

Update on Meloxicam (*Mobicox*[®]) & COX-2 Selectivity

COX-2 Selectivity/Specificity

◆ There is a lot of discussion regarding the relative COX-2 selectivity of meloxicam compared to celecoxib (*Celebrex*[®]) and rofecoxib (*Vioxx*[®]). A December 2000 *RxFiles Q&A Summary* regarding meloxicam stated that it had “relatively selective but not specific COX-2 inhibition” as discussed in a variety of literature.^{1,2,3,4,5} Boehringer Ingelheim (Canada) Ltd. (BICL) has been detailing meloxicam as an agent with COX-2 selectivity comparable to celecoxib based on data from BICL sponsored work of Warner et al.⁶ This research measured NSAID inhibition of COX-1 when COX-2 enzyme activity is inhibited by 80%. It found that both meloxicam and celecoxib were 5-50 fold selective for COX-2, with rofecoxib being >50 fold COX-2 selective. The interpretation of studies measuring relative COX-2 to COX-1 selectivity is subject to much debate due to differences in the various assays used. As with rofecoxib and celecoxib, meloxicam does not appear to affect platelet aggregation, a trait that supports high COX-2 selectivity.⁷

◆ The fight over the COX-2 market share has resulted in discussion regarding the suitability of the term “**COX-2 specific**” which has been used for both celecoxib and rofecoxib. According to a recent memorandum, the Pharmaceutical Advertising Advisory Board (PAAB) has stated that “no product has received approval for use of the term “COX-2 specific” in advertising because it is not in the product monograph of any of the three drugs” (*Mobicox*[®], *Vioxx*[®], and *Celebrex*[®]). A look at current evidence regarding actual safety data (e.g. risk of complicated GI ulcers) will be more relevant to this discussion.

GI Tolerability and Safety

◆ Unfortunately no head-to-head clinical data is available to compare rofecoxib or celecoxib to meloxicam.

◆ Two large-scale, short-term 28day trials have assessed the GI tolerability of meloxicam (see **Table**):

◆ **MELISSA**⁸ showed that compared to diclofenac SR 100mg/day, meloxicam 7.5mg/day caused less GI related adverse drug reactions (ADRs) (13% vs 19%; p=0.001). These ADRs included dyspepsia, nausea & vomiting, abdominal pain and diarrhea. There were 5 (0.1%) serious GI events defined as perforations, ulcers, or bleeds (PUBs) in the meloxicam group compared to 7 (0.15%) in the diclofenac group. While this showed a positive trend it was not statistically significant.

◆ **SELECT**⁹ showed that compared to piroxicam 20mg/day, meloxicam 7.5mg/day caused less GI related ADRs (10.3% vs 15.4%; p=0.001). There were 7 (0.16%) serious GI events (e.g. PUBs) in the meloxicam group compared to 16 (0.37%) in the piroxicam group. Again the difference lacked statistical significance.

◆ The **short duration** and **low-doses** (7.5mg OD) used make it difficult to evaluate the risk for serious GI ADRs; GI ulcer risk can increase greatly with higher NSAID dosages.

◆ A meta-analysis reporting on 12 randomized meloxicam trials suggests that compared to non-COX-2 selective NSAIDs, meloxicam has fewer GI ADRs, less dyspepsia, fewer PUBs, and less frequent discontinuation due to

adverse GI events.¹⁰ This data must be cautiously interpreted due to the inherent limitations of the meta-analysis, such as variability of trial outcomes, and the low dosage of meloxicam used in most trials.

◆ **Meloxicam appears to have better GI tolerance than non-selective NSAIDs. To what extent ulcers and complicated ulcers are also reduced remains to be established.**

◆ Major trials evaluating the safety of the other COX-2 selective drugs, **celecoxib** (*Celebrex*[®]) and **rofecoxib** (*Vioxx*[®]) have been published. These trials differ from the large-scale meloxicam trials as **dosages were 2-4X higher than usually recommended and trial length was longer** (see Table).

◆ The **CLASS**¹¹ study compared celecoxib to non-selective NSAIDs (ibuprofen and diclofenac). The risk of “GI ulcer complications + symptomatic ulcers” were significantly reduced; however significant reductions in complicated ulcers was reduced only for the study arm where patients on ASA were excluded.

◆ The **VIGOR**¹² study compared rofecoxib to naproxen and found significant reductions in complicated ulcers in rofecoxib patients. As opposed to the CLASS trial, ASA patients were excluded from the study and a small increase in risk of acute MI was seen.

◆ These trial results pose many more questions that will require further study (& more updates).

Approximate cost per 30 day prescription in SK (includes allowable markup and dispensing fee):

- ◆ naproxen 375mg po BID (~ \$16)
- ◆ meloxicam 7.5mg po OD (~ \$32)
- ◆ celecoxib 200mg po OD (~ \$52)
- ◆ rofecoxib 12.5mg po OD (~ \$52)

¹ Jackson LM, Hawkey C. COX-2 Selective Nonsteroidal Anti-inflammatory Drugs. *Drugs* 2000;59(6):1207-16.

