Effect of Indomethacin on Blood Pressure Lowering by Captopril and Losartan in Hypertensive Patients

Paul R. Conlin, Thomas J. Moore, Stephen L. Swartz, Eliav Barr, Lisa Gazdick, Charlena Fletcher, Paul DeLucca, Laura Demopoulos

Abstract—NSAIDs are known to attenuate the effects of some antihypertensive medications. It is not known whether the new class of angiotensin II receptor antagonists is similarly affected. We conducted a multicenter study assessing the effect of indomethacin on the antihypertensive effects of losartan and captopril. After 4 weeks of placebo washout, hypertensive patients received 6 weeks of active antihypertensive therapy with either 50 mg losartan once daily (n=111) or 25 mg captopril twice daily for 1 week, which was increased to 50 mg twice daily for 5 weeks (n=105). This was followed by 1 week of concomitant therapy with indomethacin (75 mg daily). The primary outcome measure was the change in mean 24-hour ambulatory diastolic blood pressure after the addition of indomethacin. Both captopril and losartan significantly lowered ambulatory diastolic blood pressure (losartan −5.3 mm Hg, P<0.001; captopril −5.6 mm Hg, P<0.001) after 6 weeks of therapy. Indomethacin significantly attenuated the 24-hour ambulatory diastolic blood pressure for both losartan (2.2 mm Hg, P<0.05) and captopril (2.7 mm Hg, P<0.001) and also attenuated the effect of captopril on trough sitting diastolic blood pressure. Changes in daytime diastolic blood pressure (7:00 AM to 11:00 PM) were similar to the 24-hour response in both groups. Nighttime diastolic blood pressure (11:01 PM to 6:59 AM) was significantly attenuated in captopril-treated patients (2.0 mm Hg, P<0.05), but losartan was unaffected (0.4 mm Hg). Thus, concurrent treatment with indomethacin similarly attenuates the 24-hour antihypertensive response to losartan and captopril. (Hypertension. 2000;36:461-465.)

Key Words: hypertension, essential ▪ indomethacin ▪ losartan ▪ captopril ▪ blood pressure

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most common classes of medications prescribed in the United States. The availability of over-the-counter formulations has increased their use further, particularly among the elderly.1 Given the high prevalence of hypertension, it is likely that concomitant use of NSAIDs and antihypertensive medication will occur in the same patient. There are numerous studies and meta-analyses that have focused on the adverse effects of NSAID medications on blood pressure and the blunting of the efficacy of antihypertensive medications. Most classes of antihypertensive drugs appear to be affected; these include diuretics,2 β-blockers,2,3 and angiotensin-converting enzyme inhibitors (ACEIs).4–7 The most widely studied of the NSAID medications is indomethacin, which has been shown to increase mean blood pressure by as much as 5 mm Hg in treated hypertensive patients.8 The clinical relevance of these blood pressure changes can be tied to the observation that NSAID use in the elderly is associated with an increased likelihood of the subsequent initiation of antihypertensive therapy.9 In part, the increase in blood pressure resulting from NSAID administration may be nonspecific (ie, related to fluid retention), and these effects may affect antihypertensive medications equally. However, given the inhibition of prostaglandin synthesis by NSAIDs, there is reason to believe that ACEIs may be particularly affected. ACEIs prevent the breakdown of bradykinin, which has been shown to increase prostaglandin synthesis.10 Not unexpectedly, concomitant administration of indomethacin in captopril-treated patients reversed 40% of the antihypertensive effect in hypertensive patients4–5 and attenuated the favorable hemodynamic effects in patients with congestive heart failure.7

The new class of antihypertensive agents, angiotensin II receptor antagonists, directly opposes the interaction of angiotensin II with its cell surface receptor. Angiotensin II receptor antagonists reduce blood pressure to a degree similar to that for most other classes of antihypertensive medications. However, in contrast to ACEI, there is no evidence from in vivo or in vitro studies that part of this antihypertensive effect of angiotensin II receptor antagonists is mediated by prostaglandins.

The present study was designed to evaluate the effect of concurrent use of indomethacin on the antihypertensive effect of losartan and captopril.
of captopril, an ACEI, and losartan, an angiotensin II receptor antagonist. It was hypothesized that both specific and non-specific effects of indomethacin would interfere with the antihypertensive efficacy of captopril and that small non-specific effects would be apparent with losartan. By using the attenuation of 24-hour ambulatory diastolic blood pressure by indomethacin for comparisons, it was also possible to gain insight into the role of vasodilator prostaglandins in the antihypertensive effect of losartan.

