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The pharmacokinetics of naproxen, its metabolite *O*-desmethylnaproxen, and their acyl glucuronides in humans. Effect of cimetidine

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1 The pharmacokinetics of 500 mg naproxen given orally were described in 10 subjects using a direct h.p.l.c. analysis of the acyl glucuronide conjugates of naproxen and its metabolite *O*-desmethylnaproxen.

2 The mean elimination half-life of naproxen was 24.7 ± 6.4 h (range 7 to 36 h).

3 Naproxen acyl glucuronide accounted for 50.8 ± 7.3% of the dose recovered in the urine, its isomerised conjugate isoglucuronide for 6.5 ± 2.0%, *O*-desmethylnaproxen acyl glucuronide for 14.3 ± 3.4%, and its isoglucuronide for 5.5 ± 1.3%. Naproxen and *O*-desmethylnaproxen were excreted in negligible amounts (< 1%).

4 Even though the urine pH of the subjects was kept acid in order to stabilize the acyl glucuronides, isomerisation took place in blood.

5 The extents of plasma binding of the unconjugated compounds were 98% (naproxen) and 100% (*O*-desmethylnaproxen), while naproxen acyl glucuronide binding was 92%; that of its isomer isoglucuronide 66%. *O*-desmethylnaproxen acyl glucuronide was 72% bound and its isoglucuronide was 42% bound.

6 Cimetidine (400 mg twice daily) decreased the $t_{1/2}$ of naproxen by 39–60% (mean 47.3 ± 11.5%; $P = 0.0014$) from 24.7 ± 6.4 h to 13.2 ± 1.0 h. It increased (10%) the urinary recovery of naproxen acyl glucuronide ($P = 0.0492$). The urinary recoveries of naproxen isoglucuronide and *O*-desmethylnaproxen acyl glucuronide remained unchanged.

Keywords naproxen pharmacokinetics acyl glucuronide cimetidine interaction

Introduction

The nonsteroidal anti-inflammatory drug naproxen is the dextrorotary isomer of 6-methoxy-α-methyl-2-naphthalene acetic acid. In humans it is oxidised to 6-*O*-desmethylnaproxen and both parent drug and metabolite are conjugated as acyl glucuronides (Todd & Clissold, 1990) (Figure 1). Descriptions of the pharmacokinetics of naproxen have been based on fluorimetric measurement of total naproxen concentration in plasma and urine after hydrolysis of the conjugates (Anttila, 1977; Anttila *et al.*, 1980; Mortensen *et al.*, 1979), g.l.c. (Runkel *et al.*, 1972a,b, 1973, 1974, 1976, 1978; Weber *et al.*, 1981), t.l.c. (Abdel-Moety *et al.*, 1988) and mass fragmentography (Gøtzsche *et al.*, 1983; Larssen & Marinelli, 1981). H.p.l.c. assay of naproxen and *O*-desmethylnaproxen is now the most commonly used method of analysis, their conjugates still being measured after enzymatic or alkaline hydrolysis (Aarbakke *et al.*, 1983; Guelen *et al.*, 1988; Shimek *et al.*, 1982; Upton *et al.*, 1980a,b). However, acyl glucuronides of naproxen have not been measured directly in human samples. Acyl glucuronides (1-*O*-glucuronides) are unstable in alkaline media (pH > 6.0) and hydrolyse back to the parent drug or isomerise to glucuronidase-resistant isoglucuronides (2-,3-, and 4-*O*-glucuronides) (Faed, 1984). Therefore, urine should be kept at pH 5.0 to prevent these reactions (Faed, 1984).

