Metabolic consequences of antihypertensive therapy

JEFFREY W. OLIN, D.O.
Cleveland, Ohio

In addition to hypertension, metabolic abnormalities such as elevated serum lipid levels, glucose intolerance, and hypokalemia, increase risk for adverse cardiovascular events. A number of commonly used antihypertensive drugs produce biochemical changes that increase the prominence of one or more of the additional risk factors as they lower blood pressure. Thiazide diuretics, for example, produce dose-related elevations in serum cholesterol and glucose values, as well as significant decreases in serum potassium. Although beta-blockers do not clinically affect potassium metabolism significantly, they do raise both cholesterol and glucose levels. The angiotensin-converting enzyme inhibitor captopril is the first of a new class of antihypertensive agents that lower blood pressure as effectively as previous therapies without adversely affecting serum levels of total, high-density lipoprotein, and low-density lipoprotein cholesterol or triglyceride, glucose, or potassium levels. In addition, captopril has been shown to blunt the adverse metabolic consequences of diuretic therapy when the two agents are administered concomitantly. It appears that the stepped-care approach is now too simplistic and that the design of antihypertensive regimens in the 1980s should be approached judiciously and on a more individualized basis.

The classic approach to antihypertensive therapy, as recommended by the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure,¹ utilizes a stepped-care framework in which treatment is begun with either a thiazide diuretic or a beta-blocking agent. If the first type of drug fails to control blood pressure adequately, the second type is added to the

therapy. If blood pressure is still not well controlled, a vasodilator is added as a step-three medication. While this treatment plan may be effective in lowering blood pressure, it discourages individualization of the antihypertensive regimen and does not fully consider the problems introduced by various therapies. In many patients, the price for lowering elevated blood pressure is an increase in other cardiovascular risk factors.

Elevated lipid levels, glucose intolerance, and hypokalemia as cardiovascular risk factors

The Framingham Study² demonstrated that cardiovascular morbidity and mortality are directly related to total cholesterol levels. In the Honolulu Heart Program,³ fatal coronary heart disease was almost twice as prevalent in patients with elevated serum cholesterol values as in random sample patients; the incidence of fatal coronary heart disease was more than two times higher for patients with elevated serum triglyceride levels as for the random sample group. The Framingham data² also indicated that the incidence of coronary heart disease is inversely related to the level of high-density lipoprotein (HDL) cholesterol, and, indeed, HDL cholesterol may be the single most powerful determinant of cardiovascular risk.

Glucose intolerance is a second identified risk factor for cardiovascular disease. In the Whitehall study,⁴ investigators demonstrated that glucose intolerance and diabetes mellitus pose a heightened risk for the development of coronary heart disease. Their data also suggested that hypertension was extremely important as a cardiovascular risk factor in these patients. Glucose intolerance also has been correlated with raised serum cholesterol and triglyceride values and may increase risk secondarily by raising blood lipid levels.⁵

A decreased serum potassium level is a third metabolic risk factor for adverse cardiovascular events. Asymptomatic hypokalemia may place the patient at increased risk for sudden cardiovascular death,⁶ especially in the presence of pre-existing electrocardiographic (EKG) abnormalities. The Multiple Risk Factor Intervention Trial Research Group⁷ found that hypertensives with resting EKG

abnormalities were at greater risk for sudden coronary heart disease deaths than were hypertensives without such phenomena. The exact reason for this is unclear.

Antihypertensive agents and serum lipid values

The antihypertensive agents that are most clearly implicated in producing elevated serum lipid levels are thiazide diuretics and beta-blockers. In a double-blind crossover study⁸ comparing hydrochlorothiazide, chlorthalidone, and placebo in patients with mild hypertension, mean plasma cholesterol increases of 14.8 ± 3.0 mg./dl. and 18.8 ± 3.6 mg./dl. were documented for patients taking hydrochlorothiazide and chlorthalidone, respectively. Increases in triglyceride levels were even more marked. This represents a clear trade-off, in that blood pressure was effectively lowered at the expense of increases in blood lipid levels. To illustrate, accumulated data⁹ suggest that a 50-year-old male nonsmoker with a diastolic blood pressure of 100 mm. Hg and a serum cholesterol level of 202 mg./dl. has a 3.2 percent risk of myocardial infarction within 5 years and an 18 percent risk within 20 years. If a thiazide diuretic were given without adequate dietary control and the diastolic blood pressure decreased to 90 mm. Hg while the serum cholesterol value rose to 238 mg./dl., the 5-year risk probability is still 3.2 percent, while the 20-year risk is 17 percent. Even though blood pressure would be lowered, there would be little change in the overall cardiovascular risk profile. Similar risk factor balancing may underlie the failure of some studies¹⁰ to demonstrate significant decreases in coronary mortality of patients with mild hypertension.