Methods

Study Subjects
This was a randomized, double-blind, parallel-design multicenter study. Participants in the present study were men and women with known essential hypertension recruited from 32 clinical centers. The protocol was reviewed and approved by Institutional Review Boards for Human Studies at each of the participating sites, and written informed consent was obtained from each participant before enrollment.

Initial screening involved a medical history, physical examination, and basic laboratory studies. Subjects were excluded if they had a history of significant cardiovascular, cerebrovascular, renal, or gastrointestinal disease, secondary hypertension, or prior documented intolerance or adverse effects from captopril, losartan, or NSAIDs.

Study Design
All personnel responsible for blood pressure measurements were certified through a standardized training program that used the American Heart Association guidelines for measurement of blood pressure. Blood pressure was measured with subjects in the sitting position after at least 5 minutes of rest; a standard mercury sphygmomanometer was used. The mean of 3 readings taken 1 minute apart (which did not differ by >5 mm Hg) was calculated. Study participants were asked not to take their dose of study medication until after clinic visits were completed.

Ambulatory blood pressure monitoring (ABPM) was performed with the use of the Spacelabs 90207 device. The device was programmed to automatically inflate every 20 minutes during the day (from 7:00 AM to 11:00 PM) and every 30 minutes at night (from 11:01 PM to 6:59 AM). The monitor initiated repeat testing if a systolic blood pressure or diastolic blood pressure reading fell outside of predefined ranges (systolic 70 to 240 mm Hg, diastolic 40 to 150 mm Hg). Participants were asked to return to the clinic the next day for removal of the device. ABPM was considered satisfactory if there were at least 50% of the anticipated readings during the 24-hour period. If there were fewer than acceptable readings, participants were asked to wear the device for an additional 24-hour period. Standard mercury sphygmomanometer readings were also obtained on the day ABPM was initiated and the following day, when the monitor was removed.

All subjects meeting eligibility criteria were withdrawn from prior antihypertensive medications and NSAID use and entered a 4-week placebo-controlled baseline period. Patients were evaluated at 2-week intervals for blood pressure and adverse experiences. Laboratory assessment was performed after 4 weeks of placebo. Only those patients whose diastolic blood pressure readings at weeks 2 and 4 of the placebo period were >95 and <115 mm Hg and did not differ by >7 mm Hg were asked to complete ABPM before randomization. Those patients whose mean 24-hour ABPM diastolic blood pressure was ≥85 mm Hg were randomized into the double-blind period of the study.

Patients were randomly assigned to double-blind treatment with either losartan (50 mg daily) or captopril (25 mg twice daily). The double-blind condition was maintained by dispensing separate bottles for losartan or matching placebo and for captopril and matching placebo. Follow-up evaluations were performed at weeks 1, 4, 6, and 7 after randomization.

After 1 week on double-blind treatment, patients who were receiving captopril had their dose increased to 50 mg twice daily, which was continued for the duration of the study. This starting dose and later dose titration were included to be consistent with the labeling for this product. After 6 weeks on double-blind treatment, ABPM was repeated with clinic blood pressures obtained on each of the 2 days that the ABPM was performed. Patients then received concomitant treatment with open-label slow-release (SR) indomethacin (75 mg daily) for 1 additional week. At the end of this week of concurrent antihypertensive and SR indomethacin treatment, the patients returned for repeat ABPM and clinic blood pressure measurements.

Statistical Analysis
The efficacy data were analyzed in subjects who completed the study without major protocol violation (per-protocol analysis). The primary outcome variable was the change in 24-hour mean diastolic blood pressure with ABPM after the addition of indomethacin. At each observation period, an individual’s 24-hour mean ABPM was obtained by averaging the hourly mean readings taken during the 24-hour period. The 24-hour mean for each treatment was then calculated by averaging the individual 24-hour means across patients. Mean changes from baseline to the end of double-blind treatment were compared between treatment groups by ANOVA with terms for treatment, investigator, and the interaction of treatment and investigator. Mean changes from the end of double-blind treatment to the end of concomitant antihypertensive and indomethacin treatment were compared between groups by ANCOVA. Within-treatment-group changes were analyzed by the paired t test. Daytime blood pressure was the mean of blood pressures obtained between 7:00 AM and 11:00 PM, and nighttime blood pressure was the mean of blood pressures obtained between 11:01 PM and 6:59 AM. The safety data were analyzed by using the all-patients-treated population. Fisher exact tests were used to compare treatment groups for the incidence of adverse experiences.

