Effects of the Fixed Combination of Manidipine Plus Delapril in the Treatment of Hypertension Inadequately Controlled by Monotherapy with Either Component: A Phase III, Multicenter, Open-Label, Clinical Trial

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ABSTRACT

Background: Failure to achieve good blood pressure (BP) control is probably the most important reason for high rates of morbidity and mortality in patients with hypertension. Combination therapy has been shown to increase the percentage of patients in whom BP control is achieved. One combination is a calcium channel blocker (CCB) and an angiotensin-converting enzyme inhibitor (ACE-I).

Objective: The aim of this study was to assess the effects of the fixed combination of the CCB manidipine and the ACE-I delapril in the treatment of hypertensive patients already given monotherapy with either component but with poor results (ie, insufficient BP control or adverse events [AEs]).

Methods: In this Phase III, multicenter, open-label, clinical trial, patients with mild to moderate hypertension were assigned to 1 of 2 groups. Group 1 comprised patients whose diastolic BP (DBP) was >90 mm Hg or who experienced AEs with manidipine 20 mg once daily. Group 2 comprised patients who had a DBP >90 mm Hg or who experienced AEs with delapril 30 mg BID. In both groups, patients aged <65 years were to be treated with a fixed combination of manidipine 10 mg plus delapril 30 mg once daily for 12 weeks, whereas patients aged ≥65 years were to be treated with manidipine 5 mg plus delapril 15 mg once daily for 2 weeks and then manidipine 10 mg plus delapril 30 mg once daily for 10 weeks. Patients were assessed at baseline and at 2, 4, 8, and 12 weeks of treatment. At each visit, systolic blood pressure (SBP), DBP, and heart rate were measured 24 hours after dosing, and AEs were recorded.

Results: Group 1 included 154 patients (80 men, 74 women; mean [SD] age, 55 [6] years); group 2 included 158 patients (79 men, 79 women; mean [SD] age, 56 [5] years). Mean BP decreased significantly in both groups ($P < 0.01$). Compared with baseline values, mean SBP/DBP decreased 16.2 (3.8)/10.1 (1.9) mm Hg in group 1 and 15.8 (3.1)/11.0 (1.5) mm Hg in group 2 at the last visit. The success rate—rate of normalized DBP (≤ 90 mm Hg) and responder rate (DBP reduction ≥ 10 mm Hg)—was 79% in group 1 and 82% in group 2. The rates of treatment-related AEs were 11% in group 1 and 8% in group 2. In group 1, heart rate significantly increased from baseline only at 2 weeks ($P < 0.05$); in group 2, at each visit ($P < 0.05$) except at week 12. However, none of these differences were clinically significant.

Conclusion: In this study population of patients whose BP was not adequately controlled by monotherapy, the fixed combination of manidipine 10 mg plus delapril 30 mg, once daily, was effective and well tolerated. (*Curr Ther Res Clin Exp.* 2003;64:422–433) Copyright © 2003 Excerpta Medica, Inc.

Key words: manidipine, delapril, hypertension therapy.

INTRODUCTION

Failure to achieve good blood pressure (BP) control is probably the most important reason for high rates of morbidity and mortality in patients with hypertension.^{1–3} Poor treatment compliance, due in part to the adverse events (AEs) associated with commonly used antihypertensive therapies, often is given as the primary reason for failing to control BP.^{4,5} A secondary reason for this failure is that many physicians do not aggressively pursue achieving the desired BP goal.^{1,3,6}

Effective BP control with any single class of antihypertensive drug is not achieved in $>50\%$ of patients, even at high doses.^{7,8} Indeed, clinical trials^{9–12} have demonstrated that 2 to 4 drugs may be needed to achieve the full benefits of antihypertensive therapy. In some studies,^{8,13–15} combination therapy with 2 drugs has been shown to increase the percentage of patients in whom BP control is achieved. The enhanced antihypertensive efficacy of combination therapy is probably related to the simultaneous effect on several of the BP regulatory systems. In addition to better BP control, combination therapy allows the use of lower doses of each drug, which results in a lower prevalence of dose-dependent AEs, thus improving treatment compliance.

