Angiotensin II receptor antagonists in hypertension

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Angiotensin II receptor antagonists in hypertension. Blockade of the renin-angiotensin system is now recognized as an effective approach to the treatment of hypertension and congestive heart failure. Today, it is possible to antagonize the effects of angiotensin II more specifically by blocking its receptors by using nonpeptide receptor antagonists. These compounds that first have been used to recognize the various subtypes of angiotensin II receptors are now available clinically. Four of them have recently been launched on the market and several others are preregistered for the treatment of hypertension. These new molecules are as effective as ACE inhibitors, calcium antagonists and beta-blockers in lowering blood pressure in hypertensive patients. When compared to ACE inhibitors, they appear to have comparable favorable effects on systemic and renal hemodynamic properties. One of the major characteristics of angiotensin II receptor antagonists as a class is the excellent tolerability with an incidence of side effects that is generally similar to that of placebo. Large clinical trials are now underway to demonstrate the long-term benefits of these agents in hypertension, heart failure and type II diabetic nephropathy.

In recent years, the trend in cardiovascular drug research has been to develop new compounds acting on very specific targets such as cell surface receptors. The increased selectivity may improve the efficacy but more often reduces the incidence of side effects. Several receptor antagonists have been developed that block receptors involved in the control of blood pressure such as the endothelin [6], bradykinin [7], vasopressin [8, 9] and angiotensin II receptors [10]. Angiotensin II receptor antagonists, which selectively compete with the binding of angiotensin II to its AT1 receptor subtype, represent the most specific way to block the activity of the renin-angiotensin system, a therapeutic approach that is now well recognized for the treatment of hypertension and congestive heart failure. The purpose of the present article is to highlight certain pharmacological and clinical aspects of this new class of antihypertensive agents.

ANGIOTENSIN II RECEPTOR ANTAGONISTS: A RAPIDLY GROWING CLASS

Since the early development of losartan, the prototype of a highly selective non-peptidic AT1 receptor antagonist, several orally active angiotensin II antagonists have entered under clinical investigation and are now available in various countries. The pharmacological characteristics of the four antagonists that have been launched are shown in Table 1 [10, 11]. Two other antagonists, eprosartan and telmisartan, are being developed but have not been launched yet.

Losartan is a highly selective antagonist with an IC50 of 20 nm in rat vascular smooth muscle. It has no affinity for the AT2 receptor subtype and no partial agonistic effect. Losartan has a major active metabolite, EXP 3174, which is 20 times more potent than losartan and has a longer duration of action (half-life of 6 to 9 hr for EXP3174 and about 2 hr for losartan). On isolated vessels, losartan produces a surmountable blockade of the contractile response whereas EXP 3174 induces an insurmountable blockade. Losartan clearance is primarily nonrenal but the clearance of its metabolite occurs through both renal and nonrenal routes. The bioavailability of losartan is 33% and the compound is highly bound to proteins (>98%). Food has no influence on drug absorption. The bioavailability of

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EXP3174 is very low. Thus, losartan is the drug on the market but most of its effects are due to EXP3174.

Valsartan has been the second AT1 receptor antagonist available clinically. It is also a potent AT1 antagonist with an IC50 of 2.7 nM on rat aorta. Valsartan does not need to be metabolized to develop its full activity and it is excreted both in the bile (70%) and by the kidneys (30%). Its bioavailability is about 25% and the half-life of six to nine hours. The compound is also highly protein-bound (95%). In acute studies, food decreases the absorption of valsartan but the interaction with food does not appear to be important during chronic administration. In experimental models, the peak effect of valsartan occurs two to four hours after dosing and the antihypertensive effect appears to last for 24 hours.

Irbesartan is a long-acting angiotensin receptor antagonist with a plasma half-life of 11 to 15 hours. Its affinity for the AT1 receptor is 1.3 nM in in rat liver. Irbesartan produces an unsurmountable blockade of angiotensin II binding. In contrast to losartan, but similar to valsartan, it has also no active metabolite. Irbesartan has a bioavailability of 60 to 80% and is only 90% bound to proteins. Food has no effect on gastrointestinal absorption of irbesartan. Irbesartan is cleared mainly by the liver (78%) and by the kidneys (22%).

