Effects of Celecoxib and Naproxen on Renal Function in the Elderly
[Original Investigation]

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Abstract

Objective: To compare the effects of celecoxib, a cyclooxygenase 2–specific inhibitor, with the nonspecific cyclooxygenase 1 and 2 inhibitor naproxen on renal function in 29 healthy elderly subjects in a single-blind, randomized, crossover study.
Methods: Subjects received either celecoxib, 200 mg twice daily, for 5 days followed by celecoxib, 400 mg twice daily, for the next 5 days, or they received naproxen, 500 mg twice daily, for 10 days. After a 7-day washout, subjects were crossed over to receive the other regimen.

Results: After the first dose, the trend was for a greater decrease in glomerular filtration rate with naproxen (-5.31 mL/min per 1.73 m²) compared with celecoxib (-0.86 mL/min per 1.73 m²). The treatment difference became statistically significant on day 6 (-7.53 vs -1.11 mL/min per 1.73 m² for naproxen and celecoxib, respectively; P=.004). Urinary prostaglandin E₂ and 6-keto-prostaglandin F₁α excretion was significantly reduced from baseline across the treatment interval with both celecoxib and naproxen (P<=.04). There were no significant differences in prostaglandin excretion between these 2 agents (P=.07). Small, transient decreases (P<.05) in urinary sodium excretion were observed after the initiation of both celecoxib and naproxen treatment. Sodium excretion values returned to baseline by the end of the study.

Conclusions: The results indicate that cyclooxygenase 2–specific inhibition in healthy elderly subjects may spare renal hemodynamic function, although the effects on sodium excretion, as well as urinary prostaglandin E₂ and 6-keto-prostaglandin F₁α excretion, appear to be similar to those of nonspecific cyclooxygenase inhibitors such as naproxen.

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ANTI-INFLAMMATORY and analgesic medications represent the most frequently used drug therapy in the adult population, and, by virtue of an age-related increase in osteoarthritis and musculoskeletal disorders, the use of these agents is particularly extensive in the elderly. 1-2 Also associated with aging is a progressive decline in renal function. 3-4 Studies of healthy men and women demonstrate a decline in glomerular filtration rate (GFR) of approximately 10 mL/min per 1.73 m² per decade beginning after 30 years of age. 3-4 This decline in renal function has particular implications for the safe use of nonsteroidal anti-inflammatory drug (NSAID) therapy in the elderly, since a decrease in renal perfusion may place these individuals at increased risk of NSAID-induced, acute renal impairment. 5-7 In addition to hemodynamically mediated acute renal failure, other renal syndromes and side effects associated with NSAID use have been characterized. 8-9

Cyclooxygenase (COX) is the enzyme responsible for initiating the formation of prostaglandins. These autacoids have multiple activities, including a renal hemodynamic “protective” effect in the setting of reduced renal perfusion. 9-10 It is now recognized that COX exists as 2 distinct isozymes, COX-1 and COX-2, which are manifestly different with regard to regulation, expression, and physiological function. 11-12 Cyclooxygenase 2 is primarily an inducible enzyme, while COX-1 is constitutively expressed in nearly all normal tissues but is especially important in the gastrointestinal tract, kidneys, and platelets. 12-15 Conventional NSAIDs are nonspecific inhibitors of COX-1 and COX-2. 16-17 It is this inhibition of COX-1 that leads to clinically undesirable effects on the gastrointestinal tract mucosa and hemostasis. 12, 15, 18-19

In the kidney, the relative physiological roles of the two COX isozymes remain unidentified. Although it is now apparent that COX-2 is constitutively expressed in the kidney, 14, 20-23 the differential expression and localization of COX-1 and COX-2 suggests that the two isozymes may have different physiological functions and also species-related differences in their functions. Therefore, some or perhaps all of the undesirable NSAID effects could be eliminated or significantly reduced by inhibiting only COX-2 while leaving COX-1–mediated renal prostaglandin production intact.

Celecoxib is the first COX-2–specific inhibitor to be approved for treating osteoarthritis and rheumatoid arthritis. 24-26 The purpose of this study was to compare the renal effects of celecoxib with those of naproxen, a nonspecific COX inhibitor, in healthy elderly subjects.

SUBJECTS AND METHODS

STUDY DESIGN

This single-center, single-blind, randomized, 2-period, crossover study compared the effects of celecoxib (200
and 400 mg twice daily [BID]) and naproxen (500 mg BID) on renal function and urinary prostaglandin (PG) E₂ and 6-keto-PGF₁α₁ excretion in healthy elderly subjects. The protocol was approved by an institutional review board, and all subjects provided written informed consent.