The most logical combinations are those that include drugs that lower BP by different mechanisms.¹⁶ One combination is an angiotensin-converting enzyme inhibitor (ACE-I) and a calcium channel blocker (CCB).^{17–25} Although these 2 drug classes have different mechanisms of action, both provide peripheral vasodilation with little direct effect on cardiac output. Moreover, the ACE-I attenuates the ankle edema frequently seen with the CCB, probably by reducing venous tone and decreasing distal arteriolar leakage of lymph.¹⁷

Delapril, a nonsulphydryl, nonprolinic, lipophilic ACE-I with high affinity for the C-terminal site of ACE, has been shown to be effective and well tolerated in the treatment of hypertension.^{26,27} Manidipine, a second-generation dihydropyridine CCB with vascular selectivity and long-lasting activity, has been shown to reduce BP effectively and to have a good tolerability profile.^{28,29} Because of the long duration of action of the 2 drugs, their association could allow effective 24-hour control of BP.

The aim of this study was to assess the effects of the fixed combination of the CCB manidipine and the ACE-I delapril in the treatment of hypertensive patients already given monotherapy with either component but with poor results (ie, insufficient BP control or AEs).

PATIENTS AND METHODS

In this Phase III, multicenter, open-label clinical trial, patients aged 18 to 75 years with mild to moderate hypertension were assigned to 1 of 2 groups. Group 1 comprised patients whose diastolic BP (DBP) was >90 mm Hg or who experienced AEs with manidipine 20 mg once daily. Group 2 comprised patients who had a DBP >90 mm Hg or who experienced AEs with delapril 30 mg BID.

The exclusion criteria were as follows: secondary hypertension, myocardial infarction <6 months before the start of the study, congestive heart failure with New York Heart Association class >I (ie, patients with limitations in activity), hemodynamically significant cardiac valve disease, diabetes mellitus, obesity, hepatic or renal insufficiency, hematologic and gastrointestinal disease, known hypersensitivity to ACE-Is or CCBs, pregnancy, possible pregnancy, and lactation. The study protocol was approved by the local ethics committees responsible for each of the 15 participating centers, and written informed consent was obtained from each patient before enrollment.

According to the study design, in both groups, patients aged <65 years were to be treated with a fixed combination of manidipine 10 mg plus delapril 30 mg once daily for 12 weeks (ie, high dose), whereas patients aged ≥65 years were to be treated with manidipine 5 mg plus delapril 15 mg once daily for 2 weeks (ie, low dose) and then switched to the high dose for the remaining 10 weeks of the study. All treatments were given orally (tablets). Patients were instructed to take the study medication at the same time each morning. In patients receiving the low dose, at 2 weeks of treatment, nonresponders (DBP reduction <10 mm Hg) were to be switched to the high dose for the remainder of the 12-week study period, whereas responders (DBP reduction ≥10 mm Hg) could continue with the low-dose combination.

Patients were assessed at baseline and at 2, 4, 8, and 12 weeks of treatment. At each visit, BP and heart rate (HR) were measured with the patient in the sitting position after 5 minutes of rest. BP measurements were performed using a standard mercury sphygmomanometer (W.H.O.M.D., Wenzu, China). Three measurements were taken at 1-minute intervals and averaged; phase V Korotkoff

sounds were designated as the DBP. BP was measured at the end of the dosing interval at trough, immediately before the daily dose of medication was dispensed (ie, 24 hours after dosing). HR was measured using pulse palpation of the wrist for 30 seconds immediately after BP measurements were performed. The daily dose of medication was dispensed just after BP and HR were measured. AEs reported spontaneously by the patient or elicited by indirect questioning by the physician were recorded, and their correlation with treatment was established.

At the baseline and final visits, laboratory specimens were collected after 8 hours of fasting, standard 12-lead electrocardiography (ECG) was performed, and body weight was measured. The specimens were used to determine serum electrolyte, creatinine, glucose, total bilirubin, uric acid, aminotransferases, total and high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels; complete blood cell count; and urinalysis.

Primary assessment of antihypertensive effect was based on quantitative reduction of DBP. Secondary assessment of antihypertensive effect was based on calculation, at the final visit, of the percentages of patients whose BP was normalized (mean DBP ≤ 90 mm Hg) and who were responders (DBP reduction ≥ 10 mm Hg). The success rate, which included responders and patients whose BP was normalized, was used to better identify the overall antihypertensive effect of the combination therapy.

