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Antihypertensive and hemodynamic effects of oxprenolol versus propranolol

Oxprenolol is an experimental beta adrenergic blocker with intrinsic sympathomimetic activity. To compare the effects of long-term administration of oxprenolol on hypertension and hemodynamics with the effects of propranolol, 20 patients with essential hypertension were divided in a double-blind random manner into two 10-patient groups and given placebo for 2 wk, followed by equipotent doses of oxprenolol or propranolol for 5 wk and by placebo for another 2 wk. Right heart cardiac catheterization was performed at the beginning and at the end of the 5-wk beta blockade. Heart rates and blood pressures fell markedly with both agents, although standing heart rate was lowered more by propranolol than by oxprenolol. Plasma renin activity was much lower after beta blockade with either drug. There was no correlation between decreases in blood pressure and renin activity. Although during the stress of repeat cardiac catheterization heart rates remained significantly lower than control, the intra-arterial pressures were not altered significantly by oxprenolol or propranolol, nor was there significant change in pulmonary pressure, vascular resistance, or cardiac output. Thus oxprenolol closely parallels the effects of propranolol in essential hypertension. The negative chronotropic action of both drugs is more marked than their antihypertensive activity.

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Oxprenolol is a relatively new beta adrenergic blocker (Fig. 1) that is still not approved for general clinical use in the United States. It has intrinsic sympathomimetic activity (ISA),[17, 19, 21, 35] and when given intravenously is reported to minimize negative inotropic effects normally seen with beta blocking agents not exerting ISA[11, 24, 45] yet may remain an effective antihypertensive[30] and antianginal agent.[29, 41, 42, 46] To compare the effects of long-term oral administration of oxprenolol on the cardiovascular system with the effects of propranolol, a beta antagonist without ISA,[13, 18] we performed a 9-wk double-blind randomized study on 20 patients with uncomplicated essential hypertension. The study was designed to compare the antihypertensive and hemodynamic effects of the 2 drugs over a prolonged period and to determine whether oxprenolol is less of a cardiac depressant than propranolol.

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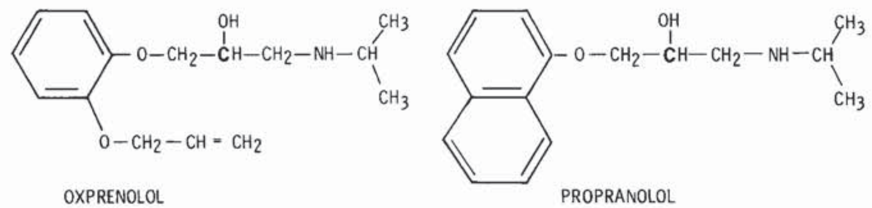

Fig. 1. Chemical structures of oxprenolol and propranolol. Presence of an active asymmetric carbon atom in the beta position gives rise to a pair of optical isomers for each drug, of which only the levo-isomer possesses beta receptor blocking activity.

Table I. *Clinical profile of patient population*

Group	Number of patients	Age (yr) (mean ± 1 SD)	Control (supine) BP readings (mean ± 1 SD)		Electrocardiogram		Cardiomegaly (CT ratio ≥ 0.50 on chest x-ray examination)
			Systolic (mm Hg)	Diastolic (mm Hg)	WNL	LVH	
Group O (oxprenolol)	10	49 ± 11	174 ± 14	113 ± 9	5 (50%)	5 (50%)	None
Group P (propranolol)	10	54 ± 4	169 ± 16	111 ± 7	8 (80%)	2 (20%)	None

CT, cardiothoracic; LVH, left ventricular hypertrophy; WNL, within normal limits.

Materials and methods

Our subjects were 20 patients with uncomplicated essential hypertension (diastolic blood pressure above 100 and below 125 mm Hg). After giving informed consent, they were divided at random into two 10-patient groups and given a placebo for 2 wk, followed by equipotent doses of oxprenolol or propranolol for 5 wk and then placebo for 2 wk. Right heart cardiac catheterization was performed before and at the end of the 5-wk beta blockade.

