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Review of gastrointestinal tolerability and safety of Meloxicam

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Abstract—Selective COX-2 inhibition relative to COX-1 has consistently been demonstrated for meloxicam in various *in vitro* test systems. In human platelets *ex vivo* COX-1-dependent thromboxane formation is partially and dose dependently inhibited, however no significant inhibition of platelet aggregation has been observed with the recommended doses of 7.5 mg and 15 mg meloxicam daily. With once daily dosing, meloxicam has demonstrated efficacy in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

Meloxicam was granted its first marketing authorization in 1995 and is now available in more than 100 countries. Meloxicam has been studied in clinical trials involving more than 30 000 patients and is estimated to have been prescribed for more than 30 million patients worldwide to date. Clinically, meloxicam offers similar efficacy to recommended doses of well-established nonsteroid anti-inflammatory drugs (NSAIDs), including diclofenac, piroxicam and naproxen.

Meloxicam distinguishes itself from established NSAIDs with a reduced risk of certain gastrointestinal adverse events. This has consistently been demonstrated in randomized clinical trials, large scale clinical outcome studies, pooled analyses and meta-analyses. Post-marketing experience is consistent with the safety profile established in these studies and analyses.

Key words: Meloxicam; selective COX-2 inhibition; gastrointestinal tolerability; osteoarthritis; rheumatoid arthritis; ankylosing spondylitis.

1. INTRODUCTION

Selective inhibition of COX-2 relative to COX-1 has consistently been demonstrated for meloxicam in various *in vitro* test systems (Churchill *et al*., 1996; Patrignani *et al*., 1997; Warner *et al*., 1999). In human platelets *ex vivo*, COX-1-dependent thromboxane formation is partially and dose dependently inhibited; however, no significant inhibition of platelet aggregation has been observed with

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the recommended doses of 7.5 mg and 15 mg meloxicam daily (De Meijer *et al.*, 1999; Panara *et al.*, 1999; Stichtenoth *et al.*, 1997; Van Hecken *et al.*, 2000). Anti-inflammatory, analgesic activity and antipyretic properties have been shown in classical models of inflammation, pain and fever (Engelhardt *et al.*, 1995). With once daily dosing, meloxicam has demonstrated efficacy in osteoarthritis (Lund *et al.*, 1998; Yocum *et al.*, 2000), rheumatoid arthritis (Furst *et al.*, 2000; Lemmel *et al.*, 1997) and ankylosing spondylitis (Dougados *et al.*, 1999). Meloxicam was granted its first marketing authorization in 1995 and is now available in more than 100 countries. Meloxicam has been studied in clinical trials involving more than 30 000 patients and is estimated to have been prescribed for more than 30 million patients worldwide to date. Clinically, meloxicam offers similar efficacy to recommended doses of well-established nonsteroid anti-inflammatory drugs (NSAIDs), including diclofenac, piroxicam and naproxen (Carraba *et al.*, 1995; Dequeker *et al.*, 1998; Dougados *et al.*, 1999; Ghozlan *et al.*, 1996; Goei The *et al.*, 1997; Hawkey *et al.*, 1998; Hosie *et al.*, 1996, 1997; Huskisson *et al.*, 1996; Linden *et al.*, 1996; Wojtulewski *et al.*, 1996; Yocum *et al.*, 2000).

Meloxicam distinguishes itself from established NSAIDs with a reduced risk of certain gastrointestinal adverse events. This has consistently been demonstrated in randomized clinical trials, large scale clinical outcome studies, pooled analyses and meta-analyses (Dequeker *et al.*, 1998; Distel *et al.*, 1996; Dougados *et al.*, 1999; Hawkey *et al.*, 1998; Schoenfeld, 1999; Yocum *et al.*, 2000). Post-marketing experience is consistent with the safety profile established in these studies and analyses (Degner *et al.*, 2000; Lanes *et al.*, 2000; Martin *et al.*, 2000).

2. CLINICAL TRIAL EXPERIENCE

2.1. Gastrointestinal tolerability

The adverse events profile including the gastrointestinal adverse events of meloxicam, have been examined in two large-scale clinical outcome studies (Dequeker *et al.*, 1998; Hawkey *et al.*, 1998). These studies demonstrated that fewer gastrointestinal adverse events were reported following the administration of meloxicam 7.5 mg daily than following the administration of the comparator NSAIDs diclofenac 100 mg SR daily ($p < 0.001$) and piroxicam 20 mg ($p < 0.001$) daily. This favourable profile was attributable predominantly to a lower reporting incidence of gastrointestinal events such as dyspepsia, abdominal pain, nausea and vomiting (Fig. 1), and was associated with significantly smaller number of meloxicam patients withdrawing from the studies for these events ($p < 0.01$). Concomitant use of salicylates during the trial was suggested as a risk factor for the development of certain gastrointestinal adverse events (Silverstein *et al.*, 2000). The favourable gastrointestinal tolerability profile of meloxicam *versus* diclofenac and piroxicam was maintained ($p < 0.001$) when adjusting for concomitant use of salicylates (Table 1).

