CURRENT MEDICAL RESEARCH AND OPINION®
VOL. 25, NO. 1, 2009, 177–185

0300-7995
doi:10.1185/03007990802597456

Antihypertensive efficacy of olmesartan medoxomil or valsartan in combination with amlodipine: A review of factorial-design studies

C. Venkata S. Ram

Dallas Nephrology Associates, Dallas, TX, USA

Address for correspondence: **C. Venkata S. Ram, MD, Dallas Nephrology Associates, University of Texas, Southwestern Medical Center, 13154 Coit Road, Suite 100, Dallas, TX 75249, USA. Tel.: +1 214 366 6412; E-mail: ramv@DNEPH.COM**

Key words: **Amlodipine – Factorial design – Hypertension – Olmesartan medoxomil – Valsartan**

ABSTRACT

Background: Most patients with hypertension require more than one drug to attain recommended blood pressure (BP) targets. Initiating therapy with two agents is recommended for patients at high risk of a cardiovascular event or with a BP > 20/10 mmHg above goal. Combination therapy is effective when comprised of agents with complementary mechanisms of action, such as calcium channel blockers (CCBs) and angiotensin II-receptor blockers (ARBs). Two fixed-dose CCB/ARB combinations are approved in the US: amlodipine/valsartan (AML/VAL) and amlodipine/olmesartan medoxomil (AML/OM).

Objectives: To review and describe the efficacy of AML/VAL and AML/OM combinations by discussing similarly designed clinical trials.

Methods: Three 8-week, randomized, double-blind, placebo-controlled, parallel-group factorial-design studies were examined (two AML/VAL; one AML/OM). The study endpoints presented in this review were: change from baseline in least-squares mean seated diastolic BP (SeDBP) and least-squares mean seated systolic BP (SeSBP). In addition to the efficacies of AML/VAL and AML/OM combinations, the efficacies of AML, VAL and OM administered as monotherapy are presented. Placebo-subtracted BP reductions were calculated for this review.

Results: Patient demographics were similar but mean baseline SeBP was higher in the OM study (163.8/101.6 mmHg) than in the VAL studies (152.8/99.3 and 156.7/99.1 mmHg), possibly suggesting that the OM study included a more difficult-to-treat patient population. AML/ARB combinations consistently produced greater mean SeBP reductions than monotherapy. Least squares (LS) mean SeDBP reductions were 19.4 mmHg (AML/OM 10/40 mg; placebo-corrected: 15.9 mmHg) and 18.6 mmHg (AML/VAL 10/320 mg; placebo-corrected: 9.8 mmHg). LS mean SeSBP reductions were 28.5 mmHg (AML/OM 10/40 mg; placebo-corrected: 25.7 mmHg) and 28.4 mmHg (AML/VAL 10/320 mg; placebo-corrected: 15.5 mmHg).

Conclusions: This review of published factorial-design studies showed that the maximal marketed doses of an amlodipine/olmesartan medoxomil combination (10/40 mg) and an amlodipine/valsartan combination (10/320 mg) produced large reductions in BP from baseline. Limitations of this review include the small number of studies analyzed and the inherent heterogeneity between patient populations. Further research is warranted to directly compare the efficacy of these combinations in a randomized, controlled trial, or additional published clinical trials are required to provide larger data sets for robust meta-analyses and to overcome heterogeneity observed within these studies.

Introduction

Poorly controlled hypertension is associated with an increased risk of cardiovascular events including stroke, renal failure, and coronary artery disease[1–3]. Cardiovascular mortality risk has been shown to double with every 20/10 mmHg increase in blood pressure (BP) above 115/75 mmHg[1]. Despite the

availability of effective antihypertensive agents, high BP remains poorly controlled and the prevalence of hypertension continues to be unacceptably high[4]. Current practice guidelines recommend a goal BP of <140/90 mmHg for the general population with hypertension and <130/80 mmHg for patients at high cardiovascular risk, including those with diabetes[2,5].

The majority of patients with hypertension will require at least two antihypertensive agents to achieve recommended BP goals[2]. For patients at high risk of a cardiovascular event or those with BP >20/10 mmHg above goal, practice guidelines advise initiating therapy with two agents[2,5]. To obtain the best possible results, in terms of both maximization of BP lowering and minimization of adverse events, combination therapy should, in principle, be comprised of agents with complementary mechanisms of action[2,5–8]. Angiotensin receptor blockers (ARBs) and dihydropyridine calcium channel blockers (CCBs) are effective classes of antihypertensive agents with distinct and complementary mechanisms of action[5,8–10]. CCB/ARB fixed-dose combinations are, therefore, emerging as a rational treatment option. Two such combinations, an amlodipine/valsartan fixed-dose combination and an amlodipine/olmesartan medoxomil fixed-dose combination, are available and approved in the US.

To date, three factorial-design studies have been undertaken in relation to CCBs in combination with an ARB[11,12]. Two of these studies investigated amlodipine and valsartan[12], and the other investigated amlodipine and olmesartan medoxomil[11]. Factorial studies are designed to evaluate whether a specific combination therapy is more effective than either of the individual components used as monotherapy. These studies have confirmed that combination CCB/ARB therapy is more effective than either agent alone. To derive information about the relative efficacy of CCB/ARB combinations and their constituent components, in the absence of direct head-to-head trials and given the similar design of factorial studies and the comparable patient population, we conducted a comparative review of results from the available factorial studies.

