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Clinical and Experimental Aspects of Olmesartan Medoxomil, a New Angiotensin II Receptor Antagonist

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ABSTRACT

Olmesartan medoxomil is a new orally active angiotensin II (Ang II) type 1 receptor antagonist. It is a prodrug and is rapidly de-esterified during absorption to form olmesartan, the active metabolite. Olmesartan is a potent, competitive and selective Ang II type 1 receptor antagonist. Olmesartan is not metabolized by the cytochrome P-450 and has a dual route of elimination, by kidneys and liver.

In patients with essential hypertension olmesartan medoxomil administered once daily at doses of 10–80 mg dose-dependently reduced diastolic blood pressure (DBP). Trough-to-peak ratios for both DBP and systolic blood pressure (SBP) were above 50%. At the recommended once-daily starting doses, olmesartan medoxomil (20 mg) was more effective than losartan (50 mg), valsartan (80 mg) or irbesartan (150 mg) in reducing cuff DBP in patients with essential hypertension. The results of cuff SBP and mean 24-h DBP and SBP were similar to those of cuff DBP measurement. In mild-to-moderate hypertensive patients the recommended starting dose of olmesartan medoxomil was as effective as that of amlodipine besylate (5 mg/day) in reducing both cuff and 24-h blood pressure. In lowering DBP olmesartan medoxomil, at 10–20 mg/day, was as effective as atenolol at 50–100 mg/day. In mild-to-moderate hypertensive patients, olmesartan medoxomil, at 5–20 mg once daily, was more effective than captopril at 12.5–50 mg twice daily. At 20–40 mg once daily olmesartan medoxomil was as effective as felodipine, at 5–10 mg once daily. Olmesartan medoxomil has minimal adverse effects with no clinically important drug interactions.

Animal studies have shown that olmesartan medoxomil provides a wide range of organ protection. Olmesartan medoxomil ameliorated atherosclerosis in hyperlipidemic animals

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and ameliorated cardiac remodeling and improved survival in rats with myocardial infarction. Olmesartan medoxomil has renoprotective effects in a remnant kidney model and type 2 diabetes models. Future investigation should reveal whether these beneficial effects of olmesartan medoxomil are applicable to human diseases.

INTRODUCTION

The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure and fluid-electrolyte balance as well as in the pathophysiology of various cardiovascular diseases. Extensive use of angiotensin converting enzyme (ACE) inhibitors has demonstrated the benefit of RAS blockade in the treatment of hypertension (41) and congestive heart failure (37) as well as in slowing the progression of chronic renal insufficiency (8,18). Although ACE inhibitors are generally well tolerated, they have some side effects, such as cough and angioedema, probably because not only angiotensin I (Ang I) but also bradykinin, substance P and enkephalins serve as substrates for ACE (9). Furthermore, the detection of angiotensin II (Ang II) and its metabolites in plasma during chronic ACE inhibition (39) implies that inhibition of the RAS is not complete. Ang II may also be produced through a non-ACE-dependent pathway, such as that involving chymase (38). These facts prompted the development of another way of blocking the RAS that has similar beneficial effects with more efficiency and a reduced risk of adverse effects.

The Ang II type 1 (AT_1) receptor mediates nearly all of the major physiological actions of Ang II such as the regulation of blood pressure, electrolyte and water balance, aldosterone secretion and renal function (32). Antagonism of the AT_1 receptor blocks, therefore, the RAS more effectively than inhibition of ACE. Orally active non-peptide AT_1 receptor antagonists such as losartan, also known as Ang II receptor blockers (ARBs), have been developed as antihypertensive agents (4). ARBs have been available in the United States since 1995, and accumulating data indicate that ARBs could be at least as effective as ACE inhibitors in the treatment of hypertension (6), congestive heart failure (29) and diabetic nephropathy (2). In April 2002, olmesartan medoxomil (also known as CS-866) (21) was approved by the Food and Drug Administration as the seventh ARB for the treatment of hypertension. This review summarizes the pharmacology, pharmacokinetics, clinical efficacy, and experimental efficacy of olmesartan medoxomil.

PHARMACOLOGY

Similar to the other ARBs, with the exception of valsartan, olmesartan medoxomil is an imidazole derivative, and a prodrug-type ARB (Fig. 1) (42). The medoxomil ester of olmesartan was developed in preference to the active compound olmesartan (RNH-6270), because the oral bioavailability of the latter is low (4.5%) and is increased (to 28.6%) by esterification with the medoxomil moiety (17).

Olmesartan inhibited [^{125}I]Ang II binding to bovine adrenal cortical membranes (AT_1 receptors) with an IC_{50} of 7.7 nM, approximately 12 and 2 times lower than those of losartan (92 nM) and EXP3174 (16 nM), an active metabolite of losartan, respectively (21). On

FIG. 1. Chemical structures of olmesartan medoxomil, olmesartan, and other angiotensin II receptor antagonists.

the other hand, olmesartan had no effect on [^{125}I]Ang II binding to bovine cerebellar membranes (Ang II type 2 receptors, AT_2 receptors) (21), indicating that olmesartan is a highly selective AT_1 receptor antagonist. In Scatchard analysis of the binding characteristics of [^{125}I]Ang II in bovine adrenal cortical membranes, olmesartan, like losartan, reduced the slope while having little effect on B_{max} (21). In Hill analysis, olmesartan caused a shift to the right of the Hill plot without changing the slope (21). The results of these two analyses suggest that olmesartan competitively interacts with AT_1 receptors. In guinea pig aortas, olmesartan reduced the maximal response of the concentration-response curve for Ang II but had no effect on the contractile response induced by phenylephrine or potassium chloride (21). Olmesartan caused a nonparallel shift to the right of the concentration-response curve for Ang II and reduced the maximal response to Ang II (21). In contrast, losartan caused a parallel rightward shift of the dose-response curve for Ang II (21). Kinetic study revealed that olmesartan had a slow onset of action and prolonged duration of its Ang II inhibitory effects, whereas losartan had a rapid onset of action (21). These data suggest that olmesartan has slow kinetics at AT_1 receptor sites and that this feature of olmesartan may be related to the reduction of the maximum response to Ang II by olmesartan.

In normotensive conscious rats, intravenously administered olmesartan, unlike saralasin, inhibited Ang II-induced pressor response dose-dependently without intrinsic agonistic activity (21). The maximal inhibition was achieved within 1 h after the administration of olmesartan medoxomil at doses of 0.01 and 0.03 mg/kg. The inhibition gradually decreased thereafter, but the Ang II pressor response did not return to pre-administration levels within 8 h (21).

When olmesartan medoxomil was administered orally to conscious normotensive rats at a dose of 0.1 mg/kg, it caused maximal inhibition of Ang II pressor response 2 h after administration. Olmesartan medoxomil inhibited the Ang II pressor response for 8 h (21). In normotensive anesthetized rats, intravenously administered olmesartan medoxomil (0.01 mg/kg) and intravenously administered losartan (1 mg/kg) inhibited the Ang II pressor response to the same degrees (70–80%) (19). Olmesartan medoxomil demonstrated its maximal inhibition within 1 hour after administration, and the inhibition gradually decreased thereafter. Losartan demonstrated a biphasic inhibitory effect and its maximal inhibitory effect occurred immediately after administration. Although SK&F-525A, a cytochrome P-450 inhibitor, suppressed the late phase of the Ang II inhibitory effect of losartan, it did not alter the effect of olmesartan medoxomil (21). This suggests that when orally administered in clinical settings, the Ang II antagonistic action of olmesartan medoxomil, unlike that of losartan, may not vary from one patient to another due to individual variations in the activity of P-450.

Quantitative *in vitro* autoradiography is a powerful technique for examining the action of ARBs at the tissue level (43). So far, there is no study, which examined the correlation of tissue AT_1 binding inhibition by olmesartan with hypotensive effect or with inhibition of the pressor response to exogenous Ang II.

Effects of a single intravenous dose of olmesartan medoxomil (0.01 or 0.1 mg/kg) or vehicle on central and regional hemodynamics were studied in anesthetized male spontaneously hypertensive rats (SHR) (15). Total peripheral resistance was decreased dose-dependently and a higher dose of olmesartan increased cardiac output. Renal blood flow was markedly and dose-dependently increased. Although testicular blood flow was slightly decreased, blood flow in other organs was unaffected by the treatment.

