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ORIGINAL ARTICLE

Efficacy and tolerability between an olmesartan/amlodipine fixed-dose combination and an amlodipine double dose in mild to moderate hypertension

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Abstract Fixed-dose combinations (FDCs) are one of the options for improving blood pressure (BP) goal attainment. We enrolled 141 patients and evaluated the efficacy and safety between a fixed dose of olmesartan/amlodipine (OA) and a double dose of amlodipine (DA) for treating mild to moderate hypertension after amlodipine monotherapy failure. After at least 2 weeks of monotherapy failure, the patients were randomized to receive either OA or DA for 8 weeks. We compared the systolic blood pressure (SBP)-lowering efficacy of the OA and DA using both an office BP and an ambulatory blood pressure monitoring (ABPM) device. The intent-to-treat analysis found that the early (2nd week) and final visit (8th week) SBP reductions were significantly greater in those patients receiving OA ($n = 70$) than DA ($n = 71$) (17.57 ± 15.49 vs. 10.46 ± 13.36 and 24.89 ± 14.09 vs. 17.03 ± 13.27 mmHg, $p = 0.002$ and 0.001, respectively). Among those using ABPM, the patients with 8-week OA had a greater SBP-lowering effect in comparison with those on DA (14.08 ± 10.74 vs. 6.32 ± 10.21, $p = 0.018$). Both treatment strategies were well tolerated. This study showed that an OA FDC is more effective than DA in reducing SBP for mild to moderate hypertension after the failure of amlodipine monotherapy.

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Introduction

Hypertension is a major risk factor for cardiovascular disease [1,2]. Unfortunately, its prevalence is increasing globally. Antihypertensive agents to decrease blood pressure (BP) have been shown to be effective in reducing cardiovascular morbidity and mortality [3]. Several international guidelines suggest BP treatment goals should be less than 140 mmHg systolic and 90 mmHg diastolic for uncomplicated hypertension and 130 mmHg systolic and 80 mmHg diastolic for the high-risk population [4—6]. However, the low rate of BP goal attainment is a worldwide problem.

Several therapeutic strategies have been proposed to improve suboptimal BP control. In one study, the percentage of patients achieving the target BP was significantly greater in the combination therapy group than in the sequential monotherapy and the stepped-care groups [7]. Combination therapy has been suggested in several hypertension treatment guidelines [4—6]. In addition, fixed-dose combinations (FDCs) can be considered for first-step treatment, provided the initial use of two drugs rather than monotherapy is indicated [4,5].

The ACCOMPLISH trial showed that an FDC with a calcium-channel blocker (CCB) and an angiotensin-converting enzyme inhibitor (ACEI) has a greater BP-lowering effect than an FDC with a diuretic and an ACEI [7]. However, an angiotensin II type 1 receptor blocker (ARB) has more tolerability than an ACEI, especially in the Asian population. This study evaluated the efficacy and safety between an FDC using an ARB and a CCB (olmesartan/amlodipine FDC, 20 mg/5 mg) and a double-dose CCB using amlodipine (10 mg) for the patients with mild to moderate hypertension not achieving their target BP after the 5-mg amlodipine monotherapy.

Methods

This was an open-label, randomized, multicenter study comparing the efficacy and safety of an olmesartan/amlodipine FDC (20 mg/5 mg, OA) and a double dose of amlodipine (10 mg, DA) for the treatment of essential hypertension. This study was conducted at four medical centers in Taiwan. The study protocol was approved by the corresponding institutional review boards and applicable health authorities.

Participant selection

To be included, the participants must have: (1) been between 20—80 years of age; (2) signed the informed consent form; (3) received amlodipine 5 mg daily for at least 2 weeks before the randomization; and (4) recorded a systolic blood pressure (SBP) between 140 and 180 mmHg or a diastolic BP (DBP) between 90 and 110 mmHg at both the screening and randomization visits. Potential participants were excluded if any of the following were found: (1) secondary hypertension; (2) pregnancy or breastfeeding; (3) complicated hypertension; (4) chronic renal insufficiency (creatinine $>$ 2.2 mg/dL); (5) serum potassium $>$ 5.5 mEq/L; (6) history of a CCB or ARB allergy; (7) other major medical abnormalities (e.g., severe drug allergy, autoimmune disease, gastrointestinal disease or malignancy); and (8) participation in another investigational drug trial in the 12 weeks before the randomization.