Candesartan cilexetil is also a long-acting antagonist of AT1 receptors. Candesartan cilexetil is an ester carbonate prodrug that is converted in vivo to CV 11974 [10]. The CV 11974 molecule is a potent antagonist of angiotensin II in vitro (IC50 for the AT1 receptor of 28 nM in rabbit aorta). The terminal half-life of candesartan is approximately nine hours. The bioavailability of candesartan is 42%. The plasma protein binding of candesartan is 98%. Candesartan is cleared mainly by the urine (60%) and to a lesser extent through the bile (about 40%).

Table 1. Pharmacological characteristics of the four angiotensin II receptor antagonists available on the market

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Trade name</th>
<th>Active metabolite</th>
<th>Bioavailability %</th>
<th>Dose recommended mg/day</th>
<th>Half-life hours</th>
<th>Protein binding %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>Cosaar</td>
<td>Yes</td>
<td>33</td>
<td>50–100</td>
<td>2</td>
<td>98.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EXP 3171</td>
<td></td>
<td></td>
<td>6–9</td>
<td>99.8</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Diovan</td>
<td>No</td>
<td>25</td>
<td>80–160</td>
<td>6</td>
<td>95.0</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>Aprovel</td>
<td>No</td>
<td>60–80</td>
<td>150–300</td>
<td>11–15</td>
<td>90.0</td>
</tr>
<tr>
<td>Candesartan</td>
<td>Atacand</td>
<td>Yes</td>
<td>42</td>
<td>4–16</td>
<td>3–4</td>
<td>99.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CV-11974</td>
<td></td>
<td></td>
<td>3–11</td>
<td></td>
</tr>
</tbody>
</table>

Numerous controlled studies have been conducted with the various angiotensin II antagonists to demonstrated their antihypertensive efficacy. Thus, in placebo-controlled studies, losartan as well as valsartan have been shown to be effective antihypertensive drugs [12, 13]. A clear dose-response relationship was not established, however, during clinical development. In double-blind placebo-controlled trials, irbesartan and candesartan also exerted a clinically significant blood pressure lowering effect, but in contrast to losartan and valsartan their effects were clearly dose-dependent [14, 15]. With irbesartan, the dose-dependent pattern was found between 75 and 300 mg whereas with candesartan, the dose-response pattern was observed between 4 and 16 mg.

When compared to other antihypertensive classes, angiotensin II receptor antagonists possess an efficacy at least equivalent to that of other antihypertensive agents including angiotensin converting enzyme inhibitors, calcium antagonists and beta-blockers [12–15]. Few studies have compared the antihypertensive efficacy of two angiotensin II receptor antagonists. In one study, candesartan (8 and 16 mg) was compared to losartan 50 mg and placebo in four groups of about 80 patients with mild to moderate hypertension [15]. Candesartan cilexetil 16 mg, that is, the highest dose of candesartan, had a clinically and statistically greater blood pressure lowering effect than losartan 50 mg 24 hours after administration, suggesting that candesartan is more effective. However, candesartan is not more effective than losartan at peak effect. Moreover, the authors have not compared the highest dose of losartan with the highest dose of candesartan. Thus, the observed difference may be due to the dose as well as to the duration of action of the drugs. The comparative efficacy of irbesartan and losartan as treatment of mild to moderate hypertension has also been assessed in a double-blind study [14]. The drugs were administered at fixed dosages that is, losartan 100 mg/day, irbesartan 150 or 300 mg/day for eight weeks. In this study, irbesartan 300 mg but not 150 mg reduced trough blood pressure to a significantly greater extent than losartan 100 mg/day, and the percentage of patients with normal blood pressure after eight weeks was higher with irbesartan 300 mg/day. The peak effects of irbesartan and losartan are again not known. The results of these two studies would suggest that long-acting angiotensin II antagonists are slightly more effective than losartan. Yet, additional studies are needed to confirm these data and to evaluate whether such differences are clinically relevant when examining hard end-points such as morbidity and mortality.