The clinical profile for the entire patient population is presented in Table I. None of the patients had a history of coronary or cerebrovascular disease, pulmonary disorder, congestive heart failure, or valvular or congenital heart disease. All had normal sinus rhythm with no conduction abnormality. Some of the patients were receiving antihypertensives, which were stopped at least 2 wk before the study. Close monitoring of these patients was instituted after the antihypertensives were discontinued to immediately detect potentially dangerous aggravation of hypertension. This did not occur in any of the subjects, and there were no new symptoms or complications.

The drug regimen began with placebo 3 times daily for the first 2 wk. Oxprenolol or propranolol therapy was started thereafter, 240 mg daily divided into 3 aliquots. Identical initial doses for both beta adrenergic antagonists were used, because it has been shown that oxprenolol and propranolol are approximately equipotent.[50] The dose of the beta blockers was titrated in increments or decrements of 40 mg so that the resting diastolic blood pressure was reduced by at least 10 mm Hg, and the resting heart rate was maintained above 50 bpm. After the completion of treatment with oxprenolol or propranol for 5 wk, placebo was given for 2 wk, concluding the study.

Three supine and standing blood pressures and heart rates were determined and averaged in all patients during the control period and thereafter at weekly intervals until the completion of the study. Blood pressure measurements were made with the Baum mercury-gravity manometer on an outpatient basis. The supine blood

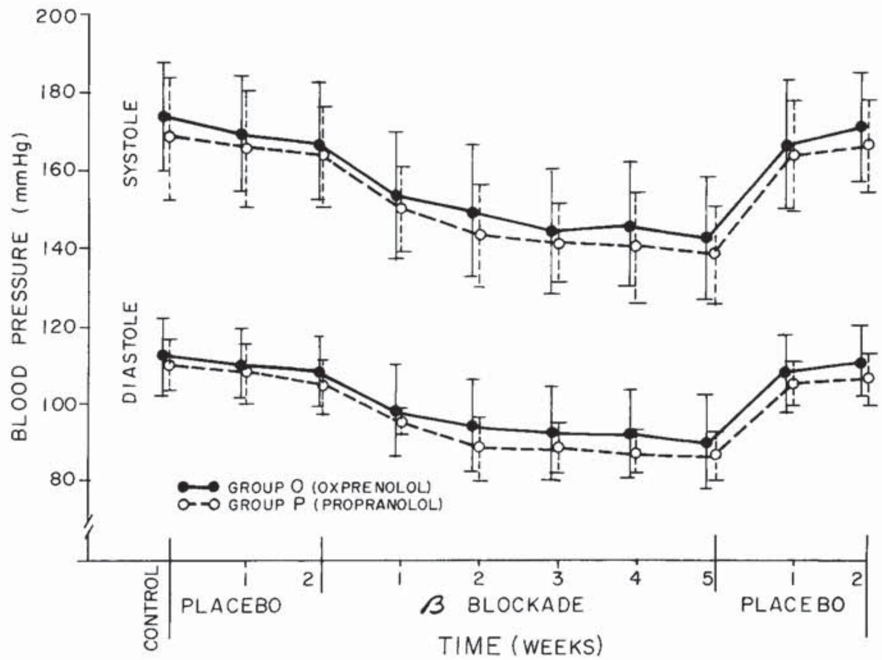

Fig. 2. Outpatient supine blood pressures during control interval, beta blockade, and 2 placebo periods. *Brackets,* ±1 SD.

pressures and heart rates were recorded after 5 min of rest at 1-min intervals and the standing pressures and rates after 2 min of relaxed standing. Right heart cardiac catheterization was performed at the end of the first placebo period and again after the completion of the 5-wk beta blockade. For this purpose all patients were hospitalized and brought to the cardiac catheterization laboratory, where hemodynamic measurements were performed in the fasting state, in the supine position, and without premedications. Cardiac output (CO) was determined with the Lyons indocyanine green indicator–dilution computer by averaging 4 sequential measurements. Cardiac index (CI) and stroke volume index (SVI) were calculated by correcting the CO for the body surface area and then dividing the results by the heart rate (HR) to obtain the SVI. All pressures—arterial (AP) systolic, diastolic, and mean; right ventricular systolic and end-diastolic; mean right atrial (RAP); mean pulmonary artery (PAP); and mean pulmonary capillary wedge pressures (PCWP)—were measured in each case with Statham model P23Db strain gauges and recorded with an Electronics for Medicine DR-12 Simultrace recorder over 3 full respiratory cycles. HR was monitored throughout. Systemic vascular resistance (SVR = [mean AP − mean RAP]/CO) and pulmonary vascular resistance (PVR = [mean PAP − mean PCWP]/CO) were calculated for each patient.

