Does the Antihypertensive Response to Angiotensin Converting Enzyme Inhibition Predict the Antihypertensive Response to Angiotensin Receptor Antagonism?

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To test the hypothesis that the antihypertensive response to angiotensin converting enzyme (ACE) inhibition can predict the response to angiotensin II type I receptor (AT₁R) antagonism, 33 hypertensive patients were randomized to receive lisinopril (20 mg) or losartan (50 mg) for 5 weeks. Patients were then crossed-over to the alternative treatment for a second 5-week period. Twenty-four-hour ambulatory BP (ABP) was measured before randomization and on the final day of each period. The agreement in ABP response between the two drugs was assessed using the following approaches: Subjects were classified as responders and nonresponders using as a threshold an arbitrary level of response (ABP fall $\geq 10 \text{ mm Hg systolic or } \geq 5 \text{ mm Hg diastolic}$) or the median ABP response achieved by each of the drugs. Disagreement between the two drugs in the responders–nonresponders classification was expressed as the proportion of subjects whose ABP responded to one of the drugs only. Lisinopril was more effective than losartan in reducing ABP (mean difference $4.7 \pm 8.1/3.3 \pm 5.7 \text{ mm Hg, systolic/diastolic, } P < .05$). Disagreement in the antihypertensive response between the two drugs was found in 39%/33% of subjects for systolic/diastolic ABP using the arbitrary response criterion (33%/39% using the median response criterion). Significant correlations were found between the responses to lisinopril and losartan ($r = 0.47/0.59$, systolic/diastolic, $P < .01$). We conclude that in more than one third of hypertensive subjects, the BP response to ACE inhibition fails to predict the response to AT₁R antagonism and vice versa. These data suggest that there are differences between these two drug classes that are not only of theoretical but also of practical significance. Am J Hypertens 2001;14:688–693 © 2001 American Journal of Hypertension, Ltd.

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Blockade of the renin-angiotensin system at different sites using angiotensin converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor (AT₁, R) antagonists is being widely used in the management of hypertension.¹,² Although these drugs block the same system, they have several important differences, as they act on different levels of the system.¹,² However, the clinical significance of most of these differences remains largely unknown¹,² and, in clinical practice, the only clear advantage of AT₁ R antagonists over ACE inhibitors is the absence of cough as a side effect.¹–³ Therefore, current guidelines recommend the use of AT₁ R antagonists in hypertensive patients in whom treatment with an ACE inhibitor is effective but poorly tolerated.³–⁵ This strategy is based on the assumption that because ACE inhibitors and AT₁ R antagonists act on the same system there is little intraindividual variation in their antihypertensive response.

There is some experimental evidence, however, supporting the view that the mechanisms of antihypertensive action of the AT₁R antagonists differ from those of the ACE inhibitors. Angiotensin converting enzyme inhibition is associated with a decrease in the breakdown of kinins⁶ and an increase in the levels of angiotensin 1–7,⁷ both of which are believed to contribute to the antihypertensive effect of these drugs.¹,² On the other hand, AT₂R antagonism is associated with activation of the AT₂ receptor, which may act synergistically with the AT₁ receptor.
blockade in reducing BP. Whether these characteristics are associated with considerable intraindividual variation in the antihypertensive effects of these two drug classes remains unknown.

To test the hypothesis that the antihypertensive response to ACE inhibition can predict the antihypertensive response to AT1 R antagonism, a prospective intraindividual comparative study was conducted in patients with essential hypertension.

**Patients and Methods**

**Study Design and Participants**

This was a randomized, open-label, crossover comparative study. Untreated subjects with essential hypertension and a diastolic blood pressure (BP) of 90 to 110 mm Hg on at least two clinic visits were assessed with 24-h ambulatory BP monitoring. Subjects with average awake ambulatory BP > 85 mm Hg were randomized to receive open lisinopril 20 mg once daily or losartan 50 mg once daily for 5 weeks. Then patients were crossed-over to the alternative treatment for a second 5-week period. Reasons for exclusion were as follows: electrocardiographic left ventricular hypertrophy; known cardiovascular, renal, or liver disease; diabetes mellitus; evidence of secondary hypertension; any change in antihypertensive medication during the study; treatment with drugs known to influence BP; repeated clinic systolic BP > 220 mm Hg and/or diastolic BP ≥ 120 mm Hg at any time during the study; or unwillingness to participate in the study.

