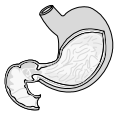
Why do need Cox-2 inhibitors ?

Conventional AINS are toxic ...

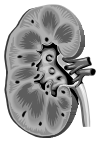
Adverse Effects of common NSAIDs

Upper - GI



- ➔ **Dyspepsia**
- ➔ **Erosions**
- ➔ **Anaemia - GI bleeding**
- ➔ **Ulcers - bleeds/perforations**

Renal

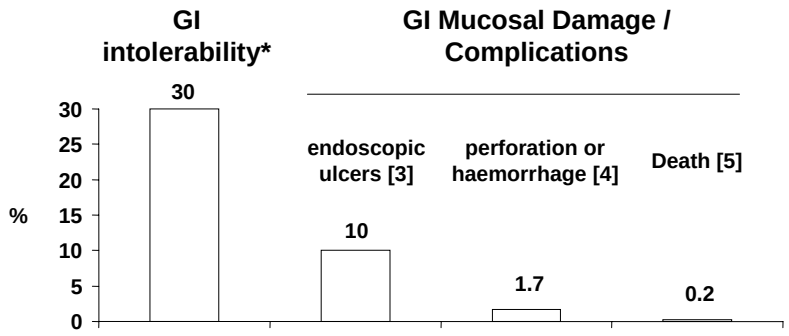


- ➔ **Renal dysfunction**
- ➔ **Renal failure - acute/chronic**
- ➔ **Blood pressure**
- ➔ **Heart failure**

Anti-platelet effects

- ➔ **Contributes to blood loss**

NSAIDs toxicity



***** Range 20-50% based on
- withdrawals for GI symptoms[1]
- community surveys for GI symptoms[2]

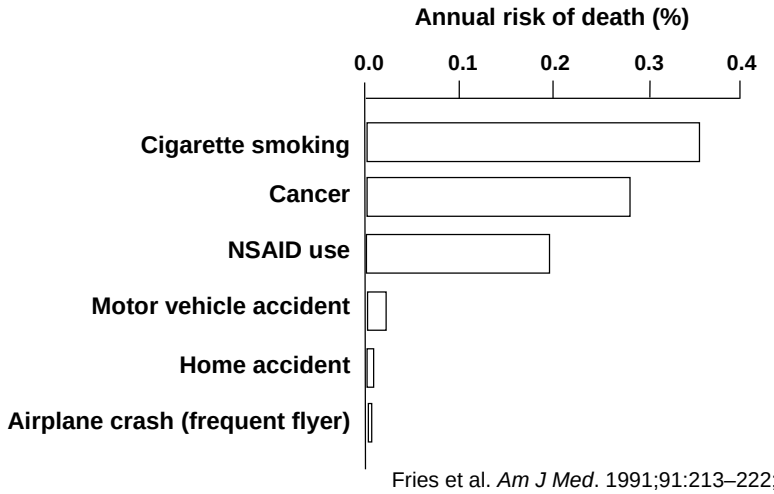
1. Kiff et al, Eur J Rheumatol, 1994; 2. Hardo et al, BJCP, 1993; 3. Graham DY et al, Am J Gastroenterol 1988; 4. Silverstein et al, Ann Int Med, 1995; 5. Blower et al, Aliment Pharmacol, 1997

NSAID Ulcers and Ulcer Complications

- **Endoscopic ulcer point prevalence: 10-30%**
- **Ulcer complications: 2-4% per year**
- **Most (>80%) hospitalizations for GI bleed occur without previous symptoms**
- **Inhibition of prostaglandin synthesis is principal mechanism for GI damage**
- **Use of antacids or H2 antagonists do not prevent NSAID induced gastric ulcers**

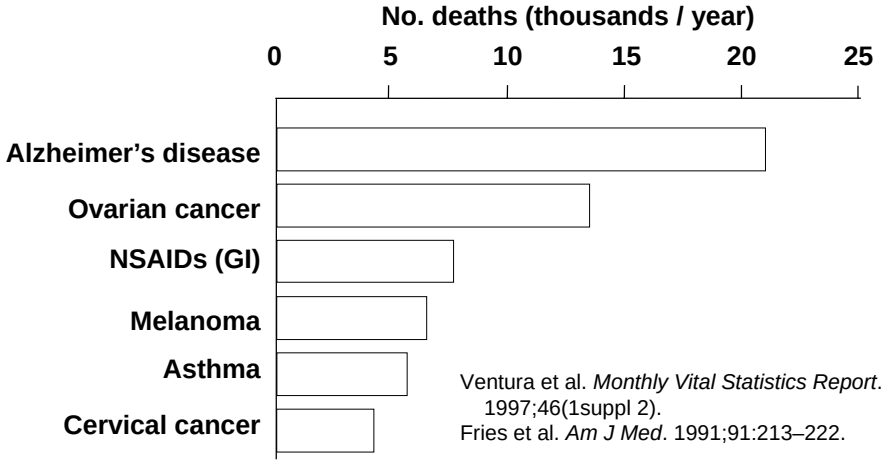
Singh G et al. *Am J Med* 1998;105(1B):31S-8S.
Geis GS et al. *J Rheumatol* 1991;18:11-14.

GI mortality associated with typical NSAIDs vs other causes in US (1of 2)



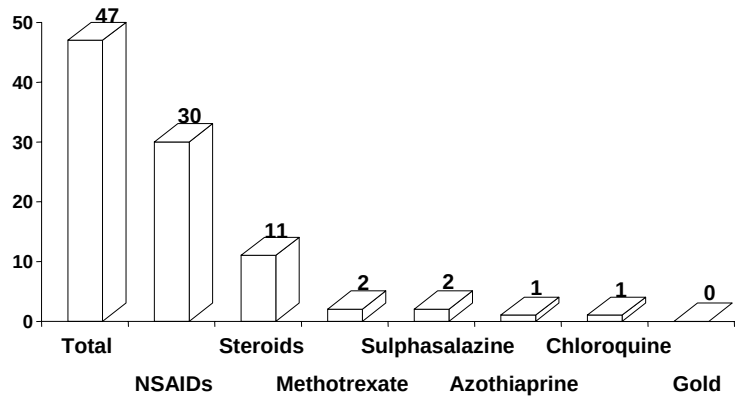
Fries et al. *Am J Med*. 1991;91:213–222;
Wilson, Crouch. *Science*. 1987;236:267–270.

GI mortality associated with typical NSAIDs vs other causes in US (2 of 2)



Ventura et al. *Monthly Vital Statistics Report*. 1997;46(1suppl 2).
Fries et al. *Am J Med*. 1991;91:213–222.

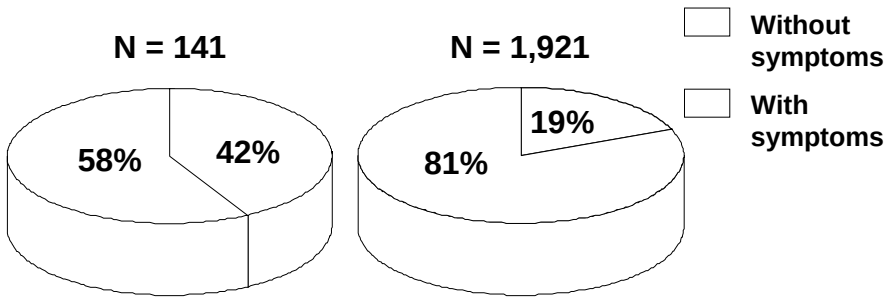
Deaths attributed to anti-rheumatic medication (series of 1666 patients with RA)



Myllykangas-Luosujarvi, J Rheum, 1995, 22, 2214-7

Most patients are asymptomatic prior to a serious NSAID-associated GI event ...

Bleeding, perforation, and gastric outlet obstruction



Armstrong &Blower. *Gut*. 1987;28:527–532.

Singh et al. *Arch Intern Med*. 1996;156:1530-1536.

*NSAIDs - Relative Risk of GI Complications

Drug	Relative Risk (95% C.I.)
None	**1**
Ibuprofen	**2.1** (0.6 - 7.1)
Diclofenac	**2.7** (1.5 - 4.8)
Other NSAID (n=16)	**2.9** (1.4 - 6.3)
Ketoprofen	**3.2** (0.9 - 11.9)
Naproxen	**4.3** (1.6 - 11.2)
Tenoxicam	**4.3** (1.9 - 9.7)
Nimesulide	**4.4** (2.5 - 7.7)
Indomethacin	**5.5** (1.6 - 18.9)
Piroxicam	**9.5** (6.5 - 13.8)
Ketorolac	*24.7 (9.6 - 63.5)*

* Rodriguez et al, Arch Intern Med, 1998, 158, 33-39

Upper GI complications in Europe

- **1000 people are hospitalised <u>every day</u> for upper GI bleeds in Europe (~400 million population)**
- **In 400 of these 1000 patients the bleed (or perforation) will be directly attributable to NSAIDs**
- **100 (10%) of these 1000 will die from their complications**

Calculated from :
Blower AL et al, Aliment Pharmacol Ther, 1997, 11, 283-291
MacDonald T et al, BMJ, 1997, 315, 1333-1337

This is why ...

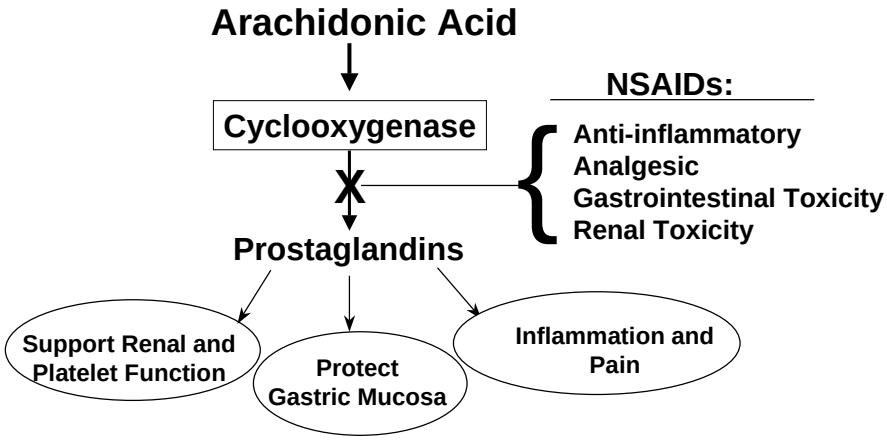
"Toxicity is the major reason for not recommending the use of NSAIDs as first-line therapy for patients with OA of the hip ….."