Chest x-ray films (posteroanterior and lateral) and electrocardiograms were obtained before and after the beta blockade. Blood samples for plasma renin activity (PRA) were drawn just before each catheterization. All subjects remained on their normal sodium diets and were instructed to stand for 3 hr before blood was drawn for the PRA. PRA was measured by radioimmunoassay[26] (Bio-Science Laboratories). Two blood samples for plasma oxprenolol or propranolol levels were drawn during each cardiac catheterization. The first sample was collected 90 min from the time of (theoretical or real) drug ingestion, and the second 30 min later. This timing for blood collection was selected because it has been shown that the peak effect of orally administered propranolol occurs between 90 and 120 min after ingestion[10, 55, 57]

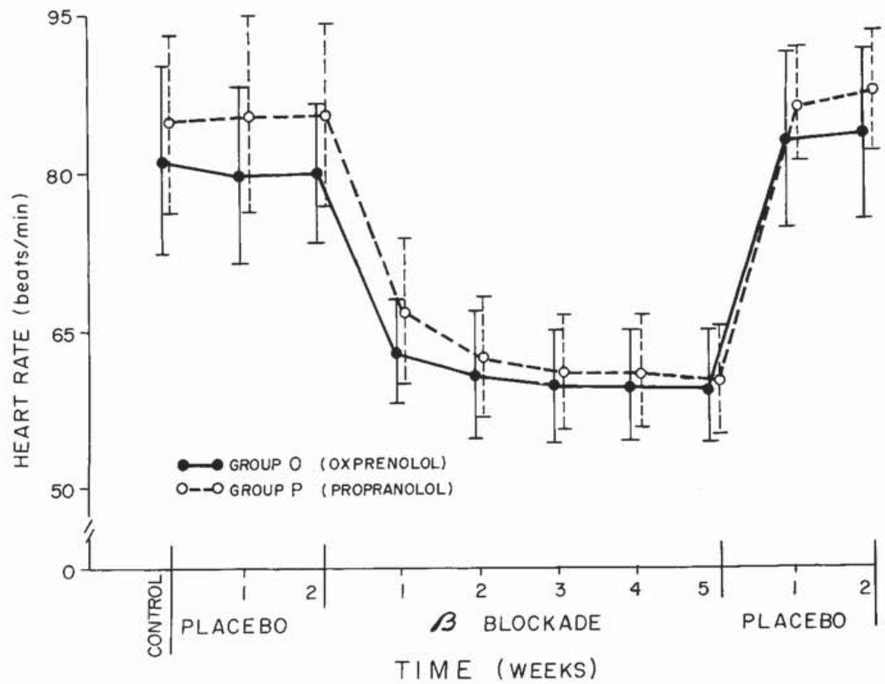

Fig. 3. Outpatient supine heart rates during control interval, beta blockade, and 2 placebo periods. *Brackets,* ±1 SD.

and that the oxprenolol plasma half-life (t½) approximates that of propranolol.[33, 48] Blood was drawn simultaneously with measurement of hemodynamic parameters. Plasma oxprenolol levels were determined by gas-liquid chromatography[15] (Ciba-Geigy) and plasma propranolol levels by high-pressure liquid chromatography[49] (Bio-Science). The results of the first and second blood samples drawn during the second cardiac catheterization were combined and averaged and then compared with the averaged results from the first cardiac catheterization. Although there was no beta blockade during the first catheterization, and plasma oxprenolol or propranolol levels determined during that period should be therefore theoretically nil, the drug level assay was performed so that the accuracy and specificity of the biochemical analysis for the 2 beta blockers could be established. Finally the arterial and central venous blood samples for the arterial-venous oxygen difference calculations were drawn just before measurement of CO.

