Advantages of Diuretics

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Our recent Veterans Administration Cooperative Study—involving 683 hypertensive male patients—showed that a diuretic was more effective than a beta blocker in controlling hypertension in most respects. In addition, in this study we failed to find evidence that thiazide-induced hypokalemia was associated with increased evidence of cardiac arrhythmias in patients without overt heart disease. We are concerned that the current desire to avoid hypokalemia at all costs may result in the prescription of ineffective dosages of diuretics for the treatment of hypertension.

When chlorothiazide became available for clinical trials in 1957, we knew that it was a breakthrough drug [1]. It was a medication that seemed to control blood pressure as well as the strictest no-salt diet, but it was much better tolerated. The diuretics were important not only because they were antihypertensive in themselves, but also because they enhanced the antihypertensive activity of other drugs. Thiazide diuretics, therefore, soon became the favored step-one agent and have largely retained that position ever since.

Hemodynamic studies revealed that thiazides caused a modest but definite reduction in plasma volume and extracellular fluid volume; furthermore, this reduction seemed to be involved in the antihypertensive effect of the drug [2]. The early fall in blood pressure was associated with a reduced cardiac output and relatively unchanged total peripheral resistance [3]. After several weeks, however, cardiac output returned to normal and total peripheral resistance decreased. This late homeostatic adjustment does not seem to be due to a direct vasodilator effect of the drug. The mechanism is unknown but may involve poorly understood autoregulatory reactions. Interestingly, these hemodynamic reactions are the opposite of the changes that have been described in the development of volume loading types of experimentally induced hypertension. In any event, the hallmark of the antihypertensive action of diuretics is a reduction in volume that lasts for as long as the diuretic is given [4,5].

The two main characteristics of interest regarding any drug are therapeutic effectiveness and toxicity. Until recently there was no question about the position of the diuretics as the step-one treatment for hypertension. In recent years, however, their premier position has been challenged. There has been increasing concern that thiazide-induced hypokalemia may contribute to cardiac arrhythmias and even to sudden death. On the other hand, beta blockers have been somewhat effective in reducing the incidence of sudden death in patients who have already sustained a myocardial infarct. Therefore, some physicians—particularly in Scandinavia—have been using a beta blocker for step-one treatment and add-

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ing thiazide second. Furthermore, the thiazide is usually added in smaller doses than in the past to minimize the possibility of hypokalemia developing.

What is the relative effectiveness of thiazides versus beta blockers as antihypertensive agents? That question was the subject of a recent VA Cooperative Study, which included 683 male patients with diastolic blood pressure averaging 95 to 114 mm Hg [6]. They were randomly assigned double-blind to receive either propranolol titrated from 40 to 320 mg twice a day or hydrochlorothiazide 25 to 100 mg twice a day.

After six months of treatment, hydrochlorothiazide lowered blood pressure by an average of 17.5/13.1 mm Hg as compared with a lowering of 8.3/11.3 mm Hg by propranolol. White patients responded better than black patients to propranolol and vice versa. Other indications of a somewhat greater effectiveness of the thiazide as compared with propranolol over the long term were as follows: (1) with thiazide, a diastolic blood pressure <90 mm Hg was achieved in 66 percent of the patients compared with 53 percent with propranolol; (2) among those taking the diuretic, fewer patients required termination for high blood pressure; (3) the need to titrate to high doses with hydrochlorothiazide was less; (4) escape from blood pressure control during treatment occurred less often with hydrochlorothiazide; and (5) after withdrawal of treatment, the blood pressure remained lower over the ensuing two weeks in those previously taking the diuretic.

None of these advantages of diuretics can be considered major; if beta blockers can be proved effective in the primary prevention of heart attack, this would outweigh all of the considerations cited and justify the use of beta blockers as primary treatment in all patients. The same policy would apply if it could be proved that thiazides increase the risk of life-threatening arrhythmias. However, at present no definitive evidence exists to justify either of these assumptions.

In considering the risks of hypokalemia, it is important to differentiate between patients who have overt heart disease and those who do not. Obvious impairment of cardiac function, particularly congestive heart failure, may be associated with a reduced potassium content in myocardial cells unrelated to diuretic treatment. In patients with asymptomatic hypertension without overt heart disease, the concentrations of potassium in their myocardial cells are normal. The following discussion concerning hypokalemic risk pertains to patients without overt heart disease.

