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Steady-State Pharmacokinetics of Enteric-Coated Naproxen Tablets Compared with Standard Naproxen Tablets

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ABSTRACT

In this open-label, randomized, crossover study, 24 healthy volunteers (12 men and 12 women) received either enteric-coated (EC) naproxen tablets 500 mg twice daily or standard naproxen tablets 500 mg twice daily for 7 days. In each of the two study periods, blood sampling began on day 8, after one last dose of the study drug was administered, to determine and compare steady-state pharmacokinetics for each of the two naproxen formulations. The plasma half-life of naproxen averaged 16.3 and 16.9 hours following EC naproxen and standard naproxen treatments, respectively. Mean time to maximum plasma concentration (T_{max}) was greater for EC naproxen than for standard naproxen (4.0 vs 1.9 hours), while the maximum observed plasma concentration (C_{max}) was slightly, but not significantly, smaller (94.9 vs 97.4 μg/mL, respectively). The mean values for average plasma concentration (C_{ave}) and minimum plasma concentration for EC naproxen were 70.4 and 60.6 μg/mL, respectively, compared with 63.9 and 44.1 μg/mL for standard naproxen. The mean plasma fluctuation about the mean was greater for standard naproxen than for EC naproxen (85.3% vs 49.3%), while the mean area under the plasma concentration-time curve (AUC) was smaller for standard naproxen (766.8 vs 845.0 μg × h/mL). At steady state, EC naproxen was similar to standard naproxen tablets with respect to C_{max}, C_{ave}, C_{max}:C_{ave}, 0- to 12-hour AUC, and half-life but differed in T_{max}. In addition, fluctuations about C_{ave} in plasma levels were considerably lower with EC naproxen than with standard naproxen.

INTRODUCTION

Naproxen is a nonsteroidal anti-inflammatory drug with analgesic and antipy-

retic properties. The efficacy and tolerability of naproxen in the management of rheumatoid diseases, gout, pain, and dysmenorrhea have been well established in many years of clinical use.[1] An enteric-coated (EC) formulation* of naproxen was developed to release naproxen at the pH level of the small intestine, where dissolution takes place.

An in vivo evaluation of EC naproxen tablets has shown that the naproxen blood levels over time were consistent with the delayed release of naproxen from the tablets,[2] but no data comparing the steady-state pharmacokinetics of EC naproxen with standard naproxen have been published. The current study was designed to compare the steady-state pharmacokinetics of EC naproxen and standard tablets† in a group of healthy men and women.

SUBJECTS AND METHODS

This was an open-label, randomized study of crossover design. Twenty-four healthy men and women whose body weights were within 15% of the average weight for their age and height, as determined from the Metropolitan Life Insurance tables, participated in the study.[3] Participants were selected on the basis of an essentially problem-free medical history, a normal physical examination, and a routine laboratory test profile showing no clinically significant abnormalities. Institutional review board approval was obtained. The study was explained to subjects in nontechnical terms, and all subjects signed a written informed consent form and an Experimental Subjects Bill of Rights before participating.

The two study regimens were: 500-mg EC naproxen tablets twice daily for 7 days plus one dose on day 8, and 500-mg standard naproxen tablets twice daily for 7 days plus one dose on day 8.

After an overnight fast (beginning at 9:30 PM the previous night), each subject received, in random order, 500 mg twice daily EC naproxen or standard naproxen for 7 days and a final dose on day 8. Adverse events were monitored at each blood drawing, and the subjects informed the study physician or trained observer of any adverse events that occurred during the study. A washout period of 8 days followed each treatment. Serial blood samples were collected after the final morning dose for up to 72 hours. To determine naproxen trough levels, single blood samples were also collected on days 6 and 7 before the morning dose. The plasma from each blood sample was separated immediately, transferred into vials, and frozen for subsequent assay of naproxen by using high-performance liquid chromatography.[4] Plasma levels below the quantification limit of 0.5 µg/mL naproxen at time zero were set to zero for the calculation of mean plasma levels and computed variables.

Statistical and Pharmacokinetic Analyses

The following pharmacokinetic variables were determined on day 8:

- T_{max}—time to maximum plasma concentration;
- Plasma half-life—computed over the 24- to 72-hour interval by using log

Trademarks: EC-Naprosyn®* and Naprosyn®† (Syntex Laboratories, Inc., Palo Alto, California).

Table I. Demographic characteristics.

Variable	Men (n = 12)	Women (n = 12)
Age (y)		
Mean ± SD	29.8 ± 4.6	30.9 ± 7.1
Range	22–35	22–47
Body weight (kg)		
Mean ± SD	82 ± 11	64 ± 6
Range	64–94	55–75
Height (cm)		
Mean ± SD	184 ± 6	168 ± 6
Range	175–193	157–176

linear regression analysis of the plasma concentration versus time data;

•C_{max}—maximum observed plasma concentration;

•0- to 12-hour AUC—area under the plasma concentration-time curve from 0 to 12 hours, computed using the linear trapezoidal rule;

•C_{ave}—average plasma concentration computed as the ratio of AUC divided by the dosing interval (12 hours);

•C_{low}—minimum (trough) plasma concentration at time of dosing computed as the mean of the zero and 24-hour values;

•C_{max}:C_{low}—peak to trough plasma ratio;

•C_{max}:C_{ave}—peak to average plasma concentration ratio;

•Fluctuation—$100 \times (C_{max} - C_{min})/C_{ave}$ (ie, percent fluctuation about average plasma concentration).

An analysis of variance (ANOVA) model appropriate for a crossover design was used,[5] and the statistical analyses were performed for the pharmacokinetic variables according to the General Linear Model procedure of the Statistical Analysis System, Version 5.16.[6] The ANOVA model included terms for sequence, subjects within sequence, formulation, and period effects.

Ninety percent classic confidence intervals[7] for the ratio of EC naproxen to standard naproxen were obtained using the *t* distribution. Confidence limits (90%) on the difference in the regimen means were computed using an error term derived from ANOVA. These limits were then expressed as percentages of the reference mean by dividing the upper and lower limits of the confidence interval by the estimated reference mean and then adding 100%. Two regimens were considered equivalent with respect to a given variable if the two means differed by less than 20% or the confidence interval was within 80% to 120%, with 90% confidence.

In addition, the trough levels on days 6, 7, and 8 were compared to demonstrate that steady-state levels had been attained by day 8. ANOVA procedures with terms in the model for subject and day were used for this comparison.

RESULTS

The demographic characteristics (Table I) were calculated separately for the 12

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