Methods

The primary efficacy endpoint in all studies was the change from baseline in mean seated diastolic blood pressure (SeDBP) at week 8. Change from baseline in mean seated systolic blood pressure (SeSBP) was a secondary endpoint. The combined goal BP in the olmesartan medoxomil study was <140/90 mmHg for most patients or <130/80 mmHg for patients with diabetes. In the valsartan studies, BP response rate was defined as SeDBP <90 mmHg or a ≥10-mmHg decrease from baseline. In all three studies, BP measurements were taken after the patient had been sitting for 5 minutes. Safety profiles were assessed via monitoring of adverse events, hematology and biochemistry parameters, vital signs, physical examinations, and 12-lead electrocardiography. The olmesartan medoxomil study was unique in that the protocol specified that the occurrence and severity of peripheral edema be proactively assessed at each visit on a 5-point severity scale (no edema = 0; mild pitting/slight indentation = 1; moderate pitting/moderate indentation = 2; deep pitting/indentation remains = 3; deep pitting/leg remains swollen = 4)[11]. In the valsartan studies, the severity of peripheral edema was not proactively assessed or specifically reported[12].

Results

Study design

All three studies were randomized, double-blind, placebo-controlled, parallel-group trials of 8 weeks' duration (Table 1). The olmesartan medoxomil study was a multicenter US study. Valsartan study 1 was a multinational study (Belgium, Canada, France, Germany, Mexico and the US), as was valsartan study 2 (Egypt, France, Germany, Korea, Malaysia, Norway, Peru, Portugal, Spain and Taiwan). All studies were conducted according to good clinical practice guidelines and in compliance with the Declaration of Helsinki. Each study received institutional review board or ethical review committee approval, and all patients followed procedures ensuring written informed consent.

Inclusion criteria were the same for both valsartan studies: patients aged ≥18 years with mean SeDBP ≥95 and <110 mmHg. Patients included in the olmesartan medoxomil study were permitted to have a higher grade of hypertension (allowable SeDBP range of 95–120 mmHg) than those in the valsartan studies. Patients with mean SeSBP ≥ 180 mmHg were excluded from the valsartan studies. SeSBP <90 mmHg was not permitted at any point throughout the olmesartan medoxomil study, but maximum allowable SeSBP was left to the discretion of the investigator. Patients with a history of cardiovascular disease or diabetes requiring insulin treatment or poorly controlled type 2 diabetes (fasting glycosylated hemoglobin > 8% at visit 1) were excluded from all of the studies.

All three studies had a 2-week washout phase during which patients discontinued any antihypertensive agents. The two valsartan studies also included a 2- to 4-week single-blind placebo run-in period before the double-blind active treatment phase. The olmesartan

Table 1. Design and methodology of the amlodipine/ARB factorial studies

Drug combination	Study design	Entry criteria	Treatment arms/drug doses	Primary efficacy endpoint
Amlodipine/olmesartan medoxomil[11]	Multicenter, randomized, double-blind, placebo-controlled 4 × 3 factorial design	SeDBP 95–120 mmHg	Placebo AML 5 or 10 mg OM 10, 20, or 40 mg AML/OM 5/10, 5/20, 5/40, 10/10, 10/20, or 10/40 mg	Change from baseline in mean SeDBP at week 8
Amlodipine/valsartan[12] (study 1)	Multicenter, randomized, double-blind, placebo-controlled 5 × 3 factorial design	SeDBP ≥ 95 and < 110 mmHg	Placebo AML 2.5 or 5 mg VAL 40, 80, 160, or 320 mg AML/VAL 2.5/40, 2.5/80, 2.5/320, 5/40, 5/80, 5/160, or 2.5/160 (1 week) → 5/320 mg	Change from baseline in mean SeDBP at week 8
Amlodipine/valsartan[12] (study 2)	Multicenter, randomized, double-blind, placebo-controlled 3 × 2 factorial design	SeDBP ≥ 95 and < 110 mmHg	Placebo AML 10 mg VAL 160 or 320 mg AML/VAL 10/160, 5/160 (1 week) → 10/320 mg	Change from baseline in mean SeDBP at week 8

AML, amlodipine; ARB, angiotensin receptor blocker; OM, olmesartan medoxomil; SeDBP, seated diastolic blood pressure; VAL, valsartan

medoxomil study employed a 4 × 3 factorial design in which 1940 patients were randomized to one of 12 treatment groups: placebo, olmesartan medoxomil 10, 20, or 40 mg/day, amlodipine 5 or 10 mg/day, or combination therapy with one of the six possible combinations of active drug. Valsartan study 1 employed a 5 × 3 factorial design in which 1911 patients were randomized to one of 15 groups: placebo, valsartan 40, 80, 160, or 320 mg/day, amlodipine 2.5 or 5 mg/day, or combination therapy with one of the eight possible combinations of active drug. Valsartan study 2 employed a 3 × 2 factorial design in which 1250 patients were randomized to one of six treatment groups: placebo, valsartan 160 or 320 mg/day, amlodipine 10 mg/day, or combination therapy with one of the two possible active drug combinations. To minimize the potential for orthostatic adverse events, patients randomized to receive amlodipine 5 or 10 mg/day plus valsartan 320 mg/day underwent forced titration after 1 week of treatment with amlodipine 2.5 or 5 mg/day plus valsartan 160 mg/day.

