International Journal of Pharmaceutics, 75 (1991) 55–62

ADONIS 037851739100300Q

IJP 02491

Pharmacokinetics and bioavailability of Naprosyn CR 500 mg tablet, a new controlled-release formulation of naproxen, after single and multiple dosing

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(Received 8 August 1990)
(Modified version received 20 February 1991)
(Accepted 19 April 1991)

Key words: Non-steroidal anti-inflammatory drug; Bioavailability; Pharmacokinetics; Naproxen; Naprosyn; Controlled-release formulation

Summary

Naprosyn CR 500 mg, a new controlled-release (CR) tablet formulation of naproxen, is suggested for use once daily for the treatment of arthritic diseases. The aim of this study was to evaluate the bioavailability (F) and pharmacokinetics of 500 mg CR tablets using standard Naprosyn (2 × 250 mg) tablets as the reference standard. A random crossover design was used in 15 healthy male volunteers. In phase I, the subjects ingested either one 500 mg CR tablet in the morning or one 250 mg Naprosyn tablet in the morning followed by one 250 mg standard Naprosyn tablet 12 h later. The plasma naproxen concentration–time profile was monitored for 48 h from the time of the initial dose. From day 3 the subjects continued to take the same formulation for 5 days. On day 8 a further 72 h of blood sampling was started (phase II). After a 5-day washout period subjects returned and the 9-day procedure was repeated using the other formulation. In phase I of the study, mean values of maximum plasma naproxen concentration (C_{max}) for the standard Naprosyn tablets after the morning and evening doses were 39.3 and 44.7 $\mu g\ ml^{-1}$, respectively, and were significantly higher than the mean C_{max} (33.6 $\mu g\ ml^{-1}$) for CR tablets ($P < 0.01$). The time to maximum plasma naproxen concentration (t_{max}) for standard Naprosyn tablets averaged 2.5 and 3.1 h after the morning and evening doses, respectively. The mean t_{max} for the CR tablets was 9.8 h and was significantly greater than the values for the standard Naprosyn tablets. The total area under the plasma concentration–time curve ($AUC_{0-\infty}$) was not significantly different between these two formulations after the single dose study. The mean elimination half-lives were 15.2 and 15.3 h for the standard Naprosyn tablets and the CR tablets, respectively. In phase II of the study, the mean C_{max} values for the 250 mg Naprosyn tablets were 64.2 and 55.4 $\mu g\ ml^{-1}$ after the morning and evening doses, respectively and the C_{max} was 52.6 $\mu g\ ml^{-1}$ for the 500 mg CR tablets. The mean t_{max} for the CR tablets (6.0 h) was greater than that for the Naprosyn tablets (2.2 and 3.7 h). The relative F of the 500 mg CR tablets assessed during the dose interval at steady-state was, on average, 96% of the 250 mg Naprosyn tablets.

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Introduction

Naproxen is a non-steroidal anti-inflammatory drug with analgesic and antipyretic properties. It

is a widely used anti-inflammatory drug for the treatment of rheumatoid arthritis and other forms of arthritis (Brodgen et al., 1979). While naproxen is effective in the management of rheumatoid arthritis, osteoarthritis and allied conditions when taken in the standard formulation of 250 mg twice a day, patient compliance is often enhanced if the dosage schedule is decreased to once a day (Mroszczak et al., 1988).

Naprosyn CR, a new 500 mg controlled-release (CR) tablet formulation of naproxen, was developed by Syntex Research Laboratories. Naprosyn CR dosage forms of 750 mg and 1000 mg have been on the market for several years (Ling et al., 1987; Ryley and Lingam, 1988; Kelly et al., 1989). The preparations are to be used once daily for the treatment of arthritic diseases. The determination of bioavailability of a new drug formulation relative to an established product on the market is essential to ensure that they are equally bioavailable. The objective of the present study was to evaluate the relative bioavailability and pharmacokinetics of 500 mg Naprosyn CR tablets using the standard Naprosyn (2×250 mg) tablets as the reference standard. The bioavailability was assessed by comparing plasma naproxen concentration–time data resulting from a single dose and under steady-state conditions with multiple dosing of these two formulations of naproxen in healthy volunteers.

