Hemodynamic Effects of Labetalol, an Alpha and Beta Adrenergic Blocking Agent, in Hypertensive Subjects

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SUMMARY Labetalol was administered to six hypertensive subjects in increasing doses for seven days. A decrease in both supine and standing arterial pressure and heart rate was observed with no change in cardiac output and few side effects. Exercise tolerance was unaltered by the drug, but the heart rate and arterial pressure response to exercise were significantly blunted. The infusion rate of isoproterenol required to produce tachycardia was increased sevenfold by 800 mg/day labetalol and tenfold by 1600 mg/day. More than twice the control dose of phenylephrine was required during labetalol therapy to produce a rise in diastolic arterial pressure. The overshoot of arterial pressure following the Valsalva maneuver was blocked and the reflex tachycardia to amyl nitrite-induced hypotension was attenuated. These studies indicate that labetalol is an anti-hypertensive drug that exerts both alpha and beta adrenergic blocking properties. It deserves further clinical trials in the treatment of hypertension and angina pectoris.

BETA ADRENERGIC RECEPTOR BLOCKING DRUGS are now widely employed for the treatment of hypertension1, 2 and angina pectoris, 3 but alpha blockers have not found much clinical application. Although the latter drugs reduce arterial pressure, their unpleasant side effects of reflex tachycardia and orthostatic hypotension have limited their use in the management of hypertension. 4 Labetalol (Sch 15719W), 5-[1-hydroxy-2-[1-methyl-3-phenylpropyl] amino] ethyl] salicylamide, is a recently developed drug which, like propranolol, blocks both beta-1 cardiac and beta-2 vascular and bronchial receptors and also has alpha blocking properties. 5 6 Animal and human studies have revealed that this drug exerts effects similar to those observed with the combination of propranolol and hydralazine. 7

In the present study, we report clinical and hemodynamic effects of labetalol in six patients with essential hypertension. We also studied the effect of the drug on phenylephrine-induced diastolic hypertension and isoproterenol-induced tachycardia to test the degree of alpha and beta adrenergic blockade produced.

Materials and Methods

Six male patients from 25 to 56 years old (mean 45 years) were studied. All patients had essential hypertension based on clinical and laboratory evaluation. In four the hypertension was mild and somewhat labile; the other two subjects had fixed hypertension of moderate severity. Patients with a history of heart failure, ischemic heart disease, bradycardia, diabetes mellitus requiring insulin, liver disease, asthma or renal failure (serum creatinine over 2 mg/100 ml) were excluded from study. All patients gave their informed consent for use of the experimental drug and for performance of the invasive studies. All prior medications were discontinued at least two weeks before the study period.

The patients were hospitalized in the Clinical Research Center and were placed on a regular diet. Their activities in

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the hospital were not restricted except on the day of hemodynamic study. Auscultatory blood pressure and heart rate were recorded at three hour intervals in the supine and standing positions. All patients were given three placebo capsules every six hours for the first three days of hospitalization, and thereafter three capsules every six hours containing gradually increasing doses of labetalol (day 4, 50 mg; day 5, 100 mg; day 6–7, 200 mg; day 8, 300 mg; and day 9–10, 400 mg). On days 11 and 12, placebo was again administered. The patients and the nursing staff were unaware of the content of the capsules.

Hemodynamic studies were carried out on day 2 (placebo phase), day 7 (low dose therapy, 200 mg every 6 hours) and day 10 (high dose therapy, 400 mg every 6 hours). An indwelling plastic catheter was placed percutaneously in the brachial artery and another catheter was placed percutaneously in the superior vena cava through an antecubital vein. Arterial pressure was recorded on a Honeywell recorder using Statham P23 Db strain gauge transducers. Cardiac output was determined by the indicator dilution technique using indocyanine green dye injected into the superior vena cava and sampled from the brachial artery through a Gilford cuvette densitometer. Systemic vascular resistance was calculated using the formula MAP × 80/CO, where MAP is the mean arterial pressure in mm Hg and CO is cardiac output in liters/minute.

