Risk of Serious Upper Gastrointestinal and Cardiovascular Thromboembolic Complications with Meloxicam

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PURPOSE: To assess the risk of serious gastrointestinal and thromboembolic complications with approved doses of meloxicam.

METHODS: We pooled data from clinical trials of meloxicam at doses of 7.5 or 15 mg/d. A blinded gastrointestinal adjudication committee used prespecified criteria to identify gastric or duodenal perforation, gastric outlet obstruction, or hemodynamically important upper gastrointestinal bleeding. For analysis of thromboembolic complications, investigator-reported events were analyzed without adjudication.

RESULTS: We analyzed data from 24,196 patients from 28 trials, most of whom had been followed for up to 60 days. Of these patients, 13,118 received meloxicam (10,158 received a daily dose of 7.5 mg and 2960 received 15 mg), 5283 were treated with diclofenac 100 mg, 181 received diclofenac 150 mg, 5371 were treated with piroxicam 20 mg, and 243 received naproxen 500 mg twice daily. Patients who received 7.5 mg of meloxicam daily had a 0.03% risk of serious upper gastrointestinal events, which was significantly lower than the risk in those who received diclofenac, naproxen, or piroxicam ($P < 0.02$). With the 15 mg daily dose of meloxicam, this risk was significantly different only when compared with piroxicam ($P = 0.03$). The risk of thromboembolic events in patients treated with meloxicam at either dose was lower than with diclofenac, but similar to that observed with piroxicam and naproxen.

CONCLUSION: This pooled analysis of 24,196 patients demonstrates that meloxicam has a favorable gastrointestinal and thromboembolic safety profile. However, only a small number of patients were followed for more than 60 days, and meaningful comparisons were not possible in this subgroup. **Am J Med. 2004;117:100–106.** ©2004 by Elsevier Inc.

Gastrointestinal complications related to nonsteroidal anti-inflammatory drug (NSAID) therapy are an important public health issue (1–4). We estimated that serious gastrointestinal complications result in nearly 103,000 hospitalizations and 16,500 deaths every year in the United States (1,2). It is believed that these serious complications are related to the NSAID-induced inhibition of cyclooxygenase-1 (COX-1) in the gastrointestinal mucosa. The newer NSAIDs that preferentially inhibit cyclooxygenase-2 (COX-2) in the joints are presumably less likely to cause such problems (5). However, recent studies have raised concerns about the association between one of the COX-2 selective NSAIDs—rofecoxib—and serious cardiovascular thromboembolic events (6).

Meloxicam is an NSAID that has been shown to spare COX-1 activity at approved doses (7). In clinical trials, it has been shown to be effective and to be associated with lower rates of gastrointestinal adverse events as compared with diclofenac and piroxicam (8–11). In addition, meloxicam does not inhibit platelet function (12). Although the drug has now been studied in more than 150 clinical trials in over 100 countries, individual trials have been too small to yield reliable estimates of the risk of clinically important gastrointestinal complications, and no large, prospective, randomized clinical trial has been performed to evaluate this outcome. In this study, we report the results of a blinded pooled analysis of 28 clinical trials (published and unpublished) and assess the risk of serious upper gastrointestinal complications. In contrast to a previous meta-analysis (10), we examined "primary information" directly from the case report forms and evaluated *prima facie* all available data in an effort to focus on serious, clinically important events, including gastrointestinal toxicity and thromboembolic events (10).

METHODS

Study Sample

We analyzed clinical trials of meloxicam (Mobic; Boehringer-Ingelheim Pharmaceuticals Inc., Ridgefield, Connecticut) that met the following criteria: use of the oral formulation of meloxicam at doses (7.5 and 15 mg) approved by the Food and Drug Administration; planned duration of treatment of at least 21 days; planned trial size of at least 20 patients per treatment group; North American or Western European study; and study completed

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and data available on April 1, 1999. Trials included patients who might have been at increased risk of gastrointestinal bleeding due to asymptomatic ulcers or a history of ulcer disease. Our primary analysis was a comparison of meloxicam 7.5 and 15 mg with the traditional NSAIDs diclofenac, naproxen, and piroxicam.