Materials and Methods

Materials

Naproxen, 250 mg Naprosyn® tablets and 500 mg Naprosyn CR tablets were supplied by Syntex Australia Ltd (Sydney, Australia). Flurbiprofen, an internal standard for a high-performance liquid chromatographic (HPLC) assay, was a gift from the Boots Co. Ltd (Sydney, Australia). All chemicals were of analytical grade. HPLC grade acetonitrile was purchased from Fisher Scientific Company (Fair Lawn, NJ, U.S.A.).

Protocol

Fifteen healthy male volunteers between 18 and 34 years of age (mean 24.3 ± 6.0 years (S.D.)) completed the study. All subjects were non-smokers and were within 10% of the average weight for their age and height. Their weight ranged from 65 to 96 kg (mean 78.0 ± 7.9 kg (S.D.)). The subjects were selected on the basis of negative medical history. Subjects with a history of hypersensitivity to aspirin or other non-steroidal anti-inflammatory drugs were excluded. In addition, prior to the study and at the end of the study, subjects had a normal physical examination and normal blood chemistry, haematology and urinalysis. No hypnotics, sedatives, antihistamines or other enzyme-inducing drugs were used for a month prior to the study. No medications (including over the counter drugs) or alcohol were allowed 72 h before or throughout the study.

All subjects signed an informed consent form. The study was approved by the Otago Area Health Board Ethical Committee, Dunedin, New Zealand.

The study was an open crossover randomized design and was conducted over a 23-day period. On day 1 the subjects received either a single morning dose of the naproxen CR 500 mg formulation or two Naprosyn 250 mg tablets, one in the morning and one 12 h later. The morning doses were taken orally with 200 ml of water after an overnight fast of at least 10 h. The subjects were required to fast until after the 4 h blood sampling time. The evening dose was taken orally with 200 ml of water without fasting. The plasma naproxen concentration–time profile was monitored for 48 h from the time of the morning dose.

On day 3, i.e., following the 48 h blood sampling period, the subjects were required to continue dosing on the *same* formulation; either one CR tablet each morning or one Naprosyn 250 mg tablet every 12 h for 5 days. They were given the tablets to take home and also were given a diary card on which to record exactly the time medication was taken on each day (note: doses were to be taken at approximately the same time every day). They then returned to the clinic on the morning of day 8 for 48 h of further blood sampling. The volunteers fasted overnight for at least 10 h before attending on day 8 and then continued fasting until after the 48 h blood sampling. Dosing was continued on day 8 as for the previ-

ous 5 days although blood sampling continued until the end of day 9 (note: no dosing on day 9). Days 10–14 were a washout period. On day 15, subjects were required to return and repeat the 9-day procedure using the other formulation.

During the 48 h blood collection periods (i.e., days 1–2, 8–9, 15–16 and 22–23) 4 ml of whole blood was collected via a cannula inserted into a forearm vein immediately before the morning dosing and then at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 13, 14, 16, 18, 20, 22, 24, 36 and 48 h post-dosing. In addition, a 72 h blood sample post-dose was also collected on day 11 and day 25. Other blood samples (4 ml each) were also collected immediately prior to the morning dose on days 4, 5, 6, 7 and 18, 19, 20, 21. These later samples were analysed for the trough concentration of the drug to ensure the achievement of steady-state. Blood samples were heparinised immediately and centrifuged. Plasma was separated and frozen at −20°C in Eppendorf® tubes for later assay of the naproxen concentrations. Routine laboratory work and physical examination were repeated within approx. 48 h of the end of the study.

Analytical methods

Plasma concentrations of naproxen were determined by an HPLC method (Wanwimolruk, 1990). The assay was based on a direct plasma protein precipitation before chromatographic separation. The sensitivity of this assay was 0.1 μg ml^{-1}. The standard calibration curve was linear over the concentration range of 0.1–150 μg ml^{-1}. Coefficients of variation for within-day and between-day analyses were less than 6%.

