Pharmacology and Clinical Efficacy of Angiotensin Receptor Blockers

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The treatment of hypertension has become increasingly refined during the past decade. Although a variety of antihypertensive medication classes exist, drugs that interrupt the renin-angiotensin axis have gained a favored position in the treatment of hypertension and its attendant end-organ complications. In this regard, two drug classes, angiotensin converting enzyme inhibitors and angiotensin receptor blockers, are most commonly used. Angiotensin receptor blockers have proven highly effective in the management of hypertension. This class is fairly heterogeneous with individual class members having somewhat distinctive pharmacologic properties. Eprosartan is a recent entry into this class. This compound compares favorably to others in this class relative to blood pressure reduction. In addition, preliminary studies indicate that this compound may uniquely interrupt the sympathetic nervous system and thereby preferentially reduce systolic blood pressure. Am J Hypertens 2001;14:242S–247S © 2001 American Journal of Hypertension, Ltd.

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Considerable resources have been devoted to developing pharmacologic treatments for hypertension during the past 40 years and we now have several classes of drugs with which to treat this condition. These drugs vary in their mechanisms of action and are often uniquely directed at different sites or receptors within the circulatory system, with varying degrees of success in controlling blood pressure (BP) and limiting end-organ damage. Of the different classes of antihypertensive agents, a number now have as a primary mechanism of action an interruption of the renin-angiotensin system (RAS) with the angiotensin II receptor blockers (ARB) being the newest class in this regard.

Angiotensin II plays a pivotal role in hypertension and end-organ disease. Both angiotensin converting enzyme (ACE) inhibitors and ARB temper the untoward effects of angiotensin II by targeting the RAS. Each does this in a distinct manner. Although ACE inhibitors repress the conversion of angiotensin I to angiotensin II, ARB work at a more distal site, at the level of the AT₁ receptor. The BP reduction that occurs with ARB occurs in a highly selective manner whereby these compounds hinder the activity of angiotensin II independent of its source. Thus, whether angiotensin II is generated by the action of ACE or by ACE-independent pathways involving either chymostatin-sensitive angiotensin II-generating enzyme (CAGE) or chymase, the action of angiotensin II is blocked. ¹ Although ARB accomplish comparable BP reductions to what is seen with ACE inhibitors,² their high degree of selectivity may afford the ARB a therapeutic advantage over a drug class like the ACE inhibitors relative to end-organ disease. The ACE inhibitors have a broader range of effects, which includes their ability to interfere with bradykinin and substance P metabolism. This latter property has been implicated in the genesis of dry cough, a not uncommon side effect with ACE inhibitors.³

Pharmacokinetics/Pharmacodynamics

Understanding the therapeutic use of a class of drugs requires having a firm grasp of the pharmacokinetics and pharmacodynamics of individual class members. Of late, the pharmacotoxicology and the pharmacogenetics of drugs have also begun to enter into the physician’s decision on which agents to use in the management of hypertension. In brief, the ARB are a diverse group of drugs whose individual class members have distinctive pharmacologic features of which the most important include absolute bioavailability, volume of distribution (Vₐ), protein binding, plasma half-life, and mode of elimination.⁴

The absolute bioavailability of a compound is commonly viewed as a major determinant of drug effect but may not accurately predict the extent of therapeutic effect. For example, eprosartan, which at a value of 13% has the
lowest absolute bioavailability of the ARB, yet remains a highly effective agent. The V_D is a pharmacokinetic parameter that often correlates with the degree of protein binding for a compound. All ARB are more than 90% protein bound, with eprosartan being 98% protein bound, which accounts for its very small V_D. Two of the ARB, irbesartan and telmisartan, have a larger V_D than the others despite equally extensive protein binding. This may reflect “looser” protein binding, particularly for telmisartan.

The ARB exhibit considerably different half-lives. This is a difficult pharmacokinetic parameter to interpret as the plasma half-life of an ARB only roughly approximates its duration of effect. A more accurate estimate of duration of effect for an ARB could be made if sampling at tissue-based AT1 receptors were feasible. In the absence of such sampling capability, the duration of BP control with an ARB becomes the best gauge for there being effective plasma/tissue concentrations.

The mode of elimination for ARB perhaps has greater value than the other pharmacokinetic parameters with regard to clinical implications. The mode of elimination for the ARB is predominantly hepatic, in contrast to the ACE inhibitors, which are cleared from the body primarily through the kidneys (Table 1). This may make them better suited than ACE inhibitors for the treatment of hypertension in patients with impaired renal function as drug accumulation will be negligible. The hypothesis that nonaccumulating drugs, such as the ARB, are safer in patients with renal failure remains to be formally tested. The ACE inhibitors and ARB must be used cautiously, if at all, in patients with bilateral renal artery stenosis or unilateral renal artery stenosis and a solitary kidney.

