Strategies to Meet Lower Blood Pressure Goals With a New Standard in Angiotensin II Receptor Blockade

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The continued poor rates of blood pressure (BP) control to the recommended target BP of <140/90 mm Hg in patients with hypertension indicate a persistent need for improved antihypertensive therapy. Angiotensin II receptor blockers (ARBs) constitute the newest approved class of antihypertensive agents. As with angiotensin converting enzyme inhibitors, ARBs block the renin-angiotensin-aldosterone system, but do so through a more specific mechanism.

Angiotensin converting enzyme inhibitors block the conversion of angiotensin I to angiotensin II, but angiotensin II may be produced by several alternate pathways. Angiotensin II receptor blockers, by contrast, inhibit the binding of angiotensin II to the angiotensin II type 1 (AT1) receptor, independent of the pathway of angiotensin II production. Comparative safety and efficacy trials indicate that ARBs are similar to other antihypertensive drugs in terms of BP-lowering effectiveness and have superior tolerability.

Olmesartan medoxomil is the newest and one of the most effective of the ARBs. In controlled trials, it has been shown to provide 24-h BP control with antihypertensive efficacy at least as good as that of the calcium channel blockers amlodipine besylate and felodipine and the β-blocker atenolol. In a comparative study, olmesartan medoxomil demonstrated significantly greater reductions in diastolic BP than did three other leading ARBs—losartan potassium, irbesartan, and valsartan.

With the convenience of placebo-like tolerability and once-daily dosing, combined with excellent antihypertensive efficacy, olmesartan medoxomil may be a useful addition to our management of hypertension. Am J Hypertens 2002;15:108S–114S © 2002 American Journal of Hypertension, Ltd.

Key Words: Hypertension, olmesartan medoxomil, angiotensin II receptor blockers.
mortality that is independent of their BP-lowering effect.\textsuperscript{15–18}

Olmesartan medoxomil is the newest of the ARBs. This recently approved agent has been shown in clinical trials to have a safety and tolerability profile similar to that of placebo, as well as antihypertensive efficacy at least as good as that of drugs in other antihypertensive classes.\textsuperscript{19,20} Olmesartan medoxomil has also been shown to have antihypertensive efficacy superior to that of other ARBs.\textsuperscript{19,21} As one of the most effective agents in a promising class of drugs, olmesartan medoxomil may be useful for helping clinicians to meet increasingly aggressive standards for treatment of hypertension.

\section*{Mechanism of Action}

As an ARB, olmesartan medoxomil lowers BP by blocking the action of angiotensin II (Ang II), the main peptide effector of the renin-angiotensin-aldosterone system (RAAS).\textsuperscript{22} High plasma renin activity is well known as a major risk factor for hypertension and for cardiovascular and renal morbidity and mortality.\textsuperscript{13}

The RAAS is an enzymatic cascade involving the conversion of angiotensinogen to angiotensin I and angiotensin I to Ang II, a potent vasoconstrictor.\textsuperscript{13,23} Angiotensin II can bind to several receptors, most notably the angiotensin II type 1 (AT\textsubscript{1}) and angiotensin II type 2 (AT\textsubscript{2}) receptors. The AT\textsubscript{1} receptor is known to mediate virtually all of the deleterious actions of Ang II; the role of the AT\textsubscript{2} receptor, however, is poorly understood.\textsuperscript{13,23,24}

The effects of inhibiting the RAAS were first demonstrated with the use of angiotensin converting enzyme (ACE) inhibitors, which block the enzyme principally responsible for converting angiotensin I to Ang II.\textsuperscript{13} Angiotensin converting enzyme inhibitors have been found to lower BP significantly while providing greater target organ protection than that of agents in other leading antihypertensive drug classes.\textsuperscript{1,25–30} However, Ang II can be generated by other pathways.\textsuperscript{27} Moreover, ACE inhibitors inhibit the breakdown of plasma bradykinin, thereby promoting the accumulation of bradykinin, which may be associated with two common adverse effects associated with ACE inhibitor therapy: a dry cough and increased risk of angioedema.

