Combined *Enalapril* and *Felodipine* Extended Release (ER) for Systemic Hypertension

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This multicenter, placebo-controlled, double-blind trial of factorial design evaluated the safety and efficacy of combination treatment with the angiotensin-converting enzyme inhibitor, enalapril, and the vascular selective calcium antagonist felodipine extended release (ER) in patients with essential hypertension. After a 4-week, single-blind placebo baseline period, 707 patients with sitting diastolic blood pressures (BPs) in the range of 95 to 115 mm Hg received placebo, enalapril (5 or 20 mg), felodipine ER (2.5, 5, or 10 mg), or their combinations for an 8-week double-blind treatment period. All doses of enalapril and felodipine ER had a statistically significant ($p < 0.05$) additive effect in reducing both systolic and diastolic BP. The trough to peak ratios for the combinations ranged from 0.63 (enalapril 5 mg–felodipine ER 2.5 mg) to 0.79 (enalapril 20 mg–felodipine ER 10 mg) and were consistent with effective BP control with 1 dose/day. Patients aged ≥65 years demonstrated a greater reduction in diastolic BP. Combinations of enalapril–felodipine ER were associated with less drug-induced peripheral edema (4.1%) compared to felodipine ER monotherapy (10.8%). There were no serious drug-related adverse effects observed during the study. In this trial, the combination of enalapril and felodipine ER effectively lowered BP and was generally well tolerated with an excellent safety profile when used in the treatment of hypertension.

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According to the traditional stepped care approach for hypertension, the initial step in treatment consists of selecting a single drug and, if necessary, titrating its dosage upward in an attempt to reach treatment goals. Additional drugs are added only if blood pressure (BP) control cannot be obtained with a single agent. It is increasingly recognized, however, that upward dose titration of antihypertensive agents can result in a significant increase in side effects with little additional BP reduction.[1–3] Many authorities now advocate combination therapy with low doses of multiple agents as an alternative strategy for achieving BP control with minimal adverse effects.[4–10] In this study, the clinical utility of combination treatment with the angiotensin-converting enzyme (ACE) inhibitor, enalapril, and the vascular selective dihydropyridine calcium antagonist, felodipine extended release (ER), was explored in a multicenter, placebo-controlled, double-blind randomized trial of factorial design.

METHODS

Patient selection and study design: Seven hundred seven patients (457 men [65%], 548 white [78%]), mean age 53.5 years, with essential hypertension and sitting diastolic BP in the range of 95 to 115 mm Hg were enrolled in a multicenter, placebo-controlled, double-blind, parallel, randomized 3 × 4 factorial design study after giving informed consent. Patients with evidence of significant renal (calculated creatinine clearance <60 ml/min) or hepatic dysfunction, recent myocardial infarction, or congestive heart failure were excluded. After a 4-week single blind placebo baseline period, qualifying patients were randomized to receive placebo, enalapril (5 or 20 mg), felodipine ER (2.5, 5 or 10 mg), or their combinations for the 8-week double blind treatment period. The number of patients enrolled in each treatment group is detailed in Table I. Patients randomized to felodipine ER 10 mg either alone or in combination with enalapril received felodipine ER 5 mg/day for the first 3 days of treatment before titration to the 10-mg dose.

Sitting (trough) BP and heart rate were measured at all visits 24 hours (range 22 to 26 hours) after receiving the dose. Sitting (peak) BP was measured 4 hours (range 3 to 5 hours) after drug administration at the end of the baseline and double-blind periods to assess peak BP response. Each recorded BP was the average of 3 measurements obtained 1 minute apart after 5 minutes of rest. Korotkoff phase V was used as the criterion for diastolic BP. Adverse signs or symptoms (volunteered) were documented at each visit and serial laboratory tests and electrocardiograms were obtained during the study to assess the occurrence of adverse events. Adverse events were classified as drug-related if, in the opinion of the investigator,

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*A list of participating investigators appears in the Appendix.

TABLE I Number of Patients Enrolled in Each Treatment Group

Dose (mg)	Placebo	Felodipine ER 2.5	Felodipine ER 5	Felodipine ER 10	Total
Placebo	79	46	84	46	255
Enalapril 5	85	48	84	46	263
Enalapril 20	48	48	45	48	189
Total	212	142	213	140	707

ER = extended release.

