Comparison of Candesartan and Felodipine Alone and Combined in the Treatment of Hypertension: A Single-Center, Double-Blind, Randomized, Crossover Trial

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ABSTRACT

Background: In the past decade, many studies have indicated that the combination of low doses of different classes of antihypertensive agents may be more efficacious than monotherapy while minimizing the likelihood of dose-dependent adverse effects (AEs).

Objective: The aim of this study was to determine whether combination therapy with lower doses of candesartan and a calcium antagonist, felodipine, would be more effective and tolerable in controlling mild to moderate hypertension compared with either drug used alone.

Methods: In this 18-week, single-center, double-blind, crossover study, patients with mild to moderate essential hypertension were randomized to 1 of 2 treatment groups after a 2-week placebo washout period. Patients in group 1 received candesartan 16 mg once daily and patients in group 2 received felodipine 5 mg once daily, for 6 weeks. All patients then received half-dose combination therapy (candesartan 8 mg plus felodipine 2.5 mg, once daily) for 6 weeks. Finally, patients received 6 weeks of monotherapy with the alternate medication (group 1 received felodipine 5 mg once daily and group 2 received candesartan 16 mg once daily).

Results: Thirty patients (18 men, 12 women; mean [SD] age, 54.0 [4.9] years; range, 39–62 years) were included in the study. During both monotherapy periods, candesartan and felodipine significantly reduced blood pressure (BP) (both $P < 0.001$). BP further decreased with combination therapy ($P < 0.001$ in both groups). Overall, 90.0% (27/30) of the patients achieved the target BP at the end of combination therapy. The incidence of AEs was similar with combination therapy compared with either monotherapy.

Conclusions: In this study population, candesartan and felodipine had additive effects when used in combination, even at low doses, in the treatment of

hypertension. Therefore, the combination of candesartan and felodipine is an effective alternative to that of candesartan and hydrochlorothiazide. (*Curr Ther Res Clin Exp*. 2003;64:380–388) Copyright © 2003 Excerpta Medica, Inc.

Key words: candesartan, felodipine, hypertension, combination therapy.

INTRODUCTION

Over the past few decades, reducing blood pressure (BP) in patients with hypertension has been shown to decrease the risk for cardiovascular accident, chronic renal failure, and the overall morbidity and mortality of cardiovascular disease.^{1,2} However, first-line antihypertensive monotherapy is effective in reducing BP to the normal range (<140/<90 mm Hg) in <60% of patients, leaving the remainder with inadequately controlled hypertension and at continued risk.¹ Furthermore, increasing the dose of most antihypertensive agents used as monotherapy results in limited efficacy and poorer tolerability.¹

An alternative strategy for improving BP control is to combine 2 or more drugs with different but complementary mechanisms of action. Combination therapy (at lower doses of each drug) may result in fewer adverse effects (AEs) and enhanced patient efficacy plus compliance.^{3,4} Normalization of BP has been achieved in up to 80% of patients treated with different combination therapies.^{5–8}

Combinations include a beta-blocker or an angiotensin-converting enzyme (ACE) inhibitor with a diuretic,^{9–12} and a beta-blocker with an alpha-blocker.^{13,14} Calcium antagonists used in combination with beta-blockers,^{15–17} diuretics,^{18,19} ACE inhibitors,^{20–23} and even with other types of calcium antagonists,²⁴ also have been reported.

Candesartan cilexetil is a highly potent and long-acting selective angiotensin 1-receptor blocker (ARB). The antihypertensive effects of candesartan alone^{25–27} or combined with a diuretic^{28,29} have been assessed in several studies. However, few studies of the combination of candesartan and other types of antihypertensive drugs, such as calcium antagonists, have been reported.³⁰

The purpose of this study was to determine whether combination therapy with lower doses of candesartan and a calcium antagonist, felodipine, would be effective and tolerable in controlling mild to moderate hypertension compared with either drug used alone.

PATIENTS AND METHODS

Patients

Patients aged ≥ 18 years with mild to moderate essential hypertension refractory to or with intolerance to monotherapy with diuretics or beta-blockers were eligible for the study. Mild hypertension was defined as a BP of 140 to 159/90 to 99 mm Hg, and moderate hypertension was defined as a BP of 160 to 179/100 to 109 mm Hg. The target BP for the study patients was <140/<90 mm Hg.

Exclusion criteria included clinical evidence of severe hepatic or renal impairment, organ tumors, or any of the known contraindications to the individual study drugs. Patients with coronary artery disease or diabetes mellitus also were excluded because other types of antihypertensive agents are preferable for the treatment of patients with these conditions. Patients also were excluded if they had secondary hypertension, which was determined by clinical examination, measurement of plasma electrolytes, serum creatinine, and urine catecholamine levels. Finally, pregnant, possibly pregnant, or breastfeeding women were not eligible for the study.