When the renin-angiotensin system is blocked, blood...
pressure becomes salt-sensitive. Thus, diuretics represent a logical combination to enhance the blood pressure response in patients treated with angiotensin converting inhibitors or angiotensin II antagonists. Several clinical studies have demonstrated that angiotensin II antagonists are highly effective when co-administered with hydrochlorothiazide [14–16]. The antihypertensive efficacy of angiotensin II antagonists has also been examined in special populations. No differential effect of the antagonists was observed on the basis of age and gender. The blood pressure response to angiotensin II receptor blockade appears to be slightly less pronounced in black hypertensive patients.

**ANGIOTENSIN II RECEPTOR ANTAGONISTS: AN EXCELLENT TOLERABILITY PROFILE**

The adverse event profile of a new therapeutic agent is very important. One of the major characteristics of angiotensin II receptor antagonists as a class is the excellent tolerability with an incidence of side-effects that is generally similar to that of placebo. Studies performed with losartan and valsartan have clearly demonstrated that in contrast to ACE inhibitors, these agents do not induce cough [17, 18]. This observation confirms that dry cough is due to the lack of specificity for the renin-angiotensin system of ACE inhibitors. The only difference among angiotensin II antagonists is the ability of losartan to increase urinary uric acid excretion and hence to lower plasma uric levels [19]. Whether this uricosuric effect of losartan, but not EXP 3174, represents an advantage or an inconvenience is still not clear. In patients pretreated with thiazide diuretics, losartan has been shown to blunt significantly the diuretic-induced increase in plasma uric acid [16]. In cyclosporine-treated heart transplant patients, losartan has also been shown to lessen the cyclosporine-induced hyperuricemia [20]. Thus, in some clinical situations—if not always—the uricosuric effect of losartan may be rather beneficial. Uric acid stone formation is not a complication of losartan because urinary pH tends to become slightly more alcaline during angiotensin II receptor blockade.

**RENAL EFFECTS OF ANGIOTENSIN II ANTAGONISTS: COMPAREABLE TO THOSE OF ACE INHIBITORS**

In contrast to ACE inhibitors, angiotensin II receptor antagonists are not expected to be associated with any effect related to the inhibition of kininase II or with an increase in prostaglandins. Thus, the influence of angiotensin II antagonists on renal hemodynamics and urinary electrolyte excretion and their ability to protect renal function might possibly differ. The results obtained so far in experimental and clinical studies suggest rather that ACE inhibitors and angiotensin II receptor antagonists have similar effects on the kidney [19, 21–23]. Indeed, several studies have demonstrated that angiotensin II antagonists have no effect on glomerular filtration and increase renal blood flow. This renal hemodynamic response to angiotensin II receptor blockade has been found in normotensive subjects [19–21] as well as in hypertensive patients [22, 23]. Angiotensin II antagonists also increase urinary sodium excretion [19, 21]. It has once been postulated that the inhibition of prostaglandin metabolism is responsible for the ACE-inhibitor-induced natriuresis. In a recent study, we have found that indomethacin similarly abolishes the natriuretic response to ACE inhibition and angiotensin II receptor blockade in normotensive subjects [24]. This suggests that the anti-natriuretic effect of nonsteroidal anti-inflammatory drugs (NSAIDs) is not class-specific. Thus, one could expect clinically that NSAIDs blunt the antihypertensive effect of angiotensin II antagonists as they do with ACE inhibitors and diuretics.

Finally, ACE inhibitors are known to have a favorable impact on renal function because they reduce proteinuria. Preliminary experimental and clinical studies obtained with the angiotensin II receptor antagonists on small groups of patients suggest that these agents have the same capacity to lower urinary albumin excretion [22].