Patients

A total of 1940 patients were randomized to treatment in the olmesartan medoxomil study and 1911 and 1250 patients in valsartan studies 1 and 2, respectively. Demographic characteristics of patients in the three studies are shown in Table 2. In light of the BP inclusion criteria, not surprisingly, the mean SeBP was highest in the olmesartan medoxomil study (163.8/101.6 mmHg vs. 152.8/99.3 and 156.7/99.1 mmHg in the two valsartan studies). Although the patients in the olmesartan medoxomil study would be predominantly described as a stage 2 hypertension population (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg) and patients in the valsartan studies would be predominantly described as a stage 1 hypertension population (SBP 140–159 mmHg or DBP 90–99 mmHg) standard deviations for these values were not provided and substantial heterogeneity is likely to exist.

The gender ratios were similar among the studies with the proportion of men ranging from 50.3% in the valsartan study 2 to 54.3% in the olmesartan medoxomil study. The mean age ranged from 54 in the olmesartan medoxomil study and valsartan study 1 to 57 in valsartan study 2. Patients aged ≥ 65 years comprised 18.2% and 28.6% of patients in the valsartan studies 1 and 2, respectively, and 19.8% of patients in the olmesartan medoxomil study. The mean weight of patients was highest in the olmesartan medoxomil study (95.1 kg vs. 88.8–79.7 kg in the valsartan studies).

Table 2. *Demographic and baseline characteristics of patients in the amlodipine/ARB factorial studies*

Treatment group	Mean age (years)	% ≥ age 65	Mean weight (kg/m^2)	Mean BMI	Sex (%)		Race (%)			Mean sitting BP (mmHg)	
					Male	Female	White	Black	Other	Diastolic	Systolic
AML/OM	54.0	19.8	95.1	33.5	54.3	45.7	71.4	24.8	4.4	101.6	163.8
AML/VAL (study 1)	54.4	18.2	88.8	29.8*	53.5	46.5	79.5	10.4	10.1	99.3	152.8
AML/VAL (study 2)	56.9	28.6	79.7	29.8*	50.3	49.7	79.4	0.4	20.3	99.1	156.7

*Mean BMI (kg/m^2) for combination of study 1 and study 2
AML, amlodipine; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; OM, olmesartan medoxomil; VAL, valsartan

Two-thirds of patients in the olmesartan medoxomil study were overweight or obese (body mass index [BMI] ≥ 30 kg/m^2) with a mean BMI of approximately 33.5 kg/m^2 and the combined mean BMI for the two valsartan studies was 29.8 kg/m^2. The proportion of white patients ranged from 71.4% in the olmesartan medoxomil study to 79% in the valsartan studies with the olmesartan medoxomil study having the highest proportion of black patients (24.8 vs. 10.4% in valsartan study 1 and 0.4% in valsartan study 2). Patients with diabetes comprised 13.5% of patients in the olmesartan medoxomil study. The proportion of patients with diabetes was not reported in either of the valsartan studies. At baseline, 13.6% of patients in the olmesartan medoxomil study had peripheral edema. Edema was not reported at baseline as part of the valsartan studies.

Review of the evidence of efficacy

The primary population for analysis in both studies was the intent-to-treat (ITT) population (all randomized patients who had a baseline BP measurement and ≥ 1 post-baseline BP measurement after taking double-blind study medication). Standard errors of the mean (SE) were reported individually for each dosage in the olmesartan-based study and were pooled for SeDBP and SeSBP reductions in the valsartan-based studies.

SeDBP

Placebo was associated with least squares (LS) mean reductions in SeDBP that ranged from 3.5 mmHg (SE 0.75) in the olmesartan medoxomil study (Figure 1) to 6.8 (SE 0.65–0.67) and 8.8 mmHg (SE 0.62–0.63) in valsartan studies 1 and 2, respectively (Figures 2 and 3)[12].

All active treatments produced greater LS mean SeDBP reductions than placebo. For the purposes of this overview, placebo-corrected values were calculated and presented. For monotherapy with amlodipine 5 mg, the LS mean reduction in SeDBP was 10.0 mmHg (SE 0.75) in the olmesartan study and 11.5 mmHg in the valsartan study 1 (SE 0.65–0.67) (placebo-corrected values of 6.5 and 4.7 mmHg, respectively). For monotherapy with amlodipine 10 mg, the LS mean reduction in SeDBP was 13.3 mmHg (SE 0.74) in the olmesartan study and 15.6 mmHg (SE 0.62–0.63) in the valsartan study 2 (placebo-corrected values of 9.8 and 6.8 mmHg, respectively) (Table 3). Olmesartan medoxomil produced LS mean reductions ranging from 8.8 mmHg (SE 0.75) with the 10-mg dose to 10.9 mmHg (SE 0.75) with the 40-mg dose (placebo-corrected values of 5.3–7.4 mmHg), and valsartan produced LS mean reductions ranging from 10.1 mmHg (SE 0.65–0.67)

