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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

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SUMMARY

SELECT is a large-scale, prospective, international, multicentre, double-blind, double-dummy, randomized, parallel-group trial. Patients with exacerbation of osteoarthritis were treated with the recommended dose of meloxicam (7.5 mg) or piroxicam (20 mg) once daily for 28 days; 4320 patients were administered meloxicam and 4336 piroxicam. The incidence of adverse events was significantly lower in the meloxicam group (22.5%) compared with the piroxicam group (27.9%; $P < 0.001$), mainly due to the significantly lower incidence of gastrointestinal (GI) adverse events in the meloxicam than in the piroxicam group (10.3% *vs* 15.4%; $P < 0.001$), while the efficacy of both drugs was equivalent. Individual GI events occurred significantly less often with meloxicam than piroxicam: dyspepsia (3.4% *vs* 5.8%; $P < 0.001$), nausea/vomiting (2.5% *vs* 3.4%; $P < 0.05$) and abdominal pain (2.1% *vs* 3.6%; $P < 0.001$). There were 16 patients with perforations, ulcerations or bleeding (PUBs) of the upper GI tract in the piroxicam group compared with seven in the meloxicam group (relative risk piroxicam:meloxicam = 1.4). Four PUBs were complicated (perforations or bleedings); none of these occurred in the meloxicam group (relative risk piroxicam:meloxicam = 1.9). The outcome of SELECT is consistent with that of the large-scale clinical trial of similar design and size which compared 7.5 mg meloxicam with 100 mg diclofenac in patients with osteoarthritis, and with a previous global analysis of the safety of meloxicam. It adds further data to the proposed relationship between selective inhibition of cyclooxygenase-2 and improved GI tolerability of non-steroidal anti-inflammatory drugs.

KEY WORDS: Meloxicam, Piroxicam, Osteoarthritis, Gastrointestinal tolerability, Cyclooxygenase, Perforations, ulcerations or bleedings.

To investigate further the hypothesis of improved tolerability with selective cyclooxygenase (COX)-2 inhibitors, the present study was performed in conjunction with a separate study, with a similar design and size, comparing meloxicam 7.5 mg to diclofenac slow release (SR) 100 mg [1]. These two large-scale comparisons intended to compare at recommended equi-effective doses the overall safety of meloxicam to established non-steroidal anti-inflammatory drugs (NSAIDs), with diclofenac being among the least toxic NSAIDs and piroxicam [2] having a high ranking in comparison to other NSAIDs [3].

Meloxicam 7.5 mg and 15 mg was investigated in a number of double-blind randomized clinical trials in comparison to several NSAIDs, including piroxicam, diclofenac and naproxen, leading to international registration. Overall, meloxicam has been shown to have a favourable gastrointestinal (GI) tolerability profile compared with these standard NSAIDs [4]. No comparative efficacy and safety data of meloxicam to ibuprofen have been obtained so far in patients with acute flares of osteoarthritis (OA).

Significant advantages with regard to efficacy were observed for meloxicam 15 mg in one study compared to piroxicam 20 mg [5]. In short- and long-term treatment, meloxicam 15 mg showed, although not statistically significantly different, larger improvements in pain scores than piroxicam 20 mg [6, 7].

On the basis of these studies, international registration for meloxicam was granted with meloxicam 7.5 mg being the recommended dose for the symptomatic treatment of acute flares of OA. Hence, meloxicam 7.5 mg was selected for comparison to piroxicam 20 mg, which was thought to be of comparable efficacy based on the results of previous trials.

For ibuprofen, so far no equi-effective dose in the treatment of acute flares of OA compared to meloxicam has been established.

In particular, the aim of this large-scale trial was to identify possible differences between meloxicam and the standard NSAID, piroxicam, in overall safety and particularly in terms of GI tolerability, and to provide further data on the potential role of NSAIDs which display selectivity towards inhibition of COX-2 relative to COX-1.

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PATIENTS AND METHODS

This was a prospective, large-scale, double-blind, double-dummy, randomized trial conducted internationally in 12 countries. The trial protocol was developed and the trial was monitored by a steering committee consisting of the authors with representatives from Boehringer Ingelheim. The trial was approved by the appropriate ethics committees and was conducted in accordance with the Declaration of Helsinki and good clinical practice. Most patients were recruited from general practice. All patients gave written informed consent.

