Effects of COX Inhibition on Blood Pressure and Kidney Function in ACE Inhibitor-Treated Blacks and Hispanics

Munavar Izhar, Tunji Alausa, Amy Folker, Elena Hung, George L. Bakris

Abstract—Cyclooxygenase (COX) inhibitors attenuate the antihypertensive effects of angiotensin-converting enzyme (ACE) inhibitors and reduce kidney function. The study tests the hypothesis that these two classes of drugs have similar effects on glomerular filtration rate (GFR) and 24-hour blood pressure. The primary endpoint was change in 24-hour systolic blood pressure. Using a randomized crossover design, 25 black and Hispanic hypertensive participants (mean age 58 ± 3 years) with osteoarthritis were studied. All participants received an ACE inhibitor at baseline. Once systolic blood pressure was <140 mm Hg, either celecoxib 200 mg/d or diclofenac 75 mg twice daily for 4 weeks was started. After measurements were obtained, all participants underwent a 2-week washout period and crossed over to the other drug for 4 weeks. A significant difference in mean 24-hour systolic blood pressure was noted between groups at 4 weeks (+4.1 ± 1.1 mm Hg diclofenac versus +0.6 ± 0.6 mm Hg celecoxib; \( P = 0.01 \)). However, because celecoxib has duration of action shorter than 24 hours, we compared ambulatory values at celecoxib trough and peak activities. At peak, no difference in systolic blood pressure was noted between agents (+3.6 ± 0.04 mm Hg diclofenac versus +4.2 ± 1.9 mm Hg celecoxib; \( P = 0.67 \)). GFR was also differentially affected at 24 hours (−9.9 ± 2.4 mL/min diclofenac versus −0.4 ± 1.2 mL/min celecoxib; \( P = 0.01 \)). We conclude that diclofenac and celecoxib increase systolic blood pressure at peak levels; however, these agents differ in their 24-hour effects. Differences observed in blood pressure response between COX inhibitors may not be related in their sensitivity but rather their dosing frequency. (Hypertension. 2004;43:573-577.)

Key Words: kidney ▪ hypertension ▪ glomerular filtration rate

Hypertension and arthritis are common conditions that co-exist in the elderly population. These two conditions represent common co-morbid causes leading to frequent administration of nonsteroidal anti-inflammatory agents (NSAIDs) and antihypertensive medications. Conventional NSAIDs used commonly in the management of arthritis nonspecifically inhibit isoforms of the cyclooxygenase (COX) system. Nonselective COX inhibition results in the inhibition of prostaglandin synthesis and is associated with anti-natriuretic and vasoconstrictor effects and also causes significant gastrointestinal side effects and frequently reduces glomerular filtration rate (GFR). The sensing mechanisms of sodium are largely through the COX-2 enzymatic pathway located in the macula densa of the kidney.\(^1\) Hence, inhibition of this enzyme would lead to an anti-natriuretic effect.

The consequences of nonselective COX inhibition on blood pressure (BP) control are particularly relevant in patients with preexisting hypertension and osteoarthritis. Two separate meta-analyses that examine the effects of nonselective COX-1 inhibitors including over-the-counter preparations such as naproxen, indomethacin, and ibuprofen implicate them as contributing to loss of BP control and reduction in efficacy of antihypertensive drug therapy, as well as reported gastrointestinal side effects and changes in renal function.\(^2\)\(^,\)\(^3\)

Celecoxib is indicated for the management of osteoarthritis or rheumatoid arthritis.\(^4\) It specifically inhibits the COX-2 enzyme while sparing COX-1, resulting in an improved gastrointestinal safety and tolerability profile compared with nonselective NSAIDs.\(^5\) While there is a plethora of literature regarding the effects of COX-1 inhibitors on BP, there are conflicting reports regarding the adverse effects of COX-2 inhibitors on BP control and kidney function.\(^6\)\(^–\)\(^8\)

