Br. J. clin. Pharmac. (1987), **23**, 15S–19S

Rationale for combination therapy

L. HANSSON
Department of Medicine, University of Göteborg, Östra Hospital, S-416 85 Göteborg, Sweden

1 Cardiovascular morbidity and mortality is higher in treated hypertensive patients than in normotensive subjects of the same age, sex and from the same populations.
2 A possible and logical explanation for this could be that arterial pressure in treated hypertensive patients usually is significantly higher than in matched normotensive subjects.
3 For these reasons it would appear logical to identify a therapeutic goal in the treatment of hypertension: to obtain normotensive blood pressure levels.
4 In order to obtain this goal, combined treatment with more than one antihypertensive drug would appear to be required.
5 Therapeutic combinations consisting of an ACE-inhibitor plus a diuretic or an ACE-inhibitor plus a calcium antagonist constitute two examples of antihypertensive drug combinations that would appear to offer potent antihypertensive efficacy and good tolerability.

Keywords arterial hypertension drug treatment

Introduction

The benefits of antihypertensive therapy were demonstrated already in the 1950s when treatment of patients with malignant hypertension was shown to improve 5 year survival from 0% in the untreated state to approximately 30% in treated patients (Harington *et al.*, 1959; Björk *et al.*, 1960). As a result of improved antihypertensive drugs and perhaps also better overall care, 5 year survival in treated malignant hypertension is now about 75% (Gudbrandsson *et al.*, 1979). These improvements in survival for the most severe form of hypertension are impressive since they have occurred over a relatively short period of time. However, much more important, at least from a quantitative aspect are the reductions in hypertension-induced cardiovascular mortality and morbidity demonstrated in non-malignant forms of hypertension. In one of the earliest controlled intervention trials in non-malignant hypertension, it was shown that significant benefits could be obtained through antihypertensive therapy at least in patients with diastolic blood pressures (phase IV) above 110 mm Hg (Hamilton *et al.*, 1964). Later, the placebo-controlled Veterans Administration Trials confirmed the benefits of antihypertensive therapy in patients with diastolic blood pressures (phase V) $\geq$ 105 mm Hg (Veterans Administration Study, 1967, 1970). In recent years, the benefits of antihypertensive treatment have been demonstrated also in milder forms of hypertension. Thus, large-scale, multicentre trials from Australia (Australian National Blood Pressure Study, 1980) and the United States (Hypertension Detection and Follow-up Program Study, 1979) and Great Britain (Medical Research Council Study, 1985) have clearly shown that antihypertensive therapy is of value also in mild hypertension.

Similar results have been obtained in the treatment of elderly hypertensive patients. Thus, in 1985 a multicentre European trial in patients aged 60 years or above clearly showed therapeutic benefits expressed as reduced cardiovascular mortality and morbidity (Amery *et al.*, 1985). These findings are in agreement with results of subgroup analysis in the Australian study discussed above. In the age-group 60–69 years the Australian data demonstrated significant reductions in cardiovascular morbidity when patients

on active treatment were compared to those receiving placebo (Australian National Blood Pressure Study, 1981).

Based on studies of this kind, antihypertensive therapy has been widely accepted and treatment of elevated arterial pressure constitutes an important part of today's medical care.

Suboptimal therapeutic effects

The positive aspects of antihypertensive therapy, briefly discussed above, are to a certain extent overshadowed by results from some recent reports, which indicate that treated hypertensive patients are still at substantial risk as compared with matched normotensive subjects.

One of the first reports in this direction was presented by Lindholm, who in his thesis investigated the whole adult population of the small community Dalby near Lund in southern Sweden (Lindholm, 1984). He found that in several age-groups treated hypertensive patients had significantly higher cerebro-cardiovascular morbidity than carefully matched normotensive subjects of the same age and sex and from the same population. However, an equally important finding was that the blood pressure in the treated hypertensive patients, although adequate by most standards, was still significantly higher than the blood pressure measured in the matched normotensive subjects (Table 1).

The findings from the Glasgow Blood Pressure Clinic are of a similar nature. In the Glasgow Blood Pressure Clinic, almost 4,000 patients with non-malignant hypertension were studied for 6.5 years (Isles *et al.*, 1986). It was found that cardiovascular mortality was 2–5 times higher than in subjects from control populations in Renfrew and Paisley as well as from the Strathclyde region in the greater Glasgow area. The findings from the Glasgow Blood Pressure Clinic clearly indicate that risk was reduced most in those patients in whom blood pressure was lowered most effectively. However, in patients in whom diastolic blood pressure was lowered to below 90 mm Hg, mortality was still higher than in the matched control population. The authors themselves attribute this to the possibility that the high mortality in the clinic patients was not wholly explained by high blood pressure before or during treatment but that some other factor might have contributed. Another equally plausible explanation is of course that even in patients in whom diastolic blood pressure was reduced to 90 mm Hg or lower, strict normotension was not obtained, which could explain the higher mortality also in this reasonably well treated stratum of patients.

