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Clinical Pharmacokinetics of Meloxicam

A Cyclo-Oxygenase-2 Preferential Nonsteroidal Anti-Inflammatory Drug

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Abstract

Meloxicam [4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide] is a nonsteroidal anti-inflammatory drug (NSAID) of the oxicam class which shows preferential inhibition of cyclo-oxygenase-2.

Meloxicam has a plasma half-life of approximately 20 hours, making it convenient for once-daily administration. Meloxicam is eliminated after biotransformation to 4 pharmacologically inactive metabolites, which are excreted in urine and faeces. Meloxicam and its metabolites bind extensively to plasma albumin. Substantial concentrations of meloxicam are attained in synovial fluid, the proposed site of action in chronic inflammatory arthropathies.

Neither moderate renal nor hepatic insufficiency significantly alter the pharmacokinetics of meloxicam. Dosage adjustment is not required in the elderly. Drug-drug interaction studies are available for some commonly co-prescribed medications. Concentration-dependent therapeutic and toxicological effects have yet to be extensively elucidated for this NSAID.

Meloxicam [4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-*2H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide] is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits prostaglandin synthesis via relatively selective inhibition of cyclo-oxygenase-2 (COX-2), imparting analgesic, antipyretic and anti-inflammatory properties.[1] Meloxicam is a zwitterion in the pH range 1 to 4 and an anion above pH 4.[2,3]

Meloxicam is currently marketed in more than 30 countries worldwide.[4] Therapeutic doses of meloxicam have proven to be equally effective compared with other commonly used NSAIDs in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and other rheumatological conditions.[5] The good tolerability profile of meloxicam in basic, clinical and epidemiological studies has been attributed to its COX-2 selectivity.

General review articles are available describing the pharmacological properties, therapeutic uses, selectivity for COX-2 and pharmacokinetics of meloxicam.[5,6] In this article, the clinical pharmacokinetics of meloxicam and its metabolites are updated and reviewed.

1. Pharmacokinetic Properties

1.1 Absorption

Meloxicam is most often administered orally, with conventional regular-release tablets being commercially available. Meloxicam has also been administered as an intravenous or intramuscular solution and as a rectal suppository. Tables I and II show the pharmacokinetic properties of meloxicam when administered in different formulations and in different disease states.

Parenteral, oral or rectal doses of meloxicam are almost completely absorbed with an absolute bioavailability of 89%.[7,8] There were no detectable differences in bioavailability when meloxicam was given following food.[9] Maximum plasma concentrations (C_{max}) were achieved 9 to 11 hours (t_{max}) after 30mg of meloxicam was given orally.[9] Rectal administration produced similar t_{max} values.[8] In a crossover study, 30mg of ^{14}C-labelled meloxicam was given to 4 healthy men as a 15-minute intravenous infusion and as an oral solution. After intravenous administration, t_{max} was 1 to 1.5 hours[8] with an absolute median bioavailability of 97%. The area under the concentration-time curve (AUC) is proportional to dose in the range 7.5 to 30mg.[7]

Because of its long half-life (22 to 24 hours), steady-state blood concentrations of meloxicam are not achieved for 3 to 4 days with oral administration of meloxicam. Assessment of clinical utility should account for this delay. Tablets, capsules and rectal suppositories are bioequivalent.[8]

For situations requiring rapid analgesia (such as acute mechanical lower back pain, sciatica and acute flares of osteoarthritis) a parenteral form of meloxicam has been developed. Meloxicam is rapidly and completely absorbed after intramuscular administration with a mean absolute bioavailability of 102%. In 32 non-obese healthy adults, intravenous infusion of meloxicam 15mg over 1 minute resulted in mean plasma concentrations 3 minutes after the start of intravenous injection ($C_{3\ min}$) of 2.99 ± 0.75 mg/L, higher than the mean peak concentrations (C_{max}) observed after intramuscular administration of the same dose (1.62 ± 0.20 mg/L).[10]

1.2 Distribution

The apparent volume of distribution (Vd/F) determined after oral administration is between 10 and 15L in humans (0.1 to 0.2 L/kg), approximates to the extracellular fluid volume, and is consistent with that of other similar oxicams.[11]

Meloxicam is strongly bound to serum albumin (>99%) and thus has a small mean steady-state volume of distribution (V_{ss}) of 0.2 L/kg after intravenous administration.[11] Since meloxicam is essentially confined to the actual distribution volume of albumin, its tissue binding is far less important than its plasma binding in determining V_{ss}.