Patients receiving naproxen chronically may develop

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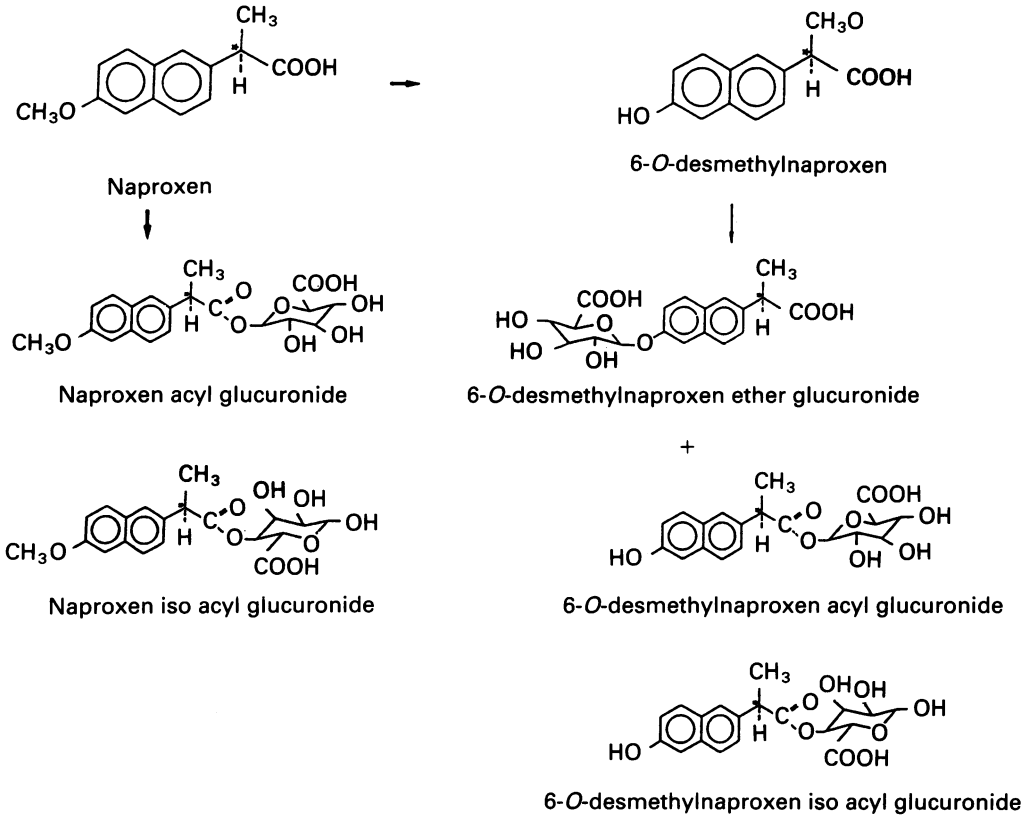


Figure 1 The chemical structures of naproxen and its possible metabolites.

gastric or duodenal ulcers, which may be treated with H_2-histamine receptor inhibitors such as cimetidine.

However, concomitant administration of cimetidine with naproxen may result in inhibition of the *O*-demethylation reaction (Aymard *et al.*, 1988; Nazario, 1986; Powell & Donn, 1984; Sedman, 1984).

The aims of this study were to assess the pharmacokinetics of naproxen in humans using a direct h.p.l.c. analysis of the acyl glucuronide conjugates of naproxen and its metabolite *O*-desmethylnaproxen and to assess the effects of cimetidine on the kinetics of naproxen.

Methods

Drugs

Naproxen and its metabolite *O*-desmethylnaproxen were obtained from Sarva-Syntex, Palo Alto, California, USA. Naprosyne® and cimetidine (Tagamet®, SKF) were obtained from the hospital pharmacy.

Naproxen acyl glucuronide and *O*-desmethylnaproxen acyl glucuronide and their isoglucuronides were identified in and isolated from human urine after oral administration of 500 mg naproxen (Vree *et al.*, 1992a).

Subjects

Ten subjects (four males, six females, ranging in age from 20 to 50 years) took 500 mg naproxen orally (Naprosyne®). On a separate occasion (1 month later) six of the same subjects took 500 mg naproxen while receiving cimetidine (Tagamet®) 400 mg twice daily orally. Cimetidine dosing started 2 days before naproxen was administered and was continued during the 4 days of its elimination.

On a separate occasion one subject took orally 100 mg *O*-desmethylnaproxen. All drug administrations took place simultaneously after an overnight fast.

The study had the approval of the hospital ethics committee and informed consent was obtained from the volunteers.

Sampling

Fingertip blood samples (2 ml) were drawn at 1, 2, 4, 6 and 8 h on the first day after administration of naproxen and twice at 12 h intervals on the following 4 days. After centrifuging, the plasma was stored at −20° C pending analysis.

Urine was collected by spontaneous voiding up to 140 h (seven times the expected $t_{1/2}$ of naproxen). Urinary pH was kept acidic (pH 5.0–5.5) by oral intake of 1 g ammonium chloride three times daily (Ammonchlor®, Südmedica, München, Germany). Four urine samples of 5 ml from each void were stored at −20° C pending analysis.

