alteration of the heart rate response to intravenous isoproterenol or to exercise (4, 5), both of which are techniques too difficult for ready clinical applicability. However, if the extent of pharmacologic blockade were established in a group of patients and compared with dose, or better still to blood levels of the drug, one could then extend these findings to other patients similarly treated. The comparison to blood levels is particularly appropriate with propranolol where almost 10-fold differences in blood levels can be demonstrated among patients after a standard oral dose of the drug (6).

We have examined these questions in hypertensive patients where the pharmacodynamic activity of beta blockade was compared with the blood level of drug, and have contrasted our findings with propranolol to those obtained in the same patients with a new beta adrenergic antagonist, practolol. The latter drug differs from propranolol in that it has been reported to have a greater antagonist action on beta I as opposed to beta II adrenergic receptors (7). Therefore, we wished to compare further the relative activity of these two

antagonists on both cardiac (beta I) and peripheral vascular (beta II) adrenergic receptors. The potencies of the two drugs also were evaluated in terms of their activities against two types of adrenergic stimulation, isoproterenol infusion and the adrenergic activation of muscular exercise.

METHODS

Eight patients with essential hypertension were admitted to the Clinical Research Center of the University of Colorado Medical Center where they were hospitalized during the 3 wk required for these studies. They ranged in age from 23 to 49 yr, two were female, and three were Negroes. Fully informed and written consent was obtained from these patients. During this time the patients received no other drugs and were maintained on a constant dietary intake with a sodium content which varied between 60 and 120 meq/day among the individual patients. The patients were treated sequentially with both beta antagonists in increasing doses over 7 days. Practolol was given first in incremental doses of 25, 50, 100, 200, 400, and 600 mg orally at 6-h intervals. This was followed by at least a 5 day recovery period during which time control cardiovascular responses were re-established. Thereafter, propranolol was administered in incremental doses of 10, 20, 40, 60, 80, and 120 mg orally at 6-h intervals. Increases were terminated when maximum blockade was achieved or the development of bradycardia prevented further increases. Each dose level was given for 24 h before study. After stopping practolol blood samples, timed urine collections were made for 5-7 days to insure that all of the administered drug had been cleared from the body before the second study with propranolol.

Patients were studied daily 2 h after their last oral dose of beta antagonist and 1.5 h after their meal. At least three control measurements were made before giving antagonists in order to insure a consistent heart rate at rest and exercise during the last two measurements. Recovery measurements were made after practolol, and heart rates at rest and exercise were equivalent to control values. The heart rates and blood pressures are reported separately for this second control. Measurements were made at each drug level during incremental dosing. Venous blood was obtained for practolol and propranolol determination. Measurements of forearm blood flow, blood pressure, heart rate, and systolic time intervals were made after 15 min of recumbency. Then the patients' heart rate and blood pressure responses to tilt and treadmill exercise were measured. The patients walked at a 10% grade for 3-min intervals starting at 1.5 mph and increasing to their maximal tolerable exercise level at 0.5-mph increments. The minimal heart rate achieved with this exercise was 133 min⁻¹. Two normal subjects (G. B. and C. A. C.) were also studied at exercise during control and propranolol administration orally. In the patients, the hemodynamic response to isoproterenol was evaluated once during the control period and once during both practolol and propranolol administration. Isoproterenol was infused in 0.89% sodium chloride solution at 0.5 ml/min starting with an initial level of 0.001 µg/kg per min. During a saline infusion and at the incremental dose levels maintained for 6 min each (0.001, 0.003, to 1.0 µg/kg per min), we measured heart rate, blood pressure, systolic time intervals, and forearm blood flow. Isoproterenol administration was increased until an increment in heart rate of 20-30 min⁻¹ had been achieved. A minimal effective dose was considered as that amount of iso-

proterenol which produced the initial responses in heart rate (Δ HR = 20), in the pre-ejection period (PEP) of the systolic time interval (Δ PEP = 25%), or in forearm vascular resistance (Δ FVR = 25%), and which could be compared with the isoproterenol responses observed during administration of antagonist. In one patient only a 10 min⁻¹ increase occurred before the development of a transient nodal arrhythmia precluded further infusion. Cardiac output was measured in seven patients during the control period and during practolol administration.