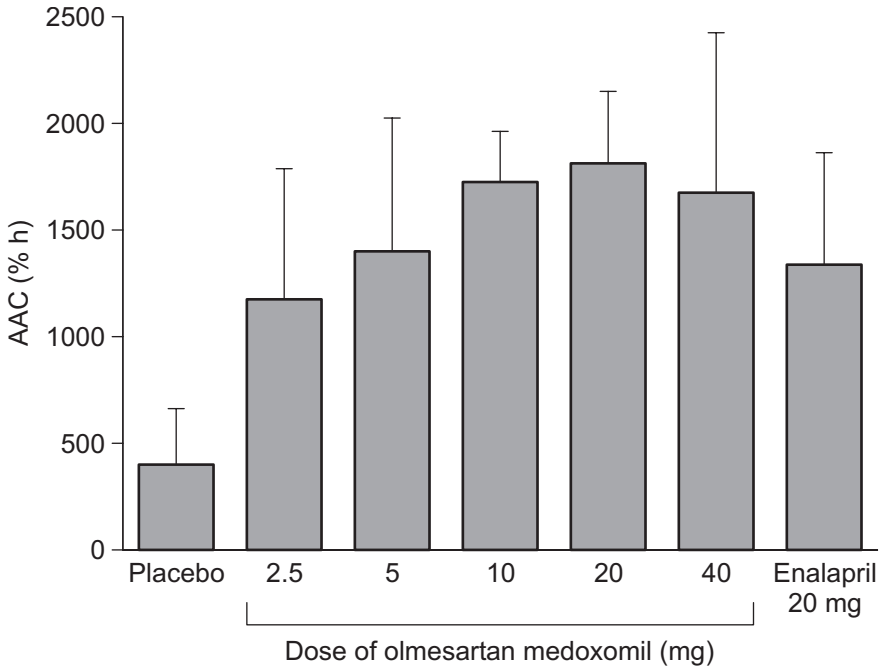

FIG. 2. Area above the curve (AAC) values for the plots of percentage response (compared with baseline) vs. time in the angiotensin I challenge study in healthy male volunteers. Data from ref. 3.

In healthy volunteers, 2.5–40 mg olmesartan medoxomil administered in single doses significantly inhibited the pressor response to exogenous Ang I (3). A dose-response relationship was observed with relevant (>75%) inhibition occurring at doses of 10 mg and higher (Fig. 2). The effects of olmesartan medoxomil at a dose of 5 mg were similar to those of 20 mg of enalapril, an ACE inhibitor (Fig. 2).

PHARMACOKINETICS

As mentioned previously, olmesartan medoxomil is a prodrug-type ARB. Olmesartan medoxomil is hydrolyzed very rapidly to olmesartan in rat and human plasma and by rat liver microsomes (14). The hydrolysis proceeds very rapidly in human plasma with a half-life of only a few seconds (14). *In vivo*, olmesartan medoxomil is rapidly and completely de-esterified during absorption to form olmesartan, the only major metabolite (17). No metabolites of olmesartan have been identified in humans. Olmesartan is highly bound to serum albumin (>99%) and α-1 acid glycoprotein (>96%) and does not enter red blood cells (7).

In a randomized, double-blind, placebo-controlled, ascending single-dose trial, healthy adult males (aged 24 ± 4 years [mean ± SD]) were randomly assigned to one of five olmesartan medoxomil dose groups (10, 20, 40, 80, or 160 mg) (31). In that study, the maximal plasma concentration (C_{max}) and area under the concentration-time curve (AUC)

for olmesartan increased with increasing dose of olmesartan medoxomil (Table 1). At a dose of olmesartan medoxomil of 10 mg, C_{max} was 224 ng/mL and increased to 2100 ng/mL in the 160 mg group. Analysis of the AUC values indicated that the effects of olmesartan at doses between 10 mg and 160 mg were dose-proportional. The time after administration at which C_{max} occurred (t_{max}) ranged from 1.4 to 2.8 h and did not vary systematically with dose (31). The terminal elimination half-life ($t_{1/2}$) was 11.8–14.7 h (31). Approximately 7.8–11.9% of the administered dose was excreted in the urine within 48 h after administration (31). In a single-dose study, 6 healthy males (aged 49–54 years) received 20 mg of [^{14}C]olmesartan orally (17). Fecal excretion accounted for 64.58–89.59% of the administered radiolabeled dose and urinary excretion accounted for 9.94–16.31% of the administered radiolabeled dose. Olmesartan was the only radiolabeled component found in both, feces and urine (17).

In a multiple-dose study, 30 healthy males (aged 25 ± 5 years) were randomly assigned to receive oral olmesartan medoxomil at doses of 20, 40, or 80 mg for 10 days (31). On day 1, t_{max} ranged from 1.7 to 2.4 h and from 1.7 to 1.9 h on day 10 (Table 2). On day 1, C_{max} values of olmesartan in subjects who received 20 mg and 80 mg of olmesartan medoxomil were 479 ng/mL and 1380 ng/mL, respectively. On day 10, C_{max} values of

TABLE 1. Plasma and urinary pharmacokinetic parameters of olmesartan in an ascending single-dose study of olmesartan medoxomil

Dose (mg)	C_{max} (ng/mL)	t_{max} (h)	AUC (ng · h/mL)	$t_{1/2}$ (h)	% dose excreted in urine
10	224 ± 45	2.4 ± 0.9	1631 ± 266	11.8 ± 2.3	11.9 ± 2.5
20	419 ± 56	2.5 ± 0.9	2678 ± 479	12.1 ± 3.8	10.5 ± 3.2
40	752 ± 223	1.4 ± 0.5	5163 ± 1230	13.0 ± 2.6	9.8 ± 2.1
80	1095 ± 280	2.0 ± 0.0	9159 ± 2760	13.2 ± 3.4	7.8 ± 1.6
160	2100 ± 532	2.8 ± 1.1	19905 ± 4370	14.7 ± 5.0	8.4 ± 1.8

C_{max}, maximal plasma concentration; t_{max}, time after administration at which C_{max} occurred; AUC, area under the concentration-time curve; $t_{1/2}$, elimination half-life. Values are means ± S.D. Data from ref. 31.

TABLE 2. Plasma and urinary pharmacokinetic parameters of olmesartan in a multiple-dose study of olmesartan medoxomil

	Dose (mg)	C_{max} (ng/mL)	t_{max} (h)	AUC (ng · h/mL)	$t_{1/2}$ (h)	% dose excreted in urine
Day 1	20	479 ± 210	1.7 ± 0.8	2613 ± 675	—	10.3 ± 3.0
	40	693 ± 78	2.4 ± 1.0	4229 ± 500	—	9.1 ± 1.6
	80	1380 ± 454	1.9 ± 0.7	9330 ± 3128	—	7.2 ± 2.6
Day 10	20	507 ± 58	1.7 ± 0.5	2950 ± 378	14.9 ± 5.9	12.4 ± 2.9
	40	733 ± 160	1.9 ± 0.4	4366 ± 626	14.5 ± 7.5	10.2 ± 2.0
	80	1379 ± 255	1.8 ± 0.8	9382 ± 2056	14.1 ± 7.0	9.3 ± 1.8

C_{max}, maximal plasma concentration; t_{max}, time after administration at which C_{max} occurred; AUC, area under the concentration-time curve; $t_{1/2}$, elimination half-life. Values are means ± S.D. Data from ref. 31.

olmesartan were 507 ng/mL and 1379 ng/mL in subjects who received 20 mg and 80 mg of olmesartan medoxomil, respectively. The plasma concentration of olmesartan approached a steady state after 5 days of treatment (31). Despite the relatively long half-life of olmesartan medoxomil, comparison of C_{max} values on day 1 and 10 shows that drug accumulation does not occur with a single daily dose up to 80 mg.

