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.
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[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 tolerbility of the selective cyclogenase (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.

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)	◆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**	◆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 <u>don't</u> 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 <u>not</u> statistically significant and the **<u>low-dose</u> (1/2 usual maximum) and <u>short duration</u> (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 ◆**supratherapeutic doses used to definitively test safety** ◆**'ulcer complications' defined as: upper GI bleeding, perforation, or gastric obstruction**
CLASS [11] (n=7968) Mean **age**=60 (~12% >75) (range 18-90)	**<u>Celecoxib</u>** 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% .	◆dose of celecoxib <u>2X usual max</u> 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**				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)		
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**	◆dose of rofecoxib <u>2X usual max</u> 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

ASA appeared to be an independent cause of ulcers in celecoxib pts, but <u>not</u> for NSAIDs (RR =4.5).

~22% of each treatment arm had concurrent ASA

ASA patients were excluded from the study; ASA would have been indicated in ~4% of pts & these pts accounted for ~28% of confirmed cardovascular thrombotic events

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 <u>not</u> significantly different from those on non-selective NSAIDs and ASA.

What we <u>don't</u> 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.

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