

Clinical Pharmacokinetics of Naproxen

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Summary

Naproxen is a stereochemically pure nonsteroidal anti-inflammatory drug of the 2-arylpropionic acid class. The absorption of naproxen is rapid and complete when given orally. Naproxen binds extensively, in a concentration-dependent manner, to plasma albumin. The area under the plasma concentration-time curve (AUC) of naproxen is linearly proportional to the dose for oral doses up to a total dose of 500mg. At doses greater than 500mg there is an increase in the unbound fraction of drug, leading to an increased renal clearance of total naproxen while unbound renal clearance remains unchanged.

Substantial concentrations of the drug are attained in synovial fluid, which is a proposed site of action for nonsteroidal anti-inflammatory drugs. Relationships between the total and unbound plasma concentration, unbound synovial fluid concentration and therapeutic effect have been established.

Naproxen is eliminated following biotransformation to glucuroconjugated and sulphate metabolites which are excreted in urine, with only a small amount of the drug being eliminated unchanged. The excretion of the 6-*O*-desmethylnaproxen metabolite conjugate may be tied to renal function, as accumulation occurs in end-stage renal disease but does not appear to be influenced by age.

Hepatic disease and rheumatoid arthritis can also significantly alter the disposition kinetics of naproxen. Although naproxen is excreted into breast milk,

the amount of drug transferred comprises only a small fraction of the maternal exposure.

Significant drug interactions have been demonstrated for probenecid, lithium and methotrexate.

Naproxen [S-(+)-2-(6-methoxynaphth-2-yl)propionic acid] is a 2-arylpropionic acid (2-APA) nonsteroidal anti-inflammatory drug (NSAID). Naproxen is a potent inhibitor of prostaglandin synthesis,^[1] and is now marketed as an over-the-counter medication in the US. Naproxen is prescribed for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and acute gouty arthritis. Therapeutic doses of naproxen have proven to be equi-efficacious when compared with other commonly used NSAIDs.^[2-4] Naproxen also has antipyretic activity and is effective in the treatment of dysmenorrhoea.^[4] Naproxen exhibits analgesic effects and is used clinically for short term alleviation of post-operative pain, as well as migraine attacks.^[5] Gastrointestinal complications are the most common adverse effect, although renal dysfunction and hypersensitivity reactions also occur.^[4]

The clinical pharmacokinetics and pharmacodynamics of several of the chiral NSAIDs have been well established.^[6-11] However, as each member of this pharmacological class demonstrates unique pharmacokinetic features which distinguish them from each other, assessment of the pharmacokinetics of each NSAID, on an individual basis, is essential.

General review articles are available dealing with the pharmacological properties and therapeutic utility of naproxen.^[2-4] However, these articles do not give detailed information on the unique features ascribed to the clinical pharmacokinetics of naproxen. This article comprehensively reviews the clinical pharmacokinetics of naproxen and its metabolites.

1. Pharmacokinetic Properties

1.1 Absorption

Naproxen is usually administered orally, but has also been administered topically, intravenously,

intramuscularly and rectally. Conventional regular release tablets, capsules, enteric-coated tablets, suspensions, sustained and controlled-release preparations, gels and suppositories are commercially available.

Table I shows the absorption properties of naproxen when administered in different formulations in various disease states. Naproxen appears to be completely absorbed, whether given as a suspension, capsule or tablet.^[63] Following oral administration, the extent of naproxen absorption results in a similar area under the concentration-time curve (AUC) compared with intravenous administration.^[63,64] Following single dose administration of regular release preparations, doses of up to 4g are rapidly absorbed, with peak plasma or serum drug concentrations ($C_{\max}$) observed between 0.5 and 3 hours after administration.^[15,23,64]

The AUC is linearly proportional to dose up to a total dose of 500mg.^[64] Multiple dose administration yields absorption characteristics similar to those seen after single doses.^[57]

Naproxen is a weak acid ($pK_a = 4.15$). Attempts have been made, based on this physicochemical characteristic, to enhance the rate of absorption from different naproxen formulations and thereby provide an earlier onset of pharmacological effect. The sodium salt tablets have been shown to be absorbed at a higher rate with higher plasma concentrations when compared to naproxen free acid tablets in healthy volunteers.^[65] However, this pharmacokinetic feature did not result in an earlier onset of analgesia. In fact, statistically significant differences in analgesic effects were not seen until 4 or 5 hours after medication in patients with postpartum pain.^[65]

1.1.1 Routes of Administration

When compared with the bioequivalent formulations of regular release tablets, enteric-coated, sustained release and controlled-release preparations have

Table I. Absorption characteristics of naproxen (single doses of oral formulations administered to healthy adults except where indicated)						
No. of patients (type)	Age ^a (y) [range]	Dose (no. of days)	C _{max} (mg/L)	t _{max} (h)	AUC (mg/L • h)	Reference
6	NR	(3 x 100mg)	~57	~2	653	12
		150mg CW supp	~42	~4	345	
		300mg CW supp	~23	~4	641	
		150mg WS supp	~48	~2	393	
		300mg WS supp	~32	~2	633	
9 RD children	10.8 [5-14]	5 mg/kg, <50kg and 250mg >50kg	59.4	1-3	774	13
6	23 [22-25]	500mg	77.6	2	NR	14
		500mg supp	65.7	2	NR	
16	20 [18-23]	1000mg	110	NR	1402	15
		2000mg	155	NR	2187	
		3000mg	169	NR	2614	
		4000mg	210	NR	2796	
12	NR	Sequence 1				16
		250mg bid x 7 D	55.5	NR	1155	
		250mg bid & PB 500mg bid x 7 D	67.7	NR	1926	
12	NR	Sequence 2				16
		250mg bid x 7 D	64.5	NR	1604	
		250mg bid & PB 500mg bid x 7 D	43.5	NR	821	
NR	26.6 [23-43]	250mg	52.63	1.78	269.96	17
	63.8 [54-74]	250mg	49.8	2.5	241.742	
	61.25 [50-71]	250mg	40.85	1.05	187.05	
8	34 [24-45]	250mg	44.3	2	797	18
8 MRF	56 [34-79]	250mg	31.5	2	763	
8 SRF	56 [42-67]	250mg	27.0	2	475	
11 hepatic disorders	NR	250mg	44.69	2.59	NR	19
9 NH	57 [34-77]	250mg	18.89	5	566.73	20
11	28 [21-39]	250mg	34.8	2.6	580	21
		250mg + AlOH, 200 mg/ml; MgOH, 200 mg/5ml; and SIM, 20 mg/5ml	37.2	2.5	579	
3 febrile children	[6-13]	10 mg/kg suspension	55	NR	821	22
7 post-op children		10 mg/kg suspension	49	NR	713	
12	[23-42]	250mg 1st time	54.8	2.9	992	23
		250mg 2nd time	65.1	1.7	1094	
12	[23-42]	250mg 1st time	53	3.1	858	24
		250mg 1st time	62.8	1.8	977	
8	28	250mg	52.63	2	NR	25
		250mg + 4g CSM in 100ml orange juice	34.49	4.11	631	
10	[20-52]	500mg EC	53.4	5.6	1494	25
		500mg	77.2	1.8	1324	
11	[19-25]	500mg EC x 5 D	66.2	4.5	1156	25
		250mg bid x 5 D	74.9	1.4	1248	
11	[21-51]	500mg EC bid x 5D	113.5	4.7	984	25
		500mg bid x 5 D	106.3	1.4	861	
11	[19-25]	500mg sodium supp	65.8	1.4	1456	26
		500mg tablets	73.4	2.4	1435	
6	[20-54]	500mg sodium supp	78.8	0.9	1675	26
		500mg supp	59.6	2.7	1448	

Table I. Contd

No. of patients (type)	Age ^a (y) [range]	Dose (no. of days)	C _{max} (mg/L)	t _{max} (h)	AUC (mg/L • h)	Reference
10	[22-39]	375mg	61.5	1.86	NR	27
		375mg × 9 days	58.2	1.46	NR	
10 E	[66-81]	375mg	59.5	2.22	NR	
		375mg × 9 days	64.2	1.84	NR	
10	29.1 [22-39]	375mg	63.2	1.4	NR	28
		375mg bid × 13 doses	94.8	1.5	NR	
10 AC	41.1 [31-59]	375mg	47.4	1.3	NR	
		375mg bid × 13 doses	84.2	1.8	NR	
7	23 [19-28]	1000mg qd × 4 days	NR	NR	1650	29
		500mg bid × 4 days	NR	NR	2780	
13 E OA	84.2 [76-93]	500mg bid × 21 days	NR	NR	487	30
6 Middle aged OA	53.9 [49-64]	500mg bid × 21 days	NR	NR	369	
1 RA	58	500mg bid active disease	90.9	NR	699	31
		500mg bid improvement	125.6	NR	1134	
6	24.3 [21-30]	500mg 500 mg + sucralfate 2g	95.6	2.2	1624	32
			84.2	4.1	1609	
12	[18-27]	500mg	82.7	1.4	1310.4	33
		500mg + sucralfate 2g	76.0	2.2	1288.8	
		500mg bid for 10 doses				
		500mg bid for 10 doses sucralfate	108.5	1.8	1761.0	
			99.3	2.3	1666.2	
5	[22-30]	500mg vaginal supp	8.1	6-8	NR	34
6	[21-30]	750mg CR	47.9	6.0	1551	35
		750mg	93.2	1.7	1435	
14	[22-30]	1000mg CR	58.5	10.2	1920	35
		500mg bid	81.2	2.0	2036	
12	[22-30]	750mg CR × 5 days	70.1	4.5	1293	35
		375mg bid × 5 days	90.4	1.7	1416	
14	[22-30]	100mg CR × 7 days	78.3	5.0	1319	35
		500mg bid × 7 days	101.7	1.4	1480	
8 RA	62 [55-65]	500mg bid	79	NR	641	36
8	24 [21-27]	500mg bid	110	NR	896	
12	32.8	500mg	63.3	0.95	685	37
		500mg + SGT 200mg	60.4	1.10	651	
14	26.5 [21-35]	500mg bid	81.3	1.4	1907.3	38
		1000mg CR	58.4	11.3	1703.2	
		500mg bid × 7 D	97.2	1.5	1397.9	
		1000mg CR qd × 7 D	72.4	3.4	1286.2	
6 OA	[63-75]	500mg bid	60.7	0.8	NR	39
23	[19-32]	375mg bid × 15 doses	79.9	[2-4]	696	40
		750mg bid × 15 doses	110.9	[2-4]	961	
25 E	[65-74]	375mg bid × 15 doses	71.6	[2-4]	670	
		750mg bid × 15 doses	109.7	[2-4]	977	
7	median 33 [26-36]	1000mg	107.3	1	2171	41
10 RA	median 69 [66-85]	1000mg	111.5	2	2073	
22	34.3 [21-44]	500mg supp	54.5	3.1	1151	42
12	[25-42]	1000mg CR fasting	63.1	9.67	2221	43
		1000mg CR postprandial	86.1	7.67	2111	

