Title: Antihypertensive and hemodynamic effects of oxprenolol versus propranolol.

Journal Issue: Clin Pharmacol Ther, 27(6)

Author: Ferlinz, J, Easthope, JL, Hughes, D, Siegel, J, Tobis, J, Aronow, WS

Publication Date: 06-01-1980

Series: UCLA Previously Published Works

Permalink: http://escholarship.org/uc/item/6xx2t936

Keywords: Adult, Antihypertensive Agents, Blood Pressure, Heart Rate, Hemodynamics, Humans, Hypertension, Middle Aged, Myocardial Contraction, Oxprenolol, Posture, Propranolol, Renin, Stress, Physiological, Time Factors

Local Identifier(s): UCPMS ID: 1037257

Abstract: 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.

Copyright Information:

Copyright 1980 by the article author(s). This work is made available under the terms of the Creative Commons Attribution 4.0 license, http://creativecommons.org/licenses/by/4.0/
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 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.

Jack Ferlinz, M.D., John L. Easthope, M.D., David Hughes, M.D., Jack Siegel, M.D., Jonathan Tobis, M.D., and Wilbert S. Aronow, M.D. Long Beach and Irvine, Calif.
Cardiovascular Section, Medical Service, Veterans Administration Medical Center, Long Beach, and the University of California School of Medicine, Irvine

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) and when given intravenously is reported to minimize negative inotropic effects normally seen with beta blocking agents not exerting ISA yet may remain an effective antihypertensive and antianginal agent.

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, 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.
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 1. 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) |
|-------------|--------------------|------------------------|--------------------------------------------|-------------------|-----------------------------------------------------------|
| Group O     | 10                 | 49 ± 11                | Systolic (mm Hg) 174 ± 14                  | 113 ± 9           | 5 (50%)                                                   | 5 (50%)                                                  | None                                              |
| (oxprenolol)|                    |                        | Diastolic (mm Hg)                           |                   |                                                           |                                                          |                                                   |
| Group P     | 10                 | 54 ± 4                 |                                             |                   |                                                           |                                                          |                                                   |
| (propranolol)|                  |                        |                                             |                   |                                                           |                                                          |                                                   |

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 1. 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. 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 propranolol 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 radioimmunoassay26 (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. 

**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 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...
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  | Results of second catheterization  | Significance (p) |
|--------------------|----------------------------------|-----------------------------------|------------------|
|                    | (mean ± 1 SD)                    | (mean ± 1 SD)                      |                  |
| 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⁻³)| 1,642 ± 654                      | 1,616 ± 830                       | NS               |
| PVR (dynes-sec-cm⁻³)| 106 ± 59                         | 87 ± 39                           | NS               |
| (A-V)O₂ (vol %)    | 4.11 ± 0.60                      | 4.03 ± 0.55                       | NS               |
| CI (l/min/m²)      | 3.14 ± 0.55                      | 3.02 ± 0.75                       | NS               |
| HR at CI (bpm)     | 76 ± 8                           | 66 ± 7                            | <0.01            |
| SVI (ml/beat/m²)   | 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)O₂, 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. 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 and abroad. In view of claims that oxprenolol appears to be as good as propranolol as an antihypertensive, 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⁻³)       | 1,576 ± 395                                   | 1,778 ± 449                                   | NS               |
| PVR (dynes-sec-cm⁻³)       | 109 ± 62                                      | 132 ± 72                                      | NS               |
| (A-VO₂) (vol %)            | 3.86 ± 0.63                                   | 5.36 ± 0.40                                   | <0.04            |
| CI (l/min/m²)              | 3.07 ± 0.79                                   | 2.60 ± 0.54                                   | NS               |
| HR at CI (bpm)             | 79 ± 10                                       | 62 ± 6                                        | <0.01            |
| SVI (ml/beat/m²)           | 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-VO₂), 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; SAP, right arterial pressure; RVEDP, right ventricular end-diastolic pressure; RVP, right ventricular pressure; SVI, stroke volume index; SVR, systemic vascular resistance.

antianginal,14, 42 and possibly even an antiarrhythmic agent,16, 32, 51 but with substantially less negative inotropic effects,11, 24, 31, 42 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.9 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.27 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 maintain 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 ex-
trapolating 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 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, and the myogenic response of the arteriolar wall to the decreased blood flow 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 and were recently confirmed in a report by Waal-Mannig.

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 suppression induced. 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 and propranolol.

