Low-Dose Quadruple Antihypertensive Combination
More Efficacious Than Individual Agents–A Preliminary Report

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Abstract—Increasingly combined antihypertensive agents are being used in practice to enhance control and improve compliance. To determine whether a capsule containing a quarter of the standard dose of 4 antihypertensive agents has greater efficacy than the standard dose of each individually, we prospectively randomized 108 untreated white hypertensive patients (55% male) aged 50±1 years (mean±SEM), with mean blood pressure 160±1/96±1 mm Hg. Patients received amlodipine (5 mg; n=22), atenolol (50 mg; n=20), bendroflumethiazide (2.5 mg; n=22), captopril (50 mg twice daily; n=22) or a capsule containing each of the 4 above at one-quarter dosage (n=22) in a parallel group design for 4 weeks. Blood pressure was measured using a semiautomated device (Omron 705), and the reduction in mean arterial pressure with the combined preparation was compared with that of the individual components. Statistical analysis used ANOVA and Tukey–Kramer honestly significant difference for multiple comparisons. The reduction in mean arterial pressure with the combination (19±2 mm Hg) was significantly greater than that with individual agents amlodipine (10±2 mm Hg; P<0.005), atenolol (10±2 mm Hg; P<0.005), bendroflumethiazide (6±1 mm Hg; P<0.005), and captopril (11±1 mm Hg; P<0.01). In addition, the percentage reduction in systolic (18±1 mm Hg; P<0.005) and diastolic (17±2 mm Hg; P=0.06) blood pressure was greater with the combination. More patients achieved a blood pressure of <140/90 mm Hg with the combination (60%) than any individual drug (15% to 45%; P<0.05). A low-dose combination of 4 agents representing 4 classes of standard antihypertensive agents was more efficacious than a standard single dose of each agent individually. (Hypertension. 2007;49:1-4.)

Key Words: antihypertensive drugs ▪ hypertension ▪ antihypertensive combinations ▪ blood pressure

Worldwide hypertension is the most prevalent risk factor for vascular disease and is predicted to affect 1 in every 3 people by the year 2010.1 Despite this, the diagnosis, management, and, particularly, control of hypertension is far from optimal, with control rates of 6% to 30% being reported from many communities.1 In part, this may be through the use of monotherapy where, in a white population, <40% may achieve a target blood pressure (<140/90 mm Hg) with standard angiotensin-converting enzyme inhibitor, β-blockers, calcium channel blockers, or diuretics.2 Increasingly, guidelines emphasize that the majority of the hypertensive population will require ≥2 antihypertensive drugs to achieve the recommended goals.3,4 Unfortunately, polypharmacy may be associated with an increased number of adverse drug effects and, possibly, decreased patient compliance.5,6 There is also some information to suggest that persistence with a single-pill combination antihypertensive is better than concurrent 2-pill therapy.7

The value of low-dose combination treatment with blood pressure drugs was examined in an analysis of 354 randomized trials8 where the average reduction using standard dosage was 9.1/5.5 mm Hg, whereas 3 drugs at half of the standard dose in combination produced a reduction of 19.9/10.7 mm Hg. The prevalence of symptoms with 2 drugs in combination was less than additive.8 Although there was considerable interindividual response to different categories of antihypertensive agents, there is evidence that certain patients will respond better to one of the following: angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists (A group); β-blocker groups of agents (B group); calcium channel antagonists (C group); or the diuretics group (D group).1,3 We, therefore, devised a combination that contained these 4 groups of agents and determined whether the combination containing a quarter of each would be superior to the standard dose of the A, B, C, or D agent.

Methods
Our population consisted of 110 untreated hypertensive patients with elevated blood pressure (>140/90 mm Hg) on 3 occasions confirmed by ambulatory blood pressure recording, with day time level >135/85 mm Hg, presenting to the Hypertension Clinic at St James’s Hospital during 2003–2005. Age was 50±1 (mean±SEM) years, and 38 were women; mean blood pressure was 160±196±1 mm Hg. None of the patients were on antihypertensive medication or any agents that influence blood pressure, such as oral contraceptives, steroids, or

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hormone replacement therapy. No patient had evidence of any vascular disease, cerebrovascular accident, coronary artery disease, or significant medical conditions. Two were receiving a statin, and 2 were on low-dose aspirin. None of the patients suffered from an associated condition that would provide a compelling indication for the exclusion of any of the agents, for example, pregnancy, heart failure, diabetes, renal disease, asthma, gout, and so forth. The participants were not blind to the form of treatment. The combined preparation using one quarter of the standard doses of each agent was prepared by cutting medicines in quarters, which were placed in an opaque capsule. The study had institutional research ethics approval, and subjects gave informed consent.

