Angiotensin II Receptor Blockade
Is There Truly a Benefit of Adding an ACE Inhibitor?

Andrei Forclaz, Marc Maillard, Jürg Nussberger, Hans R. Brunner, Michel Burnier

Abstract—We assessed the blockade of the renin-angiotensin system (RAS) achieved with 2 angiotensin (Ang) antagonists given either alone at different doses or with an ACE inhibitor. First, 20 normotensive subjects were randomly assigned to 100 mg OD losartan (LOS) or 80 mg OD telmisartan (TEL) for 1 week; during another week, the same doses of LOS and TEL were combined with 20 mg OD lisinopril. Then, 10 subjects were randomly assigned to 200 mg OD LOS and 160 mg OD TEL for 1 week and 100 mg BID LOS and 80 mg BID TEL during the second week. Blockade of the RAS was evaluated with the inhibition of the pressor effect of exogenous Ang I, an ex vivo receptor assay, and the changes in plasma Ang II. Trough blood pressure response to Ang I was blocked by 35±16% (mean±SD) with 100 mg OD LOS and by 36±13% with 80 mg OD TEL. When combined with lisinopril, blockade was 76±7% with LOS and 79±9% with TEL. With 200 mg OD LOS, trough blockade was 54±14%, but with 100 mg BID it increased to 77±8% (P<0.01). Telmisartan (160 mg OD and 80 mg BID) produced a comparable effect. Thus, at their maximal recommended doses, neither LOS nor TEL blocks the RAS for 24 hours; hence, the addition of an ACE inhibitor provides an additional blockade. A 24-hour blockade can be achieved with an angiotensin antagonist alone, provided higher doses or a BID regimen is used. (Hypertension. 2003;41:6–12.)

Key Words: angiotensin II AT1 receptor blockers, angiotensin I, angiotensin-converting enzyme, human telmisartan

Blockade of the renin-angiotensin system with angiotensin (Ang) II AT1 receptor antagonists is now recognized as an effective means of lowering blood pressure in hypertensive patients.1 In addition, several large clinical trials performed with these agents have demonstrated that blocking AT1 receptors can confer a benefit in terms of morbidity and/or mortality in patients with essential hypertension and left ventricular hypertrophy2 as well as in patients with type 2 diabetic nephropathy3–5 and congestive heart failure.6,7 Today, a similar debate is developing with Ang II receptor antagonists. Although all angiotensin antagonists have been shown to inhibit the effect of exogenous Ang I or II dose dependently at peak, the dose recommendations for the clinical use have been based on their antihypertensive efficacy, and, as for many other antihypertensive drugs, angiotensin antagonists are considered to have a rather “flat” dose-response curve.1 Yet, studies have demonstrated that the recommended doses of several Ang II receptor antagonists do not provide a full blockade of AT1 receptors around the clock and not even at peak.13,14 Thus, several investigators have proposed to associate an Ang II receptor antagonist with an ACE inhibitor to block the renin-angiotensin cascade at 2 sites and hence to obtain a greater and longer-lasting blockade of the system.15–17 However, no study has evaluated whether doses of Ang II receptor antagonists beyond those recommended for the treatment of hypertension can produce as much blockade of the renin-angiotensin system as an association of angiotensin receptor antagonists and ACE inhibitors.

To answer this question, we compared the blockade of the renin-angiotensin system produced by 2 Ang II receptor antagonists, losartan and telmisartan, administered either...
alone according to different dose regimens or in association with an ACE inhibitor in normotensive healthy volunteers.

**Methods**

**Subjects**

Thirty healthy male subjects took part in 2 consecutive studies. In the first study, 20 normotensive volunteers 26.3 years of age (range, 19 to 35), with a body mass index of 22.2±1.7 kg/m² (mean±SD; range, 19.1 to 25.3) were enrolled. The second protocol involved 10 volunteers 26.5 years of age (range, 20 to 33), with a body mass index of 21.7±2.8 kg/m² (range, 18.6 to 26.6).

All subjects were considered healthy on the basis of medical history, physical examination, routine blood and urine analyses, and an ECG. The study protocols were approved by our institutional review committee. Written consent was obtained from each volunteer after explanation of the nature, purpose, and potential risks of the study.