Subjects were admitted to the study unit (Vanderbilt University Medical Center, Nashville, Tenn) and were randomized to one of 2 treatment sequences. Each sequence consisted of two 10-day treatment periods separated by a 7-day washout period. In one sequence, subjects received celecoxib, 200 mg BID, for the first 5 days and celecoxib, 400 mg BID, for the remaining 5 days, then naproxen, 500 mg BID, for 10 days after the washout. Subjects randomized to the second treatment sequence received naproxen, 500 mg BID, initially and then celecoxib, 200 mg and 400 mg BID, after the washout.

During each treatment sequence, blood and 24-hour urine samples were collected for the determination of urinary PGE₂ and 6-keto-PGF₁α₁, urinary electrolytes, and clinical laboratory tests (Table 1). The GFR determinations were performed 2 days before drug administration and then again 3 to 5 hours after drug administration on days 1 and 6 of treatment.

## Table 1. Sampling Schedule*

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment (−16 to −3 d)</th>
<th>Admission (−2 d)</th>
<th>Baseline (−1 d)</th>
<th>Treatment, d (1−5)</th>
<th>Washout, d (1−7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Prostaglandins</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Electrolytes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Vital signs and weight†</td>
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<td>X</td>
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<tr>
<td>PK levels</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Clinical laboratory studies</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*GFR indicates glomerular filtration rate; PK, pharmacokinetic drug concentration monitoring.
†During treatment periods, performed beginning 3 hours and finishing 5 hours after morning dose.
‡Collected 15 minutes before dose and 1, 2, 3, 4, 6, 8, and 12 hours after dose.
§Sample obtained 4 hours after morning dose, following an 8-hour fast the previous evening.
¶For screening purposes only.

### SUBJECTS

Subjects between 65 and 85 years of age, weighing 45 kg or more, and who were within ±30% of ideal body weight were eligible to participate. They were required to have no clinically significant physical abnormalities, no abnormal clinical laboratory test results, blood pressure of 150/90 mm Hg or less, a GFR greater than 60 mL/min per 1.73 m², and no NSAID usage within the previous 10 days.

### ANALYTICAL TECHNIQUES

Radiolabeled iothalamate sodium I 125 (Glofil-125) was used for the measurement of GFR. 27-28 Urinary concentrations of PGE₂ and 6-keto-PGF₁α₁ were determined by means of a validated gas chromatography–mass spectrometry method (Taylor Technology, Princeton, NJ; sensitivity limit of 10 pg/mL; assay range of 10.0 to 500 pg/mL). Urinary electrolyte concentrations were determined by standard laboratory methods.

### STATISTICAL ANALYSIS

Sample size calculation was based on the ability to detect a mean GFR reduction of 10% in the celecoxib group vs a 25% reduction in the naproxen group at a significance level of .05 and a power of 80%. 29 The homogeneity of treatment sequences for sex and race was analyzed by Fisher exact test. The Kruskal-Wallis test was used to examine homogeneity with respect to age, height, weight, and vital signs.

Statistical comparisons between celecoxib and naproxen were carried out by means of analysis of variance.
Treatment sequence, subject within sequence, and treatment period were factors in the analysis of variance. All treatment-emergent adverse events were recorded. Changes in vital signs and clinical laboratory measurements from baseline and between treatment groups were compared with the Kruskal-Wallis test.

**RESULTS**

**SUBJECTS**

Twenty-nine subjects between 65 and 80 years of age (mean±SD, 70.1±4.0 years), weighing 45 kg or more, and who were within ±30% of ideal body weight were entered into the study. Baseline characteristics of the group were similar for both treatment sequences (Table 2). There were no significant differences in vital signs, GFR, or levels of urinary prostaglandins (PGE$_2$ or 6-keto-PGF$_1$[alpha]), serum creatinine, or serum electrolytes.

