

Azilsartan medoxomil: Angiotensin receptor blocker in the treatment of hypertension

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ABSTRACT

Hypertension is an important risk factor for cardiovascular and renal disease. It's early detection and control is critically important as it is an important attributable cause of stroke, coronary artery disease, heart failure, atrial fibrillation and ESRD. Recent data indicates increasing prevalence of hypertension amongst various populations. This reflects the importance of having a variety of treatment options for the management of this condition. Angiotensin receptor blockers are highly effective at reducing blood pressure, have excellent tolerability and renoprotective properties, hence they remain a useful choice in the management of hypertension. Azilsartan medoxomil has recently been approved by the FDA for the oral treatment of hypertension making it the eighth Angiotensin receptor blocker to be approved for this indication.

Key words: Hypertension, Azilsartan, angiotensin receptor blocker

Introduction

Blood pressure $\geq 140/90$ mm of Hg is an important risk factor for cardiovascular and renal disease. Many factors like sedentary lifestyle, stress, obesity, increasing age, abnormalities of renin-angiotensin-aldosterone system (raised levels of angiotensin II) and many others contribute to the development of essential hypertension. ^[1] The prevalence of hypertension is increasing ^[2] and it causes serious complications like stroke, coronary artery disease, heart failure, atrial fibrillation and end stage renal disease. ^[3] So, early detection and control of raised blood pressure is critically important. But

the blood pressure remains inadequately controlled in many hypertensive patients due to lack of aggressive treatment, improper drug selection and patient's non compliance with lifestyle changes and drug therapy. ^[2, 4] Presence of multiple causative factors and serious complications reflects the need for having a variety of treatment options for the managing this condition.

Angiotensin receptor blockers lower blood pressure by antagonizing, angiotensin II induced vasoconstriction and aldosterone release. Because of their efficacy, renoprotective properties and excellent tolerability ARB's are one of the preferred group of drugs now a days. ^[5] Currently

available ARB's are Losartan, Valsartan, Irbesartan, Candesartan, Telmisartan, Eprosartan and Olmesartan. Azilsartan medoxomil is the eighth in this group, recently approved by FDA for treatment of hypertension. It is used orally, alone or in combination with other antihypertensive drugs.^[6]

Clinical Pharmacology of Azilsartan

Azilsartan is an Angiotensin receptor blocker.

Mechanism of action

Azilsartan medoxomil is a prodrug, rapidly hydrolysed in the gastrointestinal tract to release the active moiety 'azilsartan'^[7, 8] which antagonises the vasoconstrictor and aldosterone-secreting activity of angiotensin II, by selectively blocking AT1 receptors in the vascular smooth muscles and adrenal gland. Its action is independent of angiotensin II synthesis.

Pharmacokinetics^[9]

Absorption: It rapidly hydrolysed in the gastrointestinal tract (during absorption) to release its active moiety 'azilsartan'. The peak plasma concentration is reached within 1.5 to 3 hours of oral administration.

Distribution: It is highly bound to albumin and volume of distribution is approximately 16 L.

Metabolism: Azilsartan is metabolized by CYP2C9 to two metabolites M-II(major) and M-I (minor) which do not contribute the pharmacologic activity of azilsartan.

Elimination: Excretion is in feces and urine as administration of 14C-labeled azilsartan medoxomil showed 55% of radioactivity being recovered in feces and 42% in urine. Its elimination half-life is 11 hours (approx).

Dose and administration

The recommended dose of azilsartan is 80 mg orally once daily in adults. It can be taken with or without food^[9] as food does not interfere with its absorption. In some patients 40 mg is used in combination with diuretics.

Adverse effects and contraindications

The most commonly reported adverse event is orthostatic hypotension leading to discontinuation of drug treatment.^[9] Other adverse effects include dizziness, diarrhea, nausea, asthenia, fatigue, muscle spasm and cough.^[10, 11]

In patients more than 75 years of age or with moderate to severe renal impairment at baseline a small increase in serum creatinine levels is reported with azilsartan which is reversible on discontinuing the drug.^[9]

Like other Angiotensin receptor blockers, azilsartan is contraindicated during pregnancy as it can cause fetal injury and even death during the second or third trimester.

Result of Clinical studies

Maximal dose of azilsartan (80mg) is reported to be more efficacious than the highest dose of olmesartan (40mg) in reducing mean 24- hour ambulatory systolic blood pressure. Whereas Azilsartan 40 mg has comparable efficacy as olmesartan 40 mg.^[12]

Azilsartan (40mg and 80mg) showed significantly greater reduction in mean systolic blood pressure as compared to angiotensin converting enzyme inhibitor rampril 10mg daily^[10] and also valsartan 320 mg.^[13]

Pleiotropic effects

In addition to blood pressure lowering effect azilsartan has shown pleiotropic

beneficial effects on cellular mechanisms of cardiometabolic disease in studies on experimental animals.^[14]

In a study on homogenates of the pooled aortas of ApoE knockout mice, azilsartan attenuated the evolution of atherosclerotic plaque rupture by suppressing Plasminogen activator inhibitor type-I (PAI-1).^[15]

Conclusion

Azilsartan has the advantage of improved receptor specificity and slow receptor dissociation rate. It has been found to be a safe and efficacious drug in the management of hypertension and hence provides the clinician with a newer option for managing hypertensive patients.

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