A physical examination and BP measurement were done at every visit. All BPs were measured with a mercury sphygmomanometer while the patient was sitting. Two BP measurements were taken on arrival to the hospital and at 1—2-minute intervals after 10 minutes of rest. The mean BP was recorded.

Study objective

The primary study objective was to evaluate the difference in the SBP changes from the baseline to 8 weeks between the two groups. The secondary study objectives were to evaluate the efficacy and safety features via a series of evaluated parameters including: (1) changes in the sitting SBP from the baseline to the Week 2 and Week 4 visits; (2) changes in the DBP from the baseline to the Week 2, Week 4, and Week 8 visits; (3) a successful BP control rate as defined by the proportion of patients with a final SBP less than 140 mmHg and a DBP less than 90 mmHg; (4) changes in the 24-hour mean SBP and DBP from the baseline to the Week 8 visit [only for the patients using 24-hour ambulatory blood pressure monitoring (ABPM)]; and (5) tolerability features including adverse events and abnormal blood tests.

Patients were randomly assigned to receive either OA once daily or DA once daily for the 8-week study. We required a total of five study visits consisting of a screening visit, randomization visit, evaluation Visit 1 (day 14 $\pm$ 3), evaluation Visit 2 (Day 28 $\pm$ 3), and final visit (Day 56 $\pm$ 7) (Fig. 1). A physical examination and BP measurement were done at every visit. Blood tests were performed at the randomization visit and final visit. In addition, we recorded the ABPM on 50% of the total randomized patients based on a pregenerated randomization list, with the time frame for the ABPM established on the day of randomization and on the last day of therapy.

Statistical analysis

All data were expressed as mean $\pm$ standard error mean (SEM). All tests were two-sided. A p-value $<$0.05 was

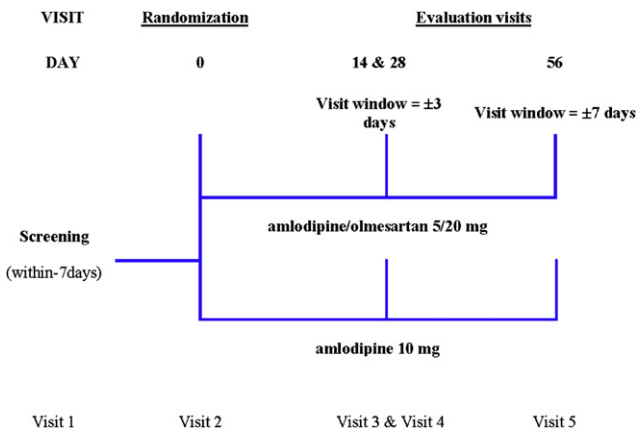

Figure 1. Study flowchart.

considered statistically significant. A χ^2 test and Wilcoxon rank-sum test were used to compare the categorical data and nonparametric data, respectively. The student *t* test was used for analysis between continuous variables. The intent-to-treat analysis was used to evaluate the efficacy and safety. SPSS 11.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Baseline data

A total of 145 prospective participants were screened; four failed the screening (3 did not meet the inclusion criteria and one met the exclusion criteria), and 141 (70 in the OA and 71 in the DA group) were finally randomized. There was no statistical significance in the medical compliance between the OA and DA groups (101.14% ± 9.47% vs. 98.94% ± 8.57%, $p = 0.124$). The extent of exposure to drugs was also similar (53.22 ± 10.43 vs. 50.62 ± 14.92 days for the OA and DA groups, $p = 0.174$).

The baseline characteristics are given in Table 1. There was no difference between the patients taking OA and DA regarding sex, age, body weight, height, biochemistry data, and baseline BP.