**Blood Pressure Measurements**

Clinic BP was measured before randomization, 2 weeks after the initiation of treatment, and on the final day of each treatment period by two physicians who fulfilled the British Hypertension Society Protocol criteria for observer agreement in BP measurement. Duplicate BP measurements were taken at trough after 5 min of sitting rest and after 1 min standing (Korotkoff phase V for diastolic BP) using a random zero sphygmonanometer (bladder size 15 × 35 cm; Hawksley, Sussex, England).

Ambulatory BP was monitored for 24 h before randomization and on the final day of each treatment period using noninvasive oscillometric devices SpaceLabs 90207 (bladder size 14 × 30 cm; SpaceLabs, Redmond, WA). The monitors were programmed to measure BP at 20 min intervals for 24 h and were always applied on a routine workday at the time of the morning dose. Participants were instructed to carry out their usual daily activities, but to stay still, with the forearm extended, during each reading. They were asked to keep a brief diary specifying the time when they were in and out of bed.

**Statistical Analysis**

The average awake, asleep, and 24-h ambulatory BP was calculated using individual patient-reported sleeping hours. Those BP measurements that were flagged by the software of the monitors as technically erroneous were excluded, as were measurements with systolic BP < 70 mm Hg or > 260 mm Hg or with diastolic BP < 40 mm Hg or > 150 mm Hg. Early readings taken < 20 min after attaching the monitor to the patient were also excluded, as these were taken in the clinic.

The possibility of a period effect or a period–treatment interaction was tested using two sample t tests. The differences in treatment induced changes in BP were analyzed. The treatment effects were compared by performing a one-sample t test on all within-subject differences between losartan and lisinopril. For each treatment effect estimation, 95% confidence intervals (95% CI) were calculated. The Oldham correction was used in the analysis of BP responses (actual BP change divided by the average of pretreatment and posttreatment BP). A probability value P < .05 was considered to be statistically significant.

The agreement in BP response between the two drug classes was assessed using the following criteria:

1. **Arbitrary response criterion:** Subjects were classified as responders and non-responders according to the magnitude of the antihypertensive response to each treatment. Responders were defined as subjects with a ≥ 5 mm Hg fall in 24-h diastolic ABP or ≥ 10 mm Hg systolic ABP. Agreement between the two drugs in the responders–nonresponders classification was regarded as the proportion of responders to both drugs plus the proportion of nonresponders to both drugs, and the level of disagreement as the proportion of subjects whose BP responded to only one of the drugs.

2. **Median response criterion:** To correct for any difference in the antihypertensive efficacy between the two drugs and to select the same proportion of responders and nonresponders in each of the two study groups, an alternative definition of responders was applied, using as a threshold for response the median BP response of all patients achieved by each of the drugs. Levels of agreement and disagreement in the response between the two drugs were calculated as for the arbitrary response criterion.

3. **Correlation criterion:** The antihypertensive responses to the two drugs were treated as continuous variables, and the association between them was examined by performing linear correlations.

**Results**

A total of 33 untreated subjects (mean age ± SD, 49.0 ± 10.2 years, BMI 28 ± 3.4 kg/m², 15 men) with elevated clinic and awake ambulatory diastolic BP were randomized. All of them completed the study. A total of 78.2 ± 4.7 readings were obtained with 24-h ambulatory BP monitoring. A fraction of 10 ± 4.4 were discarded and 3.7 ± 4.3 of time points were not represented in the ambulatory monitoring.
BP profile because both the initial and the automatically repeated reading 2 min later were considered erroneous. There was no difference in the number of acceptable BP readings obtained with 24-h ambulatory monitoring before randomization and on the final day of each treatment period. No evidence of a period effect or a treatment–period interaction was observed for any the variables studied, which included clinic and ambulatory measurements of systolic and diastolic BP.