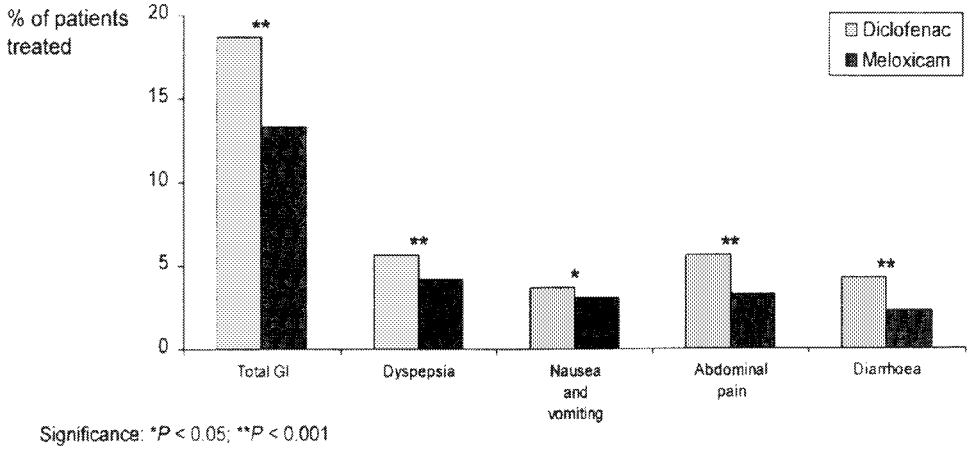

Figure 1. Favourable gastrointestinal adverse event profile for meloxicam 7.5 mg over diclofenac 100 mg in a large scale clinical outcome study (Hawkey *et al.*, 1998).

Table 1.
Effect of concomitant aspirin (ASA) intake on gastrointestinal adverse events in two large scale clinical trials with meloxicam

	MELISSA		SELECT	
	Meloxicam	Diclofenac	Meloxicam	Piroxicam
Total patients	4635	4688	4320	4336
Patients on ASA	259	224	203	226
Patients not on ASA	4376	4464	4117	4110
Patients on ASA with GI AEs (%)	15.3	23.3	13.3	19.9
Patients not on ASA with GI AEs (%)	13.2	18.6	10.2	15.2

Findings from individual placebo-controlled randomized clinical trials suggest that the favourable gastrointestinal profile of meloxicam 7.5 mg daily relative to comparator NSAIDs that was observed during treatment of osteoarthritis patients (Dequeker *et al.*, 1998; Hawkey *et al.*, 1998), also applies to meloxicam 15 mg daily (Lund *et al.*, 1998; Yocum *et al.*, 2000). In these studies, patients treated with meloxicam reported consistently fewer gastrointestinal adverse events relative to those treated with comparator NSAIDs, regardless of treatment duration at the recommended doses of 7.5 mg and 15 mg daily. The cumulative risks for gastrointestinal adverse events observed in the osteoarthritis development program for meloxicam 7.5 mg and 15 mg daily, diclofenac 100 mg and placebo are depicted in Fig. 2. While the risk was significantly different for both meloxicam 7.5 mg and 15 mg daily compared to diclofenac ($p < 0.001$), the Kaplan–Meier estimates of cumulative risk for meloxicam and placebo were shown to be similar to one another. After three months of treatment, the cumulative risk estimate for diclofenac for gastrointestinal adverse events is 27%, whereas the risk estimates for both doses of meloxicam and placebo approximated 22%.