Each trial was conducted in accordance with the principles enunciated in the Declaration of Helsinki and in accordance with Good Clinical Practices and with local guidelines defining the protection of human beings. All protocols were approved by the respective local institutional review boards or ethics committees. Informed consent was obtained from each subject.

Case Identification

Investigators were required to report all adverse events, including cases of upper gastrointestinal symptoms and complications, coded using the World Health Organization (WHO) adverse event coding system. Clinical source documents for all suspected serious upper gastrointestinal events were reviewed by a blinded, external adjudication committee. To identify potential cases for review by the committee, we created a primary list of 105 WHO codes containing terms indicating gastrointestinal bleeding, perforation, or obstruction. The primary list included diagnoses of direct interest, such as gastric ulcer, gastrointestinal hemorrhage, hematemesis, and melena, as well as related diagnoses, such as gastritis, rectal bleeding, colitis, and diverticulitis. To ensure that all potential cases of ulcer disease were identified, a secondary list was created containing 155 terms that might be consistent with signs and symptoms of gastrointestinal bleeding, such as abdominal pain, dyspepsia, nausea, and anemia. As would be expected in any study of NSAIDs, a much larger number of events were assigned codes on the secondary list (for example, for "dyspepsia") as compared with the primary list. Therefore, we identified for review patients with adverse events with diagnoses on the secondary list if they were classified as serious or if there was indication of bleeding.

Files containing medical records for potential cases were assembled by Boehringer-Ingelheim and submitted for review by two of the authors (GS and GT). The files contained all available clinical records obtained during the course of the clinical trial, and ancillary information pertaining to clinical evaluation of adverse events, including radiology, endoscopy, pathology, and hospitalization discharge summaries. Reviewers were blinded to any indication of study number, treatment, or dose.

Definitions of Serious Gastrointestinal Complications

Serious gastrointestinal complications were defined prospectively by the adjudication committee, and were based principally on those used in similar studies (13,14), with some modifications. Complications included gastric or duodenal perforation (report confirmed by endoscopy, surgery, unequivocal radiographic evaluations, or autopsy); gastric outlet obstruction (diagnosed by clinical investigator, confirmed by endoscopy, radiology, surgery, or autopsy); and hemodynamically important gastrointestinal bleeding (drop in hemoglobin level of at least 2 g/dL, decrease in hematocrit of at least 6%, or administration of a transfusion, with no evidence of any other cause). Any of these signs indicated a clinically serious bleed regardless of the presence of other clinical signs or symptoms or endoscopic findings.

Identification of Thromboembolic Events

The following were classified as thromboembolic adverse events: myocardial infarction, coronary thrombosis, coronary artery occlusion, cerebral infarction, cerebellar infarction, stroke, ischemic stroke, cerebral vascular disturbance, cerebral embolism, carotid thrombosis, transient ischemic attack, cerebral thrombosis, cerebral arterial thrombosis, and cerebellar arterial thrombosis. These adverse events were identified based solely on investigator reports.

Statistical Analysis

Time-to-event analysis of serious gastrointestinal and thromboembolic complications was performed based on Kaplan-Meier estimates of cumulative event incidences (15). Pairwise comparisons between treatment groups were assessed using the log-rank test. Analyses were performed with SAS software (SAS Inc., Cary, North Carolina).

RESULTS

We identified for inclusion 24,196 patients from 28 trials. Of these, 13,118 patients received meloxicam (10,158 received 7.5 mg and 2960 received 15 mg), 5464 patients were treated with diclofenac (5283 received 100 mg/d and 181 received 150 mg/d), 5371 patients received piroxicam 20 mg/d, and 243 were treated with naproxen 500 mg twice a day. (For analysis, all diclofenac patients were pooled together since less than 3.5% were taking the 150 mg/d dose). Thirty-nine percent of patients were at least 65 years of age, and 5% of patients reported a history of perforation, ulcer, or bleeding event (Table 1).