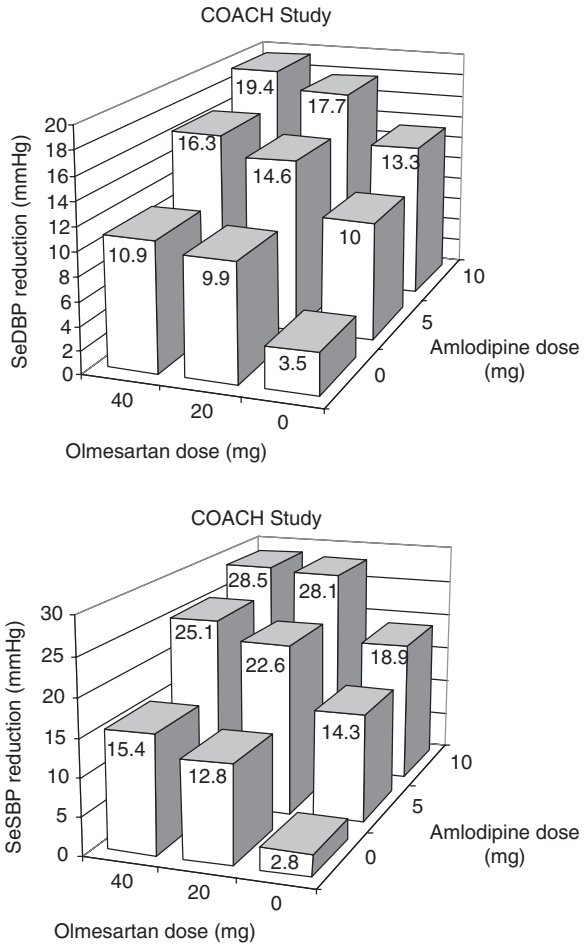

Figure 1. *LS mean reductions in SeDBP and SeSBP in patients treated with marketed dosages of amlodipine + olmesartan medoxomil*[11]

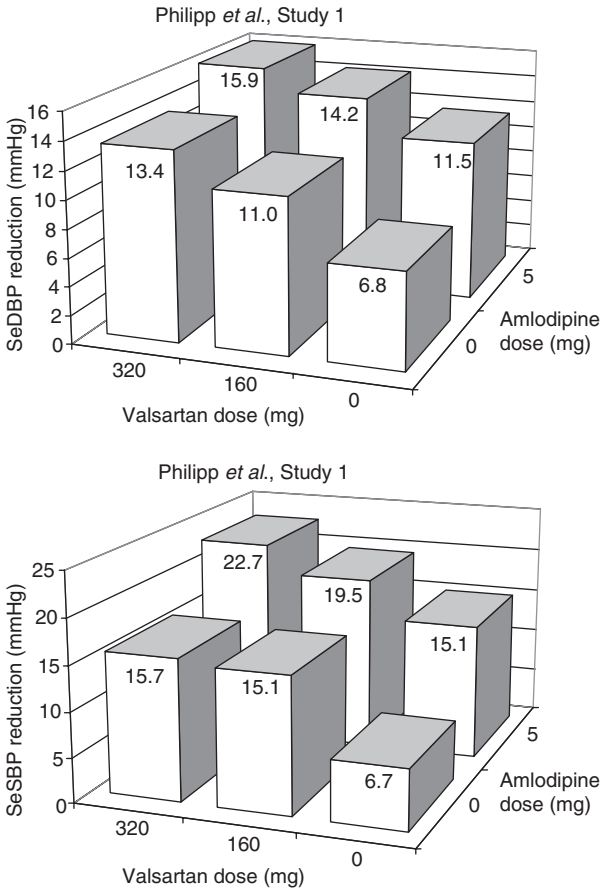

Figure 2. *LS mean reductions in SeDBP and SeSBP in patients treated with marketed dosages of amlodipine + valsartan (study 1)*[12]

with the 40-mg dose to 13.4 mmHg (SE 0.62–0.63) with the 320-mg dose (placebo-corrected values of 3.3–6.6 mmHg) (Table 4).

With the exception of the lowest amlodipine/valsartan (2.5 mg/40 mg) dose pairing, all the amlodipine/ARB combinations consistently produced greater lowering of SeDBP than monotherapy with component agents. In relation to combination therapy in the olmesartan medoxomil study, LS mean SeDBP reductions ranged from 14.3 mmHg (SE 0.74) with amlodipine 5 mg/olmesartan 10 mg to 19.4 mmHg (SE 0.74) with amlodipine 10 mg/olmesartan medoxomil 40 mg (placebo-corrected values of 10.8–15.9 mmHg) (Table 5). In the valsartan studies, LS mean reductions ranged from 10.8 mmHg (SE 0.65–0.67) with amlodipine 2.5 mg/valsartan 40 mg to 18.6 mmHg (SE 0.62–0.63) with amlodipine 10 mg/valsartan 320 mg (placebo-corrected values of 4.0–9.8 mmHg).