At the randomization clinic visit, the average sitting BP was 144.1 ± 14.7 (SD)/95.9 ± 8.1 mm Hg (systolic/diastolic) and average 24-h ambulatory BP 136.5 ± 10.2/87.6 ± 6.0 mm Hg. There was a greater reduction in clinic BP with lisinopril compared to losartan (mean difference 6.9 ± 11.1 mm Hg, 95% CI 3.0, 10.8, , 0.011 for systolic and 4.1 ± 6.5 mm Hg, 95% CI 1.7, 6.4, , 0.01 for diastolic BP). A greater reduction was also observed with lisinopril in average 24-h ambulatory BP for both systolic (mean difference 4.7 ± 8.1 mm Hg, 95% CI 1.8, 7.5, , 0.01) and diastolic BP (3.3 ± 5.7 mm Hg, 95% CI 1.3, 5.3, , 0.01). The magnitude of the difference in efficacy between the two drugs was the same during the day and the night (mean difference 4.3 ± 8.6/2.9 ± 6.0 mm Hg for daytime systolic/diastolic and 4.6 ± 9.3/3.3 ± 7.1 mm Hg for nighttime).

Analysis of responders using the median response criterion showed disagreement in the antihypertensive response between ACE inhibition and AT1R antagonism in 39% of subjects for 24-h diastolic ambulatory BP (primary endpoint) and in 33% for 24-h systolic ambulatory BP (Table 1, Fig. 1). The corresponding proportions using the arbitrary response criterion were 33% and 39% (Table 1). Those subjects in whom there was a disagreement in the response to the two drugs did not differ from subjects in whom there was agreement, in terms of age, sex, and initial clinic and ambulatory BP before treatment initiation. Strong correlations were found between the BP responses to lisinopril and losartan for clinic and ambulatory BP (Table 2, Fig. 2).

**Discussion**

The question addressed in this study was whether the antihypertensive response to ACE inhibition can predict the response to AT1R antagonism and vice versa. Studies comparing AT1R antagonists with ACE inhibitors have shown similar antihypertensive efficacy, with about 50% of the subjects responding to each treatment. However, all of these studies had parallel group designs, which does not allow for intr-individual comparison of responses. Thus, the similarity in the average antihypertensive response to these different methods of renin-angiotensin system blockade does not preclude the possibility that the same subjects respond to the treatment with both the drug classes. A cross-over design in which all patients are exposed to all treatments is appropriate to address our

**Table 1.** Responders to treatment with lisinopril, losartan, or both, and levels of agreement in the responsiveness between the two drug classes [number of subjects (%)]

<table>
<thead>
<tr>
<th>BP Fall for Definition of Responders</th>
<th>Patients With BP Response to Treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lisinopril Only</td>
</tr>
<tr>
<td>Systolic ≥ 10 mm Hg</td>
<td>11 (33.3)</td>
</tr>
<tr>
<td>Systolic &gt; median fall</td>
<td>6 (18.2)</td>
</tr>
<tr>
<td>Diastolic ≥ 5 mm Hg</td>
<td>10 (30.3)</td>
</tr>
<tr>
<td>Diastolic &gt; median fall</td>
<td>7 (21.2)</td>
</tr>
</tbody>
</table>

BP = blood pressure.
Data are given as numbers of subjects, with percentages in parentheses.

FIG. 1. Responders to angiotensin converting enzyme (ACE) inhibition and/or to angiotensin receptor (AT1R) antagonism (24-h ambulatory blood pressure [BP], median response analysis).
research question. Although the study was not blinded to the investigator, a selection bias was prevented by randomizing patients to the two treatment arms, and a placebo effect was avoided by using ambulatory BP monitoring.

**Comparison of Average Responses**

Lisinopril was more effective than losartan in reducing clinic and ambulatory BP in this study. As indicated by 95% confidence intervals, the difference between the two drugs in their effects on 24-h ambulatory BP might be either negligible (1.8/1.3 mm Hg for systolic/diastolic) or clinically important (7.5/5.3 mm Hg). The dose of 50 mg for losartan in this study was chosen because there is evidence suggesting a minimal additional effect with larger doses.\(^{14,15}\) It could be argued that by doubling the dose of losartan or by extending the duration of treatment to 6 to 8 weeks,\(^{16}\) the hypotensive effect of the drug might be stronger. Although this is probably true to some extent, the overall comparison of the two drugs was not the primary objective of the study.