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. Furthermore, the Bio-Science assay for propranolol does not measure active propranolol metabolites, whereas the Ciba-Geigy assay for oxprenolol 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. 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.

We thank Gaela Palmer and Pat Garcia for technical assistance and Kathleen Mellars for statistical analysis. Oxprenolol, propranolol, and placebos were supplied by the Ciba-Geigy Corp.

References
1. Andersson O, Berglund G, Bergman H, Cramer K, Fagerberg SE, Forsberg Å, Johnsen V, Lundkvist L, Rutle O, Sjost R: Antihypertensi-
sive effect and side-effects of treatment with beta blockers: A comparative study between oxprenolol and propranolol. Curr Ther Res 19:43-50, 1976.
2. Aronow WS, Felten J, Del Vicario M, Moorthy K, King J, Cassidy J: Effect of timolol versus propranolol on hypertension and hemodynamics. Circulation 54:47-51, 1976.
3. Barratt DW: Oxprenolol in mild to moderate essential hypertension. Scott Med J 19:51, 1974.
4. Barratt DW, Marshall AJ: Beta blockade in essential hypertension: An analysis of response to oxprenolol. Br Heart J 39:825-828, 1977.
5. Braunwald E: On the difference between the heart's output and its contractile state. Circulation 43:171-174, 1971.
6. Bravo EL, Tarazi RC, Dustin HP: Beta-adrenergic blockade in diuretic-treated patients with essential hypertension. N Engl J Med 292:66-70, 1975.
7. Bühler FR: Renin-aldosterone interaction, beta blockade, and differing antihypertensive efficacy of beta-blockers in high, normal, or low renin essential hypertension, in Schweizer W, editor: Beta-blockers: Present status and future prospects. Berne, 1974, Hans Huber Publishers, pp. 68-83.
8. Bühler FR, Laragh JH, Baer L, Vaughan ED Jr, Brunner HR: Propranolol inhibition of renin secretion: A specific approach to diagnosis and treatment of renin-dependent hypertensive diseases. N Engl J Med 287:1209-1214, 1972.
9. Bühler FR, Laragh JH, Vaughan ED Jr, Brunner HR, Gavras H, Baer L: Antihypertensive action of propranolol: Specific antiuretin responses in high and normal renin forms of essential, renal, renovascular and malignant hypertension. Am J Cardiol 32:511-522, 1973.
10. Chidsey CA, Monselli P, Bianchetti G, Morganti A, Leonetti G, Zanchetti A: Studies of the absorption and removal of propranolol in hypertensive patients during therapy. Circulation 52:313-318, 1975.
11. Choquet Y, Capone RJ, Mason DT, Amsterdam EA, Zelis R: Comparison of the beta adrenergic blocking properties and negative inotropic effects of oxprenolol and propranolol in patients. Am J Cardiol 29:257, 1972. (Abst.)
12. Colton T: Statistics in medicine. Boston, 1974, Little, Brown and Co., pp. 112-142.
13. Conolly ME, Kersting F, Dollery CT: The clinical pharmacology of beta-adrenergic blocking drugs. Progr Cardiovasc Dis 19:203-234, 1976.
14. Conway J: Beta-blocking drug therapy in hypertension. Cardiovasc Clin 9:1:253-261, 1978.
15. Degen PH, Riess W: Simplified method for the determination of oxprenolol and other beta-receptor blocking agents in biological fluids by gas-liquid chromatography. J Chromatogr 121:72-75, 1976.
16. DiBiase M, Guglielmi R, Scarca A, Chiddo A, Rizzoni P: Electrophysiologic properties of intravenous oxprenolol in man. Electrocardiology 10:267-273, 1977.
17. Dobbs W, Povalski HJ: Coronary circulation, angina pectoris, and antanginal agents, in Antonacci MJ, editor: Cardiovascular pharmacology. New York, 1977, Raven Press, pp. 461-521.
18. Dollery CT, George C: Propranolol: Ten years from introduction. Cardiovasc Clin 6:255-268, 1974.
19. Dollery CT, Paterson JW, Conolly ME: Clinical pharmacology of beta-receptor blocking drugs. Clin Pharmacol Ther 10:765-799, 1969.
20. Ester M, Zwiefker A, Randall O, DeQuattro V: Pathophysiologic and pharmacokinetic determinants of the antihypertensive response to propranolol. Clin Pharmacol Ther 22:299-308, 1977.