Heart rates were obtained using precordial electrodes and polygraphic recordings of the electrocardiograms which were also monitored continually on an oscilloscope. Blood pressures were obtained by a sphygmomanometric method using an electronic technique of detecting Korotkoff sounds (model 1950, Avionics, Inc., South Bend, Ind.) and recording these with the electrocardiogram. Systolic time intervals were obtained from the simultaneously recorded electrocardiogram, phonocardiogram, and the carotid pulse; they were calculated by the method of Weissler and associates and expressed as percent of normal predicted values (8). The pre-ejection period was used as the most sensitive index of contractility change. Forearm blood flow was measured using a water plethysmograph with the venous occlusion method (9). Cardiac output was measured using the indicator dilution technique (10) with a right atrial injection of 2 ml of cardiogreen dye and sampling from an indwelling needle in the brachial artery. Blood pressure was recorded with a Clark strain gage (no. 3047) and peripheral vascular resistance calculated from cardiac output and mean blood pressure. Propranolol was measured fluorimetrically after extraction from plasma (6) and practolol was measured after extraction from plasma and urine by a fluorimetric method recently reported from this laboratory (11). Statistical analysis of the data was performed using the Wilcoxon sign rank test (12).

RESULTS

Beta receptor blockade induced by either practolol or propranolol effected a significant reduction of heart rate (Table I). These responses will be examined first at the greatest pharmacologic effect which was achieved, as described in greater detail below. With practolol, a reduction of heart rate was observed only during tilt and exercise, whereas heart rate was unchanged at rest in the supine position. On the other hand, with propranolol, heart rate was reduced significantly at rest as well as during tilt and exercise. The extent of cardiac deceleration was comparable with these two adrenergic antagonists during tilt and exercise and, in the latter condition, the blocked heart rate at "maximum" exercise averaged 74% of the average control value during both practolol and propranolol ($P < 0.001$). This level of exercise was not equivalent to the estimated physiologic maximum of the patients since none of these individuals were conditioned. At minimum exercise (1.5 mph), the inhibition of the tachycardia response was observed to be somewhat smaller with the average blocked heart rate representing 82 and 78% of the average control value with practolol and pro-

TABLE I
Heart Rate Response during Maximal Blockade with Practolol and Propranolol

Patient	Dose Pc	Pr	Basal C_1	Pc	C_2	Pr	Tilt C_1	Pc	C_2	Pr	1.5 mph C_1	Pc	C_2	Pr	Maximum C_1	Pc	C_i	Pr
	mg/day				min^{-1}								min^{-1}					
S. E.	1600	160	80	83	71	73	92	84	80	72	122	103	120	102	151	107	148	107
C. P.	200	240	69	66	76	65	88	78	98	86	95	85	109	87	133	108	140	111
S. R.	800	160	68	63	66	54	79	76	97	75	127	107	124	98	148	124	154	120
R. G.	800	80	73	76	93	69	90	87	109	80	116	92	126	86	140	104	153	102
T. S.	2400	480	81	68	77	59	92	73	94	67	117	81	111	82	163	103	158	111
P. M.	200	80	75	59	75	56	91	64	91	61	111	83	111	82	135	100	135	99
C. F.	1600	240	59	69	73	65	64	75	77	70	115	105	116	98	137	105	128	102
E. P.	800	160	57	53	60	52	64	55	70	51	85	71	89	71	145	94	147	101
Mean =	1050	200	70	67	74	62*	83	74*	90	70*	111	91‡	113	88‡	144	106‡	145	107‡

* Mean values differ significantly from control ($P < 0.05$).

‡ Mean values differ significantly from control ($P < 0.01$).

C, control; Pc, practolol; Pr, propranolol; Maximum, maximum level that the patient could be encouraged to achieve. C_2 for P. M. was not obtained and value is taken from C_1.

pranolol, respectively ($P < 0.05$, with each drug). A comparison of these exercise responses was made with those of two normal subjects in whom exercise to the true physiologic maximum was achieved. These studies indicated that the heart rate was comparably inhibited, as a fraction of the control value, at all exercise levels beyond that necessary to achieve a tachycardia of 125 min^{-1} (Fig. 1). Furthermore, the percentage blockade of control tachycardia at all rates above 125 min^{-1} was comparable at a given dose level and it became greater as increasing doses of the antagonist propranolol were administered. There was no apparent overriding of the blockade by increasing adrenergic stimuli when maximum exercise was accomplished with control heart rate of 172 min^{-1}; this was true even at a threshold dose of propranolol which had minimal pharmacologic effect (10 mg).

