

The Journal of Clinical Pharmacology

<http://www.jclinpharm.org>

Effects of Etoricoxib and Comparator Nonsteroidal Anti-Inflammatory Drugs on Urinary Sodium Excretion, Blood Pressure, and Other Renal Function Indicators in Elderly Subjects Consuming a Controlled Sodium Diet

Jules I. Schwartz, Chau Thach, Kenneth C. Lasseter, Jutta Miller, David Hreniuk, Deborah A. Hilliard, Karen M. Snyder, Barry J. Gertz and Keith M. Gottesdiener

J. Clin. Pharmacol. 2007; 47; 1521 originally published online Oct 9, 2007;

DOI: 10.1177/0091270007307878

The online version of this article can be found at:
<http://www.jclinpharm.org/cgi/content/abstract/47/12/1521>

Published by:

 SAGE Publications

<http://www.sagepublications.com>

On behalf of:

American College of Clinical Pharmacology

Additional services and information for *The Journal of Clinical Pharmacology* can be found at:

Email Alerts: <http://www.jclinpharm.org/cgi/alerts>

Subscriptions: <http://www.jclinpharm.org/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

Citations (this article cites 25 articles hosted on the SAGE Journals Online and HighWire Press platforms):
<http://www.jclinpharm.org/cgi/content/abstract/47/12/1521#BIBL>

Effects of Etoricoxib and Comparator Nonsteroidal Anti-Inflammatory Drugs on Urinary Sodium Excretion, Blood Pressure, and Other Renal Function Indicators in Elderly Subjects Consuming a Controlled Sodium Diet

Jules I. Schwartz, PharmD, MPH, Chau Thach, PhD, Kenneth C. Lasseter, MD, Jutta Miller, BS, David Hreniuk, BS, Deborah A. Hilliard, BS, Karen M. Snyder, MS, Barry J. Gertz, MD, PhD, and Keith M. Gottesdiener, MD

This multicenter, double-blind, randomized, placebo-controlled, parallel-group study assessed renal function during dosing with etoricoxib 90 mg daily, celecoxib 200 mg twice daily, and naproxen 500 mg twice daily. Male and female subjects 60 to 81 years old ($n = 85$), in sodium balance on a controlled, normal sodium diet, were treated for 15 days. There were no clinically meaningful between-treatment differences in urinary sodium excretion, creatinine clearance, body weight, or serum electrolytes during the 2 weeks of treatment. Etoricoxib and celecoxib had no effect on the urinary thromboxane metabolite, 11-dehydrothromboxane B_2 , while significantly decreasing the urinary prostacyclin metabolite,

2,3-dinor-6-keto $PGF_{1\alpha}$. Decreases were greater for both metabolites following naproxen. Ambulatory systolic blood pressures were significantly higher than placebo for all treatments, with moderately greater increases for etoricoxib relative to other active treatments on day 14. Ambulatory diastolic blood pressures were significantly higher than placebo for etoricoxib and naproxen but not for celecoxib.

Keywords: Etoricoxib; celecoxib; naproxen; sodium excretion; blood pressure

Journal of Clinical Pharmacology, 2007;47:1521-1531
© 2007 the American College of Clinical Pharmacology

Elderly individuals between the ages of 60 and 85 years are frequent users of anti-inflammatory and analgesic agents.¹ Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit synthesis of prostaglandins (PGs), which are modulators of inflammation and of kidney function. Under normal conditions, the reliance of renal physiology on the actions of renal PGs is minimal; however, their inhibition may further

impair renal function in patients with already compromised renal function. In patients with compromised renal function, this may result in water and sodium retention and decreases in renal blood flow and glomerular filtration rate (GFR), as estimated by creatinine clearance.

In studies of renal physiology and in clinical settings, the cyclooxygenase-2 (COX-2) selective NSAIDs—celecoxib, rofecoxib,* and valdecoxib—have demonstrated effects on renal function similar to those of traditional NSAIDs.¹⁻³ Minor dose-dependent changes were noted in urinary PG excretion, GFR, and sodium retention in the presence of sodium restriction or intravascular volume depletion.^{4,5} Increases in blood

From Merck Research Laboratories, Rahway, New Jersey (Dr Schwartz, Dr Thach, Ms Miller, Mr Hreniuk, Ms Hilliard, Ms Snyder, Dr Gertz, Dr Gottesdiener) and Clinical Pharmacology Associates, Miami, Florida (Dr Lasseter). Submitted for publication March 22, 2007; revised version accepted August 5, 2007. Address for correspondence: Dr Jules I. Schwartz, Merck Research Laboratories, 126 E. Lincoln Avenue, PO Box 2000, RY34-A552, Rahway, NJ 07065-0900; e-mail: jules_schwartz@merck.com.
DOI: 10.1177/0091270007307878

*On September 30, 2004, Merck & Co, Inc announced the voluntary worldwide withdrawal of rofecoxib from the market.

pressure (BP), attenuation of antihypertensive effects, and acute renal failure, similar to those reported for traditional NSAIDs, have been observed in clinical trials with COX-2-selective NSAIDs.^{2,6-11}

In controlled clinical trials, etoricoxib has been demonstrated to be highly efficacious for the treatment of osteoarthritis, rheumatoid arthritis, chronic low back pain, gouty arthritis, ankylosing spondylitis, and acute pain.¹² It was expected that etoricoxib would have mechanism-based, dose-dependent renal function effects similar to those demonstrated by other NSAIDs.