TABLE II Patient Characteristics at Baseline (n = 707)

Age (yr)	53.5 ± 10.5
Gender	
Men	457 (65%)
Women	250 (35%)
Race	
White	548 (78%)
Non-White*	159 (22%)
Duration of hypertension (yr)	10.1 ± 8.8
Sitting diastolic BP (mm Hg)	101.86 ± 5.66
Sitting systolic BP (mm Hg)	155.48 ± 17.67

* Non-White included 58% Black, 7% Asian, and 35% designated as "other" race.
BP = blood pressure.

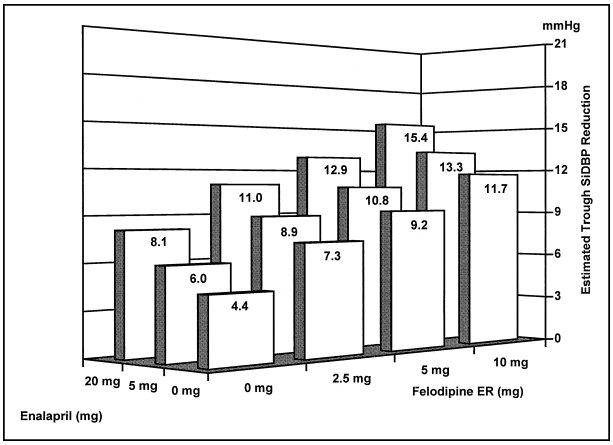

FIGURE 1. Estimated reduction in trough sitting diastolic blood pressure (SiDBP)at week 8 for all 12 treatment groups (additive model).

the event was possibly, probably, or definitely related to study medication.

Statistical methods: EFFICACY: The primary efficacy end point was the change from baseline in trough sitting diastolic BP following 8 weeks of double-blind treatment. An analysis of variance (ANOVA) characterizing a 3 × 4 factorial design with main effects and interaction term was initially performed to test for the presence of interaction (nonadditivity) between the dosage levels of the 2 drugs. Since the results indicated that there were no interactions ($p > 0.7$), the additive model as specified in the protocol was the primary approach. An ANOVA model with main effects of enalapril and felodipine ER and without the interaction term was then used to determine whether each of the dosage levels added additional benefit over placebo, and to estimate the average reduction of diastolic and systolic BP from baseline to week 8.

Subgroup analyses were performed by adding the important covariates (gender, race, and age groups) to the ANOVA model 1 at a time to determine if these covariates had significant effects on the BP reduction at week 8, but no formal statistical comparisons were made. The prespecified categories of antihypertensive response were defined as excellent (sitting diastolic BP <90 mmHg), good (sitting diastolic BP ≥90 mm Hg but a reduction of ≥10 mm Hg), or unsatisfactory (neither excellent nor good). The additive model fit ($p = 0.6$ for the goodness-of-fit statistic), indicated that the combined percentage of excellent and good responses increased with increasing dose levels of enalapril and felodipine ER. The PROC CATMOD in the Statistical Analysis System (SAS Institute, Cary, North Carolina), with main effects as the independent variables and response as the dependent variable, was used. Data were analyzed on an intent-to-treat basis. The last double-blind measurement of patients who discontinued therapy before week 8 was carried forward to subsequent time points.

Safety: All patients randomized to the study were included in the analysis of safety at week 8. The incidence of patients discontinued, adverse events (clinical and laboratory), and patients with laboratory values outside the predefined limits were analyzed for a treatment effect using the PROC CATMOD in SAS. A saturated model was used and the comparisons of interest (i.e., each combination vs placebo and its corresponding monotherapy) were made using the CONTRAST statement in SAS.

RESULTS

The baseline characteristics of the 707 patients who took part in the study are given in Table II. The 12 treatment groups were similar with respect to age, gender, race, duration of hypertension, and baseline BP. Of the 707 patients, data were available on 705 for efficacy analysis (2 patients without treatment records were excluded).

The estimated (additive model) trough sitting systolic and diastolic BP reductions at week 8 are presented in Figures 1 and 2. All doses of enalapril and felodipine ER had a statistically significant ($p < 0.05$) additive effect in reducing both systolic and diastolic BP. The additional BP reduction increased for increasing doses of each agent. The estimated trough to peak ratio for sitting diastolic BP for the treatment combinations ranged from 0.63 for enalapril 5 mg–felodipine ER 2.5 mg to 0.65 for enalapril 5 mg–felodipine ER 5 mg and 0.79 for enalapril 20 mg–felodipine ER 10 mg.

