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NEW ARBS IN THE TREATMENT OF HYPERTENSION: AN OVERVIEW

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SUMMARY

Azilsartan medoxomil (Edarbi®; Ipreziv™) is an orally administered angiotensin II receptor type 1 antagonist (blocker) used in the treatment of adults with essential hypertension. This article reviews data on the clinical efficacy and tolerability of azilsartan medoxomil in adults with essential hypertension and provides a summary of its pharmacological properties. Azilsartan medoxomil is a prodrug that undergoes rapid hydrolysis in the gastrointestinal tract after oral administration to the bioactive moiety azilsartan, before systemic absorption. Azilsartan medoxomil produces antihypertensive effects by selectively blocking the binding of angiotensin II to the angiotensin type 1 (AT(1)) receptor, thereby antagonizing the pressor response activity of angiotensin II. In vitro, azilsartan produced greater and more sustained AT(1) receptor binding/blockade activity than several comparator angiotensin II receptor antagonists. Azilsartan medoxomil reduces blood pressure (BP) in hypertensive adults. In addition, the drug has been shown to have pleiotropic effects (i.e. effects beyond AT(1) receptor blockade). In adults with essential hypertension, azilsartan medoxomil 20, 40 or 80 mg effectively reduced BP over a 24-hour period with once-daily administration in three major, randomized, controlled trials in which the primary endpoints were changes from baseline in 24-hour mean systolic BP (SBP) at week 6 (two trials) or week 24, assessed by ambulatory BP monitoring (ABPM). In the two 6-week trials, azilsartan medoxomil showed dose-dependent efficacy over all evaluated dosages and was more effective than placebo in lowering SBP. At the maximum approved dosage of 80 mg once daily, azilsartan medoxomil was significantly more effective than maximum dosages of olmesartan medoxomil (40 mg once daily) or valsartan (320 mg once daily), based on primary endpoint assessments. Mean reductions in clinic measurements of SBP and diastolic BP (DBP) measurements were also generally greater with azilsartan medoxomil 80 mg once daily than with the comparator drugs in these 6-week studies. Over a longer treatment period of 24 weeks, azilsartan medoxomil showed sustained BP-lowering efficacy, with the reduction in 24-hour mean SBP at week 24 significantly greater with azilsartan medoxomil 40 or 80 mg once daily than with valsartan 320 mg once daily. Mean reductions from baseline in mean clinic SBP and DBP as well as DBP by ABPM were also significantly greater with azilsartan medoxomil 40 or 80 mg once daily than with valsartan. Azilsartan medoxomil was generally well tolerated, with a tolerability profile similar to that of placebo in the 6-week trials. Across the three major trials, headache and dizziness were among the most common adverse events. Overall, rates of treatment discontinuation as a result of adverse events were low in the 6-week and 24-week trials. In conclusion, once-daily azilsartan medoxomil effectively lowers BP in adults with essential hypertension and has shown better antihypertensive efficacy than maximum therapeutic dosages of olmesartan medoxomil or valsartan in major trials of up to 24 weeks' duration. Azilsartan medoxomil is generally well tolerated and the low rates of discontinuation due to adverse events suggest that patients are likely to persist with long-term treatment. Azilsartan medoxomil is therefore a useful and attractive new option for lowering BP in patients with essential hypertension, particularly for those not able to tolerate other antihypertensive drugs. Further studies are required to evaluate the effects of azilsartan medoxomil on cardiovascular morbidity and mortality.

KEYWORDS: Azilsartan medoxomil azilsartan medoxomil on cardiovascular morbidity and mortality.

INTRODUCTION

Hypertension (HTN), defined as systolic blood pressure (SBP) > 140 mmHg or diastolic blood pressure (DBP) > 90 mmHg, is a major growing health problem across the globe. Hypertension, also known as high blood pressure (HBP), is a long-term medical condition in which the blood pressure in the arteries is persistently elevated.[8] High blood pressure usually does not cause symptoms.[1] Long-term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease.[2] It is the most common risk factor for cardiovascular disease

and affects nearly two-thirds of adults aged 60 years or older.[3]

High blood pressure is classified as either primary (essential) high blood pressure or secondary high blood pressure.[4] About 90–95% of cases are primary, defined as high blood pressure due to nonspecific lifestyle and genetic factors. Lifestyle factors that increase the risk include excess salt, excess body weight, smoking, and alcohol. The remaining 5–10% of cases are categorized as secondary high blood pressure, defined as high blood pressure due to an identifiable cause, such as chronic kidney disease, narrowing of the kidney arteries, an endocrine disorder, or the use of birth control pills.[4]