A comparison of the relative antagonist potency was made with practolol and propranolol during increasing dosages of each drug. The heart rate, expressed as a fraction of the control rate, decreased during "maximum" exercise as the level of antagonist in plasma increased during incremental dosing with these drugs (Fig. 2). The maximal blockade which was achieved in this study was equivalent with practolol and propranolol and approximated 25% of the control exercise heart rate. Although a plateau of the inhibitory response to propranolol was not seen as with practolol, from previous observations it appears that this is indeed a maximal or plateau level (5, 13). This maximal pharmacologic effect of the adrenergic antagonists was achieved with blood levels of practolol which averaged

2.5 ± 0.4 $\mu g/ml$ and of propranolol which averaged 0.10 ± 0.08 $\mu g/ml$. Thus, the potency of propranolol exceeds that of practolol by a factor of 25, whereas the maximal effect of the two antagonists is similar. In contrast to these blood levels, the differences between the daily doses of practolol and propranolol necessary to achieve the maximal blockade differed by only a factor of 5, 1050 mg/day for practolol and 200 mg/day for propranolol (Table I).
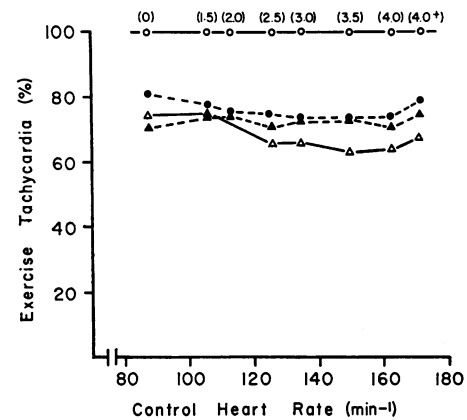

FIGURE 1 The response of heart rate to increasing amounts of propranolol at rest and during progressive exercise to the physiologic maximum heart rate in normal subject. Exercise tachycardia is expressed as a percent of the control value and plotted against the control heart rate which ranges from resting to maximum exercise values. Control (O); Propranolol, 10 mg (●), 20 mg (▲), 40 mg (△). The values in parenthesis represent the treadmill speeds (mph) at 10% grade. 4+ = 20% grade.
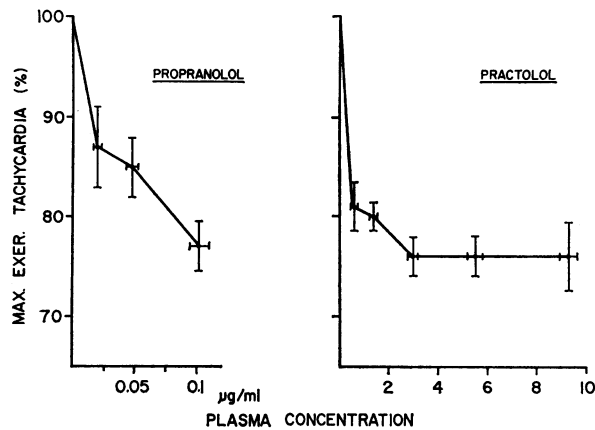
FIGURE 2 The tachycardia achieved at "maximum" exercise expressed as percent of the control value during increasing dosing of propranolol and practolol. Values are plotted against the plasma concentration of the respective antagonist. Mean values are shown with the standard error (of both response and blood level).

The antagonist activity of practolol and propranolol, in the range of doses used in these studies, was also assessed in relation to the pharmacologic adrenergic agonist, isoproterenol (Table II). The chronotropic responses of heart rate, the inotropic responses of the change in pre-ejection period, and the peripheral responses of forearm vascular resistance were all affected by these antagonists (Fig. 3). The minimal effective pharmacologic dose of isoproterenol (the minimal change in the measured variable which could be compared in control, propranolol, and practolol studies) averaged 0.015, 0.012, and 0.004 μg/kg per min, respectively at the chronotropic, inotropic, and peripheral

vascular receptors (Table II). The dose response was shifted consistently to the right during the administration of both of these competitive antagonists. However, the relative potency of propranolol appeared to differ from practolol in its capacity to antagonize isoproterenol at the three adrenergic receptors. Propranolol was much more effective in antagonizing the peripheral responses to isoproterenol than those of the cardiac receptors. These responses required 21.9 (chronotropic), > 25.0 (inotropic), and > 84.8 (vascular) times the control isoproterenol dose at these same receptors during propranolol. This differential activity was seen even when adrenergic blockade was minimal (E. P., T. S., and P. M.). In contrast practolol had a uniform effect on the receptor sites with 11.8 (chronotropic), 10.7 (inotropic), and 10.5 (vascular) times the control isoproterenol dose at chronotropic, inotropic, and peripheral receptors.

