Tailoring antihypertensive treatment: Which patients, what therapy?

WILLIAM NEAL, M.D.
Dallas, Texas

At present, several safe and effective drugs are available for the treatment of hypertension, and it is no longer appropriate to adhere to a rigid protocol when starting therapy. Each class of agents—diuretics, beta-blockers, alpha-blockers, sympatholytics, ACE inhibitors, and calcium channel blockers—are associated with potential positive and negative effects. The thoughtful physician will weigh these potential effects of each class of drugs on individual patient factors in order to optimize selection of therapy. Factors to be considered in choosing the initial antihypertensive agent include efficacy, adverse reactions profile, and appropriateness for patients, based on demographic data, metabolic and hemodynamic consequences, and concomitant diseases. Captopril, the first angiotensin-converting enzyme (ACE) inhibitor, appears to be well suited for initial therapy in uncomplicated hypertension in many patients. This drug has the advantages of specific mechanism of action and positive hemodynamic profile, a low incidence of troublesome side effects, low incidence of metabolic derangements, and the ability to preserve the patient's well being. Captopril may be the agent of choice in the hypertensive patient with a concurrent illness, such as diabetes, congestive heart failure, peripheral vascular disease, or chronic obstructive lung disease.

This paper discusses the task of selecting appropriate therapy for the individual hypertensive patient. After some basic premises regarding the use of antihypertensive medications are reviewed, the

major classes of drugs that have been used to treat hypertension will be discussed, followed by a review of the management of hypertensive patients who demonstrate specific concurrent conditions.

The first premise worth noting is that the blood pressure response to a given antihypertensive agent is not predictable with certainty in an individual patient. When we observe *mean* blood pressure changes in large clinical trials using specific antihypertensive agents, we are assured that these drugs are effective; however, when we review the cases of *individual* patients who have been so treated, there are many nonresponders. In fact, the likelihood of rendering even mildly hypertensive patients normotensive with any one form of therapy can be as low as 50 percent. Thus, on the one hand, we should accept the dual reality that the initial drug choice will often be ineffective.

The second premise is that the negative impact of the drug—the appearance of bothersome side effects, metabolic derangements, or deterioration of their quality of life—also is not predictable in the individual patient. Of course, clinical studies are quite useful here too, because if the overall incidence of any negative effect is high with a particular agent, the physician might choose to avoid that agent in initial therapy. However, it must be remembered that there is no substitute for careful monitoring of the patient for the appearance of negative effects once a regimen is begun.

The third premise is that monotherapy usually is preferable to combination therapy; this recommendation is something of a departure from stepped-care management. I propose that if the agent initially selected is less than fully effective, rather than adding a second medication, simply stop that drug and use one from another class of agents. This approach might be termed substitution therapy.

The fourth premise is that clues to which agents are more or less appropriate may be gleaned from individual patient characteristics. First, one should examine demographic factors, including age, gender, race, and level of pretreatment blood pressure. Second, one should evaluate the potential

effects of the treatment on serum chemistries, lipid profile, hemodynamics, organ function, mental function, and desired level of physical activity. Third, one should assess the potential positive and negative impact of the agent selected on any concurrent medical conditions.

Although no formula can be written that will lead the physician to an automatic answer as to which agent is most appropriate, attention to these variables should guide the thoughtful physician to the best therapy. For some patients, one variable may dominate the decision; for others, many variables may have to be weighed against one another. Some applications of this approach follow.

Classes of antihypertensive drugs

Diuretics

It should not be assumed that the advent of newer agents has rendered diuretics obsolete. For example, black and certain elderly hypertensive patients may still be appropriately treated initially with low-dose diuretics, because of the high response rate in these patients. In addition, volume-expanded hypertensives and those with renal insufficiency, enlarged hearts, or overt congestive heart failure are usually candidates for diuretics because of their efficacy not only for the hypertension but also for the associated condition. Nevertheless, the concerns raised over the potential negative effect of diuretics on cardiovascular risk deserve our attention, and in the absence of a specific indication for a diuretic, another class of agent is likely to be more appropriate. I believe that if a mildly hypertensive untreated patient demonstrates an abnormal pretreatment electrocardiogram or baseline abnormalities in lipids, glucose, or uric acid, diuretics should be avoided. Also, if the patient is physically very active, one should consider alternative therapies that do not affect potassium metabolism.

This may be the proper time to raise the issue of the relative cost of various antihypertensive therapies, because diuretics are certainly the least expensive of the antihypertensive drugs when only the cost of the drug itself is considered. However, it is worthwhile to consider also the "hidden costs" of diuretic therapy. I believe that the patient's lipids, potassium, uric acid, and glucose levels must be ascertained, and EKG should be followed to assure that no harm is being done by the diuretic. All of these incremental expenses may bring the overall costs of diuretic therapy into the same range as those of other antihypertensive agents.