Azilsartan medoxomil (AZL-M) is the eighth approved member of angiotensin II receptor blockers (ARBs), a drug class of high priority in the management of hypertensive subjects with diabetes mellitus type II (DMII).[1]

AZL-M was found to be more effective in terms of reducing indices of blood pressure over alternative ARBs or angiotensin-converting enzyme (ACE) inhibitors with minimal side effects. In vitro, azilsartan produced greater and more sustained AT1 receptor binding/blockade activity than several comparator angiotensin II receptor antagonists. Azilsartan medoxomil reduces blood pressure (BP) in hypertensive adults.[2] Preclinical studies have established pleiotropic effects for AZL-M beyond its primary antihypertensive role through differential gene expression, up-regulation of membrane receptors and favorable effect on selective intracellular biochemical and pro-atherosclerotic pathways.[1]

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Chemical Structure and Physical Properties

Azilsartan was discovered through the efforts of Takeda scientists to find a new class of AT_1 antagonists by modifying the tetrazole ring present in candesartan. The tetrazole ring is also present in many other clinically approved ARBs including irbesartan, olmesartan, losartan, and valsartan.[3] The chemical structure of azilsartan is very similar to the structure of candesartan and differs only by replacement of candesartan 5 member tetrazole ring with the 5 member oxo-oxadiazole ring of azilsartan. This chemical modification served to make azilsartan less acidic and more lipophilic than candesartan. The oxo-oxadiazole ring in azilsartan is not found in any other clinically approved ARB.[5]

Azilsartan has been shown to be effective in reducing BP when orally administered as either the ester prodrug, azilsartan medoxomil (TAK-491), or as the primary compound.[3]

Figure shows the chemical structure of azilsartan kamedoxomil, the potassium salt used in the product formulation of azilsartan medoxomil. This salt is practically insoluble in water and is freely soluble in methanol. Each white, round, unscored tablet of azilsartan medoxomil contains 42.68 mg or 85.36 mg of the potassium salt, which is equivalent to 40 mg and 80 mg of azilsartan medoxomil, respectively.[3]

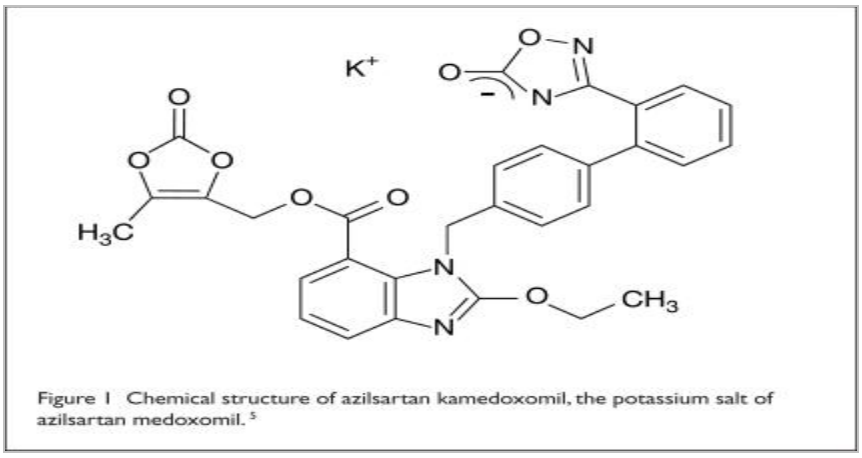

Figure 1 Chemical structure of azilsartan kamedoxomil, the potassium salt of azilsartan medoxomil.[5]

Mechanism of Action

Angiotensin II, a peptide hormone, is the principal pressor agent in the renin–angiotensin system (RAS). Angiotensin II is a potent, direct vasoconstrictor. It stimulates the synthesis and release of aldosterone and also promotes renal tubular reabsorption of sodium, resulting in water retention.[7]

Azilsartan is a selective blocker of AT1 receptors that prevents angiotensin II binding, resulting in vasodilation

and decrease in the effects of aldosterone, because of the presence of such receptors in the vascular smooth muscle and in the adrenal gland. With respect to other ARBs, azilsartan is highly selective for the AT1 receptor and not the AT2 receptor.[4]