The present study evaluated and compared the effects of oral etoricoxib 90 mg once daily, oral celecoxib 200 mg twice daily, oral naproxen 500 mg twice daily, or placebo on sodium excretion, creatinine clearance, body weight, and BP in subjects 60 to 85 years of age consuming a diet supplying a fixed amount of sodium, 200 mEq per day, which is typical of a Western diet commonly consumed in the absence of restrictions on sodium intake.¹³ The dosages of etoricoxib and celecoxib represent the maximum dosages approved for the chronic treatment of the signs and symptoms of rheumatoid arthritis.^{14,15} The dosage of naproxen is the maximum indicated for long-term treatment of osteoarthritis and rheumatoid arthritis.¹⁶

METHODS

Subjects

Eligible subjects were 60 to 85 years of age, men and postmenopausal women with a body mass index of ≤ 34 kg/m² and with creatinine clearances ≥ 40 mL/min, as estimated using serum creatinine concentrations.¹⁷ All were in good general health on the basis of medical histories, physical examinations, and routine laboratory tests. Subjects were excluded from participating in the study if they had any clinically significant past or present medical conditions or any illness that, in the opinion of the investigator, might confound the results of the study or pose additional risk in administering study drugs to the subject.

Concomitant therapeutics that were not permitted were any medications containing NSAIDs or inducers or inhibitors of drug-metabolizing enzymes.

Study Design

A double-blind, randomized, placebo-controlled, double-dummy, parallel-group study (sponsor protocol number 053) was conducted at 2 sites in the United States from June 5, 2001, to March 7, 2002. The protocol and patient consent procedures

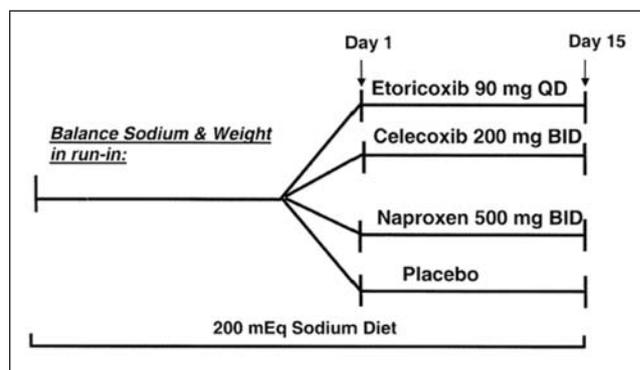


Figure 1. Study design—flowchart.

were approved by the Independent Investigational Review Board (Plantation, Florida) and the Southern Institutional Review Board (Miami, Florida). All patients provided written informed consent before participating in the study.

Subjects entered the clinical research units as inpatients to begin a run-in period to establish steady-state sodium balance prior to the first day of dosing (Figure 1). Starting on the day of admission (designated day R1), subjects were placed on an isocaloric diet that provided 200 mEq sodium, 80 to 120 mEq potassium, and approximately 0.8 g protein/kg for at least 8 days (days R1-R7 and day -1) before the start of treatment. Throughout the run-in period to establish sodium balance and the 15-day treatment period, patients remained in the clinical research units and consumed only the isocaloric diet provided by the clinical research unit. No food or beverages, other than those provided by the clinical research unit (eg, distilled or sodium-free water), were permitted during the study. Meals were consumed in their entirety.

Throughout both the dosing and evaluation periods (days 1-15), subjects continued as inpatients in the clinical research units for daily 24-hour urine collections and routine clinical measurements. Sodium balance was considered to have been achieved in the run-in period once the subject was stable in weight (within 0.5 kg on 2 successive mornings beginning on or after day R6, or starting after the sixth day on the metabolic diet) and had urinary sodium excretion within 180 to 220 mEq/24 hours. Subjects meeting these requirements began day -1 activities. For subjects who met the inclusion criteria, it was unlikely that urinary sodium excretion at day -1 would be much lower than 180 mEq or much greater than 220 mEq, although the day -1 sodium excretion value was not known until after the first dose of study drug had been administered. In the event that

the sodium excretion value for day -1 was later found to be outside the range of 130 to 270 mEq, the subject was not included in the per protocol analysis of urinary sodium excretion, body weight, creatinine clearance, and urinary potassium excretion. Subjects who did not achieve sodium balance by day R7 could continue for up to 5 additional days until balance was achieved. Subjects who failed to achieve balance after that time were discontinued from the study.

Treatment Regimens

As subjects achieved sodium and weight balance, they were sequentially assigned to an allocation number. The treatment associated with the allocation number was randomly assigned by a computer program prior to the study. The treatment groups for the study were etoricoxib (90-mg tablet once daily), celecoxib (200-mg capsule twice daily), naproxen (500-mg tablet twice daily), or matching placebos. The active treatment continued for 14 days and included the morning dose on day 15. Matching placebo capsules or tablets were provided for each active treatment, so that each subject took a total of 2 tablets and 1 capsule at ~8 AM and 1 tablet and 1 capsule at ~8 PM each day, to maintain the double-blind nature of the study.

Urinary Measurements

Twenty-four-hour urine collections commenced on day R6 and continued to the end of the study. The starting time for collection of urine was 8 AM, and the final collection was a void just prior to 8 AM on the next day. Urinary sodium and potassium excretion was measured for each 24-hour period for the duration of the study. The baseline evaluation criterion for sodium excretion was the average of the 3 days prior to drug administration. This included the day -1 value and the values for the 2 previous days.

Urinary creatinine was determined for each 24-hour period starting on day R5 and continuing until the subject was eligible for the study. The average GFR during the 3 days prior to drug administration served as the baseline value. Glomerular filtration rates for day 7 and day 15 were used to determine treatment effects.

The urinary excretion of the stable metabolites of thromboxane, 11-dehydrothromboxane B₂ (TX-M), and prostacyclin, 2,3-dinor-6-keto PGF_{1 α} (PGI-M) was quantified during corresponding 8-hour collection periods on day R5 (baseline) and on day 15 during treatment.

