Prevention of UGI Complications of NSAIDs: An Evidence Based Approach

Medical Grand Rounds

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This is to acknowledge that Walter Peterson, MD serves as a consultant to AstraZeneca and to Merck. Dr. Peterson will be discussing "off-label" uses in his presentation.

Case Scenario

- 75 y/o man presents to you with recurring osteoarthritis in his knees and hips despite acetaminophen
- Past history includes an NSAID-associated bleeding gastric ulcer 18 months previously
- Patient has also started taking 81 mg ASA per day for CV prophylaxis

Case Scenario

- You want to restart an NSAID, but are worried about the possibility of another bleeding ulcer
- You are aware of the new COX-1 sparing (COX-2 selective) NSAIDs and wonder if they would be safer for the patient instead of a non-selective NSAID

Case Scenario

What should you prescribe?

- Non -selective NSAID alone?
  + misoprostol?
  + proton pump inhibitor (PPI)?
- COX-1 sparing NSAID alone?
  + misoprostol?
  + PPI?

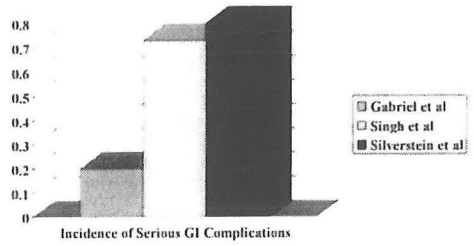
Questions of Interest

- What is the risk of UGI complications with NSAIDs?
- What is the evidence that these complications can be decreased?
  - Misoprostol
  - PPIs
  - Cox-1 sparing NSAIDs
- In whom should these agents be used?

Annual Incidence of Complications from NSAIDs in Patients With No Risk Factors

- Gabriel: meta-analysis of case-control/cohort trials
- Singh: prospective cohort trial based on ARAMIS post surveillance database
- Silverstein (MUCOSA trial): RCT of RA pts using NSAIDs with misoprostol or placebo

Annual Incidence of Complications from NSAIDs in Patients With No Risk Factors

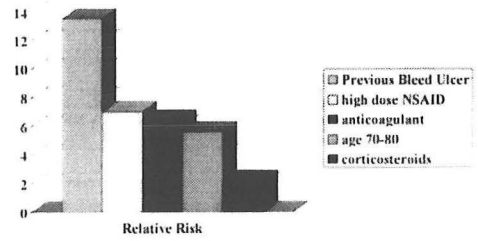


Individual Risk Factors for NSAID-Associated UGI Complications

- Case Control Trial of 1457 pts with UGI bleed and 10,000 controls
- search of computerized records of UK-GPs
- RR for any NSAID use = 4.7

Garcia Rodriguez, Lancet 1994;343 769

Relative Risks of Factors for GI Bleed



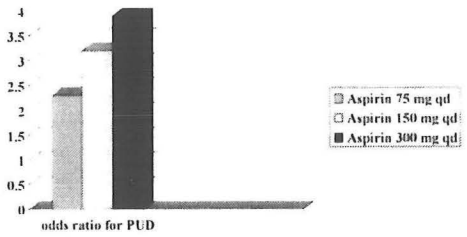
Garica Rodriguez, Lancet 1994;343 769

Low Dose Aspirin and Bleeding Peptic Ulcer

- Case control study of 1121 pts with peptic ulcer bleeds matched with community/hospital controls
- Controlled for age, gender, tobacco and etoh use
- Data on medications extracted from self-administered questionnaire at hospital admission

Weil, BMJ 1995;310:827

Aspirin and Bleeding Peptic Ulcer



Weil, BMJ 1995;310:827

Summary

- Relative risks of UGI bleeding with various factors:
  - LD-ASA = 2.3
  - Any non-aspirin NSAID = 4.7
  - High dose NSAIDs = 7.0
  - Anticoagulation = 6.4
  - Patient >70 years old = 5.6
  - History of complicated ulcer =13.5
  - NSAID + Pt. >70 + prev. comp. Ulcer + LD-ASA = ?

Questions of Interest

- What is the evidence that these GI complications can be decreased?
  - Misoprostol
  - PPIs
  - Cox-1 sparing NSAIDs

Misoprostol

- Synthetic prostaglandin analogue
- Decreases endoscopic ulcers and ulcer complications compared to placebo
- Only FDA approved drug for prevention of NSAID-induced ulcers

MUCOSA Study

- Prospective, randomized trial of 8843 patients with rheumatoid arthritis
- Patients taking one of 10 conventional NSAIDs
- Misoprostol 200 ug QID compared to placebo
- Outcome: Serious GI complications

Silverstein, Ann Intern Med 1995;123:241

Validity Criteria for Article on Therapy

- Randomized?
- Concealed allocation?
- Double blinded?
- All patients accounted for?
- Intention to treat analysis?