The reported differential effects of the COX-2 inhibitors on renal function and BP may be caused by differences in pharmacokinetics between the agents and dosage used.\(^9\)\(^,\)\(^10\) Both these agents have short half-lives but have different initial starting doses and recommended frequency of use, ie, once daily for celecoxib and twice daily for diclofenac, according to their indication for pain relief associated with arthritis.\(^9\) Given the discrepancies between the pharmacokinetics and pain-relieving actions of these two drug classes, the purpose of this study was to examine the effects of a representative agent from each class on renal function and BP as commonly prescribed and indicated for use by the Food and Drug Administration. This was performed in a group of
blacks and Hispanics, two races for which little such information is available from a randomized study.

We evaluated the effects of celecoxib, a selective COX-2 inhibitor, and the NSAID, diclofenac, in a cohort of blacks and Hispanics who had established diagnoses of osteoarthritis and hypertension to determine whether a true difference in BP effect exists between a selective COX-2 and nonspecific COX inhibitor over a 24-hour period. Moreover, these studies were performed in the presence of an ACE inhibitor and diuretic therapy administered to all participants, because these classes of drugs are recommended by recent guidelines as initial therapy for treatment of BP in blacks.11

Methods
Participants
Hispanic and black men and women between the ages of 42 and 75 years with a history of uncomplicated hypertension and osteoarthritis were recruited. Three of 25 participants had diabetes. All participants had essential hypertension. All participants received the ACE inhibitor, trandolapril, hydrochlorothiazide, and if needed clonidine was added to achieve a BP of <140/90 mm Hg. Aspirin was not allowed during the study period. Exclusion criteria included underlying peptic ulcer disease, history of myocardial infarction, stroke, cerebrovascular accident, transient ischemic attack, gastrointestinal bleed, or renal insufficiency in 6 months before the study. Need of medication that could directly or indirectly affect renal function was also an exclusion criteria. An institutional review board approval was obtained for the study. Informed consent (in English and Hispanic language when applicable) was given to all participants before enrollment to read and be discussed with the investigator and staff. All participants signed an informed consent approved by the Rush University Institutional Review Board on entering the study.

Study Design
The clinical trial design is shown in Figure 1. This was a 12-week randomized crossover trial performed in elderly hypertensive black and Hispanic participants with osteoarthritis. All participants were counseled to ingest a 3-gram sodium diet for the duration of the study. Participants were randomized to receive celecoxib 200 mg once per day or diclofenac sodium 75 mg twice per day. Current antihypertensive medications were discontinued or tapered to discontinuation. The ACE inhibitor trandolapril in doses ranging from 2 mg to 4 mg per day was started. If BP goal was not achieved, then hydrochlorothiazide in a dose ranging from 12.5 to 25 mg per day was administered. In the few who were still not at goal, clonidine in a dose ranging from 0.1 mg twice per day to 0.3 mg twice daily was used. After goal BP of <140/90 mm Hg was achieved, participants underwent randomization.

At the time of randomization, all participants had baseline measurements of 24-hour ambulatory BP and the kidney function evaluation by iothalamate (125) clearance, urinary sodium excretion, and microalbuminuria. The treatment with celecoxib and diclofenac was continued for 4 weeks. During this period, the dose of antihypertensive medications could not be altered and no other antihypertensive therapy was permitted. At the end of 4 weeks, the participants returned to the office for a repeat 24-hour ambulatory BP monitoring and iohexol clearance, as well as assessment of urinary sodium and microalbuminuria. The participants then underwent a washout period for 2 weeks. After the washout period, participants were crossed-over to the other medication (either celecoxib or diclofenac).

Participants received the trial medication for a period of 4 weeks. After 4 weeks of therapy studies of 24-hour ambulatory BP monitoring and iohexol clearance and urinary sodium and microalbuminuria were repeated. Additional clinical assessment performed at each visit included a search for gastrointestinal symptoms and an objective assessment of pedal and ankle edema. Gastrointestinal side effects like abdominal pain, dyspepsia, heartburn, nausea, vomiting, diarrhea, or constipation were recorded during all patient visits. Care was also exercised to specifically ask for history suggestive of hematemesis, melena, or hematochezia. Pedal girth was recorded in centimeters before and after the study drug.