Analyses of TX-M and PGI-M were performed separately using gas chromatography/tandem mass spectrometry (GC/MS/MS) methods with stable isotope derivatives of the analytes as internal standards. For TX-M, internal standard, 11-dehydro TXB₂-d₄, containing 4 deuterium atoms at the 3, 3', 4, and 4' positions was added to thawed urine samples, which were then activated by acidification and incubated at 37°C for 4 hours to ensure that only the lactone form was present. Samples were partially purified with solid-phase extraction columns and then underwent a second acid activation and derivatization by pentafluorobenzyl bromide esterification of the acid moiety and trimethylsilylation of the alcohols before analysis by GC/MS/MS in negative chemical ionization mode. The daughter ions of TX-M and TXB₂-d₄ (daughter ions = 243 and 247 m/z, respectively; parent ions = 511 and 515 m/z, respectively) were monitored to produce a signal with minimal background interference. The lower limit of reliable quantitation (LLORQ) ($\leq 20\%$ interassay coefficient of variation) was 39.6 pg/mL. Within- and between-day reproducibility, expressed as coefficient of variation percent (CV%), was 3% to 5% and 10% to 14%, respectively, across the range of standard concentrations.

For analysis of PGI-M, internal standard, 2,3-dinor-6-keto-prostaglandin F_{1 α} -20, 20, 20-d₃, was added to aliquots of urine samples, which then underwent an alkali treatment prior to affinity extraction using a PGI-M antibody bound to agarose beads. The samples then underwent 3 separate derivatization steps (methyloximation of the keto group using methoxyamine hydrochloride, followed by C18 solid-phase cleanup, esterification with pentafluorobenzyl bromide, and then trimethylsilylation) before analysis by GC/MS/MS in negative chemical ionization mode. The daughter ions of PGI-M and d₃-PGI-M (daughter ions = 239.5 and 242.5, respectively; parent ions = 587 and 589 m/z, respectively) were monitored to produce a signal with minimal background interference. The LLORQ was 8.5 pg/mL. Within- and between-day reproducibility (CV%) was 2.5% to 8% and 7% to 14%, respectively, across the range of standard concentrations.

Serum Electrolytes

Whole-blood samples were collected from each subject, after a midnight to 8 AM fast when only water was permitted and before any other activities, for determinations of serum levels of sodium, potassium, chloride, bicarbonate, and creatinine before the start

of the study; on days R6 and R7 (and additional days during the period of sodium stabilization, if necessary); and on days 1, 2, 3, 4, 8, 14, and 15.

Body Weight

Subjects were weighed daily on a balance beam scale that was calibrated weekly. Time of day, scale, and the person performing the measurement were the same throughout the study. The body weight on day 1 prior to the first dose was the baseline value for the study.

Blood Pressure Assessments

Ambulatory BP (systolic [SBP] and diastolic [DBP]) was measured with an ambulatory BP monitor (Model 90207, SpaceLabs Medical, Inc, Issaquah, Washington). Ambulatory BP was measured over a 24-hour period at 15-minute intervals during awake time on the dominant arm beginning at approximately 8 AM on scheduled days, immediately following the BP measurement by manual mercury sphygmomanometry. The measurement interval was every 20 minutes during the sleeping hours. The baseline values were those determined on day -1.

Manual BP was determined at 8 AM and 8 PM after the subject had been sitting for 10 minutes and at least 10 minutes after any blood draws. The average of 3 replicate measurements for SBP and DBP obtained at 1 to 2 minutes apart was recorded. The baseline values were those determined on day -1.

Safety and Tolerability Assessments

Clinical safety and tolerability were based on findings of physical examinations, electrocardiograms, clinical laboratory test results, and collection of adverse experiences (AEs) throughout the study. Drug-related AEs were those determined by the investigator to be possibly, probably, or definitely drug related.

Statistical Analyses

Between-treatment differences in least squares (LS) mean change from baseline and 90% confidence intervals (CIs) for the differences were calculated using an analysis of covariance (ANCOVA) model. The final ANCOVA model included terms for baseline, treatment, and study site. Interactions of treatment with study site and treatment by baseline were assessed but not included in the final model because

they were not statistically significant ($P < .05$) or not clinically meaningful. Results for the Shapiro-Wilks test for normality and Levene's test for homogeneity of variance did not suggest any departure from the assumption of the ANCOVA model for most analyses. If normality was not established, an ANCOVA based on nonparametric procedures was employed. Unless stated otherwise, the results from the nonparametric between-treatment comparisons were similar to the parametric results, resulting in the same conclusion.

The primary endpoint was the LS mean change from baseline in the average 24-hour urinary sodium excretion during the first 72 hours of treatment between etoricoxib and celecoxib. Power calculations were based on previous experience with studies with similar goals and similar design.^{4,10} Assuming 20 subjects per group completing the study, there was a 95% probability that during the first 72 hours, the 90% CI for the difference in mean reduction from baseline in daily average urinary sodium excretion between etoricoxib and celecoxib would fall within ± 30 mEq if the true difference was zero. Differences less than ± 30 mEq would not be considered clinically meaningful.

Secondary endpoints included LS mean changes for all treatments from baseline in urinary sodium excretion during the first 72 hours and weeks 1 and 2 of treatment, average ambulatory BP over 24 hours, body weight on day 14, creatinine clearance at days 7 and 14, and serum electrolytes at day 14. The percentage changes in urinary prostanoids from baseline (day R4) on day 15 were also analyzed. All percent change calculations were computed on log-transformed data and then back-transformed to the percent inhibition scale. The back transformation of the between-treatment mean differences from the log scale and corresponding 90% CIs were computed using previously described methods.¹⁸ Differences between values were considered significant when $P \leq .05$.