In a parallel group design, patients were randomly assigned to 1 of the 5 therapies listed in the Table. Random assignment by 1 author to 5 parallel groups was conducted independent of the observer, who was blind to the drug treatment. Blood pressure (the mean of 3 readings) was recorded after 15 minutes of supine rest using a semiautomated oscillometric device (Omron 705 CM), to avoid observer bias, at the same time in the morning, ~3 hours after drug therapy before and after 4 weeks. Blood samples were drawn at baseline for the measurement of fasting glucose, lipids, and serum creatinine.

### Statistical Analysis

The primary comparison was the reduction in mean arterial pressure. The percentage achieving a blood pressure goal of <140/90 mm Hg was also recorded. The percentage required to treat was based on estimates of blood pressure reduction in the analysis by Law et al.8

Statistical analysis was performed with JMP version 7.0 (SAS for Windows). For analysis of changes in blood pressure and heart rate, percentage reductions were also calculated using the Oldham correction, as follows: change in blood pressure = pretreatment blood pressure + posttreatment blood pressure/2, as described previously.2 Data were analyzed by ANOVA, and for differences between each treatment, Tukey–Kramer honestly significant difference was used. Data were expressed as mean ± SEM for continuous variables and as a percentage for categorical variables. Significance of 0.05 was assumed for all of the analyses.

### Results

Details of the patients randomly assigned to the 5 forms of therapy are given in the Table. There was no significant difference in baseline blood pressure, gender, or biochemical profile between the 5 different treatment groups. The absolute pretreatment and posttreatment blood pressure is also presented. Therapy was well tolerated by all of the participants, and, in particular, there was no case of hypotension. Two patients on atenolol withdrew.

As shown in the Table, all of the drugs reduced blood pressure significantly from baseline. Only atenolol and the combination significantly reduced heart rate (Table). The percentage of patients achieving target blood pressure (<140/90 mm Hg) was significantly greater with the combination (60%) compared with any individual treatment (15% to 40%).

There was a significantly greater reduction in both systolic BP (P<0.01) and mean arterial pressure (P<0.01) with the combination compared with individual drugs, although the greater reduction in diastolic BP with the combination did not achieve statistical significance (P=0.06; Figure).

Overall, there was a significant difference in the percentage fall in systolic and mean arterial pressure by treatment (P<0.001). Compared with individual agents, the combination (difference [%]; 95% confidence limits) showed a greater systolic blood pressure reduction (P<0.01) than amloidipine (8; 1 to 14), atenolol (9; 2 to 16), bendroflumethiazide (11; 4 to 18), and captopril (7; 1 to 14). Similarly, the differences in reduction in mean arterial pressure in comparison with the combination were 8% and 1% to 15% for amloidipine; 7% and 1% to 14% for atenolol; 11% and 4% to 18% for bendroflumethiazide; and 7% and 1% to 13% for captopril, reductions that were significantly less than the percentage of reduction.
seen with the combination ($P<0.01$). The difference for diastolic blood pressure was 8% and 0% to 16% for amlodipine; 6% and −3% to 13% for atenolol; 11% and 13% to 19% for bendroflumethiazide; and 7% and −1% to 14% for captopril, which did not achieve statistical significance.

Although the reduction in heart rate with the combination was greater ($P<0.01$) than that for amlodipine, bendroflumethiazide, or captopril, it was significantly less ($P<0.01$) than that with atenolol (Figure).

**Discussion**

There is now general acceptance that combined treatment will become increasingly the norm in the management of hypertension. There is abundant randomized, controlled trial data that low-dose drug combination regimens increase efficacy and reduce adverse effects. Recently, prescribers are using combinations, particularly of angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, or β-blockers with diuretics. Indeed, in the recent US Joint National Committee Guidelines, it is recommended that, in situations where blood pressure is $>20$ mm Hg above the systolic goal or $>10$ mm Hg above the diastolic goal, initiation of therapy using 2 agents, 1 of which is usually a thiazide, should be considered.

