A NEW ANTIHYPERTENSIVE STRATEGY FOR BLACK PATIENTS: LOW-DOSE MULTIMECHANISM THERAPY

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Hypertension poses serious health risks for blacks because this population presents with earlier onset and more severe forms of the disease than do nonblacks. Although diuretics are the cornerstone of antihypertensive therapy in the black population, investigators have expressed concern about adverse metabolic effects, such as hypokalemia, produced by the high doses of diuretics traditionally prescribed for blacks. Recent evidence suggests that black patients may respond equally well to the new generation of cardioselective beta-blockers and angiotensin-converting enzyme inhibitors, particularly when these agents are used together with a diuretic. A new low-dose multimechanism agent that combines the cardioselective beta-blocker bisoprolol fumarate with hydrochlorothiazide, a benzothiazine diuretic, is now available for first-line therapy for hypertension. Results of two US multicenter trials—including a subset analysis of black patients—indicate that the once-daily agent is highly effective in reducing diastolic and systolic blood pressure throughout a 24-hour period in both black and nonblack patients. The agent is well tolerated in blacks and nonblacks and has a side-effect profile comparable to placebo. Because of its efficacy and safety in black patients, bisoprolol fumarate/hydrochlorothiazide is an appropriate therapeutic option for first-line therapy of hypertension in the black population. (*J Natl Med Assoc.* 1996;88:171-175.)

Key words • hypertension • blacks • bisoprolol fumarate

Because of its earlier onset, higher prevalence rates, and greater severity in the black population compared with the nonblack population, hypertension is widely acknowledged to be a significant health hazard for adult black men and women.[1] In addition, socioeconomic factors may make blacks less likely than nonblacks to seek early treatment for the disease or to comply with the therapeutic regimen.[2] The level of compliance, as well as withdrawal from therapy, can be influenced by the impact of antihypertensive medication on the black patient's quality of life.[3] However, ample evidence shows that at comparable starting blood pressure levels, blacks will achieve similar overall reductions in blood pressure as nonblacks when provided with equal access to adequate therapy.[1] This article discusses management considerations for black patients with hypertension and reviews clinical data for black patients taking bisoprolol fumarate/hydrochlorothiazide 6.25 mg.

PHYSIOLOGIC AND PHARMACOLOGIC CONSIDERATIONS IN MANAGING BLACK HYPERTENSIVE PATIENTS

Pharmacologic management of hypertension in black patients poses special challenges for clinicians because these patients may present with salt sensitivity,

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expanded plasma volume, low renin production, and low cardiac output with increased peripheral and renal vascular resistance.[4] Because noninsulin-dependent diabetes mellitus is also twice as prevalent in blacks as in nonblacks,[1] medication must be selected carefully because certain antihypertensive drugs may impair control of diabetes. For example, decreased insulin release may occur in the presence of diuretic-induced hypokalemia.[5]

Because black patients tend to have low-renin, volume-expansion hypertension,[6] thiazide diuretics have long been the cornerstone of antihypertensive therapy for this population. The 1993 recommendations of the National Institutes of Health Fifth Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V) emphasized using thiazide diuretics or beta-blockers as preferred first-choice monotherapy for mild to moderate hypertension unless contraindicated or unacceptable, or special reasons exist for the use of other therapies.[1] The committee noted that in black hypertensive patients, diuretics should be the agent of first choice, unless other conditions prohibit their use, because they have been shown to be of particular value in long-term controlled clinical trials.[1]

Clinical data now suggest that the high doses of diuretics traditionally used to treat black hypertensives may produce metabolic adverse effects—ie, alterations in potassium and magnesium homeostasis, disturbances in glucose metabolism, and abnormalities in lipid levels—that may counterbalance the benefits derived from reducing blood pressure.[6] Furthermore, investigators have reported that black patients respond equally well to the new generation of cardioselective beta-blockers and angiotensin-converting enzyme inhibitors, particularly when these agents are used together with a thiazide diuretic.[2,5,7]

The development of cardioselective beta-blockers and angiotensin-converting enzyme inhibitors has greatly expanded pharmacologic options for treatment of hypertension in blacks. While monotherapy with beta-blockers once was perceived to be less effective in black patients than in nonblacks, recent studies have confirmed the efficacy and tolerability of cardioselective beta-blockers in black patients.[4,6] In addition, a quality-of-life study conducted by Croog et al[3] of 306 black patients with mild to moderate hypertension reported that treatment with atenolol, captopril, or verapamil SR achieved blood pressure control without negative effects on quality-of-life measurements.

