COMMENTARY

Blood pressure control and favourable pleiotropic effects of aliskiren

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Hypertension and its acute and chronic complications are one of the most important risk factors associated with significant morbidity and mortality worldwide and will increase in importance as a public health problem by 2020.[1] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7) establishes that the goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. Despite the wide range of antihypertensive agents available, less than one third of patients with hypertension have their blood pressure (BP) controlled.

The mechanism of primary (essential) hypertension includes genetic predisposition, endothelial cell dysfunction, sympathetic nervous system (SNS) hyperactivity, abnormalities in renin angiotensin aldosterone system (RAAS) function, hyperinsulinism and insulin resistance. In particular, RAAS hyperactivity is associated with the progression of renal damage. For this reason, the current guidelines indicate the pharmacological blockade of RAAS as the first choice of treatment for hypertension.

Renin is a protease mainly produced by the juxtaglomerular cells (JGC) of the kidney in the form of the pre-prohormone prorenin when BP is low and is encoded by the REN gene located on chromosome 1q32. The majority (75%) of prorenin is secreted constitutively, whereas the reminder is targeted to dense core secretory granules. Mature renin is stored in granules in the JGC and is released by an exocytotic process involving stimulus–secretion coupling between the renal and the systemic circulation. Active renin secretion is regulated principally by four interdependent factors: (1) a renal baroreceptor mechanism in the afferent arteriole; (2) changes in delivery of sodium chloride (NaCl) to the *macula densa* cells of the distal tubule (which lie close to the JGC and, together, form the juxtaglomerular apparatus); (3) sympathetic nerve stimulation via β_1-adrenergic receptors and (4) negative feedback by a direct action of angiotensin II (Ang II) on the JGC and by an increase in sympathetic activity.[2]

Angiotensinogen (Ang), a precursor of angiotensin I (Ang I), is encoded by the AGT gene located on chromosome 1q42 – q43, is mainly produced by the liver and found in the α-globulin of the plasma. Renin catalyses the first step in the activation pathway of Ang, cleaving it to obtain a decapeptide, Ang I, which is biologically inert. In fact, the biologically active molecule is obtained through hydrolysis of Ang I by the action of angiotensin converting enzyme (ACE), which forms Ang II, whereas the renin remains in the blood system for 30 to 60 min and continues to induce the production of Ang I. Other metabolites of Ang I and Ang II may have significant biological activity, particularly in tissues. Angiotensin III (Ang III) and angiotensin IV (Ang IV) are formed by the sequential removal of amino acids from the N-terminus of Ang II. Ang III is present in the central nervous system (CNS) and is involved in kidney damage in mesangial cells and renal injury.

The pharmacological inhibition of the RAAS can be obtained through three different basic mechanisms: (1) inhibition of Ang II generation from Ang I, achieved through inhibition of ACE; (2) inhibition of the action of Ang II at the level of its receptor(s) and (3) inhibition of Ang I generation from Ang obtained by direct inhibition of renin.

The rationale for the use of these three drug classes has steadily expanded beyond their proven efficacy as antihypertensive agents. In particular, they have been shown to provide special advantages in three group of patients: those with heart failure, coronary ischaemia or nephropathy.

Angiotensin converting enzyme inhibitors (ACE-Is) block the action of ACE, a bivalent dipeptidyl carboxyl metallo-peptidase that cleaves the C-terminal dipeptide from Ang I and bradykinin. The use of ACE-Is in the treatment of hypertension has steadily expanded as they have been shown to provide special advantages in a large group of hypertensive patients. Ang I receptor blockers (ARBs) displace Ang II from its specific angiotensin type 1 (AT_1) receptor, antagonising all of its known effects and resulting in both a dose-dependent fall in peripheral resistance and little change in heart rate or cardiac output. As a consequence of the competitive displacement, the circulating levels of Ang II increase and, at the same time, the blockade of the renin–angiotensin mechanism is more complete, including any Ang II that is generated through pathways that do not involve ACE. An important and obvious difference between ARB and ACE-I is the absence of an increase in kinin levels that may be responsible for some of the beneficial effects of ACE-Is and their side effects. The compounds that block the vital stages of the RAAS cascade, such as ACE-I,s ARBs and aldosterone receptor antagonists, were important in extending our treatment options. However, the positive therapeutic effects of these compounds also have certain negative consequences. Administration of ACE-Is and ARBs interrupts physiological feedback for renal renin release and leads to a reactive elevation in circulating active renin

