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Does the Clinical and Therapeutic Profile of Eprosartan Contribute to End Organ Protection?

C. V. S. Ram

Systemic hypertension is a major risk factor for premature morbidity and mortality. The diseases caused by hypertension can be serious and deadly. Therefore, various guidelines consistently recommend lower target levels of blood pressure for intervention. One important mechanism sustaining hypertension and causing target organ damage is the renin-angiotensin system. Hence, interruption of this system with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) offers a useful avenue to lower the cardiovascular risk. Of particular benefit are ARBs, which not only lower the blood pressure effectively, but also cause no side effects. Thus, ARBs provide a logical and physiological approach to treat hypertension. Among all the available ARBs, eprosartan possesses a unique mechanism of action in inhibiting both the renin-angiotensin system and also the sympathetic nervous system; this dual mechanism of action offers distinct physiological and pharmacological benefits to the patients. Studies have shown that eprosartan is not only effective in controlling hypertension, but also provides remarkable target organ protection. J Clin Basic Cardiol 2005; 8: 7–9.

Key words: angiotensin receptor blockade, systemic hypertension, MOSES trial, stroke, eprosartan, cardiovascular damage

The results of many laboratory and clinical studies have clearly established the role of the renin-angiotensin-aldosterone system (RAAS) in the development and maintenance of high blood pressure (BP) and its complications such as myocardial infarction (MI), heart failure, stroke, and kidney failure. Therapeutic approaches that target the synthesis or biologic activity of angiotensin II lower elevated BP, thereby reducing the risk of the clinical sequelae associated with high BP. A large number of clinical trials have demonstrated the ability of angiotensin converting enzyme (ACE) inhibitors to lower BP as well as to reduce the risk of recurrent MI. Although they have relatively few side effects, dry persistent cough is common with all agents in the class; angioedema is rare but potentially serious, and skin rash is sometimes seen at higher doses.

A newer, extensively studied class of antihypertensive agents is the angiotensin receptor blockers (ARBs). ARBs prevent the binding of angiotensin II to the AT₁ receptor, which regulates several physiologic processes that contribute to hypertension. In contrast with ACE inhibitors, ARBs do not interfere with the production of angiotensin II or the activity of angiotensin II at other, potentially beneficial, subtypes of angiotensin receptors. ARBs selectively target one of the central mechanisms of hypertension, and thereby reducing the risks of cardiovascular and cerebrovascular events.

ARBs have emerged as effective and safe agents for the treatment of hypertension and cardiovascular disease risk reduction either as monotherapy or in combination with other classes of drugs. Although ARBs share many common characteristics, there are some possible differences among them and such differences should be considered in clinical decision-making. While all ARBs antagonise the AT₁ receptor, there are additional mechanisms and sites involved in regulating BP. For example, some novel ARBs not only attenuate

the consequences of angiotensin stimulation, but also cause a subtle or gentle sympathetic blockade. This dual mechanism of action (MOA) provides a rational approach to treat hypertension effectively while neutralising the multiple pathophysiological mechanisms that cause the BP level to go up. By countering the mosaic of hypertensive mechanisms, ARBs might also offer greater efficacy that permits patients to achieve a target level of BP control.

Angiotensin II and Cardiovascular Damage

Angiotensin II (Ang II) dysregulation promotes harmful changes in cardiac myocytes, fibroblast proliferation and interstitial collagen formation, left ventricular hypertrophy (LVH), and pathological cardiovascular remodelling. The action of Ang II on NADPH oxidase also increases ROS. Less nitric oxide (NO) is then available to mediate vasorelaxation when the endothelium is stimulated, which leads to vasoconstriction and vascular remodelling. In addition, the redox state of cell also regulates NF- κ B, which provides another avenue by which Ang II's oxidative effects can promote inflammation and damage the cardiovascular system. Ang II also affects lipid transport and promotes vascular endothelial dysfunction by increasing the number of cellular receptors for oxidised LDL and its transport into the cell. When the stimulated macrophage takes up oxidised LDL to form a foam cell, atheromatous plaque results.

SNS Activation and Cardiovascular Damage

Like Ang II dysregulation, activation of the SNS has many harmful cardiovascular effects. For example, SNS activation increases RAAS activation and vasoconstriction, promotes endothelial injury, and decreases myocyte contractility and left ventricular efficiency. It also decreases coronary blood flow, promotes myocardial ischaemia, and increases arrhythmia.

