Drug and Dietary Intervention in Hypertension

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SUMMARY  Antihypertensive drug treatment has been shown to be efficacious in reducing mortality, morbidity, and end-organ damage from hypertension. However, the health care consequences of providing continued antihypertensive therapy for approximately one-fourth of the adult population has led to inquiry into the potential of nutritional change as an alternative therapy. The relapse rate for the return of hypertension after withdrawal of antihypertensive drugs is greater in the obese than in the nonobese patient. The relapse rate is also much greater if the hypertension was severe before antihypertensive drugs were started. A programmed course of dietary instruction enabled participants to drop sodium excretion by 50%, and to lose approximately 5% of body weight in 32 weeks. Adequate large-scale trials to determine the therapeutic success rate of dietary modification in mild hypertension have yet to be done.

Studies have been initiated in the United States and Finland to determine the feasibility of dietary modifications as a means of preventing the occurrence of hypertension. This endeavor deserves the highest priority, for the magnitude of the problem threatens to overwhelm conventional means of provision of medical care. (Hypertension 4 (supp III): III-166–III-169, 1982)

KEY WORDS • drug therapy • nutritional change • relapse after therapy

A long sequence of studies led to the recently completed drug intervention study in hypertension, the national effort to increase the number of hypertensive patients on therapy, and the beginning of large-scale studies of nonpharmacologic intervention to treat mild hypertension, and even to prevent the occurrence of hypertension.

In the early 1920s, Allen and Sherrill reported that sodium restriction benefited hypertensives. Their report aroused no enthusiasm, and it was not until 1948 that Kempner reported marked benefit from his rice/fruit diet in the treatment of severe hypertensives. The diet was very low in sodium, protein, and calories, and very high in potassium. It was undoubtedly efficacious but many patients apparently felt that the diet was worse than death. The competing therapy of that era, dorsolateral sympathectomy, had a high percentage of failure, considerable morbidity, and was frequently associated with disabling side effects such as severe postural hypotension. Schroeder used the first really successful drug therapy, a combination of hexamethonium and hydralazine in malignant hypertensive patients. It certainly saved patients who would have died otherwise. The side effects of postural hypotension, obstructive constipation, and impotence were almost universal. When I was a house officer at Johns Hopkins, Dr. Schroeder graciously answered my letter requesting suggestions for handling the problem of impotence in my patients. His final summary was "the price of vascular health is dear."

Although the studies referred to above had no real controls, they demonstrated that blood pressure could be lowered if you were willing to pay the price, and that the patient with very severe hypertension would be benefited by blood pressure lowering. The modern era started with the Freis-Veterans Administration study of hypertension. Drugs without overwhelming side effects became available. Investigators did a drug trial of antihypertensive medication using a placebo control, and demonstrated for the first time that the incidence of hypertension-related morbidity and mortality was decreased by antihypertensive therapy. A first report demonstrated that this was true for those with diastolic pressures above 115 mm Hg. The next report on benefits from antihypertensive therapy expanded these observations to patients with diastolic pressures in excess of 105 mm Hg. However, as important as this study was, it left many questions unanswered. The patients were all male, had a great deal of end-organ disease, and had been picked for compliance in taking antihypertensive medication before the study started. Would antihypertensive therapy be efficacious in mildly hypo-
pertensive patients? Would it work in women and blacks, who were relatively underrepresented in the VA study? If a population-based study including hypertensives of all severities was done, would there be compliance with antihypertensive therapy adequate to determine benefit?

Three recent studies provide an affirmative answer to the question of the overall benefit of antihypertensive therapy. The study with which I was associated, the Hypertension Detection and Follow-up Programs (HDFP), will be described in greatest detail. The HDFP differed from a standard placebo controlled trial in several ways. At the time this study was started, argument was raging on the benefits of drug therapy in mildly hypertensive patients. Part of the medical profession felt that there was inadequate evidence to recommend antihypertensive therapy for patients with only minor elevation in blood pressure. Other physicians felt that therapy for these people was mandatory. In order that patients would not be denied therapy if they and their physicians felt it was indicated, a comparison group was chosen by a sequence outlined below.

Participants were recruited from probability samples of communities of industrial populations. If initial diastolic blood pressure was equal to or greater than 95 mm Hg, individuals were referred to the project clinic. If, on arrival, their diastolic blood pressure was equal to or greater than 90 mm Hg, they were considered hypertensive for the purpose of the study. If they then agreed to participate, they were randomly assigned to either an active treatment group called stepped care (SC) because therapy was modified to achieve control of blood pressure, or to the referred care group (RC) which utilized usual sources of medical care. Participants in RC received antihypertensive therapy or not, according to decisions of their physicians and acceptance by the patients.