Continued over page

Table I. Contd

No. of patients (type)	Age ^a (y) [range]	Dose (no. of days)	C _{max} (mg/L)	t _{max} (h)	AUC (mg/L • h)	Reference
12	21.6 [18-32]	750mg CR	42.9	11.8	1524.3	44
		2 × 375mg CST	97.3	2.4	1488.4	
		2 × 375mg UST	98.6	2.3	1491.3	
6 RA	58.8 [49-64]	500mg bid	84.2	2.22	NR	28
		Active RA		1.84	NR	
		500mg bid	105.1	1.86	NR	
		Remission		1.46	NR	
6 E	73	500mg bid × 14 days	88	NR	694	45
4 RA	24	500mg bid × 4 days	110	NR	896	
2 OA 8						
12	[18-42]	500mg SR fasting	40.8	5.08	1118.7	46
		500mg SR postprandial	38.2	10.3	1156.1	
		500mg	71.0	1.58	1033.0	
18	[18-42]	250mg qid × 7 days	99.5	0.89	1640.6	46
		1000mg SR qd × 7 days	110.7	1.36	1580	
		500mg bid × 7 days	101.8	5.00	1560	
6	35 [27-49]	500mg CR	45.8	11.0	1393	47
		500mg CR	45.4	8.7	1258	
		500mg CR	47.3	9.3	1400	
18	23.2 [19-30]	500mg	71.2	2.2	1122.2	48
		500mg + standard meal	67.4	1.9	1131.4	
		2 × 1g chewable sucralfate + 500mg 30 minutes after	53.9	4.1	1148.4	
12	34.9 [20-45]	750mg	106.18	3.25	1808.73	49
		750mg CR	63.06	4.35	1990.43	
18	34.7 [20-45]	750mg CR	62.35	4.0	2010.07	49
		375mg	56.69	2.06	793.48	
		500mg	65.53	3.06	973.86	
18	34.7 [20-45]	750mg CR qd × 7 days	100.5	3.44	1741.47	49
		375mg bid × 7 days	87.62	2.39	751.54	
		500mg bid × 7 days	95.08	1.83	876.72	
8	[19-22]	250mg	23.9	7.1	677	50
		250mg EC fasted	19.4	7.2	678	
		250mg EC fed	21.0	10.4	661	
12	30.5 [27-42]	750mg	88.9	1.8	1547	51
		750mg CR	59.5	5.3	1682	
		750mg CR qd × 6	76.3	4.5	1313	
25 febrile adults	[18-55]	500mg tablet	66.3	2.9	734.5	52
25 febrile children	[10-14]	500mg suspension	53.8	2.2	692.1	
		250mg tablet	47.2	3.3	572	
		250mg suspension	49.7	2.4	548	
12	35.2 [21-52]	70mg CR fasting	69.6	4.08	1978.7	53
		750mg CR postprandial	59.9	5.0	1778.6	
12	[18-22]	500mg 10:00h	81.71	1.36	1434.8	54
		500mg 22:00h	70.458	2.70	1482.9	
7	median 22	1000mg EC fasting	106	5.0	NR	55
		1000mg fed	103	6.0	NR	

Table I. Contd

No. of patients (type)	Age ^a (y) [range]	Dose (no. of days)	C _{max} (mg/L)	t _{max} (h)	AUC (mg/L • h)	Reference
10 MA	[25-57]	500mg with attacks	68.9	2.89	786.2	5
		500mg without attacks	70.6	1.89	695.4	
12	[24-42]	250mg	46.1	1.3	691	56
		250mg supp	41.2	1.7	668	
10	[20-50]	500mg	61.5	1.3	NR	57
		500mg and cimetidine 400mg bid	59.7	1.2	NR	
6	[20-50]	500mg	61	1.4	1060	57
		500mg; cim 400mg bid	58	1.4	846	
		500mg; ran 150mg bid	68	1.4	1064	
		500mg; fam 20mg qd	65	1.4	984	
14	22.1	500mg caplet	77.9	1.02	1210.2	58
		500mg tablet	71.4	1.5	1211.0	
24	[22-47]	500mg EC	94.9	4.0	845.0	59
		500mg	97.4	1.9	766.8	
23 C	[8-14]	250mg tablet	68.5	2.67	703	60
		250mg suspension	54.6	2.16	659	
24	27 [18-38]	500mg alone day 16	113	1.3	869	61
		500mg + zileuton 800mg day 10	112	1.8	903	
		500mg + placebo day 10	99	2.0	780	
		500mg alone day 16	104	1.6	829	
28	[21-44]	250mg	35.48	2.86	560.5	62
		500mg	64.05	2.25	942.24	

a Mean age; range in parentheses.
Abbreviations: AC = alcoholic cirrhosis; AIOH = aluminum hydroxide; AUC = area under the concentration-time curve; bid = twice daily; C = children; C_{max} = peak plasma drug concentration; CR = controlled release; CSM = cholestyramine; CST = Canadian standard tablets; CW = Carbowax; DM = diabetes mellitus; E = elderly; EC = enteric coated; HF = healthy fasted; HNF = healthy non-fasted; MA = migraine attacks; MgOH = magnesium hydroxide; MRF = moderate renal failure; NH = neoplastic hypoproteinemia; NR = not reported; PB = probenecid; qd = daily; qid = 4 times daily; q6h (q12h) = every 6 (12) hours; RA = rheumatoid arthritis; RI = renal insufficiency; SIM = simethicone; SRF = severe renal failure; SGT = sulglycotide; supp = suppository; t_{max} = time taken to achieve C_{max}; UST = United States standard tablets; WS = whitesupol.

a lower C_{max} and a delayed time to attain maximum concentrations (t_{max}).^[25,35,38,44,46,47,49-51,58,59,61,67] Naproxen is rapidly and well absorbed by the lower intestinal tract from suppositories.^[12,14,26,42,56,68,69] The absorption is significantly faster for naproxen sodium suppositories when compared with bioequivalent naproxen tablets.^[34] The rate of absorption and the bioavailability are significantly higher for naproxen sodium suppositories when compared to naproxen free acid suppositories.^[26] The vaginal absorption of naproxen was investigated in 5 healthy pre-menopausal women, the study demonstrated that naproxen was absorbed, but not to therapeutically useful concentrations.^[34] After cutaneous application of gels containing naproxen

the drug is absorbed slowly, reaching a C_{max} 24 hours after application; bioavailability is between 1 and 2.1%.^[70]

1.1.2 Effects of Food
Several studies^[55,63,64] indicate that the intake of food delays the absorption of naproxen, possibly by delaying the stomach emptying time coupled with slow gastric absorption. One study^[48] indicates that administration of a standard meal with naproxen is accompanied by a significant increase in the rate of absorption, without any significant change in other pharmacokinetic variables when compared with naproxen alone.
An increase in gastrointestinal pH following food intake may facilitate dissolution of naproxen

and accelerate the rate of absorption which, by analogy, can be compared to the acceleration of naproxen absorption when taken with sodium bicarbonate.^[71] Differences between protocols may account for the differential effects of food in these studies. For example, in the initial study by Runkel et al.,^[63] naproxen was administered as a suspension in the middle of a fatty meal. The rate and extent of absorption of a naproxen controlled-release tablet is not substantially altered by the ingestion of food.^[46] However, in one study^[53] the $C_{\max}$ decreased by about 14% when taken with food and, conversely, increased by 37% with food in another study,^[43] indicating the necessity of distinguishing between different controlled-release formulations and/or diets.