Osteo-arthritis hip, Management Guidelines
Hochberg et al, 1995, Arthritis & Rheumatism

Towards new medications ...

Discovery of cyclooxygenase-2 and of cyclooxygenase-2 specific inhibitors

Role of cyclooxygenase

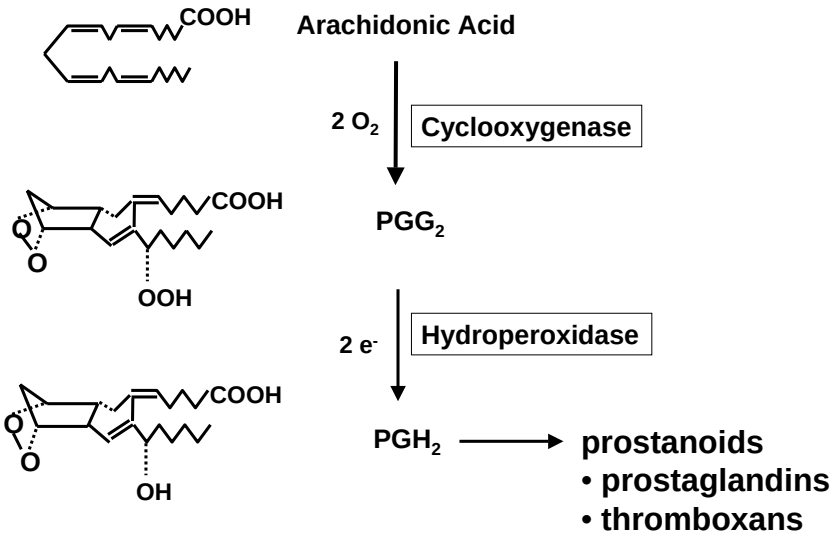


Shorrock CJ et al. *Am J Med* 1988;84 (Suppl):25-34.

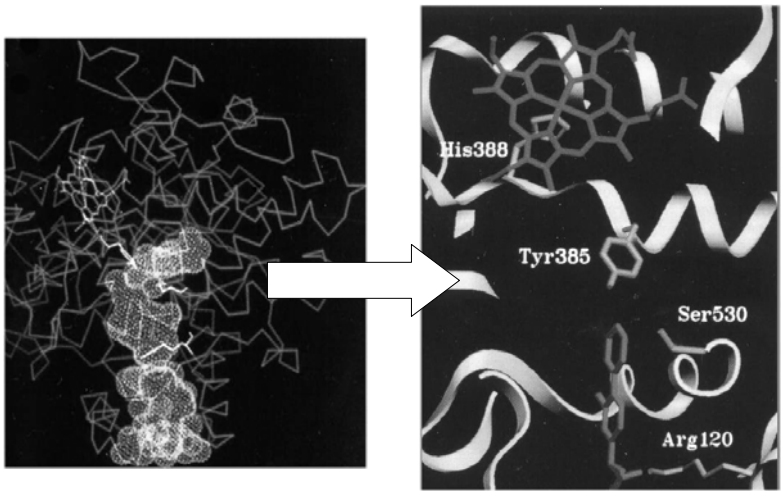
The Discovery of the role of cyclooxygenase

- **1898 … aspirin introduced**
- **1950s … corticosteroids introduced**
  - » **anti-inflammatory**
  - » **significant side effects**
- **1960s … NSAIDs introduced**
- **1971 … mode of action of NSAIDs explained on basis of COX inhibition (Vane)**
  - » **platelet activity induced by COX**
  - » **inhibited by aspirin and other NSAIDs**

Conversion of arachidonic acid to prostaglandins

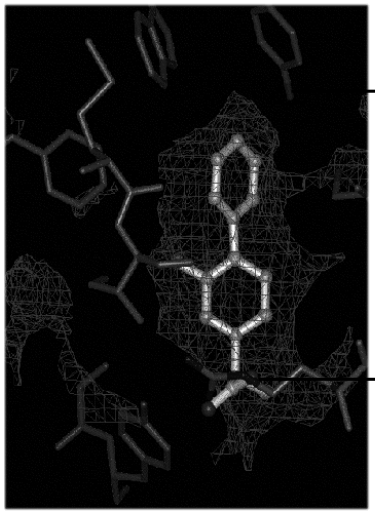


Mapping of the cyclooxygenase active site



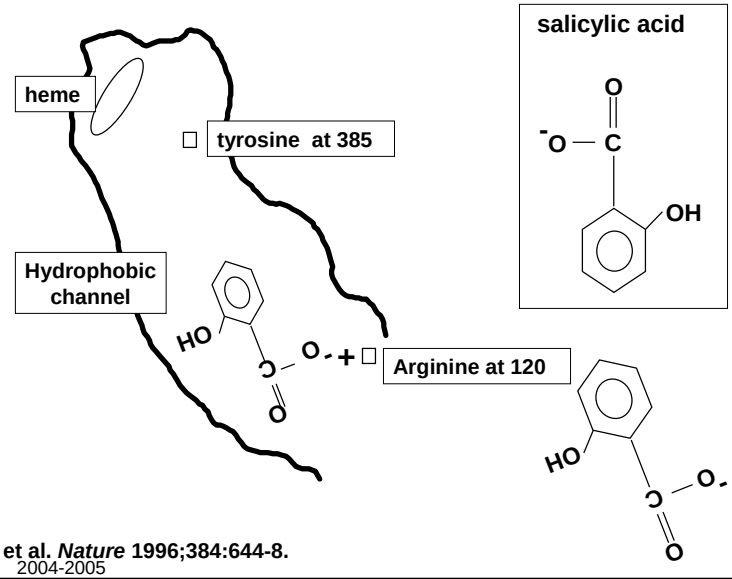
Mapping of the cyclooxygenase active site

COX-1 Active Site occupied by flurbiprofen



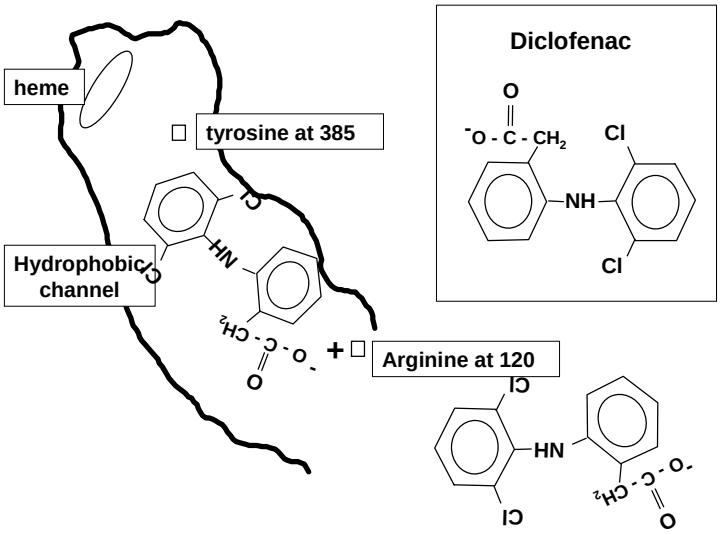
Picot, Loll and Garavito: Nature 1994; 367:243.

All conventional NSAIDs have a similar mechanism of action ...



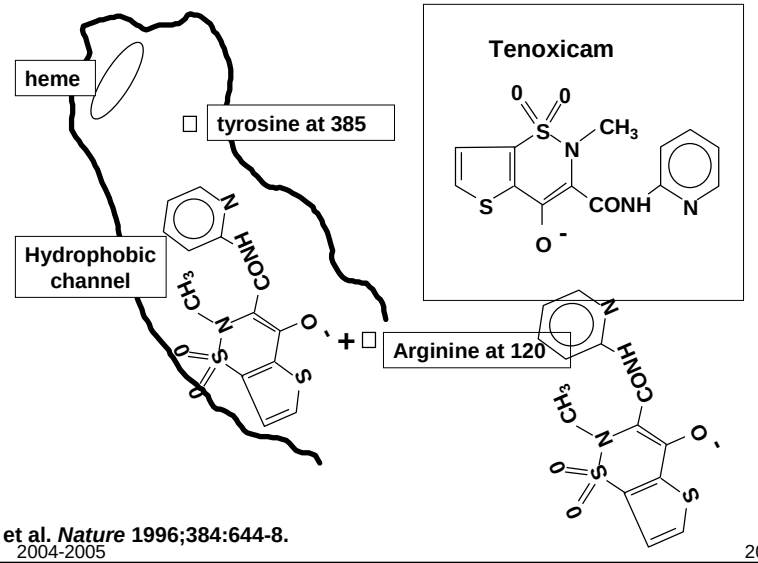
Kurumbail RG et al. *Nature* 1996;384:644-8.

All conventional NSAIDs have a similar mechanism of action ...



Kurumbail RG et al. *Nature* 1996;384:644-8.

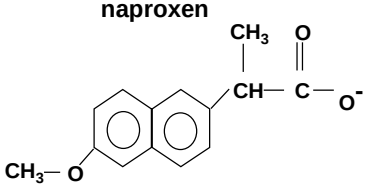
All conventional NSAIDs have a similar mechanism of action ...



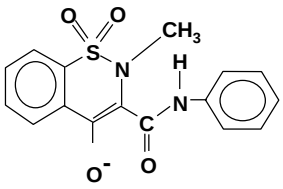
Kurumbail RG et al. *Nature* 1996;384:644-8.

Similarities of structures ...