In order to compare the relative potency of practolol and propranolol as antagonists to the agonist activity of isoproterenol the shift in threshold dose of isoproterenol was related to the plasma concentration of antagonist in these patients (Fig. 4). The logarithm of the minimal effective dose displacement for the chronotropic response was plotted against the logarithm of the molar concentration of antagonist (14). It is possible that the chronotropic response during isoproterenol is influenced by vagal withdrawal as well as adrenergic stimulation from the infused agonist. However, despite our finding of the greater sensitivity of vascular receptors to isoproterenol there was little alteration of blood pressure at the minimal dose of isoproterenol which effectively increased heart rate ($\Delta HR =$

TABLE II

Influence of Practolol and Propranolol on the Dose-Response Curve to Isoproterenol

| | Dose | | Minimal effective dose of Iso. | | | Relative change of threshold | | | | | |
| | | | | | | Pc | | | Pr | | |
Patient	Pc	Pr	HR	PEP	FVR	HR	PEP	FVR	HR	PEP	FVR
	mg/day		μg/min per kg								
S. E.	1600	160	0.01	0.01	0.003	20	30	10	60	>30	100
C. P.	1600	—	0.03	0.03	0.003	10	3	10	—	—	—
E. P.	800	160	0.01	0.01	0.001	4	6	30	10	30	>300
S. R.	800	160	0.006	0.006	0.003	6.7	5	3.3	33	50	10
R. G.	2400	80	0.006	0.01	0.003	33	20	10	17	20	66.7
T. S.	800	160	0.03	0.01	0.01	3.3	10	10	3.3	10	>20
P. M.	800	80	0.02	0.01	0.003	3	6	10	10	—	30
C. F.	2400	160	0.01	0.01	0.003	10	10	10	20	10	>100
Average	1400	137	0.015	0.012	0.004	11.3	11.3	11.7	21.9	>25	>89.5

Threshold dose amount of isoproterenol (Iso.) necessary to produce the initial response of the variable; relative change = multiple of the control threshold dose; HR, heart rate; PEP, pre-ejection period; FVR, forearm vascular resistance.

20 min^{-1}). The change in mean blood pressure at that dose averaged -10 ± 1.4 ($\pm$SE) in control, -14 ± 2.1 in practolol, and $+2\pm2$ mm Hg in propranolol periods. Thus, in control and practolol periods an equivalent vagal effect may have been present in the estimate of the minimal chronotropically effective dose of isoproterenol, but this was not present in the propranolol period. This would result only in a slight overestimation of the shift of the dose-response curve to propranolol with little or no error in that to practolol. A plot of the logarithm of the dose displacement against the blood level of antagonist allows one to make an in vivo estimate of the PA$_2$ value, a value which represents the negative logarithm of the concentration of antagonist that just doubles the amount of agonist required to achieve a given effect. This in vivo estimate of PA$_2$ for practolol was 5.3 and for propranolol 8.1 indicating that $10^{-5.3}$ and $10^{-8.1}$ M concentrations of these two antagonists were required to block the receptors to this extent. Thus, propranolol has 631 times the affinity for the adrenergic receptor in relation to the agonist activity of isoproterenol.

Precise evaluation of the effect of these antagonists on blood pressure could not be made because the design of the study was not directed toward this goal. However, it is apparent that the resting blood pressure, during the lowest dose of either antagonist which produced the maximal inhibition of exercise tachycardia, was also little changed by practolol (Table III). The decline in blood pressure during practolol was small and only significant in comparison to the pretreatment control. However, there was no significant reduction in pressure in comparison to the post-treatment control, when the drug had been cleared from the body and its pharmacologic effect on heart rate was absent (Table I). During propranolol only a small hypotensive response was present at rest. However, in contrast to the minimal effects on blood pressure in the resting state both drugs strikingly reduced systolic blood pressure during "maximal" exercise. When the hemodynamic response to practolol was examined at doses equal to or exceeding that necessary for maximal pharmacologic activity, little change was observed (Table IV). Thus, cardiac output was unchanged and there was only a small reduction in blood pressure. Vascular resistance and right atrial pressure were unaffected.