Statistical Analysis
Descriptive statistics of all variables are presented as means ± standard deviations, medians, minimums, and maximums. The paired t test was used in this data set because measurements were obtained from the same individuals before and after intervention. The paired t test was applied to test for significance differences from baseline in BP, microalbuminuria, GFR, and sodium after intervention. The same analysis was used for comparing differences between two drugs. A difference between groups or from baseline within groups at the level of P<0.05 was considered significant.

Results
Baseline Parameters
Forty participants entered the trandolapril/hydrochlorothiazide titration period (Figure 2). Ten of these participants (25%) were not randomized, primarily because of an inability to meet the BP goal criteria. Of the 30 participants randomized, no significant baseline differences in demographic or 24-hour ambulatory BPs were noted (Table 1). Most of the randomized participants (89.3%) completed the entire study.
24-Hour Ambulatory Blood Pressure Outcomes

There was a statistically significant increase in the mean 24-hour ambulatory systolic BP from baseline in diclofenac group (130±14 mm Hg to 134±15; \(P=0.019\)), whereas no increase was seen in the celecoxib group (128±11 to 129±9; \(P=0.60\)). Additionally, a relatively greater increase in mean 24-hour diastolic BP was noted in the diclofenac group (79±8 mm Hg versus 82±9; \(P=0.005\)), with no significant change in mean diastolic BP in the celecoxib group (\(P=0.57\)) (Figures 3 and 4).

An analysis of the mean 24-hour ambulatory BP changes at the most vulnerable period for cardiovascular events, ie, 6:00 AM to 11:00 AM showed an increase of systolic BP for diclofenac (129±12 mm Hg to 135±13 mm Hg; \(P=0.003\)). No effect was noted during this same period with celecoxib (129±11 mm Hg to 128±9 mm Hg; \(P=0.27\)) (Figures 3 and 4). However, during the period from 11:00 AM to 4:00 PM, when the peak effect of celecoxib is present based on the dosing regimen used, it significantly increased mean systolic BP (130±10 mm Hg to 134±9 mm Hg; \(P=0.002\)) and the diastolic BP (80±8 mm Hg to 85±8 mm Hg; \(P<0.0001\)) (Figure 3). For diclofenac, similar changes were noted for mean systolic BP (129±12 mm Hg to 133±12 mm Hg; \(P=0.004\)) and mean diastolic BP (79±8 mm Hg to 81±9 mm Hg; \(P=0.01\)) (Figure 4). Comparative effects between the changes seen at specific times in BP for celecoxib and diclofenac are displayed in Table 2. In comparison, two drugs revealed that celecoxib elevated diastolic BP more significantly than did diclofenac (\(P=0.042\)). These hourly BP changes from baseline coincide with the approximate dosing times of the study drugs in the morning for both agents and in the evening for diclofenac.

**Effects of Celecoxib and Diclofenac on Kidney Function**

GFR was not adversely affected by celecoxib (99±16 mL/min baseline versus 99±17 4 weeks; \(P=0.7\)). Conversely, diclofenac reduced GFR (100±19 mL/min baseline versus 90±16 4 weeks; \(P=0.007\)). There was no significant difference in urinary sodium excretion at baseline between groups (193±31 mmol/d diclofenac versus 171±37 mmol/d celecoxib; \(P=0.7\)). However, despite dietary counseling, the diclofenac treated participants had slightly higher urinary sodium excretion during the entire study period compared with the diclofenac group (137±36 mmol/d diclofenac versus 122±20 mmol/d celecoxib; \(P=0.009\)).