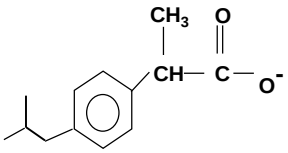
naproxen



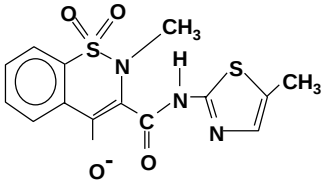
piroxicam



ibuprofen



meloxicam

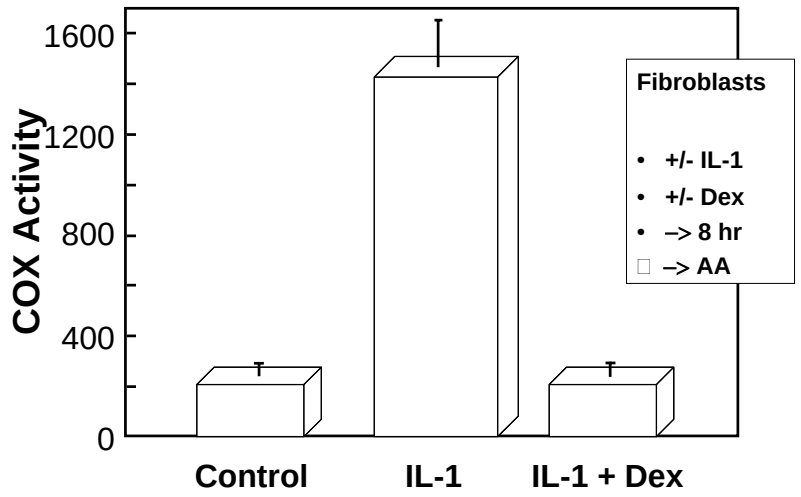


Discovery of two forms of cyclooxygenase

- **1989 ... IL-1 induces COX activity in fibroblasts [1]**
- **1990 … the inducible COX activity is inhibited by steroids [2]**
  steroids had no effect on basal cyclooxygenase activity
- **1991 … the inducible cycloxygenase (COX-2)is cloned [3]**
  - **60% identical to COX-1**
  - **certain important amino acid differences**
  - **cytokine induced and regulated by glucocorticoids**

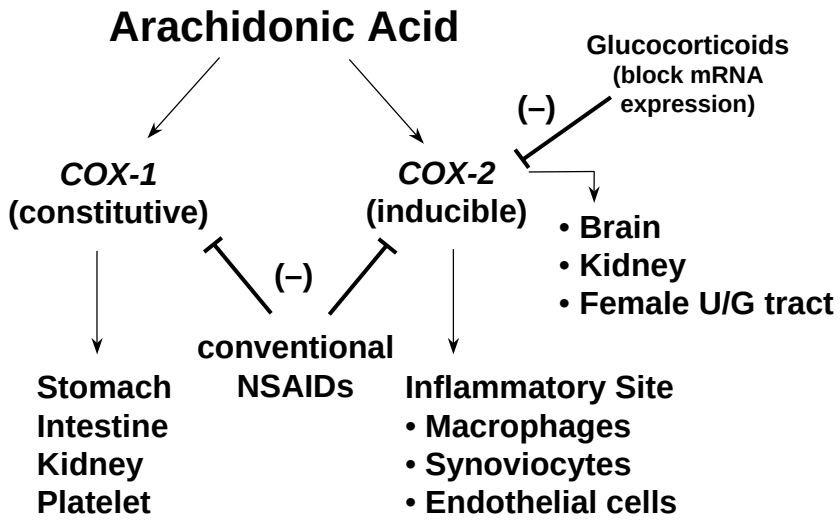
1 : Raz et al, PNAS, 1989, 86, 1657-1661
2 : Fu et al, J Biol Chem, 1990, 265. 16737-40
3 : Xie et al, 1991, PNAS, 88, 2692-6

Effect of IL-1 and dexamethasone on human fibroblast COX activity



Raz et al, PNAS, 86,1657-1661

COX-2: a new anti-inflammatory drug target

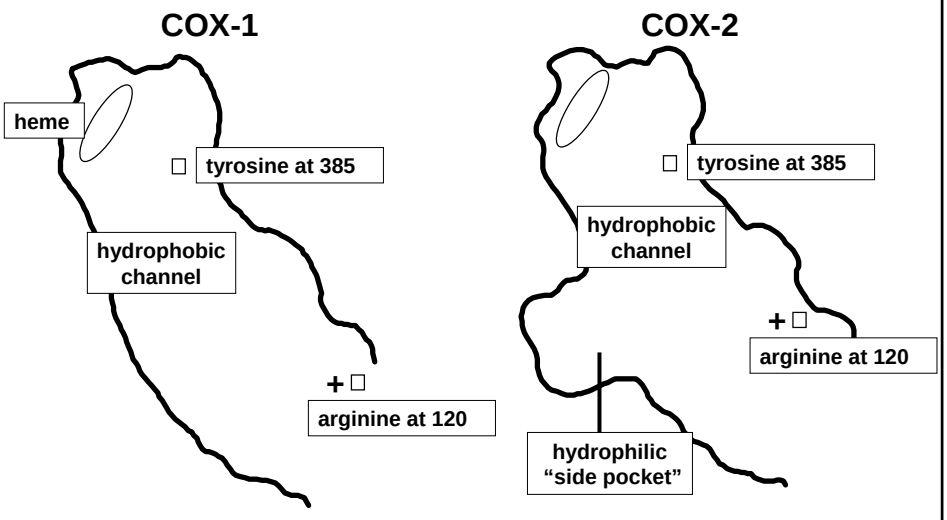


Biochemical comparisons of the Cox-1 and Cox-2

COX-1 and COX-2 are membrane-bound proteins that reside, after synthesis and transport, primarily in the endoplasmic reticulum. Although the genes for COX-1 and COX-2 are clearly different the proteins actually share 60% homology at the amino acid level; both catalyze from arachidonic acid the formation of prostaglandin (PG) G_2 followed by PGH_2 via a peroxidase function, have a similar molecular mass of 70 kDa, and are identical in length. Studies of the tertiary structures of COX-1 and COX-2 have demonstrated that the amino acid conformation for the substrate binding sites and catalytic regions are almost identical. However, there are important differences in these regions, particularly the exchanges of Ile in COX-1 for Val in COX-2 at positions 434 and 523. These substitutions result in a larger and more flexible substrate channel in COX-2 than in COX-1 and in the inhibitor binding site in COX-2, being 25% larger than that in COX-1.

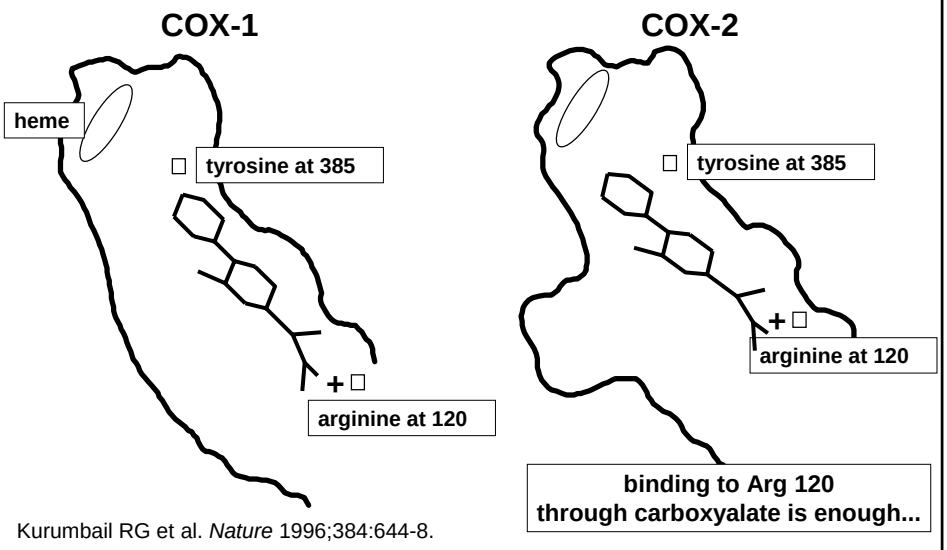
Warner TD, Mitchell JA. Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. FASEB J. 2004 May;18(7):790-804.

Structures of COX-1 and COX-2



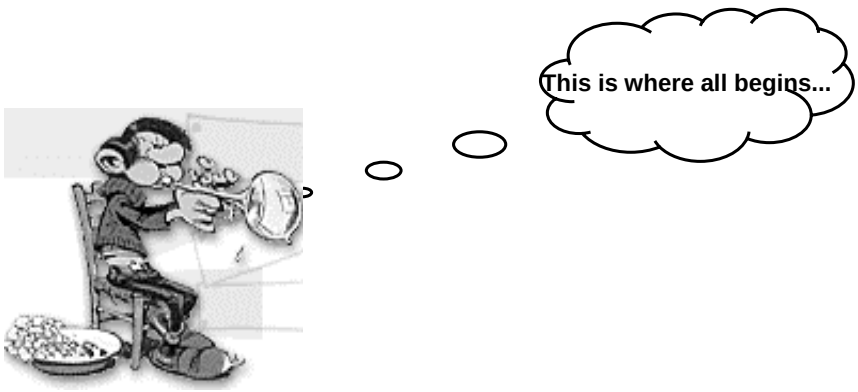
Kurumbail RG et al. *Nature* 1996;384:644-8.