The medical records of 448 potential cases were reviewed by the independent external adjudication committee. In 394 patients, the adjudication committee was able to rule out the diagnosis of a serious upper gastrointestinal event. Of the remaining 54 patients, 37 showed clear evidence of a serious gastrointestinal event. In 10 patients, there was evidence of hemodynamically important bleeding, but the site of lesion could not be confirmed. In 7 patients, there was insufficient documentation to reach a firm diagnosis. None of the patients had bleeding that was "lower" or "colonic" in origin (e.g.,

Table 1. Baseline Characteristics of Patients in the Different Treatment Groups

Characteristic	Meloxicam 7.5 mg/d (n = 10,158)	Meloxicam 15 mg/d (n = 2960)	Diclofenac* 100–150 mg/d (n = 5464)	Piroxicam 20 mg/d (n = 5371)	Naproxen 1000 mg/d (n = 243)
	Number (%) or Mean				
Duration of exposure (days)	33	179	35	41	117
Age (years)					
18–54	2822 (28)	1008 (34)	1503 (28)	1558 (29)	105 (43)
55–64	3186 (31)	853 (29)	1531 (28)	1706 (32)	73 (30)
≥65	4136 (41)	1099 (37)	2404 (44)	2095 (39)	65 (27)
Unknown	14 (<1)	0	12 (0)	12 (0)	0
Gender					
Male	3279 (32)	967 (33)	1779 (33)	1813 (34)	71 (29)
Female	6870 (68)	1993 (67)	3679 (67)	3548 (66)	172 (71)
Unknown	9 (<1)	0	6 (<1)	10 (<1)	0
History of perforation, ulcer, bleed					
Yes	406 (4)	63 (2)	157 (3)	236 (4)	12 (5)
No	7672 (76)	1938 (65)	4289 (78)	3832 (71)	156 (64)
Unknown	2080 (20)	959 (32)	1018 (19)	1303 (24)	75 (31)
Prior nonsteroidal anti-inflammatory drug use					
Yes	6625 (65)	2010 (64)	3727 (68)	3325 (62)	225 (93)
No	1913 (19)	414 (14)	986 (18)	1113 (21)	17 (7)
Unknown	1620 (16)	536 (18)	751 (14)	933 (17)	1 (<1)
Patients, by country					
France	1171 (12)	92 (3)	1194 (22)	54 (1)	32 (13)
Germany	3094 (30)	884 (30)	1116 (20)	2244 (42)	56 (23)
United Kingdom/Ireland	2310 (23)	446 (15)	1263 (23)	1059 (20)	0
United States	329 (3)	340 (11)	334 (6)	0	0
Other	981 (10)	9 (<1)	446 (8)	524 (10)	155 (63)
Indication for use					
Osteoarthritis	9411 (93)	1404 (47)	5283 (97)	4667 (87)	0
Rheumatoid arthritis	747 (7)	1433 (48)	181 (3)	554 (10)	243 (100)
Ankylosing spondylitis	0	121 (4)	0	108 (2)	0
Other	0	2 (<1)	0	42 (1)	0

* Includes 5283 patients treated with a 100-mg/d dose and 181 patients treated with a 150-mg/d dose.

hemorrhoids, diverticulosis). All 54 patients were considered cases of serious upper gastrointestinal events; of these, 38 patients were enrolled in clinical trials that met the inclusion and exclusion criteria.

Risk of Adverse Events

Meloxicam at a dose of 7.5 mg/d was associated with a 0.03% risk of serious gastrointestinal events through 60 days (Table 2; Figure 1), which was significantly lower than with diclofenac, piroxicam, and naproxen (Table 3). Only a small number of patients were followed for more than 60 days, and meaningful comparisons were not possible in this subgroup. At a daily dose of 15 mg, meloxicam was associated with a significantly lower risk of serious gastrointestinal complication only when compared with piroxicam. The risk of thromboembolic events with both doses of meloxicam was significantly lower than with diclofenac, but was not significantly different from piroxicam and naproxen (Figure 2; Table 3).

DISCUSSION

Upper gastrointestinal complications due to NSAID use are the most common serious adverse events in the treatment of patients with arthritis. Over the last few years, four new medications—celecoxib, rofecoxib, valdecoxib, and meloxicam—have been introduced in the United States with the promise of improved gastrointestinal tolerability due to limited or no inhibition of the COX-1 isoenzyme at therapeutic doses. Some studies of celecoxib and rofecoxib have demonstrated that these drugs reduce the risk of serious gastrointestinal complications compared with traditional NSAIDs (14,16–18), while others have not (13,19). Our pooled analysis of 28 clinical trials provides data on the risk of validated serious gastrointestinal complications among patients receiving meloxicam.