RESULTS

Baseline Demographics and Characteristics

Eighty-five subjects were enrolled in the study, including 44 (52%) men and 41 (48%) postmenopausal women; 22 subjects received placebo, and 21 subjects each received one of the active treatments (ie, etoricoxib, celecoxib, and naproxen). Two subjects (placebo group) were excluded from analyses of urinary sodium and potassium excretion, creatinine

Table I Baseline Demographics and Characteristics

Characteristic ^a	Etoricoxib 90 mg Daily (n = 21)	Celecoxib 200 mg Twice Daily (n = 21)	Naproxen 500 mg Twice Daily (n = 21)	Placebo (n = 20)	All Groups (n = 83)
Age					
Mean	65.7	65.0	67.4	65.5	65.8
Range	60-75	60-75	60-81	60-75	60-81
Sex (% Female)	47.6	42.8	52.3	55.0	48
Race, %					
Caucasian	57.1	33.3	47.6	36.4	43.5
Black	0	4.8	0	4.5	2.4
Hispanic	42.9	57.1	52.4	59.1	52.9
Asian	0	1	0	0	1.2
Weight, kg, mean (SD)	73.7 (12.1)	71.3 (8.3)	69.5 (11.3)	71.5 (8.7)	72.8 (9.6)
Height, cm, mean (SD)	156.9 (31.2)	157.9 (31.3)	155.8 (30.8)	157.2 (32.1)	162.3 (13.0)
Blood pressure (manual sphygmomanometry, mm Hg)					
Systolic pressure, mean (SD)	127.0 (14.6)	128.0 (14.8)	127.0 (10.1)	121.5 (11.4)	125.9 (2.95)
Diastolic pressure, mean (SD)	76.3 (6.1)	78.5 (6.5)	76.2 (6.4)	77.1 (7.8)	77.0 (1.06)
Urinary excretion					
Sodium, mEq/day, mean (SD)	186.5 (15.9)	194.9 (15.9)	189.1 (14.0)	188.3 (12.9)	189.7 (3.63)
Potassium, mEq/day, mean (SD)	51.6 (10.6)	49.6 (7.4)	51.6 (5.4)	50.6 (10.0)	50.9 (0.96)
Creatinine Cl, mL/min, mean (SD)	87.3 (15.1)	84.1 (10.6)	85.5 (13.5)	87.2 (14.3)	86.0 (1.53)
TX-M, pg/mg creatinine, mean (SD)	694 (333)	862 (509)	944 (535)	794 (278)	823 (106)
PGI-M, pg/mg creatinine, mean (SD)	86.4 (39.0)	156 (273)	127 (107)	104 (68.4)	119 (30.3)

TX-M, 11-dehydrothromboxane B₂; PGI-M, 2,3-dinor-6-keto PGF_{1α}.

a. Characteristics of patients used for analysis of primary endpoints: urinary creatinine, sodium, potassium, prostanoids, and creatinine clearance.

clearance, and body weight because they did not attain sodium balance as described by the prespecified criteria (see Methods). The resulting population had a mean age of 65.8 years (Table I). Mean weight at baseline was 72.8 kg (range, 52.2-106.6 kg), and mean height was 162.3 cm (range, 144.8-185.4 cm). The subjects were well matched in terms of SBP, DBP, urinary sodium excretion, potassium excretion, and creatinine clearance (Table I). Group mean baseline values for the urinary prostanoids are also found in Table I. Data for PGI-M analysis were not available for 2 subjects (1 each from the placebo and etoricoxib groups) due to incorrect sample preparation.

Urinary Sodium Excretion

All active treatment groups had significantly larger decreases in urinary sodium excretion from baseline during the first 72 hours of treatment relative to the placebo group (Figure 2). Etoricoxib and celecoxib were not statistically different with respect to the change in daily urinary sodium excretion during the first 72 hours of treatment and during the first and

second weeks of treatment (Table II). Even though the reduction from baseline was statistically significantly greater for naproxen when compared with placebo during the first 72 hours of treatment ($P = .005$), the lower limit of the 90% CI (-28.1 mEq/24 h) was less than the predefined value of ± 30 mEq over a 24-hour period for a clinically significant difference and was therefore considered not to be clinically meaningful. During the first 72 hours of treatment, both etoricoxib and celecoxib produced a statistically significant reduction of sodium excretion versus placebo ($P < .001$). Changes caused by both of these agents were considered clinically meaningful because the lower limit of the 90% CIs exceeded the predefined range of ± 30 mEq over a 24-hour period.

The reductions in urinary sodium excretion returned toward baseline within approximately 4 days in all treatment groups (Figure 2). When averaged over the first week of treatment (a secondary endpoint), all active treatment groups were significantly lower than their corresponding baseline, and all except naproxen had significantly greater reductions in average daily

Table II Change From Baseline for Average Daily Urinary Sodium Excretion in Elderly Subjects Treated With Etoricoxib 90 mg qd, Celecoxib 200 mg bid, Naproxen 500 mg bid, or Placebo

Parameter	Treatment (n)	LS Mean Change (SE)	Difference in LS Mean (90% Confidence Interval)	P Value
Average daily sodium excretion during first 72 hours, mEq/day	Placebo (20)	-9.7 (4.4)	E vs C -2.31 (-12.59, 7.98)	.710
	Etoricoxib (21)	-39.6(4.3)	E vs N -12.06 (-22.15, -1.98)	.050
	Celecoxib (21)	-37.3 (4.3)	C vs N -9.76 (-19.93, 0.41)	.114
	Naproxen (21)	-27.6(4.3)	E vs P -29.92 (-40.12, -19.72)	<.001
			C vs P -27.61 (-37.94, -17.29)	<.001
		N vs P -17.86 (-28.05, -7.66)	.005	
Average daily sodium excretion during first week, mEq/day	Placebo (20)	-7.7 (3.5)	E vs C -0.27 (-8.40, 7.85)	.956
	Etoricoxib (21)	-20.7 (3.4)	E vs N -9.93 (-17.90, -1.96)	.041
	Celecoxib (21)	-20.6 (3.4)	C vs N -9.65 (-17.69, -1.62)	.049
	Naproxen (21)	-10.9 (3.4)	E vs P -13.12 (-21.18, -5.05)	.008
			C vs P -12.84 (-21.00, -4.68)	.011
		N vs P -3.19 (-11.25, 4.87)	.512	
Average daily sodium excretion during first 2 weeks, mEq/day	Placebo (20)	-9.7 (3.1)	E vs C -1.38 (-8.73, 5.97)	.755
	Etoricoxib (21)	-15.3 (3.1)	E vs N -8.63 (-15.84, -1.42)	.050
	Celecoxib (21)	-13.9 (3.1)	C vs N -7.25 (-14.52, 0.02)	.101
	Naproxen (21)	-6.7 (3.1)	E vs P -5.62 (-12.92, 1.68)	.204
			C vs P -4.24 (-11.62, 3.14)	.342
		N vs P 3.01 (-4.28, 10.30)	.494	

LS, least squares; C, celecoxib 200 mg bid; E, etoricoxib 90 mg qd; N, naproxen 500 mg bid; P, placebo; SE, standard error.