SeSBP

LS mean reductions in SeSBP associated with placebo ranged from 2.8 mmHg (SE 1.25) in the olmesartan medoxomil study (Figure 1) to 6.7 mmHg (SE 1.03–1.06) in valsartan study 1 and 12.9 mmHg (SE 0.96–0.97) in valsartan study 2 (Figures 2 and 3). For monotherapy with amlodipine, the LS mean reduction was 14.3 mmHg (SE 1.24) in the olmesartan medoxomil study and 15.1 mmHg (SE 1.03–1.06) in valsartan study 1 (placebo-corrected values of 11.5 and 8.4 mmHg) for the 5-mg dose and from 18.9 mmHg (SE 1.23) in the olmesartan medoxomil study to 24.1 mmHg (SE 0.96–0.97) in valsartan study 2 (placebo-corrected values of 16.1 and 11.2 mmHg) for the 10-mg dose (Table 3).

Olmesartan medoxomil produced LS mean SBP reductions of 10.9 mmHg (SE 1.24) with the 10-mg dose and 15.4 mmHg (SE 1.24) with the 40-mg dose (placebo-corrected values of 8.1–12.6 mmHg), and valsartan produced reductions of 11.8 mmHg (SE 1.03–1.06) with the 40-mg dose and 19.8 mmHg (SE 0.96–0.97) with the 320-mg dose (placebo-corrected values of 5.1–6.9 mmHg) (Table 4). LS mean reductions in SeSBP were greater with combination therapy than with any agent given alone. In relation to combination therapy in the olmesartan medoxomil study, LS mean SeSBP reductions ranged

from 22.6 mmHg (SE 1.24) with amlodipine 5 mg/olmesartan medoxomil 20 mg to 28.5 mmHg (SE 1.24) with amlodipine 10 mg/olmesartan medoxomil 40 mg (placebo-corrected values of 19.8–25.7 mmHg) (Table 5). In the valsartan studies, LS mean reductions ranged from 15.5 mmHg (SE 1.03–1.06) with amlodipine 2.5 mg/valsartan 40 mg to 28.4 mmHg (SE 0.96–0.97) with amlodipine 10 mg/valsartan 320 mg (placebo-corrected values of 8.8–15.5 mmHg).

Attainment of BP goals

As with reductions in SeBP, goal BP (< 140/90 mmHg or < 130/80 mmHg for patients with diabetes in the olmesartan medoxomil study) was achieved to the greatest extent in the combination therapy arms. At week 8, approximately 49.1–53.2% of patients treated with the higher dose amlodipine and olmesartan combination therapies reached their BP goal[11,12]. Bearing in mind the relatively stringent definition of BP control in the olmesartan medoxomil study, the proportion of patients achieving goal DBP (< 90 mmHg) was 77.6% with amlodipine/olmesartan medoxomil 10/40 mg and 84.1% with amlodipine/valsartan 10/320 mg[11,12].

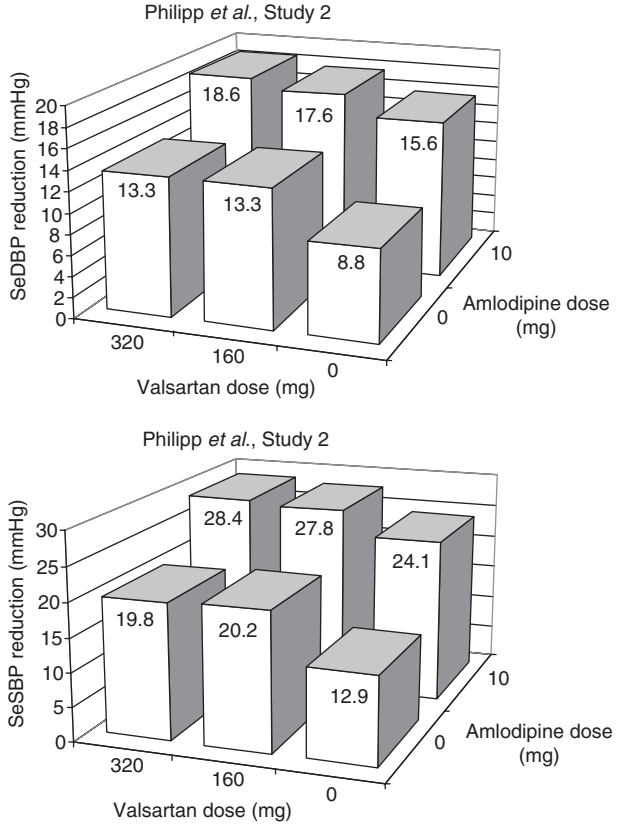

Figure 3. *LS mean reductions in SeDBP and SeSBP in patients treated with marketed dosages of amlodipine + valsartan (study 2)*[12]

Review of the evidence of the safety profiles of the two combinations

The amlodipine/ARB combinations were well-tolerated, with no unexpected safety concerns. The incidence of peripheral edema (the most common adverse event in all studies) was lower with combination therapy than with amlodipine monotherapy. The incidence of peripheral edema significantly decreased from 36.8% with amlodipine 10 mg monotherapy to 23.5% when combined with olmesartan medoxomil 40 mg ($p = 0.011$). Most occurrences of edema were of mild-to-moderate severity. The incidence of peripheral edema in valsartan studies was not broken down into dosage groups and was not as rigorously examined as in the olmesartan medoxomil study (overall incidence decreased from 8.7% with amlodipine monotherapy to 5.4% with combination amlodipine/valsartan, $p < 0.05$).

