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Olmesartan Medoxomil

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Contents

Abstract

▲ Olmesartan medoxomil is a nonpeptide angiotensin II receptor antagonist which selectively and competitively inhibits the type 1 angiotensin II receptor without affecting other receptors regulating the cardiovascular system.

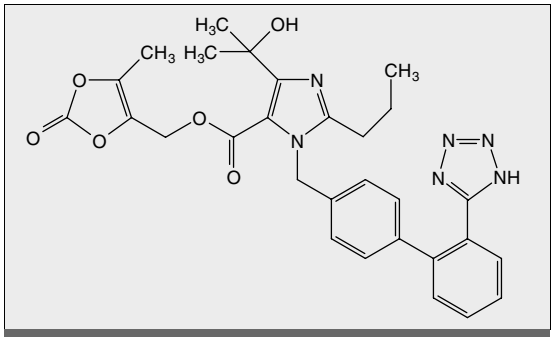
▲ In well designed randomised trials, olmesartan medoxomil was significantly more effective than placebo, and at dosages of 10 to 20 mg/day was at least as effective as atenolol 50 to 100 mg/day in reducing diastolic blood pressure (DBP). At dosages of 5 to 20 mg/day, olmesartan medoxomil was more effective than captopril 12.5 to 50mg twice daily at lowering seated DBP in patients with mild to moderate hypertension in a dose titration study.

▲ Reductions in seated DBP were greater with olmesartan medoxomil 10 to 20 mg/day than losartan 50 to 100 mg/day. Olmesartan medoxomil at 20 mg/day was more effective in lowering seated DBP than losartan 50 mg/day, valsartan 80 mg/day or irbesartan 150 mg/day, and was more efficacious than losartan 50 mg/day or valsartan 80 mg/day at reducing 24-hour ambulatory systolic blood pressure.

▲ Olmesartan medoxomil has shown no clinically important pharmacokinetic interactions with digoxin, warfarin or antacid (aluminium magnesium hydroxide).

▲ Adverse events were infrequent in clinical studies of olmesartan medoxomil and were similar to those attributed to placebo. With olmesartan medoxomil, the frequency of dizziness was higher than with placebo but similar to that occurring with losartan, valsartan and irbesartan.

Features and properties of olmesartan medoxomil (CS-866)	
Indication	
Hypertension	
Mechanism of action	
Angiotensin II receptor antagonist	
Dosage and administration	
Dosage in clinical trials	2.5 to 160 mg/day
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (20mg single dose, except where noted)	
Bioavailability	26%
Peak plasma concentration	0.475 mg/L
Time to peak plasma concentration	≈2h
Area under the plasma concentration-time curve	3.0 mg•h/L
Volume of distribution	35L
Elimination half-life (20 mg/day x 10 days)	≈15h
Adverse events	
Olmesartan medoxomil has a tolerability profile similar to that of placebo	Dizziness (2.8%)



Olmesartan medoxomil

The renin-angiotensin system (RAS) is involved in regulating blood pressure, electrolyte balance and fluid volume homeostasis. It plays a pivotal role in essential hypertension. The blockade of angiotensin converting enzyme (ACE) and of the angiotensin II (AII) receptors is the mechanism of action of numerous effective antihypertensive drugs.

Many drugs currently on the market exhibit excellent antihypertensive properties; however, adverse events and frequency of administration may decrease patient compliance,[1,2] leading to poor control of hypertension. The search for new antihypertensive agents which may improve patient compliance through an improved tolerability profile and ease of administration (i.e. once-daily) continues.

AII-receptor antagonists, unlike ACE inhibitors, have not been associated with persistent dry cough, which has caused patients to discontinue treatment. Neither have they been associated with angioedema, a less frequent but more serious adverse event, presumably because of the more specific action of the AII receptor blockade. Olmesartan medoxomil is a new AII-receptor antagonist developed for the treatment of hypertension.