1.1.3 Effect of Different Disease States

Different disease states may affect naproxen absorption. For example, post-operative patients have demonstrated a reduction in gastrointestinal absorption.^[22] Drug absorption may be slightly delayed during migraine attacks, which may be related to delayed gastric emptying, and could potentially delay the onset of analgesic effects.^[5] Patients with chronic hepatic impairment having underlying cholestasis show a significant decrease in the rate of absorption.^[19] In addition, patients with severe diabetic microangiopathy show evidence of a 30% decrease in the fraction of dose absorbed.^[17] However, absorption characteristics after both single and multiple doses are not significantly different in rheumatic disease states.^[57]

1.1.4 Drug Interactions

Antacids containing magnesium oxide, aluminum hydroxide and, to a lesser extent, magnesium carbonate appear to interfere with naproxen absorption through the formation of poorly diffusible complexes.^[71] However, a mixture of aluminum hydroxide/magnesium hydroxide and simethicone with and without naproxen after single and multiple doses in healthy volunteers did not appear to affect the bioavailability of naproxen.^[21] Concomitant administration of cholestyramine resin causes a zero-order absorptive process due to binding of naproxen.^[24] Sucralfate may delay the $t_{\max}$ of

naproxen, but does not affect bioavailability.^[32,33,52] The concomitant intake of the H_2 -histamine antagonists (e.g. cimetidine, ranitidine and famotidine) does not appear to interfere with the absorption process.^[72,73]

1.1.5 Circadian Rhythm

The influence of chronobiology has demonstrated a decrease in $C_{\max}$ and a delay in $t_{\max}$, with a corresponding lower absorption rate constant after a 22:00 hour dose when compared to a 10:00 hour dose, which is attributed to decreased gastric pH coupled with the poor water solubility of naproxen, retarded intestinal motility and lower blood flow at night.^[54]

1.2 Distribution

Table II summarises the pharmacokinetic properties of naproxen in healthy volunteers.

The apparent volume of distribution (V_d/F), determined after oral administration, is between 5 and 10L in humans (0.1 to 0.2 L/kg), which approximates plasma volume and is consistent with other 2-APA NSAIDs.^[6,8,10,11] However, since protein binding is concentration-dependent, the estimated V_d/F will vary with changes in protein binding.

1.2.1 Protein Binding

Naproxen is extensively (>99.9%) bound in plasma, serum and in solutions of human serum albumin with high affinity ($K = 5-8 \times 10^6$ L/mol) and large capacity at therapeutic concentrations.^[75-77] In human plasma and in solutions of albumin, at concentrations similar to human plasma, naproxen binding is high and not modified by pH variations (5 to 7.8) or albumin concentrations (1 to 7 g/100ml). At a plasma concentration of 100 mg/L, the degree of protein binding is 99% (96% bound to albumin), whereas at a concentration of 500 mg/L the respective percentages were 93 and 87%.

Naproxen is principally bound to albumin but also appears to be bound to globulins;^[78] it binds significantly to salivary proteins but to a lower extent (66%).^[79] Consequently, naproxen is primarily confined to the central compartment, reflected by its relatively small V_d/F (0.1 to 0.2 L/kg), which is

Table II. Pharmacokinetic properties of naproxen in healthy volunteers (oral IR dosage forms administered in single doses, except where indicated)

No. of patients	Age ^a (y) [range]	Dose (no. of days)	t _{1/2} (h)	Vd/F (L/kg) ^b	CL/F (L/h/kg) ^c	Reference
6	NR	100-300mg	13.9	0.09	NR	63
6	23 [22-25]	500mg	10.25	NR	NR	14
16	20 [18-23]	500mg supp	10.25	NR	NR	15
		1000mg	13.75	NR	0.21	
		2000mg	13.75	NR	0.21	
		3000mg	13.75	NR	0.187	
		4000mg	14.25	NR	0.18	
6	NR	500mg	13.9	NR	NR	16
12	NR	500mg and 1g PB qid day 1 and 500mg qid on days 2 and 3	36.7	NR	NR	16
		<i>Sequence 2</i>				
		250mg bid × 7 days and PB 500mg bid × 7 days	17.3	NR	NR	
		250mg bid × 7 days	12.5	NR	NR	
7	26.6 [23-43]	250mg	14.91	0.094	NR	17
11	28 [21-39]	250mg	16.4	0.057	NR	21
12	[23-42]	250mg + AlOH, 200 mg/ml; MgOH, 200 mg/5ml; and SIM, 20 mg/5ml	16.1	0.052	NR	23
		250mg 1st time	17.4	NR	4.27	
		250mg 2nd time	18.8	NR	3.97	
12	[23-42]	250mg 1st time	16.3	NR	4.93	23
8	28	250mg 1st time	16.7	NR	4.30	21
		250mg + 4g CSM in 100ml orange juice	12.66	NR	NR	
		500mg sodium supp	17.2	NR	NR	
11	[19-25]	500mg tablets	17.2	NR	NR	26
6	[20-54]	500mg sodium supp	17.3	NR	NR	25
10	[20-52]	500mg supp	16.8	NR	NR	
		500mg EC	16.7	NR	NR	
10	[20-52]	500mg	16.4	NR	NR	25
10	[20-52]	500mg EC	16.7	NR	NR	
		500mg	16.4	NR	NR	
10	29 [22-39]	375mg	NR	0.125	0.0056	27
7	23 [19-28]	375mg bid × 9 days	NR	0.164	0.0074	29
		1000mg qd × 4days	12.3	0.139	0.0084	
		500mg bid × 4 days	9.5	0.105	0.0078	
6	24.3 [21-30]	500mg	15.9	NR	NR	32
12	[18-27]	500mg + sucralfate 2g	15.7	NR	NR	33
		500mg	15.5	NR	NR	
		500mg + sucralfate 2g	14.3	NR	NR	
		500mg bid for 10 doses	14.9	NR	NR	
		500mg bid for 10 doses sucralfate	14.1	NR	NR	
6	[21-30]	750mg CR	19.8	NR	NR	35
14	[22-30]	750mg	17.2	NR	NR	35
		1000mg CR	16.4	NR	NR	
		500mg bid	14.7	NR	NR	
14	[22-30]	100mg CR × 7 days	14.8	NR	NR	35
		500mg bid × 7 days	13.7	NR	NR	Continued over page

Table II. Contd

No. of patients	Age ^a (y) [range]	Dose (no. of days)	t _{1/2} (h)	Vd/F (L/kg) ^b	CL/F (L/h/kg) ^c	Reference
12	32.8	500mg	8.39	7.63	NR	37
14	26.5 [21-35]	500mg + SGT 200mg	7.93	7.9	NR	38
		500mg bid	13.3	NR	NR	
		1000mg CR	13.9	NR	NR	
		500mg bid × 7 days	12.9	NR	NR	
23	[19-32]	1000mg CR qd × 7 days	13.6	NR	NR	40
		375mg bid × 15 doses	13.4	NR	NR	
		750 bid × 15 doses	12.2	NR	NR	
12	21.6 [18-32]	750mg CR	14.4	NR	NR	44
		2 × 375mg CST	16.1	NR	NR	
		2 × 375mg UST	16.5	NR	NR	
7	median 33 [26-36]	1000mg	16.8	0.144	0.0058	41
22	34.3 [21-44]	500mg supp	15.2	0.147	0.445	42
12	[25-42]	1000mg CR fasting	17.3	NR	NR	43
		1000mg CR postprandial	17.6	NR	NR	
8	24	500mg bid × 4 days	10.08	0.11	0.0079	45
12	[18-42]	500mg SR fasting	15.3	NR	NR	46
		500mg SR postprandial	19.1	NR	NR	
		500mg	15.5	NR	NR	
		250mg qid × 7 days	13.0	NR	NR	
18	[18-42]	1000mg SR qd × 7 days	17.9	NR	NR	46
		500mg bid × 7 days	13.6	NR	NR	
		500mg CR	16.2	NR	NR	
6	35 [27-49]	500mg CR	15.6	NR	NR	47
		500mg CR	15.6	NR	NR	
		500mg CR	15.6	NR	NR	
18	23.2 [19-30]	500mg	15.9	NR	NR	48
		500mg + standard meal	15.5	NR	NR	
		2 × 1g chewable sucralfate +	15.0	NR	NR	
		500mg 30 minutes after				
18	34.7 [20-45]	750mg CR	18.65	NR	NR	49
		375mg	8.47	NR	NR	
		500mg	9.00	NR	NR	
18	34.7 [20-45]	750mg CR qd × 7 days	21.04	NR	NR	49
		375mg bid × 7 days	8.27	NR	NR	
		500mg bid × 7 days	8.99	NR	NR	
12	34.9 [20-45]	750mg	12.17	NR	NR	49
		750mg CR	21.02	NR	NR	
8	[19-22]	250mg	15.9	NR	NR	50
		250mg EC fasted	17.8	NR	NR	
		250mg EC fed	17.5	NR	NR	
12	30.5 [27-42]	750mg	17.8	NR	NR	51
		750mg CR	18.88	NR	NR	
		750mg CR qd × 6	19.9	NR	NR	
12	35.2 [21-52]	750mg CR fasting	22.3	NR	NR	53
		750mg CR postprandial	20.9	NR	NR	
12	[18-22]	500mg 10:00h	18.32	NR	NR	54
		500mg 22:00h	17.15	NR	NR	

