Drug Treatment Considerations for the Hypertensive Black Patient

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In prior years the major differences noted between hypertension in black and white patients have been mostly epidemiological, with some suggestion that the differences were primarily quantitative and probably not qualitative. Recently, certain pathophysiological aberrations in hypertensive patients have been shown to be different in blacks and whites. Whether these differences are primary (genetic) or secondary has yet to be resolved. Nevertheless, certain racial differences may have therapeutic implications. Diuretics remain the mainstay of therapy for most hypertensive black patients. β-Blockers and angiotensin-converting enzyme (ACE) inhibitors have not shown great efficacy when used as monotherapy in black hypertensive patients. The combination of a diuretic with β-blockers or ACE inhibitors, however, has been shown to abolish black-white differences in drug response. More recently, the calcium channel blockers have been shown to be potentially effective in black hypertensive patients. In spite of the effective drug therapy that is available for hypertensive patients in general, economic and social considerations continue to contribute to the low rate of detection, treatment, and control of hypertension in the black population.

The medical consensus concerning treatment of essential hypertension has undergone considerable change in recent years. Large multicenter studies have provided evidence of the health benefits that can be gained from control of even mild degrees of hypertension.[1–3] The development of newer, more selective antihypertensive drugs has proceeded almost in parallel with a growing awareness of the possible causes of essential hypertension. As an understanding of "first causes" becomes clearer, drug therapy can be designed to target specific, crucial steps in the physiological cascade leading to development of the hypertensive state. The physician must consider many factors when tailoring an antihypertensive regimen for an individual patient. One of these factors, the patient's race, will be the subject of this paper.

ETIOLOGY OF HYPERTENSION IN BLACKS

In blacks hypertension is both more prevalent and more severe than in whites.[4,5] The elements that precipitate or predispose to hypertension in blacks and whites are qualitatively similar, differing primarily in degree. At present, the relative contributions of heredity and environment to the etiology of essential hypertension remain unresolved, but black-white differences have been noted in a variety of studies.

Some of the mechanisms responsible for the development of hypertension may be under direct genetic control. A comprehensive review of studies in black populations in South Carolina, Detroit, Brazil, and West Africa by Gillum[6] provides conflicting data on this point. Many of these studies did not control for confounding such variables as social class, education, or environmental factors. Nonetheless, in the Detroit study, darker skin color was related to blood pressure independently of other influences. This study revealed no differences between blacks and whites in heritability patterns within families. In the Brazilian population, no correlation occurred between blood pressure and the degree of black and white admixture. These results contrast with those found in a black clinic population in the United States, where diastolic blood pressure correlated with a serologically determined percentage of African admixture. Interestingly, West African blacks tend to have lower blood pressures than their United States counterparts, despite the gene pool of United States blacks originating primarily from the West African coast.

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Blood pressure tends to increase with age in both blacks and whites, but the rise is steeper in blacks. Adult white men have higher blood pressures than adult white women until about the age of 45 years, when the situation reverses. Black women tend to have higher blood pressure than black men at all ages over 35 years.[6] On the other hand, the influence of body weight on blood pressure is similar in blacks and whites, although it is proposed that weight loss may produce a better antihypertensive effect in whites than in blacks.

An examination of the influence of physiology on blood pressure yields further differences between blacks and whites that might affect the age of onset, incidence, and severity of hypertension in the two races. More blacks than whites have low levels of plasma renin, indicating suppression of the renin-angiotensin system.[7] This relationship holds true for both normotensive and hypertensive blacks. Expanded plasma volume, secondary to decreased sodium excretion in blacks, may account for some of the racial differences in hypertensive individuals. Kallikrein may mediate some of these effects. Urinary kallikrein excretion is lower in black hypertensive patients than it is in white hypertensive patients; normotensive blacks and whites show similar levels of urinary kallikrein excretion.[8]

In the United States, the fatality rate for hypertensive blacks is three times that of hypertensive whites. Vascular damage, retinal damage, and left ventricular hypertrophy are all more common and more pronounced in black than white hypertensive patients.[6,9] Blacks may have a greater incidence of adrenal cortical abnormalities than whites; this finding could have an effect on the occurrence of hypertension in these two racial groups. Levy and coworkers[10] found that although age, blood pressure, and plasma renin were not different between 19 white and eight black hypertensive subjects, the black hypertensive patients had more severe renal arterial nephrosclerosis than their white counterparts. Renal blood flow was also lower in the black subjects. These findings may be the result of an increased susceptibility to such changes in blacks or to a longer duration of undetected, untreated, or inadequately treated elevated blood pressure.

