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Role of Angiotensin Receptor Antagonists in the treatment of Hypertension, Heart Failure, and Renal Disease

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Clinical pharmacokinetics and metabolism studies show that losartan in an active, potent, and selective angiotensin II (Ang II) receptor blocker. It has a rapid and smooth onset on blood pressure, and is solely responsible for the beneficial antihypertensive effects on target organ damage.

Losartan is converted to the active metabolite E-3174 by the liver cytochrome P450 enzyme system. E-3174 exhibits significant biochemical activity and contributes to the duration of action as well as having a greater affinity for the AT_1 receptor. Losartan, the active parent compound has a mean half-life of approximately 4-6 hrs. The active metabolite, E-3174, has a half-life exceeding 9 hrs. This dual antihypertensive action of both the parent compound and its metabolite may account for the prolonged and smooth blood pressure control observed in clinical trials and in the clinical experience gained in its worldwide application.

Angiotensin II receptor blockers (ARBs) comprise a new class of antihypertensive agents whose action is mediated by prevention of binding of Ang II to the AT_1 receptor. As an agent with indications for first line therapy of hypertension, ARBs controls blood pressure and retards Ang II related target organ damage. Within the family of therapeutic agents that antagonize the pathological actions of Ang II, ARBs differ from beta-blockers and angiotensin converting enzyme (ACE) inhibitors as illustrated in table 1.

Clinically, the effects of ARBs are comparable to those obtained with ACE inhibitors, although additional long-term clinical studies are required to validate experimental conclusions. Nevertheless, the selective and specific action of ARBs in blocking the AT_1 receptor affords a greater degree of specificity in preventing the pathological actions of Ang II. There are also opportunities to combine the beneficial aspects of ACE inhibitors and ARBs by the synergistic effect that is achieved from combining inhibition of Ang II formation and receptor activity.

Table I. Similarities and Differences

Component	β-Blockers	ACE Inhibitors	ARBs
Renin Activity	(-)	(+++)	(++)
Angiotensin I	(-/+)	(+++)	(+)
Converting Enzyme	(-/+)	(-)	(-/+)
Angiotensin II		Acutely (-)	
	(-)	Chronically (-/+)	(+)
Angiotensin-(1-7)	not determined	(+++)	(++)
Kinins	(-/+)	(+++)	(-)

Keys: (-/+), no change; (+), increase; (-), inhibits.

The assumption that ARBs may represent a single class of agents may require revision because there are differences in the action and effects between various receptor blockers. This is not unexpected since variations in the chemical structure of ARBs can have significant effects on their ability to bind to target organ receptors and access AT_1 across the blood brain barrier or intracellularly.

Two examples are illustrated. Losartan, the active parent peptide has been observed to produce a significant and sustained reduction in serum uric acid, a factor associated with increase risk for cardiovascular disease and a troublesome co-morbid event in congestive heart failure. Todate, other ARBs appear not to reduce serum uric acid or augment urinary excretion of this factor. In animals, both losartan and E-3174 inhibit monocyte adhesion and act as competitive blockers of the thromboxane A_2 receptor. Valsartan and candersartan, two other Ang II receptor blockers are weak antagonists at the thromboxane A_2 receptor. Thus, losartan and its active metabolite show additional beneficial actions not shared by two other Ang II antago-

nists: reversal of hyper-uricacidemia and antithrombotic effects. In keeping with these observations, losartan has been shown to retard the development of atherosclerosis in a non-human primate model by inhibiting monocyte recruitment and retarding the oxidation of LDL. These differential effects among ARBs posits a question as to whether small changes in their chemical and pharmacokinetic profile may be associated with important differences in their ability to block the pathological actions of Ang II, independent of their effects on blood pressure.

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