Effects of Celecoxib and Naproxen on Renal Function in the Elderly

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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 (\( P \leq .04 \)). There were no significant differences in prostaglandin excretion between these 2 agents (\( P \geq .07 \)). 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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expressed in the kidney, 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. The purpose of this study was to compare the renal effects of celecoxib with those of naproxen, a non-specific COX inhibitor, in healthy elderly subjects.

## RESULTS

### SUBJECTS

Twenty-nine subjects between 65 and 80 years of age 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 I125 (Glofil-125) was used for the measurement of GFR. Urinary concentrations of PGE2 and 6-keto-PGF1α were determined by means of a validated gas chromatography–mass spectrometry method. 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%.

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.
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 PGE2 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.

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.

Urinary 6-keto-PGF$_{1a}$ excretion was significantly reduced ($P > .01$) by both treatments on each day measured (Figure 2, B). In the majority of subjects, 6-keto-PGF$_{1a}$ 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.

In women, there were sustained decreases from baseline in mean urinary PGE$_2$ and 6-keto-PGF$_{1a}$ excretion from baseline after the administration of celecoxib and naproxen. There was a trend toward greater reductions in PGE$_2$ and 6-keto-PGF$_{1a}$ in women during naproxen administration than during celecoxib administration, but this trend did not reach statistical significance.

### Table 1. Sampling Schedule*

<table>
<thead>
<tr>
<th>Pretreatment Visit (−16 to −3 d)</th>
<th>Admission (−2 d)</th>
<th>Baseline (−1 d)</th>
<th>Treatment, d</th>
<th>Washout, d</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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<td>1</td>
<td>2</td>
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<td></td>
<td></td>
<td>1-5</td>
<td>6</td>
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<tr>
<td>GFR X</td>
<td></td>
<td></td>
<td>X†</td>
<td>X†</td>
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<tr>
<td>Prostaglandins X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
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<tr>
<td>Electrolytes X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
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<tr>
<td>Vital signs and weight‡ X</td>
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<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PK levels X§</td>
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<td>X§</td>
</tr>
<tr>
<td>Clinical laboratory studies X¶</td>
<td></td>
<td></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.
‡ During treatment periods, collected 45 minutes before morning doses.
§ Collected 15 minutes before dose and 1, 2, 3, 4, 6, 8, and 12 hours after dose.
¶ For screening purposes only.

### Table 2. Characteristics of Study Participants at Baseline

<table>
<thead>
<tr>
<th>Sequence A* (n = 14)</th>
<th>Sequence B† (n = 15)</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Mean ± SD</td>
<td>69.6 ± 3.55</td>
</tr>
<tr>
<td>Range</td>
<td>65-80</td>
<td>65-79</td>
</tr>
<tr>
<td>No. (%)</td>
<td>65-70</td>
<td>11 (79)</td>
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<tr>
<td>71-79</td>
<td>2 (14)</td>
<td>7 (47)</td>
</tr>
<tr>
<td>80-85</td>
<td>1 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td>F</td>
<td>8 (57)</td>
</tr>
<tr>
<td>M</td>
<td>6 (43)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>Mean ± SD</td>
<td>70.0 ± 15.9</td>
</tr>
<tr>
<td>Range</td>
<td>49.2-112.5</td>
<td>55.0-95.9</td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min per 1.73 m² (mean ± SD)</td>
<td>80.1 ± 12.8</td>
<td>84.3 ± 14.2</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.
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.

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.

**Table 3. Renal Responses in 5 Subjects With a 20% or Greater Decrease of GFR in Response to Naproxen**

<table>
<thead>
<tr>
<th>% Reduction From Baseline, Mean ± SE</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.*
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.31 Under such conditions, renal prostaglandins are increasingly necessary for preservation of renal blood flow and GFR and for sustaining salt and water excretion.32 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 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 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

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REFERENCES