1. Pharmacodynamic Profile

In Vitro

• Olmesartan is a nonpeptide AII antagonist that is highly selective for AII type 1 (AT_1) receptors. The drug competitively inhibited binding of [^{125}I]-AII to AT_1 receptors in bovine adrenal cortical membranes, but had no effect on binding of [^{125}I]-AII to AII type 2 receptors in bovine cerebellar membranes, or on the contractile response of guinea-pig aortic tissue induced by phenylephrine or potassium chloride.[3]

• Olmesartan and EXP3174, the active metabolite of losartan, antagonised AII-induced contraction in isolated guinea-pig aortic tissue in a dose-dependent manner, with olmesartan (0.3 nmol/L) inhibiting approximately 90% and EXP3174 (0.3 nmol/L) inhibiting approximately 35% of the contractile response.[3] In contrast to the rapid diminution in the effect of EXP3174 (full contractility was restored within 60 minutes of washout), the inhibitory effect of olmesartan persisted for more than 90 minutes.

In Animals

• In conscious normotensive rats, intravenous olmesartan (0.01 to 0.03 mg/kg) and oral olmesartan medoxomil (0.1 mg/kg) inhibited the AII-induced pressor response which did not return to preadministration levels within 8 hours.[3,4]

• In a rat model, olmesartan medoxomil prevented production of certain markers of early cardiovascular inflammation,[5] myocardial remodelling[6] and cardiac fibrosis[7] induced by chronic inhibition of nitric oxide synthesis. Administration of olmesartan medoxomil (0.001 or 0.01% in the diet) to Zucker diabetic fatty rats, a model of type 2 diabetes mellitus,[8] and to spontaneously hypertensive rats[9] (3 or 10 mg/kg orally or olmesartan 100 mg/L in drinking water treatment) for 19 weeks and 6 weeks, respectively, reduced urinary protein excretion in a dose-dependent fashion.

• In rabbit and cynomolgus monkey models of atherosclerosis, oral treatment with olmesartan medoxomil (1 mg/kg/day for 32 weeks and 1 or 10 mg/kg/day for 6 months, respectively), resulted in aortic plaque lesion area reductions of 40 and 64%, respectively, compared with controls.[8] Similarly, in another model of atherosclerosis, monkeys fed a high cholesterol diet for 6 months had a mean ratio of atherosclerotic area to total area of 72 ± 6%;

whereas, the group treated concurrently with olmesartan medoxomil (10 mg/kg/day for 6 months) had a 25 ± 14% reduced ratio ($p < 0.05$ *vs* high cholesterol group).[10]

In Healthy Volunteers

• Olmesartan medoxomil inhibited the angiotensin I (AI)-induced hypertensive response in healthy volunteers.[11] The inhibitory effect of single oral doses of 2.5, 5, 10, 20 and 40mg of olmesartan medoxomil, 20mg of enalapril or placebo on an AI challenge in 16 healthy male volunteers was assessed in a randomised, double-blind, dose-escalating, crossover study. All doses of olmesartan medoxomil inhibited the AI-induced pressor response more effectively than placebo ($p \leq 0.05$), and the blockade was comparable to that produced by 20mg of enalapril. Olmesartan medoxomil 10 to 40mg produced >50% inhibition for up to 24 hours, although there was no significant gain in inhibition beyond the 20mg dose.

In Patients with Hypertension

• Single doses of olmesartan medoxomil reduced diastolic blood pressure (DBP) in patients with hypertension.[12] In a double-blind, placebo-controlled, crossover trial, 16 patients with mild-to-moderate hypertension (162 ± 13/103 ± 7mm Hg), pretreated with a moderate sodium-restrictive diet (60 mmol/day) and a single dose of furosemide 40mg to further stimulate the RAS, were randomised to one of two increasing single-dose schedules of olmesartan medoxomil 2.5, 10 and 40mg or 5, 20 and 80mg at weekly intervals, with each patient also randomly receiving placebo at one of the four treatments. Significant reductions in ambulatory DBP (6.9 to 8.9 mmHg; $p < 0.05$ *vs* placebo) were seen with doses >5mg. All doses of olmesartan medoxomil produced increases in plasma renin activity and AII levels.

2. Pharmacokinetic Profile

Olmesartan medoxomil (CS-866) is a prodrug that is rapidly and completely hydrolysed to the active metabolite, olmesartan (RNH-6270).[3] The pharmacokinetics of olmesartan have been studied in healthy male volunteers and patients with hypertension, including the young and elderly, and those with varying degrees of renal dysfunction. Most of these studies were available only as abstracts.[13-22]

Absorption and Distribution

• The absolute bioavailability after a single oral dose of olmesartan medoxomil 20mg in healthy volunteers is 26%.[23]