**Study Design**

**Protocol 1**

In this single-blind study, 20 volunteers were randomly assigned to 2 parallel groups of 10 subjects (Figure 1). During the first week, they received either losartan (100 mg OD) or telmisartan (80 mg OD). The second week, lisinopril (20 mg OD) was added to the first week’s regimen. Blockade of the renin-angiotensin system was assessed at 4 and 24 hours on day 0 without drug intake and again at 4 and 24 hours after the last drug intake at the end of the first and second week of treatment. Subjects continued their usual free sodium intake throughout the study, but consumption of caffeine-containing beverages, alcohol, or smoking was not allowed the day before and during the investigational days. On each investigational day, the volunteers were asked to come to our research facility after an overnight fast. They were comfortably installed in a supine position, and a venous catheter was placed in each forearm, one for blood sampling and the other for Ang I injections. At each time point (4 and 24 hours), the blood pressure response to exogenous Ang I was tested as described previously.13 In addition, blood was taken to measure plasma Ang II levels and the blockade of Ang II receptor-binding assay on times 0, 4, and 24 hours. During the entire study, the volunteers were asked to return every morning to receive the drug under supervision.

**Protocol 2**

In this single-blind study, 10 volunteers were randomly assigned to 2 parallel groups of 5 subjects (Figure 1). During the first week, they received either losartan (200 mg OD) or telmisartan (160 mg OD). The second week, the same dose of each drug was given, but according to a twice-a-day regimen (losartan, 100 mg BID, and telmisartan, 80 mg BID). The same assessment of Ang II receptor blockade was performed.

**Blood Pressure Measurement, In Vitro Assessment of Ang II Receptor Blockade, and Plasma Ang II**

Blood pressure and heart rate were monitored noninvasively by photoplethysmography at the finger (Finapres, Ohmeda), as described previously.18 To measure plasma Ang II levels, an immunoreactive method with monoclonal antibodies against Ang II was used.19 Ex vivo Ang II receptor blockade assessment was performed with the use of a standardized in vitro receptor assay, as described previously.20

**Statistical Analysis**

All results are mean±SD unless otherwise specified. One-way ANOVA was performed followed by either paired or unpaired t tests with the use of GraphPad Prism, version 3.00, for Windows. A probability value <0.05 was considered to indicate statistical significance.

**Results**

All subjects completed the study. The drugs were well tolerated, and no clinically significant adverse effect or change in safety parameters (hematological, hepatic, renal, or ECG) was recorded.

**TABLE 1. Protocol 1: Changes in Trough Blood Pressure After One Week of Treatment**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Systolic BP, mm Hg</th>
<th>Diastolic BP, mm Hg</th>
<th>Δ SBP, mm Hg</th>
<th>P</th>
<th>Δ DBP, mm Hg</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>112±8</td>
<td>64±6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Losartan, 100 mg o.d.</td>
<td>108±8</td>
<td>66±7</td>
<td>−3±8</td>
<td>&gt;0.05</td>
<td>2±9</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Losartan, 100 mg o.d., + lisinopril, 20 mg o.d</td>
<td>103±8</td>
<td>61±4</td>
<td>−9±7</td>
<td>&lt;0.01</td>
<td>−3±5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Baseline</td>
<td>118±8</td>
<td>70±7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telmisartan, 80 mg o.d.</td>
<td>112±7</td>
<td>65±5</td>
<td>−6±6</td>
<td>&lt;0.05</td>
<td>−5±7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Telmisartan, 80 mg o.d., + lisinopril 20 mg o.d</td>
<td>107±6</td>
<td>62±5</td>
<td>−11±7</td>
<td>&lt;0.01</td>
<td>−8±7</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are mean±SD, n=10. BP indicates blood pressure; SBP, systolic BP; DBP, diastolic BP; and Δ, changes in BP.
Protocol 1
Changes in trough systolic and diastolic blood pressure with the various treatments in the 2 groups are shown in Table 1. When given alone, 100 mg losartan once daily did not produce any significant change in blood pressure, whereas telmisartan alone induced a significant decrease in systolic blood pressure, but baseline blood pressure was higher in the telmisartan group. With the addition of the ACE inhibitor, significant changes in blood pressure were observed both with losartan and telmisartan.

