EDITORIAL

CHOICE OF DIURETICS FOR TREATMENT OF ESSENTIAL HYPERTENSION

Thiazide diuretics are recommended as first-line therapy for the treatment of essential hypertension by all the major guidelines[1-3] including those of the Southern African Hypertension Society.[4] This is based on the fact that diuretic-based therapy compared with placebo has proven benefits in reducing cardiovascular endpoints in large prospective randomised trials.[5,6] Antihypertensive therapy does not normalise coronary heart disease (CHD) morbidity and mortality in hypertensive patients. Thiazide diuretics may cause hypokalaemia, hyperuricaemia, glucose intolerance, and a worsening lipid profile, all of which are risk factors for CHD and may mitigate against the benefits of blood pressure lowering. This led to the hypothesis that the newer drugs, which are either metabolically neutral (angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers) or beneficial (α-blockers), would be superior to diuretics in the prevention of CHD in hypertensive patients. Secondly, a more metabolically neutral diuretic would also be an alternative solution.

Regarding the first issue, several major outcome studies have been completed which test this hypothesis. In the CAPPP,[7] NORDIL[8] and STOP-2[9] trials conventional therapy (diuretics and β-blockers) was compared with the newer therapies (calcium channel blockers and/or ACE inhibitors). None of these trials demonstrated any differences in the primary outcomes of cardiovascular morbidity and death. The INSIGHT trial[10] compared the fixed combination of hydrochlorothiazide and amiloride with nifedipine GITS, and showed no differences in the primary endpoints. In the ALLHAT study[11] chlorthalidone was compared with amlodipine, doxazosin or lisinopril on the primary endpoint of fatal and non-fatal CHD. The doxazosin arm was terminated early by the Data and Safety Committee because doxazosin was associated with a doubling of the risk of cardiac failure. As a result of these studies most guidelines have maintained that diuretics and/or β-blockers should be used as first-line therapy for uncomplicated essential hypertension.

Regarding the second issue, indapamide immediate release (IR), a thiazide-related sulphonamide diuretic, was developed in the early 1970s, and was found to be an effective antihypertensive at a daily dose of 2.5 mg. Initial studies showed it to have fewer adverse effects on lipid and carbohydrate metabolism, but like the thiazides it has been associated with hyperuricaemia and hypokalaemia.[12,13] However, all these initial studies tended to compare indapamide with high-dose thiazides.[13,14] Since the development of indapamide clinical practice has changed and thiazides are seldom used in doses exceeding 25 mg daily. In the recent TOMHS study[15] chlorthalidone 15 mg daily was as effective as the other major classes of antihypertensive drugs in lowering blood pressure, but was not associated with adverse effects on lipids or glucose. A recent study found no differences between hydrochlorothiazide 25 mg and indapamide IR 2.5 mg.[16]

No major outcome study has compared indapamide with hydrochlorothiazide or other classes of drug. However, in the PROGRESS study,[17] a large randomised double-blind study comparing perindopril with and without indapamide versus placebo in the secondary prevention of stroke, indapamide IR 2.5 mg was used as add-on therapy to perindopril for blood pressure control, and was found to be a very important factor in the 28% reduction of secondary stroke reported in this study.

In this edition of the *Journal* Radevski *et al.* report that indapamide IR 2.5 mg was superior to hydrochlorothiazide 12.5 mg in lowering blood pressure in black patients with essential hypertension over a 30-month period.[18] This is a well-conducted study, and its strength is that the blood pressure findings were supported by 24-hour ambulatory blood pressure monitoring. However, the findings must be read with caution as it is a small study involving only 42 patients. Larger numbers of patients are needed to show equivalence or superiority of antihypertensive drugs to avoid the inherent pitfalls of the individual variability of blood pressure response.

The introduction of the indapamide sustained release (SR) 1.5 mg may be an important advance. The SR preparation allows the lowest possible dose to be used, avoiding the adverse metabolic problems while effectively lowering blood pressure throughout the 24-hour period.[19-21] Again no large outcome studies have been conducted to determine benefits on cardiovascular morbidity and mortality, but there is evidence of benefit on a surrogate marker of cardiovascular disease. In the LIVE study[22] indapamide SR 1.5 mg was shown to be more effective in reducing left ventricular hypertrophy in hypertensive patients than the comparator enalapril over a 12-month period.

In summary, diuretics are first-line therapy in the treatment of uncomplicated essential hypertension. In doses used in current clinical practice thiazides and indapamide IR probably have similar metabolic and blood pressure-lowering effects, but in black hypertensives with poorly controlled blood pressure a switch from a thiazide to indapamide may be a reasonable change based on the report by Radevski *et al.* Indapamide SR may offer benefits because of its ultra-low-dose and SR formulation, but this remains to be proved by large outcome

studies. Currently choice of diuretics should be determined largely by cost.

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