Olmesartan medoxomil selectively blocks the binding of Ang II to the AT\textsubscript{1} receptor, thereby reducing vascular resistance and lowering BP (Fig. 1).\textsuperscript{24,31} Angiotensin II may continue to bind with the AT\textsubscript{2} receptor, which may further counteract the harmful effects of AT\textsubscript{1} receptor stimulation.\textsuperscript{24,32} This mechanism of action provides more specific and potentially more complete RAAS blockade than does ACE inhibitor therapy.\textsuperscript{33}

The inhibition of Ang II–induced contractions has been studied in aortas isolated from male Hartley guinea pigs; this is an excellent model for in vitro study of the Ang II antagonism characteristics of a particular agent. In one study, olmesartan medoxomil markedly reduced maximal Ang II–induced contractions in isolated guinea pig aortas in a dose-dependent manner, with little shift to the right of the concentration–response curve (Fig. 2).\textsuperscript{33} These results indicate noncompetitive inhibition of Ang II by olmesartan medoxomil in vascular tissue.

\section*{Pharmacokinetics}

Olmesartan medoxomil is an ARB with linear pharmacokinetics over a wide dose range.\textsuperscript{33,34} Olmesartan medoxomil is a prodrug; after oral administration, it rapidly undergoes de-esterification within the intestinal wall to release its active metabolite, olmesartan.\textsuperscript{34} Only the active metabolite is detected in plasma.\textsuperscript{35} After this hydrolytic process, olmesartan is not metabolized further. It is the only compound detected in urine and feces\textsuperscript{36}: about 35\% to 50\% of the absorbed dose is excreted in urine; the remainder undergoes elimination through the biliary tract and is excreted through feces.\textsuperscript{34} The bioavailability of

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\caption{Effect of olmesartan medoxomil on the renin-angiotensin system. Olmesartan medoxomil lowers blood pressure (BP) by selectively blocking the binding of angiotensin II to the angiotensin II type 1 (AT\textsubscript{1}) receptor. This decreases vasoconstriction and aldosterone secretion, leading to a decrease in vascular resistance.\textsuperscript{24,31} ACE = angiotensin converting enzyme; AT\textsubscript{2} = angiotensin II type 2 receptor.}
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\begin{figure}[h]
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\includegraphics[width=\textwidth]{fig2.png}
\caption{Effects of olmesartan on angiotensin II (Ang II)–induced contractions of guinea pig aorta. Olmesartan caused a marked reduction in the strength of Ang II–induced contractions in isolated guinea pig aorta. These results show slow reversibility of Ang II receptor antagonism by olmesartan in vascular tissue. (Reprinted from Mizuno M, et al: Pharmacology OT CS-866, a novel nonpeptide angiotensin II receptor antagonist. Eur J Pharmacol 1995;285:181–188. Copyright 1995, with permission from Elsevier Science.\textsuperscript{33})}
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olmesartan is approximately 25%; relatively low variability is observed for this parameter. More than 99% of a dose binds with serum albumin, >96% with α1-acid glycoproteins, and <14% with human globulin. Administration of olmesartan medoxomil in single daily doses of up to 80 mg for 10 days did not result in drug accumulation. T\textsubscript{max} is achieved in approximately 2 h.

Compared with many of the other ARBs, olmesartan has a long half-life (approximately 13 h), and it can be taken with or without meals. It is not metabolized by the hepatic cytochrome P450 enzyme system; thus, the risk of drug interactions is reduced. No clinically significant pharmacokinetic interactions were observed in studies of olmesartan medoxomil coadministered with digoxin or warfarin. Neutralization of gastric pH with antacids also did not significantly reduce the bioavailability of olmesartan medoxomil.

**Efficacy and Safety Versus Placebo**

Efficacy and safety data for olmesartan medoxomil were pooled from seven randomized, double-blind, placebo-controlled, parallel-group Phase II and Phase III studies involving 2693 subjects, 2145 of whom were included in an efficacy analysis. All were multicenter studies conducted in Europe and the US.

Enrolled subjects were men and women ≥18 years of age with a diagnosis of essential hypertension and a seated systolic blood pressure (SeSBP) of ≥100 mm Hg to ≤115 mm Hg. The primary efficacy variable for all studies was the mean change from baseline in mean trough SeDBP at the study end point, which varied from 6 to 12 weeks. Secondary variables included the change from baseline in trough seated systolic BP (SeSBP), heart rate, trough standing diastolic BP (DBP) and systolic BP (SBP), mean 24-h DBP and SBP, and responder rate (SeDBP <90 mm Hg or at least a 10-mm Hg reduction from baseline in SeDBP). Of the 2693 subjects enrolled, 2145 received olmesartan medoxomil and 548 received placebo.