The effects of the different treatment regimens on the blockade of the renin-angiotensin system as assessed by the 3 methods are shown in Table 2. Four hours after the last drug intake, the mean blood pressure response to Ang I was significant changes in blood pressure were observed both with losartan and telmisartan.

The ex vivo receptor binding assay results supported the in vivo data but differed in that the trough AT\textsubscript{1} receptor blockade results were lower in the losartan group. Because lisinopril does not interact with the AT\textsubscript{1} receptor, this assay enables us to specifically evaluate the degree of blockade attributable to the angiotensin receptor antagonist alone. Thus, as expected, no difference was observed with or without the addition of the ACE inhibitor. The reactive rise in plasma Ang II levels also supported our in vivo results. Four and 24 hours after the last drug intake, significant increases in plasma Ang II versus baseline were obtained with both 100 mg OD losartan (\(P<0.05\) and \(P<0.01\), respectively) and 80 mg OD telmisartan (\(P<0.01\) at both time points). There was no statistically significant difference when both drugs were compared. With the addition of lisinopril, Ang II levels returned to the baseline values at 4 hours in both groups, reflecting the blockade of ACE. At 24 hours, the effect of lisinopril had decreased, and, consequently, Ang II levels were significantly higher than baseline levels though markedly lower than with the Ang II antagonists alone.

Protocol 2
The changes in systolic and diastolic blood pressures are shown in Table 3. The fall in blood pressure was particularly marked when volunteers received 100 mg BID losartan (\(-11\pm4\) mm Hg systolic blood pressure and \(-10\pm3\) mm Hg diastolic blood pressure, \(P<0.01\) versus baseline), but the number of subjects is too small to demonstrate a significant difference with other treatment regimens, and baseline blood pressure was in this case higher in the losartan group.

The degree of blockade of the renin-angiotensin system in protocol 2 are presented in Table 4. At 4 hours, the blood
pressure response to exogenous Ang I was blocked by 90% with 200 mg OD losartan and 72% with 160 mg OD telmisartan. The blockade induced by telmisartan was significantly lower than that induced by losartan \((P<0.01)\). At trough, Ang I receptor blockade was similar with both compounds when these were given once per day. The twice-a-day schedule for losartan (100 mg BID) provided a degree of blockade at 4 hours similar to the once-a-day administration (200 mg OD), but the trough blockade was significantly greater with the BID regimen \((P<0.01)\). With telmisartan, 160 mg OD was equivalent to 80 mg BID.

When assessed with the ex vivo test, Ang II receptor blockade was again more sustained with the BID regimen of losartan, whereas no difference between OD and BID was found with telmisartan. The data also suggest that at 4-hour receptor blockade with telmisartan 80 or 160 mg is not complete. The changes in plasma Ang II levels were also consistent with our in vivo results in losartan group.

### Discussion

Several recent studies have suggested that combining an ACE inhibitor with an Ang II receptor blocker is more effective to block the renin-angiotensin system than either substance given alone. However, none of these studies have used doses of Ang II receptor antagonists higher than those recommended for the treatment of essential hypertension. We have therefore designed our study to assess whether higher doses of an Ang II receptor blocker could be as effective as the association of a usual dose of the antagonist combined with an ACE inhibitor in blocking the vasopressor effects of Ang II. Because the main goal of the study was to investigate the blockade of the renin-angiotensin system (including with injections of exogenous Ang I) rather than the changes in blood pressure, the study was conducted in normotensive subjects. As summarized in Figure 2, our results clearly demonstrate that a complete 24-hour blockade of the Ang II effects cannot be achieved with the recommended doses of losartan (100 mg) and telmisartan (80 mg) given once per day. Hence, with these dosing regimens of antagonists, the combination with an ACE inhibitor not surprisingly has an additive effect to provide an almost complete and long-lasting blockade of the renin-angiotensin system. However, a comparable sustained 24-hour inhibition of the system can be obtained with losartan alone when 100 mg of the drug is given twice per day. Despite its longer duration of action, 160 mg OD or 80 mg BID telmisartan did not provide a complete blockade of the system throughout the day.