Data analysis

The terminal rate of elimination (β) was determined from the slope of the terminal linear portion of the semilogarithmic plot of plasma naproxen concentration vs time by the method of least-squares best fit. The last four to six data points on the terminal portion of the semilogarithmic plot of the plasma concentration-time curve were used to estimate the β value. However, there were some difficulties regarding the data points in two subjects after a single dose of naproxen CR (i.e., phase I study). These data values did not fall to give a reasonable linear plot on the semilogarithmic scale. In these two cases, the elimination half-life and AUC were not calculated. The elimination half-life ($t_{1/2}$) was calculated from the equation:

$$t_{1/2} = 0.693/\beta \quad (1)$$

The area under the plasma concentration vs time curve (AUC) during the dosing interval(s) obtained on multiple dosing was estimated by the trapezoidal rule. AUC for the single dose study was also calculated to the last data point by the trapezoidal rule. The values for the AUC from the last data point (C_{last}) to infinity were extrapolated by C_{last}/β. The time to reach maximum plasma concentration (t_{max}) and the maximum concentration (C_{max}) of naproxen were determined from inspection of individual plasma concentration–time curves.

The two formulations were compared relative to: (a) the plasma concentration at each sampling time; (b) maximum plasma concentration, C_{max}; and (c) time to attain the maximum plasma concentration, t_{max}. The relative bioavailability (F) was determined from the 24 h AUC at steady-state on multiple dosing as follows:

$$F = \frac{AUC_{0-24}(\text{CR-naproxen})}{AUC_{0-24}(\text{S-Naprosyn})} \quad (2)$$

where AUC_{0-24} (CR-naproxen) is the AUC from 0 to 24 h for CR-naproxen tablets at steady-state and AUC_{0-24} (S-Naprosyn) is the AUC from 0 to 24 h after morning and evening doses of standard Naprosyn.

A model-dependent analysis of the plasma naproxen concentration-time data after administration of the single dose naproxen CR and standard Naprosyn tablets was also carried out assuming that naproxen disposition could be described by one-compartment open model with oral absorption. Percentage of unabsorbed drug vs time plot was defined by the method of Wagner and Nelson (1964). The first-order absorption rate constant (k_a) during phase I and phase II

studies for each formulation was obtained using the appropriate equations for first-order absorption kinetics (Gibaldi and Perrier, 1982). The data were fitted by non-linear least squares regression analysis using unweighted data with the program MINIM (courtesy of Dr. R. Purves, Department of Pharmacology, University of Otago) on an Apple MacIntosh SE30 computer.

In this study the results are given as mean values with the standard deviation (mean ± S.D.), unless otherwise stated. The difference between the bioavailability parameters after dosing with the two formulations of naproxen was assessed by means of two-way analysis of variance (ANOVA), with sequence group, subjects within sequence group, period and regimen as factors.

Results

Initially 16 subjects were entered in the study, however, during the course of the study, one subject developed a respiratory tract infection requiring the use of antibiotics. Due to the possibility of the antibiotic interfering with the study drug absorption and the HPLC assay for naproxen, the subject was excluded from the trial. The 15 subjects who completed the study reported no side effects and had no clinically significant laboratory abnormalities.

Percentages of unabsorbed drug vs time plots for the standard Naprosyn tablets and the controlled-release naproxen tablets are shown in Fig. 1. The plots for both formulations suggest first-order absorption of naproxen with no lag time or significant (consistent) dose dumping effects. The absorption rate constants (k_a) for the CR naproxen product was estimated to be 7–9-fold less than that of the standard Naprosyn tablets (Table 1).

Fig. 2 shows the mean plasma naproxen concentration-time profile after the morning and evening doses of the standard naproxen tablets compared to those after a single dose of the controlled-release naproxen tablets. There was considerable inter-subject variability in plasma naproxen concentrations.

The mean times to maximum plasma naproxen concentrations (t_{max}) following the oral administration of 250 mg Naprosyn tablets after morning and evening doses in phase I study (Table 1) were 2.5 h (range 1–6 h) and 3.1 h (range 1–8 h) respectively, and for the 500 mg Naprosyn CR the value was 9.8 h (range 1.5–24 h). The t_{max} for the CR naproxen tablets was significantly longer than those t_{max} values observed for the standard