² Kaplan-Machlis B, Klostermeyer BS. The Cyclooxygenase-2 Inhibitors: Safety and Effectiveness. *Ann Pharmacother* 1999;33:979-88.

³ Meloxicam and selective COX-2 inhibition: the evidence for improved gastrointestinal tolerability. *Drugs and Therapy Perspectives* 1996;8(2):1-4.

⁴ Hawkey CJ. COX-2 Inhibitors (New Drug Classes). *Lancet* 1999;353:307-14.

⁵ Tegeder I, Lotsch J, Krebs S, Muth-Selbach U, Brune K, Geisslinger G. Comparison of inhibitory effects of meloxicam and diclofenac on human thromboxane biosyntheses after single doses and at steady state. *Clin Pharmacol Ther* 1999;65:533-44.

⁶ Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. *Proc Natl Acad Sci USA* 1999;96:7563-8.

⁷ Hecken A, Schwartz JI, Depre M, et al. Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen, and naproxen on COX-2 versus COX-1 in healthy volunteers. *J Clin Pharmacol* 2000;40:1109-20.

⁸ Hawkey C, Kahan A, Steinbruck K, et al. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. International MELISSA Study Group. *Br J Rheumatol* 1998;37:937-45.

⁹ 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;37:946-51.

¹⁰ Schoenfeld P. Gastrointestinal safety profile of meloxicam: a meta-analysis and systematic review of randomized controlled trials. *Am J Med* 1999;107:48S-54S.

¹¹ Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of celecoxib compared with NSAIDs (CLASS). *JAMA* 1999;282:1929-33.

¹² Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis (VIGOR). *NEJM* 2000;343:1520-1528. ^{11,12}Note: additional study results (CLASS/VIGOR) - www.fda.gov/ohrms/docket

Prepared by Loren Regier BSP, BA in consultation with RxFiles advisors & reviewers.
Copyright 2001 Saskatoon District Health; All Rights Reserved.

DISCLAIMER: The content of this newsletter represents the research, experience and opinions of the authors and not those of the Board or Administration of Saskatoon District Health. Neither the authors nor Saskatoon District Health nor any other party who has been involved in the preparation or publication of this work warrants or represents that the information contained herein is accurate or complete, and they are not responsible for any errors or omissions or for the result obtained from the use of such information. Any use of the newsletter will imply acknowledgment of this disclaimer and release any responsibility of Saskatoon District Health, its employees, servants or agents. Readers are encouraged to confirm the information contained herein with other sources.

MELOXICAM (Mobicox®)

Study	Drug & Dose	Duration	# pts	Any GI adverse event – 28days (dyspepsia, etc.)	Perforations or Bleeds - 28 days	Perforations, Ulcers, or Bleeds (PUBs) - 28days	Any event causing DC	Comments
MELISSA ⁸ (n=9323) Mean age=61.5	Meloxicam 7.5mg OD Diclofenac 100mg SR OD	28 days OA	4635 4688	13% 19% (p<0.001)	0 4 not significant	0.1% 0.15% not significant	7.2% 9% (p=0.0014) (due to ADR or ↓efficacy)	<ul style="list-style-type: none"> ♦higher hospitalization rate in diclofenac group ♦diclofenac group had more pts age >65 & pts with hx of PUBs ♦more pts in meloxicam group discontinued due to lack of efficacy but less due to adverse reactions.
SELECT ⁹ (n=8656) Mean age=61.5	Meloxicam 7.5mg OD Piroxicam 20mg OD	28 days OA	4320 4336	10.3% 15.4% (p<0.001)	0 4 not significant	0.16% 0.37% not significant	6.13% 7.24% (p=0.06) NS	<ul style="list-style-type: none"> ♦piroxicam group: more >65yo; but less with a hx of PUBs ♦withdrawals due to GI adverse events less with meloxicam vs piroxicam (3.79% vs 5.26%) p<0.01%

What we know: ♦meloxicam was better tolerated and caused fewer withdrawals due to GI adverse events than non-selective NSAIDs.

What we don't know: ♦whether meloxicam significantly reduces the risk of complicated and symptomatic ulcers compared to non-selective NSAIDs can not be determined from these trials; differences shown in these studies were not statistically significant and the **low-dose (1/2 usual maximum) and short duration (28days)** of the studies makes interpretation difficult.

Meloxicam long-term data: Has been used outside of North America since 1996; >30million prescriptions in > 90 countries); One abstract reports clinically significant GI ADRs/pt-year=0.3 & 0.6 (for 7.5 & 15mg/d dose).