The synovium is the proposed primary site of action for NSAIDs in chronic inflammatory arthropathies. Meloxicam readily penetrates into

Table I. Absorption characteristics of meloxicam. All values refer to oral formulations administered as single doses to healthy adults, except where indicated

Reference	No. and type of patients	Age (y)[a]	Dose and conditions	C_{max} (mg/L)	t_{max} (h)	AUC (mg/L • h)
Busch et al.[9]	6	NR	30mg orally after 12h fasting, standard breakfast 2h later	1.5	10.7	65.0
			30mg orally 10 min after standard breakfast	1.4	9.7	71.0
Türck et al.[7]	18	NR	7.5mg	0.881	NR	13.9
			15mg	1.92	NR	30.0
Busch et al.[29]	12	(27-50)	30mg IV	NR	NR	71.8
			Cholestyramine 4g in 200ml water on the evening before the trial and then tid × 4 days, then meloxicam 30mg 1h before breakfast	NR	NR	47.4
Schmid et al.[11]	4	42	[^{14}C]Meloxicam 30mg IV over 15 min	5.35	NR	45.4
			[^{14}C]Meloxicam 30mg oral solution followed by 150ml water	3.09	NR	47.7
Busch et al.[28]	9	36 (26-53)	30mg	1.79	7.9	60.2
			30mg + aspirin 1g tid × 4 days	2.25	6.2	71.8
			30mg + cimetidine 200mg qid beginning the day before meloxicam and continuing until 4 days after meloxicam	1.70	9.2	69.5
	6	38 (27-48)	30mg with 200ml water	1.51	10.7	66.5
			30mg + Maalox-70™ [600mg $Mg(OH)_2$/900mg $Al(OH)_3$] qid × 4 days	1.45	10.3	72.1
Narjes et al.[10]	32	(23-52)	5mg IM	0.55	1.0	10.9
			10mg IM	1.10	0.5	21.9
			20mg IM	2.81	0.9	52.2
			30mg IM	3.54	0.9	62.1
	12	(21-53)	15mg IV	2.99	NR	30.6
Türck et al.[21]	10 ESRD	(22-63)	15mg	0.531	2.5	12.6
	10 controls	NR	15mg	0.901	7.0	39.3
Boulton-Jones et al.[19]	11 normal renal function[b]	43	15 mg/day × 9 days	3.2	5	55
	13 mild renal impairment[c]	51	15 mg/day × 9 days	3.1	4	55
	13 moderate renal impairment[d]	58	15 mg/day × 9 days	2.1	4	34
Türck et al.[8]	12	35 (23-47)	30mg capsule	1.72	NR	67.5
			30mg IV bolus	NR	NR	76.9
	24	37 (26-50)	15mg suppository	0.952	5.0	24.0

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perivascular spaces, including the synovial fluid. In 36 patients with arthropathies, synovial fluid concentrations of meloxicam were determined after a 60mg oral loading dose followed by either 2, 4 or 6 daily 30mg oral doses (n = 12 in each group). The mean [± standard deviation (SD)] synovial fluid concentrations of meloxicam were 49 ± 18%, 49 ± 23% and 40 ± 5% of corresponding plasma concentrations on days 2, 4 and 6 respectively; there was a statistically significant difference between days 4 and 6.[12] In a second study, 4 patients were loaded with meloxicam 60mg followed by 30 mg/day for 1 week; plasma and synovial fluid meloxicam concentrations were determined on day 7 at 0, 1, 5 and 24 hours after administration. The mean synovial fluid concentrations were 51 ± 14%, 57 ± 26%, 47 ± 10%, and 52 ± 10% of the corresponding mean plasma concentrations at 0, 1, 5 and 24 hours, respectively.[12] *In summary*, synovial fluid concentrations of meloxicam are approximately half of the corresponding plasma concentrations.

There has been considerable recent interest in the development of topical NSAIDs. When applied topically, these drugs are formulated to penetrate the skin in sufficient amounts to deliver therapeutic doses to underlying joints and muscles. Topical delivery might allow local therapeutic efficacy while minimising systemic toxicity. Currently, there are no published studies or information available concerning synovial fluid meloxicam concentrations after cutaneous application.

NSAIDs may provide relief of neuropathic pain, such as sciatica. Neural penetration has been described for several oxicam NSAIDs in preliminary animal studies.[13] Following rapid carotid infusion into rats, 19% of administered radiolabelled meloxicam was recovered from brain homogenates following decapitation 5 sec after injection. Intracellular meloxicam accounted for 23% of the total measured radioactivity. Meloxicam had similar penetration properties compared with other oxicams.

Table I. Contd

Reference	No. and type of patients	Age (y)[a]	Dose and conditions	C_{max} (mg/L)	t_{max} (h)	AUC (mg/L • h)
			15mg capsule	0.933	6.0	28.8
	24	35 (23-50)	15mg suppository od × 7 days	1.72	5.4	29.3
			15mg capsule od × 7 days	1.88	6.5	33.3
	24	35 (23-50)	15mg capsule od × 7 days	2.32	5.1	36.2
			15mg tablet od × 7 days	2.45	5.0	38.1
	18	33 (21-47)	7.5mg capsule od × 7 days	0.881	5.1	13.9
			15 mg capsule od × 7 days	1.92	5.6	22.2
			7.5mg tablet od × 7 days	1.05	4.9	15.4

a Mean age; range in parentheses.

b Creatine clearance >60 ml/min (3.6 L/h).

c Creatine clearance 41 to 60 ml/min (2.5 to 3.6 L/h).

d Creatinine clearance 20 to 40 ml/min (1.2 to 2.4 L/h).