Tolerability was assessed in terms of AEs, changes in laboratory parameters, and withdrawal rate related to treatment. Treatment compliance was assessed by counting the tablets remaining at each visit.

Statistical Analysis

Statistical analysis of the data was carried out with SAS version 6.12 (SAS Institute Inc., Cary, North Carolina). Efficacy analyses were carried out in the intent-to-treat (ITT) population (ie, patients who were treated with ≥ 1 dose of the study medications and who underwent at least the first visit during treatment) and in the per-protocol (PP) population (ie, all patients in the ITT population who also met all inclusion and exclusion criteria and who did not have any major protocol violations). Missing data were replaced using the last-observation-carried-forward method. Tolerability analysis was carried out in all patients assigned to treatment. The population of patients included in the tolerability analysis was the same as the ITT population. Mean BP changes from baseline and relative 95% CIs were calculated. Laboratory parameters were assessed using the shift tables of ranges at the end of the period versus baseline values. The incidence of patients with high values and low values was summarized using frequency counts. Statistical significance was set at $P < 0.05$.

RESULTS

Demographic and clinical data at baseline are shown in [Table I](#). In group 1, a total of 154 patients (80 men, 74 women) aged 30 to 76 years (mean [SD] age,

Table I. Baseline demographic and clinical data of study patients (N = 312).*

Characteristic	Group 1 (n = 154)	Group 2 (n = 158)
Age, y		
Mean (SD)	55 (6)	56 (5)
Range	30–76	29–78
Sex, no. (%)		
Men	80 (52)	79 (50)
Women	74 (48)	79 (50)
Body weight, kg		
Mean (SD)	73 (5)	74 (6)
Range	47–130	50–117
Height, cm		
Mean (SD)	167 (3)	166 (3)
Range	142–187	126–190
Sitting BP		
SBP, mean (SD), mm Hg	153 (12)	154 (12)
DBP, mean (SD), mm Hg	95 (5)	96 (6)
HR, mean (SD), bpm	72 (8)	73 (9)
Duration of hypertension, mean, y	5.8 (3.7)	6.2 (4.1)
Reasons for drug combination, no. (%)		
Inadequate BP control	145 (94)	149 (94)
Adverse events	8 (5)	8 (5)
Insufficient BP control + adverse events	2 (1)	2 (1)
Smokers, no. (%)	25 (16)	35 (22)
Coffee drinkers (≥ 1 cup/d), no. (%)	131 (85)	142 (90)
Alcohol drinkers (> 15 g/d), no. (%)	43 (28)	43 (27)

BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

*No statistically significant differences were found between groups.

55 [6] years) were recruited for the study. Of these, 152 patients (99%) entered into the ITT population, and 2 patients (1%) discontinued before visit 2. A total of 141 patients (93%) in group 1 completed the study, 5 patients (3%) withdrew due to AEs, 5 (3%) withdrew for logistic reasons (distance from the study center or difficulties in reaching it), and 1 (1%) withdrew due to inadequate therapeutic response. In group 2, a total of 158 patients (79 men, 79 women) aged 29 to 78 years (mean [SD] age, 56 [5] years) were recruited for the study. Of these, 155 patients (98%) entered into the ITT population, and 3 patients (2%) discontinued before visit 2. A total of 148 patients (95%) completed the study, 4 patients (3%) withdrew due to AEs, 2 (1%) withdrew due to inadequate therapeutic response, and 1 (1%) did not return for clinic visits. No statistically significant between-group differences were found in any of the baseline characteristics.

In group 1, 142 patients (93%) were aged < 65 years and so received high-dose therapy (mean [SD] treatment duration, 79.8 [1.6] days; range, 13–101 days),

whereas 27 patients (18%) were aged ≥ 65 years and so received low-dose therapy (mean [SD] treatment duration, 40.4 [1.5] days; range, 12–93 days). In group 2, 136 patients (88%) received high-dose treatment (mean [SD] treatment duration, 80.8 [2.1] days; range, 14–105 days) and 29 (19%) received low-dose treatment (mean [SD] treatment duration, 59.5 [2.2] days; range, 13–100 days).