Drug analysis

Naproxen and its metabolites were assayed by h.p.l.c. as reported elsewhere (Vree *et al.*, 1992a). The limit of quantitation (signal/noise ratio of 3) of naproxen and *O*-desmethylnaproxen in human plasma was 1.5 $\mu g\ ml^{-1}$. The respective limits of quantitation in

human urine were: naproxen, *O*-desmethylnaproxen, naproxen acyl glucuronide and *O*-desmethylnaproxen acyl glucuronide, 1.0 μg ml^{-1} and naproxen and *O*-desmethylnaproxen isoglucuronide 1.5 μg ml^{-1}.

The intraday and interday coefficients of variation in the assays of naproxen and its metabolites were < 5% (Vree *et al.*, 1992a).

Plasma samples (100 μl) were deproteinized with 0.4 ml 0.20 M perchloric acid, centrifuged at 3000 *g*, and 20 μl of the supernatant was injected onto the column. Urine samples were diluted 10 times with 0.01 M H_3PO_4, and 20 μl was injected onto the column.

Plasma binding

The protein binding of naproxen, its metabolite and the conjugates was measured in blank human plasma samples (obtained from the hospital blood bank) using the Amicon Micropartition system MPS-1 (Grace BV, Amicon Division, Capelle aan de IJssel, The Netherlands). Urine (100 μl) containing naproxen and the metabolites was added to 900 μl blank human plasma and equilibrated for 15 min at 37° C. The average protein binding (± s.d.) was calculated from six spiked plasma samples. No binding to the filters was observed.

Data analysis

The total renal clearance of naproxen acyl glucuronide (CL_R(nap)) was calculated from the total amount excreted in the urine (corrected for molecular weight) divided by the AUC of naproxen. It was assumed to be the sum of possible renal glucuronidation of naproxen and renal excretion of the acyl glucuronide, as no naproxen acyl glucuronide was detected in blood.

Curve fitting was carried out and pharmacokinetic parameters were calculated using the Medi-ware® computer program (Proost & Meyer, 1992). AUC values were calculated using the linear trapezoidal rule with extrapolation to infinity from C(last)/λ_2. Oral clearance (Cl_o) and mean residence time (MRT) were calculated by standard methods (Proost & Meyer, 1992).

Results

Plasma concentrations of naproxen, renal excretion rates and urinary recoveries of naproxen, *O*-desmethylnaproxen, naproxen acyl- and iso acyl glucuronides, *O*-desmethylnaproxen acyl- and iso acyl glucuronides in two subjects are shown in Figure 2. No acyl glucuronides of naproxen or *O*-desmethylnaproxen were detectable in plasma, nor was the metabolite *O*-desmethylnaproxen detected. Table 1 shows the mean values of the pharmacokinetic parameters of naproxen. The urinary recoveries of parent drug and metabolites were similar in all subjects. Naproxen acyl glucuronide accounted for 50.8 ± 7.3% of the dose, its isoglucuronide for 6.5 ± 2.0%, the *O*-dealkylated acyl glucuronide metabolite for 14.3 ± 3.4%, and its isoglucuronide for 5.5 ± 1.3% (n = 10). Naproxen and *O*-desmethylnaproxen were excreted in negligible amounts (< 1%).

The ratio of total naproxen/*O*-desmethylnaproxen in urine was 2.96 ± 0.75.

In the individual who was given a dose of *O*-desmethylnaproxen (100 mg), the elimination half-life of the compound was 1 h and 20% of the dose was excreted in the urine as the acyl glucuronide.

The extents of plasma binding of naproxen and its metabolites are shown in Table 2. Binding of the unconjugated compounds was greater than that of the acyl glucuronides.

Plasma concentrations in one subject receiving naproxen with and without cimetidine co-medication are shown in Figure 3.

Table 3 summarises the kinetic data for naproxen with and without cimetidine co-medication.