Conventional NSAIDs inhibit both COX-1 and COX-2

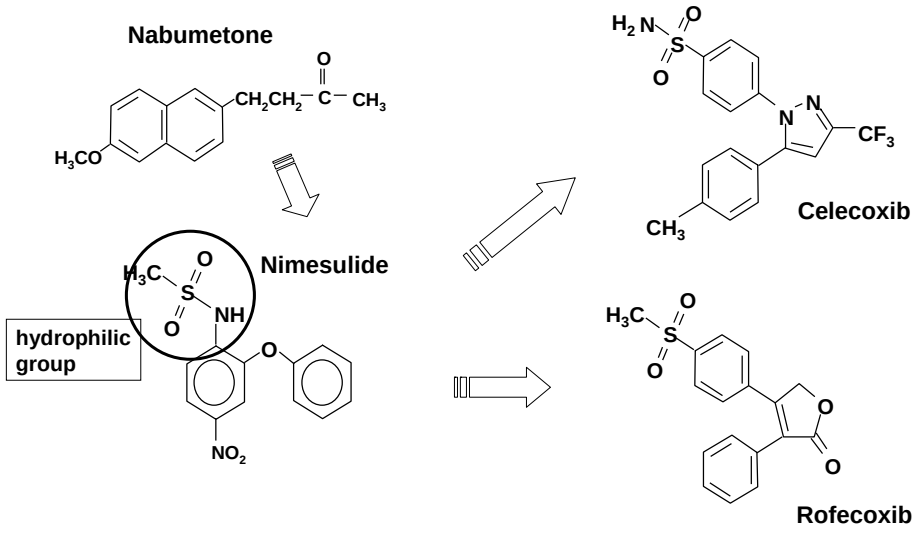


Kurumbail RG et al. *Nature* 1996;384:644-8.

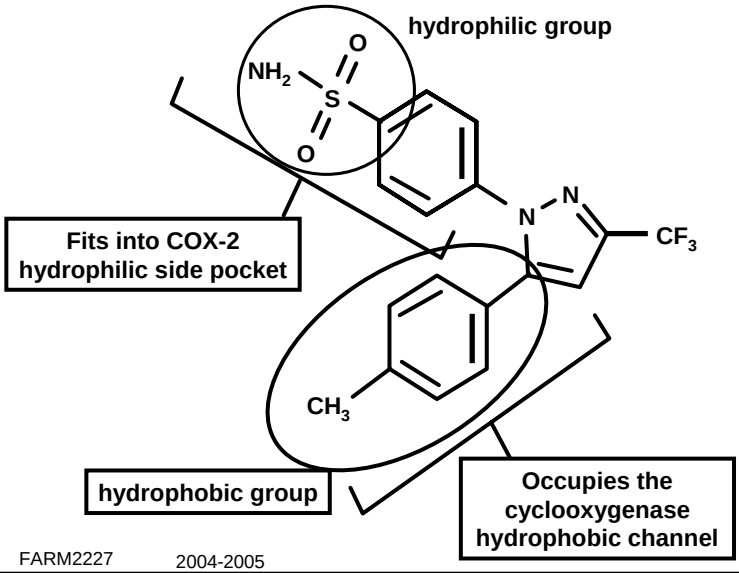
Chemistry and Activity



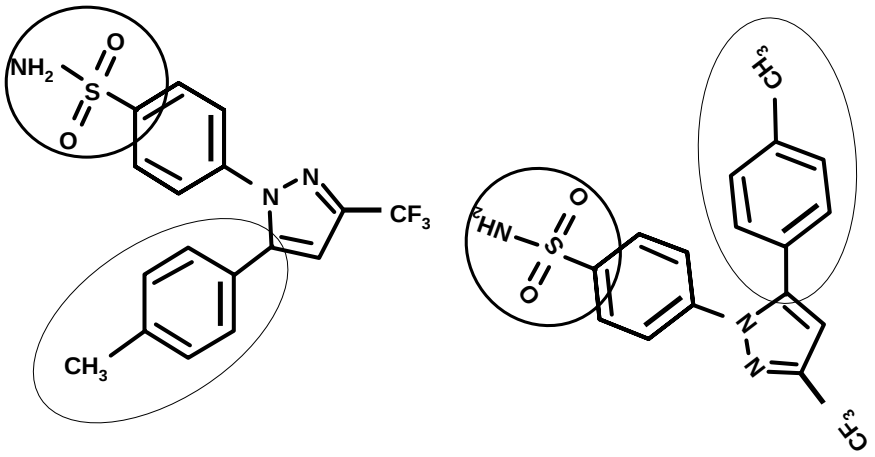
Pharmacochemistry of the COX-2 inhibitors



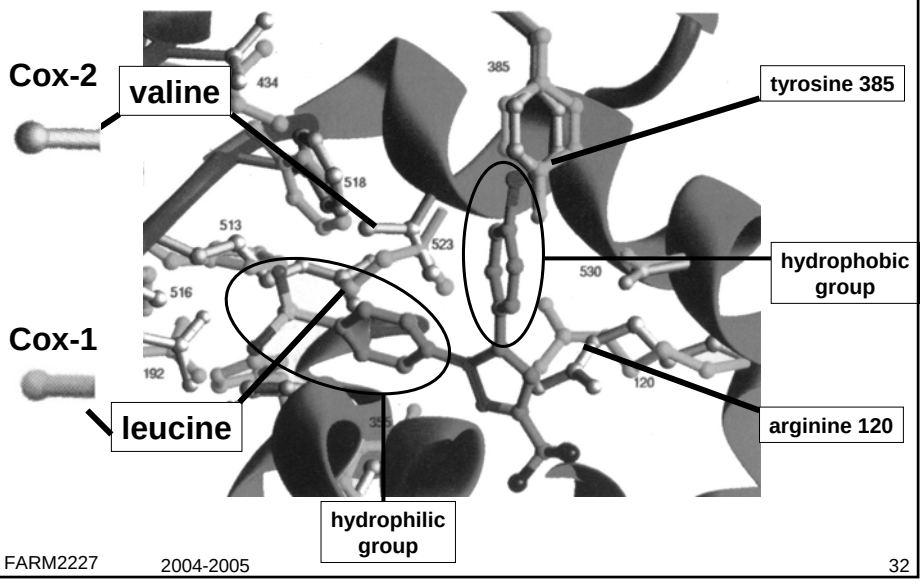
Pharmacochemical determinants in “coxibs”



Fitting “coxibs” in cyclooxygenases ...

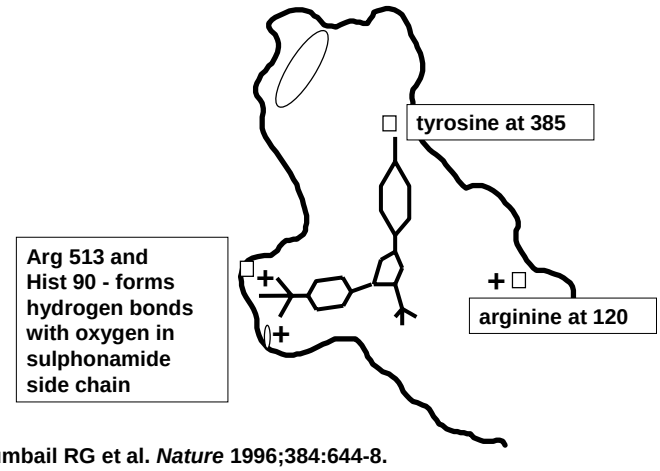


Structures of COX-1 and COX-2 with celecoxib



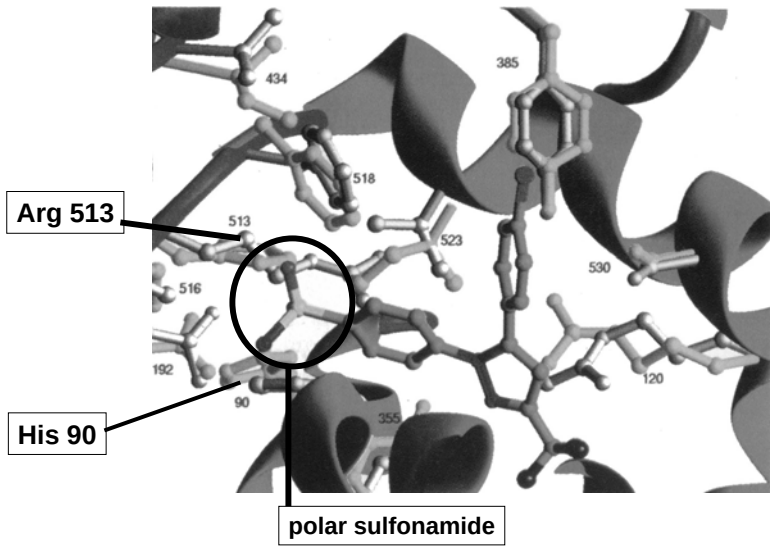
Why do “coxibs” bind so tightly to cycoloxygenase-2 ?

the polar sulphonamide side chain tightly bind to hydrophilic “side pocket”

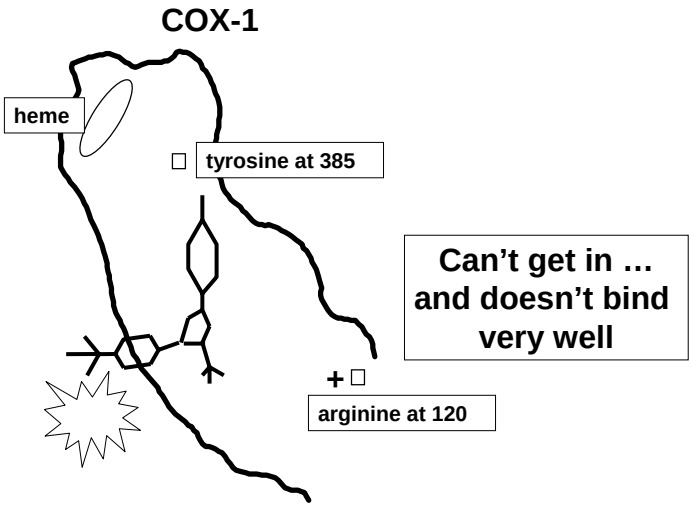


Kurumbail RG et al. *Nature* 1996;384:644-8.