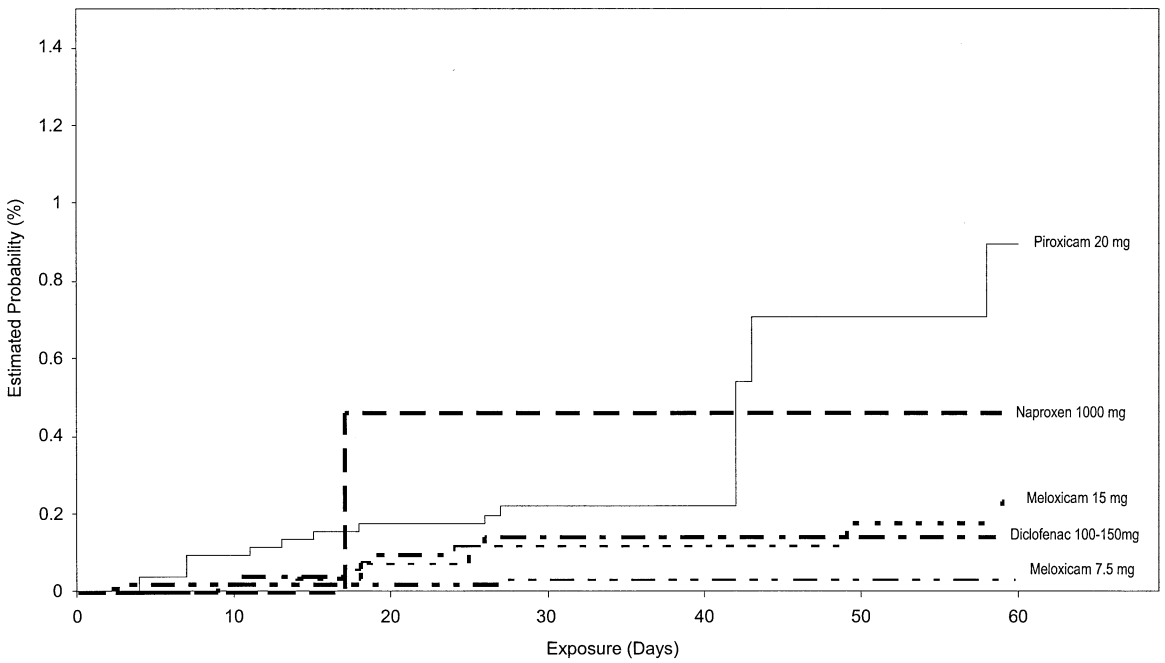
Our results suggest that there is a significant lower risk of serious gastrointestinal complications among patients taking 7.5 mg of meloxicam for up to 2 months compared

Table 2. Risk Estimates of Serious Upper Gastrointestinal and Cardiovascular Thromboembolic Complications, by Duration of Exposure and Treatment Group

Treatment (Dose)	Interval (Days)	Number of Patients Entering Interval	Serious Gastrointestinal Events	Cardiovascular Thromboembolic Events
			Number (Cumulative Risk in %)	
Meloxicam (7.5 mg/d)	0–60	10,158	3 (0.03)	8 (0.2)
	>60	551	0 (0.03)	2 (0.8)
Meloxicam (15 mg/d)	0–60	2960	5 (0.2)	5 (0.2)
	>60	1684	4 (0.6)	7 (0.9)
Diclofenac* (100–150 mg/d)	0–60	5464	7 (0.1)	13 (0.8)
	>60	493	2 (1.3)	0 (0.8)
Piroxicam (20 mg/d)	0–60	5371	15 (0.9)	5 (0.1)
	>60	532	1 (1.1)	0 (0.1)
Naproxen (1000 mg/d)	0–60	243	1 (0.5)	0
	>60	166	0 (0.5)	0

* Includes 5283 patients treated with a 100-mg/d dose and 181 patients treated with a 150-mg/d dose.