RATIONALE FOR THE USE OF LOW-DOSE MULTIMECHANISM THERAPY

Compelling scientific evidence shows that the use of low doses (10 to 12.5 mg) of hydrochlorothiazide can control blood pressure while minimizing dose-related physiologic and metabolic side effects.[8] The blunted response of hypertensive blacks to monotherapy with beta-blockers or angiotensin-converting enzyme inhibitors is reported to be negated when these drugs are used together with a diuretic.[9]

Recently, the concept has emerged of using a beta-blocker and a thiazide diuretic in doses lower than normally used to produce a greater therapeutic response than with each agent alone and to lessen the risk of dose-related side effects. The 24-hour control of blood pressure achieved would be similar to or greater than that achieved using full doses of either component as monotherapy. Results of several clinical trials have demonstrated the efficacy and tolerability of such a low-dose multimechanism agent.[10-12] It has been shown to have an additive effect in lowering blood pressure and may enhance antihypertensive efficacy in blacks, whose response to beta-blockers alone is often inadequate.[10] Further, the JNC V report has supported the theory behind this approach, noting that using two antihypertensive drugs with different modes of action "will often allow smaller doses of drugs to be used to achieve control, thereby minimizing the potential for dose-dependent side effects."[1]

AN EFFECTIVE, NEW LOW-DOSE MULTIMECHANISM AGENT

The low-dose multimechanism agent bisoprolol fumarate/hydrochlorothiazide 6.25 mg (Ziac, Lederle Laboratories, Wayne, New Jersey) is now available for first-line treatment of hypertension. It was developed specifically to offer physicians the traditional benefits of a beta-blocker and a diuretic but, due to its low-dose composition, with a side-effect profile comparable to that of placebo. Administered once daily, the new agent contains low doses (2.5, 5, and 10 mg) of the cardioselective beta-blocker bisoprolol fumarate and a low dose (6.25 mg) of the benzothiazine diuretic hydrochlorothiazide. Quality-of-life scores measured in a study of patients with hypertension indicated that bisoprolol fumarate/hydrochlorothiazide 6.25 mg therapy resulted in a significant improvement (P=.02) in overall quality-of-life scores, compared with those at baseline.[11]

The efficacy and tolerability of this agent were confirmed in two US, multicenter, randomized, double-blind, placebo-controlled trials.[10,12] Treatment effects

TABLE 1. MEAN* REDUCTIONS FROM BASELINE SITTING DIASTOLIC BLOOD PRESSURE (SDBP) 24 HOURS POSTDOSE FOR PRIMARY ANALYSIS PATIENTS AT 3 TO 4 WEEKS†

	SDBP Baseline Mean & Mean Reduction (mm Hg)			
	Black (*n*=104)		Nonblack (*n*=396)	
	Mean	Mean Change	Mean	Mean Change
Confirmatory Trial				
Placebo	100.6	−5.7	100.4	−3.5
Bisoprolol 5 mg/hydrochlorothiazide 6.25 mg	101.3	−14.1	100.4	−12.2
Hydrochlorothiazide 25 mg	100.4	−11.0	100.7	−8.1
Multifactorial Trial				
Placebo	99.3	−1.8	101.5	−4.4
Bisoprolol 2.5 mg/hydrochlorothiazide 6.25 mg	98.8	−8.4	100.0	−11.3
Bisoprolol 10 mg/hydrochlorothiazide 6.25 mg	97.5	−13.9	100.4	−14.5
Hydrochlorothiazide 25 mg	100.5	−10.6	100.0	−8.3

