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ORIGINAL REPORT

Baseline Risk of Gastrointestinal Disorders Among New Users of Meloxicam, Ibuprofen, Diclofenac, Naproxen and Indomethacin

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SUMMARY

Meloxicam (Mobic®) was introduced in the UK in 1996 as a nonsteroidal anti-inflammatory drug (NSAID). To help evaluate the postmarketing experience with meloxicam in the UK, we used the General Practitioners Research Database (GPRD) to characterize the baseline risk of an upper gastrointestinal (GI) event among new users of meloxicam, ibuprofen, diclofenac, naproxen and indomethacin. We selected for analysis a random sample of 5000 meloxicam users, and 5000 users of each of the comparator NSAIDS except indomethacin, for which we selected 2500 subjects. Comparators were matched to meloxicam subjects on age and sex. We examined for each subject history of certain GI diagnoses and recent use of anti-inflammatory drugs and acid-suppressing drugs. We found that patients receiving meloxicam were at least twice as likely as patients receiving other NSAIDs to have a recent history of GI diagnoses or treatment. We conclude that in the UK meloxicam was used more often than other popular NSAIDs among patients who were at increased baseline risk of GI events. The occurrence of GI events among users of meloxicam, even at a relatively high frequency, therefore, would be expected based solely on this increased baseline risk. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS — Meloxicam; NSAIDS; Epidemiology

INTRODUCTION

Meloxicam (Mobic®) is a nonsteroidal anti-inflammatory drug (NSAID) introduced in the UK and other countries in 1996. Clinical trials have suggested that meloxicam has better gastrointestinal (GI) tolerability than other NSAIDs, possibly due to its preferential inhibition of the COX-2 enzyme as compared with COX-1.[1,2] Despite being the largest NSAID trial conducted to date, meloxicam studies were not sufficiently large to conclude that the apparently improved GI tolerability also extends to reduced risk of upper GI perforations, ulcers and bleeds.[1,2] Thus, it was noted[3] that 'there is no convincing evidence that the risk of the severest adverse gastrointestinal events, namely peptic ulceration, perforation and bleeding, is lower with meloxicam than with other NSAIDs'. Postmarketing experience in the UK has been consistent with clinical trials in showing that the most common kinds of adverse events most frequently reported with meloxicam are GI events.[4] For this reason, the labelling for meloxicam was strengthened to be similar to other NSAIDs in alerting health practitioners to the possible risk of GI events.

It has been stated that meloxicam 'shares the common unwanted effects of other NSAIDs and the same precautions apply to its use, especially in patients at high risk for peptic ulceration'.[3] This statement could be misunderstood as suggesting that the risks associated with meloxicam are the same as the risks associated with other NSAIDs. Merely because meloxicam is associated with the same *kinds* of GI events as other NSAIDs, however, does not mean that meloxicam carries the same *risk*

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of these events as other NSAIDs. To make matters more complicated, in postmarketing surveillance, where conditions are not as well-controlled as they are in clinical trials, comparisons of disease frequency typically do not allow for valid inference. For example, if meloxicam was prescribed preferentially to patients who, at the time of receiving meloxicam, were already at increased baseline risk of GI events, one would expect to observe increased rates of GI events associated with meloxicam but unrelated to any adverse drug effect.

This study was conducted to evaluate whether or not patients receiving meloxicam soon after its introduction in the UK were at inherently greater baseline risk of GI events than patients receiving other NSAIDs. Specifically, we characterized the baseline risk of GI disorders among new users of meloxicam, ibuprofen, diclofenac, naproxen and indomethacin.