DISCUSSION

These studies have defined the pharmacologic effect of two adrenergic antagonists in terms of their blood concentrations using inhibition of the adrenergic component of exercise tachycardia as one criterion of this effect. Maximal inhibition of exercise tachycardia ob-
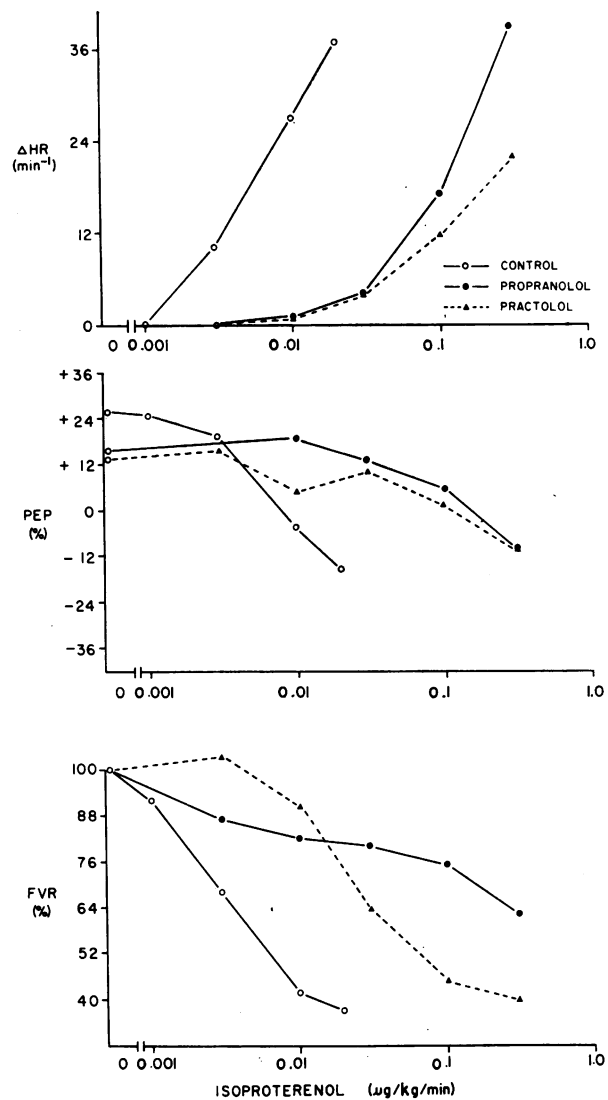

FIGURE 3 Dose-response curves to isoproterenol in a representative patient (R. G.) during the control, propranolol, and practolol periods. The change in heart rate (Δ HR) is plotted in absolute values, the pre-ejection period (PEP) is plotted as percent of normal predicated values (8), and forearm vascular resistance (FVR) as percent of values obtained immediately before isoproterenol infusion.

served in this study was achieved with a blood level of propranolol of 0.10 μg/ml whereas 2.5 μg/ml of practolol in the blood was required for the same pharmacologic effect. The value of 0.10 μg/ml of propranolol is slightly higher than 0.04 μg/ml reported by Coltart and Shand to be necessary to achieve maximal adrenergic blockade of exercise tachycardia (13). The lower blood level of Coltart and Shand may reflect the fact that their study was done after a single oral dose of the drug when there is present a pharmacologically active, 4-hydroxy metabolite not measured by the pro-
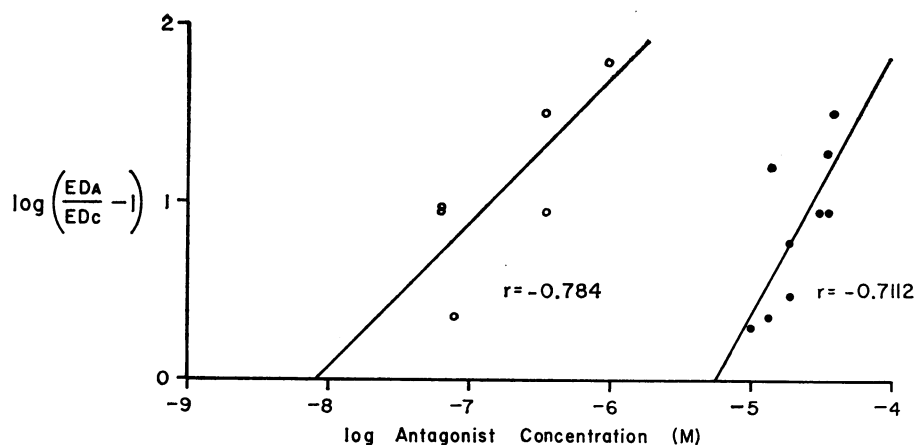
FIGURE 4 A plot of antagonist activity of propranolol ($\bigcirc$) and practolol ($\bullet$) against the concentration of drug. Antagonist activity is expressed as the logarithm of the ratio of minimum effective doses during antagonist (ED_A) and control (ED_C) minus one. Antagonist concentration is expressed as its negative logarithm. The correlation coefficients expressed are each significant ($P < 0.01$).