Thus, cimetidine decreased the $t_{½}$ of naproxen by 47.3 ± 11.5% (range 39–62%; P = 0.0014) (Table 3) and increased its oral clearance from 7.91 ± 0.87 ml min^{-1} to 9.82 ± 1.62 ml min^{-1} (P = 0.0156). It increased

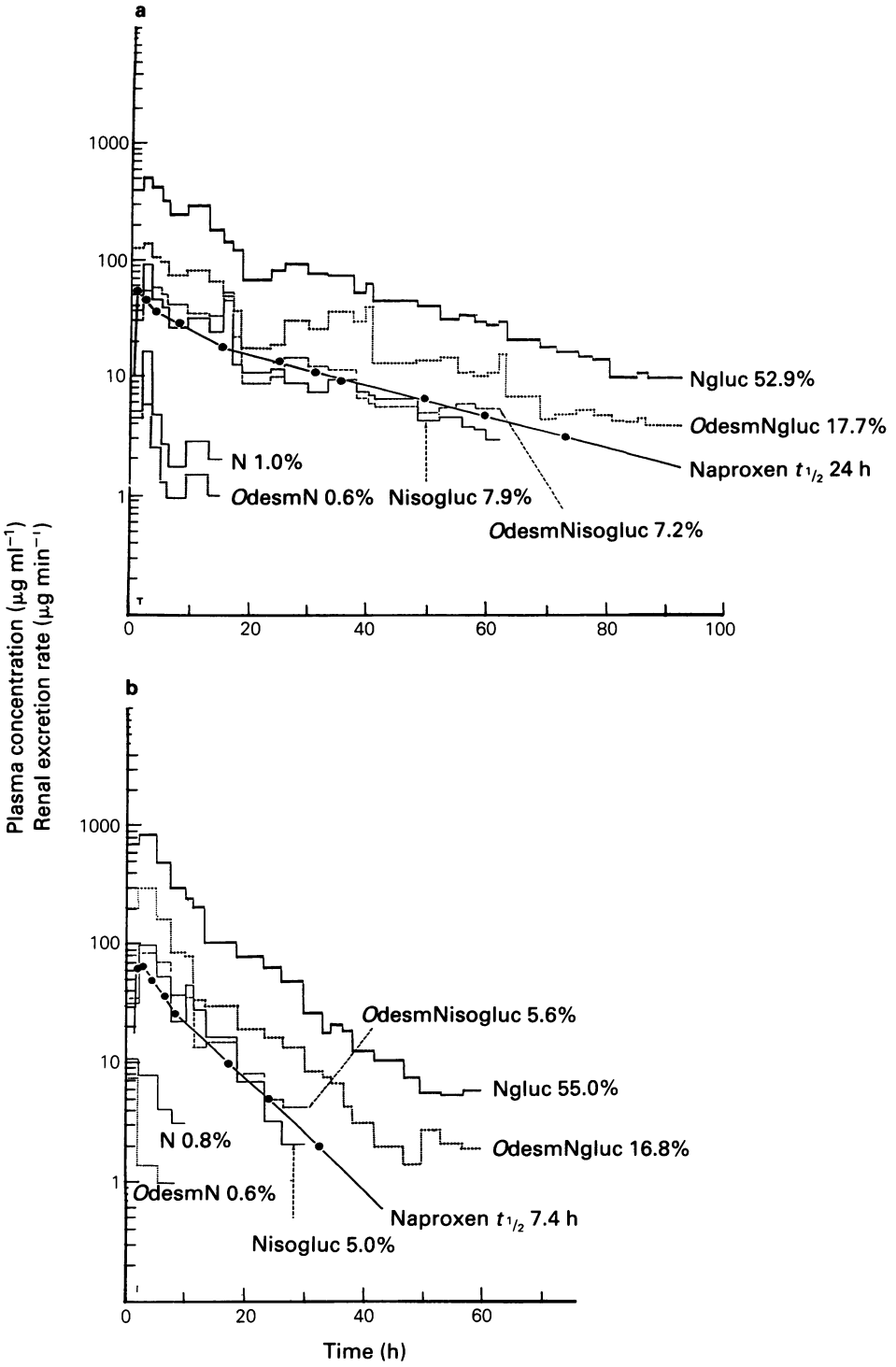
Table 1 Pharmacokinetic parameters of naproxen in 10 healthy subjects