Table II. Contd

No. of patients	Age ^a (y) [range]	Dose (no. of days)	t _{1/2} (h)	Vd/F (L/kg) ^b	CL/F (L/h/kg) ^c	Reference
12	[24-42]	250mg	15.1	NR	NR	56
		250mg supp	14.6	NR	NR	
10	[20-50]	500mg	25.8	NR	0.00678	57
		500mg; cimetidine 400mg bid	13.2	NR	0.00841	
6	[20-50]	500 mg	25.7	0.2	0.0066	57
		500mg; cimetidine 400mg bid	13.0	0.15	0.0087	
		500mg; ranitidine 150mg bid	16.0	0.11	0.0070	
		500mg; famotidine 20mg qd	13.0	0.13	0.0075	
14	22.1	500mg caplet	16.7	NR	NR	58
		500mg tablet	16.9	NR	NR	
24	[22-47]	500mg EC	16.3	NR	NR	59
		500mg	16.9	NR	NR	
6	60.91 [37-79]	500mg	63.5	2.4	1022	74
RA		UPC	0.306	2.7	3.31	
OA		SFC	18.4	12.2	710	
PSA		SFUC	0.130	14.8	4.26	
6		500 mg q12h x 7 days + single dose day 8	89.1	1.9	769	
		UPC	0.697	2.5	4.38	
		SFC	46.9	5.2	501	
		SFUC	0.514	4.0	4.93	
24	27 [18-38]	500mg alone day 16	11.0	0.117	0.0070	61
		500mg + zileuton 800mg day 10	13.3	0.135	0.0081	
		500mg + placebo day 10	10.4	0.123	0.0075	
		500mg alone day 16	10.6	0.119	0.0072	
28	[21-44]	250mg	12.27	0.115	0.0066	62
		500mg	13.34	0.138	0.0079	

a Mean age; range in parentheses.
b Vd/F = apparent volume of distribution after oral administration.
c CL/F = plasma clearance of drug after oral administration.
Abbreviations: AlOH = aluminum hydroxide; C = children; CR = controlled release; CSM = cholestyramine; CST = Canadian standard tablets; CW = Carbowax; EC = enteric coated; MgOH = magnesium hydroxide; NR = not reported; OA = osteoarthritis; PB = probenecid; PSA = psoriatic arthritis; qd = daily; qid = 4 times daily; q6h = every 6 hours; q12h = every 12 hours; RA = rheumatoid arthritis; SFC = synovial fluid concentrations; SFUC = synovial fluid unbound concentrations; SIM = simethicone; SGT = sulglycotide; supp = suppository; t_{1/2} = elimination half-life; UC = unbound concentrations; UST = United States standard tablets; WS = whitesupol.

similar to that of other chemically related NSAID structures.^[6,10,11]

Unconjugated *O*-desmethylnaproxen is fully bound to plasma proteins. Binding of acylglucuronides is less; 92% for naproxen acylglucuronide, 66% for naproxen isoglucuronide, 72% for 6-desmethylnaproxen acylglucuronide and 42% for 6-desmethylnaproxen isoglucuronide.^[57]

The plasma naproxen free fraction increases with increasing concentrations of the drug in the

23 to 800 mg/L range, resulting in a nonlinear AUC with increasing doses above 500mg.^[74,80-82] Although these results have been confirmed by other investigators, the actual free fraction values are considerably lower than those initially reported by Runkel et al.^[83] This may be due to differences in analytical methodology or between plasma and serum protein binding.

A recent study also demonstrates nonlinearity in synovial fluid protein binding. Naproxen synovial

fluid protein binding is concentration-dependent between 10 and 100 mg/L.^[74]

The protein binding of naproxen is dependent on the amount and nature of circulating protein, especially albumin, which may decrease in renal and liver disease and is lower in synovial fluid. Changes in protein binding are also attributable to an accumulation of endogenous substances, such as organic acids. Protein binding is significantly lower in patients with impaired renal function with increased serum urea, serum creatinine and total protein concentrations, and a relative increase in naproxen free fraction as well as in unbound concentrations are evident in severe renal failure.^[81]

Protein binding has also been shown to be reduced in patients with arthritis and hyopalbuminaemia,^[15] and in patients with various hepatic diseases.^[82] In contrast, the degree of plasma protein binding remains constant in patients with neoplastic hypoproteinaemia.^[20]

1.2.2 Synovial Fluid Distribution

The synovium is the proposed site of action for NSAIDs in various rheumatic diseases. Substantial concentrations of naproxen have been detected in synovial fluids and synovial tissue of patients with rheumatoid arthritis and osteoarthritis.^[39,74,84-89] Naproxen concentrations were determined in articular tissues at steady state and have been shown to concentrate in the synovial membrane and joint capsula rather than in bone and cartilage.^[90]

The synovial fluid studies indicate that naproxen has a longer $t_{\max}$, a lower $C_{\max}$ and a longer elimination half-life ($t_{1/2}$) in synovial fluid when compared with plasma.^[39,74,85-88] One study suggests that the elimination $t_{1/2}$ is longer in rheumatoid arthritis but not in osteoarthritis,^[86] which contrasts with the findings of other studies investigating patients with osteoarthritis.^[39,87] Concentrations of 6-desmethylnaproxen are reported to be extremely low in all synovial fluid samples.^[39] After repeated oral doses of naproxen, steady-state peak concentrations in synovial fluid are reported to be 65% of that in plasma,^[39,74] or even higher in synovial fluid,^[87] with a ratio of synovial fluid to plasma concentration of 2.4.

The average AUC of unbound naproxen in plasma and synovial fluid was the same over a dosage interval at steady state, but were not the same after a single dose, where the mean unbound synovial fluid AUC was 1.2 times the mean unbound plasma AUC.^[74] Free fractions of naproxen are significantly higher in synovial fluid (0.14%) when compared with plasma (0.11%), which is likely to be due to lower albumin concentrations in synovial fluid.^[74,77]

The clinical effectiveness, as demonstrated by decreases in morning stiffness and Lee Index scores (a functional index of rheumatoid arthritis), appears to correlate with the free concentration of naproxen in synovial fluid.^[91] However, a more recent investigation demonstrated that whereas prostaglandin E_2 concentrations were low after both short and long term administration, temporal and dose relationships of prostanoid concentrations with synovial fluid concentrations of naproxen could not be discerned.^[74]

There are currently no published studies or information about naproxen concentrations in synovial fluid after cutaneous application.

1.2.3 Distribution into Other Tissues

There are few data regarding the distribution of naproxen into other tissues and fluids.

Naproxen saliva concentrations in healthy individuals treated with a single 550mg dose show concentrations approximately 60% of serum concentrations (with a $C_{\max}$ of 24 mg/L, $t_{\max}$ of 4 hours, and elimination $t_{1/2}$ of 24 hours), corresponding to the clinical effectiveness of naproxen in dental pain and inflammation.^[79]

Naproxen rapidly crosses the placental barrier after oral administration to pregnant women.^[2]

1.3 Metabolism

Naproxen undergoes phase I dealkylation by cytochrome P450 (CYP) to the *O*-demethylated metabolite, followed by phase II acylglucuronidation.^[57] Hence, naproxen is oxidised to 6-*O*-desmethylnaproxen (6-DMN) and conjugated to naproxen acyl glucuronide and 6-*O*-desmethylnaproxen acylglucuronide (6-DMNG).^[64]

A preliminary report demonstrated that human liver microsomal *O*-demethylation of *S*-naproxen was decreased by the CYP2C9-specific inhibitor sulfaphenazole.^[92] A subsequent investigation has shown that sulfaphenazole reduced microsomal demethylation of *S*-naproxen by 47%, and the CYP1A2 inhibitor furafylline decreased *O*-demethylation of *S*-naproxen by 28%, suggesting that CYP2C9 and 1A2 together account for the majority of human liver demethylation of naproxen.^[93]

It has been reported that naproxen is excreted in urine unchanged (approximately 70% of the dose) and as 6-DMN (approximately 30% of the dose).^[15] It has also been reported that in adults 80% of naproxen and 97% of 6-DMN is conjugated. However, in children 60 and 63% of naproxen and 6-DMN respectively are excreted as glucuronide metabolites.^[22]

In other studies, naproxen is mainly excreted as conjugates of naproxen and 6-DMN in proportions of approximately 29 and 19% of the dose, respectively.^[94] In healthy volunteers, approximately 80 to 100% of the total dose is recovered in urine. Phase II glucuronidation consists of naproxen acylglucuronide (approximately 51%), the 6-DMN dealkylated metabolite (approximately 14%), and the respective isoglucuronides (~7% and ~6%).

Naproxen and 6-DMN are excreted in negligible amounts (<1% intact).^[57] The conflicting differences in metabolic data may be due to the instability and spontaneous hydrolysis of the glucuroconjugated metabolites of naproxen to form the parent drug, or isomerisation to form a glucuronidase resistant isoglucuronide in alkaline media. Naproxen conjugates can hydrolyse to the parent compound dependent upon the duration of frozen sample storage, freezing and thawing of samples, the analytical procedures used and urinary retention in the bladder.^[27]

The 6-DMN metabolite is 1% as active as naproxen acid in animal model anti-inflammatory tests, while the dose which kills 50% of rats (LD₅₀) is more than 12 times higher when compared with naproxen.^[95,96]

When radioactive naproxen is administered intravenously, 1 to 2% of the administered dose is recovered in the stool, most likely because of biliary excretion.^[64] The existence of *O*-desmethyl-naproxen sulphate in patients with impaired kidney function, and in healthy volunteers suggests that this metabolite may account for 10.8% of the administered dose.^[97] Neither the total 24-hour urinary recoveries, nor the metabolite profiles reveal any systemic dose-related effects.^[64]

1.4 Elimination

The excretion of the drug and metabolites occurs in both urine and faeces. In humans, more than ~80% of each daily dose is excreted as conjugates in urine. The conjugates eliminated consist of naproxen acylglucuronide (approximately 51%), 6-*O*-desmethylnaproxen acylglucuronide (approximately 14%), and their respective isoglucuronides (~7% and ~6%).^[57] After administration of ³H-labelled naproxen, approximately 1 to 2% of the injected dose is excreted in faeces.^[64] While the urinary excretion rate tends to accelerate as naproxen plasma concentrations rise between 100 and 200 mg/L, unbound clearance remains unchanged.^[15]

No studies have examined the biliary elimination pathway and the degree to which naproxen and its metabolites are enterohepatically recycled.