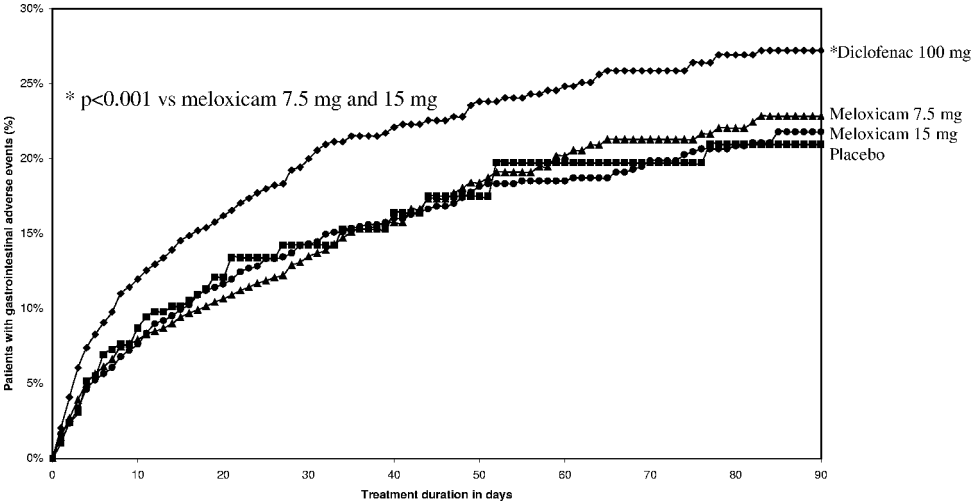

Figure 2. Gastrointestinal tolerability of meloxicam 7.5 mg ($n = 10{,}199$) and meloxicam 15 mg ($n = 977$) compared to diclofenac 100 mg ($n = 5396$) and placebo ($n = 294$) in osteoarthritis patients observed in double-blind clinical trials.

The evidence regarding the incidence of gastrointestinal adverse events with meloxicam in indications other than osteoarthritis is supported by the results from placebo-controlled clinical trials in rheumatoid arthritis and ankylosing spondylitis. These studies confirm the favourable gastrointestinal tolerability profile for doses up to meloxicam 15 mg daily (Dougados *et al.*, 1999; Lemmel *et al.*, 1997). The results of a systematic review of published clinical trial experience covering all treatment indications showed statistically significant reductions in risk following administration of meloxicam in terms of gastrointestinal adverse events, withdrawals due to gastrointestinal adverse events, and dyspepsia by 36%, 41%, and 27%, respectively for meloxicam relative to comparator NSAIDs (Schoenfeld, 1999).

2.2. Upper gastrointestinal perforation, ulcer or bleeding (PUB)

The unwanted gastrointestinal effects of NSAIDs include a broad spectrum of events from small asymptomatic peptic ulcers detected only on endoscopic examination to acute, life-threatening bleeding and perforation. The most important events clinically are also the least common. This low incidence of PUBs presents special challenges to the assessment of risk. The main problem is that most clinical trials are simply too small to allow one accurately to quantify the risk of the most serious types of gastrointestinal events.

In the two largest meloxicam trials, namely MELISSA (Hawkey *et al.*, 1998) and SELECT (Dequeker *et al.*, 1998), fewer upper gastrointestinal PUBs were reported by patients treated with meloxicam 7.5 mg daily than by patients treated with comparator NSAIDs. Following administration of meloxicam 7.5 mg daily, upper gastrointestinal PUB were reported by 5 patients treated in one trial (Hawkey *et al.*,

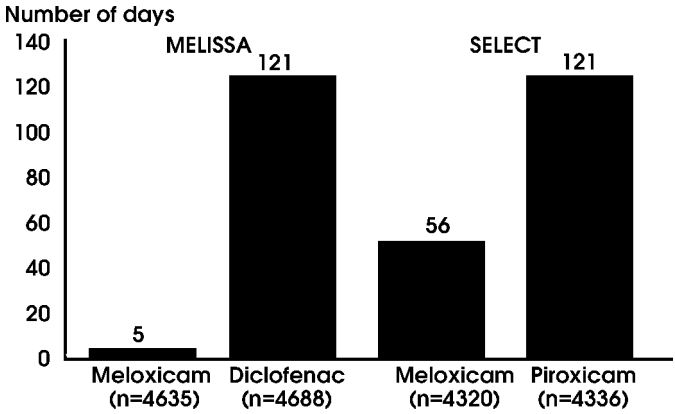

Figure 3. Number of days in hospital due to gastrointestinal adverse events for meloxicam 7.5 mg, diclofenac 100 mg SR and piroxicam 20 mg in two large scale clinical outcome studies. (Dequeker *et al.*, 1998; Hawkey *et al.*, 1998).