The mean change from baseline in both SeDBP and SeSBP was significantly greater than for placebo in all olmesartan medoxomil–treated groups (P < .001). The degree of BP reduction was dose dependent (Fig. 3). The reduction in mean SeDBP from baseline to the primary study time point was 6.2 mm Hg for placebo, 9.8 mm Hg for olmesartan medoxomil 5 mg, 12.2 mm Hg for olmesartan medoxomil 20 mg/day, and 13.1 mm Hg for olmesartan medoxomil 40 mg/day. The mean reductions in mean SeSBP from baseline to the primary study time point were 5.6 mm Hg for placebo, 12.4 mm Hg for olmesartan medoxomil 5 mg/day, 15.1 mm Hg for olmesartan medoxomil 20 mg/day, and 17.6 mm Hg for olmesartan medoxomil 40 mg/day.

The antihypertensive response to olmesartan medoxomil was evident within the first week of treatment, and the majority of the antihypertensive responses were produced within 2 weeks of initiation of treatment. These results were generally consistent across sex and age categories.

In the safety analysis, 2540 subjects received olmesartan medoxomil and 555 were given placebo. The adverse event (AE) rates were similar for the two groups: 42.2% of subjects in the olmesartan medoxomil treatment group and 42.7% of those in the placebo group experienced at least one treatment-emergent AE. Most of the events were mild and were judged by investigators to be unrelated to treatment. There was no relationship between the AE rate and the olmesartan medoxomil dose.

In one of the placebo-controlled trials, the effect of once-daily versus twice-daily dosing of olmesartan medoxomil was assessed over 24 h via ambulatory blood pressure monitoring (ABPM). Based on ambulatory BP measurements, olmesartan medoxomil 20 mg (10 mg twice daily or 20 mg once daily) produced a trough:peak ratio of 63%. Furthermore, it was effective in reducing both DBP (Fig. 4) and SBP over the entire 24-h period, whether given as 10 mg twice daily or as 20 mg once daily. Both olmesartan medoxomil dosing regimens reduced ambulatory DBP and SBP significantly compared with placebo (P < .001), and twice-daily dosing provided no clinical advantage over once-daily dosing. These results support once-daily dosing with olmesartan medoxomil.

**Efficacy Versus Other Drug Classes**

In clinical trials, olmesartan medoxomil provided similar BP-lowering efficacy compared with other leading antihypertensive agents.
Olmesartan Medoxomil Versus Atenolol

In a randomized, double-blind, 12-week comparison study, subjects (n = 326) with mild-to-moderate essential hypertension (SeDBP 95 to 114 mm Hg) were given olmesartan medoxomil 10 mg/day (n = 165) or the β-blocker atenolol 50 mg/day (n = 161). Doubling of the dose of either drug was allowed if the DBP was ≥90 mm Hg, if DBP decreased by <10 mm Hg, or both. The primary end point was the change in mean trough SeDBP from baseline to Week 12.

The reduction in SeDBP was similar for the olmesartan medoxomil group (14.0 mm Hg) and the atenolol group (14.3 mm Hg). The reduction in SeSBP was significantly greater (P = .05) in subjects given olmesartan medoxomil (20.7 mm Hg) than in subjects given atenolol (17.2 mm Hg). About one third of the subjects in each treatment group required up titration to the higher dose to reach BP goals.

Olmesartan Medoxomil Versus Amlodipine Besylate

In this double-blind, multicenter study, subjects (n = 440) with mild-to-moderate hypertension (SeDBP, 100–115 mm Hg; daytime ambulatory DBP [ADBP] 90–119 mm Hg) were randomized to 8 weeks of therapy with placebo (n = 66), the calcium channel blocker amlodipine besylate 5 mg (n = 186), or olmesartan medoxomil 20 mg (n = 188). The primary end point was the change in baseline to Week 12.

