SPECIAL ARTICLE

Appraisal of Antihypertensive Drug Therapy

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SUMMARY

Four completed prospective studies of drug-treated and control hypertensives utilizing double blind randomized protocols are reviewed for the purpose of evaluating the evidence on which the present therapeutic crusade is based. Patients studied were predominantly male, observed for short period, had complications or died at young age, had high incidence of previous target organ vascular disease, and did not include those whose blood pressure fell to normal with hospitalization alone. Incidence of complications associated with coronary artery disease was the same in control and treated patients. The rapidly progressive disease observed in these patients differs from that described in other natural history studies. Population screening for hypertension for the purpose of instituting drug therapy is premature because the value of antihypertensive drug treatment for the general hypertensive population has not been established.

Additional Indexing Words:
Double blind randomized protocol Population screening

THE MEDICAL PROFESSION is presently being asked to motivate all hypertensive patients to place themselves under medical supervision so that they may be given drugs designed to lower blood pressure to normal or near-normal levels. This therapeutic crusade represents a challenge 1) to the medical profession in terms of commitment to a program that asks that it place its hypertensive patients on one or more medications and 2) to persons with elevated blood pressure to remain on drug therapy for the rest of their lives. It means that teenagers and young adults will learn of possible complicating morbid events of heart, brain and kidney disease and of a shortened life. It would be well to re-examine the evidence on which this crusade is based before committing a large proportion of our population to life-long drug therapy.

Indirect support for the use of blood pressure lowering drugs in the treatment of hypertensive disease derives from insurance company data that indicate morbidity and mortality are increased in the hypertensive as compared to the normotensive population¹ and from a prospective study in which the presence of hypertension was found to be a "risk" factor in the course of coronary vascular disease.² These data indicate a significant relationship between hypertension and morbidity and mortality but cannot be used to examine the question whether the administration of antihypertensive drugs affects the natural history of hypertensive disease.

A more direct approach to explore the effect of blood pressure control on the course of hypertensive disease is a study of the incidence of complications and mortality in a treated group of hypertensives compared with an untreated group observed concurrently. Evaluations of antihypertensive drug therapy which attempt to overcome the difficulties of comparing two populations of hypertensives are those in which the observations are prospective in nature, in which the two groups are similar in sex, age, degree of elevation of blood pressure and presence of vascular disease, and in which patients are randomized in a double blind study. Completed studies that attempted to meet some or all of these criteria are three Veterans Administration Cooperative Group reports,² ⁴ ⁶ one by Hamilton, Thompson and Wisniewski⁶ and one by Wolff and Lindeman.⁷

The first Veterans Administration Cooperative Group study reported the effects of treatment on morbidity in 131 (not including 12 dropouts) male hypertensive patients with "moderately severe" diastolic blood pressures averaging between 115 and 129 mm Hg.⁸ The patients were randomized into two groups, one treated with the combination of hydrochlorothiazide, reserpine, and hydralazine, and

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the other given placebos. Early in the study a high incidence of complications in the placebo treated patients caused the investigators to discontinue adding patients to the control group so that it was limited to 63 patients. This study appears to demonstrate the value of the administered antihypertensive therapy (27 "severe complicating events" in 63 patients, 42.9 per cent, receiving placebo as compared to 2 in 68 patients, 2.9 per cent, receiving active therapy).

One might conclude that the difference in the incidence of end points resulted from the administration of antihypertensive drugs and that the lowering of the blood pressure prevented the high incidence of complications seen in the control group. This conclusion may be the correct one and randomization of patients may have insured the fact that both populations were identical in the incidence, extent and stage of pre-existing vascular disease at the start of the treatment period and that during the treatment period all variables (e.g. dietetic, genetic, hormonal, neurogenic) that control the rate of progression of vascular disease other than the level of blood pressure were operative to the same extent in both the control and treated groups. However, the occurrence of a complication or death in nearly one of two patients in the control group in a matter of months is surprising and the possibility exists that randomization failed to establish two groups of hypertensives identical in composition that would permit one to serve as a control for the other. The hypertensive patients in the control group had a high incidence of advanced cerebral, coronary and aortic disease prior to the study: 5 of the 63 had preceding cerebral thrombosis, 5 had diabetes mellitus and 22 had abnormal electrocardiograms; three died of dissection or rupture of the aorta. Further confirmation of the presence of advanced vascular disease is indicated by the rapidity with which complications appeared: 2 patients died in 2 months, 1 in 6 months and a fourth in 16 months from the start of the placebo treatment regimen. Eight of 15 serious morbid events occurred within 6 months or less. The duration from start of placebo treatment to complication averaged only 9.6 months. This high incidence of complications occurring in a short period of time in patients in the control group differs from that reported by Perera who observed the course of 300 hypertensive patients not receiving specific antihypertensive drug therapy and found the mean duration from cerebral vascular accident to death was 4 years with a maximum of 19 years and from myocardial infarction to death was also 4 years with a maximum of 15 years.

