



DRUG THERAPY

JAN KOCH-WESER, M.D., *Editor*

Management of Hypertension in the Elderly

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THERE is much confusion over what constitutes appropriate management of hypertension in the elderly.¹⁻⁵ Indeed, there is controversy about how one should define the terms elderly and hypertension. Bearing in mind that chronologic and biologic aging are different, one must recognize that differentiation of the two is not usually practicable. In this paper we use the chronologic index of aging and arbitrarily define the elderly as those aged 65 and over. Employing this imperfect criterion, we exclude a group who are apparently prematurely aged, while including the so-called biologically elite who show little evidence of aging into their eighth or ninth decade. Blood pressure is a continuous variable and the risks of morbidity and mortality increase with pressure, there being no clearly defined cutoff point for increased risk. Nevertheless, in this review the term hypertension is taken to mean a systolic pressure greater than 159 mm Hg, or a diastolic pressure greater than 94 mm Hg, or both.

As part of the changing demographic pattern in developed countries the elderly are steadily assuming increasing importance both in absolute numbers and as a percentage of the patient population. Cardiovascular disease and stroke account for the majority of deaths in people over 65 years of age, and morbidity from these diseases is also considerable. Since hypertension is known to be a major risk factor for cardiovascular disease, it is surprising that there is such a dearth of information on the benefits and risks associated with antihypertensive treatment and blood-pressure reduction in this age group. This point is well illustrated by Koch-Weser's observation⁶ that only 10 per cent of patients included in 41 published trials of antihypertensive drugs were over the age of 60.

In this paper we review the association between elevated blood pressure and cardiovascular disease in the elderly and the evidence that treatment with anti-

hypertensive drugs is beneficial. We also discuss the indications for lowering blood pressure and the current practice of drug usage in the elderly.

CARDIOVASCULAR DISEASE AND AGE

The Framingham study^{7,8} demonstrated unequivocally that hypertension is an important risk factor for cardiovascular disease, notably coronary-artery disease, heart failure, and stroke at all ages. Among subjects between 65 and 74 years old, those with hypertension have an annual incidence of cardiovascular disease three times greater than normotensive persons.⁸ In the Veterans Administration Study⁹ age also emerged as an important factor determining morbidity. Though only one in five of all patients in that study were older than 60 years of age, half the morbidity was in the elderly, cerebrovascular accidents and congestive heart failure being the commonest complications.

Elevated Systolic Pressure

Elevation of the systolic pressure may occur with or without a rise in the diastolic level. Most hypertensive patients have a widening of the pulse pressure, and in many the difference between systolic and diastolic pressure increases with age so that elevation of systolic pressure may predominate in the elderly. The most obvious example of this is isolated systolic hypertension in which the diastolic level is 90 mm Hg or less and systolic pressure is greater than 150¹⁰ or 160 mm Hg.¹¹ More often, elderly patients with elevation of diastolic pressure (DP) have a disproportionate increase in systolic pressure (SP). Koch-Weser¹⁰ defined disproportionate systolic hypertension as:

$$SP > (DP - 15) \times 2$$

This definition includes isolated elevation of systolic blood pressure as well as cases in which the systolic pressure is increased out of proportion to an elevation in diastolic level.

Epidemiologic studies indicate that systolic pressure has more prognostic importance than diastolic pressure.⁸ The Framingham Study has shown that systolic pressure correlates as well (or better) with the occurrence of atherothrombotic brain infarction,⁷ ischemic heart disease,¹² and congestive heart failure¹³ than do both systolic and diastolic or mean arterial pressure. Furthermore, isolated elevation of systolic pressure has been shown to be an important risk factor.^{11,14,15}

Tarazi and Gifford¹⁶ pointed out that it should not come as a surprise that cardiac complications such as congestive heart failure should be closely associated with elevation of the systolic blood pressure, since cardiac work (CW) is a function of systolic blood pressure (SP) — stroke volume (SV) and heart rate (HR) being the other two determinants:

$$CW = SV \times HR \times SP$$

When considering the other major complications of

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hypertension, stroke, and coronary-artery disease, the tension developed during systole, though briefer than that in diastole, is at a much higher level and therefore may be more damaging to vessels.