21. Fitzgerald JD: Perspectives in adrenergic beta-receptor blockade. Clin Pharmacol Ther 10:292-306, 1969.
22. Frohlich ED: The use of beta-adrenergic blockade in hypertension, in Onesti G, Kim KE, Moyer JH editors: Hypertension: Mechanisms and management. New York, 1973, Grune & Stratton, pp. 333-342.
23. Frohlich ED, Lohmüller G: A comparison of timolol and propranolol in hypertension, in Magnani B, editor: Beta-adrenergic blocking agents in the management of hypertension and angina pectoris. New York, 1974, Raven Press, pp. 45-58.
24. Grandjean T, Rivier JL: Cardio-circulatory effects of beta-adrenergic blockade in organic heart disease. Comparison between propranolol and CIBA 39, 089-Ba. Br Heart J 38:50-59, 1966.
25. Gysling E, Regoli D: Oxprenolol; Long-term effects in arterial hypertension. Clin Pharmacol Ther 14:995-1000, 1973.
26. Haber E, Koecher T, Page LB, Kliman B, Pur- node A: Application of a radioimmunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects. J Clin Endocrinol Metab 29:1349-1355, 1969.
27. Hansson L, Zweifker AJ: The effect of propranolol on plasma renin activity and blood pressure in mild essential hypertension. Acta Med Scand 185:397-401, 1974.
28. Koch G: Haemodynamic adaptation at rest and during exercise to long-term antihypertensive treatment with combination of beta-receptor blocking and vasodilator agent. Br Heart J 38:1240-1246, 1976.
29. Lecerf H, Malmberg RO: Hemodynamic effects of oxprenolol alone and combined with nitroglycerin in patients with ischemic heart disease. Acta Med Scand 192:499-506, 1972.
30. Majid PA, Sharma B, Saxton C, Stoker JB, Taylor SH: Haemodynamic effects of oxprenolol
in hypertensive patients. Postgrad Med J 46 (suppl):67-72, 1970.
31. Marshall AJ, Barratt DW: Oxprenolol in hypertension. Br J Clin Pract 27:337-340, 1973.
32. Mason DT, DeMaria AN, Amsterdam EA, Visman LA, Miller RR, Venu Z, Lee G, Zelis R, Massumi RA: Antiarrhythmic agents: Mechanisms of action, clinical pharmacology and therapeutic considerations. Cardiovasc Drugs Ther 1:75-133, 1978.
33. Mason WD, Winer N: Pharmacokinetics of oxprenolol in normal subjects. Clin Pharmacol Ther 20:401-412, 1976.
34. Materson BJ, Oster JR, Michael UF, Perez-Stable EC: Antihypertensive effectiveness of oxprenolol administered twice daily. Clin Pharmacol Ther 19:325-332, 1976.
35. McDevitt DG, Brown HC, Carruthers SG, Shanks RG: Influence of intrinsic sympathomimetic activity and cardioselectivity on beta adrenoreceptor blockade. Clin Pharmacol Ther 21:566-566, 1977.
36. Muiesan G, Motolese M, Colombi A: Hypotensive effect of oxprenolol in mild hypertension: A co-operative controlled study. Clin Sci Molec Med 45:1613-1614, 1973.
37. Nayler WG: Myocardial function during beta-adrenergic blockade. Isr J Med Sci 5:741-746, 1969.
38. Neill WA: Regulation of cardiac output, in Levine HJ, editor: Clinical cardiovascular physiology. New York, 1976, Grune & Stratton, pp. 121-142.
39. Niarhos AP, Tarazi RC: Hemodynamic effects of beta-adrenergic blocking agents in hypertension, in Onesti G, Fernandes M, Kim KE, editors: Regulation of blood pressure by the central nervous system. New York, 1976, Grune & Stratton, pp. 397-409.
40. Nies AS, Shand DG: Clinical pharmacology of propranolol. Circulation 52:6-15, 1975.
41. Prichard BNC: beta-adrenoreceptor blocking drugs in angina pectoris. Cardiovasc Drugs 2:85-118, 1978.
42. Prichard BNC, Adlig WH, Richardson GA: The action of intravenous oxprenolol, practolol, propranolol and sotalol on acute exercise tolerance in angina pectoris: The effect on heart rate and the electrocardiogram. Postgrad Med J 46(suppl):77-80, 1970.
43. Prichard BNC, Gilliam PMS: Treatment of hypertension with propranolol. Br Med J 1:7-16, 1969.
