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DOSE DEPENDENT PHARMACOKINETICS OF NAPROXEN IN MAN

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ABSTRACT

The pharmacokinetics of one of the most widely used non-steroidal antiinflammatory drugs, naproxen, were studied in 28 healthy human volunteers at the two most commonly used dose levels, viz., 250 mg and 500 mg, in a cross-over design. The plasma levels of naproxen were analysed by a modified high-pressure liquid chromatography method. The plasma concentrations at higher doses were not proportional to dose, indicating a non-linearity in the pharmacokinetics at the dose levels studied; this finding is new since earlier studies had studied only higher doses and assumed that at lower doses the pharmacokinetics would be linear. There was, however, no significant difference in the elimination half-life (rate constant), time to reach peak concentration (C_{max}), mean residence time (MRT), or area under first moment curve (AUMC). The clearance and distribution volume of naproxen were substantially increased at higher dose resulting in statistically lower proportional concentration and the total area under the curve (AUC). These observations are explained on the basis of a change in the plasma protein binding resulting in more free naproxen available for quicker clearance and wider penetration into tissues. These findings have several important clinical implications for the long-term use of naproxen as an antiarthritic drug. It is proposed that the clinical efficacy of naproxen can be increased and side-effects reduced by giving it in small divided doses instead of large doses.

KEY WORDS: naproxen; man; dose-dependence

INTRODUCTION

Naproxen belongs to the propionic acid class of non-steroidal antiarthritic drugs (NSAIDs). Chemically, it is the dextro-rotated isomer of (+)-2-(6-methoxy-2-naphthyl)-propionic acid.[1] Naproxen is used in the treatment of adult osteoarthritis and rheumatoid arthritis[2] as well as for the relief of fever[3] and moderate pain,[4,5] including the pain associated with dysmenorrhea.[6] In painful conditions such as dysmenorrhea the usual initial dose is the equivalent of 500 mg of naproxen followed by 250 mg every 6–8 h. In acute gout an initial dose of 750 mg followed by 250 mg every 8 h has been suggested.[7] In most other conditions the drug is administered twice daily at 500 mg.

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Naproxen is readily and completely absorbed from the gastrointestinal tract when administered orally. It is also well absorbed following rectal administration but at a slower rate. Effective plasma concentrations of naproxen are achieved after 20–30 min of administration and maximum plasma concentration is obtained in about 2–4 h following oral administration.[8] Naproxen is almost completely (99%) bound to plasma proteins following normal therapeutic doses and competes with aspirin for plasma protein binding sites.[9] It is extensively metabolized in humans by both oxidative and conjugation reactions. Literature reports show that the plasma concentration of naproxen increases proportionally with doses up to 500 mg daily; at higher dose there is an increase in its clearance caused by saturation of plasma proteins[7,10] resulting in proportionally lower plasma concentrations. The naproxen anion is extensively protein bound to plasma albumin and causes non-linearity in the disposition kinetics of naproxen.

Due to its high protein binding, naproxen has a relatively small volume of distribution, approximately $0{\cdot}1\ L\,kg^{-1}$.[11] Naproxen and its metabolites are almost entirely excreted in urine. The biological half-life is 12–15 h, independent of dose, plasma concentration, continued administration, or age. The reason for this very stable half-life is explainable by its strong plasma protein binding, together with the fact that only free, unbound drug is metabolized and excreted by the kidneys.[8]

The non-linearity in the disposition kinetics of naproxen has only been reported at doses exceeding 500 mg. This study reports non-linearity in the disposition kinetics of naproxen at much lower doses and makes recommendations on improving the clinical response to naproxen.

MATERIALS AND METHOD

Chemicals

Standard commercial oral dosage forms of naproxen were used. Naproxen reference standard was purchased from Zan Bon Group, Milan, Italy and ibuprofen internal reference standard was purchased from Schwelzer Hall (Pvt) Ltd, Singapore. Methanol (HPLC grade, Merck), acetonitrile (HPLC grade, Merck), glacial acetic acid (Merck), and dichloromethane (HPLC grade, BDH) were used for high-pressure liquid chromatography analysis.

Drug administration and blood sampling

Twenty-eight healthy human volunteers, aged 21–44 years, and weighing between 51 and 77 kg, were selected. A complete medical history and physical examination, urine analysis, and haematology were obtained for all volunteers within 7 days prior to the initiation of the study. The volunteers were instructed to abstain from taking any medication for 1 week prior to and during the study

period. The drug was administered orally in fasting state with 250 mL of water, immediately followed by a continental breakfast. The participants were given naproxen 500 mg tablet or 250 mg tablet in a randomized cross-over design with a washout period of 1 week between the treatments. Blood samples (10 mL) were drawn at 0, 1, 2, 3, 4, 5, 6, 8, 10, 24, 36, 48, and 72 h. Blood samples were collected by venipuncture or *via* an indwelling canula in heparinized blood collecting evacuated tubes. The blood samples were centrifuged for 10 min at 3000 rpm and plasma were separated and kept frozen at −20 °C until assayed.