Differences in the pharmacological profile of the two drugs (antihypertensive efficacy and 24-h coverage) may have affected the findings in this study. Differences in 24-h coverage did not seem to be a problem, given that the magnitude of the difference in antihypertensive efficacy between the two drugs was the same during the day and night. However, differences in the antihypertensive efficacy resulted in a higher proportion of responders to lisinopril when using an arbitrary criterion (BP fall ≥ 10/5 mm Hg for systolic/diastolic) for the responders–nonresponders classification. To select the same proportion of responders in the two study groups, an alternative definition for responders was applied using the median BP response achieved by each of the drugs as a threshold for response. Thus, for each treatment, 50% of subjects were considered to be responders. In addition, the responses to the two drugs were treated as continuous variables, and the association between them was examined by performing linear correlations.

**Intraindividual Comparison of Responses**

The responders–nonresponders analysis showed that—irrespective of the criterion used for the definition of responders—in up to 40% of individuals, the antihypertensive response to ACE inhibition fails to predict the response to AT\(_1\)R antagonism and vice versa (Table 1, Fig. 1). In other words, more than one third of individuals with poor response to treatment with one of these drug classes will respond well to the other, and vice versa. It should be mentioned, however, that the imperfect reproducibility of ambulatory BP has probably affected, at least in part, the findings of this study. The perfect design would have been to study all patients on an ACE inhibitor and then to randomize them either to receive an AT\(_1\)R antagonist or to continue the ACE inhibitor.

Regarding the correlation criterion, the high correlation

![FIG. 2. Relationship between the antihypertensive responses to ACE inhibition and to AT\(_1\)R antagonism (24-h ambulatory BP; \(r = \) correlation coefficient). Abbreviations as in Fig. 1.](image-url)
coefficients found between the antihypertensive responses to ACE inhibition and AT₁R antagonism (Table 2, Fig. 2) were expected because both drugs block the renin-angiotensin system. Previous reports from cross-over studies examining the intraindividual responses to several antihypertensive drug classes have found strong correlations between drugs that share common mechanisms of action (Table 3).17–20 Strong correlations were found between the blood pressure responses to ACE inhibitors and β-blockers, both of which are known to act on the renin-angiotensin system (correlation coefficient [r] ranging from 0.46 to 0.75),17–20 and between calcium antagonists and diuretics, both of which are known to have diuretic properties (r = 0.61).17 (Table 3). On the other hand, weak correlations were found between the responses to drug classes that act through entirely different mechanisms (ACE inhibitors versus calcium antagonists or diuretics, and β-blockers versus calcium antagonists or diuretics), with correlation coefficients ranging from 0.15 to 0.46.17–19,21 (Table 3).

It should be noted that the strength of the association found between the antihypertensive responses to ACE inhibition and AT₁R antagonism in this study does not exceed that reported between ACE inhibitors and β-blockers or between calcium antagonists and diuretics (Table 3). These findings suggest that, in fact, the intraindividual variation in the response to ACE inhibitors and to AT₁R antagonists is similar to that found between ACE inhibitors and β-blockers or between calcium antagonists and diuretics, supporting the view that there are clinically important differences between AT₁R antagonists and ACE inhibitors in their mechanisms of antihypertensive action.

### Conclusions and Practical Implications

We conclude that these findings may have considerable implications in the use of these drug classes in the management of hypertensive patients. The belief that, from a clinical point of view, AT₁R antagonists are ACE inhibitors that do not cause cough appears to be rather simplistic. The results of our study show that the antihypertensive response to one of the drugs cannot predict the response to the other. Interestingly, the combination of these drug classes has been reported to provide additive antihypertensive effects in patients with essential hypertension.22 Therefore, these drugs appear to have important similarities inasmuch as they act on the same system, but they also have important differences in their mechanisms of antihypertensive action, which are not only of theoretical but also of practical significance.

### References


