HYPERTENSION: A VIEW FROM DETROIT

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The inner-city area of Detroit, with its predominantly black population, has a high percentage of hypertensive patients. In the course of treating these patients, we have noted a distinct difference in their response to therapy as compared with their white counterparts. Frequently, the mildly hypertensive black patient will feel quite well until therapy is initiated. Then, he or she will exhibit resistance to treatment, or an increased sensitivity to the biochemical and physiologic side effects of the medication.[1]

A SECOND LOOK AT TRADITIONAL MEDICATIONS

Traditionally, thiazide diuretics have been the first choice for these patients because of their perceived efficacy, ease of use, and cost effectiveness.[2,3] In several large-scale studies, conducted over the past few years, questions have been raised, however, regarding the advisability of treating hypertensive patients for long periods with thiazides. Physiologic and metabolic side effects, hyperuricemia, hyperglycemia, hyperlipidemia, and hypokalemia may develop in addition to the problem of impotence.[4-8]

The Medical Research Council Trial (conducted in England between 1977 and 1985) studied more than 17,000 patients, aged 35 to 65 years, with mild to moderate blood pressure elevation.[9] The treated patients received either a thiazide or propranolol. Results showed that it was necessary to treat 850 patients for one year to prevent *one* stroke. Data reported no difference between treated or placebo patients in mortality from all causes, or in the occurrence of coronary artery disease. Thus, in this group, overall improvement was not great, emphasizing the importance of therapeutic agents with minimal side effects for compliance and safety.

In the Multiple Risk Factor Intervention Trial (MRFIT), 12,000 patients were studied for seven years.[10] A surprising finding emerged from this study: one subset of patients (a part of the "special intervention" group, with resting electrocardiographic abnormalities, who were treated with higher doses of diuretics) had an increased mortality rate. Although the exact reason for this response is still unclear, the possibility of sudden death as a result of hypokalemia has been suggested.[10]

The advent of beta-blocking agents appeared to offer an alternative for the initial treatment of hypertension.[11,12] Candidates for this therapy were identified as hyperadrenergic or "stress" hypertensives, typically young white men.[13,14] This subset exhibits volume constriction (normal or high renin levels) in addition to angina and electrocardiographic abnormalities. Occasionally, there is a history of episodic tachycardia. Underlying nervous tension is frequently apparent.

Beta blockers, generally effective as monotherapy in the white patient, frequently require the addition of a thiazide diuretic in the black patient to achieve normalization of blood pressure.[15,16] Again, this introduces the problems of hyperlipidemia, hyperglycemia, and hyperuricemia. It must be remembered, too, that the basic physiologic abnormality in any

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hypertensive patient is an increase in peripheral resistance, with a resultant decrease in cardiac, cerebral, and renal blood flow. In the black patient, plasma-renin activity is low; volume overload and other non–renin-related mechanisms account for the increase in peripheral resistance and associated blood-pressure elevation. Neither the thiazides nor traditional beta blockers directly reduces elevated peripheral resistance.

LABETALOL: A NEW CLASS

Labetalol is the prototype of a new class of antihypertensive drugs known as blocker-dilators.[17,18] This agent acts by blocking beta-1, beta-2, and alpha-1 adrenergic receptors. These properties permit the drug to lower blood pressure by two different mechanisms: alpha blockade reduces peripheral resistance, resulting in a fall in blood pressure at rest; beta blockade will blunt the rise in blood pressure-pulse rate product associated with exercise as the result of sympathetic nervous system activity. Beta blockade will also reduce plasma-renin activity.[19]

The reduction in total peripheral resistance, alpha blockade, occurs without significant alteration in cardiac output or resting heart rate. Renal, cardiac, and cerebral flow is unchanged.[20] This action is believed to be the reason for its enhanced effectiveness in black patients and for the increase in blood flow to the organs at risk[21] (Table 1). Long-term studies have shown this vasodilation to be persistent.[22] Studies with labetalol also have shown it to be effective as monotherapy in the treatment of black hypertensives.[23]

A SINGLE-BLIND STUDY OF LABETALOL AS MONOTHERAPY IN HYPERTENSIVE BLACK PATIENTS

This single-blind study was undertaken to confirm the effectiveness of labetalol as monotherapy in hypertensive black patients. Criteria for enrollment included chronic, mild to moderate blood pressure elevation, which was adequately controlled (140/90 mm Hg) by previous diuretic or beta-blocker therapy. Patients were excluded if they presented with uncontrolled elevated blood pressure, uncontrolled diabetes, abnormal laboratory tests (creatinine), congestive heart failure, stroke, or heart block. Approval was obtained from the Internal Review Board to conduct this study, and informed consent was obtained from each patient prior to enrollment.

TABLE 1. EFFECTS OF LABETALOL IN HYPERTENSIVE PATIENTS

Reduces
Exercise increase in heart rate
Exercise increase in blood pressure
Peripheral resistance
Elevated plasma renin
Coronary vascular resistance
Does Not Change
Cardiac output
Resting heart rate
Renal function
Cerebral blood flow

Patient Population and Methods

Twenty-one patients were initially entered into the study; however, only 18 were available for final evaluation. All patients had "responded," some for the first time, to therapy with a thiazide diuretic and a beta-blocking agent. Blood pressure levels were within normal levels at baseline. These drugs had been selected because of their once-a-day dosage regimen, which encouraged compliance. Compliance was essential, as there were minimal symptoms of hypertension present.