Efficacy

The changes in systolic BP (SBP) and DBP at 2, 4, 8, and 12 weeks of treatment with the fixed combination of manidipine and delapril are shown in Figure 1. In both groups, the fixed-combination therapy produced clinically and statistically significant ($P < 0.01$) reductions in SBP and DBP from baseline values beginning at 2 weeks and continuing throughout the treatment period. In group 1, mean

Figure 1. Changes (Δ) in sitting (A) systolic blood pressure (SBP) and (B) diastolic blood pressure (DBP) at 2, 4, 8, and 12 weeks of treatment in the intent-to-treat population of group 1 ($n = 152$) and group 2 ($n = 155$). Data are expressed as means (95% CI). No significant between-group differences were found. $P < 0.01$ versus baseline for both treatments at all time points.

(SD) SBP/DBP decreases from baseline were 9.1 (3.1)/5.8 (1.7) mm Hg at 2 weeks, 13.1 (2.2)/8.5 (1.9) mm Hg at 4 weeks, 14.8 (3.3)/9.8 (2.0) mm Hg at 8 weeks, and 16.2 (3.8)/10.1 (1.9) mm Hg at 12 weeks. In group 2, mean (SD) SBP/DBP decreases from baseline were 9.9 (2.8)/7.4 (1.2) mm Hg at 2 weeks, 12.5 (1.5)/9.3 (1.4) mm Hg at 4 weeks, 14.4 (2.3)/10.3 (1.2) mm Hg at 8 weeks, and 15.8 (3.1)/11.0 (1.5) mm Hg at 12 weeks. No statistically significant between-group differences were found in mean changes in BP at any time during the study.

BP was normalized (mean DBP ≤ 90 mm Hg) in 119 (78%; 95% CI, 70.9–84.6) patients in group 1 and 124 (80%; 95% CI, 72.8–86.0) in group 2, with no significant differences between the 2 groups. The success rate was 79% (120/152; 95% CI, 71.6–85.1) in group 1 and 82% (127/155; 95% CI, 75.0–87.6) in group 2. Among the patients aged ≥ 65 years, only 2 were responders to the lower dose.

In group 1, HR was clinically nonsignificantly, although statistically significantly, increased only at 2 weeks (mean change, 1.0 beats per minute; 95% CI, 0.1–1.9; $P < 0.05$). In group 2, HR was clinically nonsignificantly but statistically significantly increased from baseline at each visit ($P < 0.05$), except at week 12 (Figure 2).

Tolerability

The AEs considered treatment related are summarized in Table II. In group 1, 1 serious and 16 nonserious AEs were reported by 15 patients (10%) during the study. In group 1, 5 patients (3%) withdrew due to AEs (2 for ankle edema and 1 each for epigastralgia, headache, and nausea). In group 2, 4 patients (3%) withdrew due to AEs (1 each for cough, ankle edema, headache, and nausea). Two of the 8 patients (25%) who discontinued previous antihypertensive

Figure 2. Mean (SD) heart rate (HR) at baseline and at 2, 4, 8, and 12 weeks of treatment in the intent-to-treat populations of group 1 (n = 152) and group 2 (n = 155). No significant between-group differences were found. * $P < 0.05$ versus baseline.

Table II. Treatment-related adverse effects (AEs) (%) during therapy with a fixed combination of manidipine plus delapril by treatment group (intent-to-treat population, N = 307).

AE	Group 1 (n = 152)*	Group 2 (n = 155)†
Cough	3 (2)	1 (1)
Dizziness	3 (2)	0 (0)
Ankle edema	2 (1)	2 (1)
Epigastralgia/gastric pyrosis	2 (1)	0 (0)
Headache	1 (1)	1 (1)
Nausea	1 (1)	1 (1)
Palpitations/atrial fibrillation	1 (1)	1 (1)
Mental confusion	1 (1)	0 (0)
Abdominal tension	1 (1)	0 (0)
Cutaneous erythema	0 (0)	1 (1)
Fatigue	0 (0)	1 (1)

*Five of these patients (3%) withdrew due to AEs (2 for ankle edema and 1 each for epigastralgia, headache, and nausea).