All data were analyzed by the 2-tailed Student's t test.[12] The t test for the nonpaired variables was used in comparing intergroup oxprenolol and propranolol differences. Comparisons of data before and after beta blockade within a single group were analyzed by the t test for paired variables.

Results

None of the 20 patients who entered this study had to be removed because of adverse reactions to beta blockade, and none had to be reinstated on original antihypertensive therapy because the beta adrenergic antagonists failed to control the elevated blood pressures. The mean age of patients in the oxprenolol group was 49 ± 11 yr and in the propranolol group was 54 ± 4 yr (p, NS). Age-related changes in response to beta blockade[60] therefore had minimal (if any) effect on the results.

The decreases in systolic and diastolic blood pressures in outpatients after beta blockade with oxprenolol and propranolol were almost identical. Fig. 2 shows this over a 5-wk period of beta blockade (supine position). The individual readings during recumbence were always within ±2 mm Hg of those in the standing position, so

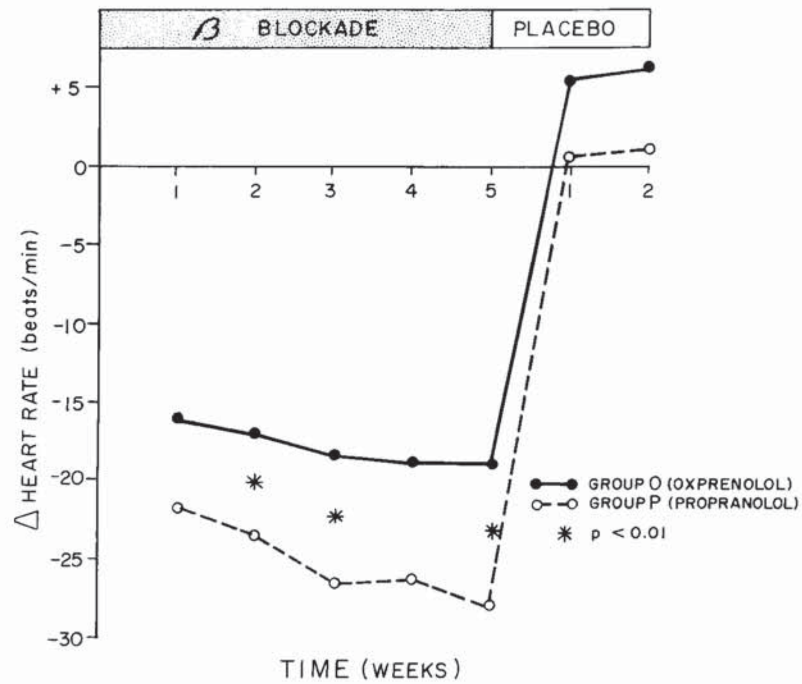

Fig. 4. Changes in standing heart rates with oxprenolol versus propranolol.

that in essence Fig. 2 effectively represents blood pressure responses for reclining and upright posture. Postural hypotension therefore is not a feature of antihypertensive therapy with either oxprenolol or propranolol.

All blood pressure readings during the 5-wk beta blockade with either drug were significantly lower than control values and those during the first 2 or the last 2 placebo weeks ($p < 0.01$). No statistically significant changes between the oxprenolol and propranolol group were detected at the beginning of the study, during the respective antihypertensive regimens, or at the end of the second placebo period when these 2 groups were compared with each other. The 2 groups therefore represented closely matched hypertensive subjects who responded to the antihypertensive effects of oxprenolol or propranolol in a virtually identical manner. If the direct comparison between the 2 groups was instituted, or if the readings at the end of the first placebo period were subtracted from the readings during each week of beta blockade and compared to adjust for possible differences that might have existed between the 2 groups at the beginning of therapy, the differences in blood pressure responses in the 2 groups were not statistically significant at any time.