1998), and by 7 in the other (Dequeker *et al.*, 1998), whereas for diclofenac 100 mg daily and piroxicam 20 mg daily, 7 and 16 cases of such events were reported, respectively (Dequeker *et al.*, 1998; Hawkey *et al.*, 1998). No ulcer complication, i.e. ulcer perforation or ulcer bleed, was observed in the meloxicam groups whereas 8 complicated cases were seen in the two comparator groups (4 with diclofenac, 4 with piroxicam). These differences did not reach statistical significance, presumably due to lack of power, in spite of the relatively large patient numbers involved. Results concerning hospital admission for gastrointestinal adverse events (Fig. 3) suggest a reduced duration of hospitalization for gastrointestinal complications in patients treated with the meloxicam (Dequeker *et al.*, 1998; Hawkey, 1999; Hawkey *et al.*, 1998). Consistent with these results, a systematic review of published randomized controlled clinical trials only, revealed a significantly lower odds ratio for upper gastrointestinal PUB of 0.52 (95% confidence interval from 0.28 to 0.96) for meloxicam compared to other NSAIDs (Schoenfeld, 1999).

Because of the extent of the meloxicam development program, the clinical database is unusually large and thus has provided the opportunity to assess the risk of the clinical events that drive the risk for NSAIDs (PUBs), by pooling data for analysis from of all clinical trials performed with meloxicam (Table 2). The recommended starting dose for meloxicam in osteoarthritis is 7.5 mg per day, although higher doses are included in the analysis for completeness. Daily doses greater than meloxicam 15 mg are neither authorized nor are they recommended.

The upper gastrointestinal PUB data from all therapeutic randomized double-blind phase II to IV clinical trials that were included in the analysis indicate a low risk for meloxicam at the recommended doses of 7.5 mg to 15 mg daily with incidences of 0.13% and 0.13%, respectively, and upper 95% confidence interval bounds that do not exceed 0.30%. The mean durations of treatment were one month for meloxicam 7.5 mg daily and two months for meloxicam 15 mg daily (Table 2).

Table 2.
Upper gastrointestinal perforation, ulcer or bleeding (PUB) in all therapeutic Phase II to IV double blind clinical trials from the meloxicam data base

	Placebo	Meloxicam			Piroxicam	Diclofenac
		7.5 mg	15 mg	22.5 mg	20 mg	100 mg*
Number of patients treated	1397	11687	3759	515	5585	5836
Number of PUB	0	15	5	3	29	10
Mean time on drug (days)	35	31	52	118	40	33
Incidence of PUB (%)	0	0.13	0.13	0.58	0.52	0.17
95% CI for PUB incidence (%)	–	[0.06–0.19]	[0.02–0.25]	[0.0–1.24]	[0.33–0.71]	[0.06–0.19]

* 343 patients receiving diclofenac 75 mg BID are included. In these 343 patients no PUB was observed.

The Kaplan–Meier estimates for the risk of upper gastrointestinal PUBs following treatment with meloxicam 15 mg daily after two and six months are low at 0.25% and 0.45%, respectively. The cumulative risks tend, however, to increase with dose and duration of treatment.

Data from multiple clinical trials were combined in this analysis to estimate the risk of clinically serious upper gastrointestinal PUB. These data should, therefore, be viewed as descriptive rather than inferential.

A strength of this analysis is that it provides direct estimation of the events that drive the risk for NSAIDs in a population that has not been screened to exclude patients at increased risk of developing such events. Endoscopy studies, for example, can be expected to underestimate the risk of clinical outcomes in patients treated with NSAIDs for two main reasons. First, patients are screened at the outset, so that patients with a detectable ulcer are excluded from participation. Second, when a patient develops an endoscopic ulcer during the study, therapy is discontinued, so these patients no longer have the opportunity to develop a symptomatic peptic ulcer or its complications. The result of this meloxicam PUB analysis can therefore reasonably be considered to be representative of risks that might be expected to occur in the general population.

3. SYSTEMATIC POST-MARKETING EXPERIENCE

A controlled pharmacoepidemiological study (Degner *et al.*, 2000) assessed the tolerability and efficacy of meloxicam under essentially normal prescribing conditions for a duration of up to six months. A total of 4526 patients received either meloxicam ($n = 2530$) or a comparator NSAID ($n = 1996$) in a multi-center prospective observational cohort study. Data from the centers randomized were analyzed in two separate groups: a meloxicam only group, and a group that was prescribed all

Table 3.
Summary of patients with gastrointestinal adverse reactions in a controlled pharmacoepidemiological study (Degner *et al.*, 2000)