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Celecoxib</th>
<th>Diclofenac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>11/14</td>
<td>11/14</td>
</tr>
<tr>
<td>Age mean, years (range)</td>
<td>57.9 (42–74)</td>
<td>57.9 (42–74)</td>
</tr>
<tr>
<td>BMI (range)</td>
<td>32.8 (21–42)</td>
<td>32.8 (21–42)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.1 (0.7–1.8)</td>
<td>1.2 (0.8–1.6)</td>
</tr>
<tr>
<td>Ambulatory BP (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour systolic BP</td>
<td>129.2±10.5</td>
<td>129.36±11.7</td>
</tr>
<tr>
<td>24-hour diastolic BP</td>
<td>79.9±9.5</td>
<td>79±8</td>
</tr>
<tr>
<td>GFR mL/min</td>
<td>100±19</td>
<td>99±16</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; GFR, glomerular filtration rate.
sus 110 ± 21 mmol/d celecoxib; \( P = 0.04 \)) at 4 weeks. This relatively higher sodium intake was also manifested clinically by increasing incidence of pedal edema in diclofenac group. Five of the 25 study participants reported pedal edema. This was especially prominent among female study participants. The increase in pedal edema was objectively demonstrated in all 5 participants with increasing pedal circumference by more than 2 centimeters after diclofenac therapy. Similar adverse profiles were observed with celecoxib. Celecoxib also causes a decrease in urinary sodium excretion although of a lesser magnitude (171 ± 37 mmol/d baseline versus 155 ± 32 mmol/d 4 weeks; \( P = 0.38 \)).

### Gastrointestinal Tolerability

One out of 25 study participants reported dyspepsia and aggravation of gastroesophageal reflux disease symptoms while using diclofenac therapy. This participant had a previous history of gastroesophageal reflux disease.

### Discussion

Our study demonstrates that diclofenac worsened overall 24-hour systolic BP control compared with celecoxib while on treatment with a long-acting ACE inhibitor and diuretic. However, we compared the commonly prescribed dose used for arthritis pain control, 200 mg of celecoxib once per day to 75 mg of diclofenac twice per day. The Physician’s Desk Reference and specific clinical studies, however, clearly indicate that celecoxib has a short half-life that may necessitate use twice daily.\(^9,^{10}\) We therefore examined hourly ambulatory BP profiles coinciding with peak plasma levels of the drug, derived from other studies, and peak time for cardiovascular events, ie, 6:00 to 10:00 AM.\(^{10,12}\) We found that during its peak activity, celecoxib and diclofenac had similar effects on systolic and diastolic BP elevation in the presence of an ACE inhibitor and diuretic. In fact, celecoxib raised diastolic BP higher than did diclofenac during the anticipated time of peak blood concentration. Celecoxib, however, did have a better renal and gastrointestinal tolerability profile compared with diclofenac. This may be explained by the fact that GFR was measured at trough level for celecoxib at 24 hours versus 12 hours for diclofenac. Dosing both agents twice daily may have given results that would have been similar between groups. Moreover, as already reported by White et al, a clear difference was noted in overall 24-hour BP response, with celecoxib not significantly raising BP.\(^{13}\) Thus, if celecoxib is used twice daily for better pain relief, then a rise in BP of similar magnitude to diclofenac would be anticipated.

In many comparative studies, celecoxib is associated with a lower incidence of hypertension when compared with nonselective NSAIDs using clinic and ambulatory BP measurements.\(^{3,13-15}\) However, COX-2 inhibitors will affect BP and sodium homeostasis in hypertensive individuals.\(^{16}\) These differences may be related to the once-daily dosing of this short half-life COX-2 inhibitor. In our study, while diclofenac raised the average 24-hour systolic BP more than celecoxib did, celecoxib elevated systolic and diastolic BP as much as diclofenac during the peak period of celecoxib action (11:00 AM to 4:00 PM), based on once-daily dosing of this agent. In fact, the diastolic BP elevation was higher than diclofenac during this later morning period. Given this observation, one could speculate that if, as suggested by the dosing recommendations, an evening dose of celecoxib was included, then a similar elevation in BP would have been noted.