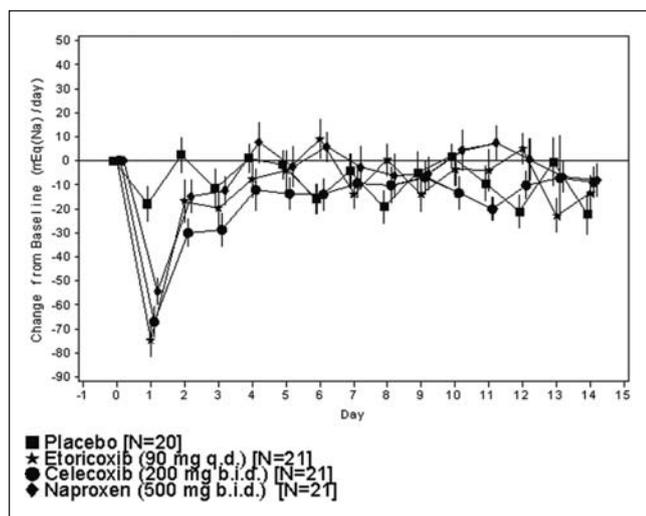


Figure 2. Change from baseline in daily urinary sodium excretion (mEq/day) over 14 days of treatment in healthy elderly subjects on a 200mEq sodium diet (mean ± SE).

urinary sodium excretion compared with the placebo group (Table II). When averaged over the entire 2-week treatment period (a secondary endpoint), there were no significant differences between any treatment group and placebo, although all groups remained at

significantly greater sodium retention levels with respect to their baseline levels (Table II).

Urinary Potassium Excretion

At day 14, the LS mean changes (SD) from baseline in urinary potassium excretion were -3.2 (7.6), -1.4 (6.4), -0.3 (6.4), and 2.0 (6.4) mEq/L for placebo, etoricoxib, celecoxib, and naproxen, respectively. Only naproxen demonstrated a significant difference compared with placebo ($P = .035$). Considering the direction of the change, it does not appear to be clinically meaningful.

Creatinine Clearance

At day 7 of treatment, the LS mean changes (SD) from baseline in creatinine clearance were not significantly different among treatment groups (-1.5 (8.0), -4.0 (6.4), 0.1 (6.4), and -3.1 (6.4) mL/min for placebo, etoricoxib, celecoxib, and naproxen, respectively). At day 14 of treatment, the LS mean changes (SD) from baseline in creatinine clearance were -4.7 (11.6), -5.8 (11.5), 4.4 (11.5), and 2.0 (11.5) mL/min for placebo, etoricoxib, celecoxib, and naproxen, respectively. The differences at day 14 between etoricoxib and celecoxib ($P = .006$) and

etoricoxib and naproxen ($P = .033$) were significant, but given the similarity between etoricoxib and placebo and the direction of the changes for celecoxib and naproxen, these differences were not considered clinically meaningful.

Body Weight

At day 14, the endpoint for body weight, LS mean changes (SD) from baseline were -0.3 (0.5), 0.1 (0.5), 0.1 (0.5), and 0.0 (0.5) kg for placebo, etoricoxib, celecoxib, and naproxen, respectively. The changes from baseline for all active treatments were small and not different among active treatments but significantly different from placebo ($P < .05$).

Urinary Prostanoids

At baseline, the urinary prostanoid metabolites excreted during the 8-hour sampling from the run-in period averaged 823 pg/mg creatinine for the thromboxane metabolite TX-M and 119 pg/mg creatinine for the prostacyclin metabolite PGI-M (Table I). Naproxen was the only active treatment associated with a statistically significant LS mean percent change (SD) from baseline of -84.5% (6.0) versus placebo for TX-M at day 15 (Figure 3). The LS mean percent changes (SD) in urinary PGI-M from baseline were not different between etoricoxib (-57.9% (18.8)) and celecoxib (-57.2% (19.3)), but both were significantly different from placebo ($P < .001$; Figure 3). For naproxen, the LS mean change (SD) from baseline was -76.2% (10.5), which was significantly ($P < .001$) different from all other treatment groups (Figure 3).

Serum Electrolytes

No significant between-treatment group differences were observed for LS mean changes from baseline for serum sodium, potassium, chloride, or bicarbonate at day 14. When compared with placebo, only a small increase (1.6%) in serum chloride with etoricoxib reached the level of a significant difference ($P = .013$).

Blood Pressure Measurements

The changes in ambulatory BP over the 24-hour period on day 14 to day 15 are presented in Figure 4. The between-treatment differences in LS mean change from baseline in SBP were significantly ($P < .05$) different for the active treatments relative to placebo (Table III). The increase in SBP with etoricoxib was

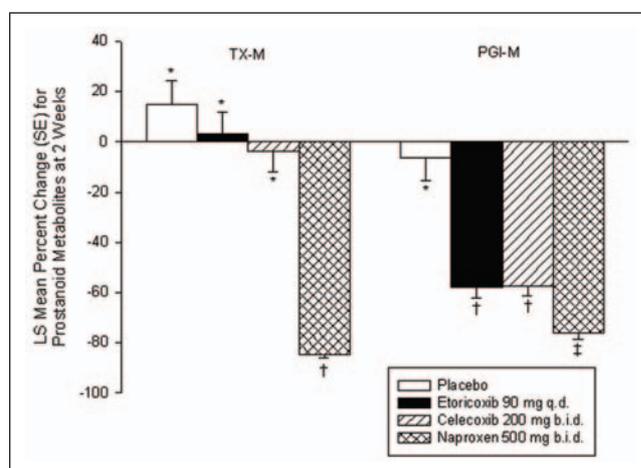


Figure 3. Day 14 least squares (LS) mean percent change from baseline for urinary prostanoid metabolites during treatment period in elderly patients consuming a controlled sodium diet. For each metabolite, significant differences between treatments ($P < .001$) are denoted by a different symbol above/below each bar; bars with the same symbol are not significantly different.

also significantly ($P < .05$) greater than the increase with celecoxib or naproxen (Table III). These results were consistent with those obtained with manual SBP at 8 AM on day 14 (Table III).