Unlike ACE inhibitors, which in certain cases are dialyzable, the ARB as a class of drugs are not dialyzable. Despite their structural similarities, the ARB block the AT1 receptor in different ways. Irbesartan, candesartan, and telmisartan are insurmountable (noncompetitive) antagonists, whereas losartan, valsartan, and eprosartan are competitive antagonists. The competitive mode of antagonism may be best viewed as an alternating current of electricity, that is, having an on/off property. Although not technically correct, this analogy is useful in understanding the interaction between receptor and agent. In patients who are very drug responsive, this quality can prove advantageous in that it may, at least in theory, temper the therapeutic effect. Of note, the losartan metabolite EXP03174 is an insurmountable antagonist. Finally, candesartan is the only ARB, other than losartan, that has an active metabolite.

### Eprosartan

Although ARB may differ in many of their pharmacologic characteristics, they are all structurally related to losartan with the exception of eprosartan. Eprosartan is the only AT1 receptor antagonist that is a nonbiphenyl, nontetrazole moiety. Eprosartan’s novel structure may, in part, explain its ability to modify preferentially sympathetic nerve activity in animal models. There is also evidence of superior efficacy in African American hypertensives when this drug is compared with the ACE inhibitor enalapril.

Eprosartan also has an apparent strong affinity for the kidney. In this regard, the recommended starting dose for the treatment of hypertension with this compound is 600 mg/day. However, a plateau is achieved for the change in renal plasma flow at substantially lower doses—approximately 100 mg/day—and changes are detectable in this parameter at doses as low as 10 mg/day. This raises the intriguing possibility of there being dose ranges for different indications with this agent. It seems reasonable to infer that this could prove to be a very valuable property in individuals at risk for change in renal function with conventional doses of an ARB. Such may be the case in patients with congestive heart failure.

### Interaction Between Angiotensin II and the Sympathetic Nervous System

Angiotensin II has profound effects on the sympathetic nervous system. In addition to directly enhancing norepinephrine release, angiotensin II attenuates normal baroreflex responses. AT1 receptors have been found on presynaptic nerve terminals as well. However, although it is known that the RAS accomplishes an increase in BP by way of several different mechanisms (Fig. 1), the precise contribution of the sympathetic nervous system to the

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**Table 1. Pharmacology of angiotensin receptor blockers**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-Life (h)</th>
<th>Bioavailability (%)</th>
<th>Volume of Distribution</th>
<th>% Renal/Hepatic Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>9</td>
<td>15</td>
<td>0.13 L/kg</td>
<td>60</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>5</td>
<td>13</td>
<td>13 L</td>
<td>30</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>11–15</td>
<td>60–80</td>
<td>53–93 L</td>
<td>1</td>
</tr>
<tr>
<td>Losartan</td>
<td>2</td>
<td>33</td>
<td>34 L</td>
<td>10</td>
</tr>
<tr>
<td>E-3174</td>
<td>6–9</td>
<td></td>
<td>12 L</td>
<td>50</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>24</td>
<td>42–58</td>
<td>500 L</td>
<td>1</td>
</tr>
<tr>
<td>Valsartan</td>
<td>6</td>
<td>≈25</td>
<td>17 L</td>
<td>30</td>
</tr>
</tbody>
</table>
pathogenesis of hypertension has proved difficult to ascer-
tain. Nonetheless, it does appear that sympathetic nervous 
system activity plays a role in the chronic alteration of the 
structure and function of target organs in hypertensive 
patients.21,22

The sympathetic nervous system and the RAS represent 
mutually reinforcing pressor systems, which may have 
evolved as a survival mechanism to operate in times of 
physiologic stress. However, the stresses of modern life 
differ considerably even from those encountered in prein-
dustrial times, and the interactions of these two systems 
can elevate BP excessively. Furthermore, in the presence 
of hypertension, their continuing activation and the effects 
of both catecholamines and angiotensin II on myocardial 
and vascular tissue can accelerate the changes in these 
structures, thus perpetuating the disease state.23

Although a number of studies have investigated the use 
of ACE inhibitors in preventing end-organ disease states 
such as renal disease and congestive heart failure, the 
results to date have been inconclusive relative to the 
contribution of the sympatholytic effect of ACE inhibitors 
to the observed findings.24–27 Given the pharmacodyna-
mics of the ARB class of drugs, it would seem natural that 
these agents might offer some therapeutic advantage over 
the ACE inhibitors in preventing end-organ disease. Al-
though both drug classes may favorably modify sympa-
thetic nervous system activity, the means by which each 
drug class accomplishes this change in sympathetic activ-
ity are likely to differ considerably. A thorough examina-
tion of this issue has yet to be undertaken.