AUC = area under the plasma concentration-time curve; **C_{max}** = peak plasma drug concentration; **ESRD** = end-stage renal disease; **IM** = intramuscular injection over 1 min; **IV** = intravenous; **NR** = not reported; **od** = once daily; **qid** = 4 times daily; **tid** = 3 times daily; **t_{max}** = time taken to achieve C_{max}.

Table II. Pharmacokinetic properties of meloxicam. All values refer to oral immediate release formulations administered as single doses to healthy adults, except where indicated

Reference	No. and type of patients	Age (y)[a]	Dose and conditions	$t_{1/2\beta}$ (h)	Vd/F (L/kg)[b]	CL/F (L/h/kg)[b]
Busch et al.[9]	6	NR	30mg orally after 12h fasting, standard breakfast 2h later	24.1	0.183	0.00756
			30mg orally 10 min after standard breakfast	22.9	0.171	0.00654
Busch et al.[29]	12	(27-50)	30mg IV	19.5	0.15[c]	0.00609[d]
			Cholestyramine 4g in 200ml water on the evening before the trial and then tid × 4 days, then meloxicam 30mg 1h before breakfast	12.7	0.14	0.00909
Schmid et al.[11]	4	42	[^{14}C]Meloxicam 30mg IV over 15 min	13.7	0.173[c]	0.0097[d]
			[^{14}C]Meloxicam 30mg oral solution followed by 150ml water	13.2	NR	NR
Busch et al.[28]	9	36 (26-53)	30mg	17.5	0.168	0.0068
			30mg + aspirin 1g tid × 4 days	16.9	0.141	0.0067
			30mg + cimetidine 200mg qid beginning the day before meloxicam and continuing until 4 days after meloxicam	19.5	0.174	0.0067
	6	38 (27-48)	30mg with 200ml water	24.3	0.217	0.0067
			30mg + Maalox-70™ [600mg $Mg(OH)_2$/900mg $Al(OH)_3$] qid × 4 days	25.3	0.2	0.0064
Narjes et al.[10]	32	(23-52)	5mg IM	18.4	NR	0.00668[d]
			10mg IM	22.1	NR	0.00695[d]
			20mg IM	16.8	NR	0.00585[d]
			30mg IM	16.9	NR	0.00696[d]
	12	(21-53)	15mg IV	15.3	NR	0.00741[d]
Türck et al.[21]	10 ESRD	(22-63)	15mg	14.4	0.351	0.017
	10 controls	NR	15mg	23.5	0.186	0.00546
Boulton-Jones et al.[19]	11 normal renal function[e]	43	15 mg/day × 9 days	21	0.119	0.0039
	13 mild renal impairment[f]	51	15 mg/day × 9 days	27	0.157	0.0039
	13 moderate renal impairment[g]	58	15 mg/day × 9 days	19	0.171	0.00626
Türck et al.[8]	12	35 (23-47)	30mg capsule	22.0	0.146	0.0055
			30mg IV bolus	20.0	0.179[c]	0.0063[d]
	24	37 (26-50)	15mg suppository	NR	0.174	0.0086
			15mg capsule	NR	0.179	0.0068
	24	35 (23-50)	15mg suppository od × 7 days	NR	0.13	0.0072
			15mg capsule od × 7 days	NR	0.122	0.0061

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1.3 Metabolism

Meloxicam is extensively metabolised in the liver to 4 pharmacologically inactive metabolites which are excreted in both urine and faeces (fig. 1).[11] Negligible amounts (<0.25%) of radiolabelled meloxicam are eliminated unchanged in urine, and only 1.6% of the parent compound is deposited in faeces. The main metabolites of meloxicam are independent of route of administration.

The 4 metabolites of meloxicam in urine account for 42.8% of an administered radioactive dose.[11] Oxidation of the 5-methyl group of the thiazolyl ring forms hydroxy (AF-UH 1 SE) and carboxylic acid (UH-AC 110 SE) metabolites. AF-UH 1 SE {2-[[(4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-yl)carbonyl]amino]-5-thiazolemet hanol *S,S*-dioxide} comprises approximately 18% and UH-AC 110 SE {2-[[(4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-yl)carbonyl] amino]-5-thiazolecarboxylic acid *S,S*-dioxide} approximately 30% of urinary metabolites. Oxidative cleavage of the benzothiazine ring yields 2 oxoacetic acid metabolites. DS-AC 2 SE [(5-methyl-2-thiazolyl)amino oxoacetic acid] comprises approximately 36%, and BI-BO 8032 NA {2-[(hydroxyacetyl)amino]-5-thiazolecarboxylic acid} approximately 11% of urinary metabolites.

Faecal and urinary metabolite distributions differed significantly. The UH-AC 110 SE metabolite comprised approximately 98% of faecal metabolites, with only traces of the remaining 3 metabolites being detected.[11] Metabolism *in vivo* and *in vitro* yields the same metabolites.