Although caution is advised with regard to starting fixed-dose combinations, specifically in some older patients and those at risk of orthostatic hypertension, in practice, the risk of adverse effects has not been greater than that of monotherapy. Fixed-dose combinations may, in addition, simplify a treatment regimen and are usually less expensive than individual components prescribed separately. Perhaps of particular importance will be the earlier achievement of blood pressure control, which has been shown recently to be an important determinant of outcome. A further advantage as shown in this study is a greater degree of efficacy. The blood pressure reduction of $26±3/15±2$ mm Hg with the combination was greater compared with that with individual agents. It is also interesting to compare the effects seen in this study with that reported in a meta-analysis of low-dose combined therapy by Law et al where a half dose of 1 drug reduced blood pressure by $6.7/3.7$ mm Hg with an increment of the same magnitude when each additional half standard dose was added, achieving a reduction of $19.9/10.7$ mm Hg with 3 agents. An extrapolation of the same magnitude to 4 drugs produces a figure very similar to that achieved in the present study. Although the number in this study is small, patient acceptability for the combined preparation was equal to that of any of the individual therapies. It should be noted that our reduction in blood pressure is not placebo adjusted.

It is clear that there is considerable individual response to antihypertensive agents. This may be influenced by age and ethnic factors. We chose a homogenous group in an effort to avoid such variables. Furthermore, the extent of blood pressure reduction achieved with the individual drugs in standard dosage is similar to that seen in the rotation study by Dickerson et al.

The present study has a number of limitations. It is not placebo controlled and is only single blind; however, the primary aim of the study was not looking at absolute reduction of blood pressure, which should ideally be placebo controlled, but in the comparison, after randomization to comparable groups, of blood pressure reduction with a low-dose combination versus full-dose monotherapy. The study was of short duration, 4 weeks, which may not represent the long-term efficacy of the different agents. In addition, we do not have data on ambulatory blood pressure recording and chose instead to look at peak effects to minimize the advantages that 1 agent may have with regard to duration of effect. In addition, the choice of individual agents and dosage may be a subject for discussion: all are in common everyday clinical usage, and the dosage chosen is the standard one.
recommended in the British National Formulary. We also chose these agents because all are now off patent, which would greatly reduce the cost if such types of preparations became commercially available. We accept, in the absence of a dose range study, that the choice of a quarter dose may not necessarily represent the optimal dose of an agent either individually or in combination given their different modes of action and the different dose–response curves already established for these agents. Furthermore, we cannot be certain that all 4 of the constituents are contributing to the antihypertensive effect or that other dual combinations of the AB/CD groups may have produced a similar effect. In addition, the use of a β-blocker in this regimen may be subject to criticism in light of the Anglo-Scandinavian Cardiac Outcomes Trial Study and the recent meta-analysis of the use of β-blockers in the treatment of primary hypertension.

The updated National Institute for Health and Clinical Excellence and British Hypertension Society guidelines no longer recommend β-blockers as initial therapy. However, we envisage the use of a β-blocker in combination therapy, and criticism to date of such agents has been as first-line therapy. One could consider substituting another drug for a β-blocker that has renin suppression effects, such as an angiotensin receptor antagonist, although our experience to date with combinations of angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists is that whereas there is an additive blood pressure reduction, it is relatively small.

We accept the need to consider other agents in an antihypertensive combination, or capsule, as in this case. There may be contraindications to its use in individual patients. However, we believe that these data show, as a preliminary observation in terms of efficacy, that a low-dose combination can produce greater blood pressure reductions than the standard dose of a single antihypertensive drug.

**Perspectives**

Cardiovascular disease will remain the major cause of death worldwide at least until 2020. Hypertension remains the most prevalent risk factor for vascular disease. Treatment of hypertension will place an increasing economic burden, not alone in developed, but also in developing countries, where its prevalence is rising rapidly. On the other hand, the economic burden of the inadequately managed hypertension is far greater. There is also an increasing recognition that adherence to therapy for many chronic asymptomatic conditions exemplified by hypertension is poor, and this significantly impacts on outcome. The problem of “pill/tablet burden” contributes to the poor patient adherence to therapy. At the same time, all of the recent studies in hypertension have emphasized the benefits of early and good blood pressure control, confirming the requirement for >1 and, commonly, 3 agents to achieve satisfactory control. We believe a combination composed of established agents ensuring both efficacy and relatively low drug acquisition costs using a low dose of individual agents reduces the likelihood of drug toxicity, will be economic, and reduces the pill burden and aid adherence. It should also be feasible to change the individual components of such a low-dose combined antihypertensive where patients are known to be sensitive to one of the constituents or where we know, based on age or ethnicity, that there may be a preferential response to different classes of agents. We believe that this study establishes a proof of concept for an increased efficacy of a multiple low-dose combination and, albeit in small numbers, no excess of adverse effects or poor adherence to therapy.

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**Disclosures**

None.

**References**

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