BP reduction

In the patients taking OA, the SBP decreased 17.57 ± 15.49, 20.80 ± 14.11, and 24.89 ± 14.0 mmHg at 2, 4, and 8 weeks, respectively (Table 2). In the patients taking DA, the SBP decreased 10.46 ± 13.36, 16.6 ± 17.65, and 17.03 ± 13.27 mmHg at 2, 4, and 8 weeks, respectively. There was a statistically significant difference in the SBP reduction between the two groups at Weeks 2 and 8 ($p = 0.002$ and 0.001, respectively; Fig. 2A).

The DBP decreased 9.53 ± 9.06, 10.80 ± 9.89, and 12.50 ± 9.78 mmHg in patients taking OA after 2, 4, and 8 weeks of treatment, respectively. In the patients taking DA, the DBP decreased 5.75 ± 7.72, 9.09 ± 7.76, and 9.29 ± 7.19 mmHg after 2, 4, and 8 weeks' treatment, respectively. There was a statistically significant difference in the DBP reduction between the two groups early in the study, at the 2nd week ($p = 0.013$).

Among those using ABPM (31 in the OA group and 25 in the DA group), the patients with 8 weeks of OA had greater SBP- and DBP-lowering effects compared with those with DA (14.08 ± 10.74 vs. 6.32 ± 10.2 and 8.62 ± 5.65 vs. 4.27 ± 5.80, $p = 0.018$ and 0.011, respectively; Fig. 2B).

After 8 weeks of treatment, a successfully controlled BP rate (as defined by the proportion of patients with a final SBP less than 140 mmHg and a DBP less than 90 mmHg) was achieved in 47 patients (67.1%) and 39 patients (54.9%) receiving OA and DA, respectively ($p = 0.117$). There were no significant changes in the pulse rate between the two groups (OA vs. DA, 0.82 vs. −1.12 beats per minute, $p = 0.678$).

Safety

Adverse events were defined as treatment related (i.e., events that first occurred or worsened after randomization). There was no statistically significant difference in the occurrence of adverse events between the two groups [OA: 28 patients (40%); DA: 31 patients (43.7%), $p = 0.582$], nor between each adverse event (Table 3). Three serious adverse events were reported (hospitalization for urolithiasis, sialolithotomy, and a tumor of the left big toe). The investigators determined the causality was unrelated or unlikely to be related to the study medication. As for the lower-leg edema, 24.3% of the patients who received OA versus 28.2% of those who received DA had edema at the randomization visit. There was no statistical significance for the changes in edema between the two groups after 8 weeks of treatment. The improved/unchanged/worsened edema statistics were: OA 10.5%, 76.1%, and 13.4% versus DA 19.7%, 72.7%, and 7.6% ($p = 0.513$) (Fig. 3).

Discussion

This study had two major findings. First, the patients with mild to moderate hypertension who received an FDC treatment with OA 20 mg/5 mg achieved greater SBP reduction than those who received the DA (10 mg). Second, among those using ABPM, the patients who received the 8-week treatment with the OA FDC also achieved a greater SBP-lowering effect. Both treatments were well tolerated.

Table 1 Baseline characteristics of the study participants.

Characteristics	Olmesartan/amlodipine	Double amlodipine	*p*
	70	71	
Age (y)	53.8 ± 10.3	52.5 ± 13.1	0.590
Sex (male, %)	64	61	0.641
Weight (kg)	73.5 ± 14.5	73.6 ± 13.9	0.971
Height (cm)	164.2 ± 8.2	163.3 ± 8.6	0.404
Fasting sugar (mg/dL)	114.9 ± 7.9	110.6 ± 28.4	0.437
Blood urea nitrogen (mg/dL)	13.1 ± 3.9	13.5 ± 4.1	0.549
Creatinine (mg/dL)	0.84 ± 0.21	0.82 ± 0.83	0.413
Cholesterol (mg/dL)	193.6 ± 31.4	200.9 ± 39.9	0.238
Systolic blood pressure (mmHg)	152.4 ± 11.4	152.4 ± 14.9	0.997
Diastolic blood pressure (mmHg)	93.6 ± 8.9	92.1 ± 7.3	0.286

Table 2 Changes in blood pressure after treatment between the two groups.