No clinically meaningful changes in heart rate were observed with monotherapy or combination therapy throughout the treatment period. At week 1, the only statistically significant heart rate changes

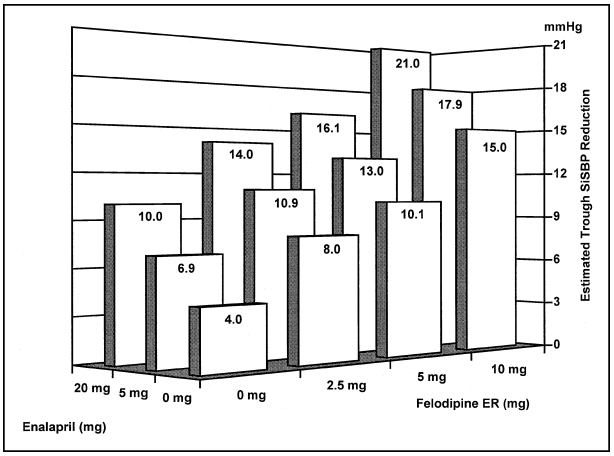

FIGURE 2. Estimated reduction in trough sitting systolic blood pressure (SiSBP) at week 8 for all 12 treatment groups (additive model).

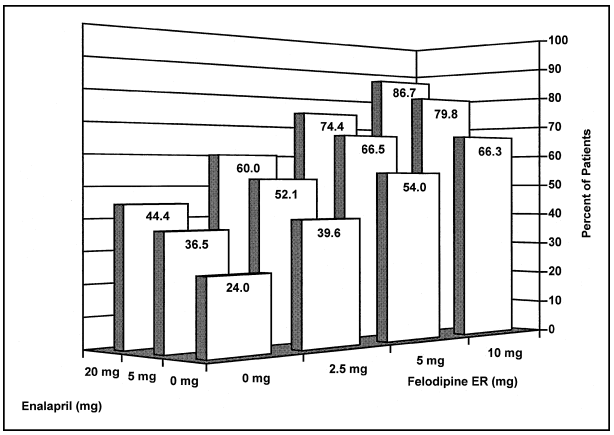

FIGURE 3. Estimated excellent/good response rates for sitting diastolic blood pressure at week 8 (intent-to-treat—last-observation-carried-forward) (additive model).

were a 2.0 beat/min reduction with the enalapril 5 mg–felodipine ER 2.5 mg combination compared to placebo, and a 2.6 beat/min increase with the enalapril 5 mg–felodipine ER 5 mg combination compared to enalapril 5 mg. At week 8, no statistically significant changes in heart rate were observed in any of the treatment groups.

Categories of blood pressure response: The estimated percentage of patients with BP reduction categorized as excellent and/or good at the end of week 8 is detailed in Figure 3. Overall, the combined percentage of excellent/good responses increased with higher doses of enalapril and felodipine ER as well as their combination. Among the treatment combinations, the estimated excellent and/or good response rate ranged from 52.1% (enalapril 5 mg–felodipine ER 2.5 mg) to 66.5% (enalapril 5 mg–felodipine ER 5 mg) and 86.7% (enalapril 20 mg–felodipine ER 10 mg).

Demographic subgroups: When patients were categorized by age as young (<50 years, n = 249), middle-aged (50 to 64 years, n = 337), or elderly (≥65 years, n = 119), age was found to be a significant ($p > 0.05$) factor in sitting diastolic BP reduction at week 8. The average sitting diastolic BP reductions were 9.3 mm Hg for the young, 9.6 mm Hg for the middle-aged, and 11.7 mm Hg for the elderly patients, although at baseline, the mean sitting diastolic BPs were similar (101.8, 102.1, and 101.2 mm Hg, respectively). Patients aged ≥65 years had greater sitting diastolic BP reductions than those <65 for all 6 treatment combinations. With respect to sitting systolic BP at week 8, the average reductions for the 12 treatment groups were 9.3 mm Hg for the young, 13.2 mm Hg for the middle-aged, and 15.2 mm Hg for the elderly patients. However, these differences were not statistically significant when adjusted for differences in baseline mean sitting systolic BPs (146.0, 158.2, and 167.3 mm Hg, respectively). It did not appear that gender or race had any meaningful effect on BP response.

Adverse events: There were no serious drug-related adverse events observed in this study. A total of 5 patients had clinical serious adverse events during the 8-week treatment period, none of which were reported as drug related by investigators. Table III shows the incidence of the 4 most frequently occurring drug-related adverse events categorized by placebo, monotherapies, and combination therapy. With regard to the monotherapies, dose-related edema and/or leg swelling occurred more frequently in patients receiving felodipine ER, whereas cough was noted more often in enalapril-treated patients. The occurrence of cough in patients receiving the combinations was similar to those receiving enalapril alone (2.2% vs 2.3%).