ACE inhibitors as well as Ang II receptor antagonists have been developed to block the multiple effects of Ang II possibly throughout the day and hence to lower blood pressure. With time, however, it became evident that continuous 24-hour blood pressure control could be achieved with ACE inhibitors despite intermittent resumption of normal ACE activity. Furthermore, during chronic ACE inhibition and particularly at trough, circulating Ang II levels are not at all suppressed, thus emphasizing the difficulty to block the

### Table 4. Blockade of Renin-Angiotensin System Assessed by 3 Different Methods in Protocol 2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Inhibition of Pressor Response to Ang I, %*</th>
<th>Displacement of Labeled Ang II, %</th>
<th>Plasma Ang II Levels, fmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time, h</td>
<td>4 24</td>
<td>4 24</td>
<td>4 24</td>
</tr>
<tr>
<td>Baseline</td>
<td>0 0</td>
<td>0 0</td>
<td>2.8±2.0 2.9±2.4</td>
</tr>
<tr>
<td>Losartan, 200 mg o.d.</td>
<td>90±4§ 54±14‡</td>
<td>87±3§ 27±8‡</td>
<td>46±43 12±9.4†</td>
</tr>
<tr>
<td>Losartan, 100 mg b.i.d.</td>
<td>92±5§ 77±8§¶</td>
<td>80±3§ 55±9§#</td>
<td>45±37 25±12∥</td>
</tr>
<tr>
<td>Telmisartan, 160 mg o.d.</td>
<td>77±12§ 57±25§</td>
<td>76±7§ 51±13§</td>
<td>48±39 23±15†</td>
</tr>
<tr>
<td>Telmisartan, 80 mg b.i.d.</td>
<td>74±13§ 59±22†</td>
<td>69±12§ 52±20§</td>
<td>29±14† 37±21†</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*Based on mean blood pressure changes.

†P<0.05; ‡P<0.01; §P<0.001 vs baseline; ||P<0.05; ¶P<0.01; #P<0.001 o.d. vs b.i.d.
renin-angiotensin system completely over a long period of time.\textsuperscript{10–12} Such an apparent discrepancy between the duration of blockade and of the antihypertensive effect appears to exist also with the use of Ang II receptor antagonists. Indeed, almost all Ang II receptor blockers including losartan and telmisartan have been shown to lower blood pressure over 24 hours when given once per day in patients with mild to moderate hypertension.\textsuperscript{1} Yet, most antagonists do not block the renin-angiotensin system around the clock.\textsuperscript{13,14} In this study, we have investigated 2 angiotensin receptor antagonists, one with a very long duration of action, telmisartan, and another with a shorter duration of action, losartan. Our data demonstrate that neither telmisartan nor losartan are capable to produce a complete blockade of the renin-angiotensin system for 24 hours when used at their maximal recommended doses of 80 and 100 mg, respectively. The results obtained with 100 mg OD losartan in this study are comparable to those reported previously that used the same methodology with a 70% inhibition at 4 hours and a 35% residual blockade at trough.\textsuperscript{24} The 36% blockade of the blood pressure response to exogenous Ang I at trough with 80 mg telmisartan was surprising. However, our results are in agreement with the recent results of Stangier et al.\textsuperscript{25} who performed a complete telmisartan dose-response curve in normotensive subjects. In this latter study, the reactive rise in plasma Ang II levels was also comparable to our results if one takes into account the methodological differences.

The blockade of the renin-angiotensin system being only partial with 100 mg losartan and 80 mg telmisartan, it is not surprising that the association with 20 mg lisinopril is additive and produces a complete blockade at 4 hours and a 75% inhibition at trough with both antagonists. These findings are therefore in agreement with previous observations suggesting that the combination is more effective in antagonizing the system than a single site inhibition in normotensive subjects.\textsuperscript{15,16} At this point, it is important to mention that the intrinsic variability of blood pressure is such that the blood pressure response to exogenous angiotensin can hardly be 100%. Indeed, even during complete blockade, there are small physiological fluctuations of blood pressure. In our hands, this spontaneous variability of blood pressure in normotensive subjects averages \(\sim 13\%\) (ie, 3 to 4 mm Hg); hence, a blockade \(\sim 85\%\) can be considered as complete.