The design, clinical protocol, assessments of tolerability, safety and efficacy, as well as statistical methods, were identical to those of another large-scale comparison of meloxicam 7.5 mg with diclofenac 100 mg SR [1], except for the selection of the comparator, which in the study reported here was piroxicam 20 mg.

RESULTS

Of 9286 patients enrolled and randomized (4645 meloxicam 7.5 mg, 4641 piroxicam 20 mg) in 922 centres in 12 countries, 630 patients (325 meloxicam 7.5 mg, 305 piroxicam 20 mg) were not treated, mainly because their eligibility could not be confirmed during the screening phase or at the baseline visit, representing 7% of the randomized population; thus, 8656 patients were evaluated on an intent-to-treat basis for safety and efficacy (Table I). Of these, 4320 were treated with meloxicam 7.5 mg and 4336 with piroxicam 20 mg. The median time on study medication was calculated to be 28 days. In both treatment groups, 79% of patients were pre-treated with NSAIDs. The trial was completed by 89% in the meloxicam group and 88% in the piroxicam group. Approximately 5% of all patients were treated with drugs for peptic diseases (antacids, proton pump inhibitors, H_2-blockers) before, and continued during, the trial (4.6% in the meloxicam group, 5.6% in the piroxicam group). Overall, the two treatment groups were comparable with respect to demographic characteristics and concomitant diseases, and were considered to be representative of the general population of patients with OA (Table I).

TABLE I
Baseline characteristics of patients

	Meloxicam $n = 4320$	Piroxicam $n = 4336$
Male:female (%)	32:68	33:67
Mean age ± SD. (yr)	61.3 ± 12.3	61.6 ± 12.3
⩽65 yr (%)	63	61
>65 yr (%)	37	39
Location of OA (%)		
Hip	14	15
Knee	46	44
Hand	12	11
Vertebral spine	28	30
Median duration of OA (months)	45	48
History of PUBs (%)	6.4	5.6
Concomitant administration of gastroprotective drugs (%)	4.6	5.6
Previous use of NSAIDs (%)	79	79

PUB, perforation, ulceration or bleeding.

Tolerability assessments

Patients on meloxicam 7.5 mg reported fewer adverse events (22.5%) than those on piroxicam 20 mg (27.9%; $P < 0.001$). The difference in adverse events between the two treatments was attributable to those affecting the GI tract. GI adverse events were found to occur significantly less commonly with meloxicam (10.3%) than piroxicam (15.4%; $P < 0.001$), as shown in Table II. Dyspepsia, nausea and vomiting, abdominal pain and diarrhoea were the most commonly reported individual events in the GI category and, with the exception of diarrhoea, occurred significantly less often with meloxicam ($P < 0.05$ at least; Fig. 1). Patients previously treated with drugs for peptic diseases showed higher incidences of GI adverse events compared to all patients. Nevertheless, in this subgroup, meloxicam also showed a lower frequency of GI adverse events than piroxicam (17.2% *vs* 21.6%).

The proportion of GI adverse events thought to be causally related to treatment was slightly higher in the piroxicam than in the meloxicam group (83% *vs* 79%). With both drugs, most of these adverse events were mild (49% piroxicam *vs* 47% meloxicam) or moderate (41% piroxicam *vs* 42.5% meloxicam) in intensity. In terms of withdrawals due to GI adverse events (Table II), the difference in favour of meloxicam was significant (3.8% *vs* 5.3%; $P < 0.01$; odds ratio 0.71, 95% CI 0.58–0.87). In subpopulations of elderly and younger males and elderly and younger females, the frequency of GI adverse events was always significantly higher (except in elderly males) in the piroxicam- than in the meloxicam-treated patients. Within treatment groups, the incidences of GI adverse events in males were comparable for those in the elderly (>65 yr) and younger (⩽65 yr) age groups (piroxicam 13.91% *vs* 13.03%; meloxicam 9.95% *vs* 10.04%). Fewer elderly than younger females treated with meloxicam reported GI adverse events (9.02% *vs* 11.42%). Although there was a small difference between elderly and younger females in the piroxicam group (16.75% *vs* 15.99%), this was less pronounced, and not statistically significant. In the piroxicam group, females suffered more GI adverse events than males (16.4% *vs* 13.3%).