44. Riesen W, Brechbühler S, Brunner L, Imhof PR, Jack DB: The metabolism of beta-blockers in relation to their pharmacokinetic and pharmacodynamic behavior, in Schweizer W, editor. Beta blockers: Present status and future prospects. Berne, 1974, Hans Huber Publishers, pp. 276-289.
45. Rivier JL, Nissiotis E, Jaeger M: Comparison of immediate haemodynamic effects of three beta-adrenoreceptor blocking agents. Postgrad Med J 46(suppl):44-49, 1970.
46. Robson RH, Fluck DC: Automatic blockade and coronary catecholamines and cyclic AMP in exercising man. J Appl Physiol 43:949-952, 1977.
47. Savetti A, Sassano P, Poli L, Pedrinelli R, Arzilli F: The effect of beta-adrenergic blockade on patterns of urinary sodium excretion, blood pressure and plasma renin activity in patients with essential and renovascular hypertension. Eur J Clin Invest 7:331-336, 1977.
48. Shand DG: Pharmacokinetic properties of the beta-adrenoreceptor blocking drugs. Cardiovasc Drugs 2:41-54, 1978.
49. Simon M, Babich-Armstrong M, Beardson R: Propranolol in serum by high pressure liquid chromatography, in Abstracts of the Tenth International Congress of Clinical Chemistry, Mexico City, 1978, p. 88. (Abst.)
50. Simpson FO: beta-adrenoreceptor blocking drugs in hypertension. Cardiovasc Drugs 2:55-83, 1978.
51. Singh BD, Lewitt DE: beta-adrenoreceptor blocking drugs in cardiac arrhythmias. Cardiovasc Drugs 2:119-159, 1978.
52. Thomas GW, Ledingham JGG, Beilin LJ, Yeates KM: Renin unresponsiveness and the effects of oxprenolol, methyl dopa and spironolactone in patients with essential hypertension. Aust NZ J Med 6(suppl):3:44-48, 1976.
53. Tuckman J, Messerli F, Holder J: Treatment of hypertension with large doses of the beta-adrenergic blocking drug oxprenolol, alone, and in combination with the vasodilator dihydralazine. Clin Sci Molec Med 45:1613-1614, 1973.
54. Van Herick R, Aronow WS: Effects of oxprenolol and propranolol on systolic time intervals. Clin Pharmacol Ther 24:678-682, 1978.
55. Vervoort E, Plum FBM, Cillissen J, Köhler K, Merkus FWWM: Propranolol serum levels during twenty-four hours. Clin Pharmacol Ther 22:853-857, 1977.
56. Waal-Manning HJ: Atenolol and three nonselective beta-blockers in hypertension. Clin Pharmacol Ther 25:8-18, 1979.
57. Walle T, Conradi EC, Walle UK, Fagan TC, Gaffney TE: The predictable relationship between plasma levels and dose during chronic propranolol therapy. Clin Pharmacol Ther 24:668-677, 1978.
58. Weber MA, Stokes GS, Gain J: Comparison of the effects on renin release of beta adrenergic antagonists with differing properties. J Clin Invest 54:1413-1419, 1974.
59. Woods JW, Pittman AW, Pulliam CC, Werc EE Jr, Waider W, Allen CA: Renin profiling in hypertension and its use in treatment with pro-
pranolol and chlorthalidone. N Engl J Med 294:1137-1143, 1976.
60. Yin FCP, Raizes GS, Guarnieri T, Spurgeon HA, Lakatta EG, Fortuin NJ, Weisfeldt ML: Age-associated decrease in ventricular response to hemodynamic stress during beta-adrenergic blockade. Br Heart J 40:1349-1355, 1978.
61. Zacest R, Gilmore E, Koch-Weser J: Treatment of essential hypertension with combined vasodilation and beta-adrenergic blockade. N Engl J Med 286:617-622, 1972.
62. Zacharias FJ, Cowen KJ, Prestt J, Vickers J, Wall BG: Propranolol in hypertension: A study of long-term therapy, 1964-1970. Am Heart J 83:755-761, 1972.

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following written statement, signed by one author: "The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C. V. Mosby Company in the event the work is published. The undersigned author warrants that the article is original, is not under consideration by another journal, and has not been previously published. I sign for and accept responsibility for releasing this material on behalf of any and all co-authors." Authors will be consulted, when possible, regarding republication of their material.