pranolol method (15). Since this is apparently only formed after an initial oral dose and not after multiple doses (16), it may be that our studies involving multiple dosing may define more accurately the blood concentration-pharmacodynamic relationship with chronic therapy. In contrast to these considerations of metabolites with propranolol, no such difficulty is present with practolol since this drug is not metabolically transformed.[1]

Although our patients were not exercised to their true physiological maximum, heart rate at their highest exercise level was maximally inhibited to 74% of the control value by both propranolol and practolol. Practolol clearly had achieved its greatest pharmacologic effect as a plateau in the response to this drug was observed. Despite the lack of response plateau to propranolol (Fig. 2), we inferred that its maximum effect was achieved since this response was equal to that of practolol and since this was the relative degree of block-

ade which Coltart and Shand achieved in studies where a response plateau was demonstrated for propranolol (13). The level of blockade of exercise tachycardia in our studies was greater than that achieved by earlier experiments using maximum exercise in normal subjects (5). This then appears to be the maximal inhibition of exercise tachycardia which can be achieved with adrenergic blockade. Furthermore, this adrenergic component of exercise tachycardia appeared to be a relatively constant fraction of the control heart rate at levels of exercise which generated unblocked heart rates from 125 min^{-1} to the true physiologic maximum exercise level as shown in normal control subjects (Fig. 1). Therefore, the responses which were observed in the patients can be considered to be comparable within the group despite the fact that their "maximum" exercise levels differed, producing control heart rates which varied between 133 and 163 min^{-1}.

A comparison of the pharmacologic activity of practolol and propranolol suggested a substantial difference

[1] Bodem, G., and C. A. Chidsey. Unpublished observations.

TABLE III

Average Blood Pressure during Maximal Blockade with Practolol and Propranolol

	Control (1)		Pc		Control (2)		Pr	
	S	D	S	D	S	D	S	D
Rest	138±8	97±4	129±8	89±4	130±5	90±4	120±8	83±3
Exer. (max)	196±9	79±10	143*±14	79±7	195±11	75±7	162*±13	79±5

* Values differ significantly from control ($P < 0.05$).

Exer. (max), maximum exercise; blood pressures represent the mean and standard error of systolic (S) and diastolic (D) measurements in seven patients during the same dose of adrenergic antagonist as in Table I Pc = 1050 mg/day and Pr = 200 mg/day). Control (1) obtained initially and control (2) after recovering from Pc.

TABLE IV

Hemodynamic Data before and during Practolol

Patient	BSA	Pc conc.	Heart rate		M Cardiac output		Blood pressure C		Pc		Vasc. res.		R. at. pres.	
			C	Pc	C	Pc	S/D	m	S/D	m	C	Pc	C	Pc
	m^2	$\mu g/ml$	min^{-1}		liters/min		mm Hg				PRU		mm Hg	
S. E.	1.49	13.6	76	77	3.7	4.9	125/94	113	129/83	103	30.5	21	—	—
T. S.	2.18	9.7	82	84	7.2	7.2	140/90	107	115/70	90	15	13	2.5	0.5
C. F.	2.2	13.2	79	69	6.5	6.7	173/105	135	175/105	135	21	20	3.5	3.0
E. P.	2.02	5.9	56	50	4.9	4.6	245/140	170	250/130	170	34.7	37	3.3	0
S. R.	1.85	3.9	65	59	5.5	4.9	128/80	100	133/70	85	18.2	17.3	2.5	5.0
R. G.	1.89	2.6	65	73	5.1	5.0	150/90	115	110/65	80	22.5	16	1.5	0
P. M.	2.45	2.6	89	79	7.7	7.5	143/93	108	138/88	105	14	14	1.5	0
Average		7.4	73	70	5.8	5.8	158/99	121	150/87*	110*	22.3	19.8	2.5	1.4

* Values differ significantly from control (<0.05).