PREVALENCE OF HYPERTENSION

The prevalence of hypertension depends on the arbitrary limits chosen to define it. In the United States National Health Survey 160/95 mm Hg was taken as the lower limit for hypertension and patients aged 65 years were designated as elderly.² According to these criteria the prevalence of hypertension was about 50 per cent. In the setting of a hypertension clinic Koch-Weser⁶ found that disproportionate systolic hypertension was present in 43 per cent of hypertensive patients over 64 years of age and that 45 per cent of these had isolated systolic hypertension. The corresponding values for patients younger than 45 years were approximately 13 per cent and 1 per cent. Colandrea et al.,¹¹ in a survey of an elderly population, found isolated systolic hypertension on initial assessment in 15 per cent, but on repeat examination the prevalence measured fell to about 3 per cent.

VALUE OF ANTIHYPERTENSIVE THERAPY IN THE ELDERLY

It is generally agreed that, irrespective of age, patients with a sustained diastolic blood pressure of 115 mm Hg or greater should receive antihypertensive therapy. Most controversy concerns drug treatment of patients with diastolic pressures in the range of 90 to 115 mm Hg. Though the number of patients over 59 years of age in the Veterans Administration Study⁹ was relatively small (81) the incidence of morbid events observed over a mean duration of 3.3 years was extremely high in the elderly group; antihypertensive treatment had a strikingly beneficial effect in those with diastolic pressures in the range 90 to 104 mm Hg. Furthermore, patients who had a major complication of hypertension before treatment benefited most.

The value of antihypertensive therapy in hypertensive survivors of stroke has been assessed in two studies. In one¹⁷ the overall recurrence of strokes was not affected by antihypertensive therapy, but data for patients aged 70 or more suggested a beneficial effect of therapy in this age group. In the study of Carter¹⁸ overall mortality was reduced by 50 per cent with treatment, and patients whose blood-pressure control was good fared best. The beneficial effect was not seen in patients over 65. However, the number of elderly patients included in this study was rather small (46).

In general, studies on the effectiveness of drug therapy in elderly patients with mild to moderate hypertension contain too few patients for us to reach valid conclusions regarding efficacy and unwanted effects of treatment. We must therefore await the results of well-designed studies containing large numbers of patients and employing various drug regimens.

WHOM TO TREAT

In the meantime there is the clinical problem of deciding which, if any, elderly patients should be given antihypertensive therapy. The associations of hypertension with morbidity and mortality do not ensure that lowering the pressure with drug therapy will be beneficial. Furthermore, drug treatment in the elderly in general can be difficult, and therapy exposes these patients to the unwanted effects of drugs. However, we believe that the evidence indicting hypertension as a major risk factor for cardiovascular problems in this age group does provide a theoretical basis at least for lowering pressure in some patients. In addition, the results so far indicate that treatment does not adversely affect prognosis, and indeed there is some evidence suggesting that treatment is beneficial. Also, the recent introduction of new drugs with fewer side effects, coupled with the rational use of older drugs, permits the treatment of elderly patients with a reasonable expectation of fewer troublesome side effects than was possible 10 or 15 years ago.

We carefully consider starting drug therapy in elderly patients whose blood pressures are greater than 160/100 on two occasions. For patients with diastolic values above 100 but below 110 mm Hg, the presence of complications or systolic values higher than 180 usually sways the balance in favor of treatment. One is then left with patients whose main hemodynamic abnormality is elevated systolic pressure. In these, the main abnormality is a decrease in aortic compliance. This type of hypertension is often resistant to therapy,¹⁶ and if an aggressive line is followed diastolic pressure may be lowered to an extent that embarrasses blood flow to vital organs.¹⁹ At present we do not treat this isolated finding, not only because of these difficulties but also because the value of treatment in this group is not known.