Results
Two hundred eighty-one patients were entered into the study; 140 were randomized to receive losartan, and 141 patients were randomized to receive captopril. A total of 216 patients (111 losartan-treated patients and 105 captopril-treated patients) completed the study according to the protocol and had valid data for analysis. The reasons for patients being excluded from analysis were (1) not completing the study (22 patients), (2) invalid or missing data either at baseline or during follow-up (22 patients), and (3) major protocol violations (21 patients). The baseline characteristics of the study population are shown in Table 1. No significant differences in baseline parameters were found between the 2 treatment groups.

Each of the antihypertensive agents, losartan and captopril, produced a significant reduction in mean 24-hour systolic and diastolic blood pressures after 6 weeks of therapy (Table 2); the reductions in blood pressures were as follows: for losartan, systolic −7.9 mm Hg, diastolic −5.3 mm Hg ($P<0.001$); for captopril, systolic −8.6 mm Hg, diastolic −5.6 mm Hg ($P<0.001$). There was no significant difference between agents in the blood pressure response produced. One week of concomitant indomethacin treatment produced a significant rise in 24-hour mean systolic and diastolic blood pressures in both the losartan- and captopril-treated patients as follows: for losartan, systolic 3.8 mm Hg, diastolic 2.2 mm Hg ($P<0.001$); for captopril, systolic 4.6 mm Hg, diastolic 2.7 mm Hg ($P<0.001$) (Figure). Within-group and between-group comparisons showed that both agents re-
sponded similarly to indomethacin. Overall, 68.5% of losartan-treated patients and 67% of captopril-treated patients had a rise in ambulatory diastolic blood pressure during indomethacin treatment. The 24-hour pulse rate did not change with antihypertensive treatment alone but fell by a small but significant amount with concomitant indomethacin to a similar extent in both groups.

Within-group comparisons showed that concomitant indomethacin treatment had its greatest effect on daytime blood pressure for both losartan and captopril. Nighttime blood pressure was also attenuated in the captopril-treated patients, whereas nighttime blood pressure was not significantly affected by indomethacin in losartan-treated patients (Table 3). Clinic blood pressures also paralleled the response of nighttime ABPM blood pressures in both treatment groups: indomethacin significantly attenuated the blood pressure response to captopril but did not have a significant effect on the losartan response. However, the between-group comparisons showed no significant difference between the 2 treatments for daytime, nighttime, or clinic blood pressure. There was no difference in the change from baseline to the end of antihypertensive treatment alone (week 6) nor was there a difference between treatment groups after the addition of indomethacin (week 7).

To determine whether baseline blood pressure affected the response to antihypertensive treatment and indomethacin, we assessed the antihypertensive effect of concomitant indomethacin in patients with higher levels of blood pressure (clinic diastolic blood pressure >100 mm Hg [losartan, n=60; captopril, n=64]). Both drug treatment groups had similar antihypertensive effects and similar blunting with indomethacin. We also analyzed the effect of indomethacin on the blood pressure response in blacks and whites. There was no significant difference in the effect of indomethacin on the blood pressure (systolic or diastolic) response to losartan or captopril in blacks or whites. Both groups had similar increases in blood pressure after indomethacin.

Patients tolerated both treatments well. Compliance with the 2 drug treatments and with indomethacin was similar. Clinical adverse experiences were significantly greater in the captopril-treated patients (51% versus 37%, P<0.03), although drug-related adverse experiences were not statistically different (losartan 18% versus captopril 25%). There were similar numbers of patients who discontinued the study.

### TABLE 1. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Losartan</th>
<th>Captopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51±1</td>
<td>51±1</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>64</td>
<td>60</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>68</td>
<td>75</td>
</tr>
<tr>
<td>Black</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>ABPM (24-h), mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>151.4±1.0</td>
<td>153.8±1.3</td>
</tr>
<tr>
<td>Diastolic</td>
<td>94.5±0.5</td>
<td>96.3±0.6</td>
</tr>
<tr>
<td>Office BP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>154.0±1.3</td>
<td>156.0±1.3</td>
</tr>
<tr>
<td>Diastolic</td>
<td>101.2±0.4</td>
<td>102.3±0.5</td>
</tr>
</tbody>
</table>

Values are mean±SE. BP indicates blood pressure; ABPM, ambulatory blood pressure monitoring.