In an ascending single-dose study, pharmacokinetics of intravenously administered olmesartan was examined in 34 healthy males (aged 28 ± 6 years) (31). C_{max} and AUC increased with increase in dose, and $t_{1/2}$ varied from 10.6 to 8.3 h. There was a steady decrease with increase in dose in the percentage of urinary excretion in 48 h following treatment (31). The percentage was 49.1% for a dose of 1 mg and 35.0% for a dose of 32 mg. These results suggest that urinary excretion is at least partially dependent on some saturable mechanism whose limit is approached at higher doses and that there is a significant hepato-biliary route of excretion for olmesartan. The volume of distribution (V_d) ranged from 14.7 to 19.7 L (31). These values of V_d suggest that olmesartan is essentially restricted to the extracellular compartment. The extensive protein binding character of olmesartan probably accounts for its relatively low V_d. In the same series of studies, however, V_d was higher (34.9 L) after oral administration of olmesartan medoxomil at a dose of 20 mg (31). Similar values of V_d were obtained in another study after oral administration of olmesartan medoxomil at a dose of 10 mg (32.4 L) and intravenous administration of olmesartan at a dose of 8 mg (29.0 L) (17). Therefore, olmesartan may be distributed throughout the intravascular, interstitial and also some transcellular compartments.

Renal clearance (CL_R) is independent of oral dose. It ranged from 0.43 to 0.92 L/h after oral administration of olmesartan medoxomil (10–320 mg) and was 0.53 L/h after intravenous administration of the drug (8 mg) (17). These values were considerably lower than the glomerular filtration rate in healthy subjects (7.5 L/h), which may reflect substantial tubular reabsorption of olmesartan.

Influence of Age on the Pharmacokinetics of Olmesartan Medoxomil

Pharmacokinetic parameters of olmesartan have been investigated in young (18–45 years old), elderly (65–75 years old), and very elderly (≥75 years old) hypertensive patients (40). Young (mean age of 37.3 years) and elderly (mean age of 67.4 years) hypertensive patients received olmesartan medoxomil orally at a dose of 80 mg/day for 10 days (40). There were no significant differences in C_{max} on days 1 and 10 and $t_{1/2}$ on day 10 between the two groups. Renal clearance (CL_R) was significantly lower and AUC on day 10 was significantly higher in the elderly group than in the young group. The pre-dose plasma concentrations of olmesartan in the elderly group were 52.5–76.0% higher than those in the young group. In another comparison, olmesartan medoxomil (10 mg/day) was administered orally to young (mean age of 35.6 years) and very elderly (mean age of 75.9 years) hypertensive patients for 14 days (40). The pre-dose plasma concentrations of olmesartan in the very elderly group were 95.5–117% higher than in the young group. On day 14, values of C_{max} and AUC were 14 and 44%, respectively, higher in the very elderly group, than in the young group. The steady state $t_{1/2}$ was longer in the elderly group (12.8 h at 80 mg/day) and very elderly group (16.5 h at 10 mg/day) than in the young groups (10.6 h at 80 mg/day and 12.3 h at 10 mg/day) (40). A dosage adjustment for elderly and very elderly patients may not be necessary. These results suggest that it may be

beneficial to start olmesartan medoxomil therapy at lower doses and titrate doses more slowly in elderly and very elderly than in younger patients.

Influence of Renal Function on the Pharmacokinetics of Olmesartan Medoxomil

Effects of renal impairment on the pharmacokinetics of olmesartan were investigated in healthy male patients with mild renal impairment (creatinine clearance [C_{Cr}] of 40–59 mL/min), patients with moderate impairment (C_{Cr} of 20–39 mL/min), and patients with severe renal impairment (C_{Cr} < 20 mL/min) (40). Olmesartan medoxomil (10 mg/day) was orally administered to these subjects for 7 days. After the first dose and at a steady state, C_{max} and AUC values increased in patients with mild, moderate and severe renal impairment compared with the values in the healthy group. Significant negative correlations were found between C_{Cr} and both C_{max} and AUC. At the steady state, the percentage of the dose excreted in urine as olmesartan in patients with mild, moderate and severe renal impairment decreased by 21, 59, and 69%, respectively, compared with the values in the healthy individuals. In the same patients CL_R values decreased by 50, 77 and 99%, respectively. As expected, there were significant positive linear correlations of CL_R with C_{Cr} after administration of single and multiple doses. Although steady-state C_{max} and AUC values in patients with mild and moderate renal impairment were up to 39 and 82% higher than in the healthy subjects, the values were much lower than in the healthy subjects or hypertensive patients who received olmesartan medoxomil at a dose of 80 mg/day (40). Therefore, dosage adjustments for patients with mild and moderate renal impairment are not necessary. Although values of C_{max} and AUC were much higher in patients with severe renal impairment, these patients can still excrete olmesartan, probably by hepato-biliary secretion. Although 40 mg is the limiting dose of olmesartan medoxomil in the general patient population, it is recommended that daily dose should not exceed 20 mg in patients with renal impairment.

Influence of Hepatic Function on the Pharmacokinetics of Olmesartan Medoxomil

Effects of liver impairment on the pharmacokinetics of olmesartan were investigated in healthy male patients with mild liver impairment (Child-Pugh score ≤6) and in patients with moderate liver impairment (Child-Pugh score >7 to ≤9) (40). Single oral doses of olmesartan medoxomil (10 mg/day) and intravenous olmesartan (8 mg/day) were administered to these subjects. Following intravenous administration of olmesartan, the pharmacokinetic profile in patients with mild liver impairment was similar to that in the healthy subjects, with similar values of CL_R (0.51 and 0.53 L/h, respectively) and similar percentages of dose excreted in urine (39.3 and 38.7%, respectively). However, higher values of these parameters were found in patients with moderate liver impairment (0.68 L/h and 58.3%, respectively). The increases in AUC and urinary excretion of olmesartan in subjects with moderate liver impairment suggest that renal clearance of olmesartan may compensate for reduced hepato-biliary secretion in patients with hepatic impairment. Compared with healthy subjects, values of AUC were increased by 30 and 48% after oral administration and by 14 and 17% after intravenous administration in patients with mild and moderate liver impairment, respectively. The increases in AUC were statistically

significant in patients with moderate liver impairment. These data suggest that dosage adjustment is necessary in patients with moderate but not in patients with mild liver impairment.

Drug Interactions

Warfarin

Pharmacokinetics of warfarin with and without administration of olmesartan medoxomil were examined in a randomized crossover study (17). Healthy male subjects received an individualized dose (titrated to a Quick value of 1.4–1.8) of warfarin combined with oral olmesartan medoxomil (40 mg/day) or placebo for 7 days and were crossed over to the alternate agent. The steady state C_{max} and AUC for both *R*- and *S*-warfarin enantiomers were unaffected by co-administration of olmesartan medoxomil. Mean pharmacokinetic parameters of the Quick value and partial prothrombin time were similarly unaffected. These results suggest that olmesartan medoxomil should not affect the response to warfarin therapy.

Digoxin

Pharmacokinetics of digoxin with and without administration of olmesartan medoxomil was examined in a randomized crossover study (17). After an oral loading dose of digoxin (1.125 mg/day), healthy male subjects received digoxin (0.375 mg/day) combined with oral olmesartan medoxomil (20 mg/day) or placebo for 7 days. After a wash-out period of 7 days, subjects were crossed over to the alternate agent. The steady state C_{max} and AUC for digoxin were unaffected by co-administration of olmesartan medoxomil.

Aluminium magnesium hydroxide

Pharmacokinetics of olmesartan with and without administration of aluminium magnesium hydroxide, an antacid, was examined in a randomized crossover study (17). Healthy male subjects received either the antacid (800 mg/day) for 8 days with co-administration of olmesartan medoxomil (20 mg/day) on days 4–8 or olmesartan medoxomil alone for 5 days. After a wash-out period, subjects were crossed over to the alternate agent. The steady state C_{max} for olmesartan was similar and the steady state AUC for olmesartan was higher when olmesartan medoxomil was administered alone compared with the values after co-administration with aluminium magnesium hydroxide. Renal excretion of olmesartan was also higher after olmesartan medoxomil alone. There were no statistically significant differences in t_{max} values. The small reduction in the bioavailability of olmesartan by co-administered aluminium magnesium hydroxide is not likely to be clinically significant.