Investigations are mainly aimed at assessing the effects rather than the cause of hypertension and should be kept to a minimum: electrocardiogram, dipstick urinalysis, serum creatinine, serum electrolytes, and urate. Even when secondary hypertension is suspected, extensive investigations should not be carried out unless surgical intervention is feasible and desirable. Attention to other risk factors for cardiovascular disease is not as important as in younger patients.⁸ In fact, blood pressure dominates as the major risk factor in this age group.

GENERAL PRINCIPLES OF TREATMENT

There are many physiologic and pathologic changes accompanying old age that may influence both the pharmacokinetics and the response of the elderly to drugs.^{20,22} Of the pharmacokinetic processes, only absorption seems not to change measurably in old age. The distribution and metabolism of certain drugs are altered, but there are at present no generally applicable rules. Renal elimination of drugs diminishes commensurate with the fall in renal func-

tion that accompanies old age. Drug sensitivity in the elderly has been studied with only a few agents, but the incidence of adverse reactions is higher than in the young. Estimates of the incidence vary, but in patients over 60 years of age it is probably two to three times greater than in younger adults,²³ and antihypertensive drugs must be included among the culprits.^{24,25}

Adherence to Therapy

Failure to adhere to the physician's instructions is now widely acknowledged to be a cause for therapeutic failure.^{26,27} In the present context there are many factors that militate against good compliance. Treatment is long-term in asymptomatic patients; consequently, the likelihood of good compliance is poor unless the benefits of adherence to treatment are carefully explained. In effect, this means a considerable demand on the physician's time. Patients' relatives may have to be advised as well, and verbal education should be reinforced with booklet instruction.

Compliance falls with increasing complexity in drug regimens, and the aim must be to use as few different medications as possible and as few doses. Ideally, not more than two doses per day should be prescribed.

Choice of Drugs

In choosing a particular drug the physician must attempt to combine efficacy with a minimum of unwanted effects. In general, it is best to avoid antihypertensive agents such as methyl dopa, reserpine, and clonidine that cause depression of the central nervous system. Though good data are lacking, it is generally held that the elderly are more prone to the unwanted central-nervous-system effects of these drugs. This generalization must be tempered by an interim report of an ongoing study by the European Working Party on Hypertension in the Elderly,²⁸ in which complications with methyl dopa do not appear to be a problem. The elderly and particularly those with cerebrovascular disease are susceptible to postural hypotension because they have less "responsive" baroreflexes.²⁹⁻³¹ For this reason, adrenergic-neuron blocking drugs (guanethidine, bethanidine, and debrisoquin) that cause postural hypotension should not be used. Using the technique of continuous intraarterial blood pressure monitoring, Goldberg and Raftery³² found dramatically low blood pressures in some older hypertensive patients on these drugs.

Vasodilators hold promise for the future, particularly in systolic hypertension. Under laboratory conditions, nitroprusside infusion causes a reduction in systolic pressure.³³ A number of mechanisms probably operate. First of all, direct action of the vasodilator may increase arterial compliance. Secondly, reduction in diastolic pressure may cause an increase in arterial distensibility. Finally, the elderly show a reduced baroreflex-mediated increase in heart rate.³³ These findings raise the interesting possibility that vasodilators such as hydralazine may be effective and

well tolerated when employed alone and in small doses.

We consider the drug of first choice to be either a beta-adrenergic blocking drug or a thiazide diuretic. Sometimes the choice is determined by the presence of a relative or absolute contraindication to one or the other, such as asthma, peripheral vascular disease, or heart failure with beta-adrenergic blocking drugs, and diabetes mellitus, hypokalemia, or hyperuricemia in the case of thiazide diuretics. In the absence of such factors the choice is more one of personal preference — ours is to use a beta-adrenergic blocking drug in the first instance.