Vasc. res., total peripheral resistance; R. at. pres., atrial pressure; BSA, body surface area; C, control; Pc, practolol; PRU, peripheral resistance units.

in their relative potencies depending on the adrenergic stimulus which was employed. The blockade of exercise tachycardia can be assumed to involve competitive antagonism of norepinephrine since measurements have demonstrated an increase only in this catecholamine during moderate to severe exercise (17, 18). A potency ratio based on blood concentrations of the antagonists at maximal or even submaximal effects would suggest a 25-fold difference in the drugs when compared with norepinephrine as the presumed agonist (Fig. 2). Although this comparison is not based on molar concentrations, the small differences of molecular weights of practolol and propranolol (266 and 259) make this comparison valid. A much greater difference in relative potency was observed when the response to the agonist activity of isoproterenol was examined (Fig. 3). Here, analysis of the dose-response curve displacements during antagonist administration using the method of Schild (14) indicated that the in vivo estimate of PA_2 values for the two antagonists differed by more than 600-fold. There are certain difficulties in defining accurately both the antagonist activity (due to potential effects of vagal withdrawal as discussed previously) as well as the actual concentration of agonist and antagonist at the receptor site. Although these difficulties make it necessary to qualify the PA_2 value as only an in vivo estimate, the value still retains practical utility as a reasonable approximation of the relative pharmacodynamic potency of a given antagonist. In fact, the estimate of PA_2 for propranolol by this in vivo method is very close to a previously reported value of 8.7 which was based on in vitro analyses using myocardial tissues (3). Thus, the in vivo estimated PA_2 value defines a very much greater potency of propranolol than of practolol in antagonizing isoproterenol. Although practolol has lesser potency than propranolol in antagonizing either exercise or isoproterenol-induced tachycardia, it would appear that practolol is a more effective antagonist against the chronotropic effect of neuronally released norepinephrine than against that produced by intravenously administered isoproterenol.

A definition of the relative affinities of three adrenergic receptor sites in the cardiovascular system was derived from these studies. We can conclude that receptors in the forearm resistance vessels have a fourfold greater affinity for isoproterenol than the cardiac receptors and that the chronotropic and inotropic receptors have equivalent affinities for this adrenergic agonist. It was of interest that the antagonists had potencies relative to these receptors which were somewhat different than that which would have been predicted from previous experimental animal studies (7, 19). Using the classification of beta receptors recently proposed (20), practolol had antagonist activity at the type II adrenergic vascular receptors which was equivalent to its activity at the type I adrenergic cardiac receptors. In contrast propranolol had more activity at the type II adrenergic receptor than at the type I receptor. Thus, our evidence does not support the concept that practolol is exclusively a type I adrenergic receptor antagonist and suggests greater type II antagonism for propranolol than had been previously recognized.

We have found no reduction in cardiac output at doses of practolol which produced blood levels of 2.6–13.6 $\mu g/ml$. Thus, no cardiodepression was observed even at doses in excess of those necessary to achieve

a full pharmacologic effect. These data are consistent with a recent report of Leon and associates (21).

The hypotensive activity of practolol and propranolol was most apparent during exercise when significant reduction of systolic blood pressure was observed with both antagonists. At rest neither drug reduced blood pressure greatly. These studies were not designed critically to evaluate the hypotensive activity of the antagonists, but the minimal blood pressure changes which we have observed are consistant with previously published observations (21). There was an apparent decline in blood pressure during practolol, but this may have been due to an initial adaptation to the study as seen in the fall in blood pressure between the first and second control periods (Table IV). This was not the consequence of residual practolol or its pharmacologic effect because the drug had been cleared from the body and heart rates had returned to control values (Table I). In contrast to practolol, propranolol did have a small but demonstrable hypotensive effect and this difference may relate to the cardiac output reduction seen with propranolol (2). Propranolol appears to have greater antihypertensive activity when administered chronically (1). Recent observations that propranolol inhibits renin release (22) may suggest a mechanism whereby its lowers blood pressure in the hypertensive patient. Another use of propranolol in hypertension has been suggested in its combination with vasodilators (10) and practolol might be of value with such combined therapy because of its lesser activity in antagonizing the beta receptors in the arterial resistance vessels.

ACKNOWLEDGMENTS

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