CLINICAL STUDIES

Effects on the Renin-Angiotensin System

The short-term effectiveness of olmesartan medoxomil in salt-restricted patients with mild-to-moderate hypertension was examined in a pharmacodynamic study (30). Prior to administration of olmesartan medoxomil, RAS was activated through sodium restriction

(60 mmol/day) and oral furosemide. A single oral dose of 10–20 mg olmesartan medoxomil resulted in almost maximal effect as assessed by ambulatory diastolic blood pressure (DBP). Olmesartan medoxomil increased plasma renin activity (PRA) and plasma Ang II concentrations, maximum values of which occurred within 3 h after dosing. At 24 h, PRA and plasma Ang II concentrations were higher than those following placebo administration. A strong positive correlation between PRA and Ang II levels was noted (30). In healthy volunteers, 2.5–40 mg olmesartan medoxomil, administered at single doses, significantly inhibited the pressor response to exogenous Ang I (3). A dose-response relationship was observed, with relevant inhibition occurring at doses of 10 mg and above. The results of these two short-term studies are comparable with those of a large-scale (n = 792), placebo-controlled, dose-ranging study in patients with mild-to-moderate hypertension (3). In this phase-II study carried out over a 12-week period, olmesartan medoxomil demonstrated significant superiority over placebo at doses of 10–80 mg once daily.

The long-term effects of olmesartan medoxomil on hypertension and the RAS were investigated in an open-label uncontrolled study (9). Oral doses of 5–40 mg olmesartan medoxomil with upward titration were given to 26 hypertensive outpatients until adequate effects were observed. Systolic blood pressure (SBP) and DBP showed significant decreases at 2 weeks after start of administration and the responses were almost maximal at about 12 weeks. After 1 year of olmesartan medoxomil treatment, the decreases in SBP and DBP were 28.8 and 15.8 mm Hg, respectively. After 1 year of treatment, PRA had increased significantly, while plasma Ang I, and Ang II concentrations as well as plasma aldosterone concentration decreased.

Placebo-Controlled Studies

Integrated safety and efficacy data from 7 randomized, double-blind, placebo-controlled, parallel group phase-II and phase-III studies were analyzed by Neutel (26). Similarities in study design, inclusion and exclusion criteria, data collection method, and efficacy endpoint allowed the data to be pooled into one integrated analysis. In these studies, patients with essential hypertension were treated with olmesartan medoxomil once daily. Sitting DBP of the patients ranged from 100 to 115 mm Hg. Data from a total of 2145 patients were included in the efficacy analysis, and data from 2540 patients in the safety analysis (26). In general, the antihypertensive effect of olmesartan medoxomil was achieved within 1 week after the start of treatment, and the majority of patients showed maximal response within 2 weeks. At 10 mg olmesartan medoxomil was more effective than at smaller doses, and there was a clear dose-response relationship at doses of 10 to 80 mg (Fig. 3). There was no difference between efficacy in the younger group (<65 years old) and that in the older group (≤65 years old) of patients. The antihypertensive effect of olmesartan medoxomil was not affected by gender. There were no differences in the responder rates to the drug at 10 mg or higher doses and they were approximately 70%. Approximately 50% of patients can be expected to achieve a DBP of <90 mm Hg and approximately 40% of patients can be expected to achieve an SBP of <140 mm Hg. In general, the adverse event profiles of olmesartan medoxomil and placebo were similar. Dizziness occurred in 2.8% of the olmesartan medoxomil-treated patients and in 0.9% of the placebo-treated patients. Dizziness was the most common adverse event responsible for drug discontinuation, and treatment was discontinued in 0.2% of the olmesartan medoxomil-treated patients.

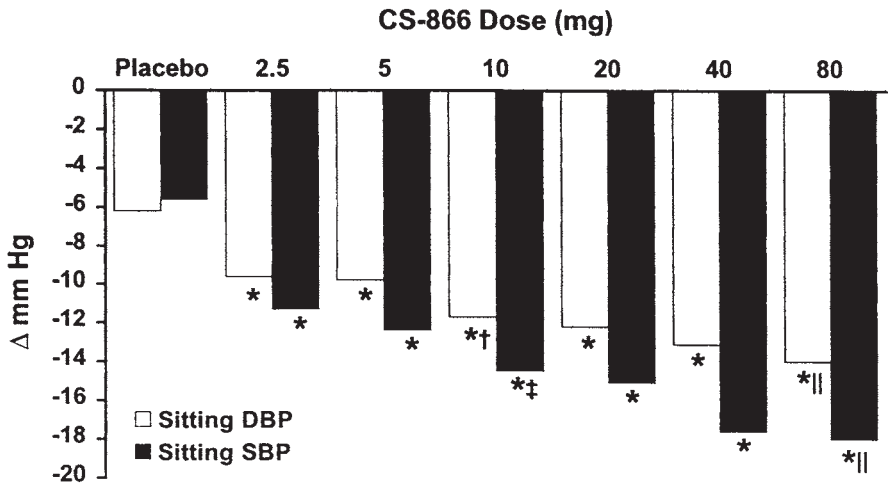

FIG. 3. Changes from baseline in least-squares mean trough sitting diastolic (DBP) and systolic (SBP) blood pressure in hypertensive patients treated with placebo, or with 1 of 6 doses of olmesartan medoxomil (CS-866). The data comprise an integrated analysis of efficacy from 7 studies. Post-treatment blood pressure values were taken at the primary study point of each study, which varied from 6 to 12 weeks after the initiation of treatment. *$p < 0.001$ vs. placebo; †$p \leq 0.019$ vs. 2.5 and 5 mg; ‡$p = 0.019$ vs. 2.5 mg; ‖$p \leq 0.050$ vs. 10 mg. Reproduced from ref. 26 with permission from Excerpta Medica, Inc.

Ambulatory blood pressure (ABP) was measured in 334 patients with moderate to severe essential hypertension (27). The patients were randomized to groups to receive a placebo; 5, 20 or 80 mg of olmesartan medoxomil once daily; or 2.5,10 or 40 mg of olmesartan medoxomil twice daily. ABP monitoring was performed prior to and after 8 weeks of treatment. Treatment with olmesartan medoxomil resulted in significant placebo-adjusted reductions in 24-h ambulatory SBP and DBP. At all comparable doses, reductions in mean SBP and DBP following once daily and twice daily dosing were not significantly different. The change in 24-h heart rate was small and not significant. In the once-daily group, placebo-adjusted trough-to-peak (T/P) ratios for SBP and DBP were 58–63 and 57–70%, respectively. These values of T/P ratio, with at least 50% of the peak effect remaining at the end of 24 h, indicate 24-h efficacy with a once-daily dose.

Comparative Trials with Other ARBs

A randomized, double-blind, parallel-group trial was carried out to assess the antihypertensive effects of four ARBs: olmesartan medoxomil, losartan potassium, valsartan, and irbesartan at recommended starting doses (28). A total of 588 essential hypertensive patients with cuff DBPs ranging from ≥100 to ≤115 mm Hg and mean daytime DBPs ranging from ≥90 to <120 mm Hg, as measured by ABP monitoring, were enrolled in this study. They were randomized to groups to receive once-daily administration of olmesartan medoxomil (20 mg/day), losartan potassium (50 mg/day), valsartan (80 mg/day) or irbesartan (150 mg/day) for 8 weeks. All drugs were provided at the starting doses recommended by the manufacturers. Cuff and ambulatory blood pressures were recorded at baseline and after 8 weeks of treatment. The primary efficacy variable was the mean

change from baseline in cuff DBP after 8 weeks of treatment. The secondary efficacy variables were the mean change from baseline in cuff SBP after 8 weeks of treatment and the mean change from baseline in 24-h ABP monitoring measurement of DBP and SBP after 8 weeks of treatment. Treatment with all four ARBs resulted in significant decreases in both cuff DBP and SBP from baseline after 8 weeks of treatment. However, treatment with olmesartan medoxomil resulted in a significantly greater reduction in cuff DBP (11.5 mm Hg) than did treatment with losartan potassium (8.2 mm Hg), valsartan (7.9 mm Hg) or irbesartan (9.9 mm Hg) (Table 3). Although differences were not statistically significant, treatment with olmesartan medoxomil resulted in a numerically greater reduction in cuff SBP (11.3 mm Hg) than did treatment with losartan potassium (9.5 mm Hg), valsartan (8.4 mm Hg) or irbesartan (11.0 mm Hg). The results of the 24-h ABP monitoring measurements were similar to those of cuff blood pressure measurements. The reductions in mean 24-h DBP and SBP obtained with olmesartan medoxomil were 8.5 and 12.5 mm Hg, respectively. These reductions were significantly greater than those obtained with losartan potassium (6.2 and 9.0 mm Hg, respectively) or valsartan (5.6 and 8.1 mm Hg, respectively) and numerically greater than those obtained with irbesartan (7.4 and 11.3 mm Hg, respectively). The T/P ratios for DBP and SBP in patients who received olmesartan medoxomil treatment were 0.68 and 0.69, respectively. These T/P ratios for DBP and SBP were numerically greater than or similar to those obtained with losartan potassium (0.69 and 0.64, respectively), valsartan (0.48 and 0.55, respectively) or irbesartan (0.60 and 0.62, respectively).