<table>
<thead>
<tr>
<th></th>
<th>Sequence A*</th>
<th>Sequence B†</th>
<th>$P$‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>(n=14)</td>
<td>(n=15)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>69.6±3.55</td>
<td>70.7±4.50</td>
<td>.60</td>
</tr>
<tr>
<td>Range</td>
<td>65-80</td>
<td>65-79</td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-70</td>
<td>11 (79)</td>
<td>8 (53)</td>
<td></td>
</tr>
<tr>
<td>71-79</td>
<td>2 (14)</td>
<td>7 (47)</td>
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</tr>
<tr>
<td>80-85</td>
<td>1 (7)</td>
<td>0 (0)</td>
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<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>8 (57)</td>
<td>11 (73)</td>
<td>.45</td>
</tr>
<tr>
<td>M</td>
<td>6 (43)</td>
<td>4 (27)</td>
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</tr>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>70.0±15.9</td>
<td>71.9±11.3</td>
<td>.56</td>
</tr>
<tr>
<td>Range</td>
<td>49.2-112.5</td>
<td>55.0-95.9</td>
<td></td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min per 1.73 m$^2$ (mean ± SD)</td>
<td>80.1±12.8</td>
<td>84.3±14.2</td>
<td>.73</td>
</tr>
</tbody>
</table>

*Celecoxib, 200 mg twice daily/400 mg twice daily, then naproxen, 500 mg twice daily, separated by 7-day washout.
†Naproxen, 500 mg twice daily, then celecoxib, 200 mg twice daily/400 mg twice daily, separated by 7-day washout.
‡Kruskal-Wallis test.

Table 2. Characteristics of Study Participants at Baseline

Twenty-four subjects (8 men and 16 women) completed both treatment sequences. Five subjects were withdrawn because of noncompliance with the study protocol.

**GLOMERULAR FILTRATION RATE**

As shown in Figure 1, GFR was relatively unchanged after the first dose of celecoxib, 200 mg (mean±SE baseline GFR, 80.1±2.6 mL/min per 1.73 m$^2$; mean±SE change from baseline, -0.8±1.7 mL/min per 1.73 m$^2$), compared with the 6% reduction with naproxen, 500 mg (mean±SE baseline GFR, 84.3±2.9 mL/min per 1.73 m$^2$; mean±SE change from baseline, -5.0±1.7 mL/min per 1.73 m$^2$).
change from baseline, $-5.3 \pm 2.4 \text{ mL/min per 1.73 m}^2$). This treatment difference was not statistically significant. By day 6, naproxen caused a 9% reduction in GFR from baseline (mean±SE change, $-7.5 \pm 2.4 \text{ mL/min per 1.73 m}^2$), and this decrease was highly significant ($P=.004$) compared with the 1% change (mean±SE change, $-1.1 \pm 1.9 \text{ mL/min per 1.73 m}^2$) after escalation of the celecoxib dose to 400 mg BID.

![Figure 1](image_url). Mean (± SE) changes in glomerular filtration rate (GFR) from baseline after celecoxib and naproxen administration on days 1 and 6 of treatment. Asterisk indicates a significant difference from celecoxib ($P=.004$). BID indicates twice daily.

Five subjects had 20% or greater reductions in GFR with naproxen on either day 1 or day 6, and 1 subject had 40% or greater reduction on both days. Mean reductions in GFR, urinary sodium excretion, and urinary PGE$_2$ excretion in these 5 individuals during celecoxib and naproxen treatment are compared in Table 3. The GFR was essentially unchanged with celecoxib in contrast to the reductions noted with naproxen treatment; urinary sodium and PGE$_2$ excretion were similar. During celecoxib treatment, none of the subjects had 20% or greater reduction in GFR; the greatest reduction was 19%, occurring in one subject on day 1 and another subject on day 6.
Table 3. Renal Responses in 5 Subjects With a 20% or Greater Decrease of GFR in Response to Naproxen*

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib</th>
<th>Naproxen</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR</td>
<td>-0.6 ± 8.4</td>
<td>-28.8 ± 5.4</td>
</tr>
<tr>
<td>Urinary sodium excretion</td>
<td>-23.2 ± 14.6</td>
<td>-20.8 ± 9.6</td>
</tr>
<tr>
<td>Urinary PGE₂ excretion</td>
<td>-54.5 ± 10.9</td>
<td>-65.3 ± 5.7</td>
</tr>
</tbody>
</table>

*GFR indicates glomerular filtration rate; PGE₂, prostaglandin E₂.

A 10% or greater reduction in GFR with naproxen was observed in an additional 6 subjects. Therefore, a total of 11 subjects (46%) experienced a 10% or greater reduction in GFR in response to naproxen. In comparison, a 10% or greater reduction in GFR was observed in a total of 5 patients during celecoxib treatment.

URINARY PROSTAGLANDIN EXCRETION

Urinary PGE₂ excretion was significantly reduced by both treatments on each day measured (P</>.04), with the exception of day 1 for celecoxib (P=.06) (Figure 2, A). Mean reductions in urinary PGE₂ excretion were similar throughout the study for celecoxib and naproxen treatments.
Figure 2. Mean (± SE) urinary prostaglandin excretion after the administration of celecoxib, 200 mg twice daily (BID) and 400 mg BID, or naproxen, 500 mg BID. Asterisk indicates P<=.05 change from baseline. PGF$_1$[alpha] indicates prostaglandin F$_1$[alpha]; PGE$_2$, prostaglandin E$_2$.