Other common adverse events in the olmesartan medoxomil study included headache (6.7%), dizziness (3.9%), and fatigue (3.2%), none of which showed consistent differences among active treatment groups. Other common adverse events in the valsartan studies included headache (5.1%), nasopharyngitis (3.8%), upper respiratory tract infection (2.3%), and dizziness (2.0%). The incidence of headache was significantly lower in the amlodipine/valsartan combination therapy arm compared with amlodipine monotherapy (4.3 vs. 7.6%, respectively; $p < 0.05$). The overall incidence of orthostatic hypotension was low in all studies (0.3–0.5%). With regard to laboratory parameters,

Table 3. *LS mean reductions in SeDBP and SeSBP after 8 weeks of treatment with amlodipine monotherapy in factorial studies*

Amlodipine doses	SeDBP, mmHg (placebo-corrected)			SeSBP, mmHg (placebo-corrected)		
	Chrysant *et al.*[11]	Philipp *et al.* study 1[12]	Philipp *et al.* study 2[12]	Chrysant *et al.*[11]	Philipp *et al.* study 1[12]	Philipp *et al.* study 2[12]
2.5 mg	NA	−9.3 (−2.5)	NA	NA	−12.4 (−5.7)	NA
5 mg	−10.0 (−6.5)	−11.5 (−4.7)	NA	−14.3 (−11.5)	−15.1 (−8.4)	NA
10 mg	−13.3 (−9.8)	NA	−15.6 (−6.8)	−18.9 (−16.1)	NA	−24.1 (−11.2)

LS, least squares; NA, not applicable; SeDBP, seated diastolic blood pressure; SeSBP, seated systolic blood pressure

Table 4. *LS mean reductions in SeDBP and SeSBP after 8 weeks of treatment with ARB monotherapy in factorial studies*

ARB	SeDBP, mmHg (placebo-corrected)			SeSBP, mmHg (placebo-corrected)		
	Chrysant *et al.*[11]	Philipp *et al.* study 1[12]	Philipp *et al.* study 2[12]	Chrysant *et al.*[11]	Philipp *et al.* study 1[12]	Philipp *et al.* study 2[12]
Olmesartan						
10 mg	−8.8 (−5.3)	—		−10.9 (−8.1)	—	—
20 mg	−9.9 (−6.4)	—	—	−12.8 (−10.0)	—	—
40 mg	−10.9 (−7.4)	—	—	−15.4 (−12.6)	—	—
Valsartan						
40 mg	–	−10.1 (−3.3)	NA	—	−11.8 (−5.1)	NA
80 mg	–	−9.7 (−2.9)	NA	—	−12.9 (−6.2)	NA
160 mg	–	−11.0 (−4.2)	−13.3 (−4.5)	—	−15.1 (−8.4)	−20.2 (−7.3)
320 mg	–	−13.4 (−6.6)	−13.3 (−4.5)	—	−15.7 (−9.0)	−19.8 (−6.9)

ARB, angiotensin receptor blocker; LS, least squares; NA, not applicable; SeDBP, seated diastolic blood pressure; SeSBP, seated systolic blood pressure

Table 5. *LS mean reductions in SeDBP and SeSBP after 8 weeks of treatment with amlodipine/ARB in factorial studies*

	SeDBP, mmHg (placebo-corrected)	SeSBP, mmHg (placebo-corrected)
Amlodipine/olmesartan medoxomil		
5 mg/10 mg	−14.3 (−10.8)	−22.6 (−19.8)
10 mg/10 mg	−16.7 (−13.2)	−24.8 (−22.0)
5 mg/20 mg	−14.6 (−11.1)	−22.6 (−19.8)
10 mg/20 mg	−17.7 (−14.2)	−28.1 (−25.3)
5 mg/40 mg	−16.3 (−12.8)	−25.1 (−22.3)
10 mg/40 mg	−19.4 (−15.9)	−28.5 (−25.7)
Amlodipine/valsartan		
2.5 mg/40 mg	−10.8 (−4.0)	−15.5 (−8.8)
5 mg/40 mg	−14.6 (−7.8)	−19.6 (−12.9)
2.5 mg/80 mg	−13.4 (−6.6)	−17.0 (−10.3)
5 mg/80 mg	−14.5 (−7.7)	−20.8 (−14.1)
2.5 mg/160 mg	−13.3 (−6.5)	−16.7 (−10.0)
5 mg/160 mg	−14.2 (−7.4)	−19.5 (−12.8)
10 mg/160 mg	−17.6 (−8.8)	−27.8 (−14.9)
2.5 mg/320 mg	−14.2 (−7.4)	−18.3 (−11.6)
5 mg/320 mg	−15.9 (−9.1)	−22.7 (−16.0)
10 mg/320 mg	−18.6 (−9.8)	−28.4 (−15.5)

ARB, angiotensin receptor blocker; LS, least squares; SeDBP, seated diastolic blood pressure; SeSBP, seated systolic blood pressure

there were no clinically significant differences between treatment groups.

