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Choice of Initial Treatment

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Summary: An important consideration in the choice of initial treatment is race. In a Veterans Administration study nadolol reduced blood pressure more in whites than in blacks, while the reverse was true with hydrochlorothiazide. Combining both drugs enhanced antihypertensive effectiveness and abolished the racial difference. The results of this and other studies suggest that for first drug selection, beta-blockers are indicated in whites and diuretics in blacks. Beta-blockers are also indicated in all patients with prior myocardial infarction or with tachycardia. Thiazides are also used in combination with other antihypertensive drugs and in patients with heart failure. Reluctance to use thiazide diuretics stems from the possibility of hypokalemia-induced arrhythmias and long-term elevations of serum cholesterol. However, a causal relationship between hypokalemia and the incidence of arrhythmias is not well supported by physiologic or clinical evidence. Elevation of cholesterol appears to be transient, reverting back to pretreatment levels after 6–12 months of treatment. An alternative regimen which is both highly effective and well tolerated is the combination of small doses of both a thiazide diuretic and captopril. Perhaps less well tolerated, but useful where cost is the major consideration, is a thiazide followed by small doses of reserpine, if needed; this is an effective, low-cost treatment. Calcium channel blockers appear promising but require further evaluation. **Key Words:** Initial treatment—Antihypertensive drugs—Thiazide toxicity—Beta-blockers.

The choice of primary treatment has become a matter of controversy. The long established primacy of the thiazide diuretics is being challenged principally by the growing popularity of the beta-adrenergic blocking drugs. This trend has been influenced, on the one hand, by the opinion that beta-blockers may protect the heart against fatal arrhythmias and on the other, by recent criticisms concerning the thiazide diuretics. The principal criticisms are the possibility of fatal cardiac arrhythmias secondary to diuretic-induced hypokalemia and the long-term increased risk of coronary artery atherosclerosis resulting from raised serum cholesterol concentrations. This review evaluates the evidence for the relative effectiveness and long-term risks of treatment with beta-blockers as compared with diuretics in primary treatment and indicates briefly some important step 2 approaches.

BETA-BLOCKER VERSUS THIAZIDE AS INITIAL TREATMENT

Is the most effective drug for the initial or primary treatment of hypertension a beta-blocker or a diuretic? Several of the recent Veterans Administration trials have addressed this question (1–3). In one such trial the beta-blocker nadolol was compared with the diuretic bendroflumethiazide and with the combination of the two (1). Both drugs are very long acting, permitting once daily dosage. Nadolol was of interest not only because of its long action but also because it exhibits no first-pass phenomenon and it induces renal vasodilatation. There were 365 patients who were randomized into the trials with pretreatment diastolic blood pressure in the range of 95–114 mm Hg. Nadolol was titrated from 80 to 240 mg once daily and bendroflumethiazide was increased from 5 to 10 mg. The reduction in diastolic blood pressure was essentially the same with the two drugs, averaging 12.4 mm Hg with nadolol and 12.9 mm Hg with bendroflumethiazide. Systolic blood pressure was reduced somewhat more with the diuretic than with the beta-blocker. The reduction with the combination was considerably greater than with either drug alone, the diastolic reduction averaging 17.9 mm Hg.

There was a significant racial difference in the response to nadolol. Diastolic blood pressure in whites was reduced by 15.6 mm Hg compared with only 9.6 mm Hg in blacks. The percentage of patients whose diastolic blood pressure was controlled below 90 mm Hg exhibited an even more striking

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difference, with 77% of whites controlled compared with 31% of blacks. The racial difference was abolished and effectiveness was enhanced in both groups when the drugs were combined, with 85% of both blacks and whites achieving control of diastolic blood pressure.

Subjective side effects were uncommon with either drug but were less with nadolol than with bendroflumethiazide. The usual biochemical side effects of the thiazide diuretics were present with bendroflumethiazide.

A related trial by the Veterans Administration group compared hydrochlorothiazide alone with propranolol alone in 683 patients with mild and moderate hypertension (2,3). With hydrochlorothiazide there were fewer patients withdrawn because of raised blood pressure, fewer required an increase in dose and, after discontinuation of treatment, fewer raised their blood pressure to above pretreatment levels. In this study, also, there were racial differences in response similar to the nadolol trial. Hydrochlorothiazide lowered blood pressure in both groups, but more in blacks than in whites, whereas the reduction in blood pressure after propranolol was significantly greater in whites than in blacks. Similar results have been reported by other investigators (4,5).

SIGNIFICANCE OF THIAZIDE-INDUCED HYPOKALEMIA AND CHOLESTEROL ELEVATION

The recent decrease in the popularity of thiazide and related diuretics as primary treatment has resulted partly from the suspicion that they exert two insidious and potentially lethal side effects. One is that hypokalemia predisposes to cardiac arrhythmias, including ventricular fibrillation and sudden death. The other is that the moderate rise in cholesterol concentration produced by the diuretics aggravates and accelerates coronary artery atherosclerosis. These beliefs are attractive because they might explain the failure of most of the clinical trials, all of which incorporated diuretics, to show a significant reduction in the incidence of coronary heart disease. Nevertheless, neither accusation seems justified, or at least each remains unproved.