with patients taking diclofenac 100 mg, naproxen 1000 mg, or piroxicam 20 mg. For patients taking the 15 mg dose of meloxicam, the risk of serious gastrointestinal complications is significantly lower than with piroxicam but not significantly different than with diclofenac or naproxen. Results from a randomized clinical trial involving 9323 patients with osteoarthritis have showed similar clinical efficacy in patients treated with 7.5 mg of meloxicam or 100 mg of diclofenac (18). Another large randomized trial of osteoarthritis patients showed that 7.5 mg of meloxicam achieved a similar clinical efficacy as 20 mg of piroxicam (9). However, Yocum and colleagues



Number at risk at the beginning of time interval (days)

Mel 7.5 mg	10,158	9827	9446	2873	616	580	552
Mel 15 mg	2960	2860	2706	2064	1999	1750	1685
Diclofenac	5464	5232	5017	1775	632	519	493
Piroxicam	5371	5185	4965	1806	703	561	532
Naproxen	243	230	215	203	189	182	166

Figure 1. Cumulative probability of serious gastrointestinal complications, by treatment group and duration of exposure. Mel = meloxicam.

Table 3. Pairwise Comparisons between Treatments for Serious Upper Gastrointestinal Complications and Cardiovascular Thromboembolic Complications during the First 60 Days of Treatment

Treatments Compared	Gastrointestinal Complications	Cardiovascular Thromboembolic Complications
	P Value*	
Meloxicam 7.5 mg vs. meloxicam 15 mg	0.06	0.8
Meloxicam 7.5 mg vs. diclofenac	0.02	0.02
Meloxicam 7.5 mg vs. piroxicam	<0.001	0.8
Meloxicam 7.5 mg vs. naproxen	0.003	0.5
Meloxicam 15 mg vs. diclofenac	0.9	0.05
Meloxicam 15 mg vs. piroxicam	0.03	0.6
Meloxicam 15 mg vs. naproxen	0.5	0.5
Diclofenac vs. piroxicam	0.09	0.06
Diclofenac vs. naproxen	0.2	0.2
Piroxicam vs. naproxen	0.7	0.6

* By log-rank test.

detected no difference in clinical efficacy among patients treated with meloxicam 7.5 mg, meloxicam 15 mg, or diclofenac 100 mg (20).

We found a similar risk of cardiovascular thromboembolic events among NSAIDs, although a somewhat higher risk was observed with diclofenac. However, results of other studies of the potential of increased thromboembolic events in patients taking certain selective COX-2 inhibitors have been conflicting. One large trial reported an incidence of myocardial infarction that was five times higher in patients taking rofecoxib as compared with naproxen (21), while other data have suggested that meloxicam may be of benefit in the prevention of acute myocardial infarctions in patients with unstable angina