• Single oral doses of olmesartan medoxomil 10 to 160mg given to 25 healthy volunteers were rapidly absorbed; mean (± standard deviation) peak plasma concentrations (C_{max}) of olmesartan ranged from 0.22 ± 0.05 to 2.1 ± 0.5 mg/L and were reached 1.4 to 2.8 hours (t_{max}) after drug administration.[23] The mean area under the plasma concentration-time curve (AUC) for the same doses ranged from 1.6 ± 0.3 to 19.9 ± 4.4 mg • h/L. There appears to be a linear relationship between prodrug dosage and active metabolite C_{max} and AUC, but not t_{max}.[16] Multiple daily dosages did not significantly increase C_{max} values. Steady-state plasma concentrations were reached within 3 days in a group of young and elderly (12 each) patients with hypertension receiving oral olmesartan medoxomil 80mg once daily for 10 days.[14]

• The volume of distribution (Vd) after intravenous administration of single doses of olmesartan 1 to 32mg in 34 healthy male volunteers was 15 to 20L.[23] The mean Vd for a single oral dose of 20mg in 24 healthy male volunteers was 34.9 ± 20.7L.

Metabolism and Elimination

• Olmesartan medoxomil is rapidly de-esterified *in vivo* to the active acid, olmesartan, the only major metabolite.[3] No metabolites of olmesartan have been identified in humans.[23]

• The mean terminal elimination half-life ($t_{½}$) of orally administered olmesartan medoxomil ranged from 9.8 ± 1.9 to 11.4 ± 2.8 hours and 14.1 ± 7.0 to 14.9 ± 5.9 hours in patients with hypertension

and healthy male volunteers, respectively, receiving dosages of 20 to 80 mg/day for 10 days.[14,23] Urinary excretion of olmesartan represented 5 to 12% of the orally administered dose.[15-17,23] In dogs and rats, >90% of the injected olmesartan dose was excreted in the faeces within 24 hours.[23]

In Elderly Patients

• In two trials comparing the pharmacokinetics of olmesartan in young (aged 18 to 45 years), elderly (aged 65 to 75 years) and very elderly (aged >75 years) patients with hypertension,[14,18] significant ($p < 0.5$) increases in AUC (≈33 and ≈44%) in the elderly and very elderly, respectively, compared with young patients, were noted. Values for C_{max}, t_{max} and $t_{½}$ showed no statistically significant differences between the groups. The authors concluded that the increases in AUC were not judged to be of clinical concern and that dosage adjustment is not recommended in this population.

In Patients with Renal Impairment

• Exposure to olmesartan is increased in patients with renal dysfunction. Renal clearance of olmesartan in a trial of eight healthy volunteers [creatinine clearance (CL_{CR}) >60 ml/min (>3.6 L/h)] was compared with that in 26 patients with varying degrees of renal dysfunction [CL_{CR} 59 to <20 ml/min (3.54 to <1.2 L/h)].[19] The AUC and C_{max} at steady state increased as renal clearance decreased, with values approximately 3 and 1.5 times greater, respectively, than those in healthy volunteers. The authors concluded that no dosage adjustment is necessary in patients with mild to moderate renal impairment.

Potential for Drug Interactions

• Coadministration of an antacid decreased the bioavailability of olmesartan; however, the authors concluded that this effect is unlikely to be of clinical significance. In a multiple dose, crossover study, 24 healthy male volunteers were randomised to coadministration of 800mg of aluminium magnesium hydroxide antacid four times daily with 20mg of olmesartan medoxomil once daily or to olmesartan medoxomil alone.[13] Mean olmesartan medoxomil AUC and C_{max} in the coadministration group were lower than those of the olmesartan medoxomil alone group (1.6 *vs* 1.9 mg • h/L and 0.29 *vs* 0.31 mg/L, respectively).

• Coadministration of warfarin and olmesartan medoxomil had no affect on coagulation values. Coagulation values and the pharmacokinetics of warfarin were not significantly affected by coadministration of 40mg of olmesartan medoxomil for 7 days in a double-blind, randomised, placebo-controlled study in 24 healthy male volunteers who received individually titrated dosages of warfarin.[20]

• Coadministration of digoxin and olmesartan medoxomil had only minor effects on digoxin pharmacokinetics. The 90% confidence interval (CI) for the ratio of mean digoxin AUC (bioequivalence defined as 0.80 to 1.25) was unaffected by coadministration of 20mg of olmesartan medoxomil (0.97) versus placebo (1.05) in healthy volunteers stabilised on a 0.375 mg/day dosage of digoxin.[21] The 90% CI for C_{max} and average plasma concentrations were also within the bioequivalence range; however, trough plasma concentrations were outside that range (0.58 for the lower boundary).