Environmental differences between blacks and whites must also be considered when examining racial variation in hypertension. Despite progress against discrimination, vastly different socioeconomic conditions still exist for many blacks in this country. Low educational and occupational status for blacks may translate into reduced awareness of medical problems and decreased accessibility to treatment. Educational level is inversely associated with the prevalence of hypertension in both blacks and whites.[4] In a recent analysis of the Hypertension Detection and Follow-up Program data,[11] blacks and whites with less than a high school education in the referred care segment of the study had a five-year death rate twice that of those with more than a high-school education. Nutritional deficiencies in some black populations, including reduced intake of potassium and calcium, may be either cultural or economic in origin.

As one might suspect, all of the variables discussed above may have an impact on the efficacy of various antihypertensive drug regimens in blacks, both from a physiological standpoint and with respect to compliance with a prescribed course of treatment. Indeed, studies confirm that responses by blacks to currently available antihypertensive agents are qualitatively different from those by whites to some drugs.

TREATMENT STRATEGIES FOR BLACK HYPERTENSIVE PATIENTS

The general approach to treating hypertension in blacks is similar to that used for whites. Many physicians use a stepped-care program[5] in which antihypertensive drugs are introduced sequentially in a pharmacologically rational manner until blood pressure is brought to a satisfactory level or until unacceptable adverse effects intervene. Thus, knowledge of racial differences in drug responses will enable the physician to avoid unproductive experimentation and to select quickly the treatment course most likely to produce the desired result.

Because therapy for essential hypertension in most cases will be lifelong, the physician must consider patient acceptance of drug treatment and the effects of therapy on quality of life in addition to therapeutic efficacy when evaluating any given antihypertensive regimen.[12] In most cases, essential hypertension produces no symptoms that would otherwise serve to motivate the patient to comply with the physician's recommendations. If patient acceptance or quality of life is significantly impaired by the antihypertensive treatment, the patient may prematurely discontinue therapy.

MONOTHERAPY

Thiazide Diuretics

Traditionally, for many hypertensive patients the first treatment step involves the use of a diuretic (usually a thiazide or thiazide-like compound) or a β-adrenergic blocker as monotherapy. In recent years, however, routine use of thiazide diuretics as initial therapy has come under close scrutiny. Thiazide diuretics, even in low doses, cause many metabolic and biochemical alterations that conceivably could place the hypertensive patient at higher risk for the development of cardiovascular complications.

TABLE 1. BLOOD PRESSURE LOWERING EFFECT OF HYDROCHLOROTHIAZIDE AND PROPRANOLOL IN BLACK AND WHITE PATIENTS

	Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)	
	Whites	Blacks	Whites	Blacks
Propranolol	−13.2*	−8.2* **	−12.6* **	−9.5* **
Hydrochlorothiazide	−15.3*	−20.3* **	−10.9* **	−13.0* **

* *Significant ($P < .005$) difference between races*
** *Significant ($P < .025$) difference between drugs*
From VA Cooperative Study Group on Antihypertensive Agents, 1982,[18] with permission

Hypokalemia and hypomagnesemia can increase the risk of ventricular ectopy or sudden death in some patients taking thiazide diuretics.[13–15] Thiazide diuretics cause increases in certain lipid components that may increase the risk of developing coronary artery disease.[16] Several large primary prevention trials have shown that, when used for hypertension, thiazide diuretics have not consistently decreased mortality from coronary heart disease.[2,3,17] Thiazide diuretics can impair glycemic control in many hypertensive patients, especially in those with pre-existing glucose intolerance.

Despite drawbacks, thiazide diuretics are effective agents in the hypertensive black population. Thiazide diuretics produce a greater fall in blood pressure at lower doses in black patients compared with white patients[18] (Table 1). At a dose of 100 mg, approximately 56 percent of white patients in this study achieved a diastolic blood pressure of ≤90 mmHg, while approximately 80 percent of blacks reached this same goal. Although thiazide diuretics are effective, easy to administer, and inexpensive, one must question whether the routine use of thiazide diuretics is appropriate for every hypertensive patient, especially those diuretics that cause potassium wasting.

β-Blockers

With all the controversy surrounding the use of thiazide diuretics, alternate agents that are effective as initial antihypertensive therapy are being sought. β-Blockers are widely used in Europe for this indication. β-Blockers are less effective in blacks than in whites[18] (Table 1); higher doses may be required to achieve comparable blood pressure control in blacks. The different response of blacks to thiazide diuretics and β-blockers may reflect racial differences in the pathophysiology of hypertension. β-Blockers, which lower plasma renin, would be less effective in low-renin or salt-sensitive hypertensive blacks, while thiazide diuretics would reduce the expanded plasma volume in blacks, and thereby produce a greater fall in blood pressure.