There are a possibility that naproxen could be eliminated in breast milk and, therefore, ingested by an infant. A case study^[98] reports that the maximum naproxen concentrations in breast milk appear 4 hours post dose administration (0.114 to 0.125 mg%) with an apparent *t*_{1/2} of 22.8 to 23.8 hours after naproxen 250mg twice daily. The corresponding *C*_{max} for 375mg twice daily administration is 0.237 mg%. The total dose recovered from urine in the infant (0.47mg) is 0.26% of the maternal dose with a *t*_{1/2} paralleling the breast milk profile. Low concentrations in breast milk may be attributable to the high degree of plasma protein binding and the lower pH of breast milk when compared with plasma. Extrapolation of this study to nursing mothers suggests that infant exposure to naproxen via breast milk is minimal.

2. Therapeutic Implications for Naproxen

2.1 Dosage and Therapeutic Range

The recommended initial dosage for naproxen is 250 to 375mg twice daily. The maintenance dose is 375mg to 750mg daily in 2 dosages as needed for the treatment of inflammatory conditions. At doses of up to 500mg twice daily, it has been suggested that a linear relationship is observed between the dose and AUC.^[15,63,64] However, a more recent study^[62] suggests the possibility of dose-dependent pharmacokinetics occurring between commonly used doses (i.e. 250 to 500mg).

At doses greater than 500mg a linear relationship is not maintained, due to an increase in the total renal clearance of naproxen, which is a consequence of the saturation of plasma protein binding sites.^[15,63,64] An increment in dosage of 500 and 1000 mg/day produces, on average, 34.5% and 14.6% increases in mean trough concentration respectively.

A study by the same group^[15] shows that AUC does not plateau in the 900mg dose region, but rises in a nonlinear fashion with incremental dosage increases up to 4 g/day and, patients show excellent drug tolerance. In addition, there is a linear increase in naproxen free fraction produced with increasing dosage, which could increase the effectiveness and/or toxicity; however, no clinical or experimental data are available to substantiate this hypothesis.

It has been difficult to establish relationships between plasma concentrations of NSAIDs and the clinical effectiveness of these drugs in chronic arthropathies, and between dose administration regimens. However, several plasma concentration-effect relationships have been elucidated for naproxen.^[74,99,100] A dose-response relationship in the range of 250 to 1500 mg/day has been demonstrated for naproxen in patients with arthritis. A serum concentration-response relationship is evident with trough naproxen concentrations, with a good therapeutic response being associated with serum concentrations of naproxen above 50 mg/L.

Rheumatoid arthritis patients with trough serum concentrations below 18 mg/L do not appear to have a clinical response to naproxen.^[99]

The relationship between the clinical response of patients with rheumatoid arthritis to naproxen 500, 1000 and 1500 mg/day and naproxen concentrations show that effectiveness, as evaluated by articular index, mean grip strength and analogue pain score, was linearly related to trough plasma concentrations of total drug, although clinical improvements were less significant with increased doses.^[100] Interestingly, the clinical effectiveness as demonstrated by decreases in morning stiffness and the Lee Index correlates with the free concentration of naproxen in synovial fluid, which is the proposed site of action of naproxen in rheumatoid arthritis.^[91] There was, however, no significant correlation with pain, this may be due to the subjective nature of clinical evaluation of pain compared to inflammation.

Other features may also help explain the lack of correlation between analgesic activity and NSAID concentrations in synovial fluid, including inter-patient variability in response to NSAIDs.^[101] In addition, several other variables have been shown to influence the clinical response to an NSAID, including the number of NSAIDs already used, duration of the disease and psychological factors.^[102] Furthermore, it appears that what characterises a responder to naproxen may not necessarily apply to another NSAID.^[103] However, a relationship between plasma concentrations of naproxen and analgesic effectiveness has been demonstrated in a rat analgesic model.^[104]

Recently, the relationships between plasma and synovial fluid naproxen concentrations and prostaglandin concentrations in these fluids have been evaluated. The data for inhibition of cyclo-oxygenase I platelet-derived thromboxane B₂ by plasma naproxen was estimated and fitted to a sigmoid E_{max} (extent of effect the drug produces) model, with a mean concentration of the drug producing 50% of E_{max} (EC₅₀) based on the total and unbound concentrations of naproxen of 7.7 ± 4.4 mg/L and 25.3 ± 22 µg/L. Although there were demonstrable

reductions in prostanoid concentrations, there were no uniform effects of naproxen on synovial fluid derived prostanoids, and many of the concentrations were at or near the detection limit sensitivity of the assays.^[74]

A sustained release preparation of naproxen has been developed which may improve patient compliance with the recommended dosage of a 300mg capsule twice daily. The sustained release preparation was as effective in controlling arthropathies as the conventional immediate release formulation.^[46] The ability of the sustained release preparations to maintain effective therapeutic concentrations in plasma has been demonstrated by several studies.^[35,67] The administration of naproxen 500mg in the evening as an enteric-coated formulation produces a significantly shorter duration of morning stiffness and higher morning plasma naproxen concentrations compared with the conventional immediate release formulation.^[105]

Pharmacokinetic differences between 2 dosage regimens of naproxen were studied^[29] at steady-state in healthy male volunteers. A twice daily regimen of 500mg results in higher serum trough concentrations and a larger AUC when compared to 1000mg once daily. The nonlinearity of naproxen pharmacokinetics at higher doses, due to the displacement of naproxen from protein binding sites, may suggest that a shorter $t_{1/2}$ and a greater total urinary excretion of unchanged drug should be apparent; however, a longer $t_{1/2}$ and a slightly larger urinary excretion when compared to twice daily administration is evident. The increase in V_d/F and total body clearance (CL_{TB}) for the once daily administration regimen results in a longer $t_{1/2}$ which, in turn, may prolong effectiveness.^[29]

In contrast to several of the reports suggesting a concentration-effect relationship, it has also been reported that there is no association between adverse effects or effectiveness with naproxen concentrations in osteoarthritis.^[106] In addition, it has been suggested that there is no significant correlation between naproxen concentrations and reduction in pain.^[91] Moreover, no published studies have related naproxen concentrations to adverse ef-

fects.^[99,100] These findings may genuinely reflect a lack of correlation, but may also suggest a lack of sensitivity in measured pharmacodynamic endpoints, and emphasises the subjective nature of some clinical data in the evaluation of inflammation and pain.

Variability in the analytical demands of monitoring unbound concentrations, disease heterogeneity, interindividual differences in disease severity, and possibly interindividual differences in penetration of naproxen into inflamed tissue, may also hinder the establishment of correlations between drug concentrations and clinical response. Continued development of more sensitive quantitative markers of clinical effectiveness and NSAID toxicity are needed in order to further establish pharmacokinetic-pharmacodynamic relationships.

Few studies have attempted to correlate clinical, pharmacokinetic and pharmacological data. A recent study^[107] has demonstrated reductions in interleukin-6 and the neuropeptide substance P in synovial fluid and plasma samples. However, this study was done in the absence of pharmacokinetic considerations. One study^[91] has attempted to correlate naproxen concentrations, clinical effectiveness and the effect of naproxen on mediators of inflammation. More studies are needed to delineate the pharmacodynamic and toxicological relevance of the pharmacokinetic data.

2.2 Disease and Naproxen Pharmacokinetics

Table III summarises the effects of disease states on the pharmacokinetic characteristics of naproxen.

Many rheumatic and elderly patients have some degree of renal function impairment, leaving them susceptible to renal failure induced by NSAIDs. Based on laboratory evidence of renal impairment, long term administration of naproxen 375mg twice daily for 4 weeks in patients at risk of renal insufficiency is not associated with further deterioration of renal function. An increase of dosage to 750mg twice daily in such patients appears to only induce small and transient changes in renal function.^[110]

Table III. Pharmacokinetic properties of naproxen in patients with disease states (oral IR dosage forms administered in single doses, except where indicated)