The cytochrome P450 (CYP) 2C subgroup of isoenzymes, possibly CYP2C9 or 2C8, appears to play a major role in oxidative metabolism of meloxicam.[11] These isoenzymes metabolise many drugs, such as other NSAIDs, warfarin and phenytoin. Drug-drug interactions are, therefore, possible. Human hepatocytes are capable of converting meloxicam to the 5-hydroxymethyl metabolite (AF-UH 1 SE) and then to the 5-carboxy metabolite (UH-AC 110 SE).[14] CYP2C9, and to a lesser extent CYP3A4, converts meloxicam to its

Table II. Contd

Reference	No. and type of patients	Age (y)[a]	Dose and conditions	$t_{1/2\beta}$ (h)	Vd/F (L/kg)[b]	CL/F (L/h/kg)[b]
	24	35 (23-50)	15mg capsule od × 7 days	NR	0.179	0.0058
			15mg tablet od × 7 days	NR	0.15	0.0055
	18	33 (21-47)	7.5mg capsule od × 7 days	20.4	0.23	0.0083
			15 mg capsule od × 7 days	22.2	0.24	0.0078
			7.5mg tablet od × 7 days	20.1	0.21	0.0074

a Mean age; range in parentheses.

b Estimate based on 70kg bodyweight.

c Volume of distribution reported.

d Clearance reported.

e Creatine clearance >60 ml/min (3.6 L/h).

f Creatine clearance 41 to 60 ml/min (2.5 to 3.6 L/h).

g Creatinine clearance 20 to 40 ml/min (1.2 to 2.4 L/h).

CL/F = apparent plasma clearance after oral administration; **ESRD** = end-stage renal disease; **IM** = intramuscular injection over 1 min; **IV** = intravenous; **NR** = not reported; **od** = once daily; **qid** = 4 times daily; **$t_{1/2\beta}$** = terminal elimination half-life; **tid** = 3 times daily; **Vd/F** = apparent volume of distribution after oral administration.

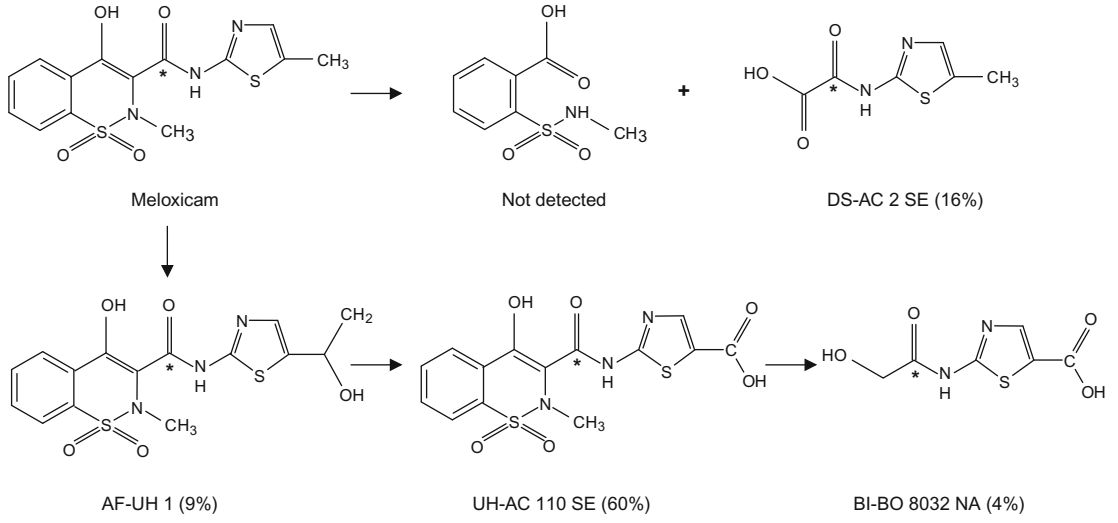

Fig. 1. The metabolism of meloxicam.[6]

5-hydroxymethyl metabolite. In human microsomes, meloxicam is an inhibitor of tolbutamide oxidation, sulfaphenazole inhibits meloxicam metabolism, and meloxicam is actively metabolised by recombinant CYP2C9, confirming the involvement of CYP2C9.[14] The involvement of CYP3A4 was demonstrated by inhibition of meloxicam metabolism by ketoconazole, a correlation between meloxicam metabolism and nifedipine oxidase activity, and metabolism of meloxicam by recombinant CYP3A4.[14]

1.4 Elimination

After administration of ^{14}C-labelled meloxicam, collected urine contained 42.8% of the administered dose of radioactivity.[11] Over 90% of the plasma radioactivity represented parent meloxicam. After both oral and intravenous administration, >50% of administered radioactivity was recovered within the first day of administration. Radioactivity in urine accounted for 45% of the dose after intravenous administration, and 43% after oral administration. Within 7 days, faecal radioactivity accounted for 49% of the dose after intravenous administration, and 47% after oral administration.[11]

The apparent oral clearance (CL/F) of meloxicam ranges from 0.42 to 0.7 L/h. The terminal elimination half-life ($t_{½\beta}$) of meloxicam in plasma ranges from 13 to 20 hours; the lower values are perhaps outliers.[11]