Pharmacokinetics

Absorption: Azilsartan medoxomil is a prodrug. It is hydrolyzed to the active moiety, azilsartan, in the gastrointestinal (GI) tract during the absorption phase. The estimated absolute bioavailability of azilsartan is 60%. Absorption is not affected by food, and peak plasma concentrations are reached within 1.5 to 3 hours.[3]

Distribution: The apparent volume of distribution of azilsartan medoxomil is 16 L. Similar to other ARBs, the drug is highly bound to plasma proteins (99%). When azilsartan was studied in rats, a minimal amount of radioactivity was found to have crossed the blood–brain barrier. In addition, azilsartan crossed the placental barrier and was distributed to the fetus.[1]

Metabolism: The enzyme principally responsible for the metabolism of azilsartan is cytochrome P450 (CYP) 2C9. And to a lesser extent by CYP2B6 and CYP2C8, resulting in the formation of two primary metabolites, M-I and M-II, by decarboxylation and *O*-dealkylation, respectively. These metabolites have low affinity for the AT_1 receptor and therefore have no effect on the pharmacologic activity of azilsartan medoxomil.[4]

Elimination: Renal clearance of this medication is estimated to be 2.3 mL/minute. The elimination half-life is 11 hours, and steady-state concentrations are reached within 5 days. Fifty-five percent of the product is eliminated in the feces, and 42% is excreted in the urine, with 15% of the drug unchanged.[7] In conclusion, the dose range of 20–320 mg does not need any adjustment based on patient's age, sex, race, or degree of renal/hepatic impairment.[3]

Pharmacology

Azilsartan medoxomil is an orally administered angiotensin II receptor type 1 antagonist (blocker) used in the treatment of adults with essential hypertension.[2]

Azilsartan medoxomil is a prodrug that undergoes rapid hydrolysis in the gastrointestinal tract after oral administration to the bioactive moiety azilsartan, before systemic absorption. Azilsartan medoxomil produces antihypertensive effects by selectively blocking the binding of angiotensin II to the angiotensin type 1 (AT1) receptor, thereby antagonizing the pressor response activity of angiotensin II.[2]

In vitro, azilsartan produced greater and more sustained AT1 receptor binding/blockade activity than several comparator angiotensin II receptor antagonists. Azilsartan medoxomil reduces blood pressure (BP) in hypertensive adults. In addition, the drug has been shown to have pleiotropic effects (i.e. effects beyond AT1 receptor blockade).[2]

In adults with essential hypertension, azilsartan medoxomil 20, 40 or 80 mg effectively reduced BP over a 24-hour period with once-daily administration in three major, randomized, controlled trials in which the primary endpoints were changes from baseline in 24-hour mean systolic BP (SBP) at week 6 (two trials) or week 24, assessed by ambulatory BP monitoring (ABPM). In the two 6-week trials, azilsartan medoxomil showed dose-dependent efficacy over all evaluated dosages and was more effective than placebo in lowering SBP.[5] At the maximum approved dosage of 80 mg once daily, azilsartan medoxomil was significantly more effective than maximum dosages of olmesartan medoxomil (40 mg once daily) or valsartan (320 mg once daily), based on primary endpoint assessments. Mean reductions in clinic measurements of SBP and diastolic BP (DBP) measurements were also generally greater with azilsartan medoxomil 80 mg once daily than with the comparator drugs in these 6-week studies.[1]

Over a longer treatment period of 24 weeks, azilsartan medoxomil showed sustained BP-lowering efficacy, with the reduction in 24-hour mean SBP at week 24 significantly greater with azilsartan medoxomil 40 or 80 mg once daily than with valsartan 320 mg once daily. Mean reductions from baseline in mean clinic SBP and DBP as well as DBP by ABPM were also significantly greater with azilsartan medoxomil 40 or 80 mg once daily than with valsartan.[2]

Azilsartan medoxomil was generally well tolerated, with a tolerability profile similar to that of placebo in the 6-week trials. Across the three major trials, headache and dizziness were among the most common adverse events. Overall, rates of treatment discontinuation as a result of adverse events were low in the 6-week and 24-week trials.[2]