The control arterial pressure, heart rate and cardiac output were recorded in the supine position and then in the erect position, after three minutes of quiet standing. Arterial pressure was continuously recorded during the Valsalva maneuver. After 30 minutes of rest, the subjects underwent treadmill exercise testing using the Bruce protocol. The electrocardiogram and arterial pressures were recorded every 30 seconds throughout the exercise period. After the exercise test the subjects rested for at least 30 minutes or until the heart rate and arterial pressure had returned to control levels. Thereafter, the patients inhaled amyl nitrate 0.3 cc held close to their nostrils in two deep breaths. After the return of arterial pressure and heart rate to control values, beta receptor sensitivity was tested by intravenous infusion of isoproterenol in graded doses starting with 1 µg/min and increasing by 0.5 µg/min at 5 minute intervals until heart rate increased by 25%. Alpha receptor sensitivity was tested by intravenous infusion of phenylephrine in graded doses starting with 0.02 mg/min which was increased by 0.01 mg/min at 5 minute intervals until diastolic pressure rose by 15 mm Hg.

Laboratory determinations including complete blood count, serum glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, lactic dehydrogenase, alkaline phosphatase, calcium, phosphorus, uric acid, creatinine, electrolytes, blood urea nitrogen, urinalysis, chest X-ray and electrocardiogram were performed on days 2 and 8. Peripheral blood for plasma renin activity was withdrawn on days 2 and 8 after the subject had been upright for two hours. Renin activity was measured by radioimmunoassay.

Results

Blood Pressure and Heart Rate

All daily determinations of blood pressure and heart rate were averaged to derive a single value for each day of observation in the supine and standing positions. As shown in figure 1, pressure fell slightly during the first three days of placebo therapy. From days 4 to 10, while the labetalol dose was being progressively increased, a further fall in arterial pressure and a decrease in heart rate were observed. The fall in supine and standing systolic and diastolic pressures was significant (P < 0.05) from days 5 to 10 when compared to the last placebo day pressures (day 3). From days 7 to 10, standing diastolic pressure was lower than supine diastolic pressure. On day 6 arterial pressure was reduced from day 3 levels by an average of 10/8 mm Hg in the supine position and 15/11 mm Hg standing. By day 10, the last day of active drug treatment, supine pressure had fallen by an average of 19/10 mm Hg and standing pressure by an average of 36/24 mm Hg. When the drug was discontinued after day 10, pressure rose promptly to return by day 12 to levels nearly identical to those observed during day 3, the last pretreatment placebo day. Heart rate was only slightly but significantly (P < 0.05) slowed during labetalol therapy. By day 10 the heart rate was slowed an average of 4 beats per minute in the supine position and 7 beats per minute while standing.

Pressures recorded at the time of hemodynamic studies also were significantly reduced during labetalol therapy (fig. 2). On day 7 when the patient was receiving 200 mg every 6 hours (low dose) supine mean arterial pressure was decreased by 15% from the pretreatment placebo period and standing blood pressure was 20% lower. Supine heart rate was reduced by 12% and standing heart rate by 18%. No orthostatic hypotensive effect was observed. On day 10 high dose therapy (400 mg every 6 hours), supine mean arterial pressure and heart rate had fallen by 19% and 13% and standing mean arterial pressure and heart rate by 26% and...
18%, respectively. In two patients, the blood pressure fell to hypotensive levels in the standing position and they complained of dizziness and weakness.

Cardiac Output

Cardiac output in the supine position in the control period averaged 6.4 ± 0.5 L/min (fig. 2). There was no alteration in cardiac output on day 7 (6.7 ± 0.7 L/min) or day 10 (6.3 ± 0.7 L/min). Cardiac output fell by 22% in the standing position in the control period, by 26% on day 7 and 25% on day 10. The change in cardiac output in response to standing was not significantly altered during drug therapy.

Systemic Vascular Resistance

Systemic vascular resistance in the control period averaged 1658 ± 176 and 2271 ± 218 dynes-sec-cm⁻¹ in the supine and erect positions, respectively. On day 7, the systemic vascular resistance fell to 1364 ± 180 and 2104 ± 181 dynes-sec-cm⁻¹ in the supine and erect positions (P < 0.01). Vascular resistance on day 10 was not significantly different from day 7 (1385 ± 157 supine and 1837 ± 243 dynes-sec-cm⁻¹ erect) (fig. 2).