Certain confounding conditions flowed from this design. Individuals assigned to SC would be seen more frequently than those in RC. Moreover, physicians taking care of the SC participant might be expected to have an unconscious bias about the outcome and therefore diagnose diseases such as myocardial infarction with greater frequency in one group than the other. Accordingly, we chose an endpoint, all-cause mortality, which was not subject to bias on the part of the investigator. The use of all-cause mortality as a primary endpoint required a large number of participants. It was necessary to screen 158,906 people, aged 30–69 years, in the 14 communities where the clinics were based to enroll 10,940 participants. The great majority of these participants (71.5%) had relatively mild hypertension (diastolic blood pressure 90 to 104 mm Hg). We saw the participants at home once yearly (with the exception of the third year), recorded their blood pressure, and noted their treatment status.

Table 1 shows treatment status at the end of the second and fifth years and average fall in diastolic blood pressure over this same time period. From the onset, there was a significant difference in mean diastolic pressure between the two groups, with lower mean diastolic pressure in SC. Also, a greater number of the SC participants than RC participants were on antihypertensive therapy. By the end of the fifth year, there was a significant difference in the total mortality between the two groups. There were 349 SC participants who died, compared to 419 RC participants. This difference was highly significant. The results in the lowest blood pressure stratum with initial diastolic blood pressures in the range of 90 to 104 mm Hg were even more significant, with 231 SC deaths by the end of 5 years compared to 291 deaths of RC participants. This represents a 20.3% reduction in mortality for the SC group (p < 0.01), and included decreased mortality in women, men, blacks, and whites. The HDFP did not show any difference in all-cause mortality in individuals aged 30–49 years.

Results from the Australian National High Blood Pressure Study further substantiate the HDFP results. This was a study of the effect of antihypertensive therapy in individuals with diastolic blood pressure of 95 to 110 mm Hg, or systolic blood pressure of 200 mm Hg or higher on two visits. The participants were carefully examined, including a chest x-ray and EKG. If no gross evidence of end-organ disease was present, they were entered into the trial. A placebo control was used. All patients were seen and examined regularly in clinics. It was possible to use a variety of events as endpoints in this study rather than total deaths alone. Included were deaths from cardiovascular diseases as well as nonfatal events attributable to hypertensive or atherosclerotic disease. The results were reported as incidence of trial endpoints per 1,000 person years at risk. There were 138 cardiovascular endpoints in the active treated group, and 168 in the placebo group. Statistically, this difference was highly significant.

The report of the United States Public Health Service treatment trial of mild hypertension is of interest in deciding whether antihypertensive therapy is of value. The USPHS study was placebo-controlled and of 10 years' duration. With the exception of hypertension, all individuals were free of cardiovascular disease on entry. There was not a significant difference in the number of the participants having major cardiovascular events (death, myocardial infarction, stroke or uremia) during the trial. However, the placebo-treated group had more cardiomegaly, changes in ECG, and changes in fundal arterioles than the drug-treated group. Participants who entered the HDFP study with

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end-organ disease, as demonstrated by ECG or chest x-ray, had a higher death rate. The hazard of fatal outcome was lowered by antihypertensive therapy but not to the level of participants without end-organ disease on entry.

The three studies referred to suggest that hypertensive patients of all ages and severity benefit from antihypertensive drug therapy. If the participant is relatively young, no benefits in mortality can be expected in the first 5 years of treatment. However, therapy will prevent the development of end-organ disease, which predicts a much greater later mortality than if the same blood pressure is present without end-organ involvement.

If we accept antihypertensive therapy as a desired goal for almost all hypertensives, what progress is being made in getting the American population under treatment? The National High Blood Pressure Education Program in conjunction with the American Heart Association and other organizations began intensive media campaigns in 1974. Investigators from three HDFP clinics (Baltimore, Maryland; Birmingham, Alabama; and Davis, California) obtained the initial participants for HDFP from a random sample of their communities. Figure 1 shows that the percent of hypertensives (defined as having elevated diastolic pressure, or on antihypertensive therapy) who were aware of their elevated blood pressure was significantly greater in each sex-race group in 1977-78 than in 1973-74. There was, in addition, a marked increase in the percent of actual hypertensives under treatment (fig. 2).

It is clear that basic and applied research has provided potent antihypertensive medication, which has been shown to be efficacious in prolonging life and reducing cardiovascular events, and that the medical profession, the public, and other interested parties have combined their efforts to increase tremendously the percentage of hypertensives receiving antihypertensive therapy.