The study consisted of three phases: phase 1 was a four-week washout period, phase 2 consisted of a one- to four-week period utilized to titrate dosage and begin treatment with labetalol, and phase 3 was a two-week labetalol maintenance period. Previous therapy was tapered off during the washout period; the diuretic was withdrawn over the first two-week period and the beta blocker over the second two-week period.

In the second phase, labetalol therapy was initiated and titrated upward until diastolic blood of $\leq$90 mm Hg and $\geq$10 mm Hg reductions were achieved. This required from one to four weeks and was accomplished slowly so as to avoid precipitation of untoward effects. Final dosages of labetalol ranged from 200 to 600 mg, administered twice daily.

In the final, or maintenance, phase, labetalol therapy was continued for another two-week period at the same dosage level established during the titration period (Figure 1).

Results

Efficacy Evaluation

A total of 18 patients were evaluated for efficacy and safety. Mean standing heart rate and mean blood

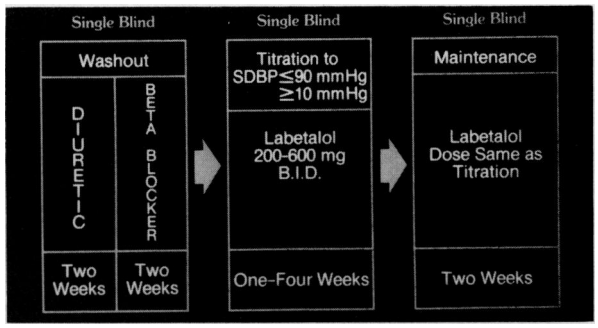

Figure 1. Protocol for single-blind study of labetalol in black hypertensive patients

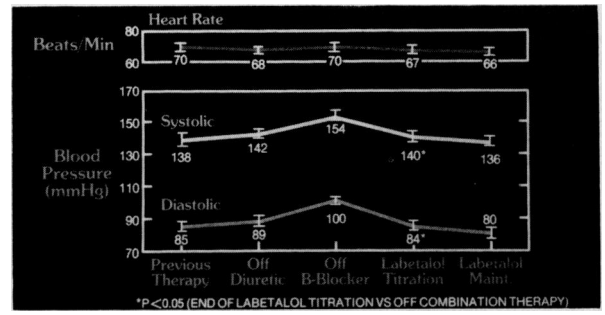

Figure 2. Mean standing heart rate and blood pressure in 18 black hypertensive patients

pressure levels for patients while on previous therapy were 70 beats per minute and 138 mm Hg (systolic) and 85 mm Hg (diastolic), respectively. After removal from diuretic and beta-blocker therapies, mean standing heart rates were 68 and 70 beats per minute, 142 and 154 mg Hg for systolic blood pressure, and 89 and 100 mm Hg for diastolic blood pressure, respectively (Figure 2).

Response to labetalol therapy was prompt. During the labetalol titration period, mean standing heart rate was reduced to 67 beats per minute, mean systolic pressure to 140 mm Hg, and mean diastolic pressure to 84 mm Hg. This trend continued during the two-week maintenance period with mean heart rate dropping to 66 beats per minute, mean systolic pressure to 136 mm Hg, and mean diastolic pressure to 80 mm Hg (Figure 2). The differences between mean blood pressure levels recorded at time of removal from previous drug therapy and those noted at the end of the labetalol titration-treatment period showed statistically significant improvement, $P < .05$.

Blood pressure control was achieved in 17 of the 18 patients treated with labetalol alone, at dosage levels of 200 to 600 mg twice daily. Thirteen patients required 300 mg twice daily or less to adequately control pressure. In eight patients, blood pressure levels were maintained at below 140/90 mm Hg.

Safety Evaluation

Labetalol was well tolerated by all patients and only minimal side effects were reported. A skin rash developed in one patient, and scalp tingling and mild bladder dysfunction were experienced by several other patients. Mild fatigue, a common side effect of beta-blocker therapy, particularly propranolol, was seen briefly in some patients as dosage levels were increased.

Other side effects usually occurring with beta-blocker therapy, ie, dizziness, gastrointestinal problems, sexual dysfunction, and edema, were not a problem with labetalol therapy. Furthermore, there were few complaints of edema or fluid retention, despite the withdrawal of diuretic therapy. No patient in the study requested a change of treatment because of problems with labetalol therapy. Thirteen of the 18 patients completing the study asked to continue therapy with this agent.

Finally, no changes were observed in laboratory tests, hemograms, chest x-ray films, or electrocardiograms in patients during labetalol therapy.

CONCLUSIONS

Labetalol is a unique antihypertensive agent that combines beta-blocking and alpha-blocking vasodilating properties in a single entity. Its alpha effect results in vasodilation that reduces peripheral resistance and increases blood flow to the target organs: the brain, kidneys, and heart. Studies have shown labetalol, used alone or in combination with a diuretic, to be an effective, safe and well-tolerated, long-term antihypertensive agent for a wide spectrum of patients.

In this study, labetalol, as monotherapy, proved to be a useful therapeutic adjunct for the control of hypertension in black patients. This agent effectively controlled blood pressure in 17 of 18 (94 percent) black patients with chronic, mild to moderate hypertension. Excellent control of both systolic and diastolic pressure levels were maintained in 13 of 17 (76 percent) patients on 600 mg or less per day. Patient acceptance of the drug was high.[24]

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