There was no statistically significant difference in the reduction in 24-h ambulatory BP achieved using olmesartan medoxomil (13.0/8.2 mm Hg) vs amlodipine besylate (12.9/7.4 mm Hg). Reductions in cuff SeSBP/SeDBP were also similar for olmesartan medoxomil (10.9/10.6 mm Hg) and amlodipine besylate (10.9/9.7 mm Hg). Both agents produced a significantly greater reduction in BP compared with placebo (P < .001). Both agents were well tolerated overall, although subjects in the amlodipine besylate group had a significantly higher incidence of nausea (2.7%; P = .039) than did subjects in the olmesartan medoxomil group (0.0%), and there was a tendency for the incidence of edema to be higher in the amlodipine besylate group (9.1%) than in the olmesartan medoxomil group (4.3%).

Olmesartan Medoxomil Versus Felodipine

In a head-to-head 12-week trial, subjects (n = 378) with moderate-to-severe hypertension (SeDBP ≥100 mm Hg to ≤120 mm Hg) were randomized to receive olmesartan medoxomil 20 mg/day (n = 186) or felodipine 5 mg/day (n = 192); the dose was doubled if the reduction in BP was <10 mm Hg by Week 8 (unpublished data, Sankyo Pharma, Inc., 2002). Blood pressure reductions at Week 12 were similar for both treatment groups (19.9/17.5 mm Hg for olmesartan medoxomil vs 19.1/17.0 mm Hg for felodipine) (unpublished data, Sankyo Pharma, Inc., 2002). Of the subjects treated with olmesartan medoxomil, 31.7% were titrated to the higher dose at Week 4, compared with 39.6% of subjects in the felodipine group. Both trial drugs were well tolerated. Peripheral edema occurred in five patients in the felodipine group and in none of the subjects given olmesartan medoxomil.

Efficacy Versus Other ARBs

Olmesartan medoxomil has been shown to have greater antihypertensive efficacy compared with that of the leading ARBs.

Olmesartan Medoxomil Versus Losartan Potassium

In a randomized, double-blind study, olmesartan medoxomil was compared with the first available ARB, losartan potassium. Subjects (n = 316) with mild-to-moderate hypertension (SeDBP between ≥95 mm Hg and ≤114 mm Hg) were randomized to treatment with olmesartan medoxomil 10 mg/day or losartan potassium 50 mg/day for 24 weeks. After 4 weeks of treatment, the dose was doubled in subjects with an SeDBP ≥90 mm Hg, a decrease in BP from baseline of <10 mm Hg, or both. At Weeks 12, 16, and 20, hydrochlorothiazide (HCTZ) was added to the regimen and subsequently up titrated if SeDBP was still not controlled. The primary end point was the change from baseline in trough SeDBP at Week 12 (when all subjects were still receiving monotherapy).

At Week 12, subjects receiving olmesartan medoxomil had a significantly greater (P < .05) reduction in SeDBP (10.6 mm Hg) than did those given losartan potassium (8.5 mm Hg). The reduction in SeDBP in patients treated with olmesartan medoxomil (9.1 mm Hg) was also significantly greater (P < .05) at Week 4 than in patients administered losartan potassium (6.4 mm Hg). Fewer subjects in the olmesartan medoxomil group than in the losartan potassium group required titration to the higher dose level (55% vs 77%) or the addition of HCTZ (35% vs 48%), and the differences in SeDBP observed at Week 24
(12.9 vs 11.6 mm Hg with olmesartan medoxomil and losartan potassium, respectively) did not reach statistical significance.

Olmesartan Medoxomil Versus Three Other ARBs

The antihypertensive efficacy of olmesartan medoxomil was compared with that of losartan potassium, valsartan, and irbesartan in a multicenter, randomized, double-blind study.21 Subjects (n = 588) with mild-to-moderate essential hypertension (SeSBP of 110 to 115 mm Hg and a mean daytime ADBP of 90 to 120 mm Hg) were randomized to the recommended starting dosages of olmesartan medoxomil (20 mg/day), losartan potassium (50 mg/day), valsartan (80 mg/day), or irbesartan (150 mg/day) once daily. The primary end point was the change from baseline in cuff SeSBP at Week 8. The reduction in SeSBP achieved by olmesartan medoxomil (11.5 mm Hg) was significantly greater than that demonstrated by each of the other three ARBs (P < .001 vs losartan potassium; P < .001 vs valsartan; P = .04 vs irbesartan) (Fig. 5).21 The reduction in 24-h mean ambulatory BP in subjects given olmesartan medoxomil (12.5/8.5 mm Hg) was significantly greater than that observed in the losartan potassium (9.0/6.2 mm Hg) and valsartan (8.1/5.6 mm Hg) groups (P < .05 for each comparison) and showed a trend toward a greater reduction than was observed in the irbesartan group (11.3/7.4 mm Hg). All ARBs were well tolerated.