• In anaesthetised, normotensive rats administered intravenous olmesartan and proadifen hydrochloride (SK&F-525A; a cytochrome P450 inhibitor), no alteration of the AII-inhibitory effect was observed.[3]

3. Therapeutic Trials

The therapeutic efficacy of olmesartan medoxomil has been evaluated in randomised, double-blind, multicentre studies in adults with varying degrees of hypertension. Most of the studies were preceded by a run-in phase (either placebo or, in one study, hydrochlorothiazide) of 2 to 4 weeks' duration. Therapeutic response was defined as a DBP of <90mm Hg or a reduction of at least 10mm Hg from baseline. Some of these studies are not yet

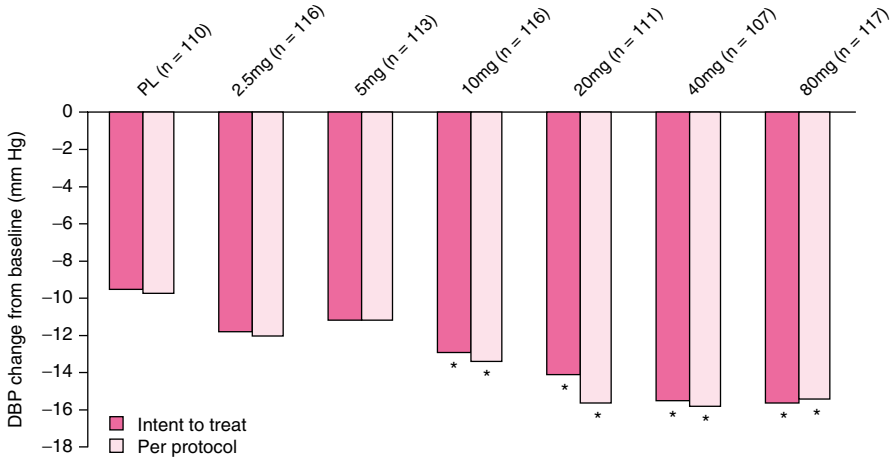


Fig. 1. Antihypertensive effects of olmesartan medoxomil given once daily in patients with mild to moderate hypertension as measured by seated diastolic blood pressure (DBP). In this randomised, multicentre, double-blind study, patients were assigned either placebo (PL) or various dosages of olmesartan for 12 weeks.[22] * $p \leq 0.05$.

published; however, preliminary data are available in abstracts.[22,24-29] In one published trial, [30] 588 patients aged 18 years or older with essential hypertension having an average cuff DBP of ≥100 and ≤115mm Hg and a mean 24-hour ambulatory daytime DBP of ≥90 and <120mm Hg after completion of a 4-week placebo run-in period were included. Patients with significant cardiovascular disease within the past 6 months or secondary hypertension were excluded from the study.

Comparisons with Placebo

• In two randomised, multicentre, double-blind studies,[22,24] olmesartan medoxomil was found to be effective in reducing DBP when compared with placebo. The first study,[22] in which 792 patients were randomised to placebo or olmesartan medoxomil for 12 weeks, showed significant reductions ($p \leq 0.05$) in seated DBP in populations receiving dosages ≥10mg (figure 1). The data suggest a dose-response relationship was evident in daily dosages from 5 to 40mg. [24] In the second study,[24] 334 patients were randomised to either placebo or varying dosages of olmesartan medoxomil given once or twice daily for 8 weeks and were evaluated by 24-hour ambulatory DBP monitoring (figure 2). All dosages produced an antihypertensive effect; however, there was no significant difference between once- and twice-daily dosages.

• In a randomised, double-blind study of 76 patients with hypertension, treatment with 20 or 80mg of olmesartan medoxomil once daily for 6 weeks significantly reduced mean 24-hour ambulatory DBP compared with placebo ($p < 0.05$).[25] The mean reduction from baseline was 9 ± 6mm Hg for the 20mg dosage, 9 ± 9mm Hg for the 80mg dosage and 3 ± 7mm Hg for placebo.