Finally, results from the Gothenburg Primary Preventive Trial were presented in 1985 (Samuelsson, 1985). In this study 686 middle-aged, male, hypertensive patients were treated for 10 years in a hospital clinic. After 10 years of treatment 525 could be followed up. During these 10 years, 31% of these patients with mostly mild hypertension had developed some cardiovascular disorder such as stroke, myocardial infarction, intermittent claudication or diabetes mellitus. Equally disturbing as this high incidence of cardiovascular morbidity was the fact that diastolic blood pressure in the patients that could be followed up was $\geq$ 105 mm Hg in 10% of all patients and $\geq$ 95 mm Hg in 34% of all patients. The morbidity in this group of treated hypertensive patients clearly exceeds the rate in normotensive, middle-aged, Swedish males.

The data from all these studies, briefly reviewed above, clearly indicate that treated hypertensive patients are at an increased risk of cardiovascular mortality and morbidity as compared to strictly normotensive subjects of the same age and sex and from the same background population. There could be several reasons for this, but the most obvious explanation appears to be that in all three instances blood pressure was not treated adequately, i.e. down to strictly normotensive levels.

Therapeutic goal

It is conceivable that the somewhat disappointing results in the three large-scale studies re-

Table 1 Morbidity in treated hypertensive patients. Male hypertensive patients, aged 40–59 years in Dalby, Sweden, compared with matched normotensive subjects

	Patients (n = 66)	*Controls* (n = 75)	P <
Blood pressure (mm Hg)	149/91	133/80	0.001
Cerebro-cardiovascular disease	21	1	0.001
Coronary disease	20	1	0.001

From Lindholm (1984).

viewed above could be attributed to the fact that blood pressure was not lowered down to the level of comparable normotensive subjects. Thus, one could argue that in order to 'normalize' the hypertension-induced risks one should demand that blood pressure is 'normalized'. There could be several reasons for the fact that blood pressure was not normalized in these three studies. One obvious reason is that today's antihypertensive therapy is not effective enough in order to make this goal possible. This seems unlikely and will be discussed further in this paper.

Another possibility is that the doctors involved in these trials, and who all have a documented interest in arterial hypertension, were satisfied if treated blood pressure in their patients had been reduced to 95 or 90 mm Hg. It appears that therapeutic goals in hypertension are not as clearly defined as for example blood pressure levels at which treatment should be commenced. This is to a certain extent surprising since several investigations have shown that the treated blood pressure level, and not the initial untreated level, is the best prognostic indicator of risk (Beevers *et al.*, 1978; the International Prospective Primary Preventive Study in Hypertension, 1985; Isles *et al.*, 1986). It appears to be justified to define a therapeutic goal for the treatment of hypertension. It also appears logical that this goal should be to obtain strict normotension, i.e. to lower blood pressure to the same level as that seen in normotensive subjects of the same age and sex in the same population.

If such a goal can be obtained, it is of course conceivable that the full therapeutic benefit of this manoeuvre would not be seen due to either negative effects caused by treatment itself, such as electrolyte or lipid changes, which could increase risk or that long-standing hypertension had caused vascular and other damage that would contribute to an increased risk even when blood pressure had been normalized. Still, the interesting possibility remains to be investigated that a complete normalization of blood pressure would also normalize risks. This interesting aspect of antihypertensive therapy is discussed in somewhat greater detail elsewhere (Hansson & Robertson, 1986).

Rationale for combination therapy

For many years stepped-care therapeutic regimens have been common although the approach as regards the choice of drugs has not been the same in all countries. In the last few years there have been advocates of a more individualized choice of drug. e.g. Zanchetti (1985). It would be fair to say that there has been a general trend towards simplified therapeutic regimens in which the aim has been to treat patients with single-drug treatment using the lowest effective dose of the pharmacological compound. This approach is not without merits, but against the background of inadequate treatment of hypertension, discussed above, it appears that at least in a substantial number of patients this approach needs to be reevaluated. It is obvious that with single drug treatment only about 50% of patients with mild to moderate hypertension become adequately controlled irrespective of whether a diuretic or a β-adrenoceptor blocker has been employed (Hansson, 1983).

If strictly normotensive levels are to be obtained it appears that combined drug treatment will have to be used more frequently than in current practice. Moreover, the choice of combination needs to be made with greater consideration for obtaining an optimal effect. The common routine prescription of a β-adrenoceptor blocker plus a diuretic does not always fulfil these more strict demands on an optimal antihypertensive drug combination.