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mia risk. In addition, it promotes the release of growth factors that contribute to progressive cardiac remodelling and can result in diastolic and/or systolic dysfunction. Finally, SNS activation not only activates cytokines but also increases the permeability of vascular cells to various factors that promote atherosclerosis.

The RAAS, the SNS, and SBP

Therapeutic interest has focused on agents that decrease the progression of atherosclerosis by inhibiting RAAS and SNS activation. For instance, beta-blockers, which reduce SNS activation, have been shown to reduce the incidence of sudden death [1]. Therapeutic interest also has focused on reducing systolic blood pressure (SBP), an important determinant of cardiovascular mortality, particularly in people with type 2 diabetes [2]. The SNS and RAAS work together to increase peripheral vascular resistance, which, over time, can decrease proximal arterial compliance. Such decreased compliance causes the proximal blood vessels to incorporate less elastin and more collagen, resulting in interstitial fibrosis and increased SBP.

Limiting the Target Organ Damage

Because Ang II-related cardiovascular damage is mediated through the AT₁ receptor, stopping the damage requires blocking the receptor or the rate-limiting enzyme with agents from one of three drug classes: renin antagonists, ACE inhibitors, or ARBs. Renin antagonists, although offering an attractive potential, will not be available for a number of years. ACE inhibitors cannot affect ACE-independent pathways, such as the kinase pathway, which can create Ang II from Ang I. Unlike ACE inhibitors, AT₁ receptor antagonists (ARBs) not only block pathways that are ACE independent, but some ARBs also may block the norepinephrine released when Ang II stimulates AT₁ receptors in the presynaptic adrenoceptor terminal. This ability has been verified experimentally by a study of pithed rats, which showed that eprosartan inhibits SNS activity and related increases in BP caused by spinal cord stimulation, and that saralasin can reverse the increase in SNS activation and BP caused by Ang II infusion [3].

Neurohormonal and Mechanistic Effects of ARBs

SNS and RAAS activation are two important factors that promote endothelial dysfunction, hypertension, and pathological cardiovascular remodelling. Stopping the cardiovascular damage that results from Ang II requires blocking the AT₁ receptor or ACE. Unlike ACE inhibitors, ARBs block both ACE-dependent and ACE-independent production of Ang II, and some ARBs may inhibit the SNS.

The side-effect profile of ARBs is equal to or better than that of placebo. ARBs have no known side effects, and their ability to reduce the incidence of headache and other often unrecognised symptoms of hypertension might explain why their side-effect profile may be better than that of placebo. Moreover, unlike beta-blockers, ARBs have no effect on the heart rate, and, unlike ACE inhibitors, ARBs do not increase the level of bradykinin, which when elevated can produce dry cough. Also, because ARBs block Ang II formed by both ACE-dependent and ACE-independent pathways, ARBs block Ang II more thoroughly than ACE inhibitors. The practical benefits of ARBs have been shown in several clinical studies, and an observational European study of 25,000 patients found that ARB therapy resulted in the highest treat-

ment persistence rate (75 %), followed by ACE inhibitor therapy (42 %) [4]. These findings suggest that the absence of side effects with ARBs may promote greater treatment duration [5].

Ang II, Aldosterone, Endothelin, and Plasminogen Activator Inhibitor-1

The deleterious effects of Ang II are not restricted to abnormal vasoconstriction and SNS activation. For example, Ang II increases the level of aldosterone, a major cause of cardiovascular fibrosis, and promotes cardiac hypertrophy. Ang II also promotes the release of endothelin, which is the most important known vasoconstrictor, and vasopressin. Together, endothelin and vasopressin can decrease vascular compliance. Ang II also promotes the release of plasminogen activator inhibitor-1, which increases the risk of thrombosis [6].

Ang II Blockade Decreases Risk of Cardiovascular Events

The importance of Ang II blockade in preventing these effects is supported by the finding that drugs blocking the RAAS are superior to other drugs in reducing the risk of cardiovascular events. For example, in the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study, the risk of reaching the primary end point – a composite of acute myocardial infarction, stroke, or cardiovascular death – was reduced by 13 % in losartan-treated patients relative to the risk for atenolol-treated patients ($p = 0.02$) and by 25 % in the diabetic subgroup of losartan-treated patients relative to atenolol-treated patients ($p = 0.03$) [7]. Moreover, LIFE found significantly greater LVH regression in losartan-treated patients than in atenolol-treated patients as indicated by percentage reduction from baseline in electrocardiographic criteria ($p < 0.0001$) [8]. These results were supported by the results of a meta-analysis of 14 studies, which found that, at a similar degree of BP reduction, LV mass was much more effectively reduced with agents that block the RAAS system than with other agents [9].