For ambulatory average 24-hour DBP, the LS mean changes from baseline for day 14 are presented in Table III and Figure 4B. Only the LS mean increase from baseline for etoricoxib was significantly different. The LS mean increases for naproxen and etoricoxib compared with placebo were significantly different. For ambulatory DBP, there were no significant differences among active treatments. These results were consistent with those obtained with manual DBP obtained at 8 AM on day 14 (Table III).

Safety and Tolerance

All treatments were generally well tolerated during the study. A total of 14 (16%) subjects had at least 1 clinical AE after the start of treatment, including 4 treated with placebo, 2 with etoricoxib, 2 with celecoxib, and 6 with naproxen. For 10 of these subjects (3 placebo, 2 etoricoxib, 1 celecoxib, and 4 naproxen), the AE was noted as mild and considered by the investigator to be possibly related to the drug; these were primarily diarrhea, constipation, and headache. Three other subjects had AEs that the investigator considered mild and not related to treatment. No laboratory AEs were identified. No subject discontinued because of an AE.

Table III Change From Baseline for Average Systolic and Diastolic Blood Pressure on Day 14 in Elderly Subjects Treated With Etoricoxib 90 mg qd, Celecoxib 200 mg bid, Naproxen 500 mg bid, or Placebo

Method and Parameter	LS Mean Change From Baseline			
	Etoricoxib (n = 22) (SD)	Celecoxib (n = 21) (SD)	Naproxen (n = 17) (SD)	Placebo (n = 20)(SD)
Ambulatory blood pressure, mm Hg ^a				
Systolic	7.7 ^{b,c,d} (6.0)	2.4 ^c (6.0)	3.6 ^{b,c} (6.0)	-2.4 (6.1)
Diastolic	3.2 ^{b,c} (3.7)	1.1 (3.7)	1.4 ^c (3.7)	-0.8 (3.3)
Manual blood pressure at day 14, mm Hg ^e				
Systolic	6.0 ^{b,c} (10.1)	1.0 (10.1)	1.4 (10.1)	-4.2 (10.3)
Diastolic	1.4 ^c (5.5)	-0.2 (5.5)	0.5 ^c (5.5)	-3.1 ^b (5.6)

LS, least squares.

a. Change from baseline (day -1) to day 14 for the average blood pressure over a 24-hour period.

b. Significant within-treatment change from baseline ($P \leq .05$).

c. Significantly different from placebo ($P \leq .05$).

d. Significantly different from celecoxib and naproxen ($P < .03$).

e. Change from baseline (day -1) to day 14 for the 8 AM blood pressure measurements.

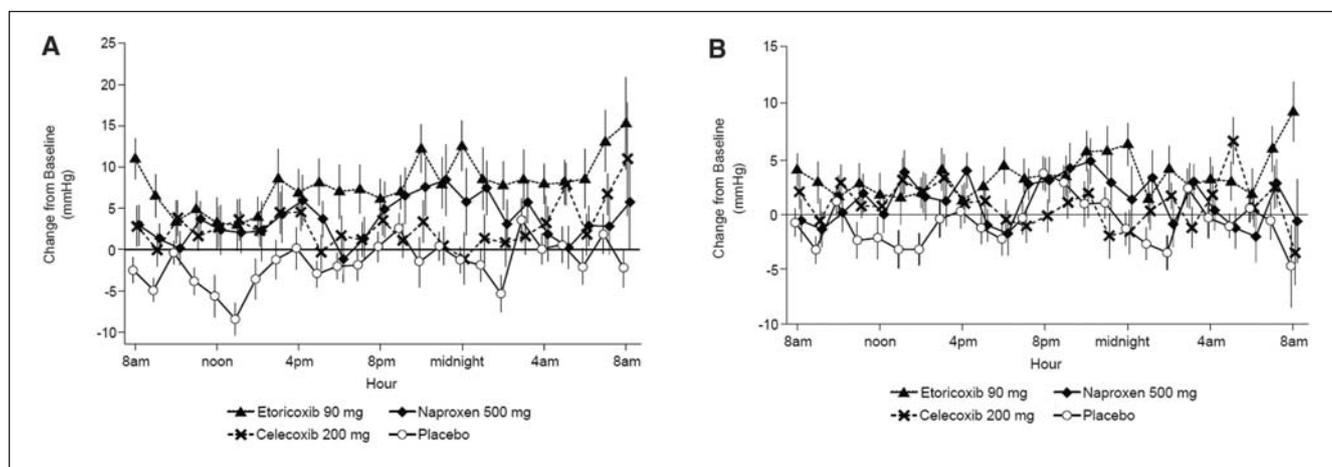


Figure 4. Hourly mean changes from baseline for ambulatory blood pressure (mm Hg) on day 14 in healthy elderly subjects on a 200-mEq sodium diet (mean \pm SE). A, systolic pressure; B, diastolic pressure.

One subject (a 72-year-old woman in the celecoxib group) experienced atrial fibrillation at the poststudy visit, which was 10 days after completing the treatment phase of the study. This adverse experience was rated by the investigator as serious but probably unrelated to study drug. The subject recovered fully after appropriate treatment at a local hospital.

