DRUG DISPOSITION

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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 dysmennorhoea.[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 (pKa = 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 × 7 D	55.5	NR	1155	
		250mg bid & PB 500mg bid × 7 D	67.7	NR	1926	
12	NR	**Sequence 2**				16
		250mg bid × 7 D	64.5	NR	1604	
		250mg bid & PB 500mg bid × 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 × 5 D	66.2	4.5	1156	25
		250mg bid × 5 D	74.9	1.4	1248	
11	[21-51]	500mg EC bid × 5D	113.5	4.7	984	25
		500mg bid × 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 84.2	2.2 4.1	1624 1609	32
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 99.3	1.8 2.3	1761.0 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	

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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	

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