Celecoxib at a dose of 200 mg daily had no effect on the GFR. This is in contrast to diclofenac, which significantly reduced GFR. Reduction in GFR was also associated with marked urinary sodium retention in the NSAID group. This has been reported in previous studies and is a probable cause for the rise in BP via volume-mediated mechanisms. This increased sodium retention occurred despite diuretic use and also resulted in ankle swelling in participants. Adverse effects of diclofenac including reduction in GFR and sodium retention have been attributed to nonspecific COX-1 inhibition that mediates renal prostaglandin synthesis.\(^{17}\) In contrast, celecoxib preserved GFR and was not associated with urinary sodium retention or ankle edema. This may be related to the fact that GFR was assessed at 24 hours in everyone in the study, that would be 12 hours after diclofenac administration and 24 hours after celecoxib.

The failure of celecoxib to decrease GFR and not alter urinary sodium excretion might suggest that GFR and urinary sodium excretion are predominantly mediated by COX-1 mechanisms. However, recent studies clearly indicate that sodium handling is mediated by the macula densa of the kidney and is under the predominant control of the COX-2 isoenzyme.\(^1\) Therefore, administered at appropriate doses at the appropriate intervals of either an NSAID or a selective COX-2 inhibitor will yield increases in sodium retention.\(^{18}\)

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**TABLE 2. Changes From Baseline in Ambulatory BP Measures After Celecoxib Versus Diclofenac**

<table>
<thead>
<tr>
<th>Ambulatory BP (time frame)</th>
<th>SBP/DBP mm Hg</th>
<th>Celecoxib Value</th>
<th>Diclofenac Value</th>
<th>( P ) Value (between drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 am–11 am</td>
<td>SBP</td>
<td>0.92 ± 1.20</td>
<td>5.2 ± 0.89</td>
<td>( 0.002 )</td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>0.24 ± 1.50</td>
<td>0.766</td>
<td>0.56 ± 0.74</td>
</tr>
<tr>
<td>11 am–4 pm</td>
<td>SBP</td>
<td>4.16 ± 1.84</td>
<td>3.60 ± 0.04</td>
<td>( 0.004 )</td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>4.32 ± 0.89</td>
<td>2.00 ± 0.89</td>
<td>( 0.010 )</td>
</tr>
<tr>
<td>24 hours</td>
<td>SBP</td>
<td>1.6 ± 0.60</td>
<td>0.596</td>
<td>4.16 ± 1.15</td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>1.9 ± 0.64</td>
<td>3.0 ± 1.15</td>
<td>( 0.005 )</td>
</tr>
</tbody>
</table>

Values indicated in **bold italics** are significantly different either from baseline or from each other.

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

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**Versus Diclofenac**
Both COX-1 and selective COX-2 inhibitors raise BP as a function of their dose, concomitant salt intake, and duration of action. No studies have assessed the changes in 24-hour BP patterns comparing these classes of agents in high cardiovascular risk groups, namely blacks and Hispanics. Moreover, in the clinical trials that evaluated outcomes of the COX-2 inhibitors, blacks and Hispanics were underrepresented. To our knowledge, ours is the only study to date that has evaluated the 24-hour ambulatory BP values and GFR in this cohort of high-risk individuals.

Although our data are consistent with previous investigators and point to some novel findings, there are limitations. Our sample size is small but the findings in this high-risk group were consistent with previous investigators. We did not administer celecoxib twice daily to fully test the assertion put forth regarding its effects on BP throughout the day.

Perspectives
In conclusion, our data provide new information regarding BP differences throughout the day comparing two commonly used medications that differ in their action to block COX isoenzymes but whose half-lives are similar. These differences are accounted for by their common use and recommendation for pain-relieving activity rather than pharmacological action. Therefore, use of selective COX-2 inhibitors in twice-daily doses can be anticipated to induce a BP profile similar to that of NSAIDs. Physicians need to be alerted to these effects on BP and kidney function and to monitor BP accordingly in all patients receiving agents that inhibit the cyclooxygenase enzyme system.

References
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