The presumption that the presence or absence of vascular disease can be established with any degree of certainty by clinical examination is unrealistic and the possibility exists that even though an attempt was made in this first Veterans Administration study to establish the incidence of vascular disease equally in the control and treated groups, disparity may have been present which accounted for the difference in the incidence of morbid events.

The nature of the 27 "severe complicating events" that occurred in the placebo treated patients also requires comment. Twelve of these 27 consisted of elevation of the blood urea nitrogen concentration, appearance of retinal changes (other than papilledema) and elevation of the blood pressure level to what was considered to be a threatening level. These end points have the inherent weakness of representing spontaneously reversible events in the course of hypertensive disease. Elevation of blood pressure to peak values may occur in the course of hypertensive disease and remain high for long periods of time without the patient progressing to the accelerated stage; retinal hemorrhage and exudate are reversible in 25 per cent of hypertensives; and blood urea nitrogen levels can rise and fall (within the limits described) without necessarily reflecting the onset of the accelerated stage. Like other instances in which "prodromata" forecast the occurrence of disease, not all patients manifesting the prodromata go on to develop the predicted pathology. Once marked proteinuria (in the absence of congestive heart failure) papilledema and azotemia occur concurrently in a hypertensive, the diagnosis of the accelerated (malignant) phase rests on solid ground. The decision to discontinue using these 12 patients as controls may have been indicated on ethical grounds but their classification as "severe complicating events" in the statistical analysis of the data can be questioned since the primary purpose of the study was to evaluate the effect of treatment on the natural history of hypertensive disease.

In a second paper the Veterans Administration Cooperative Group reported the effects of treatment of hypertensive patients with diastolic blood pressures averaging 90 through 114 mm Hg utilizing the same protocol as in the first study. Fifty-six of the 194 patients (28.9 per cent) in the control group had assessable events as compared to 22 of 186 (11.8 per cent) in the actively treated group. In the first Veterans Administration Group report the treated patients with higher blood pressures had morbidity and mortality of 2.9 per cent. One would have expected treatment to have been more effective in those with lower blood pressure levels than those with the higher pressures. This unexpected result is difficult to explain if one accepts the thesis that the degree of elevation of blood pressure determines the rate of progress of hypertensive disease. A possible explana-
tion may lie in the difficulty of categorizing patients on the basis of the degree of elevation of blood pressure alone. Marked variation in prognosis may occur since patients with modest hypertension may have a short and complicated clinical course, whereas a benign and long course may be seen in patients with marked diastolic hypertension. In general patients with marked and persistent diastolic hypertension have a poorer prognosis than those with less marked elevation but a fundamental question remains unanswered and that is whether it is the marked elevation of blood pressure that causes the poorer prognosis or whether the pathogenetic mechanism responsible for hypertensive disease is producing both the higher pressure and a rapid course of events.

The importance of the extent of pre-existing vascular disease in the second Veterans Administration Group study is indicated by the low incidence of morbid events in patients under the age of 50 in both the control and the treated groups. There were only 22 morbid events in 201 patients (10.9 per cent) under 50 years of age compared to 56 in 179 patients (31.3 per cent) in those over 50 years of age. This threefold increase in morbid events in the older group suggests that the extent of vascular disease rather than hypertension plays the dominant role in determining the natural history of combined hypertensive vascular disease.

The incidence of complications associated with coronary artery disease was the same in both control and treated groups; there were 16 complications consisting of fatal and non-fatal myocardial infarcts, atrial fibrillation, cardiac conduction defects and sudden death in the control and 15 such events in the treated group, indicating that progress of vascular disease of the coronary arteries was not influenced by reducing the level of the blood pressure. This failure to demonstrate a difference in the course of coronary artery disease in the control and treated hypertensive groups is of special interest since deaths from heart disease constitute 66.4 per cent of all deaths in patients dying of hypertensive disease.*

The influence of prior cardiovascular disease on morbidity in hypertension is stressed in the third report of the Veterans Administration Cooperative Group.9 Patients who had myocardial infarction, congestive heart failure or cerebral vascular thrombosis prior to randomization had greatly increased risk of developing morbid events, 53 per cent in the control and 26 per cent in the treated group, as compared to a not significant difference, 16 per cent in the control and 8 per cent in the treated group, of patients with no prior cardiovascular abnormalities. Although only 20 per cent of the patients were over 60 years of age these older patients contributed half of the morbid events. This further analysis by the authors of data collected in their previous work indicates the dominant role of vascular disease in determining morbidity and mortality in essential hypertension.