Out of a total of 448 patients with a history of perforation, ulceration or bleeding (PUB), 236 were treated with meloxicam and 212 with piroxicam. Adverse events were reported in 91 (38.6%) and 95 (44.8%) patients, respectively. GI adverse events were reported in 58 (24.6%) patients treated with meloxicam and in 64 (30.2%) patients receiving piroxicam.

Seven patients treated with meloxicam suffered nine PUBs, compared with 17 PUBs in 16 patients receiving piroxicam (relative risk piroxicam:meloxicam = 1.4). Four PUBs were complicated (perforations or bleedings); none of these occurred in the meloxicam group (relative risk piroxicam:meloxicam = 1.9; Table III). One patient on meloxicam developed retching,

TABLE II
Overview of adverse events

Patients	Meloxicam		Piroxicam				
	n	%	*n*	%	*P*	OR	95% CI
In trial	4320	100	4336	100	–	–	–
With any AEs	970	22.5	1211	27.9	<0.001	0.75	0.68–0.82
With GI-AEs	444	10.3	667	15.4	<0.001	0.63	0.55–0.72
Withdrawn due to any AEs	265	6.13	314	7.24	0.06	0.84	0.71–0.99
Withdrawn due to GI-AEs	164	3.79	228	5.26	<0.01	0.71	0.58–0.87

OR, odds ratio; AEs, adverse events.

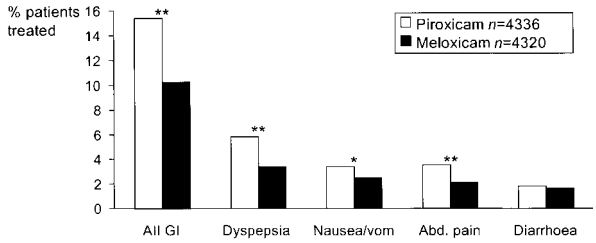

FIG. 1.—Incidence of GI adverse events. $*P < 0.05$; $**P < 0.001$ between treatments. vom, vomiting; abd., abdominal.

followed by 'coffee ground' vomiting, with a Mallory–Weiss tear, but no ulcer. Three days later, and 6 days after the last dose of meloxicam, endoscopy revealed a non-bleeding ulcer in this patient. No other patient on meloxicam had bleeding or perforation associated with ulceration.

Overall, adverse events occurred significantly less often (Table II) in patients in the meloxicam group than in the piroxicam group (22.5% *vs* 27.9%; $P < 0.001$) which was mainly due to the significantly lower incidence of GI adverse events with meloxicam. The incidences of adverse events affecting other body systems were low (<5%), differences between treatment groups for all body systems were <1%.

Out of a total of 1671 adverse events in the meloxicam group, 1471 were classified as mild or moderate and 194 as severe in intensity (six unclassified). The corresponding figures for piroxicam were 2121 adverse events in total; 1912 mild or moderate, 202 severe and seven unclassified. Overall, 54 and 59.5% of all adverse events were considered to be related to treatment with meloxicam and piroxicam, respectively; furthermore, there was a lower frequency of withdrawals due to all adverse events (Table II) with meloxicam than piroxicam, that fell short of statistical significance (6.1% *vs* 7.2%; $P = 0.06$). There was no significant difference between treatments in relation to serious adverse events (26 patients on meloxicam, 30 on piroxicam; $P = 0.69$). Serious adverse events considered related to treatment occurred rarely, and with similar frequency, in the meloxicam and piroxicam groups (7 *vs* 11). In the evaluation of global tolerability, the treatment groups were comparable (combined 'good'/'satisfactory' categories) as judged by physicians or patients (both assessments: meloxicam 90% *vs* piroxicam 88%).

Six patients in the meloxicam group and seven patients in the piroxicam group were hospitalized for GI adverse events. The mean duration of hospital stay for GI adverse events was lower in the meloxicam group than the piroxicam group (9 days *vs* 17 days, respectively), as was the total duration of hospital stay for GI adverse events (56 days *vs* 121 days).