Treatment period	Decrease in blood pressure		*p*
	Olmesartan/amlodipine ($N = 70$)	Double-dose amlodipine ($N = 71$)	
2 wk			
Systolic	17.57 ± 15.49	10.46 ± 13.36	0.002
Diastolic	9.53 ± 9.06	5.75 ± 7.72	0.013
4 wk			
Systolic	20.80 ± 14.11	16.6 ± 17.65	0.057
Diastolic	10.80 ± 9.89	9.09 ± 7.76	0.353
8 wk			
Systolic	24.89 ± 14.09	17.03 ± 13.27	0.001
Diastolic	12.50 ± 9.78	9.29 ± 7.19	0.064

Hypertension is an important public health challenge worldwide. It is recognized as one of the most significant risk factors for cardiovascular, cerebrovascular, and renal disease. The World Health Organization reported that suboptimal BP control ranks as the most common attributable risk for death in the world [8]. The effect of hypertension on cardiovascular events is greater for Asians than for Caucasians, and the treatment of hypertension results in greater cardiovascular risk reduction in Asian patients in comparison with the Caucasian population [9,10]. Although there was a significant improvement in the awareness, treatment, and rate of control in Taiwan from 1993 to 2002, the hypertension control rate was still low at only 21% in men and 29% in women [11]. After 8 weeks of treatment in our study, the BP control rate in those receiving the OA FDC was 67.1%, higher than the 53% attained by Caucasian patients in a similar study [12].

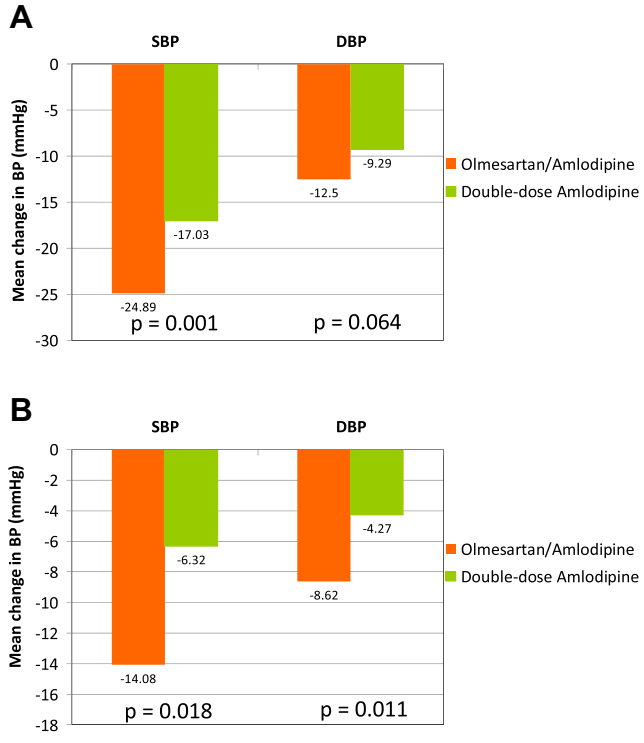

Figure 2. Blood pressure changes after 8 weeks of treatment. (A) Office BP. (B) Ambulatory blood pressure monitoring.

Although amlodipine is the most frequently prescribed antihypertensive agent in the world, clinical studies suggest that 5 mg of amlodipine alone does not control the BP of more than 50% of patients with hypertension. Although up-titration of amlodipine may improve BP control rates, it also increases the incidence of side effects that could reduce patient compliance. Several international antihypertensive treatment guidelines suggest using a combination therapy by adding an antihypertensive agent with a synergistic and complementary mechanism of action to help patients with hypertension attain their BP target [4—6]. In addition, an FDC can be considered for first-step treatment, provided the initial use of two drugs rather than one is indicated [5,6]. In this study, patients with mild to moderate hypertension who received an FDC treatment with OA 20 mg/5 mg had greater SBP reduction than those receiving DA (10 mg). After 2, 4, and 8 weeks of treatment, the SBP reductions were 17.57, 20.80, and 24.89 mmHg, respectively. Therefore, 71% and 84% of the maximal SBP reductions after the 8-week treatment period were already being observed after 2 and 4 weeks, respectively.