2. Implications of Pharmacokinetic Properties for Therapeutic Use

2.1 Dosage and Therapeutic Range

The usual recommended initial oral dosage of meloxicam for the treatment of chronic arthropathies is 15 to 30 mg/day. Meloxicam is a relatively slowly absorbed NSAID, with peak plasma concentrations attained after approximately 10 hours.[9] Clinical effects may occur less rapidly with meloxicam than with other NSAIDs that have more rapid absorption, although in general establishing relationships between plasma concentrations of NSAIDs, dosage regimens and clinical effects has been difficult. Intramuscular meloxicam relieved pain in acute sciatica more rapidly than did oral meloxicam.[15] The considerable variation reported in the t_{max} of meloxicam depending on route of

administration and the concomitant use of other drugs (see table II) complicates clinical use. Further studies addressing the effects of free meloxicam on inflammatory mediators and clinical efficacy are required to optimally guide therapy. There are likely to be tissue, plasma and urine concentration-effect relationships with meloxicam as seen with several other NSAIDs.[16]

The metabolites of meloxicam do not alter cyclooxygenase activity *in vitro* or *in vivo*. Meloxicam derivatives have neither anti-inflammatory nor analgesic activity in animal studies.[17] Although studies with meloxicam have not yet been performed, other NSAIDs have been preliminarily shown to reduce colon neoplasia and the degenerative effects of Alzheimer's disease. Consequently, meloxicam or its metabolites may possess novel pharmacological properties.

2.2 Effects of Disease and Age on the Pharmacokinetics of Meloxicam

Low extraction drugs have a low intrinsic clearance relative to hepatic blood flow; consequently, only unbound drug is available for hepatic clearance. Advanced age, hepatic dysfunction, chronic arthropathies, renal dysfunction and concomitant administration of other xenobiotics all may have the potential to affect plasma protein binding of meloxicam and alter the pharmacokinetic and pharmacodynamic properties of the drug.

Drug excretion may be prolonged in old age, and extended administration of compounds with long half-lives may result in elevated plasma concentrations in the elderly. The pharmacokinetics of meloxicam do not appear to be appreciably modified in older (>65 years) compared with younger (<55 years) men.[18] Older women (>65 years) had 59% increases in plasma meloxicam concentrations compared with younger women (<55 years), but adverse effects were similar in both groups.[18] Although no changes in dosage were recommended, the clinical implications of these gender differences warrant further study.

Therapeutic regimens in children are generally based on extrapolations from adult pharmacokinetics. There appear to be no studies of meloxicam pharmacokinetics in children.

Many patients with rheumatoid arthritis have some degree of renal impairment, and elderly patients with poor renal function are especially prone to NSAID-induced azotaemia. There were no significant differences in meloxicam pharmacokinetics between individuals with normal [creatinine clearance (CL_{CR}) >60 ml/min (>3.6 L/h)] and mildly impaired [CL_{CR} 41 to 60 ml/min (2.5 to 3.6 L/h)] renal function.[19] Similar results were noted in a 28-day trial of meloxicam 15 mg/day in patients with mild azotaemia.[20] In another study, patients with moderate azotaemia [CL_{CR} 20 to 40 ml/min (1.2 to 2.4 L/h)] had lower total plasma meloxicam concentrations and consequently higher plasma clearances compared with healthy individuals.[19] Meloxicam pharmacokinetics after a single oral 15mg capsule were compared between 12 patients with end-stage renal disease (ESRD) and age-matched controls. Patients with ESRD had increased free fractions of meloxicam (approx. 0.9% compared with 0.3% in controls), but greater relative total clearances (approx. 211% compared with controls), so that no accumulation of meloxicam occurred. Meloxicam was not dialysable. For patients with moderate to end-stage renal failure, a lower meloxicam dosage (e.g. 7.5 mg/day) may be prudent given higher C_{max} values.[21]

The pharmacokinetics of meloxicam were also similar in patients with cirrhosis and healthy controls.[22]

3. Pharmacokinetic Drug Interactions

There is little information on the effects of other drugs on the pharmacokinetics of meloxicam. Antacids or histamine (H_2) receptor antagonists are used for symptomatic relief of NSAID-induced ulcerations and gastritis. There were no changes in the C_{max}, t_{max}, half-life or AUC of meloxicam when it was given with either antacids or cimetidine.[28]

NSAIDs may potentiate the effect of oral anticoagulants by displacing them from protein binding sites or altering their metabolism. In a study of the potential interaction between meloxicam and

warfarin,[23] daily administration of meloxicam 15mg for 7 days to steady-state concentrations was initiated in healthy volunteers. Warfarin was then started to achieve stable increases in prothrombin times while continuing meloxicam. Finally, meloxicam was withdrawn and warfarin continued. Prothrombin times were not significantly altered by concomitant meloxicam treatment. The protein binding of warfarin was not affected by meloxicam. Meloxicam did not affect the pharmacokinetics of *R*-warfarin; however, for *S*-warfarin, slightly higher (+11%) plasma concentrations and steady-state AUC were observed. Meloxicam and *S*-warfarin are metabolised by the same CYP isoenzyme. Careful monitoring of prothrombin time should be undertaken if meloxicam is administered concomitantly with warfarin.[23]

Digoxin is often administered for the treatment of cardiac disease in patients with rheumatoid arthritis who are also receiving NSAIDs. In 12 healthy volunteers administered multiple doses of meloxicam and β-acetyl-digoxin in divided doses over 8 days, steady-state plasma digoxin concentrations and AUC values did not change. The $t_{½\beta}$ of digoxin was reduced by 12%, but this change was considered too small to warrant alteration of the dosage of digoxin.[24] There appear to be no studies of cardiac patients receiving digoxin and meloxicam; consequently, careful clinical and biochemical follow-up would be prudent in such patients.