Urinary 6-keto-PGF$_1$[alpha] excretion was significantly reduced (P<.01) by both treatments on each day measured (Figure 2, B). In the majority of subjects, 6-keto-PGF$_1$[alpha] concentrations in urine fell to levels below assay sensitivity (<10 pg/mL) at most time points after celecoxib or naproxen administration. This analytical limitation created uncertainty as to the true magnitude of the reduction with either treatment.

In women, urinary prostaglandin excretion reflects renal synthesis, whereas in men, it reflects combined renal and prostatic synthesis. Hence, urinary prostaglandin results in women are better reflectors of drug effects on renal prostaglandin synthesis. 30

In women, there were sustained decreases from baseline in mean urinary PGE$_2$ and 6-keto-PGF$_1$[alpha] excretion from baseline after the administration of celecoxib and naproxen. There was a trend toward greater reductions in PGE$_2$ and 6-keto-PGF$_1$[alpha] in women during naproxen administration than during celecoxib administration, but this trend did not reach statistical significance.

URINARY ELECTROLYTE EXCRETION

On day 1, urinary sodium excretion fell significantly (P<.001) from baseline after celecoxib (-30%) and naproxen (-38%) administration (Figure 3, A). On day 2, urinary sodium excretion returned toward baseline with both treatments, and on days 3 to 9 of treatment, urinary sodium excretion was largely comparable with baseline for both treatments. In general, urinary sodium excretion was unaffected by an escalation of the celecoxib dose to 400 mg BID from 200 mg BID. Celecoxib and naproxen were associated with comparable effects on urinary sodium excretion in both the magnitude of the observed changes and the temporal pattern.
Figure 3. Mean (± SE) urinary electrolyte excretion after the administration of celecoxib, 200 mg twice daily (BID) and 400 mg BID, or naproxen, 500 mg BID. Asterisk indicates P<=.05 change from baseline to naproxen treatment; dagger, P<=.05 change from baseline to celecoxib treatment; and double dagger, P<=.05 change from baseline celecoxib vs naproxen.

In both magnitude and temporal pattern, celecoxib and naproxen were associated with similar effects on urinary potassium excretion (Figure 3, B). There were no clinically or statistically significant differences between treatment groups in change from baseline at any time (P>=.12).

Urinary calcium excretion was not affected by celecoxib or naproxen administration, as evidenced by negligible differences in daily excretion compared with baseline (Figure 3, C).

SAFETY

Overall, 7 (27%) of the 26 subjects taking celecoxib, 200 mg BID; 12 (46%) of the 26 subjects taking celecoxib, 400 mg BID; and 15 (56%) of the 27 subjects taking naproxen, 500 mg BID, reported at least 1 adverse effect. The adverse effects reported most frequently were constipation, nausea, dizziness, peripheral edema, and upper respiratory tract infection. No subject withdrew from the study because of adverse events. There were no clinically significant changes in vital signs or laboratory abnormalities with either treatment. Clinical laboratory determinations including serum creatinine and serum urea nitrogen levels were performed on day 1 before the first dose of study medication and again on day 10 before the last dose of study medication. Mean (±SE) serum creatinine and serum urea nitrogen levels were unchanged in both treatment groups. For celecoxib, serum creatinine level averaged 72±2.6 µmol/L (0.81±0.03 mg/dL) and 73±3.5 µmol/L (0.83±0.04 mg/dL) on days 1 and 10, respectively, while serum urea nitrogen values were 4.7±0.3 mmol/L (13.2±0.8 mg/dL) and 5.1±0.2 mmol/L (14.2±0.8 mg/dL), respectively. For naproxen, mean serum creatinine level was 71±2.6 µmol/L (0.80±0.03 mg/dL) and 75±2.6 µmol/L (0.85±0.03 mg/dL) on days 1 and 10, respectively, and serum urea nitrogen level averaged 4.6±0.2 mmol/L (13.0±0.6 mg/dL) and 5.1±0.02 mmol/L (14.2±0.06 mg/dL) on these 2 occasions.