Exercise Tolerance

The effects of maximally tolerated exercise are shown in table 1. Although the duration of exercise varied among the patients, all subjects performed identical exercise at each of the three tests (days 2, 7 and 10). The resting heart rate and arterial pressure were significantly diminished on day 7 (low dose) as well as day 10 (high dose labetalol therapy). During exercise heart rate increased by 88.5% in the placebo phase and by only 70% and 67% on days 7 and 10, respectively (P < 0.01). With maximal exercise, the systolic pressure rise was attenuated by 20% on day 7 and by 30% on day 10. The diastolic pressure rise was reduced by 29% during low dose and 36% during high dose therapy when compared to the placebo response. The product of heart rate and systolic arterial pressure was significantly reduced at rest during labetalol therapy and rose with exercise by 117% on low dose therapy and 108% on high dose therapy as compared to a 143% rise in the pretreatment placebo phase (P < 0.01).

Effect of the Valsalva Maneuver

In all six patients studied in the control period, there was a characteristic overshoot of arterial pressure after the
Valsalva maneuver (systolic overshoot 32 ± 5 mm Hg). This overshoot response was absent in five patients and attenuated in one on day 7. The overshoot response was absent in all patients during high dose therapy on day 10.

Response to Amyl Nitrite Inhalation

The mean arterial pressure fell in response to amyl nitrite by an average of 39.3% in the control phase and by 37.9% and 46.4% on low dose and high dose therapy, respectively (NS) (table 2). The heart rate increased by 30.9% in the control period but by only 20.2% and 21.9% on low dose and high dose therapy, respectively (P < 0.01).

Response to Isoproterenol Infusion

In the control period intravenous infusion of 1.0 µg/min isoproterenol produced an 8 mm Hg fall in diastolic arterial pressure and a 5% increase in heart rate (fig. 3). A 25% increase in heart rate was achieved with infusion of 2.0 to 3.5 µg/min isoproterenol (mean 2.4 ± 0.3 µg/min) and was associated with a 15 mm Hg fall in diastolic arterial pressure. On low dose labetalol therapy, the threshold dose of isoproterenol to produce tachycardia was increased to 7.3 ± 1.7 µg/min and a dose of 15 ± 1.7 µg/min was required to achieve a 25% increase in heart rate. A 7 mm Hg elevation in diastolic arterial pressure was observed during isoproterenol infusion. On high dose therapy, the threshold isoproterenol dose was increased to 10.9 ± 2.0 µg/min and a 25% increase in heart rate required an infusion rate of 21 ± 3.8 µg/min. A 10 mm Hg elevation in diastolic arterial pressure occurred during the higher infusion rate. The increase in isoproterenol dose needed to produce tachycardia was highly significant (P < 0.001) during both low and high dose labeled labetalol therapy.

Response to Phenylephrine Infusion

In the control period 0.11 ± 0.01 mg/min (range 0.07 to 0.15 mg/min) phenylephrine infusion was required to produce a 15 mm Hg elevation in diastolic arterial pressure (fig. 4). During low dose labetalol therapy on day 7 a higher infusion rate of 0.20 ± 0.07 mg/min (range 0.14 to 0.25 mg/min) (P < 0.01) was required. A similar dose (0.21 ± 0.02 mg/min) was required on day 10 (high dose therapy).

Plasma Renin Activity

Renin activity was measured with the patients on a regular hospital diet after they were upright for two hours. Plasma renin activity on day 2 (placebo phase) in all six sub-

| Table 2. Effect of Labetalol on Response to Amyl Nitrate Inhalation |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Heart rate      | Mean arterial pressure |
|                 | (beats/min)     | (mm Hg)           |
|                 | C    | A | % change | C    | A | % change |
| Placebo         | 84   | 110±9 | -31 | 122±8 | 74±7 | -39 |
| Low dose        | 79   | 75±9 | -20 | 95   | 90±2 | -20 |
| High dose       | 73   | 89±9 | -22 | 97   | 93±2 | -22 |

Heart rate % change: placebo vs low dose, P < 0.01; placebo vs high dose, P < 0.01.
Mean arterial pressure % change: placebo vs low dose, NS, placebo vs high dose, NS.
Abbreviations: C = control; A = amyl nitrite inhalation peak effect.

