Effects of Celecoxib on Ambulatory Blood Pressure in Hypertensive Patients on ACE Inhibitors

William B. White, Jeffrey Kent, Addison Taylor, Kenneth M. Verburg, James B. Lefkowith, Andrew Whelton

Abstract—Nonselective nonsteroidal anti-inflammatory agents have been shown to attenuate the antihypertensive efficacy of ACE inhibitors with average increases in systolic blood pressure (BP) of 5 to 10 mm Hg. Less is known about the specific cyclooxygenase-2 (COX-2) inhibitors now widely used for the treatment of arthritis. The objective of this study was to determine the effects of celecoxib compared with placebo on 24-hour BP levels in ACE inhibitor–treated patients with hypertension. This was a randomized, double-blind, placebo-controlled, parallel-group clinical trial involving 178 men and women (mean age, 53 years) with essential hypertension who were treated and controlled with lisinopril monotherapy (10 to 40 mg daily). Baseline BP values were obtained using 24-hour ambulatory recordings. Patients received either celecoxib, 200 mg twice daily (twice the recommended dose for osteoarthritis) (n=91), or placebo (n=87) for 4 weeks, and changes in the 24-hour BP, body weight, and clinical laboratory parameters were assessed. Mean changes from baseline in the 24-hour systolic and diastolic BP were 2.6/1.5±0.9/0.6 mm Hg on celecoxib versus 1.0/0.3±1/0.6 mm Hg on placebo (P=0.34 for systolic BP; P=0.45 for diastolic BP). The proportion of patients whose 24-hour BP increased by at least 5, 10, 15, or 20 mm Hg were also similar on celecoxib and placebo. No changes in body weight, serum creatinine, or potassium occurred in either group. Thus, these data demonstrate that high doses of celecoxib have no significant effect on the antihypertensive effect of the ACE inhibitor lisinopril. The placebo-subtracted changes observed in 24-hour BP (1.6/1.2 mm Hg) are less than what has been reported for nonselective nonsteroidal anti-inflammatory agents in ACE inhibitor–treated patients. (Hypertension. 2002;39:929-934.)

Key Words: angiotensin-converting enzyme inhibitors ■ antihypertensive agents ■ clinical trials ■ hypertension, essential ■ cyclooxygenase

Hypertension and arthritis represent common comorbid conditions leading to the frequent coadministration of nonsteroidal anti-inflammatory agents (NSAIDs) and antihypertensive medications. Conventional NSAIDs used commonly in the management of the signs and symptoms of arthritis nonspecifically inhibit both isoforms of the cyclooxygenase (COX) system. As a result, nonselective NSAID therapy may reduce the efficacy of antihypertensive drug therapy, especially drugs that block the renin-angiotensin system.1-4

Nonselective COX inhibition results in inhibition of prostaglandin synthesis and is associated with antinatriuretic and vasoconstrictor effects.4-5 These effects have consequences on blood pressure (BP) control and are of particular relevance in patients with preexisting hypertension.1,2 Meta-analyses of the effects of many of these agents (including naproxen, indomethacin, and ibuprofen) have reported average increases in mean arterial pressure of 5.5 mm Hg.1,2 However, the relative contribution of COX-1 or COX-2 to this effect is unknown.

Angiotensin-converting enzyme (ACE) inhibitors are widely prescribed antihypertensive medicines. Like other antihypertensive therapies (with the exception of the calcium channel blockers and possibly the alpha-blockers), an important component of the mechanism of action of ACE inhibitors is the increased synthesis of vasodilatory prostaglandins.4 Celecoxib is a COX-2–specific inhibitor indicated for the management of osteoarthritis or rheumatoid arthritis.5,6 It specifically inhibits the COX-2 isoenzyme while sparing COX-1,5,6 resulting in an improved gastrointestinal safety and tolerability profile compared with nonselective NSAIDs.5,7 The COX-2 inhibitor rofecoxib has also been shown to reduce gastrointestinal toxicity compared with conventional NSAIDs8 but has recently been shown to significantly increase 24-hour systolic BP by 4.5 mm Hg over placebo in hypertensive patients on the ACE inhibitor benazepril.9,10 Because of these reported interactions of the NSAIDs and rofecoxib with BP control in ACE inhibitor–treated patients, we studied the effects of celecoxib to determine whether a similar interaction occurred.