Olmesartan Medoxomil in Combination Therapy

Major studies have shown that achieving currently recommended BP goals requires the administration of multiple antihypertensive agents in combination.4,40–42 Olmesartan medoxomil has been shown to be safe and effective when used in combination with other antihypertensive agents.

Olmesartan Medoxomil/HCTZ

In a randomized, controlled, factorial-design study, subjects (n = 502) with moderate-to-severe essential hypertension (mean SeSBP of 110 mm Hg to 115 mm Hg) were randomized to one of 12 groups for treatment with olmesartan medoxomil (0, 10, 20, or 40 mg/day) and HCTZ (0, 12.5, or 25 mg/day) (unpublished data, Sankyo Pharma, Inc., 2002). The primary efficacy variable was the mean change in SeSBP from baseline at Week 8. All olmesartan medoxomil/HCTZ combinations were welltolerated and achieved a significant (P < .001) reduction in SeSBP and SeDBP compared with placebo (unpublished data, Sankyo Pharma, Inc., 2002). Greater reductions in SeSBP and SeDBP were generally demonstrated with increasing doses of olmesartan medoxomil and with increasing doses of HCTZ (Fig. 6). The greatest reduction in BP (27.9/21.9 mm Hg) was seen with the olmesartan medoxomil 40-mg/HCTZ 25-mg combination. The incidence of emergent AEs in the olmesartan medoxomil/HCTZ combination groups (44.7% to 56.4%) was comparable to that seen in the placebo group (52.4%). The rate of response, defined as SeDBP <90 mm Hg or a ≥10-mm Hg reduction from baseline SeDBP, was as high as 92.3% in subjects treated with olmesartan medoxomil/HCTZ combination therapy and changed in a dose-dependent manner.

Treat-to-Goal Study

In an open-label, multicenter trial, 201 subjects with mild-to-moderate essential hypertension (mean SeSBP of 95 to 110 mm Hg) were initially given olmesartan medoxomil 20 mg once daily for 4 weeks.43 At subsequent 4-week
Safety Profile

In an integrated analysis of seven placebo-controlled studies, the incidence of AEs was similar for olmesartan medoxomil and placebo. Most AEs were mild and were not attributed by the investigators to the study drug. The only AE that was reported at least 1% more frequently in olmesartan medoxomil–treated patients than in the placebo group was dizziness (2.8% vs 0.9%). Serious AEs were infrequent, occurring in 0.8% of olmesartan medoxomil–treated patients and 0.7% of those given placebo. No statistically significant relationship between olmesartan medoxomil and any severe AE was identified.

Conclusions

Olmesartan medoxomil exhibits dose-related efficacy with a tolerability profile similar to that of placebo at all doses studied (Fig. 8). Olmesartan medoxomil has also been observed to provide effective BP reduction over a 24-h period with once-daily dosing. In clinical trials comparing it with other antihypertensive agents, olmesartan medoxomil has demonstrated efficacy at least similar to that of the β-blocker atenolol and the calcium channel blockers amlodipine besylate and felodipine, and greater antihypertensive efficacy than the ARBs losartan potassium, valsartan, and irbesartan, regardless of the age, sex, or ethnicity of study participants. As a component of the best-tolerated class of antihypertensive agents, olmesartan medoxomil may prove to be a useful addition to our antihypertensive armamentarium.

References


FIG. 7. Patients achieving a blood pressure (BP) target by 24 weeks with olmesartan medoxomil–based combination therapy. The percentages of patients reaching the BP goals of ≤140/90 mm Hg and ≤130/85 mm Hg with an olmesartan medoxomil–based treatment regimen were 93.3% and 87.7%, respectively (see 43; unpublished data, Sankyo Pharma, Inc., 2002).

FIG. 8. Blood pressure dose response and adverse events observed during olmesartan medoxomil therapy. Olmesartan medoxomil exhibited dose-related efficacy with a tolerability profile similar to that of placebo (unpublished data, Sankyo Pharma, Inc., 2002). *P < 0.001 vs placebo for treatment periods of 6 to 12 weeks; †All adverse events reported, with no causality attributed to the study drug. SeDBP = seated diastolic blood pressure.


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