Attenuation by NSAIDs of the hypotensive response to several antihypertensive drugs, including diuretics, has been reported. In a study of the interaction of meloxicam and furosemide (frusemide),[25] 3 daily 40mg doses of furosemide were given to 15 healthy volunteers followed by 10 daily 15mg doses of meloxicam; finally, both meloxicam and furosemide at these dosages were given for 3 days. Small reductions in furosemide-induced natriuresis were noted; no changes in the pharmacokinetics of either meloxicam or furosemide were observed. In 19 patients with moderate compensated heart failure (New York Heart Association grade II to III) on furosemide, a 21-day crossover trial of meloxicam versus placebo (7 days on each therapy with a 7-day wash-out phase) revealed only small increases in furosemide C_{max} and urinary elimination with co-administered meloxicam. These increases were not thought to be clinically significant.[26]

NSAIDs are often co-administered with disease-modifying antirheumatic drugs such as methotrexate in patients with rheumatoid arthritis. Fourteen patients with rheumatoid arthritis were given intravenous methotrexate 15mg before and after 7 daily 15mg oral doses of meloxicam. No differences in methotrexate pharmacokinetics or adverse effects were noted with or without meloxicam.[27]

The self-administration of aspirin (acetylsalicylic acid) by patients already receiving meloxicam may be cause for concern. Concurrent administration of aspirin 4 g/day increased C_{max} for meloxicam by approximately 25% and AUC by approximately 10%.[28] Although these increases were judged to be clinically insignificant, properly powered adverse effect surveillance was not reported.

Patients with rheumatoid arthritis may have dyslipidaemias, for which they may receive cholestyramine. Absorption of NSAIDs can be impaired if they bind to cholestyramine in the proximal gastrointestinal tract. Before and after taking oral cholestyramine resin 3 times daily, 12 healthy male volunteers were given intravenous meloxicam 15mg. Cholestyramine increased the clearance of meloxicam by approximately 50% and reduced its $t_{½\beta}$ from 19 to 12 hours, resulting in a 40% reduction in mean residence time; Vd remained unchanged. Together, these observations suggest that meloxicam undergoes enterohepatic recirculation.[29] Further studies are required to determine the extent of biliary or enteroenteric secretion of meloxicam.

4. Preferential Inhibition of Cyclo-Oxygenase-2

Meloxicam preferentially, but not selectively, inhibits COX-2. Most marketed NSAIDs can be

considered nonselective for the cyclo-oxygenase isoenzymes. For example, meloxicam and nimesulide can be classified as COX-2 preferential, whereas newer compounds such as SC-58125 and L-754,337 are selective for COX-2.[30] Drug plasma concentrations, protein binding and tissue-specific inhibition of prostaglandin synthesis can all influence the degree of COX-2 inhibition.[30]

The COX-2 preference of meloxicam is structurally dependent, as demonstrated by a comparison of the pharmacodynamics of meloxicam and its 4′ isomer.[31] In a human whole blood assay, the ratio of concentrations necessary to inhibit COX-1 and COX-2 by 50% (IC_{50}) was 13 for meloxicam and 1.8 for its isomer. In rat models, meloxicam was a weaker inhibitor than its 4′ isomer of gastric and renal prostaglandin synthesis, but not of paw swelling.[31]

An emerging advantage of NSAIDs that show preferential COX-2 inhibition may be reduced gastrointestinal toxicity relative to nonselective NSAIDs. The dose at which 50% of treated rats developed gastroduodenal ulcers was 2.4 mg/kg for meloxicam and 0.4 mg/kg for 4′-meloxicam.[31] In a trial comparing COX-2–selective (carprofen), COX-2–preferential (meloxicam) and COX-nonselective (ketoprofen) NSAIDs with gelatin placebo, dogs receiving carprofen and gelatin had fewer endoscopic gastroduodenal ulcerations after 7 and 28 days than those receiving the other NSAIDs, which all had similar ulceration rates.[32]

Clinical studies have shown similar trends. In a double-blind placebo-controlled comparison of meloxicam 15 mg/day or piroxicam 20 mg/day for 28 days in 44 healthy adult volunteers, piroxicam induced transient mild gastroduodenal ulcerations in 6 of 7 individuals whereas meloxicam induced no macroscopic damage.[33] In 2 large prospective comparative trials [Meloxicam Large-Scale International Study Safety Assessment (MELISSA) and Safety and Efficacy Large-Scale Evaluation of COX-Inhibiting Therapies (SELECT)], meloxicam caused significantly less gastrointestinal toxicity than nonselective NSAIDs in patients with osteoarthritis.