Decreases in outpatient heart rates in supine position were lowered ($p < 0.01$) by beta blockade with each drug; intergroup comparison again revealed no difference between oxprenolol and propranolol (Fig. 3). In marked contrast the standing heart rates were higher ($p < 0.01$) at the end of the second, third, and fifth weeks of beta blockade with oxprenolol than with propranolol (Fig. 4). In doses that lower the elevated blood pressures as effectively as propranolol, the negative chronotropic effect of oxprenolol, at least while upright, is less prominent than that of propranolol.

The complete hemodynamic data at the end of the first placebo period and again at the end of the 5-wk beta blockade are given in Tables II and III. In contrast to a marked decrease in systolic and diastolic blood pressure on an outpatient basis after beta blockade, the intra-arterial systolic, diastolic, and mean pressures recorded during cardiac catheterization were lowered

Table II. *Hemodynamic data before and after 5 wk of oxprenolol*

Parameter	Results of first catheterization (mean ± 1 SD)	Results of second catheterization (mean ± 1 SD)	Significance (p)
Systolic AP (mm Hg)	163 ± 27	157 ± 28	NS
Diastolic AP (mm Hg)	94 ± 12	88 ± 17	NS
Mean AP (mm Hg)	122 ± 16	116 ± 21	NS
Mean RAP (mm Hg)	4 ± 3	5 ± 2	NS
Systolic RVP (mm Hg)	26 ± 4	25 ± 5	NS
RVEDP (mm Hg)	5 ± 3	5 ± 2	NS
Mean PAP (mm Hg)	16 ± 3	14 ± 4	NS
Mean PWCP (mm Hg)	9 ± 4	8 ± 3	NS
SVR (dynes-sec-cm^{-5})	1,642 ± 654	1,616 ± 830	NS
PVR (dynes-sec-cm^{-5})	106 ± 59	87 ± 39	NS
(A-V)O_2 (vol %)	4.11 ± 0.60	4.03 ± 0.55	NS
CI (l/min/m^2)	3.14 ± 0.55	3.02 ± 0.75	NS
HR at CI (bpm)	76 ± 8	66 ± 7	<0.01
SVI (ml/beat/m^2)	42 ± 9	45 ± 10	NS
PRA (ng/ml/hr)	1.83 ± 1.03	0.51 ± 0.31	<0.01
Plasma oxprenolol conc. (ng/ml)	15 ± 15	1,021 ± 393	<0.001
CTR	0.47 ± 0.02	0.49 ± 0.02	<0.02

AP, arterial pressure; (A-V)O_2, arterial-venous oxygen difference; CI, cardiac index, CTR, cardiothoracic ratio; HR, heart rate; NS, not significant; PRA, plasma renin activity; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure, RVEDP, right ventricular end-diastolic pressure; RVP, right ventricular pressure; SVI, stroke volume index; SVR, systemic vascular resistance.

only slightly and not statistically significantly. The HR, however, was maintained at a lower level ($p < 0.01$) during the second cardiac catheterization with oxprenolol and with propranolol.

All right-side pressures were essentially unchanged after beta blockade, as were pulmonary and systemic vascular resistances. CI decreased with both drugs, but the decrease was less with oxprenolol than with propranolol (NS). The arterial-venous oxygen difference, although unchanged after oxprenolol, was higher after propranolol ($p < 0.04$). SVI was virtually unchanged by the drugs despite the reduction in CI, apparently because of the concomitant reduction in HR.

PRA was lowered substantially by both beta blockers ($p < 0.01$), and by approximately equal margins. There is no correlation between systolic and diastolic blood pressures and PRA with either drug, all correlation coefficients being extremely low ($r = 0.012$ and 0.079 for oxprenolol and 0.439 and 0.032 for propranolol).

The administered oral dose of oxprenolol was 418 ± 115 mg/day and propranolol 440 ± 129 mg/day (p not significantly different). The plasma levels of the 2 drugs before treatment with either drug was started were reported to be 15 ± 15 ng/ml for oxprenolol and 10 ± 0 ng/ml for propranolol, indicating that interfering substances in plasma can lead to a false impression of active beta blocking before drug is given. Such spurious values are quite low and could therefore induce only very minor aberrations in the plasma levels obtained after 5 wk of beta blockade, when the blood concentration of both drugs was many times as high. Although both drugs climbed to substantial plasma levels, the absolute level of plasma oxprenolol (1,021 ± 393 ng/ml) was almost 5 times that of propranolol (244 ± 210 ng/ml) ($p < 0.01$).