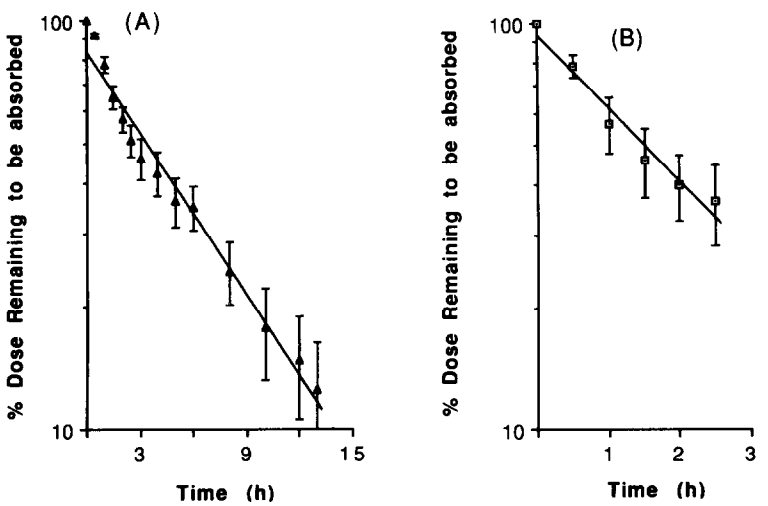

Fig. 1. Plots of percent naproxen remaining to be absorbed (log scale) vs time after oral administration of (A) 500 mg controlled-release naproxen tablets, or (B) 250 mg standard Naprosyn tablets, during a single dose study (i.e., phase I study). Vertical bars represent the standard errors of the mean value.

Naprosyn tablets ($P < 0.05$). The t_{max} for the controlled-release tablets exceeded the t_{max} for the standard Naprosyn tablets in 14 subjects and was less in one subject. Mean C_{max} values for the standard Naprosyn tablets after the morning and evening doses in phase I study were 39.3 and 44.7 $\mu g\ ml^{-1}$, respectively and were significantly higher ($P < 0.01$) than the mean C_{max} (33.6 $\mu g\ ml^{-1}$) for the controlled-release naproxen tablets (Table 1). Variability in C_{max} for controlled-release tablets (coefficient of variation, C.V.) was 19.6%. Variability in C_{max} for the standard Naprosyn tablets (C.V.) was 13.5% and 17.7% after morning and evening doses, respectively.

There was no statistically significant difference in either AUC (from 0 to 24 h) or total AUC (from 0 to ∞) between 250 mg Naprosyn tablets (after the morning and evening doses) and a single dose of 500 mg controlled-release naproxen tablet given during the phase I study (Table 1). The mean total AUC (0 to ∞) for the controlled-release tablets was 1091.3 $\mu g\ h\ ml^{-1}$ with a C.V. of 26.8% and for the standard Naprosyn tablets, 1172.4 $\mu g\ h\ ml^{-1}$ with a C.V. of 18.5%. The mean elimination half-lives for the controlled-release tablets and the standard Naprosyn tablets were 15.3 and 15.2 h, respectively, in the phase I study (Table 1). There was no significant differ-

TABLE 1

Pharmacokinetic parameters and bioavailability (F) for controlled-release (CR) and standard (S) naproxen tablets [a,b]

Parameter	Phase I study		Phase II study	
	500 mg CR	250 mg S	500 mg CR q.d.	250 mg S b.i.d.
k_a (h^{-1})	0.172 ± 0.097 [c]	1.17 ± 0.85	0.127 ± 0.105 [c]	0.97 ± 0.43
t_{max} (h)				
after morning dose	9.8 ± 5.9 [d]	2.5 ± 1.4	6.0 ± 4.6 [d]	2.2 ± 1.2
after evening dose	–	3.1 ± 1.8	–	3.7 ± 2.6
C_{max} ($\mu g\ ml^{-1}$)				
after morning dose	33.6 ± 6.6 [e]	39.3 ± 5.3	52.6 ± 19.1 [f]	64.2 ± 9.8
after evening dose	–	44.7 ± 7.9	–	55.4 ± 16.1
C_{min} ($\mu g\ ml^{-1}$) at steady-state				
after morning dose	–	–	30.3 ± 10.3	32.0 ± 7.2
after evening dose	–	–	–	28.5 ± 9.2
C_{max}/C_{min} ratio	–	–	1.82 ± 0.49	2.05 ± 0.38
C_{ss} average ($\mu g\ ml^{-1}$)	–	–	39.8 ± 14.1	40.8 ± 10.0
AUC_{0-24} ($\mu g\ h\ ml^{-1}$)	541.5 ± 137.3	574.7 ± 97.3	945.3 ± 339.1	979.7 ± 240.3
AUC_{0-48} ($\mu g\ h\ ml^{-1}$)	909.0 ± 217.3	986.1 ± 131.6	–	–
$AUC_{0-\infty}$ ($\mu g\ h\ ml^{-1}$)	1091.3 ± 292.3 ($n = 13$) [g]	1172.4 ± 217.1	–	–
$t_{1/2}$ (h)	15.3 ± 2.9 ($n = 13$) [g]	15.2 ± 2.7	16.9 ± 3.5	16.1 ± 2.7
F (relative)	–	–	0.96 ± 0.16	–