The international double-blind randomised MELISSA trial compared 4635 patients receiving meloxicam 7.5 mg/day with 4688 receiving diclofenac 100 mg/day.[34] Significantly fewer meloxicam than diclofenac recipients experienced gastrointestinal problems (13 *vs* 19%), required or remained in hospital because of adverse effects (5 *vs* 121 hospital days), or withdrew because of adverse effects (5.5 *vs* 8.0%). However, diclofenac provided more effective analgesia than meloxicam.

SELECT, a prospective international multicentre double-blind double-dummy randomised parallel-group trial, compared 4320 patients receiving meloxicam 7.5 mg/day for 28 days with 4336 patients receiving piroxicam 20 mg/day for 28 days.[35] Adverse effects were significantly lower in the meloxicam group (22.5%) compared with the piroxicam group (27.9%; $p = 0.001$). Meloxicam recipients had significantly fewer gastrointestinal complications (dyspepsia, nausea, vomiting, pain, perforation or haemorrhage) than piroxicam recipients (10.3 *vs* 15.4%; $p = 0.001$). The efficacy of both drugs was equivalent.

The COX-2 preference of meloxicam may also be clinically important in other extra-articular diseases. In an open-label uncontrolled study of meloxicam in UV dermatitis, 10 patients received UV irradiation at the minimal erythema dose (MED) with or without meloxicam 7.5mg. No differences in UV protection compared with previous studies of nonselective NSAIDs were noted.[36] In an animal study of the central effects of superfusion of indomethacin and meloxicam into rat spinal cord, only the COX-2–preferential meloxicam inhibited spinal reflexes.[37]

5. Conclusions

The long half-life and preferential COX-2 inhibition of meloxicam may provide the convenience of once-daily administration with reduced gastrointestinal adverse effects. Minimal pharmacokinetic changes have been reported in the elderly, in patients with renal or hepatic impairment, or when meloxicam is administered with other commonly co-prescribed drugs. However, enhanced

clinical vigilance in such cases is still advisable. Further study and clinical experience are required before the unique properties of this oxicam can be fully appreciated. As with other NSAIDs, further investigation of novel effects in Alzheimer's disease and colorectal cancer should be undertaken.