WHO System Organ Class Disorders & Preferred Term	Meloxicam ($n = 2530$)		NSAID ($n = 1996$)		Relative Risk [95% CI]	p-value[1]
	N	%	*N*	%		
Adverse reactions	63	2.5	71	3.6	0.70 [0.50–0.98]	0.04
Gastrointestinal (GI) system in total	45	1.8	63	3.2	0.56 [0.39–0.82]	0.003
Abdominal pain	23	0.91	38	1.90	0.48 [0.29–0.80]	0.006
Gastritis	2	0.08	12	0.60	0.13 [0.03–0.59]	0.002
Nausea	10	0.40	9	0.45	0.88 [0.36–2.15]	n.s.
Dyspepsia	2	0.08	7	0.35	0.23 [0.05–1.08]	0.049
Diarrhoea	8	0.32	5	0.25	1.26 [0.41–3.86]	n.s.
Oesophagitis	1	0.04	3	0.15	0.26 [0.03–2.53]	n.s.
Anorexia	1	0.04	1	0.05	0.79 [0.05–12.6]	n.s.
Flatulence	0	0	1	0.05	—	n.s.
Duodenitis	0	0	1	0.05	—	n.s.
Gastrointestinal disorders not other specified	3	0.12	1	0.05	2.37 [0.25–22.7]	n.s.
Vomiting	5	0.20	0	0	—	n.s.
Bleeding from GI tract (i.e. PUB, gastritis hemorrhagic or GI hemorrhage)	2*	0.08	10*	0.50	0.16 [0.04–0.72]	0.007
Any gastric or duodenal ulcer, hematemesis or melaena (PUB)	0	0	6	0.30	—	0.007
Gastric ulcer	0	0	5	0.25	—	n.s.
Gastric ulcer perforated	0	0	1	0.05	—	n.s.
Duodenal ulcer	0	0	1	0.05	—	n.s.
Melaena	0	0	1	0.05	—	n.s.
Gastritis haemorrhagic	0	0	1	0.05	—	n.s.
Gastrointestinal haemorrhage	2	0.08	5	0.25	0.32 [0.06–1.63]	n.s.

* Including one case of serious adverse reaction.
CI = confidence interval.
Number of patients do not sum up due to the possibility of multiple adverse events per individual.
[1] p-value (Fisher's exact text) of difference between treatments.
n.s. not significant.

comparator NSAIDs. Treatment groups were similar regarding efficacy. Significantly lower proportions of meloxicam patients reported gastrointestinal adverse drug reactions (1.8% *vs.* 3.2%), including dyspepsia (0.08% *vs.* 0.35%), abdominal pain (0.91% *vs.* 1.9%), gastritis (0.08% *vs.* 0.60%) and bleeding from the gastrointestinal tract (0.08% *vs.* 0.50%) relative to patients with the NSAIDs with which meloxicam was compared (Table 3).

The interpretation of these data obtained in the post-marketing setting needs to be performed with care, as bias can easily be introduced. One potential bias is selective prescription to high risk patients, which was demonstrated to have

occured in this controlled pharmacoepidemiological study (Degner *et al.*, 2000). Meloxicam was prescribed preferentially to patients who had not responded to NSAIDs previously (47% *vs.* 39%), and/or had reported NSAID induced side-effects (19% *vs.* 6%), or had a history of PUB (12% *vs.* 7%). Although selective prescribing, and the non-randomised and unblinded nature of this type of study limits the confidence one can place in the conclusions that can be drawn concerning efficacy or tolerability, the results of this study emphasize the importance of adhering carefully to recommendations.

Further systematic studies of the post-marketing experience with meloxicam have been performed, one of which employed data from the UK General Practitioners Research Database (Lanes *et al.*, 2000). The baseline risk of an upper gastrointestinal event among new users of meloxicam, ibuprofen, diclofenac, naproxen and indomethacin was estimated in this study. The authors selected for analysis a random sample of 5000 meloxicam users, and 5000 users of each of the comparator NSAIDs, except indomethacin, for which 2500 subjects were selected. Comparators were matched to meloxicam subjects on age and sex. History of certain gastrointestinal diagnoses and recent use of anti-inflammatory drugs and acid-suppressing drugs were obtained for each subject. It was found that patients receiving meloxicam were at least twice as likely as patients receiving other NSAIDs to have a recent history of gastrointestinal diagnoses or treatment. One can conclude that in the UK, meloxicam was prescribed more often than other popular NSAIDs to patients who had an increased baseline risk of developing gastrointestinal events in response to NSAIDs.

A prescription-event monitoring study involving 19,087 patients in the UK has demonstrated, furthermore, that upper gastrointestinal adverse events occurred more frequently in patients with a past history of gastrointestinal disorder and in patients who were prescribed concomitant gastroprotective agents (Martin *et al.*, 2000).

Overall, the post-marketing experience with meloxicam is consistent with the favorable gastrointestinal tolerability seen with meloxicam in double-blind comparative clinical trials. The safe and effective use of all NSAIDs depends critically on the administration of the lowest effective dose for the shortest duration necessary. For high-risk patients, alternative therapies that do not involve NSAIDs should be considered.

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