REVIEW ARTICLES

ALISKIREN –AN OVERVIEW

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Abstract

The renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS) is a major endocrine/ paracrine system that regulates blood pressure (BP) via angiotensin release as well as fluid and electrolyte homeostasis via aldosterone release. RAAS should be constantly suppressed and any degree of activity may lead to hypertension (HTN) and associated target organ damage. Activation of the RAAS in the pathogenesis of hypertension, cardiovascular disease(CVD) and renal disease is well documented. Also benefits of inhibition of RAAS, as an effective way to intervene in the pathogenesis of HTN, CVD and chronic renal failure(CRF) has been well recognized. Inhibition of renin activity and the blockage of RAAS cascade at its primary steps, has long been proposed as the optimal means of RAAS inhibition. Renin inhibitor provides more effective means of RAAS Inhibition. Aliskiren is the first in a new class of orally active, non-peptide, low molecular weight direct renin inhibitor (DRI) available for clinical use and potential new approach to the blockade of the RAAS.

Key words:- *Aliskiren; Hypertension; RAAS; Direct renin inhibitor.*

Introduction

The RAAS regulates BP via angiotensin release and body electrolyte content via aldosterone release. Renin, a circulating enzyme, with one known substrate angiotensinogenase, is a key regulator of the RAAS and is released from juxtaglomerular cells in kidneys, in response to fall in blood pressure level due to dietary sodium restriction. It establishes a short-term defense mechanism against hypovolemic hypotension. However, when dietary sodium is in excess, RAAS should be constantly suppressed and any degree of activity may lead to hypertension (HTN) and associated target organ damage. Although renin was discovered more than a century ago, the significance of this system in the pathogenesis of cardiovascular and renal disorders has gained wide acceptance only during the past 3 decades[1].

Standard treatments available for treatment of hypertension are diuretics, â-blockers, angiotensin converting enzyme inhibitors (ACEs), angiotensin II receptor blockers (ARBs), calcium channel blockers, α-blockers, vasodilators, and centrally acting drugs[2]. The drugs from the class of ACE inhibitors and ARBs act by interfering with angiotensin or aldosterone. These drugs do not block the renin–angiotensin–aldosterone system (RAAS) completely[3]. It is difficult to achieve the optimized RAAS suppression with currently available antihypertensive agents, because ACE inhibitors, ARBs, and diuretics all activate the compensatory feedback mechanism that increases renin release and increase plasma renin activity (PRA)[4,5]. ACE inhibitors cause an increase in PRA and angiotensin I, which is then converted to angiotensin II by both remaining unblock ACE and by ACE independent pathways[6]. ARBs and diuretics increase PRA, angiotensin I, and angiotensin II[7]. Hence physicians and cardiologists have been looking for a drug which directly inhibits the renin. The first orally active direct renin inhibitors (DRIs) were developed in 1980s, including enalkiren, remikiren, and zankiren. However, poor absorption from the gastrointestinal tract, less bioavailability (<2%), short half life, and low potency blocked the development of these compounds[8]. Aliskiren is the first in a new class of orally effective, nonpeptide, low molecular weight, and DRI for the treatment of hypertension.

Aliskiren is a potent and specific inhibitor of human renin with fewer adverse events[9,10]. Combination of ARBs and DRI could offer improved RAAS blockade by acting both at the receptor level and at the first step of cascade[11,12]. Aliskiren is available as 150 or 300 mg tablet meant for oral administration. The recommended initial dose of the drug is 150 mg once daily. In patients who do not have adequately controlled blood pressure, the daily dose may be increased to 300 mg[13,14].

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Role of RAAS & effects of its inhibition

Renin was first discovered, characterized and named in 1898 by Robert Tigerstedt. Half century later Braun-Menedez and colleagues and Page and Helmer independently showed that renin was a circulating aspartic proteinase that cleaves the peptide bond between leu10 and val11 in angiotensinogen 2 to yield decapeptide angiotensin I (Ang I), in the rate limiting step of the cascade. The inactive Ang I is further converted into octapeptide angiotensin II (Ang II) [Ang-(1-8)], a biologically active potent constrictor, by angiotensin-converting enzyme (ACE), primarily within the capillaries of the lungs. The Ang II a powerful vasoconstrictor thus formed acts on receptors of Ang II (AT-1 receptors); it acts on the musculature and thereby raises the resistance exerted by these arteries to the heart. In order to overcome this increase in load, heart works more vigorously, causing increase in BP. Ang II also acts on the adrenal glands and releases aldosterone, which stimulates the epithelial cells of the kidneys to increase re-absorption of salt and water, leading to increased blood volume and BP. This excessive activity of the renin system is associated with HTN and target organ damage, mediated largely through the actions of Ang II on the angiotensin AT1 receptor[15,16].

Advantages of inhibition of RAAS, as an effective way to intervene in pathogenesis of HTN, CVD and CRF have been well established[17,18]. RAAS may be blocked by drugs at various points and is important target site for five distinctive classes of antihypertensive drugs; beta blockers, renin inhibitors, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and aldosterone inhibitors. These drugs inhibit renin secretion, the enzymatic action of renin, the conversion of angiotensin I to angiotensin II, angiotensin II receptors or the effect of aldosterone, respectively[19] and have proven to be highly successful treatments for hypertension and related cardiovascular diseases[20,21].