Binding of the slide chain to Arg 513 and His 90



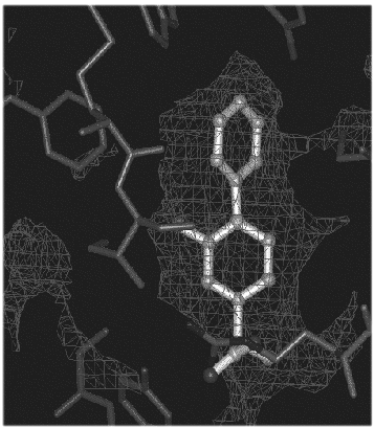
Why do “coxibs” fail to inhibit cyclooxygenase-1 ?



Kurumbail RG et al. *Nature* 1996;384:644-8.

Cox-1 vs Cox-2 ...

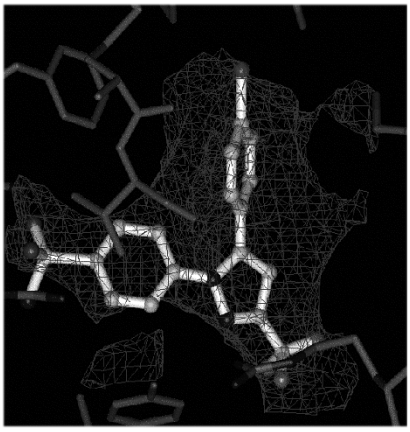
flurbiprofene in Cox-1



Picot, Loll and Garavito

Nature 1994; 367:243.

celecoxib in Cox-1



Kurumbail et al. Nature 1996;384:644-8.

Selectivity and specificity of Cox-inhibitors

(Lipsky et al, Editorial, J. Rheumatol, 1998, 25, 2298-2303)

Levels 1 & 2, Selectivity

1. **Enzymatic or biochemical**
   - **in vitro COX-1/COX- 2 ratio**
2. **Biological and pharmacologic**
   - **ex-vivo cell assays**

Level 3, Clinical specificity

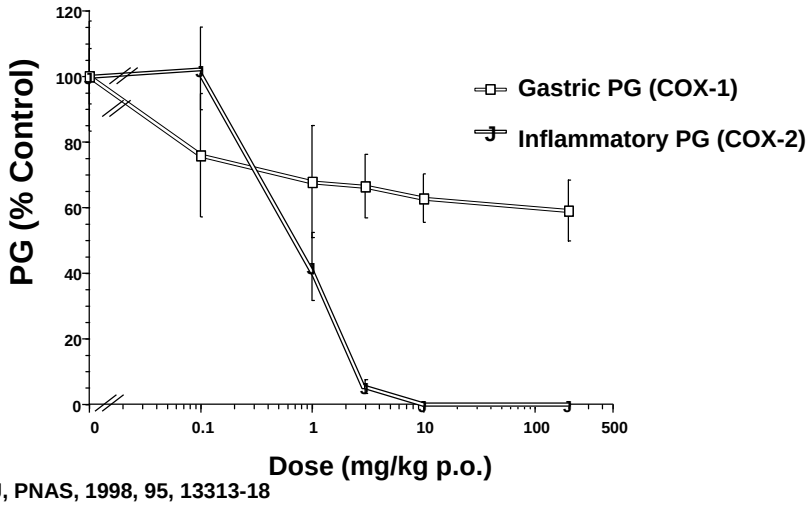
3. **At fully efficacious therapeutic concentration**
   - **No inhibition of COX-1 mediated platelet function**
   - **No clinically relevant COX-1 inhibitory effect on GI tract**

   = COX-2 SPECIFIC INHIBITION (CSI)

Categories of COX Inhibitors

1.	**COX-1 specific**	**Low dose aspirin**
2.	**COX non-specific**	**All current NSAIDs**
3.	**COX-2 preferential***	**Agent with some anti-inflammatory or analgesic activities at a dose that inhibits COX-2 but causes no significant inhibition of COX-1**
4.	**COX-2 specific**	**Agent which at maximal therapeutic dosing causes no clinically meaningful inhibition of COX-1**

Specificity of Celecoxib *in vivo*



Smith CJ, PNAS, 1998, 95, 13313-18

Selective cyclooxygenase inhibitors

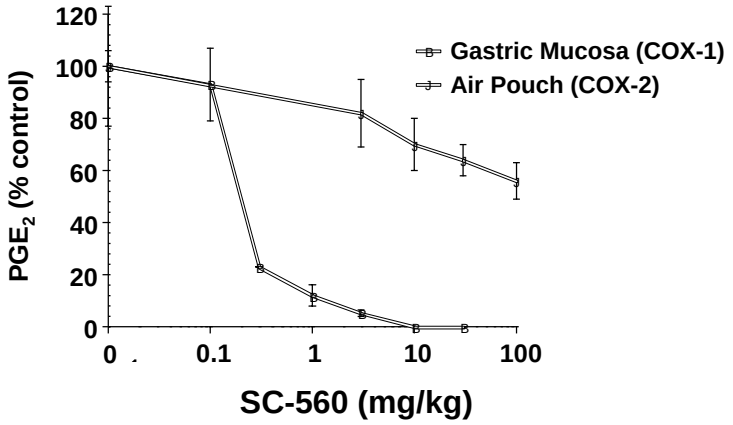
SC-560

celecoxib

IC_{50} (μM)	COX-1	0.009	15
	COX-2	6.3	0.04

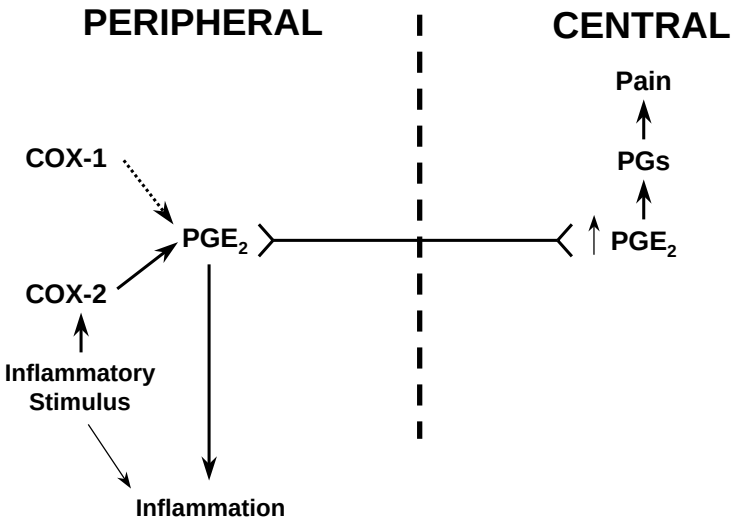
Smith CJ, PNAS, 1998, 95, 13313-18

In vivo Specificity of SC-560



Smith CJ, PNAS, 1998, 95, 13313-18

Model for COX-1 and COX-2 derived prostaglandins in inflammation and pain



Smith CJ, PNAS, 1998, 95, 13313-18

Pharmacokinetics

Pharmacokinetics of celecoxib

- **Absorption**
  - **75% bioavailable (versus oral solution)**
  - **food enhances bioavailability by 7-20%**
  - **antacids reduce bioavailability by ~25%**
- **Distribution**
  - **97% bound to plasma proteins**
  - **Protein binding is concentration independent**
  - **3% unbound with linear kinetic profile**

Potential drug interactions ...

- **Drugs that are Metabolized by the Cytochrome P450 2C9 Pathway**
  - S-Warfarin
  - tolbutamide
  - phenytoin
  - glyburide
- **Potential Protein Binding Displacement**
  - warfarin
  - phenytoin
  - glyburide
- **Drugs Eliminated by the Kidneys**
  - methotrexate
  - lithium
- **Drugs that are Metabolized by the Cytochrome P450 2D6 Pathway**
  - paroxetine
  - dextromethorphan

Actual results of drug interaction studies

Interactions observed :

- **lithium** (17% increase AUC and C_{max})
- **fluconazole** (2x increase celecoxib AUC and C_{max} by CYP $_{2C9}$ inhibition)
- **paroxetine** and **dextromethorphan** (moderate increases of PK values)

No interactions with :

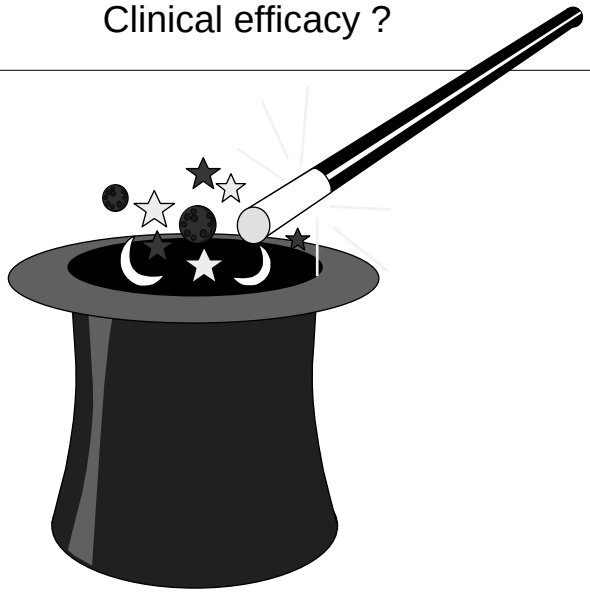
- **methotrexate**
- **glyburide**
- **warfarin**
- **phenytoin**
- **tolbutamide**
- **ketoconazole**

Karim A et al. *Arthritis & Rheum* 1998;41(9) Suppl:1698A.
Data on File: Searle (Studies 017, 038, 039, 040, 050, 051,117)

Celecoxib platelet effects

- **no alteration of aggregation or bleeding time [Lack of COX-1 inhibition] at 6 x the therapeutic dose**
- **Anaemia, ecchymoses were reduced on celecoxib vs NSAIDs (comparison with naproxen)**

Clinical efficacy ?