Discussion

A notable difference between the studies was the inclusion criteria, which led to a patient population with more severe systolic hypertension in the olmesartan medoxomil study compared with the valsartan studies (mean baseline SeSBP 163.8 mmHg vs. 152.8–156.7 mmHg). Note that, relative to DBP, goal SBP is particularly difficult to obtain, requiring drug doses and combinations that go beyond those necessary for control of DBP[13]. Mean baseline SeSBP was relatively high in the olmesartan medoxomil study, and SBP was included in the definition of goal BP (< 140/90 mmHg or < 130/80 mmHg for patients with diabetes), whereas the only goal-related results reported in the valsartan studies were response rates defined as DBP < 90 mmHg or a ≥ 10 mmHg reduction from baseline and control rates defined as DBP < 90 mmHg.

The mean baseline DBP was 99.3 and 99.1 mmHg in the valsartan study 1 and study 2, respectively. Olmesartan medoxomil study patients started with a higher baseline mean DBP of 101.6 mmHg. Consequently, a greater reduction in DBP was necessary in the olmesartan medoxomil study population in order to achieve a DBP goal of < 90 mmHg. As would be expected from these discrepancies, proportions of patients achieving their target DBP were relatively high with amlodipine/valsartan versus the proportions of patients achieving target SBP/DBP with amlodipine/olmesartan medoxomil.

Placebo response was greater in the valsartan studies (LS mean SBP reduction of 6.7 and 12.9 mmHg in study 1 and 2, respectively; and LS mean DBP reduction of 6.8 and 8.8 mmHg in study 1 and 2, respectively) compared with the olmesartan medoxomil study (LS mean SBP reduction of 2.8 mmHg and LS mean DBP reduction of 3.5 mmHg). In the valsartan studies, patients randomized to the maximum dose combination were started with 1 week of amlodipine 2.5 mg (study 1) or amlodipine 5 mg (study 2) and

valsartan 160 mg, then up-titrated. In contrast, patients in the olmesartan medoxomil study were immediately randomized to the maximum dose combination. This variation in treatment administration, and differences in washout protocols prior to study entry, may be a source of heterogeneity between the studies and in the patients' responses to therapy.

The demographics of patients differed substantially in the racial composition and BMI status between studies. These differences between study populations may potentially have had an impact upon BP-lowering efficacy due to the increased preponderance of difficult-to-treat patients in the olmesartan study as opposed to the valsartan studies. For example, hypertension management in obese individuals, who were greater in number in the olmesartan medoxomil study, is complicated by poorer response to treatment, and the increased need for multiple medications[14].

The differences in patient demographics should be considered when interpreting the observation that BP lowering in the olmesartan study was remarkably similar to that seen in the valsartan studies. Differences in demographics may also have accounted for the larger BP decreases in patients receiving placebo in the valsartan studies. The studies also recruited patients from different geographical areas, and lifestyle or dietary factors may also have contributed to heterogeneity between the studies. Inclusion and exclusion criteria were also different between the studies. For example, consumption of more than one pack of cigarettes per day was a criterion for exclusion from the olmesartan study but apparently not the valsartan studies.

However, generally the results of this analysis show that the BP-lowering efficacy of low- and high-dose combination amlodipine/olmesartan medoxomil and amlodipine/valsartan are at least comparable. At the maximal dose, amlodipine 10 mg/olmesartan medoxomil 40 mg provided the largest placebo-corrected reductions in both LS mean SeDBP and SeSBP (15.9 and 25.7 mmHg, respectively, as opposed to 9.8 and 15.5 mmHg, respectively, with maximal dose amlodipine 10 mg/valsartan 320 mg).

At lower doses, reductions in SeSBP tended to be greater with amlodipine/olmesartan medoxomil versus amlodipine/valsartan. As opposed to increasing the dose of a single agent, administering a combination of agents with complementary modes of action may result in better BP-lowering efficacy and improved adverse events profile[9]. CCBs can stimulate release of renin and increased sympathetic outflow, which is blunted by the addition of a renin-angiotensin-blocking agent, such as an ARB[9]. As opposed to monotherapy, efficacy was enhanced by CCB/ARB combination therapy in these factorial studies (additive activity consistent with the complementary mechanisms described above). Note, however, that combined therapy with valsartan 160 mg in combination with amlodipine 10 mg has been reported to be unable to attenuate amlodipine-induced sympathetic activation[15]. It is not clear whether differences between the ARBs with respect to attenuation of amlodipine-induced sympathetic activation could help to explain the difference in BP-lowering efficacy between different amlodipine/ARB combinations. Such a hypothesis requires prospective validation.

In terms of complementary mechanisms in relation to ARBs, thiazide diuretics represent another rational add-on class of antihypertensive[5,9]. Administration of a diuretic potentiates a similar cascade of events to that of a CCB[9]. In the same way that the current review of factorial-design amlodipine/ARB studies supports the rational use of this combination therapy for patients with hypertension, a previously conducted review of factorial-design ARB/HCTZ (hydrochlorothiazide) studies supports the rational use of ARB/HCTZ combination therapy[16]. Note that, in the review of ARB/HCTZ combinations, high-dose olmesartan 40 mg/HCTZ 25 mg was associated with the greatest placebo-corrected reduction in BP as opposed to other ARB/HCTZ combinations involving irbesartan, telmisartan or valsartan[16]. This finding is consistent with findings related to amlodipine/olmesartan medoxomil versus amlodipine/valsartan in the current review.