Comparisons with a β-Blocker

• In two randomised, double-blind trials,[26,27] olmesartan medoxomil was as efficacious as atenolol in reducing DBP. In a double-blind study,[26] 326 patients were randomised to either olmesartan medoxomil 10mg once daily (n = 165) or atenolol 50mg once daily (n = 161) for 12 weeks. If no response was seen after 4 weeks of treatment, the dosage of either drug could be doubled. A decrease in the mean seated trough DBP was evident by 2 weeks after initiation of treatment in both groups and became more pronounced in the following 2 weeks. The mean reduction in seated systolic blood pressure (SBP)/DBP from baseline at 12 weeks

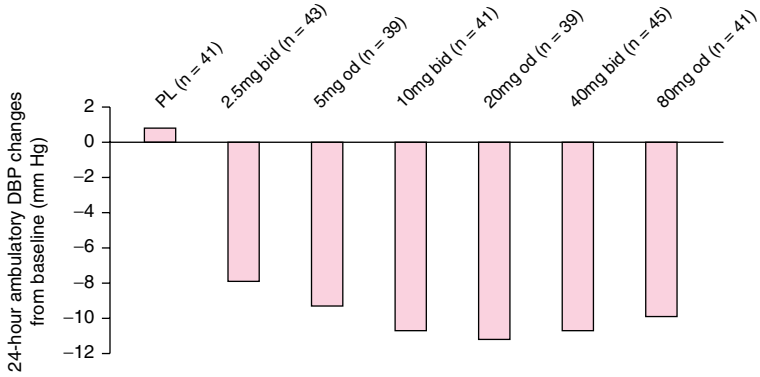


Fig. 2. Antihypertensive effects of olmesartan medoxomil in patients with hypertension as measured by 24-hour ambulatory diastolic blood pressure (DBP) monitoring. In this randomised, multicentre, double-blind study, patients were assigned either to placebo (PL) or to various dosages of olmesartan medoxomil for 8 weeks.[24] **bid** = twice daily; **od** = once daily.

was 20.7 ± 1.0/14.0 ± 0.6mm Hg for the olmesartan medoxomil group and 17.2 ± 1.0/14.3 ± 0.6mm Hg for the atenolol group. There was a small but significantly greater reduction in SBP from baseline with olmesartan medoxomil (mean difference –3.5mm Hg, 95% CI of –6.0, –0.8).

• In another double-blind study,[27] 328 patients with moderate to severe hypertension (seated DBP of 100 to 120mm Hg while receiving 25mg of hydrochlorothiazide once daily) were randomised to either olmesartan medoxomil 10mg once daily (n = 164) or atenolol 50mg once daily (n = 164) in addition to continued hydrochlorothiazide for a total of 12 weeks. If, after 4 weeks of treatment, patients did not respond, the dosage of either drug could be doubled. In this study 43 patients (26.2%) in the olmesartan medoxomil treatment group and 46 (28.1%) in the atenolol group needed the higher dosage to achieve the desired reductions in DBP. The mean reductions in SBP/DBP for olmesartan medoxomil were 20.4 ± 10.5/17.3 ± 6.3mm Hg and for atenolol were 19.6 ± 10.5/17.2 ± 6.4mm Hg.

Comparison with an ACE Inhibitor

• In a multicentre, double-blind study,[28] 291 patients with mild to moderate hypertension (mean seated DBP of 95 to 114mm Hg) were randomised to either olmesartan medoxomil 5mg once daily (n = 148) or captopril 12.5mg twice daily (n = 143) for up to 12 weeks. After 4 weeks of treatment, if patients did not respond, the dosage of either drug could be doubled, and it could be doubled again after 8 weeks if DBP remained uncontrolled. The reduction in seated trough DBP from baseline in the olemesartan medoxomil group was 9.9 ± 0.6mm Hg. This was greater than that in the captopril group (6.8 ± 0.6mm Hg; mean difference –3.1mm Hg, 95% CI of –4.8, –1.5). Reductions in mean seated SBP were also greater in the olmesartan medoxomil group than in the captopril group, 14.7 ± 1.0 *vs* 7.1 ± 1.1mm Hg (mean difference –7.6mm Hg, 95% CI of –10.4, –4.7).[31]