DISCUSSION

The primary hypothesis for this study was that the mean reduction from baseline in average daily urinary sodium excretion during the first 72 hours of

daily treatment with etoricoxib 90 mg would be the same as celecoxib 200 mg bid. This initial 72-hour period has been identified as the period when substantial decreases in urinary sodium excretion occur following dosing with traditional and COX-2-selective NSAIDs.^{4,10,19} In similar trials examining the renal function effects of COX-2-selective NSAIDs, a 90% CI for the LS mean change from baseline that falls within ± 30 mEq was determined to be an appropriate limit for declaring similarity between treatments.^{4,10} Using this prespecified criterion, maximum antiarthritic doses of etoricoxib and celecoxib do not meaningfully differ from each other with regard to

reduction in sodium excretion during the initial 72 hours of treatment.

Using the same criterion for the secondary endpoints, urinary sodium excretion over 1 and 2 weeks of treatment, etoricoxib 90 mg and celecoxib 200 mg bid did not meaningfully differ from each other or with naproxen 500 mg bid. A similar lack of differences between treatment groups was observed for the related parameter, change in body weight, over the 2 weeks of treatment.

After the initial reduction in urinary sodium excretion at day 1, excretion subsequently returned toward baseline levels. This change suggests that urinary sodium excretion pathways were reset after 24 hours, denoted by the increase in sodium excretion, which may represent up-regulation of COX enzymes or other renal homeostatic mechanisms coming into play.²⁰⁻²²

Although ambulatory SBP (a secondary endpoint) was modestly increased from baseline on day 14 for all active treatments, the increase was moderately higher for etoricoxib compared with the other active treatments. The observations for the manual SBP and DBP on day 14 were in the same rank order as that seen with the ambulatory method.

Even in a rigorously controlled study such as ours, the observed effects of treatment on blood pressure may be variable and difficult to reproduce. It is necessary to recognize that etoricoxib's effects on blood pressure could be different from the comparators in this study. Data from the MEDAL (Multinational Etoricoxib vs Diclofenac Arthritis Long Term) program²³ currently provide the largest comparison of etoricoxib's effects on blood pressure compared with a traditional NSAID (ie, diclofenac). The MEDAL program enrolled more than 34 000 arthritis patients treated with etoricoxib 60 or 90 mg, or diclofenac 150 mg daily. Mean duration of exposure was 18 months. Clinically important increases in renal function endpoints (eg, fluid retention and blood pressure) were observed with etoricoxib compared with diclofenac. Specifically, the incidence of confirmed congestive heart failure (etoricoxib 90 mg) and discontinuations due to hypertension (etoricoxib 60 and 90 mg) were higher with etoricoxib. Elevated blood pressure is a risk factor for cardiovascular events and should be carefully monitored in patients receiving chronic therapy with any NSAID. In the MEDAL program, patients with hypertension at baseline experienced higher rates of confirmed thrombotic cardiovascular events compared with those patients who did not. However, there was no difference in the rates of confirmed

thrombotic cardiovascular events between the etoricoxib and diclofenac treatment groups, regardless of baseline risk factor status.

In healthy individuals with adequate hydration, as included in the present study, PGs do not play a crucial role in the maintenance of water and sodium homeostasis; however, when renal perfusion is diminished, renal PGs are important for compensatory regulation of this function.^{1,24} No individuals with cardiovascular disease or diminished renal function were included in this study.

The most important renal PGs are PGI₂ (prostacyclin), which increases potassium secretion and is a potent vasodilator, and PGE₂, which helps to control sodium reabsorption. Measurement of urinary PGI-M excretion has become a routinely used indicator of systemic PGI₂ production.^{10,25,26} In this study, etoricoxib 90 mg and celecoxib 200 mg bid were associated with similar reductions in urinary excretion of PGI-M, whereas administration of naproxen 500 mg bid was associated with a significantly greater reduction in urinary excretion of PGI-M relative to the other treatments. These results imply that both COX-1 and COX-2 are important in the production of systemic PGI₂.^{10,25,26} The clinical relevance of reductions in PGI-M in this and other studies is unclear. Although the kidney and the lung appear to be major sources of PGI-M, the relative contributions to the total amount excreted in urine from various tissue compartments remain an area of scientific investigation.^{27,28} Hence, this biomarker serves only as a measurement of total systemic PGI₂ production.

Urinary TX-M is primarily derived from platelets. Similar to results from other trials,^{25,29} the lack of effect on urinary TX-M by etoricoxib 90 mg and celecoxib 200 mg bid relative to placebo or to the respective baseline values in this study suggests that thromboxane biosynthesis by platelets was not inhibited or stimulated. In contrast, as shown in a previous study,³⁰ treatment with naproxen 500 mg bid significantly reduced TX-M excretion.

CONCLUSION

Based on the findings in this study, it can be concluded that chronic dosing with etoricoxib 90 mg, celecoxib 200 mg bid, or naproxen 500 mg bid has similar effects on urinary sodium excretion. All active treatments demonstrated similar effects on body weight, creatinine clearance, and serum electrolytes during 2 weeks of treatment. Treatment with etoricoxib, celecoxib, and placebo did not alter urinary excretion of the COX-1-related prostanoid, TX-M;

etoricoxib and celecoxib decreased urinary excretion of the COX-2-related prostanoid, PGI-M, although the decrease in both COX-1- and COX-2-derived prostanoids was greatest for naproxen. Systolic BP was increased relative to placebo for all active treatments, with a greater increase occurring for etoricoxib on day 14. Diastolic BP was increased relative to placebo for etoricoxib and naproxen on day 14.

Because all NSAIDs have the potential to affect renal function to different extents, the present data further emphasize the importance of monitoring BP in all patients on chronic NSAID therapy.⁸

The authors thank Drs William Taggart and Paul Cavanaugh for assistance in preparing this manuscript, as well as Dr Victoria H. Castellanos for nutritional consultation for developing the diet.

Financial disclosure: This study was supported by Merck Research Laboratories. Jules I. Schwartz, Jutta Miller, David Hreniuk, Deborah A. Hilliard, Karen M. Snyder, Barry J. Gertz, and Keith M. Gottesdiener are employees of Merck Research Laboratories and own stock and/or hold stock options in the Company. Chau Thach, an employee of Merck Research Laboratories at the time of the conduct of the trial, is currently at Kos Pharmaceuticals. Kenneth M. Lasseter received grant support from Merck Research Laboratories for conduct of various phases of the study.