Patient group (dosage form)	No. of patients	Age (y) [range]	Dose (no. days)	t _{1/2} (h)	Vd/F (L/kg) ^b	CL/F (L/h/kg) ^c	Reference
RD children suspension	9	10.8 [5-14]	5 mg/kg <50kg and 250mg >50kg suspension	11.55	NR	NR	13
DM slight angiopathy	5	63.8 [54-74]	250mg	17.68	0.088	NR	17
DM severe angiopathy	4	61.25 [50-71]	250mg	21.16	0.139	NR	
Healthy	8	34 [24-45]	250mg	17.7	0.124	0.0049	18
MRF	8	56 [34-79]	250mg	20.9	0.126	0.004	
SRF	8	56 [42-67]	250mg	15.4	0.175	0.0080	
Hepatic disorders	11	NR	250mg	20.36	NR	NR	19
NH	9	57 [34-77]	250	16.4	0.114	NR	20
Febrile children	3	[6-13]	10 mg/kg suspension	10.8	NR	NR	22
Post-op children	7		10 mg/kg suspension	13.6	NR	NR	
Febrile children	25	NR	5.74 mg/kg tablet suspension	17.4 14	NR NR	NR NR	22
RA	1	23	250mg bid for 8 months	8.75 and 7.75	NR	NR	98
NM			375mg bid 3 weeks	8.5	NR	NR	
E	10	71 [66-81]	375mg	NR	0.132	0.00439	27
			375mg bid × 9 days	NR	0.193	0.00685	
AC	10	41.1 [31-59]	375mg	NR	0.147	0.0046	28
			375mg bid × 13 doses	NR	0.229	0.0076	
E OA	13	84.2 [76-93]	500mg bid × 21 days	20.4	0.18	0.006	30
Middle-aged OA	6	53.9 [49-64]	500mg bid × 21 days	18.2	0.23	0.009	
RA	1	58	500 mg bid active disease	12.3	0.175	0.0099	31
			500 mg bid improvement	14.1	0.123	0.0060	
RA	8	62 [55-65]	500mg bid	10.4	0.18	NR	36
E OA	6	[63-75]	500mg bid	11.7	NR	NR	39
E	25	[65-74]	375mg bid × 15 doses	16.9	NR	NR	40
			750mg bid × 15 doses	15.3	NR	NR	
Rheumatic patients	10	median 69 [66-85]	1000mg	16.4	0.169	0.0068	41
E RA & OA	6	73	500mg bid × 14 days	9.3	0.17	0.0125	108
RA	6	58.8 [49-64]	500mg bid active RA	13.1	0.15	0.0113	45
			500mg bid remission	13.7	0.117	0.00825	
Febrile adults	25	[18-55]	500mg tablet	15.1	NR	7.7	52
			500mg suspension	13.8	NR	7.7	
Febrile children	25	[10-14]	250mg tablet	17.4	NR	6.9	
			250mg suspension	14.0	NR	7.8	
MA	10	[25-57]	500mg with attacks	9.45	NR	0.011	5
			500mg without attacks	8.52	NR	0.016	
JRA	9	>10	Naproxen 14.6-18.8 g/kg/day + MTX 0.22-1.02 mg/kg/wk	9.13	2.91	0.234	66
				11.32	3.57	0.232	
Children	23	[8-14]	250mg tablet	7.61	0.112	0.0092	109
orthopedic surgery			250mg suspension	8.88	0.130	0.0090	

Table III. Contd

Patient group (dosage form)	No. of patients	Age (y) [range]	Dose (no. days)	t _{1/2} (h)	Vd/F (L/kg) ^b	CL/F (L/h/kg) ^c	Reference
RA, OA, PSA	6	60.92 [37-79]	500mg	14.1	0.158	0.0078	74
			UT	13.5	49.2	2.54	
			SFT	19.1	NR	NR	
			SFUT	13.4	NR	NR	
	6		500mg Q12H x 7 days + 500mg on day 8	NR	NR	0.0099	
			UCL	NR	NR	1.836	
			SFCL	NR	NR	2.436	
			SFUCL	NR	NR	0.024	

a Mean age; range in parentheses.
b Vd/F = apparent volume of distribution after oral administration.
c CL/F = plasma clearance of drug after oral administration.
Abbreviations: AC = alcoholic cirrhosis; AUC = area under the concentration-time curve; C = children; CL/F = plasma clearance of drug after oral administration; C_{max} = peak plasma drug concentration; CR = controlled release; DM = diabetes mellitus; E = elderly; EC = enteric coated; JRA = juvenile rheumatoid arthritis; MA = migraine attacks; MRF = moderate renal failure; MTX = methotrexate; NM = nursing mother; NH = neoplastic hyoproteinemia; NR = not reported; OA = osteoarthritis; PB = probenecid; PSA = psoriatic arthritis; qid = 4 times daily; q6h = every 6 hours; qd = daily; qid = 4 times daily; q12h = every 12 hours; RA = rheumatoid arthritis; RD = rheumatic disorders; RI = renal insufficiency; SFCL = synovial fluid clearance; SFT = synovial fluid half-life; SFUCI = synovial fluid unbound clearance; SFUT = synovial fluid unbound half-life; SRF = severe renal failure; t_{max} = time taken to achieve C_{max}; t_{1/2} = elimination half-life; UCL = unbound clearance; UT = unbound half-life; Vd/F = apparent volume of distribution after oral administration.

However, naproxen has been implicated in various renal syndromes, especially acute renal failure. In particular, this adverse effect develops in patients with ineffective circulatory volume of various origins.^[111] However, elimination of naproxen is dependent upon urinary excretion of conjugated metabolites, which may be influenced by reduced renal function. The pharmacokinetics of naproxen in patients with uraemia administered single doses of naproxen show a reduced urinary excretion of the drug. However, no accumulation of total naproxen in plasma occurs.^[112]

6-DMN is detected in patients with moderate and severe renal failure, showing a significantly greater C_{max} at 6 to 7 hours post-dose when compared with healthy individuals with a C_{max} at approximately 3 hours post-dose. The concentration and AUC of 6-DMN correlates with serum creatinine concentration.^[18] The 6-DMN sulphate conjugate metabolite is present in high concentrations in patients with impaired renal function. The extent of the sulphate conjugation appears to be directly related to the severity of the dysfunction in patients with renal failure.^[97] When compared to moderate

and normal renal function patients, the AUC, CL_{TB} and Vd/F of patients with severe renal failure are significantly different.^[109]

The binding of naproxen to serum proteins is significantly lower in patients with moderate and severe renal failure.^[18,81] Unfortunately, the unbound clearance of naproxen was not determined in these studies; however, it may be decreased with renal impairment. It is also possible that there may be a reduced absorption, or a compensatory increased biliary excretion with increased excretion of the drug in faeces. However, no studies to date have assessed these pharmacokinetic possibilities.

A study of 6 patients during maintenance dialysis indicates that naproxen is not dialysed. The effect of haemodialysis on naproxen plasma concentrations in an anuric man with chronic glomerulonephritis shows slightly higher plasma concentrations after dialysis, attributed to a >2kg fluid loss, and emphasises that naproxen is not cleared from the body during haemodialysis.^[109] In contrast with naproxen, the 6-DMN metabolite is dialysable. However, preliminary pharmacological assessment suggests that this metabolite has minimal

therapeutic or toxicological activity and, therefore, it is not likely to result in any clinically significant sequelae.^[112]

The pharmacokinetics of naproxen in elderly patients with arthritis on long term treatment during 1 dosage interval of 12 hours shows that the plasma concentrations and AUC of naproxen are significantly lower than the values obtained from healthy volunteers, although $t_{1/2}$ is not significantly different. Conversely, the V_d/F , unbound naproxen concentrations and oral clearance are significantly larger when studied in these 2 patient groups respectively.^[36,108]

The effect of rheumatoid arthritis on the pharmacokinetics of naproxen has not been extensively studied. Changes in serum albumin concentration and fluctuations in severity of disease can alter the pharmacokinetics of highly bound drugs. A case report of a middle-aged patient with rheumatoid arthritis suggests that total serum concentrations are much higher in the remission phase compared with the active phase of rheumatoid arthritis.^[31] The opposite is true for unbound serum naproxen concentrations, where the peak values are significantly higher in the active phase compared with values after 8 months of therapy. At the time of active rheumatic disease, a higher unbound naproxen concentration and an increased oral clearance results in a smaller AUC based on total concentrations.

Hypoalbuminaemia in patients with active rheumatoid arthritis leads to the saturation of protein binding at lower total naproxen concentrations. Upon remission, the serum albumin concentration rises from 25 g/L to 41 g/L, resulting in a 30 to 40% decrease in the volume of distribution (V_d) and clearance. The association constant between naproxen and albumin in remission and active disease shows increased binding during remission, which suggests that albumin ligand binding is affected by disease activity. There is no significant change in the renal excretion of conjugated naproxen or desmethylnaproxen. In addition, it appears that disease states such as rheumatoid arthritis affect the capacity of the liver to metabolise napro-

xen, possibly because of the effect of inflammatory mediators, hepatic uptake of unbound drug or modulation of intrahepatic processes.^[31] The disease-related changes of naproxen pharmacokinetics described in the original case report were later confirmed in a small study of 6 patients with rheumatoid arthritis.^[108]

The influence of alcoholic cirrhosis on the hepatic uptake processes in humans shows a quantitatively similar loss of unbound naproxen clearance similar to that in chronic arthropathies.^[28] The clinical sequelae of higher unbound naproxen concentrations for either effectiveness or toxicity has not been determined.