Through blockade of cardiac β-receptors, β-blockers cause a decrease in heart rate and a decrease in cardiac output, and they prevent exercise-induced increases in heart rate. β-Blockers are not free of adverse metabolic effects; noncardioselective β-blockers can adversely affect plasma lipids and glucose tolerance. Adverse central nervous system effects (sleep disturbances, lethargy, irritability, and hallucinations) have been reported, usually after chronic use of high doses of a β-blocker. Although β-blockers have been shown to decrease cardiovascular morbidity and mortality, when given after an acute myocardial infarction, this benefit has not been demonstrated prior to the appearance of clinical coronary artery disease.[2,17]

α_1-Blockers

Prazosin, an α_1-adrenergic blocker, is an effective antihypertensive agent by itself, but patients may eventually require addition of a diuretic because of prazosin's salt- and water-retaining properties. Prazosin is usually administered two or three times daily. Syncope has been reported after administration of the first dose of prazosin. This side effect can be minimized by using a small initial dose (1 mg), and by giving the first dose in the evening, before bedtime. Increases in dose should be made slowly. Prazosin may improve the lipid status of patients by lowering low-density lipoprotein (LDL) cholesterol levels; it may also increase high-density lipoprotein (HDL) cholesterol levels.[19,20]

Calcium Channel Blockers

Calcium channel blockers may provide another option for single-drug antihypertensive therapy in blacks, although experience with these agents is limited. Verapamil is the only calcium channel blocker currently approved by the Food and Drug Administration for use in hypertension, although nifedipine and diltiazem have also been used successfully. Possibly because of their direct vasodilating actions, calcium channel blockers may be more effective in low-renin hypertensive patients. Calcium channel blockers are not associated with the adverse metabolic effects of the thiazide diuretics and β-blockers and are clinically well tolerated. Common adverse reactions include constipation (verapamil) and headache or flushing (nifedipine). Diltiazem and verapamil should be used cautiously in patients with underlying cardiac conduction defects. Bradycardia and heart block have been reported in less than 1 percent of patients using these drugs. These drugs should also be used carefully when there is a potential for congestive heart failure, as they can depress systolic myocardial function.

TABLE 2. BLOOD PRESSURE RESPONSES TO CAPTOPRIL AND HYDROCHLOROTHIAZIDE IN WHITE AND BLACK PATIENTS AT FOUR WEEKS

		Supine Blood Pressure (mmHg)		Change	
	Race (n)	Before Treatment	After Treatment	mmHg	Percent
Captopril	White (154)				
Systolic		171.3	149.3	−22	−12.8
Diastolic		110.8	95.2	−15.6	−14.1
Hydrochlorothiazide	White (92)				
Systolic		167.3	145.2	−22.1	−13.2
Diastolic		109.8	94.6	−15.2	−13.8
Captopril	Black (20)				
Systolic		165.7	156.2	−9.2	−5.7
Diastolic		107.8	97.1	−10.7	−9.9
Hydrochlorothiazide	Black (10)				
Systolic		163.7	134.5	−29.2	−17.8
Diastolic		107.7	92.2	−15.5	−14.4

From Moser and Lunn, 1982,[26] with permission

Placebo-controlled trials[21–23] have demonstrated the efficacy of nifedipine and verapamil in small numbers of blacks (<50), and in a comparative study by Moser and co-workers,[24] hydrochlorothiazide and diltiazem were shown to have equivalent effects in lowering blood pressure in 20 black hypertensive patients. Halperin and associates[25] have shown that verapamil lowered blood pressure equally in blacks and whites, but propranolol was more effective in whites than blacks.

ACE Inhibitors

Initial therapy with angiotensin-converting enzyme (ACE) inhibitors (captopril, enalapril) has also been suggested as an alternative to thiazide diuretics, β-blockers, and calcium channel blockers. When used alone, blacks are somewhat less responsive to this class of drugs than are whites[26–28] (Table 2). This lower response rate may be because the complete mechanism of action of ACE inhibitors has not been entirely defined. ACE inhibitors block angiotensin-converting enzyme, which converts inactive angiotensin I to angiotensin II, a potent vasoconstrictor. Converting enzyme activity may gradually return toward normal during long-term therapy, although blood pressure reduction persists. Other mechanisms, therefore, must play a role in the antihypertensive vasodilatory effect of ACE inhibitors.