With the drugs presently available one could distinguish two or three alternative combinations that would seem to offer improved antihypertensive efficacy while at the same time maintaining an acceptable rate of side-effects. Such combinations could consist of a β-adrenoceptor blocker in combination with a calcium antagonist (not of the verapamil type), an ACE-inhibitor and a diuretic and finally an ACE-inhibitor plus a calcium antagonist. The last two of these alternatives will be discussed in somewhat greater detail although there is still not an abundance of data covering this topic.

Combination of an ACE-inhibitor and a diuretic

It is well known that combined therapy with an ACE-inhibitor and a diuretic commonly offers remarkably good control of blood pressure. Thus, captopril given in combination with hydrochlorothiazide has been shown to cause a greater reduction in arterial pressure than hydrochlorothiazide or captopril monotherapy (Veterans Administration Study, 1983). In another study the response-rate increased from 60 to 85% when a diuretic was added to treatment with captopril (Johnston *et al.*, 1984). It also appears that in patients given a very low dose of the ACE-inhibitor, e.g. captopril 12.5 mg three times daily, a diuretic is necessary to maintain an adequate antihypertensive effect (Veterans Administration Study, 1983).

It has been noted in several studies that black patients do not respond as well to ACE-inhibitor treatment as white patients. However, when a thiazide diuretic is added to the treatment with captopril the response has been quite favourable and no racial differences in the overall response rate remained (Veterans Administration Study, 1982a).

Early data from our group indicated that patients treated with captopril benefitted more from added diuretic therapy than did patients who initially were treated with atenolol (Andrén *et al.*, 1983a). An interesting aspect on the combined treatment with an ACE-inhibitor and a diuretic is the fact that a very low dose of the thiazide seems to be as effective as a normal dose, i.e. 6.25 mg of hydrochlorothiazide appears to be as effective as 25 mg during combined treatment (Andrén *et al.*, 1983b).

Against the stated goal above that hypertension needs to be treated more effectively, it is interesting to note that in the Veterans Administration trial referred to above, the goal diastolic blood pressure ($\leq$ 91 mm Hg) was obtained in 82–95% of patients with the various combinations of captopril plus hydrochlorothiazide (Veterans Administration Study, 1982b).

Other combinations of ACE-inhibitors and antihypertensive agents have also been studied. In a double-blind, cross-over trial in 15 patients with essential hypertension treated with a high dose of captopril (600 mg daily) either propranolol (240 mg daily) or bendroflumethiazide (7.5 mg daily) was added (Staessen *et al.*, 1983). Both propranolol and the thiazide diuretic caused a further reduction in arterial pressure, which tended to be greater following the addition of the thiazide.

Studies of this kind thus clearly indicate that an ACE-inhibitor given in combination with a diuretic offers a useful, potent and well tolerated therapeutic alternative.

ACE-inhibitors combined with calcium antagonists

Increasing clinical experience is being accumulated on the combined use of an ACE-inhibitor and a calcium antagonist. This combination seems to offer useful and well tolerated antihypertensive treatment with a striking degree of efficacy. So far there are very few published observations on this combination and this writer is at present not aware of any controlled studies on this topic. However, placebo-controlled, double-blind studies are underway, e.g. with the combination of captopril and the new dihydropyridine derivative calcium antagonist PN 200-110 (Hansson *et al.*, in preparation).

If the early positive clinical impressions can be confirmed in adequately designed and controlled trials, it appears likely that the combination between an ACE-inhibitor and a calcium antagonist could offer useful and effective treatment of arterial hypertension.

Conclusion

The rationale for combined treatment in hypertension has been reviewed in this paper. Against the background that several large-scale studies have shown that cardiovascular morbidity and mortality in treated hypertensive patients still is markedly higher than in untreated normotensive, matched control subjects, it appears that treatment of elevated arterial pressure needs to be improved, with the aim being to produce strictly normotensive blood pressure levels. In order to obtain this therapeutic goal, new and logical combinations of antihypertensive drugs will be required. Such useful combinations could consist of an ACE-inhibitor plus a diuretic or an ACE-inhibitor plus a calcium antagonist.

References

Andrén, L., Svensson, A. & Hansson, L. (1983a). Captopril or atenolol in essential hypertension. *Acta med. Scand.*, Suppl. 677, 115–118.

Andrén, L., Weiner, L., Svensson, A. & Hansson, L. (1983b). Enalapril with either a 'very low' or 'low' dose of hydrochlorothiazide is equally effective in essential hypertension. A double-blind trial in 100 hypertensive patients. *J. Hypertension*, **1**, Suppl. 2, 384–386.

Amery, A., Birkenhäger, W. H., Brixko, P., Bulpitt, C., Clement, D., Deruyttere, M., de Schaepdryver, A., Dollery, C., Fagard, R., Forette, F., Forte, J., Hamdy, R., Henry, J. H., Joossens, J. V., Leonetti, G., Lund-Johansen, P., O'Malley, K., Petrie, J., Strasser, T., Tuomilehto, J. & Williams, B. (1985). Mortality and morbidity results from the European Working Party on Hypertension in the Elderly Trial. *Lancet*, **i**, 1351–1354.