Treatment with agents other than candesartan or felodipine was not allowed during the study.

The study was approved by the local ethics committee at Ege University Medical School and was conducted in accordance with the principles and amendments of the Declaration of Helsinki. All patients provided written informed consent before study entry.

Study Design

This was an 18-week, double-blind, crossover study. After a placebo washout period of 2 weeks, patients were assigned, using a random number table, to 1 of 2 treatment groups. For 6 weeks, group 1 received candesartan 16 mg once daily, and group 2 received felodipine 5 mg once daily. During the second 6-week period, all patients were given a once-daily combination of half-doses of candesartan (8 mg) and felodipine (2.5 mg). For the last 6 weeks, the treatment groups were crossed over (ie, group 1 received felodipine 5 mg once daily and group 2 received candesartan 16 mg once daily) ([Figure](#)). All treatments, whether alone or in combination, were given in a single capsule of identical appearance. Patients took the capsule at home in the morning, and clinical examinations were carried out at the study site between 2 and 4 PM.

Before randomization, a medical history was taken, and patients underwent physical examination. During the 18-week treatment period, BP and heart rate were recorded weekly at each hospital visit. BP and radial pulse rate were measured after the patient had been in the hospital for at least 15 minutes and had been seated for at least 10 minutes. BP was measured with a mercury sphygmomanometer at Korotkoff's phases I and V and the mean of 3 consecutive measurements was calculated. For each patient, BP measurements were obtained from both arms at each hospital visit by the same investigators using the same cuff and equipment.

At the end of the washout period (week 0) and at weeks 6, 12, and 18 of treatment, electrocardiography, urinalysis, and blood tests were performed. Blood tests included hematocrit; red and white blood cell and platelet counts; hemoglobin levels; fasting levels of plasma glucose, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, and triglycerides; and levels of uric acid, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, plasma

Figure. Study design for the comparison of candesartan versus felodipine alone and combined. QD = once daily.

electrolytes (sodium, calcium, potassium), and magnesium. Echocardiography was performed at baseline and the end of week 18.

AEs were assessed by scripted, nonleading questions posed by the investigators during scheduled hospital visits.

Statistical Analysis

To assess within-group changes in BP, heart rate, and laboratory test results, statistical analyses were performed using 2-tailed paired Student *t* tests for comparisons between weeks 0 and 6. Two-tailed independent Student *t* tests were performed for comparisons between weeks 0, 6, 12, and 18. The latter also were used for between-group comparisons at weeks 0, 6, and 18. $P \leq 0.05$ was considered to be statistically significant for treatment effect.

RESULTS

Thirty patients (18 men, 12 women; mean [SD] age, 54.0 [4.9] years; range, 39–62 years) entered the study (Table I); 15 patients were assigned to each group. All patients completed the study.

Table I. Baseline demographic characteristics in all study patients (N = 30).

Characteristic	Value
Age, y	
Mean (SD)	54.0 (4.9)
Range	39–62
Sex, no. (%)	
Men	18 (60.0)
Women	12 (40.0)
Duration of hypertension, mo	
Mean (SD)	38.3 (13.2)
Range	9–72
Blood pressure, mm Hg	
Systolic (NV, <140)	
Mean (SD)	172.4 (8.6)
Range	152–180
Diastolic (NV, <90)	
Mean (SD)	101.2 (4.7)
Range	92–108
Heart rate, beats/min (NV, 60–100)	
Mean (SD)	76.5 (5.2)
Range	60–94

NV = normal value.

The overall mean (SD) systolic BP (SBP)/diastolic BP (DBP) at baseline was 168.7 (6.0)/100.1 (3.1) mm Hg (range, 152–180/92–108 mm Hg). Nineteen patients (63.3%) had moderate hypertension and 11 (36.7%) had mild hypertension. At study entry, 20 patients (66.7%) were refractory to treatment with their previous monotherapy with several antihypertensive drugs.

At week 0, patients in both groups had similar BPs (Table II). In group 1, the mean (SD) SBP/DBP was 168.6 (5.7)/100.2 (3.0) mm Hg; in group 2, the mean (SD) SBP/DBP was 168.8 (6.4)/100.0 (3.1) mm Hg.