In conclusion, once-daily azilsartan medoxomil effectively lowers BP in adults with essential hypertension and has shown better antihypertensive efficacy than maximum therapeutic dosages of olmesartan medoxomil or valsartan in major trials of up to 24 weeks' duration.[2] Azilsartan medoxomil is generally well tolerated and the low rates of discontinuation due to adverse events suggest that patients are likely to persist with long-term treatment. Azilsartan medoxomil is therefore a useful and attractive new option for lowering BP in patients with essential hypertension, particularly for those not able to tolerate other antihypertensive drugs.[1]

Pleiotropic effects

Although AZL-M has been approved for hypertension, it remains to be determined whether this new drug can offer clinical benefits beyond its hypertensive action. In

general, accumulating evidence suggests that ARBs could decelerate the progression of diabetic nephropathy, independently of their BP lowering effect. In addition, some ARBs may be more effective than others in reducing proteinuria in patients with diabetic nephropathy despite similar induced reductions in BP. Most important, specific ARBs are pleiotropic molecules with additional cellular actions beyond the blockade of AT1 receptors that might confer favorable cardio metabolic effects.[2] According to a relevant review study, ARBs typically have trivial impact on basal glucose and insulin levels, particularly in lean animals, but nonetheless often improve glucose and insulin sensitivity, particularly in obese animals and/or models with type II diabetes. In addition the authors mentioned that AT1R blockade can improve diabetes-induced vascular remodeling, probably independently of BP lowering.[1]

Indication and Usage

Azilsartan medoxomil is indicated for the treatment of hypertension in adults 18 years of age and older. It is approved for use alone or in combination with other antihypertensive drugs.[3]

Adverse Drug Effects

In clinical trials, 4,814 patients were evaluated for safety during azilsartan medoxomil therapy at daily doses of 20, 40, and 80 mg. A total of 1,704 patients were treated for at least 6 months, including 588 who were treated for at least 1 year. Azilsartan medoxomil was well tolerated, and the incidence of AEs was similar to that of placebo.[3]

Rates of withdrawals resulting from AEs were 2.4% for placebo, 2.2% for azilsartan medoxomil 40 mg, and 2.7% for azilsartan medoxomil 80 mg. Hypotension and orthostatic hypotension were the most common AEs leading to discontinuation of therapy. Both AEs occurred in 0.4% of the patients treated with azilsartan medoxomil compared with 0% of the patients receiving placebo.[4]

Most of the changes in standard laboratory parameters were not clinically relevant. A small, reversible increase in serum creatinine was observed with patients receiving azilsartan medoxomil 80 mg. This increase may be larger when azilsartan medoxomil is coadministered with chlorthalidone or HCTZ. In addition, serum creatinine levels may be increased in patients with moderate or severe renal impairment or in those who are 75 years of age or older.[3]

Diarrhea was the most common AE associated with azilsartan medoxomil, occurring in up to 2% of patients receiving the 80-mg dose in placebo-controlled monotherapy trials, compared with 0.5% of patients who received placebo. Other AEs with a plausible relationship to treatment with azilsartan medoxomil included nausea, asthenia, fatigue, muscle spasm, dizziness, and cough. Low hemoglobin, hematocrit, and red blood cell counts were observed in 0.2%, 0.4% and 0.3% of patients receiving azilsartan medoxomil, respectively.[3]

Drug Interactions

Because azilsartan medoxomil is metabolized by CYP2C9, caution is advised when azilsartan is administered with strong modulators of this enzyme. Other antihypertensive agents should also be used with caution in combination with azilsartan medoxomil.[7]

Nonsteroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors, may inhibit renal function when administered with ARBs. This effect is reversible and is most likely to occur in elderly, volume-depleted, or renally compromised patients.[3]

Drug interactions of azilsartan with caffeine, antacid, warfarin, digoxin, tolbutamide, glyburide, metformin, pioglitazone, chlorthalidone, amlodipine, dextromethorphan, midazolam, and fexofenandine have been studied; any other significant interactions have also been observed.[7]

In another drug interaction study, azilsartan clearance was reduced when coadministered with fluconazole (a CYP2C9 inhibitor), but not when coadministered with ketoconazole (a CYP3A4/5 inhibitor).[4]

Given that, nonsteroidal anti-inflammatory agents and COX-2 inhibitors cause prerenal acute renal failure by blocking prostaglandin production, which also alters local glomerular arteriolar perfusion, the use of these agents concurrently with azilsartan may increase the risk of renal function deterioration.[4]

Contraindications

There are no clinical contraindications to the use of azilsartan medoxomil.[3]