†Four of these patients (3%) withdrew due to AEs (1 each for cough, ankle edema, headache, and nausea).

monotherapy with manidipine due to AEs again experienced an AE. In group 2, 1 serious and 11 nonserious AEs were reported by 8 patients (5%) during the study period. One of the 7 patients (14%) who discontinued previous antihypertensive monotherapy with delapril due to AEs again experienced an AE.

No significant changes were found in the results of laboratory tests or ECG in either treatment group. A clinically nonsignificant but statistically significant decrease was found in body weight in both groups: the mean decrease from baseline was 0.4 kg (95% CI, 0.6–0.2) in group 1 and 0.3 kg (95% CI, 0.6–0.1) in group 2 ($P < 0.05$).

Based on counting the remaining tablets at each visit, 90% of the prescribed tablets were taken during combination therapy in group 1 and 91% in group 2, indicating good treatment compliance.

DISCUSSION

Fixed-dose combinations of drugs traditionally have been discouraged as initial therapy.³⁰ Reasons given included the inability to titrate individual components, difficulty in separating individual toxicities, and unnecessary exposure to superfluous therapy. However, the use of a fixed combination of small doses of 2 drugs with documented additive BP-lowering effects may offer some advantages—improved antihypertensive efficacy, improved compliance because of once-daily dosing and 1 dose unit, improved tolerability profile, fewer metabolic AEs because of lower doses of individual drugs, and less cost than individual components prescribed separately.¹⁴ For these reasons, fixed-combination

therapy is now regarded as a logical and effective alternative to standard single-agent therapy and could contribute to an increase in the percentage of patients whose hypertension is well controlled.³¹

The results obtained in the present study showed that the fixed combination of the CCB manidipine and the ACE-I delapril was effective in reducing BP values in patients with hypertension inadequately controlled with either manidipine or delapril monotherapy. The antihypertensive efficacy of the fixed combination was shown by the SBP and DBP values measured 24 hours after dosing, which were statistically significantly lower than those observed with manidipine and delapril alone. The decrease in BP values was seen throughout the trial and was similar in the 2 groups. The antihypertensive efficacy of the fixed combination was confirmed by the percentage of patients whose BP was normalized (78% in the patients who had previously received manidipine monotherapy and 80% in those who had previously received delapril). These findings are in agreement with previous observations indicating that the combination of a dihydropyridine CCB and an ACE-I has an additive effect on BP reduction.¹⁷⁻²⁵ Beyond the additive BP-lowering effect, a potentially important advantage of this type of combination therapy is that CCBs and ACE-Is are devoid of metabolic AEs.³²⁻³⁴ Indeed, in the present study no significant changes in laboratory parameters (particularly, serum glucose, uric acid, HDL-C, and TG) were observed. A slight, although significant, increase in HR was observed during fixed-combination treatment in patients previously treated with delapril alone; however, such an increase, which was not seen in patients previously treated with manidipine alone, was not considered clinically relevant.

Since CCBs and ACE-Is have been shown to produce favorable effects on structural changes complicating hypertension (eg, development of left-ventricular hypertrophy, renal damage, endothelial dysfunction, and atherosclerotic vascular lesions),³⁵⁻³⁸ another potential advantage of the CCB + ACE-I combination would be greater tissue protection than with either agent alone, thus improving the benefits of their synergistic antihypertensive action.^{39,40}

The issue of drug tolerability is especially crucial in treating an asymptomatic condition such as hypertension in which patients are usually expected to take medications on a long-term basis without obvious short-term health benefits. In the present study, the incidence of AEs was low, thereby confirming a good tolerability profile for the fixed-combination treatment. The 15 patients who discontinued previous antihypertensive treatment due to treatment-related AEs (8 who previously received manidipine and 7 who previously received delapril monotherapy) had BP levels controlled with the combination therapy, and only 3 of them experienced AEs with the combination therapy.

CONCLUSION

In this study population of patients whose BP was not adequately controlled by monotherapy, the fixed combination of manidipine 10 mg plus delapril 30 mg was effective and well tolerated.

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