REFERENCES

- Harris RC Jr. Cyclooxygenase-2 inhibition and renal physiology. *Am J Cardiol.* 2002;89:10D-17D.
- Gertz BJ, Krupa D, Bolognese JA, Sperling RS, Reicin A. A comparison of adverse renovascular experiences among osteoarthritis patients treated with rofecoxib and comparator non-selective non-steroidal anti-inflammatory agents. *Curr Med Res Opin.* 2002;18:82-91.
- Curtis SP, Ng J, Yu Q, et al. Renal effects of etoricoxib and comparator nonsteroidal anti-inflammatory drugs in controlled clinical trials. *Clin Ther.* 2004;26:70-83.
- Schwartz JI, Vandormael K, Malice MP, et al. Comparison of rofecoxib, celecoxib, and naproxen on renal function in elderly subjects receiving a normal-salt diet. *Clin Pharmacol Ther.* 2002;72:50-61.
- Swan SK, Rudy DW, Lasseter KC, et al. Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low-salt diet. *Ann Intern Med.* 2000;133:1-9.
- Murray MD, Lazaridis EN, Brizendine E, et al. The effect of nonsteroidal antiinflammatory drugs on electrolyte homeostasis and blood pressure in young and elderly persons with and without renal insufficiency. *Am J Med Sci.* 1997;314:80-88.
- Nieter PJ, Ornstein SM, Dickerson LM, Rothenberg RJ. Comparison of changes in blood pressure measurements and anti-hypertensive therapy in older, hypertensive, ambulatory care patients prescribed celecoxib or rofecoxib. *Pharmacotherapy.* 2003;23:1416-1423.
- Toto RD, Anderson SA, Brown-Cartwright D, Kokko JP, Brater DC. Effects of acute and chronic dosing of NSAIDs in patients with renal insufficiency. *Kidney Int.* 1986;30:760-768.
- Ylitalo P, Pitkajarvi T, Pyykonen M-L, et al. Inhibition of prostaglandin synthesis by indomethacin interacts with the anti-hypertensive effect of atenolol. *Clin Pharmacol Ther.* 1985;38:443-449.
- Catella-Lawson F, McAdam B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. *J Pharmacol Exp Ther.* 1999;289:735-741.
- Rossat J, Maillard M, Nussberger J, Brunner HR, Burnier M. Renal effects of selective cyclooxygenase-2 inhibition in normotensive salt-depleted subjects. *Clin Pharmacol Ther.* 1999;66:76-84.
- Matsumoto AK, Cavanaugh PF Jr. Etoricoxib. *Drugs Today (Barc).* 2004;40:395-414.
- Committee on Diet and Health (National Research Council). *Diet and Health: Implications for Reducing Chronic Disease Risk.* Washington, DC: National Academy Press; 1989:414.
- CELEBREX capsules (celecoxib). Groton, CT: Pfizer; 2005. PDR Electronic Library. Available at: <http://www.thomsonhc.com/pdrel/librarian>. Accessed July 27, 2007.
- ARCOXIA (etoricoxib). White House Station, NJ: Merck; 2004. Available at: www.emea.eu.int/pdfs/human/referral/etoricoxib/EN%20Etoricoxib.pdf. Accessed July 27, 2007.
- Naproxen. Nutly, NJ: Roche; 2005. PDR Electronic Library. Available at: <http://www.thomsonhc.com/pdrel/librarian>. Accessed July 27, 2007.
- Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31-41.
- Wong P, Mukhopadhyay S, Quan H, Larson P. *Confidence Intervals for Between-Treatment Mean Difference When Analysis Is on the Log Percent Scale.* Alexandria, Va: American Statistical Association, Proceedings of the Biopharmaceutical Section; 1999:111-116.
- Mulkerrin EC, Clark BA, Epstein FH. Increased salt retention and hypertension from non-steroidal agents in the elderly. *Q J Med.* 1997;90:411-415.
- Jaffe EA, Weksler BB. Recovery of endothelial cell prostacyclin production after inhibition by low doses of aspirin. *J Clin Invest.* 1979;63:532-535.
- Zewde T, Mattson DL. Inhibition of cyclooxygenase-2 in the rat renal medulla leads to sodium-sensitive hypertension. *Hypertension.* 2004;44:424-428.
- Hao CM, Breyer MD. Hypertension and cyclooxygenase-2 inhibitors: target: the renal medulla. *Hypertension.* 2004;44:396-397.
- Cannon CP, Curtis SP, FitzGerald GA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet.* 2006;368:1771-1781.
- Brater DC. Effects of nonsteroidal anti-inflammatory drugs on renal function: focus on cyclooxygenase-2-selective inhibition. *Am J Med.* 1999;107:65S-71S.
- McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. *Proc Natl Acad Sci USA.* 1999;96:272-277.
- FitzGerald GA, Pedersen AK, Patrono C. Analysis of prostacyclin and thromboxane biosynthesis in cardiovascular disease. *Circulation.* 1983;67:1174-1177.

27. Flavahan NA. Balancing prostanoid activity in the human vascular system. *Trends Pharmacol Sci.* 2007;28:106-110.
28. Kawka DW, Ouellet M, Hetu PO, Singer II, Riendeau D. Double-label expression studies of prostacyclin synthase, thromboxane synthase and COX isoforms in normal aortic endothelium. *Biochim Biophys Acta.* 2007;1771:45-54.
29. Dallob A, Hawkey CJ, Greenberg H, et al. Characterization of etoricoxib, a novel, selective COX-2 inhibitor. *J Clin Pharmacol.* 2003;43:573-585.
30. Van Hecken A, Schwartz JI, Depré M, et al. Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen and naproxen on COX-2 versus COX-1 in healthy volunteers. *J Clin Pharmacol.* 2000;40:1-12.