Warnings

The labeling for azilsartan medoxomil includes a boxed warning regarding the use of this drug in pregnancy. When pregnancy is detected, azilsartan medoxomil should be discontinued as soon as possible. Drugs that act on the RAS, such as azilsartan medoxomil, can cause injury and death to the developing fetus.[7]

No clinical studies of azilsartan medoxomil have been conducted in pregnant women. Azilsartan medoxomil is a Pregnancy Category C drug during the first trimester and a Pregnancy Category D drug during the second and third trimesters. It is not known whether this medication is excreted in human milk. Low concentrations of the drug have been found in the milk of lactating rats.[3]

The RAS is activated in patients who are volume-depleted or salt-depleted, including patients taking high doses of diuretics. The use of azilsartan medoxomil may

result in symptomatic hypotension in that population. Volume and salt depletion must be corrected before initiation of azilsartan medoxomil, and treatment should be started with a daily dose of 40 mg.[2]

A transient hypotensive episode does not constitute a contraindication to the use of azilsartan medoxomil. The drug may be continued when the patient's BP has been stabilized.[1]

Changes in renal function may be anticipated when patients are taking medications that inhibit the RAS. Azilsartan medoxomil, like other ARBs, may cause oliguria or progressive azotemia in volume-depleted patients, in patients with severe congestive heart failure, and in patients with renal stenosis.[3]

Dosage and Administration

In adults, the recommended dosage of azilsartan medoxomil is 80 mg taken orally once daily with or without food. A starting dose of 40 mg should be considered in patients receiving high doses of diuretics and in volume-depleted and salt-depleted patients.[3]

Azilsartan medoxomil may be used with other antihypertensive agents. It has not been studied in patients younger than 18 years of age. Dose adjustments are unnecessary in elderly patients, in those with renal impairment, or in those with mild-to-moderate hepatic dysfunction. The drug's safety and efficacy have not been established in patients with severe hepatic impairment.[2]

Comparison of Azilsartan VS Other Sartans

Bakris et al published the first study investigating the antihypertensive efficacy and safety of azilsartan in 2011. It was a placebo-controlled trial involving a total of 1,275 patients who were randomized to placebo, azilsartan 20, 40, or 80 mg daily, or olmesartan 40 mg daily for 6 weeks.[5] Twenty four-hour mean systolic BP (SBP; measured by 24 hours ambulatory blood pressure monitoring [ABPM]) was found to be significantly reduced in all azilsartan groups (−12.2, −13.5, and −14.6 mmHg) and in the olmesartan 40 mg group (−12.6 mmHg). Reductions were significantly greater with azilsartan 80 mg than olmesartan 40 mg (P=0.038), while azilsartan 40 mg was not inferior to olmesartan 40 mg. Safety profiles of both drugs were similar to placebo, although statistical comparison was not performed.[4]

Another double-blind, randomized, placebo-controlled trial compared azilsartan with olmesartan and valsartan. A total of 1,285 patients were randomized to placebo, azilsartan 40–80 mg daily, olmesartan 40 mg daily, or valsartan 320 mg daily for 6 weeks. Placebo-adjusted ABPM-SBP was lowered by azilsartan (−14.3 mmHg) significantly more than by valsartan (−10.0 mmHg; $P\leqslant 0.001$) and olmesartan (−11.7 mmHg; P=0.009). Safety profiles were not statistically investigated; nonetheless the raw data reported show similar results between study groups.[5]

Comparison of azilsartan and valsartan has been further investigated by Sica et al15 in another double-blind, randomized trial including 984 patients randomized to placebo, azilsartan 20 mg titrated to 40 mg, 40 mg titrated to 80 mg, or valsartan 80 mg titrated to 320 mg for 24 weeks. Azilsartan 40 and 80 mg lowered 24-hour mean SBP (−14.9 and −15.3 mmHg, respectively) more than valsartan 320 mg (−11.3 mmHg; $P\leqslant 0.001$ for both comparisons).[4]

Furthermore, safety and efficacy of azilsartan (20–40 mg) has also been compared to candesartan (8–12 mg) in a 16-week randomized controlled trial involving 622 patients.16 Results demonstrated a significant BP reduction among patients administered azilsartan (−12.4 mmHg diastolic blood pressure [DBP] and −21.8 mmHg SBP) in comparison with those receiving candesartan (−9.8 mmHg DBP and −17.5 mmHg SBP). This analysis of sitting BP was further confirmed by ABPM findings. The most common adverse effect was nasopharyngitis (interesting 18% vs. 16% patients, P= nonsignificant), and safety profiles were also similar between treatment groups.[5]