High-pressure liquid chromatographic (HPLC) analysis of plasma samples

Plasma levels of naproxen were analysed by an HPLC method developed during this study. Analysis was performed using a system consisting of an auto-injector (SIL-6B Shimadzu, Japan) fitted with a 20 μL loop, a high-pressure pump (LC-6A, Shimadzu, Japan), a spectrophotometric detector (SPD-6A, Shimadzu, Japan) and a data integrator (C-R4A, Shimadzu, Japan). The stainless steel column (300 mm length × 3·9 mm i.d.) was used packed with reversed-phase C-18 Microbondapak (Waters Associates, Millipore, U.S.A.) base and acetonitrile:water (40:60 v/v in 0.1% glacial acetic acid) was used as an eluant with a flow rate of 2·5 mL/min. The eluant was monitored at 232 nm wavelength. Ibuprofen was used as the internal standard in this study.

Extraction of plasma samples was performed by protein precipitation with phosphoric acid, followed by addition of 5 mL extraction solution (internal standard in dichloromethane). After centrifugation at 3000 rpm for 10 min, 4 mL of the upper layer was separated and evaporated to dryness under a nitrogen stream. The residue was reconstituted in 0·5 mL of methanol and 20 μL was injected onto the column. Naproxen and ibuprofen showed excellent separation and resolution at 6·5 and 15·5 min respectively.

Pharmacokinetic analysis

The plasma concentration profiles of naproxen at the two dose levels studied are shown in Figure 1. Pharmacokinetic parameters of these profiles were obtained by both compartmental and non-compartmental analysis using non-linear regression computer fitting software and also manually since the profile at low dose contained recycling of drug. The pharmacokinetic parameters were calculated through following relationships:

$$\text{Elimination half-life } (t_{1/2}) = 0{\cdot}693/\beta \ (\beta = \text{terminal rate constant}) \quad (1)$$

$$\text{Volume of distribution } (V_d/F) = (Cl_p/F)/\beta \ (F = \text{fraction absorbed}) \quad (2)$$

$$\text{Plasma clearance } (Cl_p/F) = \text{dose}/AUC_{0-\infty} \quad (3)$$

$$\text{Area under the curve (AUC)} = [(t_2 - t_1)(C_1 + C_2)/2)] + \ldots + [(t_n - t_{n-1})(C_{n-1} + C_n)/2] \quad (4)$$

$$\text{Area under the moment curve (AUMC)} = [(t_2 - t_1)(C_1 t_1 + C_2 t_2)/2] + \ldots + [(t_n - t_{n-1})(C_{n-1} t_{n-1} + C_n t_n)/2] \quad (5)$$

$$\text{Mean residence time (MRT, h)} = \text{AUMC/AUC} \quad (6)$$

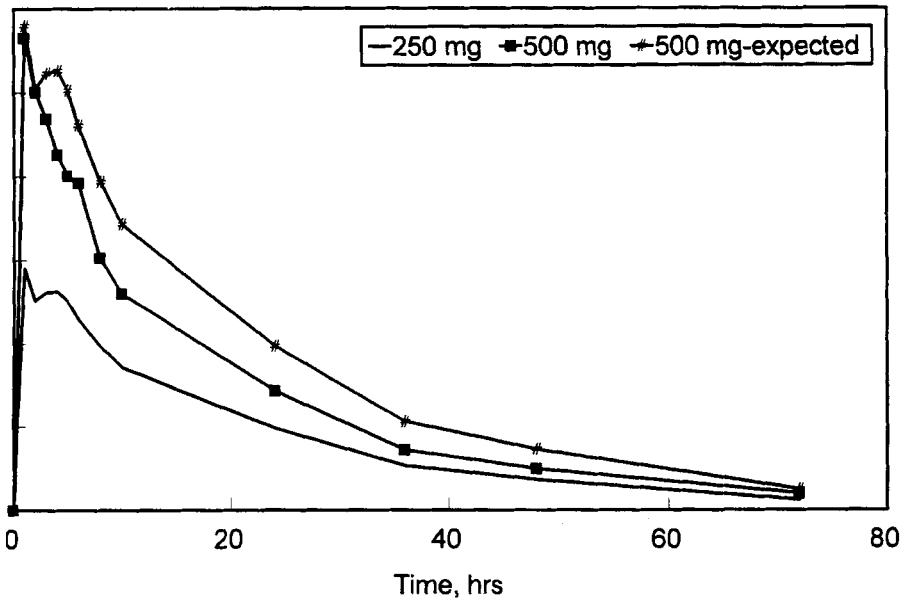

Figure 1. Plasma level profiles of naproxen at 250 mg (bottom), 500 mg (middle), and 500 mg — theoretical (top) doses

The AUC was calculated by trapezoidal rule to 72 h and then extrapolated to infinity using the terminal rate constant value.[12] The derived parameters were subjected to Student's *t* test to evaluate the significance of difference.[13]