Beta-Adrenergic Blocking Drugs

If care is taken to exclude patients in whom these drugs might be contraindicated, beta-adrenergic blocking agents do not cause many unwanted effects. It is possible that the clinical response in the elderly will be different from that seen in younger patients,³² but properly designed studies of these drugs have not been carried out in elderly hypertensives. There is some evidence³⁴ that responsiveness to beta-adrenergic blocking drugs is reduced in the elderly. On the other hand, there are important pharmacokinetic alterations in the elderly. Propranolol plasma levels³⁵ are much higher in old persons than in the young, and this applies both to the acute and chronic situation. Distribution to tissue is slower, and there is an increase in bioavailability after oral administration owing to a diminution in first-pass metabolism. Metoprolol is eliminated mainly by metabolism, and Kendall and his colleagues³⁶ found marked variation between individuals, particularly among the elderly who tended to have higher and later peak plasma levels than young patients. Thus, the available evidence indicates that higher plasma levels are to be expected in the elderly, and this is consistent with the finding of an increased incidence of adverse reactions with propranolol in elderly patients.³⁷

Diuretics

In the absence of adequate response to beta-adrenergic blocking drugs we add a thiazide diuretic. It may be just as reasonable to start with a thiazide diuretic (which will be cheaper) and, if blood-pressure control is not satisfactory, to add a beta-adrenergic blocking drug. In the Working Party study³⁸ a thiazide (combined with a potassium-sparing diuretic, triamterene) is the basis of treatment. Although this study is not complete, an interim report²⁸ indicates that the diuretic is effective in lowering blood pressure in most patients and that therapy is well tolerated. In a minority of patients (15 per cent) it was necessary to add methyl dopa. A thiazide is preferred to the "loop" diuretic when renal function is good. The evidence is that thiazide diuretics are at least as effective in lowering blood pressure as furosemide.³⁹ The longer duration of action of the thiazide may result in nocturia in some patients. On the other hand, furo-

semide is more likely to cause acute retention or urinary incontinence in susceptible patients.

The question of routine administration of potassium-sparing diuretics or potassium supplements with thiazides in the elderly is a difficult one.⁴⁰ Since the elderly are more sensitive to the potassium-losing effect of thiazide diuretics, potassium supplementation may be necessary. This is in contrast to younger persons with uncomplicated hypertension,⁴¹ who generally do not require potassium supplementation. Unfortunately, the elderly are more prone to hyperkalemia when potassium supplementation is used. If elderly patients are taking digoxin in addition to a thiazide, the case for added potassium-sparing diuretic is stronger. The elderly often find effervescent potassium unpalatable and have difficulty in swallowing large tablets containing potassium. A reasonable approach, used in the Working Party study,³⁸ is to prescribe a combined thiazide/potassium-sparing diuretic preparation. In addition to counteracting potassium loss such a regimen has the advantage of simplicity (one tablet per day), an important consideration from the point of view of adherence to treatment. Other possibilities include a low-dose thiazide (e.g., chlorthalidone, 12.5 mg per day) or combined thiazide/potassium preparations.

The deterioration in glucose tolerance associated with thiazide diuretics occurs to a varying extent in all elderly patients after some years.⁴² This adverse effect occurs sooner and may be more severe than in young patients. Clinical diabetes is unlikely in patients other than those who already have borderline diabetes. Modest increases in serum uric acid can be expected with thiazides; however, such hyperuricemia rarely leads to secondary gout, and in the light of present knowledge it seems to have little importance as a risk factor for cardiac complications.

Usually the goal for therapy is to maintain blood pressure in the region of 150/90 to 160/95 mm Hg. One rarely has to increase treatment above the conventionally accepted maximum doses of beta-adrenergic blocking drugs and thiazide diuretics. In the small group of patients resistant to this line of therapy the addition of a vasodilator such as hydralazine may be appropriate. However, vasodilators may produce an exaggerated hypotensive response, since the usual compensatory response to blood-pressure lowering is attenuated in old people. As in all cases of resistant hypertension, one must steer a sensible course between complicated and expensive high-dose regimens with their attendant risk of adverse reactions and poor compliance on the one hand and ideal blood pressure on the other.

In conclusion, hypertension in the elderly is associated with a high incidence of cardiovascular disease. There is not yet definitive proof that treatment of hypertension in this age group improves prognosis, but a review of the available data does suggest that treatment is beneficial. This being so, we advocate an active, although cautious, approach. There are many areas that require further study, including the prob-

lems of systolic hypertension, the efficacy and safety of various antihypertensive drugs, and compliance with therapeutic regimens in this age group.

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