ABPM has become increasingly important for the management of hypertension [13]. In addition to reducing the white-coat effect, ABPM provides more reproducible BP readings and represents more accurate predictors of future cardiovascular risk than office BP measurement [14,15]. Among the patients using ABPM in this study, those with the 8-week OA FDC showed greater SBP-lowering effects than those receiving DA. Furthermore, the ABPM SBP reduction in our patients receiving the OA (20 mg/5 mg) FDC was greater than for the patients in another study receiving valsartan/amlodipine FDC (160 mg/5 mg) for 8 weeks where their BPs were uncontrolled by amlodipine (5 mg) [16].

There were three limitations in our study. First, our investigation had only a small number of patients. Second, we did not have a placebo group because of the ethical issues. Third, all of the participants did not agree to the ABPM. However, our study results are consistent with previous data in the Caucasian population.

In conclusion, we showed that using an OA FDC in the Asian population provides more powerful SBP reduction, as measured by both the office BP and the ABPM, than a double-dose of amlodipine for patients with mild to

Table 3 Incidence of adverse events.

Adverse events		Treatment		Total
		Olmesartan/amlodipine	Double-dose amlodipine	
	N	70	71	141
Blood and lymphatic system disorders	Anemia	1 (1.4%)	0 (0.0%)	1 (0.7%)
Cardiac disorders	Palpitations	2 (2.9%)	1 (1.4%)	3 (2.1%)
Ear and labyrinth disorders	Cholesteatoma	1 (1.4%)	0 (0.0%)	1 (0.7%)
Eye disorders	Borderline glaucoma	1 (1.4%)	0 (0.0%)	1 (0.7%)
	Cataract	1 (1.4%)	0 (0.0%)	1 (0.7%)
	Conjunctivitis (allergic)	1 (1.4%)	0 (0.0%)	1 (0.7%)
	Lacrimation decreased	1 (1.4%)	0 (0.0%)	1 (0.7%)
	Visual field defect	1 (1.4%)	0 (0.0%)	1 (0.7%)
Gastrointestinal disorders	Constipation	0 (0.0%)	3 (4.2%)	3 (2.1%)
	Enteritis	1 (1.4%)	0 (0.0%)	1 (0.7%)
	Gastroenteritis	1 (1.4%)	1 (1.4%)	1 (1.4%)
	Nausea	0 (0.0%)	1 (1.4%)	1 (0.7%)
	Periodontitis	0 (0.0%)	1 (1.4%)	1 (0.7%)
	Reflux esophagitis	1 (1.4%)	1 (1.4%)	2 (1.4%)
	Salivary gland calculus	1 (1.4%)	0 (0.0%)	1 (0.7%)
	Sialoadenitis	1 (1.4%)	0 (0.0%)	1 (0.7%)
General disorders and administration site conditions	Chest discomfort	1 (1.4%)	0 (0.0%)	1 (0.7%)
	Chest pain	1 (1.4%)	0 (0.0%)	1 (0.7%)
	Edema	11 (15.7%)	11 (15.5%)	22 (15.6%)
	Edema peripheral	0 (0.0%)	1 (1.4%)	1 (0.7%)
Hepatobiliary disorders	Liver disorder	1 (1.4%)	0 (0.0%)	1 (0.7%)
Infections and infestations	Cellulitis streptococcal	0 (0.0%)	1 (1.4%)	1 (0.7%)
	Helicobacter infection	0 (0.0%)	1 (1.4%)	1 (0.7%)
	Upper respiratory tract infection	1 (1.4%)	1 (1.4%)	2 (1.4%)
Injury, poisoning, and procedural complications	Contusion	0 (0.0%)	1 (1.4%)	1 (0.7%)
	Foreign body	0 (0.0%)	1 (1.4%)	1 (0.7%)
	Open wound	0 (0.0%)	2 (2.8%)	2 (1.4%)
Investigations	Creatinine increased	1 (1.4%)	0 (0.0%)	1 (0.7%)
	Non-HDL cholesterol increased	1 (1.4%)	0 (0.0%)	1 (0.7%)
Metabolism and nutrition disorders	Hyperthyroidism	1 (1.4%)	0 (0.0%)	1 (0.7%)
	Hyperuricemia	1 (1.4%)	0 (0.0%)	1 (0.7%)
	Hypokalemia	1 (1.4%)	0 (0.0%)	1 (0.7%)
Musculoskeletal and connective tissue disorders	Arthralgia	0 (0.0%)	2 (2.8%)	2 (1.4%)
	Chondromalacia	0 (0.0%)	1 (1.4%)	1 (0.7%)
	Gout	1 (1.4%)	1 (1.4%)	2 (1.4%)
	Intervertebral disc disorder	1 (1.4%)	0 (0.0%)	1 (0.7%)
	Musculoskeletal disorder	0 (0.0%)	1 (1.4%)	1 (0.7%)
	Musculoskeletal stiffness	0 (0.0%)	1 (1.4%)	1 (0.7%)
	Neck pain	1 (1.4%)	0 (0.0%)	1 (0.7%)
	Tendinitis	1 (1.4%)	0 (0.0%)	1 (0.7%)
Neoplasms benign, malignant, and unspecified	Benign neoplasm of skin	1 (1.4%)	1 (1.4%)	2 (1.4%)
Nervous system disorders	Dizziness	2 (2.9%)	4 (5.6%)	6 (4.3%)
	Headache	0 (0.0%)	1 (1.4%)	1 (0.7%)
	Vertigo	0 (0.0%)	1 (1.4%)	1 (0.7%)
	Vertigo positional	0 (0.0%)	1 (1.4%)	1 (0.7%)
Psychiatric disorders	Anxiety	1 (1.4%)	0 (0.0%)	1 (0.7%)
	Insomnia	0 (0.0%)	1 (1.4%)	1 (0.7%)
	Sleep disorder	0 (0.0%)	2 (2.8%)	2 (1.4%)
Renal and urinary disorders	Calculus urinary	0 (0.0%)	1 (1.4%)	1 (0.7%)
	Nocturia	0 (0.0%)	1 (1.4%)	1 (0.7%)
Respiratory, thoracic, and mediastinal disorders	Bronchitis	1 (1.4%)	0 (0.0%)	1 (0.7%)
	Dyspnea	1 (1.4%)	0 (0.0%)	1 (0.7%)
	Nasopharyngitis	0 (0.0%)	1 (1.4%)	1 (0.7%)