RESULTS AND DISCUSSION

Table 1 summarizes the pharmacokinetic parameters of naproxen at the two dose levels studied. Figure 1 shows the plasma concentration profile of naproxen as a function of time at two doses. Both doses showed secondary peaks around 2–4 h after drug administration. No significant difference was observed in the half-life ($t_{1/2}$) or time to peak concentration (T_{max}) at the two dose levels studied. The values of the pharmacokinetic parameters of naproxen calculated in this study were in good general agreement with earlier studies.[14–17]

The peak plasma levels were proportionally lower at the higher dose (500 mg) studied since there was only an 80% increase in the peak plasma level instead of the doubling of peak concentration obtained at 250 mg. This observation is in concordance with values reported earlier for higher doses.[14–16] For example, when comparing a dose of 500 mg to a 1000 mg dose, the increase in peak plasma level was only 34·5% and when comparing to 1500 mg the increase was only 14·6% compared to a 1000 mg dose.[14–16]

Table 1. Dose-dependent pharmacokinetic parameters of naproxen in man

Parameters	Naproxen 250 mg	Naproxen 500 mg	% change observed[a]	% change expected
AUC (mcg mL^{-1} h^{-1})	560·5 ± 29·7	942·24 ± 41·64	60	100
AUMC (mcg mL^{-1} h^{-2})	10 545·1 ± 891·9	18 262 ± 1466·7	68	100
$t_{1/2}$ (h)	12·27 ± 0·64	13·34 ± 1·29	NS	NS
MRT (h)	18·2 ± 0·91	18·87 ± 1·36	NS	NS
C_{max} (mcg mL^{-1})	35·48 ± 1·54	64·05 ± 2·12	80	100
T_{max} (h)	2·86 ± 0·32	2·25 ± 0·33	NS	NS
CL_p/F (L h^{-1})	0·465 ± 0·017	0·556 ± 0·022	16·4	NS
V_d/F (L)	8·03 ± 0·38	9·63 ± 0·87	16·6	NS

[a]Values different from expected at $p < 0·05$.
NS, non-significant.

The area under the curve showed only 60% increase when the dose was doubled from 250 to 500 mg. The non-linear relationship between the naproxen dose and plasma concentration has been described previously in healthy volunteers after the single and repeat oral dose.[17,18] It was observed in these studies that the AUC increased less than proportionately at higher doses. This non-proportional increase can be attributed to two possible factors: changes in the fraction of naproxen dose absorbed (F) and clearance (CL_p). The absorption of naproxen has been previously reported as 100%,[15,20] so such large differences in the area under the curve cannot be attributed to the differences in fractions absorbed. The clearance (CL_p) was however found to be dependent on dose, increasing by almost 16% at the higher dose of 500 mg (Table 1). These changes in clearance are generally attributed to non-linear binding of naproxen to plasma albumin giving rise to a higher free fraction at higher dose.[8,17,19] Studies reported in patients with alcoholic cirrhosis showed that there was a marked reduction of approximately 60% in the clearance based on unbound drug fraction.[21] Therefore the availability of free fraction of drug plays an important role in the total clearance of naproxen.

The change in the free fraction of naproxen at higher doses is further responsible for the changes in the distribution volume at the higher dose. We observed a 16% increase in the distribution volume, parallel with the increase in the clearance. Literature values report large variation but generally agree well with our studies. For example, at the 500 mg dose, reported values of V_d were 15·7 ± 10·4 L and 10·0 ± 2·6 L in the elderly.[18] In another comparative pharmacokinetic study[19] of naproxen in young volunteers and elderly rheumatoid patients, the reported V_d was in the range of 9·7–12 L in the young and 10·8–13·2 L in elderly patients following a 1 g dose of naproxen orally.

The half-life of naproxen in our study falls within the range of the half-lives reported in adult subjects in the literature.[7] Runkel *et al.*[22] reported a serum half-life ranging from 10 to 17 h with a mean of 13·9 in adult volunteers. In

another study by the same authors a mean serum half-life of 13–15 h in adult subjects was reported.[21] In a study conducted in elderly and young volunteers, observed half-lives were in the range of 13·3–18·7 h and 13·1–19·0 h in the young and elderly patients respectively, indicating no significant difference in the half-life of naproxen in young healthy volunteers and elderly patients.[19] No significant difference is found in the half-life at the two dose levels of naproxen studied. There was also no change observed in the mean residence time at the two dose levels studied (Table 1). This lack of change in the half-life despite changes in the clearance is explained on the basis of a proportional change in the distribution volume. At the higher dose, a proportionally higher fraction is being distributed out of the central compartment, which takes longer to clear the drug out of the body despite faster clearance.

We have demonstrated that even at the low dose levels of 500 mg the pharmacokinetics of naproxen is non-linear. This finding corroborates earlier reports where non-linear pharmacokinetics of naproxen were reported at doses higher than 500 mg. There can be several clinical implications of this finding including the recommendation to administer naproxen at smaller divided doses to reduce toxicity in long-term use.

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