CELECOXIB (Celebrex®) & ROFECOXIB (Vioxx®) Detailed study results for CLASS & VIGOR obtained from submission to FDA arthritis advisory committee Feb01 - <http://www.fda.gov/ohrms/doCKET>

Study	Drug & Dose	Duration	# pts	Any GI adverse events	GI ulcer complications / 100 pt-yrs	GI ulcer complications + symptomatic ulcers / 100 pt-yrs	Any event causing DC	Comments
CLASS ¹¹ (n=7968) Mean age=60 (~12% >75) (range 18-90)	Celecoxib 400mg BID Ibuprofen 800mg TID Diclofenac 75mg BID	≤6mo; ave 4.2mo OA or RA 72%	3987 1985 1996	45.6% 46.2% NS 55.0% (p<0.05)	0.76 1.45 (p=0.09) not significant	2.08 3.54 (p=0.02) NNT=68.5	22.4% 23.0% NS 26.5%	<ul style="list-style-type: none"> ♦supratherapeutic doses used to definitively test safety ♦'ulcer complications' defined as: upper GI bleeding, perforation, or gastric obstruction ♦dose of celecoxib 2X usual max daily dose ♦only 4573 completed full 6 month trial; high drop out rate ♦ > withdrawal rate due to GI ADR in diclofenac group (16.6% vs 12.2% for celecoxib) may have underestimated its GI risk ♦differences in GI ulcers/complications were found for celecoxib versus ibuprofen (2.08 vs 4.31/100 pt-yrs; p=0.005) but not celecoxib vs diclofenac (possibly due to > withdrawal rate) ♦pts at ↑ risk for GI events also had ↑ withdrawal rates ♦fewer celecoxib pts had GI blood loss, GI intolerance ♦no difference in CV events (but ASA allowed in study) ♦celecoxib arm had more pts > 65yo & hx of upper GI bleeds ♦rash with high-dose celecoxib (6.2%); appears to be dose-dependent ↑ from previous data; (sulfa allergy pts excluded)
	Subgroup: as above but excluding patients on ASA ≤325mg/d	ASA appeared to be an independent cause of ulcers in celecoxib pts, but not for NSAIDs (RR =4.5).			0.44 1.27 (p=0.04) NNT=120	1.40 2.91 (p=0.02) NNT=66		
	Subgroup: as above but including patients on ASA ≤325mg/d				2.01 2.12 (p=0.92) not significant	4.7 6.0 (p=0.49)		
			~22% of each treatment arm had concurrent ASA					
VIGOR ¹² (n=8076) Mean age 58; (only ~5% >75) (range 34-89)	Rofecoxib 50mg OD Naproxen 500mg BID	≤13mo; mean 8mo RA	4047 4029	32.6% 36%	0.59 1.37 (p=0.005) NNT=128	2.08 4.49 (p=0.001) NNT=41.5	15.9% 15.8% NS	<ul style="list-style-type: none"> ♦dose of rofecoxib 2X usual max daily dose ♦acute MI > in rofecoxib than naproxen (0.5% vs 0.1%) ♦DC due to hypertension > in rofecoxib (0.7% vs 0.1%); HTN & edema appear to be dose dependent (previous data) ♦DC due to GI ADR lower in rofecoxib (RR = 0.73; p<0.001) ♦similar incidence of rash (rofecoxib vs naproxen 3.5% vs 3%) ♦better GI safety but some adverse outcomes related to non-GI events; ASA pts excluded; ♦rofecoxib arm had less pts age >65

What we know: ♦rofecoxib reduced the risk of complicated &/or symptomatic ulcers but increased the risk of acute MI compared to the non-selective NSAID, naproxen.

♦celecoxib significantly reduced the risk of complicated &/or symptomatic ulcers compared to ibuprofen

♦risk of serious ulcer complications in patients on celecoxib and low-dose ASA was not significantly different from those on non-selective NSAIDs and ASA.

What we don't know: ♦whether risk of serious GI toxicity in patients on rofecoxib and ASA would be reduced compared to patients on non-selective NSAIDs and ASA.

♦whether the safety profile would be significantly improved in patients on a usually recommended or lowest effective dose as opposed to supratherapeutic doses from trials.

♦whether COX-2 selective agents are significantly safer in high-risk patients (e.g. the very elderly ≥75yrs or patients with previous hx of ulcers).

♦how the selective COX-2 agents compare to each other in terms of overall safety or efficacy. (No head-to-head trials; different trial designs.)

Celecoxib long-term data: Study 024: ulcer complication rate of 0.23% (≤2 years exposure); postmarketing surveillance incidence of ulcer complications <0.02%; 30 fatal GI events in 1999; acute renal failure 0.0039%.

Rofecoxib long-term data: postmarketing surveillance - 59 complicated PUBs in 1999 (but only approved May/1999); complicated upper GI events = 0.014 per 100 pt-yrs;

Background rate of ulcers: estimated to be approximately 0.1 to 0.4 events per patient years (varying as function of patient age); general ulcer rate for NSAIDs is thought to be ~2-4% per year; risk ↑'s with ↑d dose;

acute renal failure secondary to NSAIDs = 15-20 per 100,000 pt-yrs; NSAIDs account for 16,500 deaths/year in the USA

Of interest, MUCOSA study: misoprostol (200mcg po qid) ↓d the rate of serious complicated upper GI events from 0.95% to 0.56% for NSAID users with RA over 6 months (ARR =0.4%; NNT=250)

DC=discontinuation; OA=osteoarthritis; RA=rheumatoid arthritis; yo=years old; NS=not (statistically) significant; GI=gastrointestinal; ADR=adverse drug reaction; CV =cardiovascular; pts =patients; hx =history.