### TABLE 2. Ambulatory BP and Pulse Rate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Week</th>
<th>Systolic BP, mm Hg</th>
<th>Diastolic BP, mm Hg</th>
<th>Pulse, bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>111</td>
<td>Baseline</td>
<td>150.0±1.2</td>
<td>93.2±0.6</td>
<td>81.9±1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>142.0±1.6*</td>
<td>87.9±0.8*</td>
<td>81.6±1.0</td>
</tr>
<tr>
<td></td>
<td>+Indomethacin</td>
<td>7</td>
<td>145.8±1.6†</td>
<td>90.0±0.8†</td>
<td>79.5±1.0†</td>
</tr>
<tr>
<td>Captopril</td>
<td>105</td>
<td>Baseline</td>
<td>152.2±1.5</td>
<td>95.0±0.8</td>
<td>78.0±1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>144.1±1.6*</td>
<td>89.8±0.9*</td>
<td>78.3±1.0</td>
</tr>
<tr>
<td></td>
<td>+Indomethacin</td>
<td>7</td>
<td>148.3±1.6†</td>
<td>92.2±0.9†</td>
<td>75.7±1.0†</td>
</tr>
</tbody>
</table>

Values are mean±SE.

*P<0.05 vs baseline; †P<0.05 vs week 6.
because of adverse events with losartan (n=5 [4%]) and captopril (n=9 [6%]).

Discussion

The present study shows that the NSAID indomethacin blunts the 24-hour antihypertensive effects of both captopril and losartan. ABPM was chosen as the primary outcome measure because it can produce reliable and reproducible measurements without observer bias and therefore increases the power to detect small differences in blood pressure. Indomethacin blunted the antihypertensive effect of captopril for daytime, nighttime, and in-clinic measurements by standard mercury sphygmomanometry. Indomethacin also attenuated the 24-hour blood pressure response to losartan, although this was largely due to effects on daytime blood pressure. Nighttime and clinic blood pressures were less affected in the losartan-treated patients.

The effect of indomethacin on the antihypertensive effect of captopril and losartan was quantitatively small (=2 to 3 mm Hg increase in diastolic blood pressure and 3 to 5 mm Hg increase in systolic blood pressure), but this represented a loss of ~40% of their antihypertensive effect. These observations may have implications for the antihypertensive effect of these 2 agents when taken concomitantly with indomethacin.

There are a number of studies that have identified an effect of NSAID medications on blood pressure in both normotensive and hypertensive individuals. In general, the effect is small but is most evident with β-blockers and vasodilators, whereas diuretics or calcium channel blockers are less affected. This may imply that the mechanism of effect is nonspecific rather than a direct interruption of the mechanism of action of the antihypertensive agent. In fact, the actual mechanism(s) of the role of NSAIDs in blood pressure regulation is poorly understood; therefore, the mechanism of the attenuation of the antihypertensive effect is equally unclear. Effects on renin secretion, sodium reabsorption, and free water clearance are all described in the mechanism of action of these NSAID medications. However, a specific effect of vasodilator prostaglandins in the antihypertensive effect of ACEIs was suggested from in vitro studies that showed increased prostaglandin synthesis with captopril. It has also been presumed that this effect was mediated by bradykinin. The blood pressure lowering of angiotensin II receptor antagonists does not appear to involve bradykinin as it does captopril. It was for this reason that we positied that there would be less blunting of the antihypertensive effect of losartan by indomethacin.

We observed that indomethacin significantly blunted the 24-hour blood pressure response to both captopril and losartan. These findings are at variance with a recent report that showed no effect of indomethacin on the efficacy of losartan in hypertensive patients and also used ABPM as the primary outcome measure. Olsen et al. used a crossover study design, with indomethacin administered in double-blind fashion to 10 losartan-treated hypertensive patients. They observed an increase in body weight and increased intravascular volume with indomethacin treatment but no change in blood pressure. The major differences between our findings and those of Olsen et al may lie in the study design (we did not include a placebo arm) and the greater number of patients we studied.