TABLE III
Perforations, ulcerations or bleeding of the upper GI tract*

	Number of patients	
	Meloxicam $n = 4320$	Piroxicam $n = 4336$
Gastric ulcers		
Bleeding	0	1
Perforated	0	2
Uncomplicated	2	4‡
Duodenal ulcers		
Bleeding	0	1
Uncomplicated	0	1
Haematemesis	1†	1
Melaena	4	6§

*The presence of ulceration or bleeding was confirmed by endoscopy. The presence of perforation was confirmed by endoscopy, surgery or X-ray. Patients who were reported to have experienced melaena were also regarded as PUB even if no endoscopy was performed or clinical evidence of bleeding given. One patient in the meloxicam group had a history of GI ulcer at screening and four patients in the piroxicam group had a history of PUBs (two gastric ulcer, one perforated GI ulcer, one GI and duodenal ulcer).

†Patient suffered from concomitant duodenal and gastric ulcer, and haematemesis.

‡One patient had both gastric and duodenal ulcer.

§One patient had concomitant duodenal ulcer and melaena.

The median laboratory values of the blood chemistry, haematology and differential blood cell count did not indicate any relevant changes between baseline and the end of the treatment period. The values showed significantly fewer increases of serum creatinine (2.4% *vs* 3.4%; $P < 0.01$) and urea (8.8% *vs* 17.7%; $P < 0.01$) from the normal into the range above the upper limit of normal in favour of meloxicam compared with piroxicam. There were no significant differences in relevant changes of haemoglobin and haematocrit between the two treatment groups.

Efficacy assessments

The reduction in pain on active movement, assessed by 100 mm visual analogue scale (VAS), was comparable with meloxicam and piroxicam and not signifi-

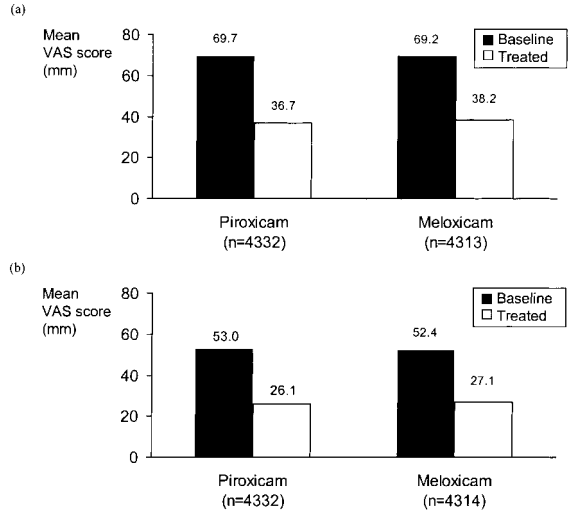

FIG. 2.—(a) Pain on active movement and (b) pain at rest (last observation carried forward, LOCF). Measured on 100 mm VAS where 0 mm = no pain and 100 mm = unbearable pain.
Footnote: Seven patients in the meloxicam group [six in graph (b)] and four patients in the piroxicam group were not included in the LOCF analyses of VAS scores because baseline values were not available.

cantly different (Fig. 2a). The mean reduction from baseline to the end of the trial was −31 mm (−45%) with meloxicam and −33 mm (−47%) with piroxicam. The mean treatment difference at the end of the trial was 1.97 mm (95% CI 1.01–2.94 mm) which is within the predefined equivalence region of 17 mm [8]. A similar pattern was observed with pain at rest, with no significant difference between treatments; the mean change from baseline to the end of treatment was −25 mm (−48%) with meloxicam and −27 mm (−51%) with piroxicam (Fig. 2b). The mean treatment difference at the end of the trial was 1.54 mm (95% CI 0.54–2.54 mm) which is again within the predefined equivalence region of 10.5 mm [8].

Seventy-five meloxicam-treated patients (1.7%) and 68 piroxicam-treated patients (1.6%) withdrew prematurely due to lack of efficacy.

Based on the predefined equivalence boundaries [8], meloxicam and piroxicam were also shown to be equivalent with regard to all other efficacy assessments, with no significant differences between treatments (Table IV). The change in patients' arthritic condition improved from a mean value of 3.2 at baseline to 2.0 at the end of treatment with both drugs. The final judgement of the patients' arthritic status was comparable with meloxicam and piroxicam (66% *vs* 70% of patients improved, respectively). In addition, at the end of treatment, the percentage of patients rating global efficacy with meloxicam and piroxicam as 'good' or 'satisfactory' was 70 and 73%, respectively; the corresponding proportions for physician-rated global efficacy were 71 and 75%, respectively.