In this regard, promising research findings have 
emerged on the sympathetic nervous system effects of the 
ARB eprosartan. Ohlstein et al20 found that eprosartan 
inhibited the pressor response induced by spinal cord 
stimulation in pithed rats. Equivalent doses of other ARB, 
including losartan, valsartan, and irbesartan, had little ef-
flect on this pressor response to spinal cord stimulation. It 
was suggested that the greater systolic BP-lowering effect 
with eprosartan observed in several studies could have 
originated from the more profound sympathetic nervous 
system inhibitory effect with eprosartan.

Although the results remain less than conclusive, the 
data obtained are instructive and may ultimately help 
elucidate the interaction between the sympathetic nervous 
system and angiotensin II. More recently, human studies 
with the compound eprosartan have demonstrated a 
heightened effect for the agent on systolic BP.6,28 These 
findings indicate that a unique interaction may exist be-
tween the sympathetic nervous system and eprosartan, 
which may, in part, relate to its affinity for the presynaptic 
AT1 receptor (Fig. 2).

**Trough:Peak Ratios Versus the Smoothness Index**

Although frequently used to establish the therapeutic effect 
of an agent throughout a dosing period, trough:peak ratios 
pose difficulties. There is a serious question as to whether 
this measure adequately gauges BP control. The BP is 
measured 4 to 6 h after the initial dose and then again at 
the end of the dosing interval. Although the ratio of these 
two values gives some indication of an agent’s perform-
ance, this indication is oftentimes inadequate. Evidence 
suggests that the end-organ damage resulting from hyper-
tension is significantly related not only to 24-h average 
BP, but also to BP variability within that period.29,30 Thus, 
it has been suggested that optimal antihypertensive ther-
apy should have a constancy of effect that maintains BP 
reduction during a 24-h period with minimal fluctua-
tions.31

In accordance with this observation, the Sixth Joint 
National Committee on Prevention, Detection, Evaluation,
and Treatment of High Blood Pressure (JNC VI) has formulated a number of recommendations for desirable qualities for an antihypertensive agent, including 24-h efficacy with once-daily dosing and at least 50% of the peak effect remaining at the end of the 24 h. JNC VI further states that control of hypertension should be “persistent and smooth rather than intermittent,” and should protect against the risk of sudden death, heart attack, and stroke caused by an abrupt increase in BP upon arising in the morning.32

Recently, a new measure of antihypertensive effect was developed—the smoothness index (SI). The SI of a particular agent is determined by taking the inverse of the standard deviation of all hourly BP changes over a 24-h period.33 Although trough:peak ratio has a nonnormal distribution of values and limited reproducibility, the normal distribution of SI values provides meaningful data for evaluation of drug performance in individual patients and for application to clinical practice.34,35 Furthermore, the SI is more reproducible than the trough:peak ratio and, unlike the trough-peak ratio, has been found to correlate with regression of left ventricular hypertrophy.34 The trough:peak ratio, however, does allow a time-related analysis of performance, and it remains an element of the Food and Drug Administration guidelines for determining once-daily dosing.

At this time, the SI has yet to become standard, and most agents have data given in terms of trough:peak ratio. Eprosartan has a favorable performance for this measure. Hedner et al.36 found that, given in a once-daily dose of 400 to 800 mg or a twice-daily dose of 200 to 400 mg, eprosartan achieved trough:peak ratios of 67% and 87%, respectively. These findings demonstrate that once-daily dosing of eprosartan is an effective regimen for maintaining BP control (Fig. 3).14,15

Conclusion

The ARB class in general, and eprosartan in particular, has been found to be both safe and well tolerated in the treatment of hypertension, with a side effect profile similar to that seen with placebo.14,15,37 In clinical studies, eprosartan has demonstrated efficacy equal to or greater than that of enalapril in controlling BP.3,6 The potential for the ARB class of drug to exert a favorable effect on both sympathetic nervous system mechanisms involved in BP control and on the RAS gives hope that an effective means of preventing end-organ disease in hypertension is now within our means. As data become available from studies on the efficacy of the ARB in preventing tissue damage, their pharmacodynamic and pharmacokinetic parameters can be put into perspective. Although at this point BP data are very promising, and the safety and tolerability profiles are excellent, it is ultimately the reduced morbidity and mortality that will be the most significant considerations with the ARB. Given the success of the ACE inhibitors and the specificity of the ARB in blocking the same RAS pathways, it is reasonable to believe that the ARB could surpass the ACE inhibitors in reducing both the morbidity and the mortality associated with hypertension. Eprosartan’s apparent greater affinity for presynaptic AT1 receptors, its ability to act on the sympathetic nervous system, and its efficacy in reducing systolic BP may make it an especially valuable agent in modifying the consequences of this disorder.
References