Parameter	*Mean ± s.d.*	*Range*
C_{max} (μg ml^{-1})	62.2 ± 11.1	46.0–78.1
t_{max} (h)	1.5 ± 0.68	0.5–1.9
$t_{½,z}$ (h)	24.7 ± 6.4	7.5–35.8
MRT (h)	29.2 ± 7.3	10.2–39.7
CL_o (ml min^{-1})	7.44 ± 1.07	5.75–14.40
CL_R(nap) (ml min^{-1})	4.02 ± 0.74	2.89–6.78
Urinary recoveries (% dose)		
Naproxen acyl gluc	50.8 ± 7.3	39.2–61.7
O-desmethylN acyl gluc	14.3 ± 3.4	10.7–21.4
Naproxen isogluc	6.5 ± 2.0	2.2–10.1
O-desmethylN isogluc	5.5 ± 1.3	2.5–7.2
Naproxen	1.10 ± 0.87	0.5–1.7
O-desmethylnaproxen	0.63 ± 0.29	0.2–1.1
Total	78.8 ± 7.8	64.3–87.5
N/*O*-desmethylN	2.96 ± 0.75	2.00–4.53

C_{max} = maximum plasma drug concentration, t_{max} = time at which C_{max} occurs. CL_o oral clearance, CL_R(nap) = renal clearance naproxen (= $excretion_{naproxen}$ + $mgNgluc_{urine}$/$AUC_{naproxen}$). mgNgluc = mg of naproxen acyl glucuronide excreted.

Table 2 Extent of plasma binding of naproxen and its metabolites *in vitro*

Compound *Plasma concentration range (μg ml^{-1})*	*% binding (mean ± s.d.)*
Naproxen 8–20	98.2 ± 4.5
Naproxen isoglucuronide 33–130	66.0 ± 9.2
Naproxen acyl glucuronide 670–1300	92.0 ± 3.5
O-desmethylnaproxen 5–13	100.0 ± 0.0
O-desmethylnaproxen acyl glucuronide 100–500	72.8 ± 4.6
O-desmethylnaproxen isoglucuronide 15–65	42.1 ± 5.8



Figures 2a,b Plasma concentrations of naproxen (N), renal excretion rates, and urinary recoveries (%) of naproxen acyl glucuronide (Ngluc), its isoglucuronide (Nisogluc), *O*-desmethylnaproxen acyl glucuronide (*O*desmNgluc), its isoglucuronide (*O*-desmNisogluc), naproxen (N), and *O*-desmethylnaproxen (*O*desmN) in two subjects after an oral dose of 500 mg naproxen.

(10%) the amount of naproxen acyl glucuronide excreted in the urine ($P = 0.0492$). The urinary recoveries of both naproxen isoglucuronide and *O*-desmethylnaproxen acyl glucuronide remained unchanged.

Discussion

Naproxen is renally excreted to a negligible extent (< 1% dose) when the urine is kept acidic (Upton *et al.*, 1980b). It is extensively reabsorbed (Cox *et al.*, 1990) and may be glucuronidated in the kidney tubules like probenecid (Vree *et al.*, 1992b). Acyl glucuronidation of naproxen is three times more extensive than *O*-demethylation, as shown by a mean urinary ratio of total naproxen:total *O*-desmethylnaproxen of about 3. It appears that about 5 to 6% of the acyl glucuronides of both parent drug and the *O*-desmethyl product isomerise.

6-*O*-desmethylnaproxen given orally is eliminated rapidly partly by formation of its acyl glucuronide. This

Table 3 Differences (mean ± s.d.) in pharmacokinetic parameters of naproxen, its metabolite *O*-desmethylnaproxen and acyl glucuronide conjugates in six subjects with and without co-administration of cimetidine (400 mg twice daily)

Parameter	*Without cimetidine*	*With cimetidine*	P	*95% confidence interval of difference*
C_{max} (μg ml^{-1})	61.5 ± 9.5	59.7 ± 6.0	0.3528	−29–33
t_{max}(h)	1.3 ± 0.7	1.2 ± 0.8	0.4123	−2.1–2.3
$t_{½,z}$ (h)	25.8 ± 5.4	13.2 ± 1.0	0.0014	−2.9–28.1
MRT (h)	29.0 ± 6.2	18.7 ± 2.1	0.0042	−9.2–29.9
CL_o (ml min^{-1})	7.91 ± 0.87	9.82 ± 1.62	0.0156	−5.7–1.9
CL_R(nap) (ml min^{-1})	4.32 ± 0.68	5.67 ± 1.25	0.0224	−5.2–2.5
Urinary recoveries (% dose)				
Naproxen acyl gluc	50.9 ± 6.9	60.4 ± 10.8	0.0492	−24.3–5.1
O-desmethylN acyl gluc	14.3 ± 4.3	14.2 ± 3.8	0.4945	−4.7–4.7
Naproxen isogluc	6.8 ± 2.6	6.3 ± 2.1	0.3694	−8.1–9.0
O-desmethylN isogluc	5.0 ± 1.5	5.0 ± 2.0	0.4945	−3.5–3.6
Naproxen	1.3 ± 1.1	0.58 ± 0.38	0.0937	−1.9–3.3
O-desmethylnaproxen	0.63 ± 0.38	0.42 ± 0.33	0.1605	−1.2–1.7
Total	78.9 ± 7.9	86.9 ± 8.9	0.0665	−21.9–5.8
N/*O*-desm (total)	3.12 ± 0.88	3.67 ± 1.49	0.2279	−2.6–1.5