Combinations of enalapril–felodipine ER were associated with less drug-induced peripheral edema than felodipine ER alone. The incidence of edema was highest, and dose related, in patients receiving

TABLE III Drug-Related Adverse Events

	Treatment Group			
Adverse Events	Placebo (79 patients)	Felodipine ER Monotherapy (176 patients)	Enalapril Monotherapy (133 patients)	Combination Therapy (319 patients)
Headache	6 (7.6%)	18 (10.2%)	5 (3.8%)	33 (10.3%)
Dizziness	0 (0.0%)	5 (2.8%)	2 (1.5%)	14 (4.4%)
Edema swelling	1 (1.3%)	19 (10.8%)	3 (2.3%)	13 (4.1%)
Cough	0 (0.0%)	1 (0.6%)	3 (2.3%)	7 (2.2%)

ER = extended release.

felodipine ER monotherapy (overall 10.8%) and lowest in those receiving enalapril alone (2.3%). However, edema occurred in only 4.1% of patients receiving combinations of enalapril–felodipine ER. Overall, dizziness was reported slightly more often with the combination (4.4%) than with felodipine ER (2.8%) or enalapril (1.5%), but this finding was not consistent across doses.

Of the 707 patients entered into the study, 641 (91%) completed the 8-week treatment period. Only 3% discontinued for a clinical adverse event, whether or not it was drug related. Discontinuations due to adverse events included 2 of 79 patients (3%) in the placebo group, 1 of 133 patients (1%) receiving enalapril monotherapy, 7 of 176 patients (4%) taking felodipine ER monotherapy, and 10 of 319 patients(3%) receiving the combination therapy.

DISCUSSION

In this study, the combination of enalapril and felodipine ER effectively lowered BP and was generally well tolerated with an excellent safety profile when used in the treatment of hypertension. Moreover, both efficacy and tolerability were enhanced when these drugs were used in combination compared to their monotherapies. At each combination dose, both drugs contributed significantly to lowering BP. The trough to peak ratios were consistent with 1dose/day in that BP reduction 24 hours after receiving the dose was not accomplished at the expense of excessive BP reductions at peak. The additive effect of the 2 drugs on BP presumably results from the distinct pharmacologic mechanism of each drug.[7] ACE inhibitors and calcium antagonists have complimentary mechanisms of action, and their use in combination is particularly appealing in patients whose hypertension is multifactorial with respect to pathophysiology, as well as those patients who do not respond adequately to initial therapy with a single agent. Enalapril reduces peripheral vascular resistance and BP by inhibiting the renin-angiotensin-aldosterone system via blockade of ACE. Felodipine produces vasodilation by reducing calcium entry via L-type calcium channels during smooth muscle cell depolarization. Because of its vascular selectivity, felodipine does not depress myocardial contractility at clinically administered doses.[11]

Peripheral edema has been a potential limiting factor in the use of dihydropyridine calcium antagonists, particularly at higher doses. Edema associated with the use of calcium antagonists is not related to fluid retention but is thought to be secondary to arteriolar dilation and resulting increases in capillary hydrostatic pressure which causes a fluid shift into the surrounding tissues.[12] By inducing concomitant venodilatation, enalapril is believed to reduce capillary pressures and the tendency for extravasation of fluid into interstitial spaces. The results of this study confirm earlier reports of reduced edema in patients concomitantly treated with enalapril and felodipine ER[9] as well as other combinations of calcium entry blockers and ACE inhibitors.[12]

Because of their effectiveness in low renin hypertension, calcium antagonists are widely utilized in blacks and elderly hypertensive patients.[13] Additionally, calcium antagonists have been shown to produce greater reduction in BP in the elderly compared with younger individuals.[14,15] In 1 study on felodipine ER, age was found to influence felodipine pharmacokinetics and an increased antihypertensive response was documented in the elderly.[16] This age-related effect on BP is preserved when enalapril and felodipine ER are combined. Patients >65 years of age exhibited greater reduction in BP compared with younger hypertensive patients. With respect to race, the efficacy of the combination was similar in whites and nonwhites.

Clinical implications: The combination of enalapril and felodipine ER had significant additive BP reducing effects compared to each of the monotherapies over a wide range of doses. This combination may be particularly useful for patients who fail to respond adequately to an ACE inhibitor or a calcium antagonist.

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APPENDIX

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