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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 sequela 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 nitricoxide (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-κB, 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 ischemia, and increases arrhyth-
From Ang I. Unlike ACE inhibitors, AT1 receptor antagonists
years. ACE inhibitors cannot affect ACE-independent path-
agents from one of three drug classes: renin antagonists, ACE
inhibitors, or ARBs. Renin antagonists, although offering an
ACE-dependent and ACE-independent pathways, ARBs
increased SBP.

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 sud-
den death [1]. Therapeutic interest also has focused on re-
ducing systolic blood pressure (SBP), an important determin-
ant 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 com-
pliance 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 path-
ways, 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
during Ang I stimuliates AT1 receptors in the presynaptic
adrenoreceptor terminal. This ability has been verified ex-
perimentally 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 re-
verse 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 pro-
mote endothelial dysfunction, hypertension, and pathologi-
cal 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 abil-
ty to reduce the incidence of headache and other often un-
recognised 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 pa-
tients 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 du-
ration [5].

Ang II, Aldosterone, Endothelin, and
Plasminogen Activator Inhibitor-1
The deleterious effects of Ang II are not restricted to abnor-
mal vasoconstriction and SNS activation. For example, Ang II
increases the level of aldosterone, a major cause of cardio-
figrosis, and promotes cardiac hypertrophy. Ang II also pro-
motes the release of endothelin, which is the most important
known vasoconstrictor, and vasopressin. Together, endothe-
lin 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 ef-
fects is supported by the finding that drugs blocking the
RAAS are superior to other drugs in reducing the risk of car-
diovascular events. For example, in the LIFE (Losartan In-
tervention 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 per-
centage reduction from baseline in electrocardiographic cri-
teria (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 ef-
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, un-
like other ARBs, has a dual mechanism of action: it not only
blocks the AT1 receptor but also blocks SNS discharge by in-
hibiting the presynaptic noradrenergic release stimulated by
Ang II. In an animal model, eprosartan, unlike other ARBs,
was found to significantly inhibit the sympathetically stimu-
lated increase in BP [10]. In addition, long-term administra-
tion of eprosartan significantly reduced heart rate in rats
made hypertensive by eating a hypercaloric diet, which in-
duces 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 valu-
able. Such ability has been shown for the combination of
eprosartan and a diuretic, which potentiates eprosartan’s an-
thypertensive effects [12]. The effectiveness of this combi-
nation 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-κB, 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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