The reasons why the hypokalemia hypothesis is poorly supported are as follows: Firstly, hypokalemia after diuretics does not imply potassium depletion, as is commonly stated (6,7). A review of the many studies of changes in total body potassium after thiazides indicates that, with the exception of only a few contrary reports, the total body losses of potassium are in the range of 5 to 7%, far below the level that could be considered biologically important. The hypokalemia represents in part a movement of potassium from the extracellular fluid into cells secondary to the volume depletion. Therefore, there is little change in intracellular concentration despite the extracellular hypokalemia.

Secondly, the sensitivity of the heart to depolarization depends in part on the ratio of the concentration of potassium inside the cells to the concentration outside (6,7). An increase in this ratio raises the threshold to depolarization, that is, it reduces irritability. Therefore, thiazide-induced hypokalemia should make the heart more resistant to arrhythmias, since the ratio will be increased by the decrease in extracellular potassium concentration with little change in the intracellular concentration.

Thirdly, recent studies with 24- or 48-h monitoring of the electrocardiogram refute previous work claiming a relation between hypokalemia caused by thiazides and the incidence of arrhythmia. Papademetriou, in one laboratory, has recently found that induction of hypokalemia failed to increase the frequency of arrhythmic activity as compared with the pretreatment state (8). Also, correction of the hypokalemia with potassium supplements and/or triamterene did not reduce the frequency of arrhythmias (9). Lief *et al.* also investigated this question using 48-h monitoring before and after inducing hypokalemia (10). They also found no increase in arrhythmic activity during the period of hypokalemia.

The principal support for the concept that hypokalemia secondary to thiazides increases arrhythmic activity comes from Holland *et al.* (11), who found an increase in arrhythmias in 7 of 21 patients subjected to 24-h monitoring. The validity of this conclusion is questionable, however, because of the experimental design. Holland accepted only patients who showed fewer than six ventricular premature beats per hour. However, there is considerable spontaneous variability in the frequency of ectopic activity from day to day. When Holland selected only those with minimal arrhythmic activity in a single 24-h monitoring he increased the chances of observing greater activity on the second or post-treatment monitoring simply on the basis of spontaneous fluctuation or deviation toward the mean.

Fourthly, the Multiple Risk Factor Trial (MRFT) is often referred to as providing evidence that thiazide-induced hypokalemia may be responsible for the increased incidence of sudden death found in a subgroup of the trial (12). This evidence also is not very convincing. First, the correlation was found on hindsight by examining multiple subsets after the study was completed. This approach carries a high risk of finding one or two positive correlations simply on the basis of chance. Second, and more importantly, they found no correlation between the presence of hypokalemia and sudden death. Data from the Medical Research Council trial of Great Britain also failed to show any correlation between

hypokalemia induced by thiazides and the incidence of arrhythmias (13).

It would appear from the above brief review that the concept of thiazide-induced hypokalemia as a cause of ventricular fibrillation and sudden death is poorly supported. This conclusion, however, applies only to hypertensive patients without overt heart disease. Thiazides do increase digitalis-induced arrhythmias, and their safety in the treatment of patients with overt heart disease, where there may be losses of intracellular potassium, has not been either proved or disproved by well controlled trials (6,7).

The second objection to the use of thiazide diuretics has concerned their effects on serum cholesterol. During the early months of treatment with thiazides serum cholesterol rises to a modest degree (14,15). Even though the rise is relatively small, it might increase the risk of coronary artery atherosclerosis if the increase persisted over many years. Nevertheless, other evidence indicates that the rise reverts back to pretreatment levels over the long term. When serum cholesterol concentrations are measured after one or two years of thiazide treatment in large drug-intervention trials the cholesterol level is unchanged from the pretreatment control (16,17).

Since the large-scale preventive trials often added other antihypertensive drugs, possibly the addition of these agents might have moderated the cholesterol-raising effects of the thiazides. For example, prazosin (18), reserpine (19), and hydralazine (20) have all been reported to prevent the rise in serum cholesterol concentrations induced by thiazides. However, Alcazar et al. (21), who employed hydrochlorothiazide and amiloride without other drugs, found a rise of serum cholesterol at 1–3 months of treatment, which returned to baseline levels at 6 months to 2 years of follow-up. The Veterans Administration study of hydrochlorothiazide versus propranolol (8) used no other antihypertensive agents and no dietary interventions in 343 patients treated with hydrochlorothiazide alone. During the first 3 months of treatment serum cholesterol was raised but at 12 months it had fallen to slightly below the baseline value. Further evidence, therefore, indicates that the rise in serum cholesterol concentration is short lived and, therefore, could not be an important factor influencing mortality from coronary heart disease in hypertensive patients.