[a] k_a = absorption rate constant; t_{max}, time to peak concentration; C_{max}, peak plasma concentration; C_{min}, trough concentration during steady-state; C_{ss} average, average steady-state plasma concentration = AUC during dose interval/dose interval; AUC, area under the plasma concentration vs time curve; $t_{1/2}$, elimination half-life; F, relative bioavailability = AUC_{0-24} (CR)/AUC_{0-24} (S).

[b] Data are mean ± S.D. ($n = 15$).

[c] Significantly less than value for the standard naproxen tablet ($P < 0.005$).

[d] Significantly greater than value for the standard naproxen tablet ($P < 0.05$).

[e] Significantly less than value for the standard naproxen tablet ($P < 0.01$).

[f] Significantly less than value for the standard naproxen tablet after the morning dose ($P < 0.01$) but not significantly different from those after the evening dose.

[g] The plasma naproxen concentrations in two subjects were not markedly decreased from 24 to 48 h post-dose, so the data from these subjects were excluded.

ence ($P > 0.05$) in the half-life of naproxen between the two tablet formulations. During the phase I study the plasma naproxen concentrations for two subjects increased (but not exceeded the C_{max} value) from 24 to 48 h after a single dose of Naprosyn CR. This may be due to variability in the controlled-release characteristics of the CR-naproxen formulation. Also it may be due to the effect of food on drug absorption and gastrointestinal motility since it occurred around their meal times. The elimination half-life and AUC (0 to ∞) for these two subjects was not determined while taking CR-naproxen tablets.

After multiple dosing of each formulation (phase II study), the plasma naproxen concentration–time profiles (Fig. 3) were similar to those seen in the phase I study. Plasma naproxen concentrations after the standard Naprosyn tablets were greater than those for the Naprosyn CR tablets at 1, 1.5, 2 and 2.5 h (Fig. 3). Following

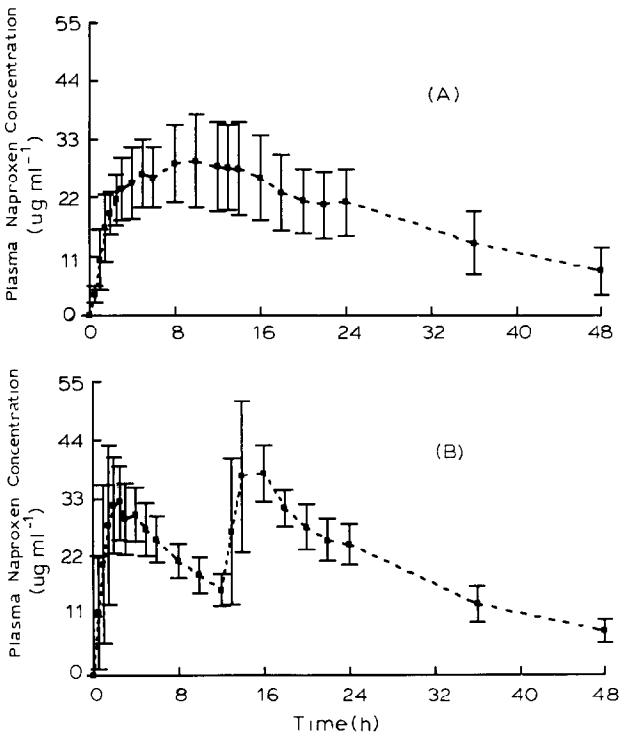

Fig. 2. Mean plasma concentrations of naproxen after a single dose of (A) one 500 mg controlled-release naproxen tablet vs (B) one 250 mg standard Naprosyn tablet b.i.d., (i.e., phase I study). The vertical cross-hatched bars represent the S.D.