Patients with neoplastic hypoproteinaemia also demonstrate a significantly reduced maximal concentration of naproxen when compared with healthy volunteers; however, in this case it appears to be a consequence of a 45 to 55% reduction in oral bioavailability.^[83]

Although drug absorption may be delayed in migraine attacks, there does not appear to be an effect on the clinical effectiveness or pharmacokinetics of naproxen, as no differences in bioavailability during and between migraine attacks was evident.^[5]

The course of diabetes mellitus may cause a vasculopathy of capillaries with calcification, leading to capillary microangiopathy which, in turn, may affect the intestinal epithelium and the pharmacokinetics of xenobiotics. The pharmacokinetics of naproxen in patients with diabetic microangiopathy show a reduction in the fraction of dose absorbed. Furthermore, the glomerular impairment of some patients leads to a decrease in the elimination rate constant.^[17]

In addition, disease states such as diabetes mellitus, acute myocardial infarction and hyperthyroidism are linked with increased serum concentrations of free fatty acids. This could potentially lead to an increase in the free fraction of naproxen, which may increase the distribution into tissues. The *in vitro* displacement of naproxen from albumin binding sites by palmitic acid demonstrates

an increase in free naproxen with increasing concentration of fatty acid.^[78]

As naproxen undergoes significant hepatic metabolism, there may be important pharmacokinetic variations in patients with hepatic disorders (e.g. hepatitis, cholestasis, cirrhosis and ascites). Serum albumin, globulin, and total protein decrease in patients with hepatic disease, which tends to increase the free fraction of naproxen. The pharmacokinetics of naproxen in patients diagnosed with various hepatic and biliary disorders with underlying cholestasis show a significant delay in absorption after oral administration of a single 250mg dose. In the majority of these patients, elimination is clearly diminished due to a decrease in metabolic capacity. Unfortunately, the degree of plasma protein binding was not determined in these patients.^[19]

Plasma protein binding is reduced by 60% in alcoholic liver cirrhosis.^[28] Patients with hepatic impairment, specifically with Laennec's cirrhosis and alcoholic cirrhosis, are also found to possess a diminished intrinsic clearance of naproxen, suggesting that both conjugation and demethylation are affected.^[28,82] Oral clearance of naproxen is reduced after a single dose in alcoholic liver cirrhosis when compared with a healthy controls group; however, this difference is not significant at steady-state.

There is a significant negative correlation between serum bilirubin concentration and the serum protein binding of naproxen. Bilirubin, however, is not exclusively responsible for reduced naproxen binding, as *in vitro* studies fail to show binding changes upon the addition of bilirubin to the media.^[28,82]

2.3 The Influence of Age on Naproxen Pharmacokinetics

Therapeutic regimens in paediatric patients are generally based on the extrapolation of pharmacokinetic data in adults. The single and multiple dose pharmacokinetics of naproxen in young patients with rheumatic disorders suggest no significant difference in peak plasma concentrations and Vd

between adults and children.^[13,60,113,114] An initial study^[52] suggests that there are no significant differences between pharmacokinetic parameters in febrile adults and children. However, a later study^[60] suggests that compared with adults, children aged 8 to 14 years appear to eliminate naproxen more rapidly and, therefore, some children may require more frequent doses to maintain a clinical response.

It appears that renal clearance of naproxen is significantly decreased in the elderly. However, renal clearance averages only 10% of CL_{TB} and is only a minor pathway of drug removal in comparison to metabolism. In a study of 629 patients with osteoarthritis given naproxen 750 mg/day, after 4 weeks of therapy there was a significant increase (20%) in plasma concentrations which correlated with increasing age in females (with samples taken 3 and 12 hours post-dose).^[106] In another study,^[30] AUC, mean bound, and mean unbound trough concentrations were higher in elderly patients with osteoarthritis when compared to middle-aged patients, with a corresponding reduction in clearance.

In single and multiple dose studies with oral naproxen 375mg twice daily in healthy young and elderly male volunteers,^[27] the mean steady-state plasma concentrations were indistinguishable. However, the unbound naproxen fraction was doubled in the elderly males, along with a 50% decrease in intrinsic clearance, possibly because of the loss of hepatic and renal function as well as an impaired ability to eliminate urinary excretion of ester conjugates.^[27] A significant decrease in serum albumin in elderly patients explains the lower C_{max} , smaller AUC, and larger Vd/F seen in this study.

Naproxen binding affinity to albumin is also significantly reduced in the elderly. Other proteins may be partly responsible, or the nature of albumin might be altered with age. Diminished renal or hepatic function and uptake processes or both in elderly individuals probably allow accumulation of higher levels of endogenous compounds competing for or otherwise inhibiting naproxen binding which leads to an increase in serum unbound naproxen.

A follow-up study of naproxen 500mg twice daily in young healthy adults and elderly patients also demonstrated higher unbound fractions, higher peak and trough unbound concentrations, and a 40% reduction in unbound clearance in elderly patients.^[45] After a single 1000mg dose there were no pharmacokinetic differences between young volunteers and elderly patients with rheumatism.^[41] After 500mg twice daily, the trough concentrations were higher in young volunteers when compared with elderly patients with rheumatism, which corresponds to higher unbound trough concentrations in the elderly. There is evidence of an increase in naproxen free fraction, an inverse correlation between serum albumin and free fraction, and a 37% reduction of intrinsic clearance in elderly patients.^[41]

One study^[41] shows that there are no significant age group differences for naproxen 375mg or 750mg twice daily doses in terms of $C_{\max}$ or 12 hour AUCs. Although the terminal plasma $t_{1/2}$ was longer in the elderly, the authors concluded that advanced age does not alter naproxen pharmacokinetics.^[41] These data differ from the report of Upton et al.,^[27] although the participants in this study had a mean creatinine clearance of 2.87 L/h, which is considerably below normal values and far lower than in the Cohen and Basch study.^[40]

In addition, Upton et al.^[27] reported that the mean steady-state plasma concentrations of naproxen were indistinguishable between elderly and young healthy individuals, but the elderly generated twice the mean steady-state unbound plasma concentrations.

3. Drug Interactions

3.1 Effect of Other Drugs on the Pharmacokinetics of Naproxen

The clinical relevance of NSAID-drug interactions has been well described.^[115] There is sparse information regarding the effects of other xenobiotics on the pharmacokinetics of naproxen. Naproxen and probenecid have been used simultaneously in the treatment of chronic gouty arthritis. As naproxen and its metabolites are primarily ex-

creted in urine, probenecid alters the kinetics of naproxen if used concomitantly. The plasma $t_{1/2}$, AUC, and drug concentration at steady-state (C^{ss}) are significantly greater when probenecid is administered with naproxen, although the rate and extent of absorption are not affected.^[16]

Urinary excretion of conjugated and unconjugated naproxen was studied in the presence and absence of probenecid in healthy male volunteers.^[16,116] Urinary excretion of conjugated and unconjugated naproxen decreases, while urinary excretion of conjugated and unconjugated 6-DMN increases, in the presence of probenecid. Inhibition of glucuronide formation may be the result of competition for conjugative processes, as a larger percentage of both drugs are eliminated from plasma by conjugation.

Renal clearance of naproxen administered alone is 14.28 L/h (twice the glomerular filtration rate) and is only 2.16 L/h when naproxen and probenecid are administered concomitantly. The inhibition of renal clearance by probenecid supports the assertion that naproxen is actively secreted by the renal tubules.^[15] As the concomitant administration of probenecid increases the plasma concentration of naproxen, enhanced pharmacodynamic effects can be expected when these 2 drugs are combined.

Combinations of NSAIDs are inadvisable, and even contra-indicated in some countries. It has been shown that concurrent administration of 2 NSAIDs resulted in an increased risk of major gastrointestinal complications.^[117,118] Aspirin (acetylsalicylic acid), when given concomitantly with naproxen, causes a small but significant decrease of naproxen plasma concentrations and a 15% reduction in AUC. This effect is caused by the displacement of naproxen from protein binding sites and a transient increase in renal clearance of naproxen or its 6-DMN metabolite.^[119] This may be a concern because of the potential for self-administration of aspirin by patients already receiving naproxen.

Combinations of NSAIDs are sometimes used in the treatment of chronic arthropathies. The co-administration of the NSAID diflunisal and napro-

xen show no significant pharmacokinetic effect.^[120] However, co-administration of choline magnesium trisalicylate 45 mg/kg/day with naproxen 1500 mg/day for 1 month led to a 26% decrease in the naproxen C^{ss} with a 56% increase in naproxen clearance.^[121,122]

It is sometimes necessary to give NSAIDs to patients on anticoagulant therapy. The mean C^{ss} of naproxen with a single dose of warfarin shows a small but significant decrease in naproxen concentrations.^[123] The serum free fraction concentrations of naproxen are lower with continued administration of warfarin when compared with healthy individuals not taking warfarin.^[83] These results are consistent with the findings that warfarin can cause a concentration-dependent increase in the serum protein binding of naproxen *in vitro*.^[123]

Antacids and H_2 histamine receptor blockers are sometimes co-administered with NSAIDs. Although neither antacids nor H_2 antagonists are effective in preventing NSAID-induced gastric ulcers, they may exert beneficial effects on dyspepsia symptoms related to NSAID therapy.^[118] Cimetidine is known to inhibit phase I *N*-dealkylation and may, therefore, affect the *O*-demethylation of naproxen. The urinary recoveries, however, of parent drug and metabolites are similar in all patients treated with either cimetidine, ranitidine, or famotidine. Cimetidine has no effect on *O*-dealkylation.^[72,73] It appears, however, that cimetidine, ranitidine and famotidine all decrease the serum elimination $t_{1/2}$ and V_d of naproxen, corresponding to an increase in naproxen oral clearance. The mechanism(s) of these findings are unknown, but it has been speculated that the inhibition of gastric acid secretion, which affects duodenal and ileal pH, leads to an acceleration of enterohepatic recycling because of the enhanced hydrolysis of biliary excreted naproxen acylglucuronide. However, there are no available pharmacokinetic data definitively confirming biliary excretion of naproxen and this hypothesis. The clinical significance of this interaction is speculative, but could possibly affect the duration of pharmacodynamic effects.