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Methods

Patients
Men and women between the ages of 18 and 75 years were included if they had a history of uncomplicated hypertension and were treated with no more than 2 antihypertensive agents. Because aspirin has been shown to attenuate the hemodynamic effects of the ACE inhibitors,11,12 aspirin was not allowed during the study. Acetaminophen (up to 4 grams/daily) was permitted.

Study Design
The study was a double-blind, placebo-controlled, parallel-group multicenter trial (Figure 1). The primary objective was to evaluate the effects of high doses (200 mg dosed twice daily) of celecoxib on 24-hour BP in hypertensive patients whose BP was controlled with the ACE inhibitor lisinopril. Current antihypertensive medication(s) were discontinued or tapered to discontinuation. When seated diastolic BP in the doctor’s office or clinic was stable (defined as 2 consecutive measurements, taken 2 weeks apart and varying by no more than 5 mm Hg) at 95 to 109 mm Hg, patients were eligible for the open label lisinopril titration period.

Lisinopril was titrated weekly (10, 20, to 40 mg once daily in the morning) to stabilize the hypertension (defined as a seated diastolic BP [DBP] <90 mm Hg if the untreated DBP was 95 to 104 mm Hg or <95 mm Hg if the untreated DBP was 105 to 109 mm Hg). During this ACE-inhibitor treatment period, all patients received single-blind placebo to match celecoxib, 200 mg twice daily. When patients met the criteria for diastolic BP stabilization at 2 separate weekly visits on a stable dose of lisinopril in the clinic or office, 24-hour ambulatory BP monitoring was performed, providing baseline measures. If BP could not be stabilized adequately with lisinopril 40 mg QD, or if ambulatory BP monitoring was not adequate after 2 attempts during the single-blind period, then patients were withdrawn from the study.

Patients with stable BP on lisinopril and complete 24-hour ambulatory BP recordings at baseline were randomized to treatment with either celecoxib 200 mg twice daily (twice the recommended dose for osteoarthritis) or placebo twice daily. During the double-blind period, the dose of lisinopril that had controlled the BP during the baseline period was maintained. Following 4 weeks of double-blind therapy, 24-hour ambulatory monitoring was repeated. During the double-blind period, the lisinopril dose could not be altered, and no other antihypertensive therapy was permitted.

Statistical Analyses
The comparability of patients in the 2 treatment groups was determined from the demographic data and baseline hemodynamic values. Continuous variables were analyzed using the nonparametric Kruskal-Wallis method. Discrete variables were compared using the chi-squared test method for homogeneity of proportions for categorical data. The primary variable for assessing the attenuation of ACE inhibitor control of hypertension was the change in 24-hour diastolic BP from baseline after 4 weeks of celecoxib or placebo. Secondary analyses included the changes from baseline in the 24-hour systolic BP and several other ambulatory monitoring parameters, including daytime mean, nighttime mean, and the changes in ambulatory heart rate. Furthermore, the proportion of patients whose 24-hour systolic and diastolic BP increased by <5, 5 to 9, 10 to 14, 15 to 19, and >20 mm Hg on celecoxib and placebo compared with the baseline values were calculated.

Treatment groups were compared with respect to change from baseline to the week 4 endpoint using an analysis of covariance (ANCOVA) that included treatment, center, and baseline measures as the covariates in the model. Treatment comparisons were based on the least square means obtained via a SAS Type III analysis (SAS 6.09 VMS operating system, SAS Institute). A power analysis was based on a single effect variable, ie, the change from baseline in the 24-hour mean diastolic BP as determined at the final visit of the double-blind period. It was determined that a sample size of 80 patients per treatment group would give 80% power to detect a 3 mm Hg difference between celecoxib and placebo in the 24-hour diastolic BP assuming a standard deviation of 6.5 mm Hg and a 2-tailed α of 0.05.

Results

Baseline Parameters
As shown in Figure 2, there were 242 patients who entered the lisinopril titration period; 64 patients (26%) were not randomized, the majority of the discontinuations before randomization occurred because of an inability to meet the BP stability criteria. Of the 178 patients who were randomized in the double-blind treatment period, there were no significant baseline differences in demographic characteristics, or in baseline ambulatory BPs or heart rates between the celecoxib (n=91) or placebo (n=87) groups (Table 1). The majority of the randomized patients completed the entire 4-week double-blind treatment period (97.7% in the placebo group and 94.5% in the celecoxib group). The average daily doses of lisinopril were similar in the celecoxib treatment group (23 mg) and the placebo group (21 mg).