Dual Mechanism of Action of Eprosartan

Eprosartan is chemically distinct from other ARBs and, unlike other ARBs, has a dual mechanism of action: it not only blocks the AT₁ receptor but also blocks SNS discharge by inhibiting the presynaptic noradrenergic release stimulated by Ang II. In an animal model, eprosartan, unlike other ARBs, was found to significantly inhibit the sympathetically stimulated increase in BP [10]. In addition, long-term administration of eprosartan significantly reduced heart rate in rats made hypertensive by eating a hypercaloric diet, which induces sympathetic activation [11]. This ability of eprosartan to block SNS discharge may be particularly valuable because inhibition of neurohormonal activity may reduce the risk of cardiovascular complications.

ARBs in Combination Therapy

Many patients require more than one antihypertensive agent to reach new target blood pressure levels, which makes the ability of agents to complement each other particularly valuable. Such ability has been shown for the combination of eprosartan and a diuretic, which potentiates eprosartan's antihypertensive effects [12]. The effectiveness of this combination also was shown by the finding that adding a low dose of hydrochlorothiazide (12.5 mg or 25 mg) to eprosartan therapy resulted in a statistically significant additional reduc-

tion in blood pressure. Moreover, this combination was as effective in reducing blood pressure in the elderly as it was in the young.

The effects of eprosartan therapy in stroke patients were compared with those of nitrendipine in MOSES (Mortality and Morbidity After Stroke – Eprosartan versus Nitrendipine in Secondary Prevention study) [13]. Nitrendipine was chosen as the comparator agent in MOSES because it was found to reduce the frequency of stroke and dementia [14, 15] in the Syst-Eur study. MOSES assessed the impact of antihypertensive therapy on morbidity, mortality, functional state, and cognitive function after stroke in about 700 men and an equal number of women (mean age: 68) recruited at 312 sites in Germany and Austria. Average follow-up was 2 to 4 years. In the MOSES study, the clinical outcomes were superior with eprosartan compared to nitrendipine suggesting a possible advantage for ARBs in cerebro-protection.

Therapeutic Advantages of ARBs

Although SBP reduction reduces almost all cardiovascular end points, elevated SBP is widely undertreated. Moreover, even when treatment is initiated, persistence rates are low because patients are reluctant to accept drug side effects for an asymptomatic condition. Because they have a side-effect profile similar to that of placebo, ARBs can lengthen the duration of antihypertensive treatment. The ARB eprosartan may have advantages over other antihypertensive agents in its class because of its dual mechanism of action, which not only blocks Ang II but also blocks SNS activation related to its effects at the presynaptic level.

Summary

Hypertension and atherosclerosis are inflammatory diseases. Ang II, well known as a vasoconstrictor hormone, also promotes inflammation, which contributes to hypertension and atherosclerosis. Ang II does this by activating NF- κ B, the hub of inflammatory signaling; by increasing oxidative stress; by promoting the accumulation of the adhesion molecule VCAM-1 and the chemoattractant molecule MCP-1; and by increasing the production of IL-6, which signals the liver to produce CRP.

Ang II dysregulation damages cardiac myocytes, promotes LVH and pathological cardiovascular remodelling, and increases the transport of oxidised LDL into vascular cells. Because Ang II is more harmful to the cardiovascular system than was previously noted, controlling Ang II production appears particularly crucial for improving clinical outcomes. By blocking both ACE-dependent and ACE-independent pathways, ARBs block Ang II production more completely than ACE inhibitors do.

Like overproduction of Ang II, SNS activation increases vasoconstriction, activates inflammatory cytokines, decreases myocyte contractility, and promotes endothelial injury and

cardiac remodelling. In addition, by activating the RAAS, SNS activation can also increase Ang II levels. Because of these adverse effects, controlling blood pressure by inhibiting both RAAS and SNS activation may improve cardiovascular outcomes more than RAAS inhibition alone.

Unlike other ARBs, eprosartan not only blocks Ang II but also blocks SNS activation by Ang II at the presynaptic level. Eprosartan thus may be especially beneficial in improving clinical outcomes, particularly in patients with stress-related hypertension and a high degree of associated SNS activation. It can be thus speculated with confidence that the clinical and therapeutic profile of eprosartan may contribute to target organ protection in patients with hypertension.

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