Discussion

The use of propranolol in essential hypertension is widely accepted.[14, 22, 39, 61, 62] Although not yet accepted in the United States, oxprenolol has also been reported to be an effective antihypertensive agent in numerous studies from this country[34] and abroad.[3, 4, 25, 28, 36, 50, 53] In view of claims that oxprenolol appears to be as good as propranolol as an antihypertensive,[1] an

Table III. *Hemodynamic data before and after 5 wk of propranolol*

Parameter	Results of first catheterization (mean ± 1 SD)	Results of second catheterization (mean ± 1 SD)	Significance (p)
Systolic AP (mm Hg)	162 ± 19	158 ± 25	NS
Diastolic AP (mm Hg)	89 ± 8	83 ± 8	NS
Mean AP (mm Hg)	118 ± 9	112 ± 14	NS
Mean RAP (mm Hg)	5 ± 3	5 ± 2	NS
Systolic RVP (mm Hg)	28 ± 7	29 ± 8	NS
RVEDP (mm Hg)	5 ± 3	6 ± 3	NS
Mean PAP (mm Hg)	17 ± 6	17 ± 5	NS
Mean PCWP (mm Hg)	10 ± 2	10 ± 4	NS
SVR (dynes-sec-cm^{-5})	1,576 ± 395	1,778 ± 449	NS
PVR (dynes-sec-cm^{-5})	109 ± 62	132 ± 72	NS
(A-V)O_2 (vol %)	3.86 ± 0.63	4.36 ± 0.40	<0.04
CI (l/min/m^2)	3.07 ± 0.79	2.60 ± 0.54	NS
HR at CI (bpm)	79 ± 10	62 ± 6	<0.01
SVI (ml/beat/m^2)	39 ± 7	40 ± 7	NS
PRA (ng/ml/hr)	1.34 ± 1.07	0.42 ± 0.57	<0.01
Plasma propranolol conc. (ng/ml)	10 ± 0	244 ± 210	<0.001
CTR	0.48 ± 0.02	0.50 ± 0.01	<0.01

AP, arterial pressure; (A-V)O_2, arterial-venous oxygen difference; CI, cardiac index; CTR, cardiothoracic ratio; HR, heart rate; NS, not significant; PRA, plasma renin activity; PAP, pulmonary arterial pressure; PWCP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVEDP, right ventricular end-diastolic pressure; RVP, right ventricular pressure; SVI, stroke volume index; SVR, systemic vascular resistance.

antianginal,[41, 42] and possibly even an antiarrhythmic agent,[16, 32, 51] but with substantially less negative inotropic effects,[11, 24, 31, 45] interest in oxprenolol is understandable. Some studies, however, use CO as an index of myocardial contractility,[24, 25] ignoring the fact that CO and the contractile state of myocardium cannot be related to one another in a simple manner.[5] The extent of differences in heart disease between the 2 treatment groups (oxprenolol and propranolol) in some studies is often so great as to preclude meaningful conclusions.[24, 25] When an identical experimental preparation was used to compare the effects of oxprenolol and propranolol on myocardial function, the doses of the 2 drugs were so different as likely to cause divergent results to result from failure to use equiactive doses rather than from the true difference in biologic activity.[37] Our study shows that CI and arterial-venous oxygen difference are slightly less compromised with oxprenolol than with propranolol. That these changes indicate that oxprenolol really exerts substantially less negative inotropic effect on the myocardium than propranolol is doubtful, but it cannot be completely excluded.