Student's *t*-test significance at $P < 0.05$.

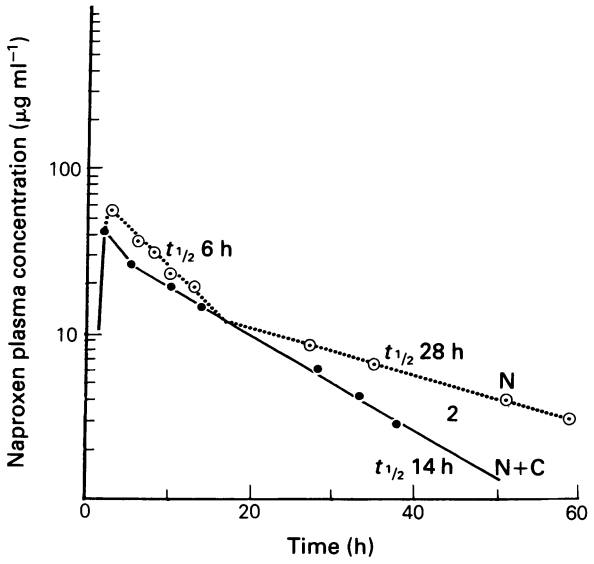


Figure 3 Plasma concentrations of naproxen (N) in one subject after an oral dose of 500 mg naproxen without (N) and with (NC) concomitant administration of cimetidine (400 mg twice daily).

rapid elimination may explain why no *O*-desmethylnaproxen was detected in plasma after administration of naproxen. Unconjugated plasma concentrations of *O*-desmethylnaproxen are 100 times less than those of naproxen (Runkel *et al.*, 1972a,b, 1973, 1976; Spahn-Langguth & Benet, 1992).

The long $t_{½}$ (18–35 h) of naproxen may reflect enterohepatic cycling as a result of biliary excretion of the acyl glucuronide followed by hydrolysis in the intestines.

Although Ziemniak *et al.* (1986) reported that cimetidine had no effect on naproxen kinetics we found an increase in naproxen clearance accompanied by a decreased $t_{½}$, and an increased urinary recovery of naproxen acyl glucuronide. The mechanism of these changes is unknown but may involve acceleration of the enterohepatic cycle. Cimetidine inhibits gastric acid secretion and may affect the pH in the ileum and duodenum of the intestines. Although this should not affect the biliary excretion of the glucuronides, an alkaline pH could enhance the hydrolysis of biliary excreted naproxen acyl glucuronide and hence increase the rate of enterohepatic cycling.

Neuvonen (1991) reported that the gastro-intestinal absorption of ibuprofen was accelerated greatly by the concomitant ingestion of magnesium hydroxide. However, this accelerated absorption was not observed for ketoprofen and diclofenac. In this study cimeditine did not affect the C_{max} and the t_{max} of naproxen and the total amount absorbed as reflected by urinary recoveries. Cimetidine had no effect on the *O*-dealkylation ($P = 0.49$) of naproxen. The slight increase in the urinary recovery of naproxen acyl glucuronide, while that of its isoglucuronide remained unaffected, suggests that renal glucuronidation of naproxen may occur (Baldassare *et al.*, 1986).

In conclusion, naproxen is *O*-demethylated and the parent drug and metabolite are conjugated as acyl glucuronides. These acyl glucuronides isomerise to stable isoglucuronides when released by the liver into the blood for excretion by the kidney. The half-life of naproxen shows a wide variation between 7 and 35 h (27%CV), which may be attributed to differences in the rate of enterohepatic cycling. Cimetidine reduces the half-life and its variability (7%CV).

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