Changes in the extracellular concentration of potassium do not reliably reflect changes in the intracellular concentration of potassium. Most of the studies indicate that even during long-term treatment with thiazide, losses of total body potassium remain small, averaging 5 to 10 percent in most reports [7,8]. Thus, the percentage reduction of intracellular potassium is considerably less than the reduction in extracellular potassium.

Recent studies from our clinic do not provide any evidence that thiazide-induced hypokalemia leads to the development of increased ventricular arrhythmias [9]. Hypertensive patients with no overt heart disease were chosen for study. All had hypokalemia while taking diuretics, with plasma potassium concentrations of 3.2 mEq per liter or less (average 2.8 mEq per liter). Holter monitoring for 24 hours was carried out on each patient during the hypokalemia, as well as after it was corrected with potassium supplements and/or triamterene. There was no improvement in ventricular ectopy after correction of hypokalemia. Ventricular ectopic activity improved in five patients but worsened in 10. This response is not too surprising since the sensitivity of myocardial cells to disturbances in rhythm depends upon the relative concentrations of potassium inside and outside the cell. An increase in this ratio produced either by an increase in intracellular potassium concentration or a decrease in extracellular concentration results in a more negative resting membrane potential, that is, the cell becomes more resistant to excitation [10]. This change should reduce rather than increase the incidence of ventricular ectopy.

An additional concern has been the small but definite increase in serum cholesterol that occurs with diuretic treatment. Possibly, this could increase the risk of atherosclerosis over the long term. In the VA trial [6], however, it was found that the elevation did not persist, returning to baseline after one year of treatment. Others have found similar returns to baseline over the long term [11,12].

An important consideration in the choice of initial treatment is the racial difference in response to diuretics as compared with beta blockers. Although diuretics are definitely more effective in black people, beta blockers may be as effective or more effective than diuretics in white people. In a recent VA trial of the beta blocker nadolol versus the diuretic bendroflumethiazide, nadolol lowered blood pressure to a greater extent in white people than did the diuretic [13]. In the trial of propranolol versus hydrochlorothiazide, the reduction of diastolic blood pressure was nearly the same with each drug in white people but not in black people, in whom the diuretic was definitely superior [6].

Are small doses of thiazide diuretics equally as effective as large doses? According to some of the recent reports in the literature they are. It is currently popular, for example, to give 25 mg hydrochlorothiazide or even less once daily and not to increase the dose beyond that point since it is believed that the dose-response curve has already plateaued. This does not agree with data from our VA Cooperative Study [6]. In two-thirds of 312 patients, a diastolic blood pressure <90 mm Hg was attained with hydrochlorothiazide titrated from 25 mg twice a day to 100 mg twice a day. Of this number, goal diastolic blood pressure was achieved in 50 percent with the 25 mg twice a day dose (50 mg a day), in an additional 30 percent with 50 mg

twice a day, whereas in the remaining 20 percent 100 mg twice a day was required. In a recent study by others, doses as low as 6.25 mg a day have been given [14]. It seems possible that no reduction of plasma volume or extracellular volume would result from such a small dose. A double-blind placebo-treated group would be required to be certain that the decrease in blood pressure was due to drug effects rather than to the gradual downward drift of blood pressure that occurs with repeated visits to the clinic.

In summary, diuretics lower blood pressure by reducing plasma and extracellular fluid volume. This is a unique mechanism that is shared by no other antihypertensive agents. Our evidence indicates that thiazide diuretics still are the keystone of antihypertensive drug treatment not only for primary treatment, but also in enhancing antihypertensive effectiveness when combined with other drugs. Because of racial differences in response, beta blockers have a slight edge over diuretics for initial treatment of white patients, although diuretics are still the preferred primary treatment for black patients. Also, studies from this clinic failed to find evidence that thiazide-induced hypokalemia was associated with an increased incidence of cardiac arrhythmias in patients without overt heart disease. It is possible that, because of the current desire to avoid hypokalemia at all costs, doses of diuretics are being reduced in some cases to below the effective therapeutic level.

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