Inhibition of renin activity and the blockage of RAAS cascade at its primary steps, has long been proposed as the optimal means of RAAS inhibition. Aliskiren provides more effective means of RAAS inhibition, unlike with ACE inhibitors or ARBs[22,23]. As it blocks formation of both Ang I and Ang II, with no activation of the AT receptors and no interference with bradykinin metabolism, thus enhancing its therapeutic potential.

Pharmacology

Aliskiren is an orally active, competitive inhibitor of human renin. Its extremely high affinity for human renin (50% inhibitory concentration [IC50] 0.6 nM) compensates for its low bioavailability (2.6% for the hard gelatine 75-mg capsule)[24]. Its affinity for related aspartic peptidases is more than 10,000 times lower than its affinity for human renin. Its free base has the molecular formula C30H53N3O6 and a molecular mass of 551.8 g/mol, and it is highly soluble in water (> 350 mg/mL at pH 7.4). In its tablet form, aliskiren is present as its hemifumarate salt. Aliskiren is a nonpeptide, low-molecular-weight, orally active renin inhibitor designed through a combination of molecular modeling techniques and crystal structure elucidation[25]. It binds with high specificity to the proteolytic active sites of renin. It has an extended half-life allowing once daily oral administration. It lowers blood pressure by inhibiting renin and therefore the circulating levels of Ang I and Ang II[26,27]. Its mechanism of action leads to a reduced Ang II level, a compensatory rise in plasma renin concentration, a reduced functional plasma renin activity and a reduced urinary aldosterone excretion. In healthy normotensive volunteers, it does not change heart rate and has a duration of action of 48 hours[28].

Pharmacokinetics & pharmacodynamics

Aliskiren has a very low bioavailability (<"2.5%) and reaches the peak plasma concentration within 1 to 6 hours[29]. High fat meals reduce the drug exposure and peak plasma concentration by 71% and 85%, respectively. Diminished drug exposure was also noted in the elderly. It has a small volume of distribution (2 L/kg) and a half-life of approximately 24 hours with a steady-state drug level achieved in 5–8 days[28]. It has modest water solubility with moderate protein binding (50%)[30]. It is metabolized by liver cytochrome P450 enzyme 3A4. More than 90% of aliskiren is eliminated unchanged in the feces, 2% is eliminated as oxidized metabolites, and 1% is eliminated in the urine. Diabetic patients have a higher drug exposure due to a slower drug clearance (205 vs. 234 L/h) and a longer elimination half-life (44 vs. 40 hours)[31,32].

Adverse effects[26]

Some patients may experience angioedema with or without respiratory symptoms. Edema of the face, hands or whole body and diarrhea have also been reported. Other gastrointestinal side effects include abdominal pain and dyspepsia, etc. Cough has been observed in clinical studies, but it occurs less frequently unlike ACE inhibitors. Derangement of renal function and anemia occurs occasionally. Other adverse effects reported in clinical trials include rash, hyperkalemia, elevated uric acid, gout, renal stones,

tonic-clonic seizures with loss of consciousness and myositis.

Precautions[26]

Hyperkalemia can occur when used in combination with an ACE inhibitor or ARB. Hypotension may occur, especially when used in combination with other antihypertensive agents. It should be used with great caution in patients with renal dysfunction (serum creatinine 1.7 mg/dL for women; 2.0 mg/dL for men and/or estimated glomerular filtration rate 30 mL/min), a history of dialysis, nephritic syndrome or renovascular hypertension. It is contraindicated during pregnancy and in patients who experience angioedema with its use.

Drug Interactions

Aliskiren is metabolized by liver enzyme cytochrome P450 3A4. Co-administration of other 3A4 substrates, such as atorvastatin and ketoconazole, can significantly increase its plasma level due to competitive enzyme inhibition. Studies report that there are no drug interactions with lovastatin, atenolol, celecoxib, cimetidine or warfarin[33,34]. Aliskiren decreases the plasma drug concentration of furosemide for which its dose needs to be increased. In addition, risk for hypotension should be monitored when aliskiren is used in combination with other antihypertensives. High-fat meals may reduce drug absorption of aliskiren, but the clinical significance remains unclear[35].

In a study conducted by Stanton et al, aliskiren (at doses 37.5, 75, 150, and 300 mg once daily) and losartan (100 mg once daily) were compared in a 4-week trial in 226 patients with mild-to-moderate essential hypertension. It was found that aliskiren showed dose-dependent reduction in BP, with the changes in patients getting 75–300 mg of aliskiren similar to those receiving 100 mg of losartan[36]. In a similar trial with the ARB irbesartan, 652 hypertensive subjects were randomized to receive either irbesartan (150 mg) or aliskiren (150, 300 and 600 mg). It was observed that at a dose of 150 mg, aliskiren was as effective as irbesartan (150 mg) in lowering blood pressure with similar safety and tolerability over the short term[37].

In a study carried out in KEM hospital, Mumbai, it was observed that aliskiren effectively reduced the blood pressure as a mono therapy as well as in combination therapy. It showed renoprotective effects thereby preventing myocardial end organ damage, and various other effects[38]. Similar study from India conducted by Patel et al confirmed above findings[39].

Conclusion

Aliskiren is the first drug in a class of DRI. Aliskiren effectively reduces the blood pressure as a mono therapy as well as in combination therapy. From the above clinical and preclinical studies, aliskiren showed renoprotective effects; prevents myocardial end organ damage and various other effects. These effects of aliskiren are needed to be studied in more detail. Very few studies were conducted in Indian population, so it is advisable to perform more clinical studies in Indian population to evaluate safety and efficacy of aliskiren in more detail.

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