FIGURE 3. Heart rate response to isoproterenol infusion before and during labetalol administration. Isoproterenol dose-response curve shifted progressively to the right with increasing dose of labetalol.

FIGURE 4. Diastolic pressure response to phenylephrine infusion before and during labetalol administration. Phenylephrine dose-response curve is shifted to the right during labetalol administration.

Side Effects

Three patients complained of gastrointestinal symptoms (nausea, constipation, diarrhea) during therapy with labetalol. Weakness was reported by five of the patients while tak-
ing the highest dose (1600 mg/day) and two developed orthostatic dizziness on one or more occasions during the day.

No significant alterations in the chest X-ray, electrocardiogram, hemogram, urinalysis or blood chemistries were observed. An S₁ gallop present initially in two patients disappeared during therapy. Body weight was unaltered during labetalol treatment.

Discussion

The most effective drug therapy of hypertension usually involves the administration of combinations of agents that have differing pharmacologic effects.² Beta adrenergic antagonists have recently proved to be effective antihypertensive agents especially when they are combined with diuretics or vasodilators.¹ ² ₉ ₁₂ ₁₄ Since beta blockade alone usually exerts only a mild antihypertensive effect, and alpha blockade is often associated with tachycardia and orthostasis, combined alpha and beta blockade has been advocated as a rational approach to the management of hypertension.¹₅

In previous European studies labetalol has been shown to possess both alpha and beta adrenergic blocking properties.⁶ ⁷ This pharmacologic effect of the drug was confirmed in the present study, which demonstrated attenuation of both isoproterenol-induced tachycardia and phenylephrine-induced hypertension during short-term labetalol therapy. The dose-response curve to isoproterenol was shifted tenfold to the right and the beta adrenergic blockade appeared to be dose related. The alpha adrenergic blockade was more moderate, with an increase of two to three-fold in the dose requirement for phenylephrine. Therefore, at a dose of 800 to 1600 mg/day, labetalol appeared to be 4-6 times more potent as a beta adrenergic antagonist than as an alpha adrenergic antagonist, assuming that the tests used for evaluating receptor response are equisensitive. It has been reported previously that labetalol is 5-18 times less potent than propranolol in blocking beta receptors⁶ - ⁷ and 2-7 times less potent than phentolamine in blocking alpha receptors.⁷

In the present study labetalol therapy resulted in significant reduction in the supine and standing arterial pressure with only slight slowing of heart rate in hypertensive subjects. Orthostatic dizziness occurred occasionally on high dose therapy, but in moderate doses (800 mg/day) the antihypertensive effect was well tolerated. The decrease in blood pressure and heart rate appeared within the first day after therapy was initiated and disappeared within 48 hours after the drug was discontinued. Cardiac output in the supine and upright position was unchanged from the control period during treatment with the drug, and therefore the antihypertensive effect was due to a fall in systemic vascular resistance. This response is quite different from that usually observed to propranolol, which results in a more delayed antihypertensive effect, a greater slowing of heart rate, a fall in cardiac output and a rise or no change in vascular resistance.¹₈ ¹₇

The mechanism of the hemodynamic effect of labetalol is not entirely clear. The maintenance of cardiac output, despite beta adrenergic blockade, could be attributed to the peripheral vasodilator effect of the alpha adrenergic blocking properties of the drug. Prichard et al. also reported that intravenous administration of labetalol produced acute lowering of blood pressure without a change in cardiac output or heart rate.⁹ They found the hemodynamic response to labetalol to be quite similar to that when hydralazine was administered after induction of beta blockade. Similarly, Sannerstedt et al. studied a group of hypertensive patients whose cardiac outputs had been reduced by treatment with a beta adrenergic blocking agent. Addition of hydralazine resulted in a further fall in blood pressure associated with no change in heart rate but a rise of cardiac output toward pretreatment levels.¹₃ The rise in output in response to the vasodilator drug could be attributed to either a subtle reflex inotropic effect not completely inhibited by the beta blockade or to the mechanical effect on left ventricular output of a reduced aortic outflow resistance.¹₉ There is no evidence that labetalol possesses beta adrenergic agonist activity as does practolol.¹⁹