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and greater production of Ang I and Ang II, with a subsequent return of aldosterone secretion to the pretreatment levels ('escape' phenomenon). These possible adverse effects of the intermediary products of incomplete RAAS blockade leading to organ complications have facilitated efforts to develop compounds that block the initial stages of the renin–angiotensin cascade, such as aliskiren, which reduces plasma renin activity (PRA) and neutralises hydrochlorothiazide-induced RAAS activation. Once-daily administration of the drug leads to activity over more than 24 h, and its prolonged blocking effects on the kidneys are the basis for its renal protection. Aliskiren, the most advanced of the new class of orally active, non-peptide, low-molecular weight renin inhibitors, has demonstrated favourable effects on vascular inflammation, remodelling and neurohumoral mediators of various forms of cardiovascular complications, including chronic heart failure (CHF) and proteinuria in diabetic patients. Many published studies have demonstrated a relationship between PRA and acute myocardial infarction (AMI), CHF, left ventricular hypertension (LVH), modification of function renal indexes and development of hypertension in obese subjects.[3] Large randomized controlled clinical trials have demonstrated the efficacy of once-daily administration of aliskiren in the treatment of patients with mild-to-moderate hypertension, either as a monotherapy or in combination with diuretics, calcium channel blockers (CCBs), ACE-Is, ARBs, β-blockers or as a monotherapy in the treatment of severe hypertension, CHF and diabetic nephropathy.[4]

Microvascular complications of hypertension such as nephropathy, retinopathy and neuropathy represent important aspects of hypertension disease. It is important to diagnose and treat these conditions before they manifest themselves as microvascular diseases of the retina, kidneys and nervous system. A growing body of evidence suggests that shared pathophysiologic mechanisms initiate and promote dysfunction in the micro/macrovasculature in individuals with diabetes and hypertension. Despite the frequent concomitance of nephropathy, retinopathy and neuropathy, it is increasingly apparent that these three conditions may progress independently of one another.

The specific pathophysiologic mechanisms of microvascular damage are not well understood. In studies of spontaneously hypertensive rats early inflammatory responses were documented in the retina, and these were directly attributable to diabetes and exacerbated by hypertension, suggesting that the AT_1 receptor activation contributes to blood–retinal barrier dysfunction. Other animal studies documented an enhanced expression of fibronectin and vascular endothelial growth factor, breakdown of the blood–retinal barrier and withdrawal of neuroprogenitor cells from the cell cycle.

In an important study by *Chou et al.*[5] published in *Hypertension Research* the authors demonstrated many favourable effects of aliskiren treatment in fructose-fed rats. In particular, the authors showed a significant reduction in systolic blood pressure (SBP) after aliskiren treatment with values similar to those of control rats. The treatment with aliskiren demonstrated an improvement in glycolipidic metabolism indexes. In particular, the treatment with aliskiren ameliorates the rise in plasma glycaemia and glucose intolerance, insulin resistance, triglycerides and total cholesterol profiles. The treatment does not alter food intake, body weight gain, water intake or urine flow throughout the entire study period. Another important aspect of this study regards the effects of aliskiren on endothelial function and the nitrergic system. The treatment with aliskiren resulted in higher plasma nitrite levels than those in fructose-fed rats, suggesting that aliskiren has the ability to stimulate nitric oxide (NO) release, significantly reduces vascular wall hypertrophy and decreases lipid peroxide levels compared to those seen in rats on a high-fructose diet.

A more complete inhibition of RAAS may be the object for new therapeutic targets for the treatment of hypertensive disease. Published studies suggested that alternative pathways to the ACE exist for Ang I generation in the heart, large arteries, and the kidney. *Hollenberg et al.*[6] studied the renal vasodilator response to three ACEIs, two renin inhibitors and two ARBs at the top of their respective dose–response relationships in young and healthy human volunteers. Both renin inhibitors and both ARBs that were studied induced a renal vasodilator response of 140 to 150 ml min per 1.73 m^2, ∼50% larger than the maximal renal hemodynamic response to ACE inhibition, which was 90 to 100 ml min per 1.73 m^2. These findings indicate that in the intact human kidney, virtually all Ang II generation is renin-dependent but at least 40% of Ang I is converted to Ang II by pathways other than ACE, presumably a chymase, although other enzyme pathways exist. One implication of this study is that at the tissue level, direct renin inhibitors and Ang II antagonists have much greater potential for blocking the RAAS than does ACE inhibition.

Aliskiren suppresses the RAAS by directly inhibiting PRA. Both animal and human studies have shown much evidence suggesting that aliskiren is effective for BP control, inhibits the progression of chronic kidney and cardiovascular diseases, and has favourable pleiotropic effects by exerting action in improving glycolipidic metabolism profile and endothelial wall function.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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