Archives of Gerontology and Geriatrics 57 (2013) 423–427

Contents lists available at SciVerse ScienceDirect

Archives of Gerontology and Geriatrics

journal homepage: www.elsevier.com/locate/archger

Clinical effects of combined olmesartan medoxomil and amlodipine on clinic and ambulatory blood pressure in elderly patients with resistant hypertension

Shunjing Ding [a], Jin Liu [a], Qiang Fu [a], Ying Zheng [b,*]

[a] Department of Cardiology, Beijing Tiantan Hospital Affiliated to Capital Medical University, China
[b] Department of Gastroenterology, Beijing Tiantan Hospital Affiliated to Capital Medical University, China

ARTICLE INFO

Article history:
Received 4 December 2012
Received in revised form 12 April 2013
Accepted 16 April 2013
Available online 10 May 2013

Keywords:
Olmesartan medoxomil
Amlodipine
Resistant hypertension
Blood pressure

ABSTRACT

Elderly patients with resistant hypertension are at increased risk for cardiovascular events. Clinical trials suggest that resistant hypertension involves perhaps 10–15% of hypertension study participants. In this study, 157 resistant hypertension patients older than 60 years were randomized to 8 weeks double-blind treatment with placebo, AML 10 mg/day, OM 40 mg/day and AM × L (10 mg/day) + OM (40 mg/day). Research outcomes suggested that ALM + OM combination therapy had superior efficacy than ALM or OM monotherapies in terms of the clinic blood pressure and 24-h ambulatory blood pressure. In addition, more patients receiving combination therapy (62.5%) achieved BP goal than those treated with placebo (18.4%), AML (37.5) or OM (38.5%) monotherapies. The adverse events in both groups were comparable. Thus, the combination of AML + OM provides a safe and effective option for the treatment of resistant hypertension in challenging elderly patient populations.

1. Introduction

Hypertension, which is the leading cause of cardiovascular (CV) disease worldwide (Barrios, Escobar, Calderon, & Bohm, 2009), is typically associated with other risk factors such as diabetes, hyperlipidemia and obesity. According to NHANES III Study, its prevalence rate for subjects > 60 years old is estimated to be >60% (Ong, Cheung, Man, Lau, & Lam, 2007). It is widely recognized that effective control of blood pressure (BP) in patients with hypertension could reduce the risk of CV events (Chobanian et al., 2003; Mansia et al., 2007). 30% cut of ischemic heart disease and 40% decrease of stroke mortality might occur for every 20 mgHg reductions in systolic blood pressure (SBP) (Lewington, Clarke, Qizilbash, Peto, & Collins, 2002).

Resistant hypertension is defined as blood pressure that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes. Ideally, one of the 3 agents should be a diuretic and all agents should be prescribed at optimal dosages (Calhoun et al., 2008). Patients requiring ≥4 antihypertensive medications (even if controlled) are also classified as having resistant hypertension. The reasons for failure to achieve BP goals are various, including inexpertly selected treatment regimens, poor adherence to treatment regimens by the patient or conflicting effects of concomitantly administered drugs (Calhoun et al., 2008; Gradman, Basile, Carter, & Bakris, 2011; Sarafidis & Bakris, 2008). The exact prevalence of resistant hypertension is unclear, but it is estimated from clinical trials to affect at least 10–15% of all hypertensive patients (Black et al., 2003; Cushman et al., 2002).

During the past decade, Blockade of the angiotensin II type 1 (AT1) has become popular in the treatment of hypertension, because it not only effectively reduces BP (McGill & Reilly, 2001), but also reduces the proportion of hypertensive patients with type 2 diabetes mellitus (DM) and chronic kidney disease (CKD) (Brenner et al., 2001; Lewis et al., 2001). Meanwhile, the potent arterial vasodilatory effects of calcium channel blockers (CCBs) lower blood pressure without causing significant chronic reflex tachycardia and without interfering with autonomic baroreflex cardiovascular responses (Scholz, 1997). Besides, CCBs could decrease renovascular resistance and increase glomerular filtration rate (Kendall & Luscombe, 1987). A recent long-term clinical trial suggested that the combination of renin–angiotensin system blockade (angiotensin-converting enzyme inhibitor-benazepril) with a CCB (amlodipine) was more effective in reducing cardiovascular complications than the combination of renin–angiotensin system blockade (benazepril) with a diuretic (hydrochlorothiazide) (Jamerson et al., 2008; Kjeldsen et al., 2008). European Society of Hypertension and the European Society of Cardiology recommended combination of Angiotensin Receptor

* Corresponding author at: Tiantan Hospital affiliated to Capital Medical University, Tiantan Xili 6, Dongcheng District, Beijing 100050, China.
Tel.: +86 1067096611.
E-mail address: zhengyingtt@yahoo.cn (Y. Zheng).

0167-4943/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.archger.2013.04.006

Blockers (ARBs) and CCBs as an effective and well-tolerated therapeutic option (Mancia et al., 2007). Therefore, the present proof-of-concept study aims to investigate the effect on BP and the safety of combination of olmesartan medoxomil (ARB) and amlodipine (CCB) in elderly patients with resistant hypertension.