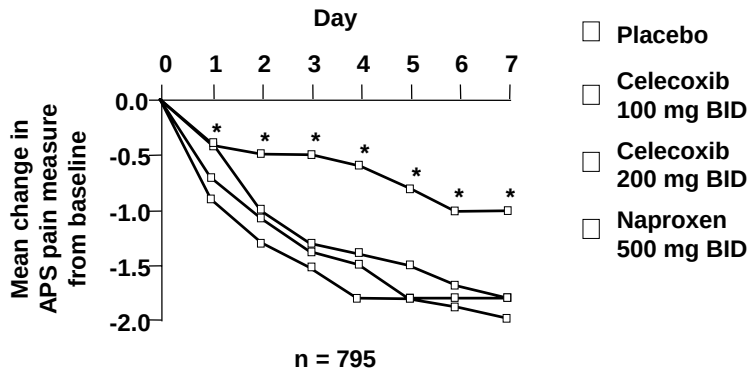


Pain Measure Questionnaire
of the American Pain Society (APS)

1. **Have you experienced any pain in the last 24 h? (yes or no)**
2. **How much pain are you having right now? (0–10)**
3. **Indicate the worst pain you have had in the past 24 h. (0–10)**
4. **Indicate the average level of pain you have had in the past 24 h. (0–10)**
5. **Indicate how pain has interfered with you in: (7 daily activities; each scored 0–10)**

Patient's assessment of average arthritis pain in last 24h

OA Knee Trial: Celecoxib vs Naproxen

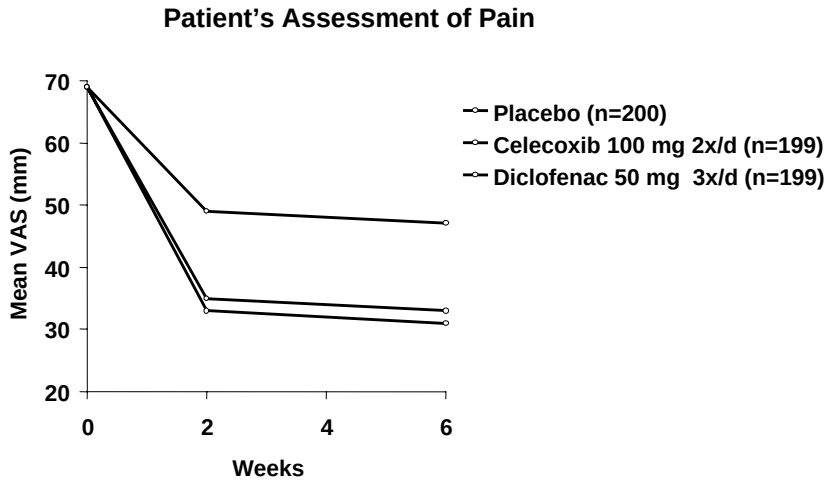


n = 795

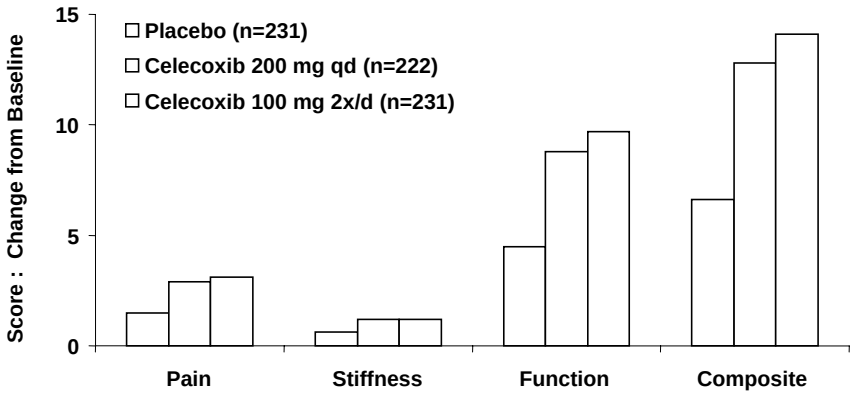
***P* < 0.05 vs all treatments (except naproxen at Day 1 and celecoxib 100 mg at Day 2)**

Data on file : Searle Study 020

Celecoxib vs Diclofenac in OA

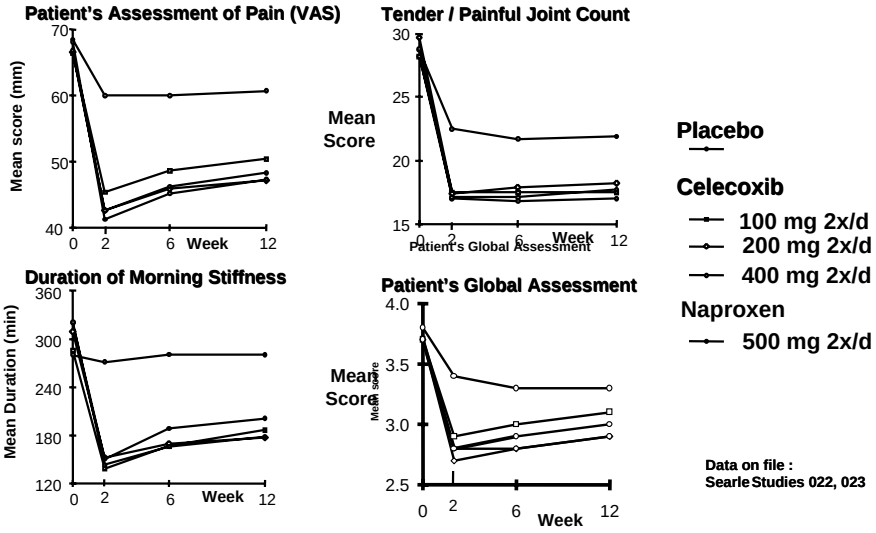


Efficacy of celecoxib 200 mg once a day (qd) in OA

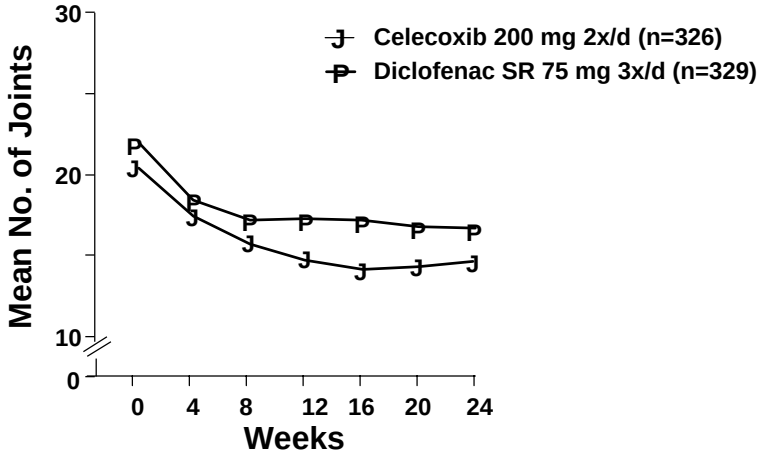


Searle Study 060

Celecoxib Efficacy in RA - Combined Results from 2 Studies (n = 400 per treatment group)



Number of tender / painful joints
6 Months International Study in RA



Data on File : Searle Study 041
Emery P et al, Lancet, 1999,2106-2111

Toxicity ??

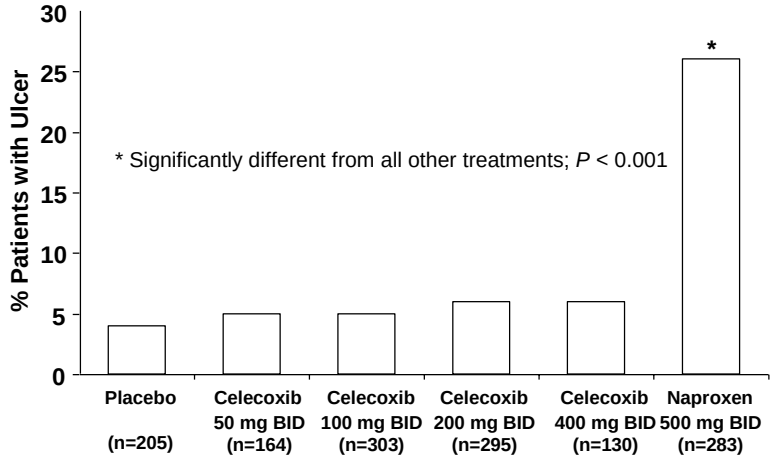
Gastrointestinal Safety and Tolerability Celecoxib vs NSAIDs

- **Gastroduodenal ulceration**
  - 6 endoscopy studies in >4000 individuals
- **Clinically significant upper GI events**
  - 4004 patient-years exposure data (All treatments)
- **Changes in haemoglobin**
- **GI Symptoms**

>11,000 patients with OA or RA in 14 Phase II / III

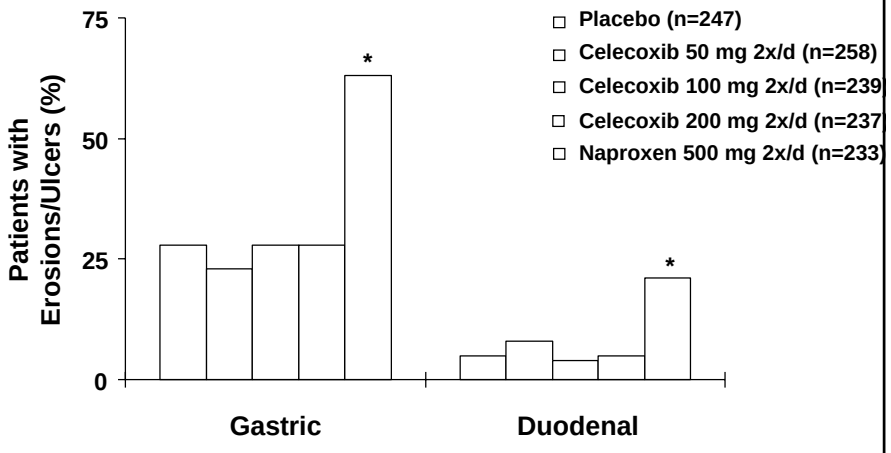
Incidence of gastroduodenal ulcers - week 12

Celecoxib - Phase III RA and OA UGI Safety Trials



Searle (Studies 021 & 022)

