

LETTER TO THE EDITOR

ALISKIREN : A NOVEL RENIN INHIBITOR FOR HYPERTENSION

Sir,

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The renin-angiotensin system (RAS) is an important participant in both short- and long-term regulation of arterial blood pressure (1). It acts synergistically with the sympathetic nervous system and stimulates aldosterone secretion; it plays a central role in the control of sodium excretion and fluid volume as well as of vascular tone (2). Thus, abnormalities of the RAS are apparent in several forms of human hypertension, edematous states such as congestive heart failure and renal failure (3).

Renin is an enzyme that acts on angiotensinogen (renin substrate) to catalyze the formation of the decapeptide angiotensin I. This decapeptide is then cleaved by angiotensin converting enzyme (ACE) to yield the octapeptide angiotensin II which is a most potent vasoconstrictor (1).

Most of the biological effects of this vasoconstrictor agent (angiotensin II) are mediated by the specific membrane bound G-protein-coupled receptor called angiotensin II subtype 1 receptor (AT₁ receptor). The main actions of angiotensin II include generalized vasoconstriction, increased release of noradrenaline from sympathetic nerve terminals, stimulation of proximal tubular reabsorption of sodium and alteration in cardiovascular structures (1, 2).

Further, it is claimed that morbidity in the hypertensives is related to plasma renin activity (PRA) (4). Some effective antihypertensive drugs such as hydralazine, diazoxide, sodium nitroprusside, thiazide

diuretics, angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) increase PRA in hypertensive patients (1, 4).

As renin catalyzes the first and rate-limiting step of the RAS and has high specificity for angiotensinogen, blockade of production of angiotensin II by direct inhibition of renin has long been a therapeutic goal (5). Aliskiren, a novel renin inhibitor has been found to cause a dose-dependent decrease in PRA, effectively block the formation of both angiotensin I and angiotensin II and decrease plasma and urine aldosterone levels (6).

Chemistry

Aliskiren (SPP100) is a potent, low-molecular weight, nonpeptidic renin inhibitor, readily soluble in water and consists of 2(S), 4(S), 5(S), 7(S), -N-(2-, 7-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-3(methoxypropoxy) phenyl]-octanamid hemifumarate salt (6).

Pharmacodynamics

Renin inhibitor (Aliskiren) prevents the initiation of biochemical reactions in the RAS cascade. Renin inhibitors block the renin-catalyzed hydrolytic cleavage of angiotensinogen by competitively binding to the active site and subsites of renin and remaining bound but noncleavable by the enzyme. So the generation of angiotensin I is inhibited and consequently, angiotensin II

becomes unavailable to maintain its biological effects. Thus, renin inhibitors decrease PRA, systemic vascular resistance and systemic blood pressure (7) and consequently decrease cardiovascular morbidity.

Pharmacokinetics

Aliskiren has good water solubility and low lipophilicity and is resistant to biodegradation by peptidases in the intestine, blood circulation and the liver (8). The trough to peak (T:P) ratio is commonly used as an index of the duration of action of antihypertensive agents, and previous guidelines for the treatment of hypertension have recommended the use of drugs with a T:P ratio >0.5 (9). The high T:P ratio of aliskiren in hypertensive patients was found consistent (10) with the long plasma half-life (approximately 24 hours) observed after oral administration of the drug to healthy subjects (6). Ambulatory blood pressure measurements also indicated a sustained antihypertensive effect of aliskiren (10) over the 24-hour period after dosing (5).

Adverse effects

The most common adverse effects reported by Gradman et al (10) were headache, dizziness, diarrhoea and musculoskeletal system related adverse events comparable to those of placebo and irbesartan, while fatigue/weakness, gastrointestinal disorders and headaches were reported by Stanton et al (5). Generally, the overall incidence of each adverse effects reported was relatively low (5, 10).

Clinical trials

1. Once-daily oral doses of aliskiren of upto 640 mg were well tolerated and caused dose dependent and sustained RAS inhibition in human healthy volunteers (6).

2. Another study in 226 patients with mild-to-moderate hypertension showed that aliskiren 300 mg daily lowered blood pressure with efficacy and tolerability similar to those of the ARB-losartan at twice the recommended dose (5).
3. A recent randomized, multicenter, double-blind, placebo-controlled, active-comparator, 8 week trial in 652 patients with mild to moderate hypertension done by Gradman et al concluded that once-daily oral treatment with aliskiren 150 mg lowers blood pressure effectively, with a safety and tolerability profile comparable to that of irbesartan and placebo (10).

Use

Aliskiren 150 mg once-daily is as effective as irbesartan 150 mg in lowering blood pressure in patients with mild to moderate hypertension (10). US-FDA has not yet approved the use of aliskiren.

Advantages

1. As renin inhibitors prevent the formation of both angiotensin I and angiotensin II, they may offer a therapeutic profile distinct from both ACE inhibitors and ARBs (10).
2. ACE inhibition causes an increase in angiotensin I, which is then available for conversion to angiotensin II by ACE-independent pathways not blocked by ACE inhibitors (11). Further, renin inhibitors also do not affect kinin metabolism and hence would not be expected to cause dry cough or angioneurotic edema, which are characteristic side effects of ACE inhibitors (12).
3. Although the AT₂ receptor generally is conceptualized as a cardiovascular

protective receptor, its activation may contribute to cardiac fibrosis (13). ARBs increase levels of angiotensin II and indirectly stimulates angiotensin II subtype 2 receptor (AT₂), an effect that does not occur with renin inhibitors and thus prevents unexpected effects of AT₂ receptor stimulation (1, 10).

4. No evidence of withdrawal effect (10).

Disadvantages

Adverse effects reported with aliskiren are headache, dizziness, diarrhoea, musculoskeletal system related adverse events, fatigue/weakness, and gastrointestinal disorders (5, 10).

Conclusion

As aliskiren is effective in lowering blood pressure with once-daily dose and has low incidence of adverse effects reported (10), it has the potential to become first orally effective renin inhibitor that provides a true alternative to ACE-inhibitors and ARBs in therapy for hypertension and other cardiovascular and renal diseases (6).

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