Effects of Treatment on Ambulatory BP and Heart Rate
The effects of celecoxib and placebo on ambulatory BP and heart rate parameters are shown in Table 2. There were small increases in 24-hour ambulatory systolic and diastolic BP (2.6/1.5 mm Hg) in the celecoxib group compared with the placebo group (1.0/0.3 mm Hg). However, these were not statistically significant. These numerical differences between celecoxib and placebo were more notable during the daytime,
awake hours than during the nighttime sleep period (Table 2). There were no changes in the 24-hour mean heart rates on placebo or celecoxib.

Visual evaluation of the hourly ambulatory BP profiles showed a 2-to-4-mm Hg, transient increase in ambulatory systolic BP for approximately 4 hours post-dosing of celecoxib, both in the morning (9 AM to 1 PM) and in the evening (7 PM to 10 PM) (Figure 3). These hourly changes from baseline coincide with the approximate dosing times of study drug in the morning and 12 hours later in the evening. The changes from baseline in diastolic BP were smaller on celecoxib.

An analysis of the proportion of individuals whose 24-hour BP increased by clinically relevant threshold values is shown in Figure 4. Most of the patients whose BP rose in either the celecoxib or placebo group were in the range of 1 to 10 mm Hg. There were no significant differences in the proportion of patients whose BP was elevated at any particular threshold value on celecoxib versus placebo.

**TABLE 1. Baseline Demographic Characteristics of All Randomized Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Celecoxib (n=91)</th>
<th>Placebo (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>51/40</td>
<td>49/38</td>
</tr>
<tr>
<td>Age, mean yr (range)</td>
<td>54.5 (30–70)</td>
<td>52.9 (29–69)</td>
</tr>
<tr>
<td>Weight, mean kg (range)</td>
<td>87.6 (55–153)</td>
<td>87.5 (54–140)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>51 (56%)</td>
<td>55 (63%)</td>
</tr>
<tr>
<td>Black</td>
<td>17 (19%)</td>
<td>10 (12%)</td>
</tr>
<tr>
<td>Hispanic/Latin American</td>
<td>19 (21%)</td>
<td>19 (22%)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (4%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>70.1</td>
<td>73.7</td>
</tr>
</tbody>
</table>

Ambulatory BP measurements (mm Hg)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Celecoxib</td>
</tr>
<tr>
<td>24-hour systolic BP (mm Hg)</td>
<td>134.7±1.5</td>
</tr>
<tr>
<td>24-hour diastolic BP (mm Hg)</td>
<td>83.8±0.9</td>
</tr>
<tr>
<td>Daytime systolic BP (mm Hg)</td>
<td>137.4±1.4</td>
</tr>
<tr>
<td>Daytime diastolic BP (mm Hg)</td>
<td>86.7±0.9</td>
</tr>
<tr>
<td>Nighttime systolic BP (mm Hg)</td>
<td>125.8±1.8</td>
</tr>
<tr>
<td>Nighttime diastolic BP (mm Hg)</td>
<td>74.6±1.0</td>
</tr>
</tbody>
</table>

Data are expressed as the mean±standard error of the mean.
Safety Analyses
There were no deaths or serious adverse events in the celecoxib treatment group. There were 2 serious adverse events in the placebo group (suicide attempt and acute myocardial infarction that occurred post-study). There were no differences in nonserious adverse event rates between the celecoxib and placebo treatment groups. The mean change from baseline in body weight was $-0.06\pm0.47$ kg in the placebo group and $0.16\pm0.37$ kg in the celecoxib group ($P=\text{NS}$). There were also no differences in the proportion of patients who developed a prespecified 5% increase or decrease in body weight. No patient in the placebo group developed significant peripheral edema, whereas one subject (1%) developed edema in the celecoxib group. There were no differences in any of the safety laboratory parameters with the exception of the blood urea nitrogen which increased $0.67\pm0.13$ mmol/L on celecoxib versus decreasing by $0.24\pm0.13$ mmol/L on placebo ($P<0.01$). However, no patient in either group developed a blood urea nitrogen above the upper limits of normal.