MUCOSA Study: Validity

- Randomized — Yes
- Allocation concealed — Yes
- Double blinded — Yes
- Complete follow-up? — No
- Intention to treat analysis: — Yes

MUCOSA Study: Results After Six Months

End Point	Placebo (n=4439)	Misoprostol (n=4404)	RRR
Complicated UGI Events	33 (0.74%)	16 (0.36%)	51%
Above + Sxic Ulcers	59 (1.33%)	27 (0.61%)	54%

Silverstein, Ann Intern Med 1995;123:241.

Absolute Risk Reduction (ARR)

- Actual reduction in bad outcomes between treatment group patients & control group patients
- (% bad outcome: control group) - (% bad outcome: treatment group)

Relative Risk Reduction (RRR)

- Decreased risk of bad outcome in treatment (tx) group patients *compared* to risk of bad outcome in control group patients
  - $\frac{\text{(\% bad outcome control group) - (\% bad outcome tx group)}}{\text{(\% bad outcome control group)}}$

Number Needed to Treat (NNT)

- Number of patients that need to be treated to prevent one additional bad outcome over a given period of time
- $\text{NNT} = \frac{1}{\text{ARR}}$

MUCOSA Study: Results

- Relative Risk Reduction = 51%
  (0.74% - 0.36%/0.74%)
- Absolute Risk Reduction = 0.38%
  (0.74%-0.36%)
- Number Needed to Treat = 263
  (1/0.0038)

ARR vs. RRR

- Since RRR is comparison of treatment benefits. RRR may be misleadingly high if frequency of bad outcomes is low
- Since ARR *directly* measures the decrease in bad outcomes. ARR may be a more accurate estimate of treatment benefits

Proton Pump Inhibitors

- Known to heal NSAID-induced ulcers
  - When NSAIDs discontinued
  - When NSAIDs continued
- Few side effects
- Once daily dosing

OMNIUM Study

- 935 patients who developed NSAID ulcers or >10 erosions
- Ulcers healed with either omeprazole or misoprostol
- 725 patients with healed lesions randomized to receive placebo. omeprazole (20 mg QD) or misoprostol (200 ug BID)
- Endoscopic evaluation after 6 months for ulcers

Hawkey. New Engl J Med 1998;338:727

OMNIUM Study: Validity

- Randomized Yes
- Allocation concealed Yes
- Double blinded Yes
- Complete follow-up ?
- Intention to treat analysis: Yes

Omnium Study: Results after Six Months

- Percent of patients with ulcers :
  - Placebo: 69/155 (45%)
  - Misoprostol: 61/296 (21%)
  - Omeprazole: 42/274 (15%)
- Omeprazole tolerated better

Hawkey, New Engl J Med 1998;338:727

Omnium Study: Results

- Omeprazole compared to placebo
  - RRR: 67%
  - ARR: 30%
  - NNT (six months) = 3
- Omeprazole compared to misoprostol
  - RRR: 40%
  - ARR: 6%
  - NNT (six months) = 17

Omnium Study: Other Issues

- Clinically significant complications (bleeds, perforations) not an endpoint
- Low dose of misoprostol

H. pylori Study

- Study designed to compare Hp eradication with PPI therapy
- 330 patients on low-dose ASA for CV prophylaxis or Naproxen for arthritis with past ulcer bleeding
- Ulcers healed with omeprazole
- Randomized to H pylori therapy (BMT) or omeprazole
- 6 month follow-up for rebleeding
- BMT group surrogate control for PPI

Chan, Gastroenterology 2000; 118:A1228

Hp Study: Validity

- Randomized — Yes
- Allocation concealed — ?
- Double blinded — No
- Complete follow-up — 7% drop-out
- Intention to treat analysis: — Yes

Hp Study: Results after Six Months

- Naproxen (n=150)
  - BMT 17.3% rebleeding
  - Omeprazole 4% rebleeding (p=0.008)
- LD-ASA (n=180)
  - BMT 2.1% rebleeding
  - Omeprazole 1.1% rebleeding (NS)

Chan, Gastroenterology 2000; 118 A1228

Hp Study: Results

- Naproxen: Omeprazole compared to BMT
  - RRR: 75%
  - ARR: 13%
  - NNT (six months) = 8

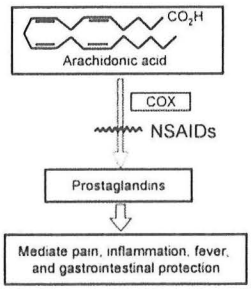
Summary

- Misoprostol reduces the risk of complicated UGI events (RRR ~ 50%), but the absolute risk reduction is small (<0.5%)
- Large numbers of patients must be treated to prevent one event (NNT = 263).