METHODS

The study was conducted using the population included in the General Practice Research Database (GPRD), formerly VAMP Research in the UK.[5] The GPRD contains computerized medical information recorded by general practitioners for more than 3 million people in the UK.[5] The Office of National Statistics organizes this information so that it can be used for research projects. The computerized information includes demographics, details of all general practitioners' visits, diagnoses from specialists' visits and hospitalizations, results of laboratory tests and a free text section. In addition, prescriptions written by the general practitioner are issued directly from the computer. For coding purposes, a modification of the OXMIS classification system is used to register medical diagnoses. A drug dictionary based on data from the Prescription Pricing Authority is used to record medicines. The accuracy and completeness of recorded data have been documented in previous validation studies of the GPRD database.[6,7] For instance, it has been found that over 90% of all referrals are entered on the general practitioners' computers with a code with reflects the specialists diagnosis.[6]

We identified all users of meloxicam in the GPRD from the time of its introduction in September 1996 until November 1997, the most recent date for which data were available. We selected for analysis a random sample of 5000 meloxicam users from among all people with at least 1 year of information prospectively recorded in the database before they received meloxicam. We then identified for comparison users of four other NSAIDs (ibuprofen, diclofenac, naproxen and indomethacin) who had their first ever prescription for that particular NSAID recorded in the database between September 1996 and November 1997. From among people with at least 1 year of prospectively recorded information in the database before receiving the NSAID, we selected a stratified random sample of 5000 patients each among users of ibuprofen, diclofenac, and naproxen. Owing to smaller numbers of users of indomethacin, we selected a stratified random sample of 2500 users of indomethacin. The comparison groups were frequency-matched to the meloxicam group according to age and sex. The index date for each subject was the date of first prescription for meloxicam or one of the four comparator NSAIDs.

To characterize baseline risk of GI events, we searched the records of each patient for the period before the index date. Specifically, we searched for a history of diagnosis of dyspepsia, gastritis, duodenitis, or peptic ulcer during the prior year. We also examined history of use of medications related to GI events and their treatment, including gastroprotective agents (antacids, H_2-blockers, proton-pump inhibitors) and analgesics/anti-inflammatory medications (aspirin, NSAIDs, oral corticosteroids). We categorized medications according to use within 6 months (recent use) and more than 6 months before the index date. We compared baseline GI risk at the time of receiving a new NSAID by computing the ratio of the odds of having a GI history for new users of meloxicam divided by the odds of having a GI history for new users of each of the other NSAIDs. We repeated this approach for patients who had either a GI history or recent use of acid-suppressing medication. Odds ratios and 95% confidence intervals were computed from logistic regression models using the SAS (version 6.12) statistical package.

RESULTS

Table 1 presents the distribution of the five study groups by age, sex, smoking status, and body mass index (BMI). Owing to the use of matching in study design, age and sex distributions were similar among the five cohorts. In addition, there were no major differences among the five study groups in smoking habits or BMI.

Table 2 presents for each study group the pro-

Table 1 — Distribution of study groups by age, sex, smoking status and body mass index

	Meloxicam		Ibuprofen		Diclofenac		Naproxen		Indomethacin	
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)
Age										
<24	35	(0.7)	35	(0.7)	35	(0.7)	40	(0.8)	31	(1.2)
25–34	262	(5.2)	262	(5.2)	262	(5.5)	274	(5.5)	212	(8.5)
35–44	585	(11.7)	585	(11.7)	585	(11.7)	613	(12.3)	397	(15.9)
45–54	1028	(20.6)	1028	(20.6)	1028	(20.6)	1071	(21.4)	566	(22.7)
55–64	1210	(24.2)	1210	(24.2)	1210	(24.2)	1264	(25.3)	566	(22.7)
65–74	1145	(22.9)	1145	(22.9)	1145	(22.9)	1161	(23.2)	471	(18.8)
75–84	715	(14.3)	715	(14.3)	715	(14.3)	559	(11.2)	251	(10.0)
85+	20	(0.4)	20	(0.4)	20	(0.4)	18	(0.3)	6	(0.2)
Sex										
Male	1677	(33.5)	1677	(33.5)	1677	(33.5)	1758	(35.2)	1274	(51.0)
Female	3323	(66.5)	3323	(66.5)	3323	(66.5)	3242	(64.8)	1226	(49.0)
Smoking status										
Non-smoker	2935	(58.7)	2901	(58.0)	2882	(57.6)	2914	(58.3)	1344	(53.8)
Smoker	1119	(22.4)	1160	(23.2)	1150	(23.0)	1175	(23.5)	646	(25.8)
Ex-smoker	468	(9.4)	394	(7.9)	415	(8.3)	434	(8.7)	235	(9.4)
Unknown	478	(9.6)	545	(10.9)	553	(11.1)	477	(9.5)	275	(11.0)
Body Mass Index										
<20	168	(3.4)	240	(4.8)	217	(4.3)	153	(3.1)	74	(3.0)
20–24	1389	(27.8)	1480	(29.6)	1449	(29.0)	1483	(29.7)	621	(24.8)
25–29	1599	(32.0)	1504	(30.1)	1530	(30.6)	1548	(31.0)	821	(32.9)
30+	930	(18.6)	703	(14.1)	745	(14.9)	824	(16.5)	464	(18.6)
Unknown	914	(18.3)	1073	(21.5)	1059	(21.2)	992	(19.8)	520	(20.8)