The purpose of the study reported by Hamilton, Thompson and Wisniewski10 was to evaluate the role of blood pressure control in the incidence of strokes. The small population studied was judged by these authors to have symptomless, uncomplicated benign essential hypertension. In the control group 7 of 31 patients had a stroke as compared to 3 in 30 in the treated group. This small difference in the control and treated groups, not considered significant by the authors, stimulated them to examine the blood pressure response to drug therapy in the treated group. Of 16 patients with good or fair control none had a stroke as compared to 6 strokes in 23 patients with poor control of blood pressure. In this latter analysis the treated group is no longer being compared to the control group, the 23 patients being composed of treated patients in whom blood pressure level was not significantly reduced and of control patients. The danger in adding patients in the treated group to the control group lies in the possibility that their complications may have been due to rapidly progressive disease rather than to poor blood pressure control. This study then is no longer a comparison of results in a randomly selected treated group with those of a control group. The high incidence of complications (21 in 61 patients) in the relatively short period of time of 2 to 6 years in the Hamilton et al. report is most surprising since the patients were carefully selected to avoid including those with vascular disease. The criteria employed were that the patients be under 60, that they be asymptomatic, that they be free of previous complications, that the ocular fundi be free of papilledema, exudates or hemorrhages, that clinical, radiologic and cardiographic evidence of cardiac involvement be absent, that proteinuria be absent, and that serum urea levels be normal. It is difficult, therefore, to explain the rapid progress of vascular disease in these patients, a course not in keeping with the relatively benign natural history of hypertensive disease in patients carefully screened for evidence of disease in the heart, brain and kidneys.8,12 The small number of hypertensives studied by Hamilton et al. might account for the atypical course of the disease in so many of their patients.

Wolff and Lindeman reported their observations of the effect of drug therapy on the course of hypertensive disease in patients studied over a two year period utilizing the double blind technique.7 There were 45 patients in the treated group of whom 28 completed the study, and 42 in the control group of whom 20 completed the study. The hypertensive population
studied was predominantly black (89.7 per cent) with a high incidence of previous disease (cardiac 67.8 per cent; cerebral 33.3 per cent; and renal 52.9 per cent). The original design of the study was to include only hypertensives without complications but the clinic population was so small that they added patients with target organ involvement. There were 6 treatment failures in the 45 treated patients and 19 failures in the 42 patients in the control group. Since the purpose of the study was to determine whether effective reduction of blood pressure prevents or delays the progress of target organ deterioration 8 of the 19 patients classified as failures deserve comment. Two of the 8 developed clinical diabetes; one died of pulmonary insufficiency in the course of chronic lung disease; two had temporary increase in serum urea nitrogen to 42 and 49 mg % which returned to normal with therapy; two developed the anginal syndrome which improved with treatment; and one developed headache that cleared with therapy. Classifying these 8 patients as treatment failures is questionable.

The significance of the Wolf and Lindeman study is limited by the small number of patients, by the population being predominantly black, by the mixture of uncomplicated hypertensives with patients with cardiac, cerebral and renal disease, by the relatively short period of observation (less than 2 years) and by the high incidence (greater than 50 per cent) of patients diagnosed as having chronic pyelonephritis, a figure well above the occurrence of this renal disease in most clinic hypertensive populations. Whether or not the presence of intrinsic renal disease is related to the early occurrence of complications (11 of 19 within one year in the control group), the population studied in this report is not representative of the general hypertensive population.

Discussion

As we have pointed out before, there is a need for convincing proof of the clinical usefulness of antihypertensive drugs in essential hypertension. Even if the data reviewed in this report were to be interpreted as indicating that administration of antihypertensive drugs decreases morbidity and mortality of hypertensive patients, the characteristics of the patients who supplied the data in the four studies are different from those of the general hypertensive population and therefore should not be used to establish the basis for recommending such therapy to all hypertensives, whether they be female, adolescent, young or aged. The large majority of patients who formed the control and treated groups were male, had complications or died at the relatively young age of 50 years, had a high incidence of previous coronary artery, cerebral artery and aortic vascular disease, and had a psychological make-up such that they attended clinic regularly and took their medicine religiously. In the Veterans Administration Group studies exclusion of patients whose diastolic blood pressure fell below 90 mm Hg after 4 to 6 days of hospitalization further limited their sample since it has been shown that a significant percentage of hypertensives have a fall in blood pressure when removed from their home and work. Since many of the patients had advanced vascular disease at age 50 it is probable that arterial pathology started at a relatively young age and suggests that the population studied included patients in whom the primary disease was atherosclerosis rather than essential hypertension.