Australian National Blood Pressure Study (1980). Report by the management committee. *Lancet*, **i**, 1261–1267.

Australian National Blood Pressure Study (1981). Treatment of mild hypertension in the elderly. *Med. J. Austr.*, **2**, 398–402.

Beevers, D. G., Johnston, J., Devine, B. L., Dunn, F. G., Larkin, H. & Titterington, D. M. (1978).

Relation between prognosis and the blood pressure before and during treatment of hypertensive patients. *Clin. Sci. mol. Med.*, **55**, 333s–336s.

Björk, S., Sannerstedt, R., Angervall, G. & Hood, B. (1960). Treatment and prognosis in malignant hypertension: clinical follow-up study of 93 patients on modern medical treatment. *Acta med. Scand.*, **166**, 175–187.

Gudbrandsson, T., Hansson, L., Herlitz, H. & Andrén, L. (1979). Malignant hypertension—improving prognosis in a rare disease. *Acta med. Scand.*, **206**, 495–499.

Hamilton, M., Thompson, E. N. & Wisniewsky, T. K. M. (1964). The role of blood pressure control in preventing complications of hypertension. *Lancet*, **i**, 235–238.

Hansson, L. (1983). Drug treatment of hypertension. In *Handbook of Hypertension*, I. *Clinical aspects of essential hypertension*, ed., Robertson, J. I. S., pp. 397–436. Amsterdam: Elsevier.

Hansson, L. & Robertson, J. I. S. (1986). Is hypertension treated adequately? Report from the North Cape Meeting. *J. Hypertension* (in press).

Harington, M., Kincaid-Smith, P. & McMichael, J. (1959). Results of treatment in malignant hypertension: a seven-year experience in 94 cases. *Br. med. J.*, **2**, 969–980.

Hypertension Detection and Follow-up Program Cooperative Study (1979). Five year findings of the HDFP. I. Reduction in mortality in persons with high blood pressure including mild hypertension. *J. Am. med. Ass.*, **242**, 2562–2571.

The IPPPSH Collaborative Group (1985). Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta blocker oxprenolol: The International Prospective Primary Preventive Study in Hypertension (IPPPSH). *J. Hypertension*, **3**, 379–392.

Isles, C. G., Walker, L. M., Beevers, G. D., Brown, I., Cameron, L. M., Clarke, J., Hawthorn, V., Hole, D., Lever, A. F., Robertson, J. W. K., Wapshaw, J. A. (1986). Mortality in patients of the Glasgow Blood Pressure Clinic. *J. Hypertension*, **4**, 141–156.

Johnston, C. I., Arnolda, L. & Hiwatari, M. (1984). Angiotensin converting enzyme inhibitors in the treatment of hypertension. *Drugs*, **27**, 271–277.

Lindholm, L. (1984). Hypertension and its risks, pp. 1–84. *Epidemiological studies in Swedish primary health care*. Thesis, University of Lund.

Medical Research Council Working Party (1985). MRC trial of treatment of mild hypertension: principal results. *Br. med. J.*, **291**, 97–104.

Samuelsson, O. (1985). Hypertension in middle-aged men. *Acta med. Scand.*, Suppl. 702, 1–79.

Staessen, J., Fagard, R., Lijnen, P., Verschueren, L. J. & Amery, A. (1983). Double-blind comparison between propranolol and bendroflumethiazide in captopril-treated resistant hypertensive patients. *Am. Heart J.*, **106**, 321–328.

Veterans Administration Cooperative Study Group on Antihypertensive Agents (1967). Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressure averaging 115 through 129 mm Hg. *J. Am. med. Ass.*, **202**, 1028–1034.

Veterans Administration Cooperative Study Group on Antihypertensive Agents (1970). Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *J. Am. med. Ass.*, **213**, 1143–1152.

Veterans Administration Cooperative Study Group on Antihypertensive Agents (1982a). Racial differences in response to low dose captopril are abolished by the addition of hydrochlorothiazide. *Br. J. clin. Pharmac.*, **14**, Suppl. 2, 97S–101S.

Veterans Administration Cooperative Study Group on Antihypertensive Agents (1982b). Captopril: Evaluation of low doses, twice daily doses and the addition of diuretic for the treatment of mild to moderate hypertension. *Clin. Sci.*, **63**, 443s–445s.

Veterans Administration Cooperative Study Group on Antihypertensive Agents (1983). Low dose captopril for the treatment of mild to moderate hypertension. *Hypertension*, **5**, Suppl III, 139–144.

Zanchetti, A. (1985). A re-examination of stepped care. A retrospective and prospective analysis. *J. cardiovasc. Pharmac.*, **7**, Suppl. 1, S126–S130.