portion of subjects who used analgesic and anti-inflammatory medications (aspirin, NSAIDs and oral corticosteroids) during the 6 months before the index date, subjects who used medications intended to prevent or treat the GI effects of analgesic and anti-inflammatory medications during the same period, and subjects who had a history of GI diagnoses in the prior year. The proportion of subjects who used aspirin, and especially NSAIDs or oral corticosteroids, during the past 6 months, was greater for subjects who received meloxicam than for subjects who received each of the other NSAIDs. In addition, subjects prescribed meloxicam were more likely than subjects prescribed each of the other NSAIDs to have had a history of dyspepsia, gastritis/duodenitis and peptic ulcer.

Table 3 presents the estimates of odds ratios comparing meloxicam with each of the other NSAIDs with regard to history of GI diagnoses or recent use of H_2-blockers or proton-pump inhibitors. The results indicate that patients with a history of dyspepsia, gastritis, duodenitis, or peptic ulcer, had about twice the odds of receiving meloxicam as receiving each of the other NSAIDs. For patients with a history of GI diagnoses in the past year or treatment with H_2-blockers or proton-pump inhibitors during the past 6 months, the odds ratios of receiving meloxicam as compared with each of the other NSAIDs were two- to three-fold. Each of these odds ratios is estimated with good precision, as indicated by the width of the confidence intervals.

DISCUSSION

In the UK from September 1996 through November 1997, meloxicam was more likely than either ibuprofen, diclofenac, naproxen or indomethacin to be prescribed to patients who had a recent diagnosis of or treatment for a GI event and who, therefore, were at increased baseline risk of having a GI event before receiving the NSAID. Baseline risk

Table 2 — Distribution of study groups by recent use of analgesic/anti-inflammatory drugs, gastrointestinal protecting drugs, and history of gastrointestinal diagnosis

	Meloxicam		Ibuprofen		Diclofenac		Naproxen		Indomethacin	
	$N = 5000$	%	$N = 5000$	%	$N = 5000$	%	$N = 5000$	%	$N = 5000$	%
Recent use* of analgesic/anti-inflammatory drugs										
Aspirin	496	9.9	374	7.5	389	7.8	386	7.7	205	8.2
NSAIDs	2489	49.8	396	7.9	1109	22.2	1413	28.3	942	37.7
Oral corticosteroids	515	10.3	191	3.8	246	4.9	255	5.1	149	6.0
Recent use* of acid-suppressing drugs										
Antacids	503	10.1	270	5.4	301	6.0	269	5.4	129	5.2
H_2 blockers	620	12.4	202	4.0	242	4.8	222	4.4	137	5.5
Proton-pump inhibitors	555	11.1	151	3.0	195	3.9	158	3.2	113	4.5
History of GI diagnoses†										
Dyspepsia	1922	38.4	1016	20.3	1097	21.9	1128	22.6	602	24.1
Gastritis/duodenitis	440	8.8	205	4.1	210	4.2	235	4.7	132	5.3
Peptic ulcer	305	6.1	156	3.1	147	2.9	129	2.6	97	3.9

GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.
* Recent use in past 6 months.
† History in past year.