In most individuals, there is a diurnal variation of blood pressure, with daytime levels being higher than nighttime levels. This is related in part to changes in posture as well as diurnal changes in the activity of blood pressure–regulating systems, including the renin-angiotensin system and the sympathetic nervous system. When the 24-hour period was separated into daytime and nighttime intervals, the effect of indomethacin was different between the 2 drugs. We chose arbitrary times to define daytime and nighttime because awake and sleep times were not obtained from the study participants. However, in a recent study, we measured ambulatory blood pressure in 354 participants and observed that 90% of the participants reported that their awake and asleep times fell within 2 hours of these fixed time intervals. The 24-hour blood pressure effects of indomethacin were similar between captopril and losartan. However, the antihypertensive effect of captopril was attenuated during both daytime and nighttime hours, and the effect of losartan was blunted mainly during daytime hours. This was not due to a smaller nighttime antihypertensive effect of losartan. A similar pattern was observed with the results of clinic blood pressures, which were measured in the morning, 24 hours after the last dose of medication. Despite these differences in the response of each agent, the comparison of captopril and losartan showed that both behaved similarly.

**TABLE 3. Daytime, Nighttime, and Clinic BPs**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Week</th>
<th>Daytime Systolic BP, mm Hg</th>
<th>Daytime Diastolic BP, mm Hg</th>
<th>Nighttime Systolic BP, mm Hg</th>
<th>Nighttime Diastolic BP, mm Hg</th>
<th>Clinic Systolic BP, mm Hg</th>
<th>Clinic Diastolic BP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>111</td>
<td>Baseline</td>
<td>155.0±1.2</td>
<td>97.5±0.6</td>
<td>138.5±1.3</td>
<td>83.8±0.8</td>
<td>154.0±1.5</td>
<td>101.2±0.5</td>
</tr>
<tr>
<td>+Indomethacin</td>
<td>6</td>
<td>151.1±1.6</td>
<td>94.3±0.8</td>
<td>133.3±1.6</td>
<td>80.3±1.0</td>
<td>148.7±1.8</td>
<td>94.5±0.8</td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>105</td>
<td>Baseline</td>
<td>157.2±1.4</td>
<td>99.1±0.8</td>
<td>140.6±1.8</td>
<td>85.7±1.0</td>
<td>156.0±1.5</td>
<td>102.3±0.5</td>
</tr>
<tr>
<td>+Indomethacin</td>
<td>7</td>
<td>153.8±1.5</td>
<td>96.7±0.8</td>
<td>135.7±1.9</td>
<td>81.9±1.0</td>
<td>150.2±1.8</td>
<td>96.5±0.9</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SE. Daytime (7:00 AM to 11:00 PM) and nighttime (11:01 PM to 6:59 AM) BPs were measured with ABPM. Clinic BP was measured by mercury sphygmomanometry.

*P<0.05 vs baseline; †P<0.05 vs week 6.
We assessed the possibility that higher blood pressures were more sensitive to prostaglandin inhibition with indomethacin. To address this possibility, we evaluated the effect of indomethacin in patients with sitting diastolic blood pressure ≥100 mm Hg at study entry to determine whether a greater attenuation with indomethacin was observed. We saw the same amount of blood pressure attenuation in these subjects as in the entire group. Likewise, indomethacin had similar effects in blacks and whites.

Although NSAIDs such as indomethacin clearly affect blood pressure, it is not known whether the new class of NSAID agents, cyclooxygenase (COX)-2 inhibitors, will have the same effect. Both COX-1 and COX-2 are expressed in the kidney. Unpublished data suggest that edema formation is increased with the use of celecoxib and rofecoxib. The effect of COX-2 inhibitors on blood pressure has not been reported.

In conclusion, the present study shows that indomethacin blunts the 24-hour antihypertensive effects of losartan and captopril. Thus, hypertensive patients receiving either captopril or losartan who require concomitant therapy with indomethacin should be monitored for alterations in blood pressure.

Acknowledgment
This study was conducted with a grant from Merck and Co, Inc, US Human Health Division.

References
Effect of Indomethacin on Blood Pressure Lowering by Captopril and Losartan in Hypertensive Patients
Paul R. Conlin, Thomas J. Moore, Stephen L. Swartz, Eliav Barr, Lisa Gazdick, Charlena Fletcher, Paul DeLucca and Laura Demopoulos

Hypertension, 2000;36:461-465
doi: 10.1161/01.HYP.36.3.461

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/36/3/461

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/