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Table 3 (*continued*)

Adverse events		Treatment		Total
		Olmesartan/ amlodipine	Double-dose amlodipine	
	N	70	71	141
Skin and subcutaneous tissue disorders	Dermatophytosis	0 (0.0%)	1 (1.4%)	1 (0.7%)
	Rash papular	0 (0.0%)	1 (1.4%)	1 (0.7%)
Surgical and medical procedures	Promotion of wound healing	1 (1.4%)	0 (0.0%)	1 (0.7%)

HDL = high-density lipoprotein.

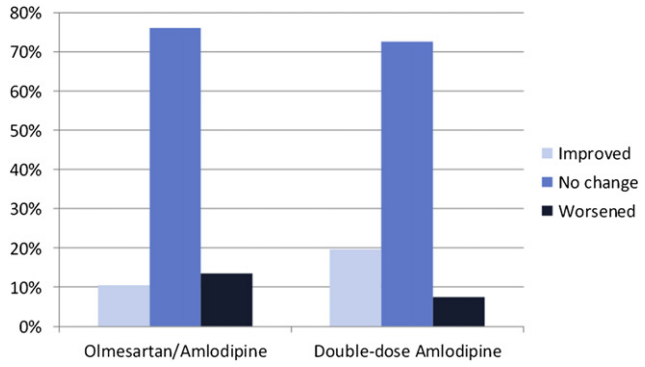

Figure 3. Lower-leg edema between the two groups.

moderate hypertension after the failure of amlodipine monotherapy.

Acknowledgments

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