Dietary Modification and Withdrawal of Antihypertensive Drugs

A continuing question in the care of the hypertensive patient whose blood pressure has been brought under control by drugs is whether the drugs are still needed. We know that hypertension produces vascular hypertrophy, as well as changes in endothelium and mural connective tissue of blood vessels. These changes apparently act to maintain elevated blood pressure. If experimental animals are treated with antihypertensive drugs, one finds that many of these vascular changes will regress. In fact, hypertensive rats of the Okomota strain which have been treated with antihypertensive drugs will have blood pressures well below their littermates if the antihypertensive medication is discontinued. The University of Mississippi School of Medicine, the University of Alabama at Birmingham, Einstein College of Medicine, and the coordinating center at the University of Texas School of Public Health, Houston, Texas, participated in such a study. Participants who had taken part in the HDFP were enrolled from the three clinics. They were eligible to participate in the new study if they had no major end-organ disease, were well controlled on antihypertensive medication, and planned to remain in the vicinity of the clinics for the next 2 years. The experimental design called for randomization of patients who were obese (120% or greater ideal weight) into four groups: 1) continue medication; 2) withdraw from medication with no further intervention; 3) discontinue medication and restrict sodium and increase potassium dietary intake; or 4) withdraw from medication and reduce weight. The nonobese were randomly assigned to groups to 1) continue antihypertensive medication, 2) withdraw medications with no intervention, or 3) withdraw medications, while restricting sodium and increasing potassium intake.
Conduct of such a study requires a major effort to organize. A program devised by Drs. Arlene Caggulia and Renee Wing of the University of Pittsburgh School of Public Health was used to evaluate and change dietary intake. This was administered by trained nutritionists at each of the centers. All participants were expected to attend weekly group sessions for eight weeks, then at monthly intervals thereafter. Baseline dietary data were obtained, as well as 24-hour collections of urine for analysis of sodium, potassium and creatinine. These measurements were repeated at 8, 32, and 56 weeks.

The data from this study are still being analyzed. The most complete information is available from the group randomized to withdrawal of drug therapy without nutritional intervention. Even in this group, a nutritional component is evident. The nonobese individuals who were only mildly hypertensive at the beginning of the study (90 to 104 mm Hg, with medication) had a 32-week failure rate of 23.7%. The obese, mildly hypertensive individuals had a slightly higher failure rate, 26.3%. Differences in failure rate between obese and nonobese individuals was more marked in those persons who were severely hypertensive at the start of the HDFP program, even though their blood pressure had been subsequently well controlled for 5 years. Of the obese individuals, 64% had failed by the 32nd week, compared to 45% of nonobese individuals. While we feel that we will be able to reduce these failure rates in individuals who have been assigned to the dietary modification groups, these data have not been analyzed. As yet, we cannot say whether the results for the dietary modification group will be significantly better than those for the control drug withdrawal group. We can say that we have been effective in inducing dietary change. Obese individuals excreted 153 ± 80 mEq Na and 49 ± 36 mEq K on a daily basis as expected. By 32 weeks, they had reduced their excretion to 93 ± 53 mEq Na and 48 ± 23 mEq K per day (n = 33). The nonobese excreted 143 ± 109 mEq Na and 52 ± 28 mEq K per day at baseline, and 86 ± 32 mEq Na and 56 ± 26 mEq K per day at 32 weeks (n = 20). Obese individuals randomized to a weight reduction program lost approximately 5% of their weight by 32 weeks.10

**Dietary Modification as Sole Therapy for Hypertension**

A few recent studies involving small numbers of subjects have shown that reduction in sodium intake will lower blood pressure. MacGregor and co-workers11 have shown in 19 patients that lowering dietary sodium intake so that urinary sodium excretion fell from 162 ± 9 mEq per 24 hours to 86 ± 9 mEq per 24 hours lowered mean blood pressure by 7.1 mm Hg (6.1%).11 There is a paucity of large-scale, long-term studies of the effect of either sodium restriction or weight loss on blood pressure. Such studies are urgently needed, although they will be difficult to perform, and perhaps disheartening for the investigator and participant.

**Prevention of Hypertension**

Can a diet relatively low in sodium and high in potassium prevent hypertension from occurring? Can the prevention of obesity prevent the occurrence of hypertension? Studies to answer these questions are just beginning. Dr. Oberman heads a relatively small multiclinic first-phase study to see if dietary modification will prevent the occurrence of hypertension. An ambitious public health project has been mounted in Karelia, Finland, to see if the entire communities can be induced to reduce their sodium intake, increase their potassium intake, and decrease the prevalence of obesity. While this type of public health approach is extremely attractive, it remains to be demonstrated whether we can change peoples' habits; and if behaviors change, will hypertension be abolished?

**References**

4. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension: Results in patients with diastolic blood pressure averaging 115 through 129 mm Hg. JAMA 202: 1028. 1967
5. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 213: 1143. 1970
6. Five-year findings of the Hypertension Detection and Follow-up Program: I. Reduction in mortality of persons with high blood pressure, including mild hypertension. II. Mortality by race-sex and age. JAMA 242: 2562. 1979
Drug and dietary intervention in hypertension.
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