Previous studies with ACE inhibitors and Ang II receptor antagonists have shown that increasing the dose once daily has little effect on the peak inhibition but tends to prolong the duration of the inhibition.\textsuperscript{14,18,26} In accordance with this observation, increasing the dose of losartan to 200 mg OD and that of telmisartan to 160 mg OD significantly improved the trough blockade, with only a slight improvement in the degree of blockade measured 4 hours after drug intake. Yet, even though both drugs were administered for 1 week, the trough blockade remained far from being complete, whatever the method of assessment.

The main goal of these experiments was to demonstrate that an Ang II receptor antagonist alone can be as effective as an ACE inhibitor–Ang II receptor blocker association, provided that it is administered at the right dose and dosing interval. Our results show that this is indeed the case. When 100 mg losartan was given twice per day, the degree of antagonism was similar to that of the combination of 100 mg losartan with 20 mg lisinopril. Interestingly, this was not the case with 80 mg BID telmisartan. The difference is possibly explained by the very long half-life of telmisartan.\textsuperscript{27} With long-acting drugs, a twice-a-day regimen does not provide any benefit, and it would certainly be more adequate to increase the dose further. It is conceivable that higher doses of telmisartan (>160 mg/d) once daily would enable the same degree of antagonism to be reached as with 100 mg BID losartan.

Taken together, our results demonstrate that an equal 24-hour blockade of the renin-angiotensin cascade can be obtained with an Ang II receptor blocker alone as with an ACE inhibitor/Ang II receptor blocker combination. However, to achieve this goal with a monotherapy, it implies the use of higher doses of the antagonists and in some cases a twice-a-day regimen. One may also be concerned by safety considerations when administering higher doses of AT\(_1\) receptor blockers. This is hardly an issue, since AT\(_1\) receptor antagonists do not exhibit any dose-dependent adverse effects. Indeed, AT\(_1\) receptor blockers have been used safely at higher doses. For example, in the ValHeft trial, many patients received 160 mg valsartan twice a day without any safety concerns,\textsuperscript{7} and the high doses used in this trial probably explain the marked efficacy observed in the ACE-intolerant patients. On the other hand, the use of angiotensin receptor antagonists alone rather than in association with ACE inhibitors avoids all the side effects associated with this latter class of drugs. This study has some limitations. First, it was conducted in young normotensive subjects who have a reactive renin-angiotensin system. One may thus argue that our observations do not necessarily apply to patients with a less active renin-angiotensin system, such as older hypertensive patients or patients receiving concurrent \(\beta\)-blockade.

Second, subjects have been studied on a free sodium intake and the degree of blockade of the renin-angiotensin system by AT\(_1\) receptor antagonists may well vary, depending on the baseline activation of the system. Last, inhibition of the renin-angiotensin system hardly causes a decrease in blood pressure in normotensive subjects. Hence, it is difficult to demonstrate that a greater inhibition provides a greater antihypertensive efficacy. Yet, in our subjects, a significant correlation was found between the percent inhibition at trough and the percent change in systolic blood pressure (\(r = -0.25, P = 0.05, n=60\)).

**Perspectives**

Although they were obtained in normotensive subjects, our observations may have some clinical implications, as they may help defining the most adequate dose of Ang II receptor blocker to use clinically. Indeed, today, the recommended doses of ACE inhibitors and Ang II receptor blocker have been chosen on the basis of their ability to lower blood pressure. However, the recent trials investigating the ability of these agents to protect patients against target organ damage have now repeatedly shown that the highest doses were most effective,\textsuperscript{2–5,7,28} thus recommending more aggressive treatment in the future. These studies have also suggested that
there may be benefits of blocking the effects of Ang II beyond blood pressure control.2 This would indicate that the doses used for blood pressure control are not those needed for target organ protection. If this hypothesis is true, a complete 24-h blockade of the renin-angiotensin system would definitely be a better target for treatment, and the results obtained with one antagonist may not necessarily be assumed to be obvious for all others. However, whether a full 24-hour blockade of the renin-angiotensin system provides a better organ protection than a transient blockade remains to be further investigated prospectively in clinical trials.

Acknowledgments
This work was supported by a grant from Boehringer-Ingelheim (Switzerland). The authors thank Monique Salvi and Françoise Nicoud for excellent assistance.

References


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Hypertension. published online December 2, 2002;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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