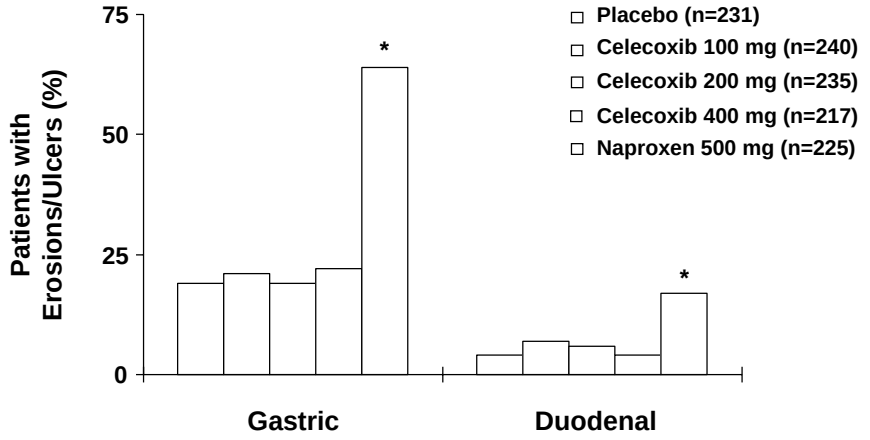
Incidence of erosions / ulcers in patients with OA



*** Significantly different from all other treatments; *P* < 0.001**

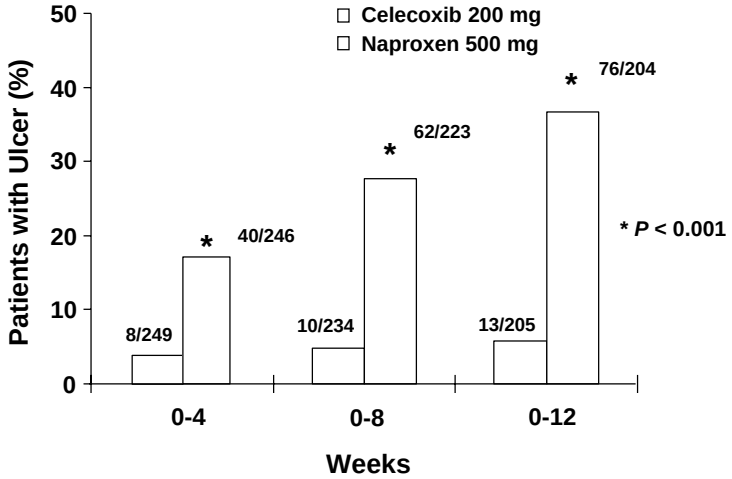
Searle Study 021

Incidence of Erosions / Ulcers in Patients with RA



*** Significantly different from all other treatments; *P* < 0.001**
Searle Study 022

Cumulative Incidence of Gastric Ulcers



Goldstein et al., Reduced incidence of gastroduodenal ulcers with celecoxib, a novel cyclooxygenase-2 inhibitor, compared to naproxen in patients with arthritis. Am J Gastroenterol. 2001 Apr;96(4):1019-27.

Celecoxib vs Diclofenac plus omeprazole

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ORIGINAL ARTICLE

◄ Previous Volume 347:2104-2110 December 26, 2002 Number 26 Next ►

Celecoxib versus Diclofenac and Omeprazole in Reducing the Risk of Recurrent Ulcer Bleeding in Patients with Arthritis

Francis K.L. Chan, M.D., Lawrence C.T. Hung, M.D., Bing Y. Suen, R.N., Justin C.Y. Wu, M.D., Kenneth C. Lee, Ph.D., Vincent K.S. Leung, M.D., Aric J. Hui, M.D., Ka F. To, M.D., Wai K. Leung, M.D., Vincent W.S. Wong, M.D., S.C. Sydney Chung, M.D., and Joseph J.Y. Sung, M.D., Ph.D.

From the Department of Medicine and Therapeutics (F.K.L.C., L.C.T.H., J.C.Y.W., A.J.H., W.K.L., V.W.S.W., J.J.Y.S.), the Department of Surgery (B.Y.S., S.C.S.C.), the Department of Pharmacy (K.C.L.), and the Department of Anatomical and Cellular Pathology (K.F.T.), Prince of Wales Hospital, Chinese University of Hong Kong, and the Medical Unit, United Christian Hospital (V.K.S.L.) — all in Hong Kong, China.

Celecoxib vs Diclofenac plus omeprazole

ABSTRACT

Background **Current guidelines recommend that patients at risk for ulcer disease who require treatment for arthritis receive nonsteroidal antiinflammatory drugs (NSAIDs) that are selective for cyclooxygenase-2 or the combination of a nonselective NSAID with a proton-pump inhibitor. We assessed whether celecoxib would be similar to diclofenac plus omeprazole in reducing the risk of recurrent ulcer bleeding in patients at high risk for bleeding.**

Methods **We studied patients who used NSAIDs for arthritis and who presented with ulcer bleeding. After their ulcers had healed, we randomly assigned patients who were negative for *Helicobacter pylori* to receive either 200 mg of celecoxib twice daily plus daily placebo or 75 mg of diclofenac twice daily plus 20 mg of omeprazole daily for six months. The end point was recurrent ulcer bleeding.**

Results **In the intention-to-treat analysis, which included 287 patients (144 receiving celecoxib and 143 receiving diclofenac plus omeprazole), recurrent ulcer bleeding occurred in 7 patients receiving celecoxib and 9 receiving diclofenac plus omeprazole. The probability of recurrent bleeding during the six-month period was 4.9 percent (95 percent confidence interval, 3.1 to 6.7) for patients who received celecoxib and 6.4 percent (95 percent confidence interval, 4.3 to 8.4) for patients who received diclofenac plus omeprazole (difference, –1.5 percentage points; 95 percent confidence interval for the difference, –6.8 to 3.8). Renal adverse events, including hypertension, peripheral edema, and renal failure, occurred in 24.3 percent of the patients receiving celecoxib and 30.8 percent of those receiving diclofenac plus omeprazole.**

Conclusions **Among patients with a recent history of ulcer bleeding, treatment with celecoxib was as effective as treatment with diclofenac plus omeprazole, with respect to the prevention of recurrent bleeding. Renal toxic effects are common in high-risk patients receiving celecoxib or diclofenac plus omeprazole.**

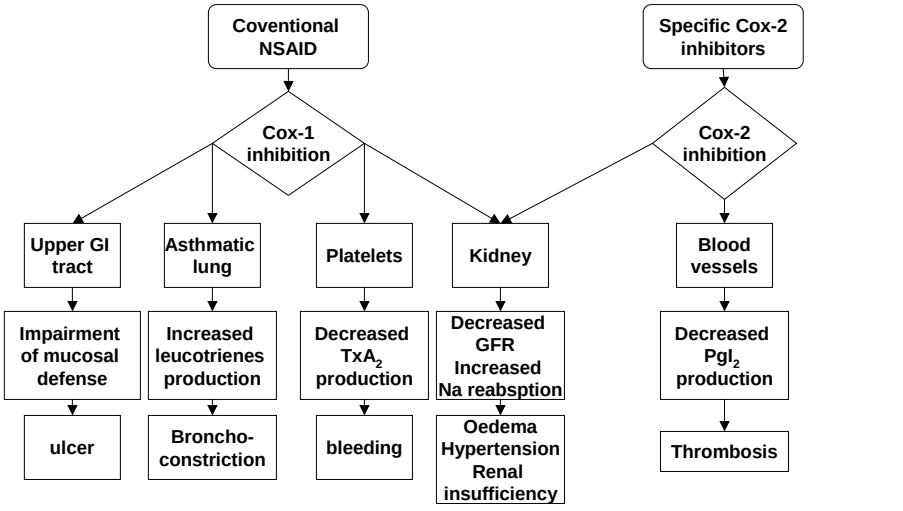
Localization of COX-1 and COX-2 in the kidneys

+=COX-1 present +=COX-2 present	Dog	Rat	Monkey	Man
Renal Vasculature **(Arteries, Arterioles, Veins)**	+ ±	+	+ +	+ +
Glomerulus			+ +	+ +
Macula Densa	+ (+++)	+ (+++)	(-)	
Interstitium	+ +	+ +	+	+
Thick Ascending Loop	+ (+++)	+ (+++)		
Collecting Ducts	+ + +	+ + +	+ +	+ +

(+++) = expression with volume depletion

Khan KN et al. *Toxicol Pathol* 1998;26(1):137-42.

Present views on adverse-effects of Cox-1 / Cox-2 inhibitors



Modified from : Warner TD, Mitchell JA. Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. FASEB J. 2004 May;18(7):790-804.

The hypertension story starting in 2001 ...

Cyclooxygenase-2-Specific Inhibitors and Cardiorenal Function: A Randomized, Controlled Trial of Celecoxib and Rofecoxib in Older Hypertensive Osteoarthritis Patients.
American Journal of Therapeutics. 8(2):85-95, March/April 2001.
Whelton, Andrew 1; Fort, John G. 2; Puma, Joseph A. 3; Normandin, Diane 4; Bello, Alfonso E. 2; Verburg, Kenneth M. 5; SUCCESS VI Study Group*

Abstract:
Background: Arthritis and hypertension are common comorbid conditions affecting elderly adults. Use of nonsteroidal anti-inflammatory drugs in patients treated with antihypertensive medication can lead to destabilization of blood pressure control and other cardiorenal events. The potential for similar interactions with cyclooxygenase-2-specific inhibitors has not been fully explored. The authors evaluated the cardiorenal safety of two new cyclooxygenase-2-specific inhibitors, celecoxib and rofecoxib.

Methods: This study was a 6-week, randomized, parallel-group, double-blind trial in patients with osteoarthritis who were >=65 years of age and were taking antihypertensive agents. Patients received once-daily celecoxib 200 mg or rofecoxib 25 mg. The primary endpoints were the development of edema, changes in systolic blood pressure, and changes in diastolic blood pressure as measured at any time point in the study. Measurements occurred at baseline and after 1, 2, and 6 weeks of treatment.