A question that requires studies of longer duration before the general population is placed on drug therapy is the psychological impact on the course of the disease of young adults being told of their prognosis. The potential adverse effects (e.g. gout, diabetes) of long-term administration of drugs on metabolic and biochemical functions also requires further observations.

Another disturbing aspect of the studies reviewed in this report is the rapidly progressive course of the disease in the patients who constituted both the treated and control hypertensive populations. There was a high incidence of complications in the combined placebo groups (82 of 330, 24.8 per cent) that occurred in a relatively short period of time (one out of every 4 patients died or had a complication some months from randomization). This experience is quite different from the natural history of the disease described by observers of hypertensive patients not treated with antihypertensive drugs followed over extended periods of time. Ranges observed reports made on a group of 241 individuals (130 females and 111 males) with hypertensive disease followed for from 10 to 25 years (average, 14 years). This group remained working and all 241 were alive and ambulatory at the end of the long period of observation. In 161 of the 241 patients normal blood pressure was known to be present from 5 to 10 years before hypertension was first noted. Bechgaard, Kopp and Nielsen followed 1000 hypertensive patients whom they regarded as untreated for from 16 to 22 years and reported that the first remarkable finding in this investigation was that so many still survived at the end of the period of observation.” Perera followed 150 persons from before the onset of hypertension throughout the course of their disease and found the mean duration to be 20 years; these patients were not given hypotensive drugs nor was their diet sodium free. When one compares these observations with those of Hamilton et al whose therapy was administered for 2 to 3 years, with those of Wolff and Lindeman whose therapy was ad-

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ministered for less than 2 years, with those of the first Veterans Administration Group study where therapy was administered for less than 2 years and with the second Veterans Administration Group study whose average duration of therapy was a little over three years, the conclusion one must draw is that the patients selected for these studies represented a special hypertensive population. This disparity between the course of events in the patients selected to evaluate the effect of therapy on morbidity and mortality and the course of disease in 1391 (Ranges, 241, Bechgaard et al., 1000, and Perera, 150) untreated hypertensives is particularly striking in the Hamilton et al. series because the investigators in this study made every attempt to exclude patients with detectable vascular disease or with a prior complication of hypertensive disease. It is difficult to understand why these 4 groups of hypertensives manifested rapid progressive disease to the extent they did and had a course so disparate from that known to characterize the general hypertensive population. The explanation, to some extent, may be attributed to the fact that hypertensive patients who seek medical help at a clinic or hospital facility are more apt to be farther along in their disease than persons found to have elevated blood pressure in routine examination or in a survey directed at identifying hypertensives.

One of the problems faced in the use of a protocol that proposes to evaluate the effect of blood pressure control on the course of hypertensive disease is that the events that complicate or terminate the disease are vascular in origin and the factors that affect the progress of vascular disease other than the level of systemic arterial pressure are multiple and complex. The primary event in the vascular wall that initiates arterial disease is unknown and factors such as diet, genetics, environment and hormones have been suggested as playing a pathogenetic role. In view of the multiplicity of factors, known and unknown, primary and secondary, that may be involved in determining the occurrence and progress of vascular disease, the experimental approach that affects one variable, i.e., the level of blood pressure, and assumes that randomization has equaled all other variables, may lead to unwarranted conclusions.

Conclusions

Four completed prospective studies have been reviewed that evaluated antihypertensive drug therapy by comparing a treated with a control hypertensive population utilizing a double blind randomized protocol. From this review the following questions arise:

1. Since both the control and treated patients selected to evaluate the effect of drug therapy manifested rapidly progressive disease, a course quite different from that observed in the general hypertensive population, should the results in these studies be used to establish the basis for recommending such therapy to all hypertensives?

2. In view of the multiplicity of factors, known and unknown, primary and secondary, that determine the occurrence and progress of vascular disease, can an experimental approach that affects only one variable, i.e., level of blood pressure, lead to unwarranted conclusions because of the failure of randomization to equally distribute all other variables?

3. Since antihypertensive drug therapy fails in coronary artery disease and since 2 out of 3 hypertensives die of heart disease, should not potential benefit be balanced against potential harm before all hypertensives be treated with antihypertensive drugs?

It is concluded that the ultimate value of antihypertensive drug treatment has not been established for the general hypertensive population. Population screening for hypertensives for the purpose of instituting drug therapy is premature.

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