Beta-blockers

There are subsets of the hypertensive population

for which initial beta-blocker monotherapy remains appropriate, because of the greater likelihood of effectiveness in these patients or because of associated conditions that also are benefited by beta-blockade. These subsets include younger white patients, who should not or will not exercise vigorously, postmyocardial infarction hypertensives, and hypertensives with angina, migraine, or asymmetric septal hypertrophy. In addition to the usual contraindications to beta-blockers, I would include the presence of lipid abnormalities; it is appropriate to follow lipid values in patients on beta-blocker therapy. For highly active patients, I usually consider beta-blockers to be inappropriate, because beta-blockade critically impacts on the patient's ability to respond maximally to exercise.

Sympatholytics

Sympatholytic drugs have ever-decreasing popularity because of their high incidence of central nervous system side effects, and I regard them as the least preferable of the available agents because of this. These traditional step-2 agents, including methyl dopa, clonidine, guanabenz, and reserpine, are only marginally effective without the concomitant use of a diuretic. It may be surprising that, for the small number of patients for whom I continue to use sympatholytics (those who need a multiple-drug regimen for control), I favor reserpine over the others because of its low cost, long duration of action, and low incidence of side effects at low doses.

Alpha-blockers

The alpha-blocker prazosin has been shown to be effective monotherapy in some studies,¹ although it traditionally is used with a diuretic. The incidence of side effects is low with prazosin use. The drug is particularly useful in hypertensive patients with lipid abnormalities, and because of its ability to decrease peripheral resistance, to correct the hemodynamic abnormality present in most hypertensives. There are virtually no negative effects on any other concomitant diseases.

Calcium channel blockers

Calcium channel blockers are effective as antihypertensive monotherapy. They are suitable for low-renin patients, the elderly,² and hypertensives with another indication for calcium channel blockade, such as angina. They offer the advantage over diuretics in these groups of not stimulating renin or aldosterone.³ The new sustained release form of verapamil, which allows for once daily dosing, makes this calcium channel blocker as convenient to take as other antihypertensives. However, they

are one of the most expensive forms of antihypertensive therapy. Also, the diffuse effects of these agents on the numerous cellular processes dependent on calcium entry may be reason for concern; they are negative inotropes, may affect atrioventricular conduction, and may impair insulin secretion. In addition, the incidence of bothersome side effects of headache, flushing, and edema is high (about 15 percent).⁴

Angiotensin-converting enzyme (ACE) inhibitors

Both of the ACE inhibitors captopril and enalapril effect reductions in blood pressure in all types of hypertensive patients. However, the experience with captopril has been much more extensive than that with enalapril. The magnitude of the antihypertensive effect achieved with these agents depends on the degree of activation of the patient's renin-angiotensin system, but adequate control is also often obtained in low-renin patients, presumably because of non-renin-mediated mechanisms.⁵ Because diuretics stimulate this system, they "prep" the patient for the maximal therapeutic response to captopril, in addition to their own antihypertensive effect per se. Therefore, this combination is attractive, and a low dose of a thiazide diuretic is often added to ACE inhibitor monotherapy early during titration.

What sets ACE inhibitors apart from other agents is what they do not do. Because of their unique mechanism of action, these drugs are essentially free from the symptomatic effects that can interfere with a patient's feeling of well-being,⁶ which are so common in all other classes of agents. In addition, ACE inhibitors do not cause the metabolic abnormalities associated with diuretics—hypokalemia, hyperlipidemia, glucose intolerance, and hyperuricemia.⁷ In fact, when captopril is combined with a thiazide diuretic, many of the derangements related to diuretic monotherapy are actually blunted.⁷ Because ACE inhibitors suppress aldosterone, they can preserve serum potassium, thus making the concomitant use of a potassium supplement or potassium-sparing diuretic less likely.⁷

Selecting patients for ACE inhibition. ACE inhibitors can be considered for first-line therapy for almost all hypertensive patients. Special caution is advised in patients with renal impairment or collagen-vascular disease; while the drugs are valuable, even lifesaving for these patients, their use must be monitored closely because of increased incidence of toxicity in these two groups. ACE inhibitors can be used for newly diagnosed hypertensives and are also appropriate for patients who are

experiencing unacceptable side effects from other antihypertensive agents. This class of drugs can be especially valuable in certain special patient groups:

Hypertension with heart failure. Captopril currently is approved for the treatment of heart failure, while enalapril is not. Captopril is a highly appropriate addition to initial diuretic therapy in patients with both hypertension and congestive heart failure. The drug lowers blood pressure by reducing peripheral resistance and unloading the left ventricle, improving cardiac function, and increasing exercise tolerance.

Hypertension with diabetes. There is a relative contraindication to the use of diuretics, beta-blockers, and calcium channel blockers in diabetics. Diuretics disturb potassium metabolism, which in turn may produce a deterioration in glucose tolerance; beta-blockers may interfere with glucose tolerance and may mask the symptoms that allow the patient to be aware of hypoglycemia. Calcium channel blockers may interfere with insulin release. In contrast, captopril does not disturb glucose metabolism and has no effect on the perception of hypoglycemia. Also, it has no known adverse interactions with the therapy for diabetes, and, in a recent preliminary study,⁸ captopril has been shown to be associated with reduced proteinuria in some diabetic patients. Diabetics with renal insufficiency, hyporeninemic hypoaldosteronism, or proteinuria should be appropriately monitored when captopril is initiated.