ADVERSE DRUG EFFECTS

Adverse effects of antihypertensive drugs are well-documented,[5,13] and can be minimized by adjusting the dosage or substituting a different drug from the same class. For instance, thiazide-induced hypokalemia can be alleviated by substituting a potassium-sparing diuretic. A noncardioselective β-blocker such as propranolol is contraindicated in patients with bronchial asthma; substitution with low doses of a cardioselective β-blocker such as metoprolol or atenolol may be a more appropriate treatment strategy if no alternatives are available. With larger doses, though, these agents lose their cardioselectivity and should not be used in those with bronchial asthma. Low doses of ACE inhibitors effectively reduce the incidence of adverse effects without compromising blood pressure control.[27,29,30] In blacks, however, larger doses or the addition of a diuretic may be required. ACE inhibitors are useful in patients unable to tolerate the adverse metabolic or biochemical adverse effects of thiazides or β-blockers. To avoid postural hypotension, ACE inhibitors should be used with care in patients who are volume- or sodium-depleted from diuretic use. ACE inhibitors do not cause hypokalemia, hyperuricemia, impaired glucose tolerance, or changes in lipid status.

COMBINATION THERAPY

Patients whose blood pressure does not respond adequately to monotherapy become candidates for combination therapy. When drugs are used in combination, doses of the individual agents often can be reduced. Most cases of essential hypertension in blacks can be controlled by second-step combination therapy. Racial differences in response to both β-blockers and ACE inhibitors are abolished when combined with a diuretic.[27,28,31,32]

TABLE 3. THERAPEUTIC EFFECT OF CAPTOPRIL AND HYDROCHLOROTHIAZIDE (HCTZ), ALONE AND IN COMBINATION

	Placebo		Monotherapy		Captopril-HCTZ Treatment	
	Captopril	HCTZ	Captopril	HCTZ	3 mos	12 mos
Number of patients	11	7	11	7	15	12
Blood pressure (mmHg)						
Supine						
Systolic	159 ± 4	161 ± 5	154 ± 4	128 ± 6	120 ± 2**	125 ± 1.9**
Diastolic	103 ± 1	103 ± 2	99 ± 2	86 ± 4	80 ± 2**	83 ± 1.1**
Standing						
Systolic	151 ± 4	156 ± 4	146 ± 4	121 ± 6**	111 ± 3**	116 ± 2.2**
Diastolic	100 ± 1	101 ± 1	96 ± 2*	83 ± 3**	76 ± 2**	81 ± 0.8**

*$P < .05$ compared with placebo
**$P < .01$ compared with placebo
From Holland et al, 1983,[31] by permission of the American Heart Association, Inc

In blacks a thiazide diuretic plus a β-blocker has been shown to be a useful combination.[32] Addition of a thiazide diuretic to a β-blocker may prevent the water retention that may accompany β-blocker use. The effects of captopril and hydrochlorothiazide alone and in combination in blacks with salt-sensitive hypertension are shown in Table 3.[31] ACE inhibitors ameliorate the potassium depletion caused by thiazide diuretics and blunt the changes in uric acid, glucose, and cholesterol induced by diuretic therapy.[33] Neither captopril alone nor in combination with low-dose hydrochlorothiazide has been shown to negatively influence quality of life.[12]

Advanced stages of stepped-care therapy involving the use of multiple drug combinations should be reserved for special cases of refractory hypertension. Hydralazine, minoxidil, and guanethidine are generally more potent, more likely to be used in combination with other drugs, and more likely to produce serious, unacceptable adverse effects.[5]

COMMENT

Black hypertensive patients present a special challenge for the physician. They are not only more likely than whites to be hypertensive but also more likely to suffer from the secondary consequences of the disease: congestive heart failure, stroke, and accelerated nephrosclerosis. Added socioeconomic factors may make blacks less liable to seek or continue treatment for hypertension. Although the black-white ratio with respect to the incidence of hypertension appears to be decreasing over time, the reasons for this development are not clear.[34]

Perhaps the greatest need for the black population is in the area of high blood pressure education. Increased awareness of the complications of hypertension and the need for treatment should be encouraged in the black community. Many cases of mild hypertension can initially be controlled by weight loss and salt-restricted diets. If these individuals are identified early in the course of the disease, the need for pharmacological intervention may be reduced or eliminated entirely.

Newer antihypertensive agents, such as ACE inhibitors and calcium channel blockers, make more options available to the physician for the management of black hypertensive patients. Clinical studies have confirmed the efficacy of thiazide–ACE inhibitor and thiazide–β-blocker combinations in blacks. With a thiazide diuretic–ACE inhibitor combination, blood pressure can be normalized without the burden of adverse metabolic and subjective effects that might lead to discontinuation of therapy. Early data also suggest that calcium channel blockers may be effective in black hypertensives. In years to come these advances will have positive public health consequences as morbidity and mortality from hypertension-related causes decrease.

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