The efficacy of olmesartan medoxomil was compared with that of losartan potassium in patients with mild-to-moderate hypertension (mean sitting DBP, 95–114 mm Hg) (33). A total of 316 patients were randomized to groups to receive olmesartan medoxomil at a dose of 10 mg once daily or losartan potassium at a dose of 50 mg once daily. After 4 weeks, the dose was doubled if required, for up to 6 months, with addition of 12.5 or 25 mg hydrochlorothiazide (HCTZ) as necessary after week 12. Olmesartan medoxomil treatment resulted in significantly greater reductions in both DBP and SBP after 12 weeks

TABLE 3. Clinical efficacy trials comparing olmesartan medoxomil with other Ang II receptor blockers

Study (ref.)	Diagnosis	Duration	Regimen	Results of primary efficacy variable
Oparil et al. (28)	Essential hypertension Cuff DBP 100–115 mm Hg Mean day time DBP 90–120 mm Hg	8 weeks	Once-daily administration Olmesartan medoxomil 20 mg Losartan potassium 50 mg Valsartan 80 mg Irbesartan 150 mg	Changes in sitting cuff DBP –11.5 mm Hg –8.2 mm Hg –7.9 mm Hg –9.9 mm Hg
Stumpe and Ludwig (33)	Mild-to-moderate hypertension Sitting DBP 95–114 mm Hg	12 weeks	Once-daily administration Olmesartan medoxomil 10–20 mg Losartan potassium 50–100 mg	Changes in sitting DBP –10.6 mm Hg –8.5 mm Hg

DBP, diastolic blood pressure.

than losartan potassium treatment. The mean reductions in DBP in the olmesartan medoxomil group and losartan potassium group were 10.6 and 8.5 mm Hg, respectively (Table 3), and the mean reductions in SBP in the olmesartan medoxomil group and losartan potassium group were 14.9 and 11.6 mm Hg, respectively. The responder rates after 12 weeks were 63 and 52% in the olmesartan medoxomil group and losartan potassium group, respectively. The proportion of patients requiring dose titration and concomitant HCTZ therapy in the losartan potassium group was greater than that in the olmesartan medoxomil group.

Comparative Trials with Other Antihypertensive Drugs

Comparison with atenolol in patients with moderate-to-severe hypertension

The efficacy of olmesartan medoxomil was compared with that of atenolol, a β-adrenoceptor antagonist, in patients with moderate-to-severe hypertension (mean sitting DBP, 100–120 mm Hg) (1). A total of 328 patients receiving 25 mg of HCTZ and having completed a 4-week HCTZ run-in phase were enrolled in the study. The patients were randomized to groups to receive olmesartan medoxomil at 10 mg once daily plus HCTZ at 25 mg once daily or atenolol at 50 mg once daily plus HCTZ at 25 mg once daily. The dose was doubled after 4 weeks if required, for up to 12 weeks. After 12 weeks, decreases in sitting DBP were 17.3 and 17.2 mm Hg in the olmesartan medoxomil with HCTZ group and atenolol with HCTZ group, respectively (Table 4). Values for sitting SBP, a secondary variable, were also comparable (20.4 and 19.6 mm Hg, respectively). Significant decreases of about 12 mm Hg were achieved in both DBP and SBP after 2 weeks of treatment. Maximum decreases in blood pressure had essentially been reached by week 8. The responder rates after 12 weeks were 86.0% for patients receiving olmesartan medoxomil and 84.8% for patients receiving atenolol.

Comparison with Atenolol in Patients with Mild-to-Moderate Hypertension

The efficacy of olmesartan medoxomil was compared with that of atenolol in patients with mild-to-moderate hypertension (mean sitting DBP, 95–114 mm Hg) (33). After a 3-week placebo run-in phase, a total of 326 patients were randomized to groups to receive olmesartan medoxomil at a dose of 10 mg once daily or atenolol at a dose of 50 mg once daily. After 4 weeks, the dose was doubled for non-responders in each group. After 12 weeks, the mean changes in DBP in the two groups were comparable (Table 4). Olmesartan medoxomil treatment resulted in a significantly greater reduction in SBP after 4 weeks than did atenolol treatment (18.6 and 15.8 mm Hg, respectively), and the superiority was significant up to week 12. The responder rates after 12 weeks were 78% for patients receiving olmesartan medoxomil and 79% for patients receiving atenolol.

Comparison with Captopril in Patients with Mild-to-Moderate Hypertension

The efficacy of olmesartan medoxomil was compared with that of captopril, an ACE inhibitor, in patients with mild-to-moderate hypertension (mean sitting DBP, 95–114 mm Hg) (33). After a 3-week placebo run-in phase, a total of 291 patients were randomized to groups to receive olmesartan medoxomil at 5 mg once daily or captopril at 12.5 mg twice daily. The dose was doubled after 4 weeks and after 8 weeks if required, for up to 12 weeks. After 12 weeks, treatment with olmesartan medoxomil resulted in significantly greater reductions in both DBP (9.9 mm Hg) and SBP (14.7 mm Hg) than in pa-

TABLE 4. Clinical efficacy trials comparing olmesartan medoxomil with other antihypertensive drugs

Study (ref.)	Diagnosis	Duration	Regimen	Results
Ball et al. (1)	Moderate-to-severe hypertension Sitting DBP 100–120 mm Hg	12 weeks	Once-daily administration	Changes in sitting DBP
			Olmesartan medoxomil 10–20 mg + HCTZ 25 mg	–17.3 mm Hg
			Atenolol 50–100 mg + HCTZ 25 mg	–17.2 mm Hg
Stumpe and Ludwig (33)	Mild-to-moderate hypertension Sitting DBP 95–114 mm Hg	12 weeks	Once-daily administration	Changes in sitting DBP
			Olmesartan medoxomil 10–20 mg	–14.2 mm Hg*
			Atenolol 50–100 mg	–13.9 mm Hg*
Stumpe and Ludwig (33)	Mild-to-moderate hypertension Sitting DBP 95–114 mm Hg	12 weeks	Once-daily administration Olmesartan medoxomil 5–20 mg	Changes in sitting DBP –9.9 mm Hg
			Twice-daily administration Captopril 12.5–50 mg	–6.8 mm Hg
Stumpe and Ludwig (33)	Mild-to-moderate hypertension Sitting DBP 100–120 mm Hg	12 weeks	Once-daily administration	Changes in sitting DBP
			Olmesartan medoxomil 20–40 mg	–17.5 mm Hg
			Felodipine 20–40 mg	–17.0 mm Hg
Chrysant et al. (5)	Mild-to-moderate hypertension Sitting DBP 100–115 mm Hg	8 weeks	Once-daily administration	Changes in mean 24-h DBP
			Olmesartan medoxomil 20 mg	–7.7 mm Hg
			Amlodipine besylate 5 mg	–7.0 mm Hg
			Placebo	–1.4 mm Hg

DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide. *values of at 8 weeks.

tients treated with captopril (6.8 and 7.1 mm Hg, respectively) (Table 4). The superiority of olmesartan medoxomil treatment was already evident after 4 weeks. The responder rates after 12 weeks were 53% for patients receiving olmesartan medoxomil and 38% for patients receiving captopril. The number of olmesartan medoxomil-treated patients who needed the highest dose was smaller than the number of captopril-treated patients who needed the highest dose (25.0 and 54.9%, respectively).

Comparison with Felodipine in Patients with Mild-to-Moderate Hypertension

The efficacy of olmesartan medoxomil was compared with that of felodipine, a calcium antagonist, in patients with mild-to-moderate hypertension (mean sitting DBP, 100–120 mm Hg) (33). After a 3-week placebo run-in phase, a total of 381 patients were randomized to groups to receive olmesartan medoxomil at 20 mg once daily or felodipine at 5 mg once daily. The dose was doubled after 4 weeks for non-responders in each group. After 12 weeks, reductions in both DBP and SBP in the olmesartan medoxomil group (17.5 and 19.9 mm Hg, respectively) were similar to those in the felodipine group (17.0 and 19.1 mm Hg, respectively) (Table 4). The responder rates after 12 weeks were 82.8% for patients receiving olmesartan medoxomil and 83.3% for patients receiving felodipine. The percentages of patients in the olmesartan medoxomil group and in the felodipine group who were receiving a higher dose by week 12 were 31.7 and 39.6%, respectively.

