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.