Comparisons with Other Angiotensin II-Receptor Antagonists

• In a multicentre, double-blind study,[31] 316 patients with mild to moderate hypertension (mean seated DBP of 95 to 114mm Hg) were randomised to olmesartan medoxomil 10mg once daily (n = 158) or losartan 50mg once daily (n = 152) for 12 weeks. After 4 weeks of treatment, if patients did not respond, the dosage of either drug was to be doubled. At week 12, the mean reduction in seated trough DBP in the olmesartan medoxomil group was significantly greater than in the losartan group, 10.6 ± 0.5 *vs* 8.5 ± 0.6mm Hg (mean difference

–2.1mm Hg, 95% CI of –3.6, –0.5). The reduction in mean seated SBP was also greater in the olmesartan medoxomil group than in the losartan group, 14.9 ± 1.0 *vs* 11.6 ± 1.0mm Hg (mean difference –3.3mm Hg, 95% CI of –6.0, –0.6).

• In a multicentre, double-blind study,[30] 588 patients (mean age of 51.9 years) with hypertension (mean seated DBP of 100 to 115mm Hg) were randomised to one of four AII-receptor antagonists for 8 weeks. Patients were assigned to olmesartan medoxomil 20 mg/day or the recommended starting doses of either losartan, valsartan or irbesartan (50, 80 and 150 mg/day). Patients in the active treatment phase of the trial had their blood pressure and heart rate measured at weeks 2, 4 and 8. At week 8, the mean reduction in seated cuff DBP from baseline in olmesartan medoxomil recipients (11.5mm Hg) was significantly greater than in patients treated with losartan (8.2mm Hg; p = 0.0002), valsartan (7.9mm Hg; p < 0.0001)or irbesartan (9.9mm Hg; p = 0.0412) (figure 3). The reduction in mean seated cuff SBP was also greatest in the olmesartan medoxomil group (11.3mm Hg) than in the other groups (9.5, 8.4 and 11.0mm Hg for losartan, valsartan and irbesartan, respectively); however, the difference was deemed statistically insignificant. At week 8, olmesartan medoxomil reduced mean 24-hour ambulatory SBP significantly more than did losartan and valsartan (12.5 *vs* 9.0 and 8.1mm Hg; p < 0.05) but not irbesartan (11.3mm Hg). There was no significant effect on heart rate with the use of any of the AII-receptor antagonists in this study.

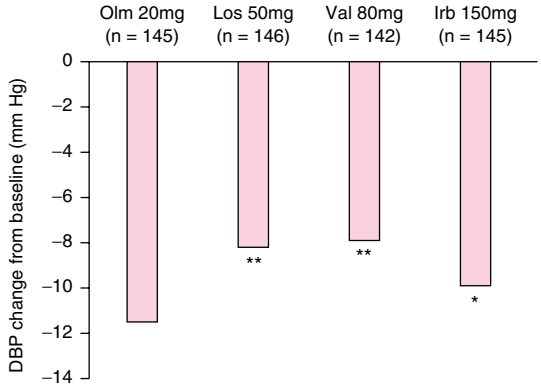


Fig. 3. Antihypertensive effects of olmesartan medoxomil (Olm) versus losartan (Los), valsartan (Val) or irbesartan (Irb) as measured by seated cuff diastolic blood pressure (DBP). In this multicentre, double-blind study,[30] patients in the intent-to-treat population were randomised to the recommended starting dose of one of four angiotensin II receptor antagonists for 8 weeks. All drugs were given once daily. * p < 0.05; ** p < 0.0005.

Meta-analysis

• In a meta-analysis[32] of data from studies in which 3055 patients with mild to moderate hypertension were randomised to either placebo (n = 544) or 2.5 to 80mg of olmesartan medoxomil (n = 2511) once daily, clinically relevant reductions in DBP were achieved at dosages of 20 mg/day and above. The mean 5mm Hg placebo-corrected reductions from baseline in seated trough DBP with olmesartan medoxomil after 12 weeks were: –2.36mm Hg (2.5mg), –2.74mm Hg (5mg), –3.58mm Hg (10mg), –5.08mm Hg (20mg), –5.02mm Hg (40mg) and –5.00mm Hg (80mg).