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References

1. Engelhardt G, Homma D, Schlegel K, et al. Anti-inflammatory, analgesic, antipyretic and related properties of meloxicam, a new non-steroidal anti-inflammatory agent with favourable gastrointestinal tolerance. Inflamm Res 1995; 44 (10): 423-33
2. Luger P, Daneck K, Engel W, et al. Structure and physiochemical properties of meloxicam, a new NSAID. Eur J Pharm Sci 1996; 4 (3): 175-87
3. Albengres E, Urien S, Barre J, et al. Clinical pharmacology of oxicams: new insights into the mechanisms of their dose-dependent toxicity. Int J Tissue React 1993; 15 (3): 125-34
4. Roszko P. Meloxicam: a COX-2 preferential NSAID. IBC's Industry Symposium on COX-2 Inhibitors. Applications in Inflammation, Cancer, and Alzheimer's Disease: 1998 Aug 6-7; San Diego. In press
5. Noble S, Balfour JA. Meloxicam. Drugs 1996; 51 (3): 424-30; discussion 431-32
6. Türck D, Roth W, Busch U. A review of the clinical pharmacokinetics of meloxicam. Br J Rheumatol 1996; 35 Suppl. 1: 13-6
7. Türck D, Busch U, Heinzel G, et al. Basic clinical pharmacokinetics of meloxicam, a new NSAID [abstract]. Scand J Rheumatol 1994; S98: A120
8. Türck D, Busch U, Heinzel G, et al. Clinical pharmacokinetics of meloxicam. Arzneimittel Forschung 1997; 47 (3): 253-8
9. Busch U, Heinzel G, Narjes H. Effect of food on pharmacokinetics of meloxicam, a new non steroidal anti-inflammatory drug (NSAID). Agents Actions 1991; 32 (1-2): 52-3
10. Narjes H, Türck D, Busch U, et al. Pharmacokinetics and tolerability of meloxicam after i.m. administration. Br J Clin Pharmacol 1996; 41 (2): 135-9
11. Schmid J, Busch U, Heinzel G, et al. Pharmacokinetics and metabolic pattern after intravenous infusion and oral administration to healthy subjects. Drug Metab Dispos 1995; 23 (11): 1206-13
12. Degner F, Heinzl G, Busch U. Transsynovial kinetics of meloxicam [abstract]. Scand J Rheumatol 1994; S98: A121
13. Jolliet P, Simon N, Bree F, et al. Blood-to-brain transfer of various oxicams: effects of plasma binding on their brain delivery. Pharm Res 1997; 14 (5): 650-6
14. Chesne C, Guyomard C, Guillouzo A, et al. Metabolism of meloxicam in human liver involves cytochromes P4502C9 and 3A4. Xenobiotica 1998; 28 (1): 1-13
15. Auvinet B, Ziller R, Appelboom T, et al. Comparison of the onset and intensity of action of intramuscular meloxicam and oral meloxicam in patients with acute sciatica. Clin Ther 1995; 17 (6): 1078-98
16. Davies NM, Anderson KE. Clinical pharmacokinetics of diclofenac: therapeutic insights and pitfalls. Clin Pharmacokinet 1997; 33 (3): 184-213
17. Engelhardt G, Trummlitz G. Biological activity of the main metabolites of meloxicam. Drugs Exp Clin Res 1990; 16 (2): 53-6
18. Sander O, Hübner G, Türck D, et al. Meloxicam pharmacokinetics in elderly compared to younger male and female patients with rheumatoid arthritis. Rheumatol Eur 1995; 24 (S3): 221
19. Boulton-Jones JM, Geddes CG, Heinzel G, et al. Meloxicam pharmacokinetics in renal impairment. Br J Clin Pharmacol 1997; 43 (1): 35-40
20. Bevis PJ, Bird HA, Lapham G. An open study to assess the safety and tolerability of meloxicam 15 mg in subjects with rheumatic disease and mild renal impairment. Br J Rheumatol 1996; 35 Suppl. 1: 56-60
21. Türck D, Schwarz A, Hoffler D, et al. Pharmacokinetics of meloxicam in patients with end-stage renal failure on haemodialysis: a comparison with healthy volunteers. Eur J Clin Pharmacol 1996; 51 (3-4): 309-13
22. Busch U, Heinzel G, Narjes H, et al. Pharmacokinetics of meloxicam in patients with liver insufficiency associated with liver cirrhosis. Rheumatol Eur 1995; 24 (S3): 177
23. Türck D, Su CA, Heinzel G, et al. Lack of interaction between meloxicam and warfarin in healthy volunteers. Eur J Clin Pharmacol 1997; 51 (5): 421-5
24. Degner FL, Heinzel G, Narjes H, et al. The effect of meloxicam on the pharmacokinetics of beta-acetyl-digoxin. Br J Clin Pharmacol 1995; 40 (5): 486-8
25. Muller FO, Schall R, de Vaal AC, et al. Influence of meloxicam on furosemide pharmacokinetics and pharmacodynamics in healthy volunteers. Eur J Clin Pharmacol 1995; 48 (3-4): 247-51
26. Muller FO, Middle MV, Schall R, et al. An evaluation of the interaction of meloxicam with frusemide in patients with compensated chronic cardiac failure. Br J Clin Pharmacol 1997; 44 (4): 393-8
27. Hubner G, Sander O, Degner FL, et al. Lack of pharmacokinetic interaction of meloxicam with methotrexate in patients with rheumatoid arthritis. J Rheumatol 1997; 24 (5): 845-51
28. Busch U, Heinzel G, Narjes H, et al. Interaction of meloxicam with cimetidine, Maalox, or aspirin. J Clin Pharmacol 1996; 36 (1): 79-84
29. Busch U, Heinzel G, Narjes H. The effect of cholestyramine on the pharmacokinetics of meloxicam, a new non-steroidal anti-inflammatory drug (NSAID), in man. Eur J Clin Pharmacol 1995; 48 (3-4): 269-72
30. Pairet M, van Ryn J. Experimental models used to investigate the differential inhibition of cyclooxygenase-1 and cyclooxygenase-2 by non-steroidal anti-inflammatory drugs. Inflamm Res 1998; 47 Suppl. 2: S93-101
31. Pairet M, van Ryn J, Schierok H, et al. Differential inhibition of cyclooxygenases-1 and -2 by meloxicam and its 4′-isomer. Inflamm Res 1998; 47 (6): 270-6
32. Forsyth SF, Guilford WG, Haslett SJ, et al. Endoscopy of the gastroduodenal mucosa after carprofen, meloxicam and ketoprofen administration in dogs. J Small Anim Pract 1998; 39 (9): 421-4
33. Lipscomb GR, Wallis N, Armstrong G, et al. Gastrointestinal tolerability of meloxicam and piroxicam: a double-blind

placebo-controlled study. Br J Clin Pharmacol 1998; 46 (2): 133-7
34. Hawkey C, Kahan A, Steinbruck K, International Meloxicam Large-Scale International Study Safety Assessment (MELISSA) Study Group, et al. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. Br J Rheumatol 1998; 37 (9): 937-45
35. Dequeker J, Hawkey C, Kahan A, et al. Improvement in gastrointestinal tolerability of the selective cyclooxygenase (COX)-2 inhibitor, meloxicam, compared with piroxicam: results of the Safety and Efficacy Large-scale Evaluation of COX-Inhibiting Therapies (SELECT) trial in osteoarthritis. Br J Rheumatol 1998; 37 (9): 946-51
36. Bayerl C, Pagung R, Jung EG. Meloxicam in acute UV dermatitis: a pilot study. Photodermatol Photoimmunol Photomed 1998; 14 (5-6): 167-9
37. Lopez-Garcia JA, Laird JM. Central antinociceptive effects of meloxicam on rat spinal cord in vitro. Neuroreport 1998; 9 (4): 647-51

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