2. Materials and methods

2.1. Patient population

After the authors received approval of ethics committee, Beijing Tiantan Hospital affiliated to Capital Medical University, and obtained informed patient consent for this study, patients older than 60 years suffering from resistant hypertension were enrolled. The inclusion criteria were as followed: (1) office BP $\geq$ 140/90 mmHg ($\geq$130/80 mmHg if they had DM or CKD) in spite of treatment with $\geq$3 antihypertensive drugs from different drug classes, including a diuretic, an optimized doses; (2) daytime average ambulatory BP $\geq$ 130/80 mmHg on the current antihypertensive drug regimen within 6 months of the start of the study. For safety reason, patients were excluded if (1) age $<$ 60; (2) absence of informed consent; (3) with severe hypertension (SBP $\geq$ 180 mmHg or DBP $\geq$ 110 mmHg); (4) renal insufficiency with serum creatinine $\geq$ 180 μmol/L glomerular filtration rate $\leq$ 40 mL/min calculated by the Modification of Diet in Renal Disease formula; (5) anemia; (6) liver dysfunction; (7) a history of coronary, arrhythmic, or stroke events within the past 6 months; or (8) pregnant women or women of childbearing potential. The clinical trial was conducted in compliance with Good Clinical Practice guidelines and the ethics principles set out in the Declaration of Helsinki.

2.2. Study design

After screening for eligibility, a placebo run-in lasted for 2 weeks was used to wash out of their current antihypertensive drugs and make sure that their BP maintained stable and continued to meet entry criteria. Then, eligible patients were randomly assigned using a simple randomization procedure to receive placebo, amlodipine monotherapy (Group AML, 10 mg/day), olmesartan medoxomil monotherapy (Group OM, 40 mg/day) or combination therapy with amlodipine and olmesartan medoxomil (Group AML + OM, 10 + 40 mg/day) for 8 weeks. Randomization was generated using a computer-generated, random sequence concealed in consecutively numbered opaque sealed envelopes. All the investigators and patients were blinded to treatment during the whole research period from July 2008 to June 2012, until the randomization codes were opened.

After randomization, all patients were required to take their blinded study drugs at the same time every day. Clinical visits would be conducted at 2, 4, 6 and 8 weeks. The prespecified primary efficacy variables were to show the change from baseline in the average 24-h SBP after 8 weeks of treatment. The key secondary end points were the changes from baseline to week 8 in mean siting SBP and DBP. Additional secondary end point included changes from baseline in mean siting SBP and DBP at weeks 2, 4 and 6; and the percentage of patients who achieved BP goal ($\leq$140/90 mmHg or $\leq$130/80 for patients with DM or CKD) after 8 weeks of treatment.

2.3. BP measurement

Clinic BPs were measured and recorded at each study visit by a calibrated mercury sphygmomanometer in seated patients with their arm supported. The value was recorded as the average of three consecutive measurements, each separated by 3 min between the measurements.

Ambulatory BP monitoring was completed at baseline and the end of the study. The automatic ambulatory BP monitor (ABPM, SpaceLabs 90207 monitor, SpaceLabs Inc.) was set to record every 15 min during the day (7:00 AM to 11:00 PM) and every 30 min at night (11:00 PM to 7:00 AM). Hourly averages were calculated, and the following predefined day and night periods were used: day, 9:00 AM to 9:00 PM and night 12:00 AM to 6:00 AM.

2.4. Monitoring of adverse events

Patients were questioned about possible adverse events at baseline and all subsequent visits.

2.5. Statistical analyses

The distribution of all continuous variables that followed a normal Gaussian distribution are presented as mean $\pm$ SD and compared among these groups by the one-way Analysis of Variance (ANOVA). Student–Newman–Keuls (SNK) procedure was used for multiple comparison when significant difference occurred in ANOVA. Repeated measure analysis of variance would be conducted for evaluating the difference in the changes of blood pressure among these four groups over time. Categories data were compared by the Pearson chi-square test. Fisher exact test was used to test differences in proportions based on small numbers in two-by-two table, such as percentage of patients in each group suffering from side effects. Statistical significance was defined as p values $<$ 0.05. All statistical analyses were performed with the SPSS statistical software program package (SPSS version 15.0 for windows, SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient enrollment and disposition

Fig. 1 shows the recruitment/participant disposition. Of the 226 screened patients for this study, 170 patients were enrolled in the double-blind, placebo run-in period, and 56 were not included for reasons specified in Fig. 1. These enrolled patients were randomized into each group. Finally, the vast majority of patients completed the treatment: (1) 38 patients to placebo; (2) 40 patients to 10 mg/day of AML; (3) 39 patients to 40 mg/day of OM; (4) 40 patients to combination therapy with 10 mg/day of AML and 40 mg/day of OM. The most common reasons for discontinuing the study were adverse events, lack of efficacy and voluntary withdrawal.

3.2. Baseline characteristics of the study population

The baseline characteristics of all of the randomized patients in the 4 treatment arms are shown in Table 1. Consistent with entry criteria, all of these patients received a diuretic at baseline. Treatment groups were balanced with respect to all patient characteristics, such as age, gender, body weight, Body mass index, medical history, heart rate and SBP and DBP level.

3.3. Changes in the 24-h ambulatory blood pressure

Table 2 shows the primary study outcomes. Evident declines can be observed in all patients after 8 weeks of treatment comparing with baseline. A post hoc analysis using SNK method suggested that changes from baseline in 24-h, day and night mean SBP were significant greater with AML + OM versus placebo, AML and OM group, whereas AML was noninferior to OM. Fig. 2 shows the hourly averages of SBP over the 24-h recording period at baseline and end-of-study point. The SBP increment in all these patients was present during the daytime, and steadily declined over the night. Hourly reductions in ambulatory SBP were lower