Comparison with Amlodipine in Patients with Mild-to-Moderate Hypertension

The efficacy of olmesartan medoxomil was compared with that of amlodipine besylate, a calcium antagonist, in patients with mild-to-moderate hypertension (mean sitting DBP, 100–115 mm Hg) (5). After a 4-week placebo run-in phase, a total of 440 patients were randomized to groups to receive olmesartan medoxomil at 20 mg once daily, amlodipine besylate at 5 mg once daily, or placebo for 8 weeks. These doses were the recommended starting doses. The patients were evaluated by 24-h ABP monitoring and by seated cuff blood pressure measurement at trough. Both olmesartan medoxomil and amlodipine besylate induced significantly greater reductions in mean 24-h ambulatory DBP than that in the placebo group (7.7, 7.0, and 1.4 mm Hg, respectively) (Table 4) and significantly greater reductions in mean 24-h ambulatory SBP than that in the placebo group (12.2, 12.3, and 2.3 mm Hg, respectively). Similar to the ABP monitoring results, both olmesartan medoxomil and amlodipine besylate induced significantly greater reductions in seated cuff DBP than that in the placebo group (10.8, 10.1, and 3.6 mm Hg, respectively) and in significantly greater reductions in seated cuff SBP than that in the placebo group (10.3, 10.3, and 0.8 mm Hg, respectively). The placebo-adjusted T/P ratios for DBP with olmesartan medoxomil and amlodipine besylate were 0.7 and 0.8, respectively, suggesting that both drugs were effective with a once-daily dose. Significantly more patients in the olmesartan medoxomil group achieved the more rigorous SBP goal of <130 and the more rigorous DBP goal of <85 mm Hg. Amlodipine besylate was associated with a numerically higher incidence of edema compared with olmesartan medoxomil and placebo (9.1, 4.3, and 4.5%, respectively).

ANIMAL STUDIES

Organ protective effects of olmesartan in animal models are summarized in Table 5.

Vasculoprotective effects

Endothelial dysfunction in aged rats was caused primarily by increased production of vasoconstricting eicosanoids derived from cyclooxygenase (COX)-2 and of super oxide anion. Inhibition of the RAS with olmesartan medoxomil or temocapril, an ACE inhibitor,

TABLE 5. Organ protective effects of olmesartan in animal models

Study (ref.)	Animal model	Organ protective effects
Vasculoprotection		
Mukai et al. (23)	Aged Wistar-Kyoto rats (12-month-old)	Amelioration of endothelial dysfunction
Koike et al. (15)	Cynomolgus monkeys fed a high-cholesterol diet	Reduction in the atherosclerotic lesion area
Koike et al. (15)	Watanabe heritable hyperlipidemic rabbits	Reduction in the atherosclerotic lesion area
Miyazaki and Takai (20)	Monkeys fed a high-cholesterol diet	Reduction in the atherosclerotic lesion area and intimal area, and improvement in relaxation response of carotid arteries
Kim et al. (13)	Balloon-injured rat carotid arteries	Prevention of intimal thickening
Liu et al. (19)	Polyethylene cuff placement around mouse femoral arteries	Inhibition of neointima formation
Cardioprotection		
Nakamura et al. (24)	Rats with myocardial infarction	Amelioration of heart weights, hemodynamics and ventricular dimensions
Taniyama et al. (36)	Cardiomyopathic hamsters	Inhibition of myocardial fibrosis
Jia et al. (12)	Stroke-prone SHR	Reductions in cardiac hypertrophy
Koike et al. (15)	Rats with myocardial infarction	Improvement of the survival rate at the higher dose
Koike et al. (15)	Rats with an aorto-caval shunt	Reductions in cardiac hypertrophy and LVEDP
Koike et al. (15)	Rats with pulmonary hypertension	Improvement of the survival rate
Koike et al. (15)	SHR	Reduction in cardiac hypertrophy
Takemoto et al. (35)	Chronic inhibition of nitric oxide synthesis in rats	Attenuation of cardiovascular remodeling
Renoprotection		
Mizuno et al. (22)	Zucker diabetic fatty rats	Suppression of proteinuria, glomerular sclerosis, and tubular injury
Nangaku et al. (25)	Spontaneously hypertensive/NIH-corpulent rats	Suppression of proteinuria and segmental glomerulosclerosis
Yoshida et al. (44)	SHR with five-sixth nephrectomy	Suppression of proteinuria, glomerular sclerosis, and relative interstitial volume
Other organ protection		
Kurikawa et al. (16)	Ligation of the common bile duct in rats	Improvement of liver fibrosis
Iwasaki et al. (11)	Sciatic nerve transection in rats	Prevention of the death of spinal motor neurons

SHR, spontaneously hypertensive rats; LVEDP, left ventricular end-diastolic pressure.

effectively ameliorated endothelial dysfunction in aged aortae by decreasing the production of vasoconstricting eicosanoids and superoxide (23). Inhibition of the RAS suppressed the increase in expression level of COX-2 in the aortae of aged rats (23). Therefore, inhibition of the RAS may be an effective strategy for treating aging-related endothelial dysfunction in humans.

Antiatherosclerotic effects of olmesartan medoxomil were examined in monkeys (15). Olmesartan medoxomil was administered orally at 1 or 10 mg/kg/day to male cynomolgus monkeys fed a high-cholesterol diet (4% cholesterol and 6% corn oil) for 6 months. Control monkeys received a normal cholesterol diet. Treatment and diet were initiated simultaneously. SBPs measured 6 months after the start of treatment were 111 ± 5, 112 ± 5, 110 ± 5, and 109 ± 4 mm Hg in the vehicle, low-dose olmesartan medoxomil, high-dose olmesartan medoxomil, and normal cholesterol diet groups, respectively. Plasma total cholesterol concentrations in these groups were 606 ± 49, 534 ± 32, 536 ± 45, and 112 ± 17 mg/dL, respectively. Despite the similarities in blood pressures and plasma cholesterol concentrations, treatment with olmesartan medoxomil reduced the size of the atherosclerotic lesion area in the aorta dose-dependently, the reduction in the high-dose group being 65% (15).

In another study, monkeys (*Macaca fascicularis*) were fed a high-cholesterol diet (4% cholesterol and 6% corn oil) for 6 months (20). Half of the monkeys received olmesartan medoxomil (10 mg/kg/day, orally) and the remaining half of them received the high-cholesterol diet only. A control group received a normal diet (20). The level of low-density lipoprotein (LDL) cholesterol was increased by the high-cholesterol diet, whereas the level of high-density lipoprotein (HDL) cholesterol was decreased. Olmesartan medoxomil did not affect the cholesterol levels in the monkeys fed a high-cholesterol diet. Atherosclerotic lesions in the thoracic aortae were not observed in the normal-diet group. In the high-cholesterol diet group, the mean atherosclerotic lesion area was 72%, and treatment with olmesartan medoxomil significantly reduced the atherosclerotic lesion area to 25%. Olmesartan medoxomil also significantly reduced the intimal area and the ratio of intimal area to medial area. The relaxation response of isolated carotid arteries to acetylcholine was suppressed in the high-cholesterol group, but this was improved by olmesartan medoxomil. Olmesartan medoxomil inhibited the accumulation of macrophages in the intimal layer and suppressed serum levels of transforming growth factor-β1 (TGF-β1), macrophage colony-stimulating factor and intracellular adhesion molecule-1.

Olmesartan medoxomil, both alone and in combination with pravastatin (an HMG-CoA reductase inhibitor), was given to Watanabe heritable hyperlipidemic (WHHL) rabbits (15). The WHHL rabbit is a genetic model of hyperlipidemia with elevated plasma LDL that develops atherosclerosis from an early age. WHHL rabbits were treated with olmesartan medoxomil (1 mg/kg, orally), pravastatin (50 mg/kg/day, orally), or the combination of both for 32 weeks beginning at the age of 2 to 3 months. Olmesartan medoxomil reduced the atherosclerotic lesion area in the aorta without lowering plasma total cholesterol level (670 ± 28 in the vehicle group and 659 ± 38 mg/dL in the olmesartan medoxomil group). Olmesartan medoxomil tended to reduce intimal thickening. Pravastatin, on the other hand, did not reduce the atherosclerotic lesion area but lowered plasma total cholesterol level (437 ± 27 mg/dL, $P < 0.01$). The combination of olmesartan medoxomil and pravastatin did not further reduce plasma total cholesterol level compared with that in the group given pravastatin alone. However, the combination of both drugs induced a greater

reduction in atherosclerotic lesion area than did olmesartan medoxomil alone and significantly suppressed intimal thickening.