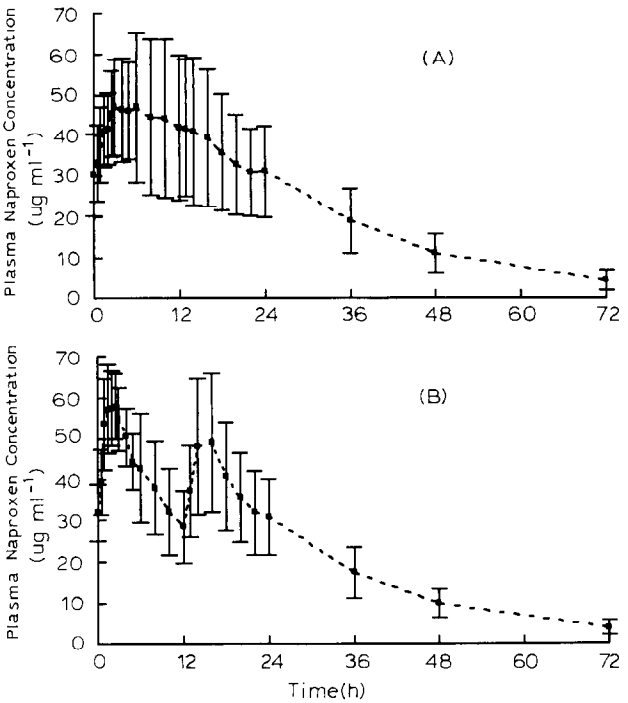

Fig. 3. Mean plasma concentrations of naproxen on the sixth day after (A) once-daily administration of 500 mg controlled-release naproxen tablets, or (B) twice-daily administration of 250 mg standard Naprosyn tablets (i.e., phase II study). The vertical cross-hatched bars represent the S.D.

the morning and evening doses of the standard 250 mg Naprosyn tablets during steady-state, the mean t_{max} values were 2.2 h, range 1–6 h, and 3.7 h, range 1–10 h (Table 1). The mean t_{max} after multiple dosing of the 500 mg Naprosyn CR was 6.0 h, range 1–16 h. The mean t_{max} for the CR-naproxen was significantly greater than that for standard Naprosyn tablets ($P < 0.05$). During the steady-state study (phase II), the C_{max} values for both tablet formulations were considerably greater than those observed during the phase I study. The mean C_{max} after multiple dosing of 250 mg Naprosyn tablets was 64.2 and 55.4 μg ml^{-1} after the morning and the evening doses, respectively (Table 1). After multiple dosing of 500 mg Naprosyn CR tablets, the mean C_{max} was 52.6 μg ml^{-1} which was significantly less than the mean C_{max} for the standard Naprosyn after the morning dose ($P < 0.01$) but this was not significantly different from the mean C_{max} after the

evening dose of the standard Naprosyn tablets ($P > 0.2$).

Mean trough plasma naproxen concentration (C_{min}) values for the 500 mg Naprosyn CR tablets were similar to those for the standard 250 mg Naprosyn tablets (Table 1). Fluctuation in plasma naproxen concentrations during the steady-state after the Naprosyn CR tablets was comparable to that after the standard Naprosyn tablets. Mean C_{max}/C_{min} ratios after multiple dosing of 500 mg Naprosyn CR tablets and the standard Naprosyn tablets were 1.82 (range 1.23–3.13) and 2.05 (range 1.55–2.96), respectively (Table 1), and there was no significant difference in the mean C_{max}/C_{min} ratios between the two tablet formulations despite the difference in dosing intervals. Multiple daily dosing of 500 mg Naprosyn CR yielded average steady-state concentrations (C_{ss} average) of naproxen similar to those after multiple dosing of the standard 250 mg Naprosyn tablets twice a day. The mean C_{ss} average of naproxen was 39.8 and 40.8 $\mu g\ ml^{-1}$ for Naprosyn CR tablets and the standard Naprosyn tablets, respectively, and were not significantly different (Table 1).

The AUC estimated at steady-state (phase II study) is more valuable in the assessment of the relative bioavailability of the controlled-release naproxen tablets. There was no significant difference in the AUC_{0-24} calculated over two dose intervals of 250 mg Naprosyn and over a single dose interval of 500 mg CR naproxen (Table 1).