*Means are estimated based on analysis of variance models.
†Data from Lederle Laboratories.

were consistent across racial groups. In a 24-center multifactorial study, 512 patients received: placebo; bisoprolol 2.5, 10, and 40 mg alone; hydrochlorothiazide alone (6.25 and 25 mg); and all possible pairings of the two agents at these doses.[10,12] One goal of this trial was to determine whether using the medications together had an additive effect. In a 30-center confirmatory trial, which was designed to verify the additive effect and focused on middose efficacy, 547 patients received placebo; hydrochlorothiazide 25 mg alone; bisoprolol fumarate 5 mg alone; or bisoprolol fumarate 5 mg/hydrochlorothiazide 6.25 mg.[10,12]

Overall response rates at 24 hours postdose for the bisoprolol fumarate 2.5, 5, and 10 mg/hydrochlorothiazide 6.25 mg treatment groups were 61%, 73%, and 80%, respectively.[10] Side effects were mild and transient, and comparable to those of placebo. In both studies, bisoprolol fumarate/hydrochlorothiazide 6.25 mg was found to be more effective than monotherapy in all subsets of patients, including men and women, blacks, the elderly, and smokers.[12] Moreover, treatment with bisoprolol fumarate 5 mg/hydrochlorothiazide 6.25 mg resulted in an incidence of hypokalemia comparable to that of placebo and significantly less than that observed with hydrochlorothiazide 25 mg (0.7 versus 6.5).[10] The incidence of hyperuricemia was significantly less ($P<.01$) with bisoprolol fumarate/hydrochlorothiazide 6.25 mg than with 25 mg of hydrochlorothiazide.[12]

Bisoprolol fumarate/hydrochlorothiazide 6.25 mg also minimizes adverse effects on serum lipids. In a short-term 4-week study, treatment with this agent resulted in no significant change in mean total cholesterol, an increase in mean serum triglycerides (14%), and a small decrease in mean high-density lipoprotein cholesterol (5%) versus placebo (Lederle Laboratories, unpublished data). However, a long-term study of bisoprolol fumarate monotherapy showed no significant changes in total cholesterol or triglycerides in up to 3 years of therapy.[13] Another study showed no significant changes in total cholesterol, low-density lipoprotein, or high-density lipoprotein after 2 years of therapy.[14]

RESULTS IN BLACK PATIENTS

The safety and efficacy of bisoprolol in black patients has been determined previously.[15] To determine the efficacy and safety benefits of bisoprolol fumarate/hydrochlorothiazide 6.25 mg in black and nonblack patients, a subset analysis of the multicenter studies described above was conducted. Results at weeks 3 to 4 showed that once-daily therapy with bisoprolol fumarate/hydrochlorothiazide 6.25 mg was effective in reducing diastolic and systolic blood pressure throughout a 24-hour period in both racial groups. Mean reductions in sitting diastolic blood pressure in black patients ranged between 8.4 and 14.1 mm Hg; nonblacks showed a range between 11.3 and 14.5 (Table 1) (Lederle Laboratories, unpublished data). Mean reductions in sitting systolic blood pressure ranged from 12 to 17.5 mm Hg in black patients and from 13.7 to 16.8 mm Hg in nonblack patients (Table 2) (Lederle Laboratories, unpublished data).

At weeks 3 to 4, pairwise comparisons of sitting diastolic blood pressure in the bisoprolol 5 mg/-hydrochlorothiazide 6.25 mg group versus the hydrochlorothiazide 25 mg group showed a mean difference of −1.5±2.56 between patient pairs in black

TABLE 2. MEAN* REDUCTIONS FROM BASELINE SITTING SYSTOLIC BLOOD PRESSURE (SSBP) 24 HOURS POSTDOSE FOR PRIMARY ANALYSIS PATIENTS AT 3 TO 4 WEEKS†