Differences between placebo-corrected BP changes in amlodipine monotherapy-treated patients may be due in part to the higher mean baseline BP of patients entering the olmesartan study (Table 2). As well as reviewing the antihypertensive effects of different amlodipine/ARB combination therapies, this comparison also provided information on the comparative efficacy of ARB monotherapies. For example, olmesartan medoxomil 40 mg produced a placebo-corrected LS mean reduction in SeDBP of 7.4 mmHg, and valsartan 320 mg produced placebo-corrected LS mean reductions of 6.6 and 4.5 mmHg in valsartan studies 1 and 2. As well as improving efficacy, administering a combination of agents with complementary modes of action may also result in an improved adverse events profile[9]. Risk of edema with CCBs can be ascribed to potent unopposed arterial vasodilation[17], but this can be counterbalanced by dilation of the venous circulation with renin-angiotensin system blockade[9]. In the amlodipine/olmesartan medoxomil and amlodipine/valsartan factorial studies, safety profiles of both combination therapies were consistent with the known pharmacologic properties of each of their components, and amlodipine-induced peripheral edema was partially reduced by combining with an ARB at some dose combinations.

Conclusions

This comparison of findings from the literature supports the rational use of amlodipine/ARB combination therapy for patients with hypertension. Contextual comparison of the combinations of amlodipine/olmesartan medoxomil and amlodipine/valsartan evaluated in similarly designed factorial studies revealed that BP was effectively reduced at the maximal marketed doses of 10 mg/40 mg and 10 mg/320 mg, respectively. This comparison of findings is limited by the small number of studies analyzed and differences between patient populations. Determination of which of the two combinations is more efficacious could be achieved by a meta-analysis comprising further published studies. Such an analysis would negate many of the sources of heterogeneity inherent within the three studies compared here. Due to the current unavailability of additional study data, an alternative would be a clinical study encompassing a direct head-to-head trial of amlodipine 10 mg/olmesartan medoxomil 40 mg with the maximal marketed dose of amlodipine 10 mg/valsartan 320 mg in order to eliminate potentially confounding aspects of the current analysis.

Acknowledgments

Declaration of interest: Funding for editorial assistance was provided by Daiichi Sankyo, Inc. The authors thank Jennifer M. Kulak, PhD, and Christopher J. Jones, PhD, Wolters Kluwer Health, for their editorial assistance in the preparation of this manuscript. Figures 2 and 3 reprinted from Clin Ther, 29(4), Philipp T, et al, Two multicenter, 8-week, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension, 563-580, Copyright (2007), with permission from Excerpta Medica, Inc.

References

1. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903-13
2. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560-72
3. Rosendorff C, Black HR, Cannon CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. Circulation 2007;115:2761-88
4. Ong KL, Cheung BM, Man YB, et al. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. Hypertension 2007;49:69-75
5. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105-87
6. Sica DA. Rationale for fixed-dose combinations in the treatment of hypertension: the cycle repeats. Drugs 2002; 62:443-62
7. Weber MA. Creating a combination antihypertensive regimen: what does the research show? J Clin Hypertens (Greenwich) 2003;5:12-20
8. Weir MR. Targeting mechanisms of hypertensive vascular disease with dual calcium channel and renin-angiotensin system blockade. J Hum Hypertens 2007;21:770-9
9. Epstein BJ, Vogel K, Palmer BF. Dihydropyridine calcium channel antagonists in the management of hypertension. Drugs 2007;67:1309-27
10. Swales P, Williams B. Calcium channel blockade in combination with angiotensin-converting enzyme inhibition or angiotensin II (AT(1)-receptor) antagonism in hypertensive diabetics and patients with renal disease and hypertension. J Renin Angiotensin Aldosterone Syst 2002;3:79-89
11. Chrysant SG, Melino M, Kariki S, et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double blind, placebo-controlled, 8-week factorial efficacy and safety study. Clin Ther 2008;30:587-604
12. Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. Clin Ther 2007;29:563-80
13. Mancia G, Grassi G. Systolic and diastolic blood pressure control in antihypertensive drug trials. J Hypertens 2002;20:1461-4
14. Chrostowska M, Szczech R, Narkiewicz K. Antihypertensive therapy in the obese hypertensive patient. Curr Opin Nephrol Hypertens 2006;15:487-92
15. de Champlain J, Karas M, Assouline L, et al. Effects of valsartan or amlodipine alone or in combination on plasma catecholamine levels at rest and during standing in hypertensive patients. J Clin Hypertens (Greenwich) 2007;9:168-78
16. Ram CV. Antihypertensive efficacy of angiotensin receptor blockers in combination with hydrochlorothiazide: a review of the factorial-design studies. J Clin Hypertens (Greenwich) 2004;6:569-77
17. Messerli FH. Vasodilatory edema: a common side effect of antihypertensive therapy. Curr Cardiol Rep 2002;4:479-82

CrossRef links are available in the online published version of this paper:
http://www.cmrojournal.com
Paper CMRO-4776_4, *Accepted for publication:* 4 November 2008
Published Online: 8 December 2008
doi:10.1185/03007990802597456