Table 3 — Odds ratios for receiving meloxicam as compared with other NSAIDs by GI history* and recent use† of acid-suppressing drugs‡

	Ibuprofen		Diclofenac		Naproxen		Indomethacin	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
GI history	2.4	(2.2–2.7)	2.2	(2.0–2.4)	2.2	(2.0–2.4)	1.9	(1.8–2.2)
GI history or recent use of acid-suppressing drugs	2.8	(2.6–3.1)	2.6	(2.4–2.8)	2.6	(2.4–2.8)	2.2	(2.0–2.4)

* GI history is dyspepsia, gastritis, duodenitis, or peptic ulcer in past year.
† Recent use in past 6 months.
‡ Acid-suppressing drugs are H_2 blockers or proton-pump inhibitors.

was characterized by a history of dyspepsia, gastritis, or peptic ulcer in the past year, or treatment with acid-suppressing drugs during the past 6 months. Previous GI events are assumed to be markers for future GI events, including GI perforations, ulcers and bleeds.[8] Consequently, patients who received meloxicam would be expected to have higher rates of GI events than other commonly used NSAIDs based solely on their baseline risk and apart from any adverse effect of meloxicam.

The reasons that meloxicam was prescribed preferentially to high-risk patients are unclear, but could reflect many factors. For instance, a new NSAID might be expected to attract patients who recently stopped using an NSAID because they experienced adverse effects. This hypothesis is supported by our observation that meloxicam subjects were more likely than others to be recent users of NSAIDs. In addition, meloxicam was promoted as gentler on the GI tract than other NSAIDs, based on clinical studies[1,2] and certain pharmacologic properties (i.e. preferential inhibition of COX-2 versus COX-1) that offer theoretical safety advantages but which have not yet been demonstrated conclusively to result in improved clinical safety.

Because these results pertain to medical histories of subjects before they received meloxicam, the data are not directly informative about the safety or efficacy of meloxicam. However, insofar as they relate to the underlying baseline risk of GI events among patients who received meloxicam as compared with patients who received other NSAIDs during the same calendar period, these data bear on the interpretation of reports of GI events associated with meloxicam in the UK.[4] In particular, the tendency to use meloxicam in high-risk patients means that there will be more GI events in users of meloxicam than would otherwise be expected. Further, these results demonstrate that non-comparability with regard to baseline risk can occur even among drugs in the same therapeutic class. Any postmarketing comparison of GI risks among users of meloxicam with users of other NSAIDs, therefore, needs to take into account the underlying baseline risk of the populations being compared. Currently, the most valid information about the safety of meloxicam comes from clinical studies in which subjects are assigned by random allocation to different treatment groups.[1,2]

The study has several limitations. Although the GPRD has been shown to be fairly complete and accurate,[5–7] automated data do not measure perfectly the medical histories and drug use of the study population. In particular, not every patient with a GI illness would necessarily have such history recorded, so the data may underestimate the proportion of patients with a history of GI illness. In addition, recording of drugs prescribed does not correspond perfectly to actual use of prescription medications and even less so to use of non-prescription medications such as aspirin. We suspect that to the extent that these errors occur, however, the data are probably similarly accurate for meloxicam subjects as for users of other NSAIDs. If these kinds of errors occur to the same degree across study groups, then they would not bias the effect estimates and would not affect our conclusions.

The results of this study, if valid, cannot necessarily be generalized beyond the population covered by the GPRD, the comparators selected, or the time of the study. That is, the GPRD population may not be representative of the UK population with regard to some factor related to NSAIDs or GI illness. We are unaware of any such factor, however; indeed, there is every indication that the GPRD data reflect accurately the UK population.[5] Nevertheless, the results of this study depend on many factors that change over time, including physician prescribing patterns, disease management practices, the patient population, alternative therapies available, etc. Therefore, these results should not be expected to be uniform over time, nor can they easily be compared with studies conducted in different populations at different times.

In conclusion, this study found that in the UK meloxicam was used more often than other popular NSAIDs among patients at increased risk of GI events. This increased baseline risk needs to be considered when using postmarketing data to evaluate the safety of meloxicam or, more generally, when comparing the risks among individual NSAIDs in epidemiological studies. The occurrence of GI events among users of meloxicam, even at a relatively high frequency, would be expected based solely on this increased baseline risk.

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