Elevated levels of total serum cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides increase the risk of coronary artery dis-

ease; HDL cholesterol, in contrast, aids in removing lipids from tissues.¹¹ Generally, beta-blockers (except pindolol, acebutolol and labetalol) have been shown to increase triglycerides and to decrease HDL cholesterol.^{11,12} The Australian Risk Factor Prevalence Study¹³ showed that metoprolol produces a significant decrease in HDL cholesterol levels, a significant elevation in serum triglyceride values, and a significant increase in the ratio of total cholesterol to HDL cholesterol.

The centrally-acting antihypertensive agents do not seem to raise total cholesterol levels.¹⁴ However, methyl dopa has been shown to reduce HDL cholesterol levels significantly and to elevate the ratio of total cholesterol to HDL cholesterol.¹⁵ The alpha-adrenergic drug guanabenz appears to decrease total serum cholesterol.¹⁶ Agents not known to alter serum lipid profiles or decrease serum lipid levels include prazosin^{11,17} and calcium entry blockers.^{18,19} Among vasodilators, hydralazine and minoxidil are direct-action agents that have no effect on lipid levels.¹¹ However, they stimulate the sympathetic nervous system, causing tachycardia, and they also may cause significant salt and water retention. Thus, a diuretic and/or a beta-blocker frequently must be used with one of these two vasodilators, thereby altering lipid metabolism.

Captopril, an angiotensin-converting enzyme (ACE) inhibitor, does not alter total cholesterol (Fig. 1).²⁰ Moreover, when captopril is added to thiazide diuretic therapy, the diuretic-associated rise in serum cholesterol may be effectively blunted.²¹

Antihypertensive agents and glucose tolerance

Thiazide diuretics cause increases in blood glucose levels that are generally reversible when therapy is discontinued.²² Similarly, increases in both fasting blood sugar and 2-hour postprandial blood glucose values have been demonstrated in patients receiving propranolol monotherapy.²³ Beta-blockers also produce a decrease in serum insulin; this effect is observed with both cardioselective and noncardioselective agents.^{24,25} Labetalol, which has alpha-blocking as well as beta-blocking activity, has no apparent effect on serum glucose values.²⁶

Among centrally-acting agents, clonidine has been associated with early reductions in glucose tolerance,²⁷ while guanabenz has not.²⁸ The peripheral alpha-blocker prazosin increased plasma glucose in a short-term trial,²⁹ but not on longer administration.³⁰ The ACE inhibitor captopril has no effect on serum glucose, as confirmed in patients treated for several years.³¹ In addition, the expected rise in blood glucose levels following administration of a thiazide diuretic is often blunted by cap-

Fig. 1. Effects of hydrochlorothiazide, captopril, and both in combination. (Adapted from Weinberger,²⁰ with permission.)

topril during combination therapy²⁰ (Fig. 1).

Antihypertensive agents and hypokalemia

Hypokalemia continues to be one of the more worrisome derangements observed during diuretic therapy. Studies by Hollifield and Slaton⁷ and Holland and Associates³² point toward higher risk of cardiac arrhythmias during periods of diuretic-induced hypokalemia. Most other antihypertensive drugs have not been associated with low-potassium levels. Captopril does not affect serum potassium levels and lessens the degree of hypokalemia produced by concomitantly administered diuretics (Fig. 1).²⁰ Similar effects on serum potassium, as with lipid and glucose levels, may be anticipated with the ACE inhibitor enalapril. Potassium-sparing diuretics and dietary potassium supplements generally are unnecessary during ACE inhibitor therapy, therefore, except for patients in whom hypokalemia has been recorded.

Conclusion

In summary, all of the available antihypertensive agents effectively lower elevated blood pressure. However, many of these agents have concurrent adverse effects on other known cardiovascular risk factors, including lipid profiles, glucose tolerance, and potassium metabolism. The impact of such antihypertensive medications on cardiovascular morbidity and mortality may be substantially negated by their secondary results. The addition of an ACE inhibitor, which does not produce such side effects, to the antihypertensive armamentarium makes it possible to set aside the outdated constraints of the stepped-care approach and to formulate antihypertensive therapy on an individualized basis.

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At the time this paper was written, Dr. Olin was director of the Hypertension Clinic, Western Pennsylvania Hospital, and clinical instructor of medicine, University of Pittsburgh. He is now an associate staff member in the Department of Peripheral Vascular Disease, Cleveland Clinic Foundation, Cleveland, Ohio.

Dr. Olin, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106.