DISCUSSION

The large-scale SELECT (Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies) trial demonstrated that there was a significant advantage for meloxicam compared with piroxicam with regard to the frequency of GI adverse events in a population of OA patients representative of those found in clinical practice. Individual GI adverse events, including dyspepsia, nausea and vomiting, and abdominal pain, occurred significantly less frequently with meloxicam, and patients receiving meloxicam were significantly less likely to be withdrawn due to GI adverse events. The overall adverse event rate was significantly lower in meloxicam- than piroxicam-treated patients, mainly due to the lower GI adverse event rate with meloxicam. Meloxicam was associated with fewer ulcerations of the upper GI tract, including fewer complications (perforation or bleeding) than piroxicam, but, as expected in a trial of 4 weeks duration [9], the incidences were too low to show a statistically significant difference ($P < 0.1$).

In respect of GI tolerability, our findings are consistent with those of another large-scale trial, the Meloxicam Large-scale International Study Safety Assessment (MELISSA). Like SELECT, MELISSA was a prospective, randomized, double-blind trial; 4635 OA patients received treatment with meloxicam 7.5 mg once daily and 4688 received diclofenac 100 mg SR for 28 days. In common with SELECT, there were fewer GI adverse events reported for meloxicam compared with the comparator group (13% *vs* 19%; $P < 0.001$). Moreover, individual events (dyspepsia, nausea and vomiting, abdominal pain and diarrhoea) occurred significantly less often with meloxicam than diclofenac

TABLE IV
Efficacy assessments

Assessment	Meloxicam $n = 4320$	Piroxicam $n = 4336$	Mean Δ between treatments (95% CI)
Arthritic condition (mean change from baseline*)	−1.18 ± 1.07	−1.25 ± 1.07	0.07 (0.03–0.11)
Final judgement of arthritic status (mean score†)	1.37 ± 0.57	1.32 ± 0.54	0.05 (0.03–0.07)
Final global efficacy (mean score*)			
Patient assessment	1.93 ± 0.92	1.86 ± 0.91	0.07 (0.03–0.10)
Physician assessment	1.90 ± 0.88	1.83 ± 0.87	0.07 (0.04–0.10)
Patients withdrawing due to lack of efficacy	75/4320 (1.7%)	68/4336 (1.6%)	

*Based on four-point scale (1 = good; 2 = satisfactory; 3 = not satisfactory; 4 = bad).
†Based on three-point scale (1 = improved; 2 = unchanged; 3 = deteriorated).

($P < 0.05$ at least). Efficacy was comparable for both NSAIDs.

Furthermore, the results of both SELECT and MELISSA confirm a global analysis of safety data from meloxicam clinical trials [10]. In this analysis, meloxicam 7.5 mg and 15 mg ($n = 4175$) were compared with piroxicam 20 mg ($n = 906$), diclofenac 100 mg SR ($n = 324$) and naproxen 750–1000 mg ($n = 243$). Both doses of meloxicam were significantly better tolerated than all comparator NSAIDs in terms of all GI adverse events, and, in most cases, significantly better tolerated than comparator drugs with respect to severe GI events, discontinuations due to GI events, individual GI events (dyspepsia, abdominal pain), and unspecified upper GI adverse events. After 30 days of treatment, 13% of patients on meloxicam 7.5 mg reported GI adverse events compared with 19% on diclofenac, 17.6% on piroxicam and 11% on placebo [4].

The number of patients affected by PUB-related complications during SELECT was lower in the meloxicam group than in the piroxicam group (7 *vs* 16) and the number of complications (perforations or bleeding) was also lower (one questionable ulcer complication on meloxicam *vs* four definite ulcer complications on piroxicam), although the difference did not achieve statistical significance ($P < 0.1$). These figures for meloxicam support those from MELISSA, where five patients reported PUBs on meloxicam, all of which were uncomplicated, i.e. no perforations or bleeding, compared with seven reports on diclofenac, four of which were complicated. The low incidences of PUBs in both these studies may be accounted for by the short (4 week) duration of treatment. In the global analysis of safety data already reported from meloxicam clinical trials, the incidence of PUBs was significantly lower with meloxicam 7.5 mg than with piroxicam 20 mg (0.1% *vs* 1.2%; $P < 0.05$) over a period of 6 months [10]. Consistent with these results is the observation that treatment with meloxicam was associated with a lower average duration of hospital stay, and a lower total duration of hospital stay, for GI adverse events.