The 2 drugs are unquestionably different in their effects on heart rate of patients in the standing position. The adrenergic tone is normally enhanced in the upright position, probably as a compensatory mechanism for the decrease in the cardiac filling pressure.[38] One consequence of this increased sympathetic stimulation is increase in HR. Oxprenolol is less able to block this response than propranolol, because it does not maintain low heart rates as effectively as propranolol. Observations that oxprenolol induces less resting bradycardia than propranolol were made by others.[1, 54] This property of oxprenolol may make it potentially more desirable than propranolol when the intrinsically slow heart rates preclude the use of propranolol. On the other hand, oxprenolol may not be as effective as propranolol when it is essential to mainain low heart rates.

Both oxprenolol and propranolol exerted marked antihypertensive effects on outpatient subjects, but a significant "antihypertensive" effect ($p < 0.01$) was noted after the first 2 wk on placebo regimen and before either of the 2 beta blockers was given (Fig. 2).

This experiment points to the danger of extrapolating conclusions from data obtained without taking into account the psychologic consequences of observing patients for a long period, during which each patient receives a great deal of unusual personal attention.

After the first placebo period was completed and oxprenolol or propranolol therapy started, there was additional fall in outpatient blood pressure. A clear trend of continuing decrease in the systolic and diastolic pressures throughout the 5 wk of beta blockade is seen in Fig. 2. This observation is in agreement with the observation of Prichard and Gillam[43] that antihypertensive therapy with beta blockers requires several weeks before blood pressure reaches its lowest point. Yet this substantial antihypertensive response was not maintained when the patients were brought to the cardiac catheterization laboratory for repeat examination.

Many mechanisms have been suggested to explain why beta blockers lower elevated blood pressure; among these the negative inotropic effect that lowers CO, the resetting of baroreceptors, the effect mediated through the central nervous system, decrease in renin output, reduction in venous return or plasma volume,[50] and the myogenic response of the arteriolar wall to the decreased blood flow[23] have been suggested. Although some (or most) of these mechanisms may account for the decrease in blood pressure in our outpatient subjects, they failed to maintain their antihypertensive effects when the patients were subjected to the stress of the repeat cardiac catheterization. In contrast to the heart rates, which continued to be lower during the entire second hemodynamic study, the systolic, diastolic, and mean intra-arterial pressures rose to levels virtually identical to those during the first catheterization (which took place before any beta blockers were administered). A significant stress can therefore almost eliminate the antihypertensive effect of beta blockade, but it cannot overcome its negative chronotropic effect. Similar observations were made during our earlier study with timolol[2] and were recently confirmed in a report by Waal-Manning.[56]

Oxprenolol and propranolol markedly lowered PRA after 5 wk. Some investigators have postulated that the antihypertensive effectiveness of beta blockers correlates closely with both the control renin levels and the degree of renin supression induced.[7-9] Our study did not substantiate this relationship for either oxprenolol or propranolol. There was an almost total lack of correlation between the decreases in blood pressures and PRA, all coefficients being exceedingly low. Similar problems were encountered by other investigators when they tried (but failed) to establish a close relationship between the antihypertensive and hyporeninemic effects of oxprenolol[47, 52, 58] and propranolol.[6, 20, 27, 59]

The doses of oxprenolol and propranolol were almost identical, and the antihypertensive and hemodynamic effects induced by each were also of the same order. Yet the plasma level of oxprenolol was almost 5 times as high as that of propranolol. This large difference in plasma levels of the 2 drugs is probably the result of differences in oxprenolol and propranolol kinetics. Whereas propranolol undergoes extensive presystemic metabolism by the liver (the "first-pass effect"), oxprenolol is almost completely devoid of first-pass elimination.[44] Furthermore, the Bio-Science assay for propranolol[49] does not measure active propranolol metabolites, whereas the Ciba-Geigy assay for oxprenolol[15] does. An active metabolite of propranolol, such as 4-hydroxy-propranolol, was therefore not measured by us. Yet because it is equipotent with propranolol and can achieve approximately the same circulating concentrations as the parent drug shortly after an oral dose, its effects are added to those of propranolol.[40] A simple comparison between the plasma levels of oxprenolol and propranolol (at least by the assays we used) can therefore not be used as an index of the absolute bioavailability of the 2 drugs or as a predictor of the eventual antihypertensive and hemodynamic potency of oxprenolol and propranolol.

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