Discussion
Principal Findings of the Study
Our study demonstrates that celecoxib, a novel COX-2-specific inhibitor, had no clinically significant interaction with the 24-hour antihypertensive effect of lisinopril. In this study, change in the 24-hour ambulatory BP in an ACE inhibitor–treated population was chosen as the primary end-point, because ambulatory BP has recently been shown to have an important and independent association with target organ disease and prognosis in patients with hypertension.\textsuperscript{13–16} In addition, the 24-hour BP curves are superior to the clinic measurements as an effective method for assessing any potential pharmacodynamic interactions occurring during the entire dosing interval of the drugs under evaluation, ie, the ACE inhibitor and the COX-2 inhibitor (Figure 3). The other clinically relevant finding from our study was that celecoxib at maximal doses of 400 mg per day was not associated with increases in body weight, edema rates, or clinically important changes in renal function or potassium homeostasis in hypertensive patients treated with an ACE inhibitor.

Comparative Findings With Conventional NSAID and ACE Inhibitors
Celecoxib appears to have effects that are different from those reported with conventional NSAIDs on BP control in ACE inhibitor–treated patients. The changes observed in 24-hour BP (1.58/1.22 mm Hg, Table 2) are substantially less than those that have been reported for nonselective NSAIDs in ACE inhibitor–treated patients.\textsuperscript{1–4} For example, in a study by Morgan et al,\textsuperscript{4} indomethacin was given at a dose of 50 mg twice daily to 60 patients whose BP had been controlled by the ACE inhibitor enalapril and the dihydropyridine calcium antagonist amlodipine. The difference caused by indomethacin between the 2 groups was a 10/5 mm Hg increase in

![Figure 4. The proportion of patients whose 24-hour systolic (top) and diastolic (bottom) blood pressure increased by <5, 5–9, 10–14, 15–19, and >20 mm Hg above baseline following celecoxib 200 mg twice daily or placebo. There were no significant differences in the proportions at any of the given thresholds.](http://hyper.ahajournals.org/articles/2002/14/1/437/f4.jpg)
Comparisons Between COX-2 Inhibitors Added to Antihypertensive Therapy

Our study represents the only trial to date that has evaluated the ambulatory BP effects of celecoxib in patients treated exclusively with ACE inhibitors. Whelton et al.19 performed a randomized study in which 812 much older patients with osteoarthritis and controlled hypertension received either celecoxib (200 mg daily) or rofecoxib (25 mg daily). Approximately 40% of the patients randomized to the celecoxib group had been treated chronically with ACE inhibitors, whereas 30% of the rofecoxib-treated patients were on ACE inhibitors. The proportion of patients whose systolic BP increased by a clinically significant amount (>20 mm Hg) was significantly greater on rofecoxib (17%) compared with patients on celecoxib (11%). These findings are supported in part by a 36-patient crossover design study that evaluated the COX-2 inhibitor rofecoxib, 25 mg daily, indomethacin sustained-release, 75 mg daily, and placebo in hypertensive patients controlled with the ACE inhibitor benazepril.8,10 In that study, rofecoxib was associated with a significant 4.5 mm Hg sustained increase in 24-hour systolic BP compared with placebo and an approximately 2.5 mm Hg increase in 24-hour systolic pressure compared with indomethacin.

Conclusions

Our study demonstrates that celecoxib, even at maximal doses, is not associated with clinically or statistically significant attenuation of the 24-hour BP control in patients treated exclusively with an ACE inhibitor. Based on several studies in the literature, celecoxib appears to be associated with a lower incidence of hypertension than nonselective NSAIDs using both clinic and ambulatory BP measurements.1-4,8 Recent data directly comparing celecoxib to rofecoxib in older hypertensive patients also confirm a significant difference between these agents in terms of their effects on systolic BP in the clinic and edema.19 Differences in the level of BP control or stability in patients with hypertension clearly have the potential to drive overall cardiovascular morbidity, especially in terms of congestive heart failure and stroke.20 The mechanisms associated with the apparent difference in the COX-2-specific inhibitors, as well as the differences between celecoxib and the conventional NSAIDs, remains to be elucidated. Nevertheless, variations in the cardiovascular effects of celecoxib versus conventional NSAIDs, which may be molecule-specific rather than mechanism-specific, are demonstrable.8,21 Further, direct comparative trials with the COX-2 inhibitors and conventional NSAIDs in patients with hypertension are needed.

Acknowledgments

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References

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