There is a trend at present to prescribe quite small doses of diuretics such as 25 mg or even 12.5 mg hydrochlorothiazide once daily. The principal reasons—to avoid hypokalemia and a rise in plasma cholesterol concentration—are not well justified, as indicated above. It is also doubtful whether such doses are effective in most patients. This question was examined in the Veterans Administration Study of propranolol versus hydrochlorothiazide (2). Doses of hydrochlorothiazide alone were titrated from 25 mg twice daily, the time interval between dosage increments being about 2 months. Of the patients whose diastolic blood pressures were reduced below 90 mm Hg, about half responded to the dose of 25 mg twice daily, 30% required 50 mg twice daily, and the remaining 20% needed 100 mg twice daily. If, as the evidence suggests, diuretics lower blood pressure by volume reduction, it is difficult to see how the very small doses employed by some physicians can be effective. As with other antihypertensive drugs, titration of doses with thiazides should be based on blood-pressure response versus valid side effects rather than on prevention of hypokalemia, rise of the plasma cholesterol concentration, or other unsubstantiated claims of toxicity

OTHER DRUG TREATMENTS

Thiazides and beta-blockers are not the only drugs which should be considered for primary care. Several newer agents deserve consideration. The calcium channel blockers may become candidates but there is still insufficient experience with them to make such a judgment at present. Minoxidil given with a diuretic is probably the most effective treatment for severe hypertension with renal failure.

Captopril

The angiotensin-converting enzyme inhibitors probably represent the leading new candidates for primary or step 2 treatment. It is appropriate, therefore, to review the results of the recent Veterans Administration trial of captopril with and without a diuretic (22,23). Doses of captopril alone of 12.5, 25, and 50 mg three times daily or 37.5 mg twice daily or placebo were randomly assigned, double blind to 475 patients with pretreatment diastolic blood pressures of 92–109 mm Hg. After 7 weeks hydrochlorothiazide, 25 mg twice daily, was added in two-thirds of the patients and in all of the placebo group. Treatment was then continued for 8 to 10 months.

Small doses appeared to be as effective as the large doses after 7 weeks of treatment, although there was some waning of the response to the lowest (12.5 mg) dose after 8 months of treatment. Reductions in diastolic blood pressure averaged 8 to 17 mm Hg with the various doses. Addition of hydrochlorothiazide considerably enhanced the antihypertensive effect, with diastolic reductions averaging 16 to 19 mm Hg below pretreatment levels with the various doses of captopril. These reductions were significantly greater than with hydrochlorothiazide alone. With this combined therapy there were no significant differences between any doses of captopril, including the 12.5 mg dose.

There were no life-threatening toxic effects. Re-

versible proteinuria appeared in two patients taking the active drug and in one taking placebo. Reversible loss of taste occurred in two patients. A reduction of white blood count from a pretreatment value of 3.6–2.6 × 1,000/mm^3 after captopril was found in one alcoholic patient and was probably not drug related. A few patients developed rashes or urticaria. Overall, however, the drug was extremely well tolerated. The usual complaints that may occur with other antihypertensive drugs, such as loss of energy, weakness, or impotence, were rarely noted. In fact, many patients experienced a sense of well being.

The favorable subjective profile makes captopril a promising candidate for primary treatment. In addition, the drug does not appear to be toxic when given in small doses to patients with mild to moderate hypertension and it is effective in lowering blood pressure in these doses, particularly when combined with a thiazide diuretic.

Thiazide plus reserpine

Another effective treatment for hypertension is the combination of a small dose of the long-acting drug reserpine with a long-acting diuretic. This choice can be considered when cost is a major obstacle to effective treatment, such as in countries where funds for medical care are severely restricted. Moreover, because the patients in such countries are often poorly educated, compliance may be a major problem and once-daily dosage becomes particularly important. A long-acting diuretic should be tried first such as bendroflumethiazide or chlorthalidone which can be given once daily. If this is ineffective a combination tablet of a long-acting diuretic with reserpine can then be substituted.

Reserpine has considerable antihypertensive effect when given with a diuretic. The principal objection to its use is the possibility of subjective complaints. Nevertheless, the incidence of side effects is less with lower doses. In the recent Veterans Administration study of reserpine (24) it was shown that doses as low as 0.125 mg per day were as effective as the standard dose of 0.25 mg per day. Thus, a combination tablet of 0.1 or 0.125 mg reserpine plus 25–50 mg chlorthalidone or 5–10 mg bendroflumethiazide should provide effective treatment when cost is a major consideration.

CONCLUSION

Diuretics have not been replaced in the step 1 position but their range of application has been somewhat narrowed. This is not because of hypokalemia or hypercholesterolemia but because of the possibly greater effectiveness of some beta-blockers in white patients. Beta-blockers also are preferred as primary treatment in patients with prior myocardial infarcts and in patients with rapid heart rates. Diuretics are the drug of first choice in black patients, in all hypertensive patients with a history of congestive heart failure, and in patients with renal failure where loop diuretics may be indicated. They are also preferred over other drugs for use in combination with captopril, reserpine, or any step 2 drug. Captopril provides an effective and well tolerated alternative primary treatment of hypertension.

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