The mildness of the orthostatic effect observed with moderate doses of this drug, despite the prominent reduction in supine blood pressure, suggests that alpha adrenergic blockade is not the major cause of its antihypertensive properties. Indeed, one might expect the orthostasis of alpha blockade to be accentuated if compensatory reflex cardiac stimulation were inhibited by concomitant beta receptor blockade. Therefore, the alpha blockade produced by these moderate doses of labetalol must be of a degree adequate to contribute importantly to the antihypertensive effect of the beta blockade but not great enough to produce symptomatic orthostasis. Alternatively, labetalol may have antihypertensive properties not confined to peripheral adrenergic receptor blockade.

Beta adrenergic blocking drugs like propranolol have been found to be useful in angina pectoris.⁵ ²⁰ The beneficial response in angina pectoris appears to be dose-related and is manifested by decreased heart rate, blood pressure and the double product (heart rate X systolic blood pressure) both at rest and during exercise.⁵ ₁₄ In hypertensive subjects as well, propranolol administration attenuates heart rate and arterial pressure responses to exercise.¹₆ ¹₇ During labetalol therapy, all hypertensive subjects could perform the same level of exercise as before therapy and the blood pressure responses seemed to be blocked to a greater degree than has previously been reported with propranolol,¹⁶ ¹₇ probably because of the concomitant alpha adrenergic blockade.

The effect of labetalol on plasma renin activity (PRA) was variable in this study. Although the number of subjects was small, it is interesting to observe that plasma renin activity was suppressed in subjects with elevated control PRA and elevated in those with normal PRA. Such a response is not surprising, since beta blockade would be expected to decrease renin whereas vasodilatation or alpha adrenergic blockade might increase it.²¹ ²²

These preliminary observations suggest that labetalol may be useful in the therapy of both hypertension and angina pectoris. The prominent antihypertensive effect at moderate dose levels (800 mg/day) without significant side effects or reduction in cardiac output offers potential advantages over currently available drugs. The striking reduction in heart rate-blood pressure product during exercise provides a rationale for its use in angina pectoris. Chronic therapeutic trials in these disorders appear to be justified.
Superiority of Dobutamine over Dopamine for Augmentation of Cardiac Output in Patients with Chronic Low Output Cardiac Failure

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SUMMARY Dobutamine is a newly developed catecholamine reported to have minimal direct vascular effects relative to its inotropic activity and to have less chronotropic and arrhythmogenic properties than dopamine. It has been used in the treatment of low output states. In this study, the acute hemodynamic effects of dobutamine were compared to those of dopamine in 13 patients with chronic low output cardiac failure. At dosages adjusted to achieve similar increments in cardiac output, dobutamine reduced left ventricular filling pressure (LVEDP) from 25 ± 2 mm Hg (SEM) to 17 ± 2 mm Hg, while dopamine increased LVEDP to 30 ± 3 mm Hg and in six patients caused arterial O₂ saturation to fall below 90%. This poor response to dopamine was probably the result of its vasconstrictive effects and illustrates the potential advantages of using a cardioselective agent such as dobutamine when the desired goal of therapy is to improve ventricular function by direct inotropic stimulation.

OF THE MANY AGENTS capable of improving cardiac output in patients with low output cardiac failure, the catecholamines are among the most widely used. As a group, these drugs exert similar direct cardiac effects mediated by stimulation of beta adrenergic receptors. Important differences in their peripheral vascular actions are found among them. At times, these vascular effects are undesirable and can offset benefits gained from the inotropic actions. In addition, the catecholamines currently used for treatment of heart failure frequently cause tachycardia and/or arrhythmias. Newer agents have been developed and tested under laboratory conditions with the purpose of finding one that would retain the inotropic activity of the earlier catecholamines without direct vascular, chronotropic and arrhythmogenic actions. Of many such compounds tested, dobutamine appears to come close to fulfilling these criteria. We and others² ³ have previously described the acute hemodynamic effects of dobutamine in patients with severe left ventricular dysfunction. In the present study, we compared the effects of dobutamine to those of dopamine in 13 such patients. Our studies suggest that dobutamine has important
Hemodynamic effects of labetalol, an alpha and beta adrenergic blocking agent, in hypertensive subjects.
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