COMMENT

The purpose of this study was to investigate the comparative renal effects of celecoxib (200 mg and 400 mg BID) and naproxen (500 mg BID) in subjects representative of a healthy elderly population. Specifically, baseline GFR measurements in our study reflected the diminution relative to younger subjects that is characteristic of the elderly population. These age-related changes can lead to greater susceptibility of elderly patients to the undesirable renal effects of NSAIDs. Under such conditions, renal prostaglandins are increasingly necessary for preservation of renal blood flow and GFR and for sustaining salt and water excretion. The relative importance of COX-1 and COX-2 in these compensatory processes has not been established.

Celecoxib at therapeutic (200 mg BID) and supratherapeutic (400 mg BID) doses had no effect on GFR, in contrast to the effect of naproxen, 500 mg BID, which is the standard therapeutic dose of naproxen for arthritis in adults. Reductions in GFR were apparent beginning with the initial dose of naproxen, and this decrease became statistically significant compared with celecoxib with continued treatment. However, in this 10-day study period, serum creatinine level did not become significantly elevated such that naproxen-treated patients required modification of their NSAID regimen. Nonetheless, for long-term treatment, additional interval monitoring of serum creatinine level would be appropriate particularly during the use of conventional NSAIDs.

Celecoxib and naproxen were associated with similar and sustained reductions in urinary PGE$_2$ and 6-keto-PGF$_1[alpha]$ excretion. Increasing the dose of celecoxib from 200 mg BID to 400 mg BID, however, produced no further decrease.

The effect of naproxen on renal function in older patients with mild to moderate renal dysfunction has previously been described. In that study, urinary excretion of PGE$_2$ fell to 28% of baseline values after naproxen therapy (375 mg BID for 2 weeks), but, in contrast to our findings and those of Eriksson et al, who also studied naproxen at 375 mg BID, there was no significant decrease in urinary 6-keto-PGF$_1[alpha]$ excretion or GFR.
Based on the premise that urinary PGE$_2$ and 6-keto-PGF$_1$[alpha] reflect predominantly renal synthesis, our results are consistent with previous reports that COX-2 is constitutively expressed in the kidney and that COX-2 enzyme activity is responsible for the synthesis of some renal prostaglandins. 12, 14, 20-22

The possibility that the reductions in urinary PGE$_2$ and 6-keto-PGF$_1$[alpha] excretion with celecoxib are the result of renal COX-1 inhibition is not supported by evidence gathered to date. Other studies have shown that celecoxib administration at single doses up to 800 mg and multiple doses of 600 mg BID do not inhibit platelet COX-1 activity. 24, 34 Additionally, tissue distribution studies indicate that plasma concentrations generally reflect tissue concentrations of celecoxib within the kidney in animal models. 35

Mean urinary sodium levels fell significantly on the first 1 to 2 days of dosing with both celecoxib and naproxen. Thereafter, urinary sodium excretion returned to baseline and remained within the normal range for the duration of the study. Celecoxib was not associated with large or persistent reductions in sodium excretion, and it remains to be established whether celecoxib is associated with a degree of sodium retention comparable with that of other COX-2–specific inhibitors or conventional, ie, nonspecific, NSAIDs. Sodium retention and edema formation have been characteristically observed in 2% to 5% of patients in clinical trials with NSAIDs, and patients prone to edema formation likewise experience an exacerbation while taking conventional NSAIDs. 8-10

The observation that celecoxib is GFR sparing, but has effects on sodium excretion similar to those of naproxen, suggests that control of GFR may be predominantly COX-1 mediated, whereas COX-2–mediated activity is reflected by changes in sodium and water balance, likely controlled by interglomerular redistribution of blood flow and or renal tubular processing of sodium chloride and water. Comparable effects on GFR in the elderly with the COX-2–specific inhibitor rofecoxib have recently been reported. 36

In conclusion, it is evident from our study that celecoxib (200 mg BID and 400 mg BID) is not associated with detrimental changes of GFR in healthy elderly subjects, unlike the effects observed with naproxen. These observations suggest that celecoxib may afford benefits to those, such as the elderly, who are susceptible to the acute renal hemodynamic changes that may occur when both of the COX isozymes are inhibited. Despite sustained inhibition of renal prostaglandin synthesis, as evidenced by reductions in urinary PGE$_2$ and 6-keto-PGF$_1$[alpha] excretion with celecoxib, only transient decreases in sodium excretion were detected. Finally, the differential effects of celecoxib on GFR combined with similarity of activity on sodium excretion when compared with naproxen suggests that prostaglandins formed through COX-1 are important for preservation of GFR, whereas COX-2 activity may be of more importance in the regulation of renal sodium and water balance.

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Celecoxib; Cyclooxygenase Inhibitors; Elderly; Kidney Failure; Naproxen; Prostaglandins; Renal Failure