After the first monotherapy treatment period, the mean (SD) SBP/DBP in the candesartan-treated patients (group 1) decreased significantly (to 141.4 [6.9]/88.2 [3.3] mm Hg) compared with baseline (both $P < 0.001$). In the felodipine-treated patients (group 2), the mean (SD) SBP/DBP decreased significantly (to 140.5 [6.7]/88.2 [4.3] mm Hg) (both $P < 0.001$). Nine patients (60.0%) in the candesartan group and 8 (53.3%) in the felodipine group achieved the target BP at the end of the first 6-week treatment period (week 6). No statistically significant differences in BP were found between the 2 treatment groups at that time.

After 6 weeks of combination therapy (week 12), BP in both groups combined (N = 30) was further reduced. The mean (SD) SBP/DBP found with combination therapy was significantly reduced to 134.8 (5.9)/85.6 (3.0) mm Hg (both $P < 0.001$

Table II. Mean (SD) blood pressure (mm Hg) at week 0 and after 6, 12, and 18 weeks of treatment.

Study Week	SBP	DBP
Week 0		
Group 1	168.6 (5.7)	100.2 (3.0)
Group 2	168.8 (6.4)	100.0 (3.1)
Week 6		
Group 1 (candesartan; n = 15)	141.4 (6.9)*	88.2 (3.3)*
Group 2 (felodipine; n = 15)	140.5 (6.7)*	88.2 (4.3)*
Week 12		
Combination therapy (candesartan + felodipine; N = 30)	134.8 (5.9) [†]	85.6 (3.0) [†]
Week 18		
Group 1 (felodipine; n = 15)	140.4 (6.5) [‡]	87.9 (3.1) [§]
Group 2 (candesartan; n = 15)	140.0 (5.7) [‡]	88.5 (4.2) [§]

SBP = systolic blood pressure; DBP = diastolic blood pressure.

* $P < 0.001$ versus week 0.

[†] $P < 0.001$ versus week 0; $P < 0.02$ versus week 6.

[‡] $P < 0.02$ versus week 12.

[§] $P < 0.05$ versus week 12.

versus week 0; both $P < 0.02$ versus week 6). Overall, 90.0% (27/30) of the patients achieved the target BP at the end of combination therapy.

On reverting to monotherapy with the alternate medication for the last 6 weeks of treatment (week 18), the mean (SD) SBP in group 1 (felodipine) increased significantly to 140.4 (6.5) mm Hg ($P < 0.02$), and the mean (SD) DBP increased to 87.9 (3.1) mm Hg ($P < 0.05$) compared with week 12. Also, in group 2 (candesartan), the mean (SD) SBP increased to 140.0 (5.7) mm Hg ($P < 0.02$) and the mean (SD) DBP increased to 88.5 (4.2) mm Hg ($P < 0.05$) compared with week 12.

No significant changes in mean heart rate were found at weeks 6, 12, or 18 for either treatment group compared with week 0. No significant changes in laboratory test results occurred in either group. In general, both drugs were well tolerated. The incidence of AEs was similar with combination therapy compared with either monotherapy (Table III). The most common AEs were gastrointestinal disorders, headache, and fatigue. AEs were mild, and all patients continued with their medication. All AEs were considered treatment related.

DISCUSSION AND CONCLUSIONS

Monotherapy with an antihypertensive drug is likely to achieve a desirable decrease in BP in <60% of patients. Those remaining are likely to be unresponsive, even if appropriate dosage adjustments are made. For these patients, combination therapy usually results in better BP control.¹

Table III. Number (%) of patients reporting ≥ 1 adverse effect.*

Adverse Effect	Candesartan (n = 15)	Felodipine (n = 15)	Combination (N = 30)
Gastrointestinal disorders	2 (6.7)	1 (3.3)	1 (3.3)
Headache	1 (3.3)	2 (6.7)	1 (3.3)
Fatigue	1 (3.3)	1 (3.3)	1 (3.3)
Flushing	0 (0.0)	3 (10.0)	0 (0.0)
Edema	0 (0.0)	2 (3.7)	0 (0.0)

*All adverse effects were considered treatment related.

This study demonstrated that combination therapy with half-doses of candesartan, an ARB, and felodipine, a calcium antagonist, is an effective treatment for hypertension. Combination therapy produced significantly greater decreases in BP than either medication alone, which suggests a clinical additive effect of these 2 drugs. Furthermore, combination therapy was associated with a lower incidence of AEs than either monotherapy.

Candesartan is a novel, long-acting, selective ARB. In the past decade it has been used as monotherapy or in combination therapy for the treatment of hypertension. When it was used in combination therapy, hydrochlorothiazide was recommended as the second agent.^{28–32} Our study showed that the combination of candesartan and felodipine is an effective alternative therapy for the treatment of hypertension. It can be used when patients cannot tolerate the AEs of hydrochlorothiazide. Further studies with larger numbers of patients are needed to confirm our results.

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