The relative bioavailability of Naprosyn CR was estimated at the steady-state (phase II study) using the AUC_{0-24} and Eqn 2. The mean results are presented in Table 1. The relative bioavailability values ranged from 0.60 to 1.16. The mean relative bioavailability of the CR-naproxen was 0.96 with a C.V. of 16.3%. The results indicate that the bioavailability of the new 500 mg controlled-release naproxen formulation is 96% of that of the standard Naprosyn tablets.

After multiple dosing of each formulation (phase II) study, the elimination half-lives of naproxen were similar to those previously observed after the single dose study. The mean half-lives of naproxen were 16.9 and 16.1 h for Naprosyn CR tablets and the standard Naprosyn tablets, respectively (Table 1), and were not significantly different.

Discussion

There is an increasing interest in the simplification of drug dosage schedules, mainly in terms of reducing the frequency of dosing, which is thought particularly important for the treatment of chronic diseases. It has been demonstrated that when drugs can be given less frequently, e.g., once a day, patient compliance to the treatment is improved. These considerations apply also to the therapy of rheumatoid arthritis, osteoarthritis and other chronic inflammatory joint diseases with non-steroidal anti-inflammatory drugs (Koch-Weser and Schechter, 1981; Mroszczak et al., 1988).

Drug formulations with controlled release (CR) or 'slow-release' properties have played an important role in clinical therapeutics for several different products (Koch-Weser and Schechter, 1981). Theoretically, the advantages include the convenience of a less frequent dosing regimen and the maintenance of therapeutic drug concentrations at steady-state in a less variable or equally variable range than concentrations following more rapidly absorbed formulations. These properties have been demonstrated for the previously available 750 mg and 1000 mg dosage forms of CR naproxen (Ling et al., 1987; Mroszczak et al., 1988; Ryley and Lingam, 1988; Kelly et al., 1989).

The present study was designed to evaluate the relative bioavailability of the new controlled-release 500 mg tablet given once daily, in comparison with twice-daily administration of the standard 250 mg naproxen tablets. The Naprosyn CR tablet produced a plasma concentration-time profile typical of the prolonged dissolution characteristics of a controlled-release formulation. The 500 mg CR Naprosyn tablets demonstrated a longer time to reach a peak concentration than the standard 250 mg Naprosyn tablets and appeared to be more consistent in overall performance as indicated by a lower variation in plasma naproxen concentrations, longer time to peak and lower peak plasma naproxen concentration. The extent

of absorption, assessed by measurements of AUC was very similar for the Naprosyn CR tablet and the standard Naprosyn tablet. This demonstrates that bioavailability of naproxen was not reduced by its incorporation in a controlled-release system. The relative bioavailability of the CR Naprosyn tablet, calculated as the ratio of AUC (0–24 h) over a dosage interval at the steady-state and compared to the standard Naprosyn formulation, was 96%. This is in agreement with earlier studies with different doses of naproxen formulation (Ling et al., 1987; Mroszczak et al., 1988, Ryley and Lingam, 1988). Following repeated administration of the sustained-release naproxen formulation (1 g once a day), the relative bioavailability was found to be 98.7% of the same daily dose of 500 mg conventional naproxen formulation given twice daily (Mroszczak et al., 1988). Ling et al. (1987) reported that the bioavailabilities of the 750 and 1000 mg CR naproxen tablets were 91.3 and 98.1%, respectively, as compared to the same daily dose of the standard naproxen tablets. Ryley and Lingam (1988) also found that the 750 mg CR naproxen tablets were bioequivalent to the standard naproxen tablets, with the relative bioavailability of 102%.

Conclusion

The AUC during the dosage interval (24 h) for the controlled-release Naprosyn tablets was not significantly different from the AUC (0–24 h) during two dosage intervals for the 250 mg Naprosyn tablets. This new controlled-release formulation has a relative bioavailability of 96% as compared to the 250 mg Naprosyn tablets. It is anticipated, therefore, that this new 500 mg once-daily controlled-release formulation of naproxen will be an alternative to the currently available 250 mg standard Naprosyn tablets in cases where compliance with twice-daily dosing is of particular concern.

Acknowledgements

This study was supported by a grant from Syntex Australia Ltd, Sydney, Australia. The authors wish to thank Professor A.J. Campbell of Otago University Medical School for his clinical support.

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