This is the first trial comparing piroxicam 20 mg, a dose commonly used in general practice for OA, with meloxicam 7.5 mg. The efficacy of meloxicam and piroxicam was equivalent, as shown in a range of standard efficacy parameters. This finding confirms the results from previous studies [5–7] which were the basis for the dose recommendation of meloxicam in international registrations. These results of SELECT are consistent with those of the MELISSA trial in which the efficacy of meloxicam 7.5 mg was shown to be equivalent to diclofenac 100 mg SR. NSAIDs should be used cautiously in patients known to be at risk of upper GI tract bleeding, including the elderly or those with a history of peptic ulcer. In SELECT, the number of elderly patients (>65 yr old) and the number of patients with a peptic ulcer history was similar in both treatment groups. When subgroups of younger (≤65 yr) and elderly (>65 yr) male and female patients were analysed, the incidence of GI adverse events was found to be lower with meloxicam than piroxicam in every group.

The results of SELECT, together with the results of MELISSA and the global analysis of meloxicam studies, are supportive of the view that meloxicam has a GI tolerability profile superior to that of piroxicam and other standard NSAIDs. The importance of the superiority of the tolerability profile and the related improvement can be approximated by calculating the relative differences of adverse event incidences, which are of the order of 19–30%. For adverse events in general, this figure is 19% (22.5 *vs* 27.9), for GI adverse events it is 33% (10.3 *vs* 15.4), and for GI adverse events in patients with a previous history of PUB it is 19% (24.6 *vs* 30.2). For increases in creatinine and urea above the upper limit of normal, the respective figures are 29 and 50%. These approximations are somewhat conservative as they do not take the placebo incidences into account. GI adverse events have been observed to occur under 3 weeks of placebo treatment with an incidence of around 11% [4].

The reason for the difference in tolerability between meloxicam and piroxicam may lie in differences in their relative inhibition of COX-1 and COX-2 [11]. Meloxicam is a member of a new class of NSAIDs that have been shown to be more selective for COX-2 than COX-1 [11, 12], and this property may explain its improved GI tolerability. Piroxicam, on the other hand, strongly inhibits both COX-1 and COX-2 at therapeutic concentrations, and shows some preference for COX-1 *in vitro* [13, 14], possibly explaining the associated greater risk of serious GI side-toxicity, compared with some other NSAIDs, seen in epidemiological studies [3]. The results of SELECT lend further support to this theory, since the major difference in tolerability between the two drugs lay in those effects thought typically to be mediated by COX-1. A longer study duration might have been expected to show even greater differences between the two drugs with respect to serious GI toxicity.

NSAIDs that selectively inhibit COX-2 relative to COX-1 may prove to be an important step forward in developing better tolerated treatment for OA, and thus reducing the morbidity and mortality associated with standard NSAIDs.

CONCLUSIONS

In SELECT, one of the largest prospective, double-blind trials to compare the tolerability of two NSAIDs, meloxicam induced significantly fewer GI adverse events than an equi-effective dose of piroxicam. Meloxicam treatment was also associated with fewer perforated or bleeding ulcers than treatment with piroxicam. These findings were consistent with the results of the MELISSA study and a pooled analysis of double-blind clinical trials, which have demonstrated that meloxicam has an improved GI tolerability profile compared with equi-effective doses of the standard NSAIDs piroxicam, diclofenac and naproxen.

The COX concept predicts that COX-2 inhibition underlies the efficacy of NSAIDs, whilst their toxicity

is due to inhibition of COX-1. Standard NSAIDs are equipotent against COX isoforms, or selective towards COX-1; selective COX-2 inhibitors therefore promise to deliver equivalent efficacy, and an improved tolerability profile, compared with standard NSAIDs. Meloxicam is the first of a new class of NSAIDs with selectivity towards COX-2 rather than COX-1, which may explain its superior GI tolerability compared with other NSAIDs. The results of SELECT support the relevance of the COX concept to improved therapy for arthritic disease.

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