	SSBP Baseline Mean & Mean Reduction (mm Hg)			
	Black (*n*=104)		Nonblack (*n*=396)	
	Mean	Mean Change	Mean	Mean Change
Confirmatory Trial				
Placebo	152.4	−3.6	151.9	−2.8
Bisoprolol 5 mg/hydrochlorothiazide 6.25 mg	152.3	−17.5	151.7	−15.5
Hydrochlorothiazide 25 mg	151.3	−12.1	150.3	−9.8
Multifactorial Trial				
Placebo	148.9	+0.5	150.8	−4.3
Bisoprolol 2.5 mg/hydrochlorothiazide 6.25 mg	154.1	−14.8	147.8	−13.7
Bisoprolol 10 mg/hydrochlorothiazide 6.25 mg	148.2	−12.0	151.0	−16.8
Hydrochlorothiazide 25 mg	153.9	−12.2	146.3	−12.0

*Means are estimated based on analysis of variance models.
†Data from Lederle Laboratories.

patients, indicating no significant difference between the two treatments (P=.51). For the other dosages of bisoprolol fumarate/hydrochlorothiazide 6.25 mg (2.5 and 10 mg), the pairwise comparisons with hydrochlorothiazide 25 mg also showed no significant difference in sitting diastolic blood pressure in black patients (P=.61 and P=.11, respectively). For nonblack patients, such pairwise comparisons indicated a significant difference between the response to bisoprolol fumarate/hydrochlorothiazide 6.25 mg and hydro-chlorothiazide 25 mg in favor of bisoprolol fumarate for the following doses: 5 mg, −4.86±0.88 (P<.01) and 10 mg, −6.09±2.27 (P<.01).

With regard to reductions in sitting heart rate, in black patients pairwise comparisons between bisoprolol fumarate/hydrochlorothiazide 6.25 mg and hydrochlorothiazide-treated patients indicated no significant difference in the patients treated with the 2.5 mg dose (P=.44) and the 10 mg dose (P=.24), but a significant difference was noticed in those treated with the 5 mg dose (−6.62±2.23; P<.01). For nonblack patients, comparisons showed a significant difference between the following bisoprolol fumarate and hydrochlorothiazide doses: 5 mg, −8.33±1.07 (P<.01) and 10 mg, −14.01±2.89 (P<.01).

Bisoprolol fumarate/hydrochlorothiazide 6.25 mg was safe in black and nonblack patients and provided a side-effect profile comparable to placebo. Dizziness and fatigue were the most common side effects, occurring in 2.1% and 2.1% of black patients, respectively, and in 3.5% and 4% of nonblacks, respectively. The changes in potassium and uric acid were comparable to placebo in both groups of patients.

SUMMARY

Because they present with earlier onset and more severe forms of the disease than do nonblacks, black hypertensive patients pose a management challenge to clinicians. Recent clinical evidence suggests that the use of a cardioselective beta-blocker with a thiazide diuretic is an efficacious therapeutic option for black patients. A new low-dose multimechanism beta-blocker/diuretic—bisoprolol fumarate/hydrochlorothiazide 6.25 mg—is now available for first-line treatment of hypertension. Two US multicenter studies have confirmed that the once-daily agent is effective in reducing systolic and diastolic blood pressure throughout a 24-hour period in black patients.

The low fixed dose of hydrochlorothiazide (6.25 mg) avoids the metabolic and physiologic side effects experienced with full-strength diuretic therapy while providing a substantial increase in efficacy over that demonstrated by beta-blockers alone. The agent is well tolerated in black patients, with a side-effect profile comparable to that of placebo. This held true for hypokalemia and hyperuricemia, problems typically associated with diuretics.

Thus, the efficacy and once-daily dosing regimen of bisoprolol fumarate/hydrochlorothiazide 6.25 mg, combined with its side-effect profile comparable to placebo and its lack of negative impact on quality-of-life scores, may help promote compliance in the black population. This, in turn, may translate into fewer complications and an overall decrease in the cost of care.

CONCLUSION

Bisoprolol fumarate/hydrochlorothiazide 6.25 mg is an appropriate first-line therapeutic option for black

patients with hypertension. Based on favorable direct comparisons to full-strength diuretic therapy in black patients, physicians may want to reevaluate their current treatment preferences in this patient population.

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