Effects of olmesartan medoxomil, temocapril, and their combination on neointimal hyperplasia in balloon-injured rat carotid arteries were compared (13). Olmesartan medoxomil (5, 10, or 20 mg/kg/day), temocapril (10, 20, or 40 mg/kg/day), or a combination of olmesartan medoxomil (10 mg/kg/day) and temocapril (20 mg/kg/day) were given to rats orally from 3 days before balloon injury until 14 days after balloon injury. The maximal preventive effects of olmesartan medoxomil and temocapril on arterial intimal thickening were obtained at doses of 10 and 20 mg/kg/day, respectively. Compared with either drug alone, however, the combination of olmesartan medoxomil and temocapril prevented intimal thickening to a large extent. Furthermore, compared with either drug alone, the combination of the two drugs prevented vascular smooth muscle cell proliferation in the intima more effectively (13). The results suggest that either bradykinin or nitric oxide contributes to the beneficial effects of the combination therapy.

It is known that placement of a polyethylene cuff around the femoral artery of a mouse induces neointima formation and DNA synthesis in the artery. In this model, olmesartan medoxomil and estrogen synergistically attenuated vascular remodeling. This was accompanied by marked inhibition of extracellular signal-regulated kinase (ERK) and signal transducer and activator of transcription (STAT) activity (19). These findings provided insights into the negative crosstalk between the actions of estrogen and Ang II *in vivo*. A combination of ARB and estrogen replacement might be a useful and effective therapy for the treatment of cardiovascular diseases associated with menopause.

Cardioprotective Effects

Myocardial infarction (MI) frequently produces left ventricular (LV) dilatation associated with myocyte hypertrophy and interstitial fibrosis of the noninfarcted myocardium. These changes in LV geometry, referred to as remodeling, contribute to the development of depressed cardiac performance and subsequent cardiovascular events. Olmesartan medoxomil (1 or 10 mg/kg/day), temocapril (3 or 30 mg/kg/day), or a combination of olmesartan medoxomil and temocapril (0.5 or 5 and 1.5 or 15 mg/kg/day, respectively) was administered to rats after MI (24). MI was produced by ligation of the left coronary artery. At 4 weeks after MI, all tested drugs lowered mean blood pressure in rats. LV end-diastolic pressure (LVEDP) and right ventricular (RV) weight were significantly higher in rats with MI than in control rats. LV end-diastolic dimension (LVDD) and LV end-diastolic volume (LVEDV) were significantly increased and LV ejection fraction (LVEF) was significantly decreased in rats with MI compared to control rats. Treatment with olmesartan medoxomil, temocapril, or a combination of the two drugs ameliorated heart weights, hemodynamics and dimensions to the same extent. However, the combination of the two drugs suppressed atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and other gene expression related to contractile proteins of fetal type and collagens more effectively than did either drug alone (24). These findings suggest that a combination of olmesartan medoxomil and temocapril, independent of the hemodynamic effect, improves left ventricular phenotypic change, collagen accumulation and diastolic function.

In another study, rats underwent left coronary artery ligation and were treated with either temocapril (5 mg/kg/day) or a vehicle for 2 weeks (34). The rats treated with temocapril were further randomly assigned to groups to receive either high-dose temocapril

(10 mg/kg/day) or a combination of temocapril and olmesartan medoxomil (5 and 2.5 mg/kg/day, respectively) for another 6 weeks. Both treatments significantly and equally reduced blood pressure, improved survival and ameliorated LV enlargement. Several parameters of LV systolic and diastolic function, however, were significantly ameliorated by the high-dose temocapril but not by the combination therapy (34).

Twelve-week-old cardiomyopathic hamsters were treated with a vehicle, olmesartan medoxomil (1 or 10 mg/kg/day), temocapril (20 mg/kg/day), or hydralazine (8 mg/kg/day) up to 20 weeks of age (36). Control Bio F1b hamsters were also treated with a vehicle. Cardiac fibrotic area and mRNA level of collagen III were increased in the cardiomyopathic hamsters compared with those in the control hamsters. On the other hand, cardiac hepatocyte growth factor (HGF) mRNA expression and HGF concentration were significantly decreased in the cardiomyopathic hamsters compared with the control hamsters. Treatment of cardiomyopathic hamsters with olmesartan medoxomil, temocapril or hydralazine decreased blood pressure compared with that in the vehicle-treated hamsters. Administration of olmesartan medoxomil or temocapril resulted in significant inhibition of myocardial fibrosis compared with that in the vehicle-treated hamsters (36). Cardiac HGF mRNA expression and HGF concentration were significantly increased and mRNA expression of collagen III was markedly decreased in cardiomyopathic hamsters treated with olmesartan medoxomil or temocapril compared with those in the vehicle-treated hamsters. In contrast, hydralazine treatment did not affect fibrotic area or cardiac HGF concentration (36). These findings suggest that Ang II blockade prevented myocardial fibrosis in cardiomyopathic hamsters, accompanied by a significant increase in cardiac HGF production.

Olmesartan medoxomil (10 mg/kg/day), temocapril (10 mg/kg/day), or a combination of the two drugs (3 mg/kg/day for both) were administered to stroke-prone spontaneously hypertensive rats (SHRSP) from 6 to 12 weeks of age (12). A control group received a vehicle only. Treatments with olmesartan medoxomil, temocapril, and a combination of the two drugs significantly and similarly reduced SBP. The reduction in cardiac hypertrophy, however, was greater in SHRSP treated with olmesartan medoxomil or a combination of the two drugs than in the animals treated with temocapril only (12). The mRNA levels of ANP, AT_1 receptor, and integrin β_1 (a cell surface receptor linked to cardiac hypertrophy and the development of cardiomyopathy) were significantly higher in vehicle-treated SHRSP than in normotensive Wistar-Kyoto rats (WKY). All active treatments reduced mRNA levels of ANP, AT_1 receptor, and integrin β_1 in SHRSP. Olmesartan medoxomil and a combination of olmesartan medoxomil and temocapril produced greater reductions in the mRNA levels than did temocapril (12).

Koike et al. demonstrated cardioprotective effects of olmesartan medoxomil in a series of experiments (15). The effects of olmesartan medoxomil on long-term survival rate of rats that had undergone coronary ligation were examined. Olmesartan medoxomil mixed in the diet (0.001 or 0.01%; approximately equivalent to 0.5 or 5 mg/kg/day, respectively) was given to rats with MI for 9 months. At the higher (but not lower) dose olmesartan medoxomil improved the survival rate (15). Rats with an aorto-caval shunt, a high output heart failure model, were treated with olmesartan medoxomil (3 or 10 mg/kg) or a vehicle for 4 weeks. LVEDP was elevated in the vehicle-treated rats compared with the sham-operated rats and was decreased in rats treated with both the lower and higher doses of olmesartan medoxomil. LV hypertrophy developed in the vehicle treated rats, but was sup-

pressed by the 4-week treatment with olmesartan medoxomil. LV*dp/dt* was unchanged despite the reduced LVEDP in the olmesartan medoxomil-treated groups, suggesting that olmesartan medoxomil improved cardiac function in this heart failure model (15). A single subcutaneous administration of monocrotaline (MCT), a plant alkaloid, produces pulmonary hypertension and, hence, right heart failure and ultimately death. MCT injection in rats caused death from 21 days after injection and all rats had died within 30 days. Administration of olmesartan medoxomil (3 or 10 mg/kg/day) 7 days after MCT injection resulted in a dose-related prolongation of the time to death. The survival rate 37 days after MCT injection was as high as 90% in rats treated with the higher-dose olmesartan medoxomil (15). Sixteen-week-old SHR were treated with olmesartan medoxomil (0.3 or 1 mg/kg/day) for 6 weeks, and age-matched WKY were used as controls. Heart weight-to-body weight (HW/BW) ratio in the vehicle-treated SHR was much greater than that in the WKY. Chronic treatment with olmesartan medoxomil reduced the HW/BW ratio dose-dependently (15).