4. Tolerability

• Olmesartan medoxomil was well tolerated by patients with hypertension during clinical trial (section 3).[22,24,27,33] In a meta-analysis of seven randomised trials, the occurrence of adverse events in patients treated with olmesartan medoxomil was similar to the occurrence in those receiving placebo (42.2 and 42.7%, respectively, figure 4).[33] Headache, upper respiratory tract infections and influenza-like symptoms were the most commonly reported adverse events in both groups. Hyperglycaemia was more commonly reported in the placebo than the olmesartan medoxomil group (2.7 *vs* 1.3%; p = 0.02). Dizziness was more common in the olmesartan medoxomil than the placebo group (2.8 *vs* 0.9%; p = 0.01). In the Oparil et al. study,[30] the rate of dizziness in the olmesartan medoxomil group was similar to that in the losartan, valsartan and irbesartan groups (1.4, 0.7, 1.4 and 3.4%, respectively).

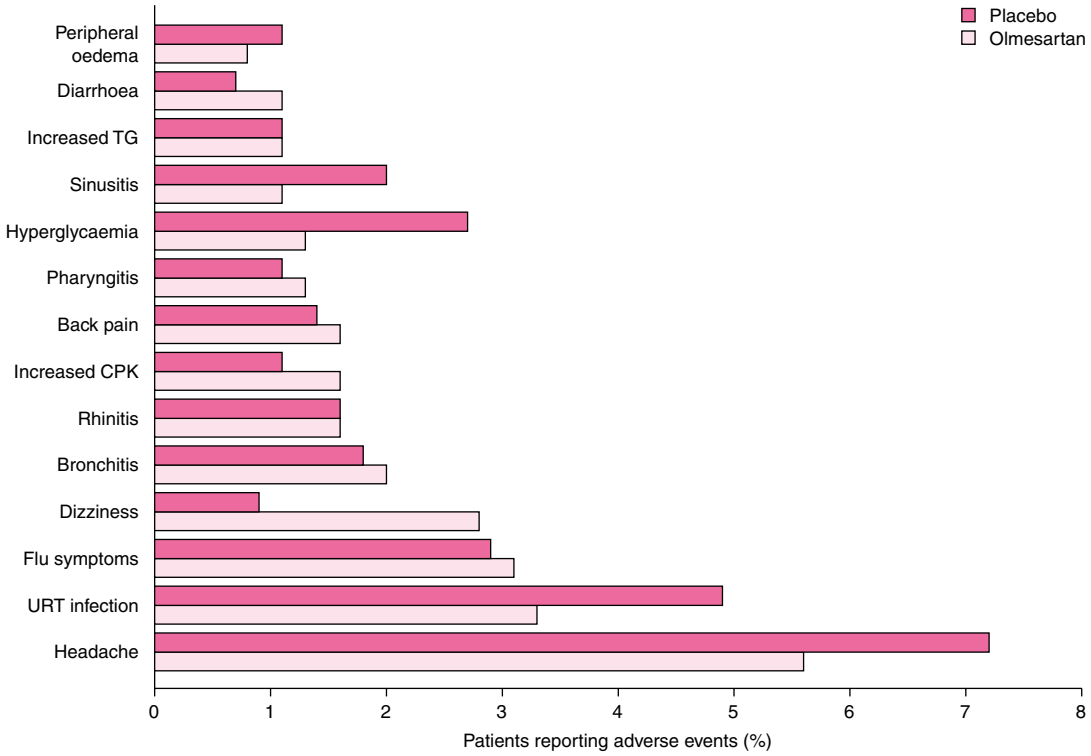


Fig. 4. Adverse events reported by >1% of patients with hypertension in a meta-analysis of seven randomised clinical trials.[33] Patients with hypertension in these double-blind studies were randomised to either various dosages (2.5 to 80 mg/day) of olmesartan medoxomil (n = 2540) or placebo (n = 555) for 6 to 12 weeks. **CPK** = creatine phosphokinase; **TG** = triglyceride; **URT** = upper respiratory tract.

• Dizziness was also the most common reason for drug discontinuation in these studies, with a total of six olmesartan medoxomil recipients discontinuing treatment.[33] Of those six patients, one was still experiencing dizziness 7 months after discontinuation, and another patient had a 4-year history of dizziness and headache. Total discontinuation rates were 1.6% in the olmesartan medoxomil treatment group and 0.7% in the placebo group.

5. Olmesartan Medoxomil: Current Status

Olmesartan medoxomil is an AII-receptor antagonist that has been approved by the Food and Drug Administration in the US for the treatment of hypertension,[34] and is being reviewed for registration in Europe. The efficacy of olmesartan medoxomil in the treatment of various stages of hypertension has been demonstrated in well designed clinical trials. Olmesartan medoxomil is well tolerated and its adverse event profile is similar to that of placebo.

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