Anti-Hypertensive Effects of Azilsartan Medoxomil In Comparison To Other Drug Classes

For comparisons with different classes of antihypertensive drugs, data on the efficacy, and safety of AZL-M. As far as comparisons with ACE inhibitors are concerned, a trial evaluated the efficacy and safety of AZL-M vs. Ramipril after 24 weeks of treatment. AZL-M was superior to Ramipril in reducing all measured indices of BP (trough, clinic, and ambulatory). The safety profile was similar to that of Ramipril, with fewer discontinuations due to adverse events. Albeit not randomized, the one-year outcomes of the EARLY registry, a prospective observational study that was designed to compare AZL-M with ACE-inhibitors under real life settings, further reinforce the results of the aforementioned clinical trials and confirm the greater BP-lowering effect of AZL-M.[4]

Two randomized trials compared AZL-M in combination with amlodipine with their individual monotherapies, and with amlodipine plus placebo respectively. Changes from baseline in the sitting, trough, diastolic BP and 24 h systolic BP were considered the primary end point and combination of the two drugs was found to be a more efficient regimen than individual monotherapy and placebo along with a similar safety profile. In contrast, when AZL-M was compared with amlodipine in a randomized, open-label study (N = 718), AZL-M failed to induce a greater reduction in night systolic BP than amlodipine after 8-weeks of treatment.[4]

DISCUSSION

Azilsartan medoxomil (Edarbi®; Ipreziv™) is an orally administered angiotensin II receptor type 1 antagonist (blocker) used in the treatment of adults with essential hypertension. This article reviews data on the clinical efficacy and tolerability of azilsartan medoxomil in adults with essential hypertension and provides a summary of its pharmacological properties. Azilsartan medoxomil is a prodrug that undergoes rapid hydrolysis in the gastrointestinal tract after oral administration to the bioactive moiety azilsartan, before systemic absorption. Azilsartan medoxomil produces antihypertensive effects by selectively blocking the binding of angiotensin II to the angiotensin type 1 (AT1) receptor, thereby antagonizing the pressor response activity of angiotensin II.

In adults with essential hypertension, azilsartan medoxomil 20, 40 or 80 mg effectively reduced BP over a 24-hour period with once-daily administration in three major, randomized, controlled trials in which the primary endpoints were changes from baseline in 24-hour mean systolic BP (SBP) at week 6 (two trials) or week 24, assessed by ambulatory BP monitoring (ABPM0. Over a longer treatment period of 24 weeks, azilsartan medoxomil showed sustained BP-lowering efficacy, with the reduction in 24-hour mean SBP at week 24 significantly greater with azilsartan medoxomil 40 or 80 mg once daily than with valsartan 320 mg once daily. Mean reductions from baseline in mean clinic SBP and DBP as well as DBP by ABPM were also significantly greater with azilsartan medoxomil 40 or 80 mg once daily than with valsartan.

Azilsartan medoxomil was generally well tolerated. Headache and dizziness were among the most common adverse events.

CONCLUSION

Azilsartan medoxomil is the eighth ARB to be approved for the treatment of hypertension. Recent studies have demonstrated that azilsartan is more effective than the ARBs olmesartan and valsartan and the ACE inhibitor Ramipril at lowering systolic BP. A recent study also showed that the combination of azilsartan medoxomil and the calcium-channel blocker amlodipine is effective at lowering systolic BP, with a reduced incidence of peripheral edema.

The antihypertensive effects of azilsartan medoxomil are dose-related. This characteristic was observed after an infusion of angiotensin II in healthy subjects. A 32-mg dose of azilsartan medoxomil decreased the maximal pressor effect of angiotensin II by approximately 90% when the drug reached peak plasma concentration. Twenty-four hours after administration, azilsartan medoxomil lowered the pressor effect by approximately 60%.

In healthy subjects, single and repeated doses of azilsartan medoxomil increased the plasma concentrations of both angiotensin I and angiotensin II. Renin activity also increased, whereas plasma aldosterone levels decreased.

In conclusion, Azilsartan medoxomil is an effective and safe BP lowering drug for patients with hypertension and metabolic co-morbidities, including DM or prediabetes mellitus.

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