**ANGIOTENSIN II ANTAGONISTS AND ACE INHIBITORS: A USEFUL COMBINATION?**

Acute inhibition of ACE results in a marked decrease in plasma angiotensin II levels to almost undetectable levels [25, 26]. However, this is not the case during chronic ACE inhibition. Indeed, although blood pressure is reduced throughout the day with the repeated administration of an ACE inhibitor, plasma angiotensin II levels are still measurable. The lack of complete disappearance of angiotensin II from plasma during chronic treatment can be explained in several ways. First, plasma renin activity and plasma angiotensin I levels increase markedly during ACE inhibition. Since ACE activity is rarely inhibited around the clock with ACE inhibitors, even a small percentage of enzyme activity can lead to the generation of angiotensin II if the substrate, that is, angiotensin I, is available in large amounts [27]. Second, during chronic ACE inhibition, angiotensin II can be formed by other enzymatic pathways including for example the heart chymase [28]. Thus, additional antihypertensive effects could be theoretically expected from the combination of an ACE inhibitor with an AT₁ receptor antagonist because the antagonist blocks angiotensin II at its receptor independently of its source. However, if the antagonist effectively blocks all the effects of angiotensin II independently of the level of circulating angiotensin II, the need for an ACE inhibitor would be doubtful. Plasma angiotensin II levels increase markedly during chronic blockade of AT₁ receptors. The elevated plasma angiotensin II levels can be expected to compete with the antagonist at the receptor site and to displace the antagonist from the receptor. In this situation, the added
ACE inhibitor could blunt the rise in plasma angiotensin II and thereby increase the antihypertensive efficacy of the receptor antagonist. Whether this hypothesis holds true in clinical hypertension, and more precisely, whether high circulating angiotensin II levels are indeed able to compete with the mostly unsurmountable receptor blockade, certainly deserves further investigation. A preliminary study conducted in salt-depleted normotensive volunteers has already suggested that the combined administration of a standard single oral dose of an ACE inhibitor and an angiotensin II antagonist induces an additional blood pressure reduction and has a major additive effect on the rise in plasma renin activity [29]. Similar results were found in transgenic rats with a renin dependent hypertension [30]. However, in rats with 5/6 renal mass ablation, enalapril, losartan and the combination of both agents had similar renoprotective effects that were closely related to the magnitude of the antihypertensive effects [31]. Further studies are need to decide whether the combination of an ACE-inhibitor with an AT1 receptor antagonist provides additive, or even synergistic, therapeutic benefits in patients with hypertension, heart failure of diabetic nephropathy. In congestive heart failure, high doses of ACE inhibitors are often necessary to block the renin-angiotensin system. In this condition, the association of an ACE inhibitor and an AT1 receptor antagonist could seem attractive to improve the overall blockade of the system. However, to demonstrate the advantages of the ACE inhibitor-AT1 antagonist combination, it should be compared clinically with a full titration of each individual drug and also with using long-acting angiotensin II antagonists.

THE FUTURE OF ANGIOTENSIN II RECEPTOR ANTAGONISTS

Non-peptide, orally active angiotensin II antagonists represent an important new development in the treatment of hypertension and probably congestive heart failure and chronic renal failure. These agents are very effective in lowering blood pressure and present a unique tolerability profile. Additional studies are now necessary to evaluate their impact on the long-term morbidity and mortality of patients with various cardiovascular diseases. Several large trials are underway in various populations. The LIFE study (Losartan Intervention For End-point reduction in hypertension) is evaluating the effect of losartan on cardiovascular morbidity and mortality in hypertensive patients [32] and the RENAAL study examine the renal protective effect of losartan in patients with type II diabetes. The ELITE trial (Evaluation of Losartan In The Elderly) has compared the safety and efficacy of losartan and captopril in elderly patients with heart failure [33]. The first results of this study have shown that losartan is as safe as captopril, and no difference in renal dysfunction was found between the two drugs. Surprisingly, however, after one year of follow-up the mortality was significantly lower in the losartan than in the captopril group. A second study (ELITE II) is now underway to confirm these promising preliminary results. Large interventional trials are also conducted with other angiotensin II receptor antagonists. Together, the results of these studies will help to more clearly define the future role of angiotensin II receptor antagonists in the management of patients suffering from hypertension, congestive heart failure and chronic nephropathies. At the same time, they will contribute significantly to further elucidate the role of angiotensin II in causing cardiovascular morbidity and mortality.

REFERENCES


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