Findings: Eight hundred ten patients received study medication (celecoxib, n = 411; rofecoxib, n = 399). Nearly twice as many rofecoxib-compared with celecoxib-treated patients experienced edema (9.5% vs. 4.9%, P = 0.014). Systolic blood pressure increased significantly in 17% of rofecoxib-compared with 11% of celecoxib-treated patients (P = 0.032) at any study time point. Diastolic blood pressure increased in 2.3% of rofecoxib-compared with 1.5% of celecoxib-treated patients (P = 0.44). At week 6, the change from baseline in mean systolic blood pressure was +2.6 mmHg for rofecoxib compared with -0.5 mmHg for celecoxib (P = 0.007).

Conclusions: Patients taking antihypertensive therapy and receiving cyclooxygenase-2-specific inhibitors should be monitored for the development of cardiorenal events. Patients receiving celecoxib experienced less edema and less destabilization of blood pressure control compared with those receiving rofecoxib.

The hypertension story reviewed in 2004...

Bull Cancer. 2004 May;91 Spec No:S117-24. Related Articles, Links

Bulletin du Cancer

[Safety of selective inhibitors of inducible cyclooxygenase-2 taken for a long period]

[Article in French]

Lamarque D.

Unite d'hepato-gastroenterologie et service de chirurgie generale, Hotel-Dieu, 1 place du Parvis de Notre-Dame, 75004 Paris. dominique.lamarque@htd.ap-hop-paris.fr

The serious digestive side effects of the selective inhibitors the inducible cyclooxygenase-2 are reduced by 60% as compared to the nonselective non-steroidal anti-inflammatory drugs. The main risk factors associated with gastro-intestinal ulcers caused by the latter were found also with the selective inhibitors taken for long period (age > 60 years, antecedents of gastro-duodenal ulcers, concomitant aspirin treatment). In contrast, H. pylori infection was not found as risk factor apart from past history of gastro-duodenal ulcers. The complications in the lower digestive tract are twice less frequent with the selective inhibitors than with nonselective anti-inflammatory drugs. Nevertheless, it seems that the risk of exacerbation of inflammatory colitis is not reduced. The cardiovascular complications are discussed. Rofecoxib taken at supra-therapeutic dosage was recognised to increase the incidence of myocardial infarction. A such increase was not found with usual dosage or with celecoxib. The selective inhibitors may reduce the renal sodium excretion and increase the blood pressure, particularly in hypertensive patients whose the blood pressure has to be regularly checked.

The hypertension story ... ending on Sept. 30th, 2004

Important Information for Patients and Healthcare Professionals

"We are taking this action because we believe it best serves the interests of patients."

Raymond V. Gilmartin
Chairman, President & Chief Executive Officer

Merck Announces Voluntary Worldwide Withdrawal of VIOXX®

WHITEHOUSE STATION, N.J., Sept 30, 2004 - Merck &. Co., Inc. today announced a voluntary worldwide withdrawal of VIOXX® (rofecoxib), its arthritis and acute pain medication. The company's decision, which is effective immediately, is based on new, three-year data from a... »More

http://www.merck.com/

The hypertension story ... ending on Sept. 30th, 2004

Merck Announces Voluntary Worldwide Withdrawal of VIOXX®

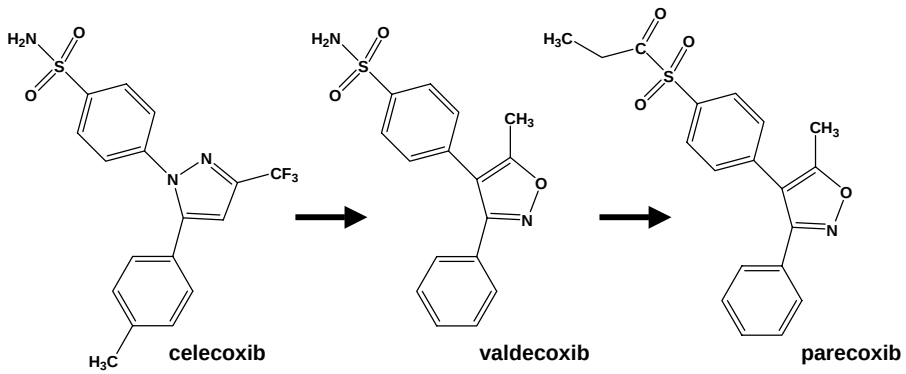
WHITEHOUSE STATION, N.J., Sept. 30, 2004 - Merck &. Co., Inc. today announced a voluntary worldwide withdrawal of VIOXX® (rofecoxib), its arthritis and acute pain medication. The company's decision, which is effective immediately, is based on new, three-year data from a prospective, randomized, placebo-controlled clinical trial, the APPROVe (Adenomatous Polyp Prevention on VIOXX) trial.

The trial, which is being stopped, was designed to evaluate the efficacy of VIOXX 25 mg in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas. In this study, there was an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking VIOXX compared to those taking placebo. The results for the first 18 months of the APPROVe study did not show any increased risk of confirmed cardiovascular events on VIOXX, and in this respect, are similar to the results of two placebo-controlled studies described in the current U.S. labeling for VIOXX.

http://www.merck.com/newsroom/press_releases/product/2004_0930.html

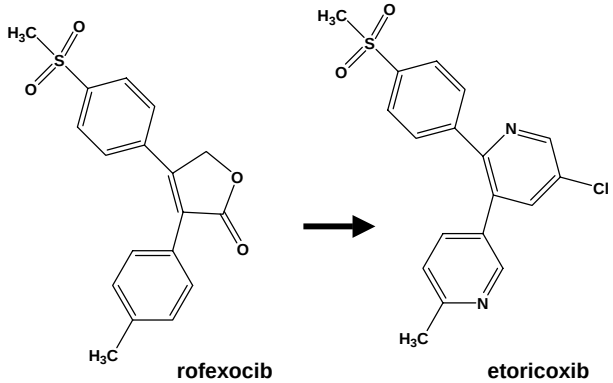
And the other coxibs…

The Searle's series …

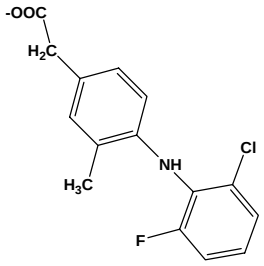


And the other coxibs…

The MSD series …



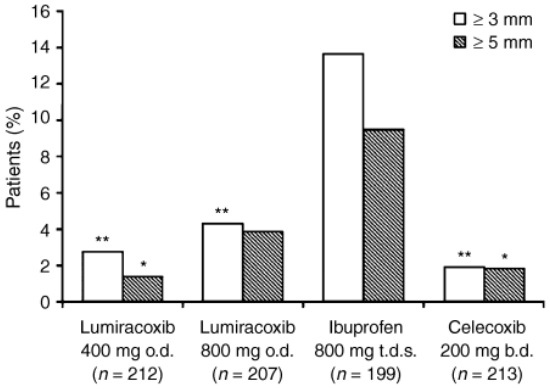
The Novartis little boy…



Current evidence points to a marginal, if any, gain of safety compared with the first generation of COX-2 inhibitors. However, trials with the new COX-2 inhibitors offer the chance to address these open questions of highly selective COX-2 inhibition; that is, thrombogenic risk, sodium and water retention, and interference with tissue repair, in particular, healing of mucosal damage.
Drom: Stichtenoth DO, Frolich JC. Drugs. 2003;63(1):33-45. The second generation of COX-2 inhibitors: what advantages do the newest offer?

Lumiracoxib gastrointestinal safety

Kivitz, A. J., Nayiager, S., Schimansky, T., Gimona, A., Thurston, H. J. & Hawkey, C. Reduced incidence of gastroduodenal ulcers associated with lumiracoxib compared with ibuprofen in patients with rheumatoid arthritis. *Alimentary Pharmacology & Therapeutics* 19 (11), 1189-1198, 2004. doi: 10.1111/j.1365-2036.2004.01956.x

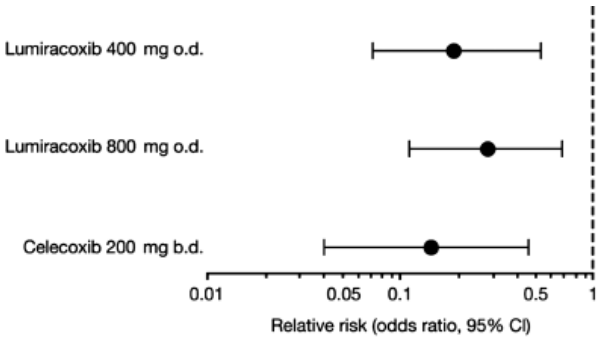


*$P < 0.05$, **$P < 0.01$ – vs. ibuprofen
≥ 5 mm – lumiracoxib 800 mg o.d. vs. ibuprofen $P = 0.09$
Lumiracoxib 400 or 800 mg o.d. vs. celecoxib – N.S.
Lumiracoxib 400 mg o.d. vs. lumiracoxib 800 mg o.d. – N.S.
n = modified safety population (all safety patients who underwent at least one post-baseline upper gastrointestinal endoscopy)

Cumulative incidence of gastroduodenal ulcers 3 and 5 mm at study end (week 13) by treatment group.

Lumiracoxib gastrointestinal safety

Kivitz, A. J., Nayiager, S., Schimansky, T., Gimona, A., Thurston, H. J. & Hawkey, C. Reduced incidence of gastroduodenal ulcers associated with lumiracoxib compared with ibuprofen in patients with rheumatoid arthritis. *Alimentary Pharmacology & Therapeutics* 19 (11), 1189-1198, 2004. doi: 10.1111/j.1365-2036.2004.01956.x



Ibuprofen 800 mg t.d.s., relative risk = 1
Odds ratios all $P < 0.01$ vs. ibuprofen

Relative risk from developing gastroduodenal ulcers 3 mm in diameter.