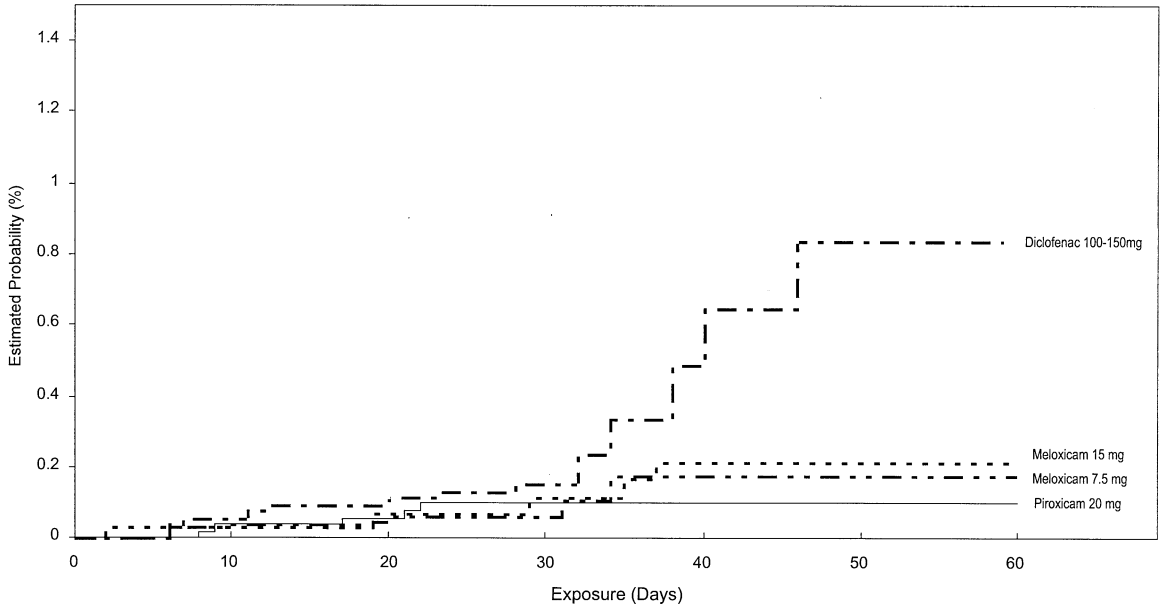


Figure 2. Cumulative probability of cardiovascular thromboembolic complications, by treatment group and duration of exposure. Mel = meloxicam.

because of its anti-inflammatory activity (22). Further, the role of specific doses of each of these drugs is not understood.

Our analysis combines strengths of epidemiological and clinical studies while overcoming some of their typical limitations. The meloxicam database was large, including more than 20,000 patients, which compares favorably with large epidemiological studies and allows us to evaluate the clinical outcome of interest instead of a "surrogate" outcome. The study included patients who were at risk of gastrointestinal bleeding, including those with a history of ulcer disease or asymptomatic ulcers, and the elderly; thus, the study sample is more representative of the population at large. This is in contrast to several analyses of celecoxib and rofecoxib (16,17), which excluded patients who had the potential to develop a serious upper gastrointestinal event because of an endoscopic ulcer or a prior history of complication (perforation, ulcer, or bleeding). At the same time, our data contained detailed information about medication use (e.g., precise dose) and outcomes (laboratory values to assess clinical importance) to permit blinded evaluation of all serious gastrointestinal outcomes by an adjudication committee.

Still, our study has several limitations. Most of the patients were treated for less than 2 months, so the risk estimates for longer durations of use are unreliable. Several trials did not include a control group. Pooling treatment groups from different studies does not preserve the benefits of randomization for making comparisons between treatment groups, even though the treatment groups were similar with regard to the major risk factors for gastrointestinal complications. The trials did not have any protocol-defined workup guidelines for suspected gastrointestinal complications, except as may be considered appropriate by the treating physician. It is also possible that relevant clinical data may not have been collected in all cases. Therefore, we used a liberal set of adjudication criteria designed to include patients if a serious upper gastrointestinal complication could not be ruled out. The final analysis included all indeterminate cases to avoid underestimating the risk. Because of the serious nature of the outcome, it seems unlikely that a case of gastrointestinal bleeding would go undetected or unrecorded. More likely, our strategy of including potential cases classified as "unknown" may have resulted in our overestimating the risk of having a serious upper gastrointestinal bleeding event.

Further, it is difficult to make comparisons without head-to-head randomized clinical trials. Currently available studies of the newer NSAIDs use different patient samples with varying risk factors. An important difference among analyses of upper gastrointestinal events in outcome studies is the definition of endpoints and the method used to come to a conclusion. Until recently, most published studies on NSAID-related gastrointestinal toxicity did not use predefined endpoints or adjudication committees. Observational studies relied on a post hoc identification of codes from the *International Classification of Diseases, Ninth Revision* or hospitalizations for gastrointestinal complications. Recent outcome trials have used predefined endpoint criteria and introduced important monitoring and workup guidelines (13,14,18,19). The criteria used to identify upper gastrointestinal events in some studies (13) require direct visualization of a lesion (either by upper gastrointestinal endoscopy or radiography).

In conclusion, we found that the risk of serious gastrointestinal complications was generally lower with meloxicam than with diclofenac, naproxen, and piroxicam, and that this risk was dose dependent. In contrast, the risk of thromboembolic events among the NSAIDs was generally similar, although diclofenac was associated with the highest risk. Given that most patients were treated for less than 2 months, the long-term risk estimates for gastrointestinal and cardiovascular complications are not certain.

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