Hypertension with chronic pulmonary disease. Diuretics probably should not be used in these patients unless there is also overt right heart failure. The reasoning is that patients with chronic lung disease are borderline or overtly hypoxemic, which constitutes a risk factor for cardiac arrhythmias. Adding diuretics can result in a fall in serum potassium, thus creating an additional risk for arrhythmias. The contraindication for beta-blockers in this population is the risk of bronchospasm. The choice of captopril as primary monotherapy in this subset of patients seems particularly attractive, because it has no deleterious effects on airway function or on common therapies for pulmonary disease.

Hypertension with peripheral vascular disease. If a hypertensive patient also demonstrates a significantly compromised peripheral blood flow, it clearly would be preferable to administer captopril and increase flow rather than to further decrease flow, such as would occur with a beta-blocker. The

concept of peripheral vascular disease is used here in its most generic sense, that is, whether one is considering transient ischemic attacks, completed strokes, angina pectoris, or claudication. In all cases, one should attempt to increase flow while lowering blood pressure.

Hypertension with renal insufficiency. In such cases, loop diuretics should be considered initially, because virtually all of these patients are volume expanded. Following the diuretic, judicious use of captopril may be appropriate because of its potentially beneficial effects on renal function.⁹ Urine protein, blood urea nitrogen, serum creatinine, and serum potassium values should all be followed in these patients. When captopril is considered in this patient group, it should be started at very low doses, because it is cleared through the kidneys. If blood urea nitrogen or serum creatinine levels rise during treatment, hypoperfusion states, such as heart failure, volume depletion or bilateral renal artery stenosis should be considered. This is usually reversible with reduction of the diuretic or discontinuation of the captopril.

Elderly patients

Older patients are very susceptible to the adverse effects of antihypertensive agents, such as fatigue and drowsiness. While diuretics historically have been recommended for elderly patients, more recently concerns have arisen about increased metabolic risk factors and hypokalemia-induced arrhythmias. Calcium channel blockers and ACE inhibitors both appear to be good alternatives to diuretics in elderly patients, or, allowing smaller doses of each drug than if used alone, one of these may be used in combination with a diuretic.

Black patients

Generally, black patients respond best to diuretics; however, a large percentage of these patients will not be controlled by diuretic therapy alone and require the addition of a second agent. For these

more difficult patients, the combination of a diuretic and an ACE inhibitor or calcium channel blocker may prove extremely effective.

Conclusion

Even with a judiciously selected step-one agent, many patients will not respond adequately to the initial monotherapy, and a trial with a second, third, or even fourth drug will be required. Moreover, when a response can be achieved only with combination therapy, reducing the dosage of the initial drug or removing it will determine whether the step-two drug is responsible for all of the therapeutic effect. In addition, one must remain sensitive to the issue of negative effects of the drugs, and constantly work toward the goals of achieving good control of blood pressure without either imposing additional risk or compromising the patient's sense of well being.

1. Okun, R.: Effectiveness of prazosin as initial antihypertensive therapy. *Am J Cardiol* 51:644-50, 24 Feb 83
2. Bühler, F.R., et al.: Renin profiling to select antihypertensive baseline drugs. Renin inhibitors for high-renin and calcium entry blockers for low-renin patients. *Am J Med* 77:36-42, 20 Aug 84
3. Lederballe Pederson, O., et al.: Effect of nifedipine on plasma renin, aldosterone, and catecholamines in arterial hypertension. *Eur J Clin Pharmacol* 15:235-40, 1979
4. Ebner, F., and Donath, M.: Fourth International Adalat Symposium, Excerpta Medica, Amsterdam, 1981, p. 25
5. Zusman, R.M., et al.: Renin- and non-renin-mediated antihypertensive actions of converting enzyme inhibitors. *Kidney Intl* 25:969-83, 1984
6. Croog, S.H., et al.: The effects of antihypertensive therapy on the quality of life. *N Engl J Med* 314:1657-64, 26 Jun 86
7. Weinberger, M.H.: Blood pressure and metabolic responses to hydrochlorothiazide, captopril, and the combination in black and white mild-to-moderate hypertensive patients. *J Cardiovasc Pharmacol* 7:S52-5, 1985
8. Taguma, Y., et al.: Effect of captopril on heavy proteinuria in azotemic diabetics. *N Engl J Med* 313:1617-20, 26 Dec 85
9. Jenkins, A.C., et al.: Captopril in hypertension. Seven years later. *J Cardiovasc Pharmacol* 7:S96-S101, 1985

Dr. Neal is a participating investigator, VA Cooperative Studies Program on Antihypertensive Agents, Dallas VA Medical Center, Dallas, Texas.

Dr. Neal, Dallas VA Hospital, 4500 South Lancaster Road, Dallas, Texas 75216.