Chronic inhibition of nitric oxide (NO) synthesis with N^{ω}-nitro-L-arginine methyl ester (L-NAME) induces myocardial remodeling (hypertrophy/fibrosis), vascular remodeling (medial thickening/perivascular fibrosis), and hypertension in animals. Cardiovascular remodeling in rats induced by chronic inhibition of NO synthesis was attenuated by chronic treatment with olmesartan medoxomil mixed in the diet (7.5 or 75 μg/g) (35).

Renoprotective Effects

Renoprotective effects of olmesartan medoxomil were examined in Zucker diabetic fatty (ZDF) rats, an animal model of type 2 diabetes (22). Beginning at 12 weeks of age, olmesartan medoxomil mixed in the diet (0.001 or 0.01%; approximately equivalent to 0.6 or 6 mg/kg/day, respectively) was administered to ZDF rats for 19 weeks. Another group of ZDF rats served as vehicle controls, and lean non-diabetic rats were used as controls. ZDF rats developed progressive hyperglycemia, hyperinsulinemia, proteinuria, glomerulosclerosis, and moderate hypertension. Plasma glucose, insulin concentration, and body weight were not affected by either dose of olmesartan medoxomil, but SBP was lowered significantly by the higher dose of olmesartan medoxomil. Progressive proteinuria in ZDF rats was suppressed by both the lower and higher doses of olmesartan medoxomil (about 30 and 70%, respectively). Hyperlipidemia and hypoalbuminemia in ZDF rats were substantially corrected by the treatment with olmesartan medoxomil. Extensive glomerular sclerosis and tubular injury were present in the vehicle-treated ZDF rats, and both of these histological changes were significantly suppressed by treatment with olmesartan medoxomil (22). These results suggest that olmesartan medoxomil could be an effective agent for the prevention and treatment of nephropathy in type 2 diabetes.

The spontaneously hypertensive/NIH-corpulent rat [SHR/NDmc-cp (fat/fat)] is another animal model of type 2 diabetes that develops diabetic nephropathy. Beginning at 13 weeks of age, olmesartan medoxomil (1 or 5 mg/kg/day) was administered to SHR/NDmc-cp (fat/fat) for 20 weeks (25). Control SHR/NDmc-cp (fat/fat) received a vehicle only. Age-matched SHR (hypertensive, nondiabetic) were treated with olmesartan medoxomil or the vehicle (25). Compared with SHR, SHR/NDmc-cp (fat/fat) were obese and had developed hyperglycemia with hyperinsulinemia and hyperlipidemia. Plasma glucose, insulin concentration, and body weight were not affected by olmesartan medoxomil. Olmesartan medoxomil lowered SBP dose-dependently. The higher dose of

olmesartan medoxomil corrected hyperlipidemia. At the end of the study, proteinuria in SHR/NDmc-cp (fat/fat) was suppressed by both the lower and higher doses of olmesartan medoxomil (about 33 and 57%, respectively). Control SHR developed mild proteinuria, which was significantly reduced by olmesartan medoxomil. Segmental glomerulosclerosis was observed only in a small number of glomeruli in SHR. Much more severe segmental glomerulosclerosis was present in the vehicle-treated SHR/NDmc-cp (fat/fat) and was dose-dependently suppressed by olmesartan medoxomil (19 and 48% reduction for the lower and higher doses, respectively) (25). 4-hydroxynonenal-protein adduct, an oxidative protein product generated during lipid peroxidation, was not detected in glomeruli of SHR, but it accumulated in glomeruli of the vehicle-treated SHR/NDmc-cp (fat/fat). The higher dose of olmesartan medoxomil abolished the accumulation of 4-hydroxynonenal-protein adduct in glomeruli. Pentosidine, an advanced glycation end product, accumulated in the glomeruli and arterial wall of the vehicle-treated SHR/NDmc-cp (fat/fat) to a greater extent than in SHR. The higher dose of olmesartan medoxomil reduced pentosidine content in both tissues (25). In the SHR/NDmc-cp (fat/fat), the renal pentosidine content was significantly correlated with proteinuria and with SBP. These results suggest that prevention of diabetic nephropathy might depend not only on the reduction in blood pressure but also on the inhibition of protein modifications induced by advanced glycation.

Organ protective effects of olmesartan medoxomil and temocapril, alone or in combination, were examined in a remnant kidney rat model (44). When renal mass is reduced in rats, the remaining nephrons undergo hypertrophy, with a concomitant increase in glomerular plasma flow and an increase in glomerular capillary pressure. Eight-week-old male SHR were subjected to five-sixth nephrectomy. At the age of 10 weeks, the rats were randomly allocated to groups that received two doses of olmesartan medoxomil (3 or 10 mg/kg/day), temocapril (10 mg/kg/day), olmesartan medoxomil plus temocapril (3 and 10 mg/kg/day, respectively), or a vehicle alone as an untreated control group. The treatments were continued for up to 18 weeks of age. All drug treatments significantly reduced SBP, proteinuria, glomerular sclerosis index (GSI), relative interstitial volume (RIV) and heart weight. The hypotensive effects were in the following order: combination therapy > high-dose olmesartan medoxomil = temocapril > low-dose olmesartan medoxomil. Proteinuria, GSI and RIV were found to be highly correlated with SBP among the individual rats pooled from all groups, and the correlation was maintained among the group means. A similar correlation was found between heart weight and SBP. The results suggest that the organ protective effects of olmesartan medoxomil, temocapril, or a combination of the two drugs are closely related to the magnitude of their antihypertensive effects (44).

Protective Effects on Other Organs

Ligation of the common bile duct induces liver fibrosis in rats. Liver fibrosis is characterized by excess production of extracellular matrix (ECM), and hepatic stellate cells (HSCs) are a major source of the ECM. Starting one week after bile duct ligation, rats were treated with olmesartan medoxomil (1 mg/kg/day) or a vehicle for 2 weeks (16). Treatment with olmesartan medoxomil significantly reduced the fibrotic area of the liver, the liver hydroxyproline content, an index of liver collagen accumulation, the mRNA expression of collagen I and α-smooth muscle actin (α-SMA), as well as the plasma levels of TGF-β1. Interestingly, AT_1 receptors were expressed in α-SMA-positive cells in the fibro-

tic area of the liver. Treatment with olmesartan medoxomil reduced the number of these cells. In rat primary HSCs, treatment with Ang II-induced proliferation and collagen synthesis and upregulated the profibrogenic cytokines, TGF-β1 and connective tissue growth factor. Olmesartan blocked all of these effects of Ang II (16). These results suggest that olmesartan medoxomil may act as a potent antifibrotic drug in this model of liver fibrosis.

Experiments have been carried out to determine whether olmesartan has neurotrophic effects on spinal motor neurons *in vitro* and *in vivo* (11). Olmesartan increased the neurite outgrowth and choline acetyltransferase activity in primary explanted cultures of ventral spinal cords of fetal rats. This neurite promoting effect was dose-dependent. *In vivo* experiments also demonstrated that treatment with olmesartan (1, 5, or 10 mg/kg/day, intraperitoneally) for 14 consecutive days prevented the death of spinal motor neurons caused by sciatic nerve transection in rats (11). These findings suggest a potential therapeutic use of olmesartan in treating diseases that involve degeneration and death of motor neurons.

SUMMARY AND CONCLUSIONS

Olmesartan medoxomil is an orally active, potent and selective prodrug-type ARB. It is rapidly de-esterified during absorption to form olmesartan, the active metabolite. Olmesartan is not metabolized by the cytochrome P-450 and has a dual route of elimination by the kidney and liver. Dosage adjustment is not necessary in patients with mild-to-moderate renal impairment or patients with mild liver impairment. In head-to-head clinical studies, olmesartan medoxomil has been shown to be more effective than other ARBs when administered at recommended starting doses. The antihypertensive effect of olmesartan medoxomil is comparable or superior to those of other classes of antihypertensive agents. Olmesartan medoxomil is well tolerated and has a good safety profile similar to that of placebo. In animal models of atherosclerosis, chronic renal diseases and various types of heart diseases, olmesartan medoxomil has demonstrated a wide range of organ protective effects. These effects in animal models are promising, and future investigation should reveal their applicability to human diseases.

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