Antacids containing magnesium oxide, aluminum hydroxide and, to a lesser extent, magnesium carbonate appear to interfere with naproxen absorption through the formation of poorly diffusible complexes.^[71] Co-administration of naproxen with commonly used antacids containing aluminum-magnesium hydroxides and simethicone has no effect on the rate or extent of absorption in single dose or multiple dose pharmacokinetics in healthy volunteers.^[21]

The influence of sucralfate on the pharmacokinetic parameters of naproxen show a decrease in C_{max} and increase in t_{max} without any effect on bioavailability.^[32] However, another study^[33] does not show any significant pharmacokinetic differences between the administration of naproxen alone or with sucralfate. However, when compared with the administration of naproxen alone, a significantly lower C_{max} and longer t_{max} is attained with repeated administration of naproxen in combination with sucralfate.^[52]

In addition, a chewable sucralfate tablet reduces C_{max} and delays t_{max} due to a decrease in the rate of absorption, which is likely to be a consequence of a delay in gastric emptying. However, there is no difference in relative bioavailability when compared with administration of naproxen alone.^[48] The concomitant administration of sulglycotide with naproxen does not show any discernible differences in naproxen pharmacokinetic parameters.^[37]

Rheumatic disease may also be associated with type II hyperlipidaemias, for which patients may receive cholestyramine. Concomitant administration of cholestyramine with naproxen causes a delay in the systemic availability of naproxen, with no other pharmacokinetic effects.^[24]

NSAIDs are often co-administered with disease modifying antirheumatic drugs, such as methotrexate, for the management of patients with rheumatoid arthritis (also see section 3.2). In a small study of 9 patients, methotrexate caused a >30% increase in the clearance of naproxen (2 patients) or AUC (3 patients) as well as a >30% decrease in the clearance (2 patients) or AUC (2 patients) of

naproxen. However, this study does not allow any conclusion to be drawn regarding a methotrexate-naproxen interaction.^[124]

Inhibitors of 5-lipoxygenase may be concomitantly prescribed for asthmatic patients with inflammatory disease states who may already be receiving NSAIDs. It is, therefore, important to assess the effect of coadministration of 5-lipoxygenase inhibitors on the pharmacokinetics of NSAIDs. The 5-lipoxygenase inhibitor zileuton had no effect on the plasma concentration-time curve compared to administration of naproxen administered alone. However, there was a statistically significant increase in AUC (16%) and naproxen concentrations in the elimination phase upon zileuton coadministration when compared with naproxen alone. These differences were too small to be clinically significant.^[61]

Lastly, there is a report suggesting bioequivalency of a formulation of naproxen sodium plus pseudoephedrine in capsules for alleviation of the symptoms caused by rhinovirus (i.e. headache, nasal congestion and fever) compared with the administration of naproxen alone.^[125]

3.2 Effect of Naproxen on the Pharmacokinetics of Other Drugs

Simultaneous administration of naproxen and aspirin show a slight decrease of 2.6% in the salicylate AUC, with the total quantity of salicylates recovered in urine unchanged.^[119] Following coadministration of choline magnesium trisalicylate 45 mg/kg/day and naproxen 1500 mg/day for 1 month, the plasma salicylate concentrations were minimally affected, with clinical effectiveness not being significantly improved, although toxic reactions were more prevalent.^[121,122]

Concomitant naproxen administration with tolbutamide in maturity onset diabetes shows no significant difference in blood glucose concentrations nor any demonstrable effect on serum tolbutamide concentrations.^[126]

The effect of naproxen on the pharmacokinetics of free and total plasma concentrations of valproic acid (valproate sodium) demonstrates a slight, but

significant, decrease in total plasma valproic acid and AUC, corresponding to an increase in clearance of the total drug. Naproxen moderately displaces valproic acid from protein binding sites, but free valproic acid concentrations, while elevated, are not significantly changed. Therefore, no change in the clearance of the drug is evident.^[127] The magnitude of this interaction does not appear to be clinically relevant.

A subsequent report suggests significant displacement of valproic acid from protein binding sites when the study was conducted using a normal serum pool. In a uraemic serum pool, no significant displacement of valproic acid was evident even at high naproxen concentrations, suggesting that uraemic serum may contain an inhibitor that blocks this displacement interaction.^[128] In addition, statistically significant displacement of carbamazepine from protein binding sites was evident in normal and uraemic serum.

Twice daily administration of naproxen 375mg causes a small, but significant, increase in the free fraction of warfarin in serum, but has no effect on the pharmacokinetics and anticoagulant activity of a single large dose (50mg) of warfarin in healthy adults.^[123] Patients controlled on long term warfarin show no difference in free and total C_{ss} of warfarin in serum when given naproxen, despite a statistically significant increase of warfarin free fraction. Naproxen is highly protein bound and has been shown to displace warfarin from binding sites in plasma.^[83] This is consistent with *in vitro* studies demonstrating that the free fraction of warfarin in serum increases linearly with increasing naproxen concentrations, which may cause an increase in warfarin CL_{TB} . A transient increase in anticoagulant activity may occur due to this displacement, although no such phenomena has been demonstrated in humans.^[129] At a constant daily dosage of warfarin, blood coagulation parameters, as assessed by prothrombin times, do not show any difference after administration of naproxen.^[83]

Patients with human immunodeficiency virus (HIV) are often administered NSAIDs for relief of nonspecific fever and musculoskeletal pain. The

pharmacokinetics of zidovudine do not appear to be altered with co-administration of naproxen in patients with HIV.^[130,131] However, naproxen significantly decreases the AUC of the glucuronidated metabolite of zidovudine. This may reflect an increase in zidovudine clearance by other metabolites, a decrease in the formation of glucuronidated metabolite of zidovudine, and/or an increase in the clearance of the glucuronidated metabolite of zidovudine. A decrease in formation of the glucuronidated metabolite of zidovudine is consistent with *in vitro* studies where naproxen inhibits zidovudine glucuronidation.^[132] The clinical significance of this interaction remains unclear.

NSAIDs are often co-administered with disease modifying antirheumatic drugs, such as methotrexate, for the management of patients with rheumatoid arthritis. A severe, and often fatal, interaction between naproxen and methotrexate has been documented.^[133] Whether NSAID-methotrexate interactions play a major role in methotrexate toxicity in patients with rheumatoid arthritis remains unclear. This toxic interaction may be due to displacement of methotrexate from plasma proteins, altered hepatic metabolism of methotrexate, altered renal prostaglandin synthesis resulting in a decrease in glomerular filtration rate and methotrexate clearance, and/or competition for renal tubular secretion between naproxen and methotrexate.^[133] However, the exact mechanism of this interaction still remains a matter of speculation.

It has been suggested that, as the 7-hydroxy metabolite of methotrexate and naproxen are highly protein bound, displacement of 7-hydroxy-methotrexate by naproxen may increase the concentration of the 7-hydroxy-MTX eligible for renal filtration, which could promote renal damage. Indeed, naproxen reduces the binding of 7-hydroxy-methotrexate in a concentration-dependent fashion *in vitro*. After ingestion of naproxen 1000mg, the percentage of unbound 7-hydroxy-methotrexate in sera from volunteers increases 2- to 3-fold, which is positively correlated with naproxen concentrations.^[134] Several studies of methotrexate kinetic

disposition with co-administered naproxen have been published with conflicting results.

A decrease in oral clearance of methotrexate with concomitant administration of naproxen to adults with rheumatoid arthritis has been reported, with a trend towards reduced renal clearance.^[135] Conversely, no alterations in methotrexate kinetics in rheumatoid arthritis patients treated with naproxen have been found.^[124,135-137] There are, however, apparent methotrexate-naproxen interactions in individual patients,^[136] with variability in the renal clearance of methotrexate.^[133,135] Moreover, an alteration in methotrexate Vd/F is evident after naproxen administration.^[124]

The small number of patients and high variability limits sensitivity for detection of these differences, which may be clinically significant for some patients. The significance of this interaction may increase if high dose methotrexate is being used, as in the treatment of cancer, as opposed to low dose therapy used in rheumatic diseases. It may be hypothesised that an interaction between naproxen and low dose methotrexate may also enhance methotrexate toxicity.^[138]

Naproxen may also inhibit the renal clearance of lithium, which may cause an increase in serum lithium concentrations and overdose.^[139] Careful monitoring and titration of lithium dosage is, therefore, required in patients who receive naproxen and lithium concurrently. This is a concern for psychiatric outpatients with the potential for self-administration of over-the-counter NSAIDs.

A report suggests bioequivalency of a formulation of naproxen sodium plus pseudoephedrine in capsules as compared to the administration of pseudoephedrine alone.^[125] Finally, the concomitant administration of naproxen had no effect on the pharmacokinetics of the 5-lipoxygenase inhibitor zileuton.^[61]

4. Conclusions

Naproxen is an effective NSAID which is now available in the US as an over-the-counter medication. Naproxen shows dose-dependent pharmacokinetics at doses greater than 500mg, attributable

to the saturation of protein binding sites. Relationships between the anti-inflammatory effect, analgesic effect, and plasma concentrations of the drug have been established. Future research should try to delineate the role of enterohepatic recirculation and the therapeutic and toxicological relevance of nonlinearity in the pharmacokinetic data.

Since many patients may not respond to a certain NSAID, and toxicological profiles between NSAIDs may differ, there is a continued need for therapeutic alternatives. Naproxen appears to be an effective, well tolerated and suitable NSAID for a variety of indications.

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