Summary

- Study endpoints with PPIs are primarily endoscopic ulcers, not complicated UGI events
- PPI therapy appears to be at least as effective as misoprostol in preventing endoscopic lesions in high risk patients.
- Data on PPI for prevention of complicated UGI events are limited, but the H. pylori study suggests a RRR of .75 in high-risk patients.

Mechanism of Action of NSAIDs: Old Concept

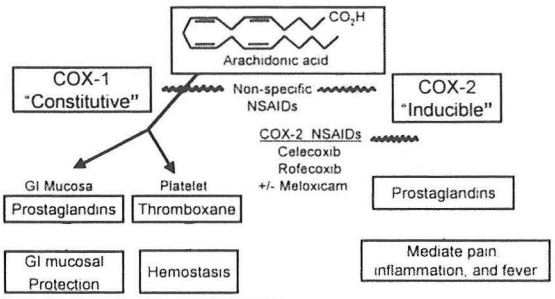


Vane *Nature New Biol* 1971;231 232-235
Vane et al *Inflamm Res* 1995;44 1-10

Comparison of Cyclooxygenase (COX)-1 and COX-2

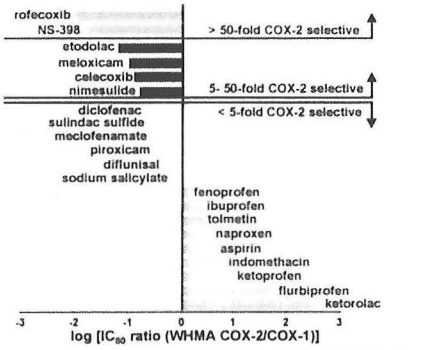
	COX-1	COX-2
Regulation	Constitutive	Inducible
Range of Expression	2 to 4 fold	10 to 80 fold
Tissue Expression		
	Most tissues Notably found in: Platelets Stomach	Inflammatory Sites Synoviocytes Fibroblasts Monocytes

Mechanism of Action of NSAIDs: New Concept



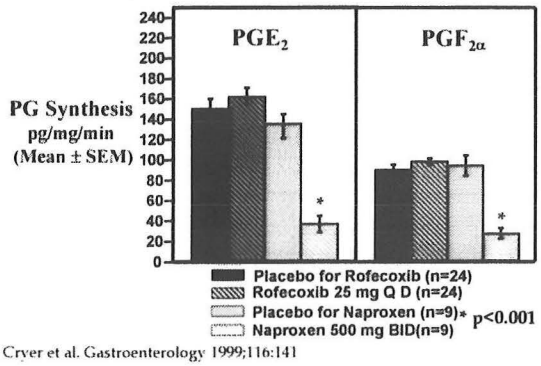
Bakhle et al *Med Inflamm* 1996 5 305-323
Vane et al *Inflamm Res* 1995 44 1-10

In Vitro Selectivity: COX-2/COX-1 Ratio



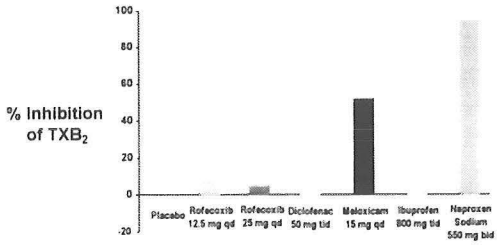
Warner *et al. Proc. Natl. Acad. Sci.* USA 96

PG Synthesis in Gastric Mucosal Biopsies



Cryer et al. Gastroenterology 1999;116:141

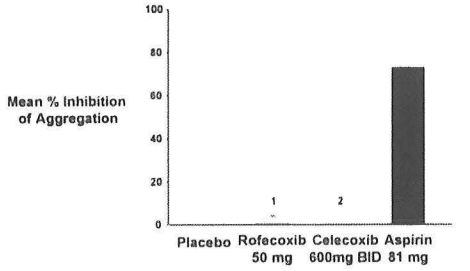
In vivo COX-1 Inhibition with Therapeutic Dosing



Schwartz et al. *Ann Rheum Dis* 1999;58:206. Abstract 857.

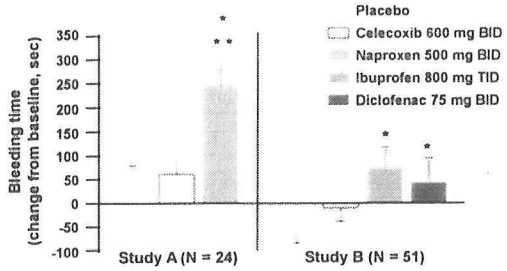
Platelet Aggregation

Inhibition (1mM Arachadonic Acid Agonist)



1-data on file Merck Research Labs
2-data on file G. D. Searle & Co.

Bleeding Time at Steady State



*$P < 0.05$ vs placebo; **$P < 0.05$ vs celecoxib
[1]Mengle-Gaw et al. *Arthritis Rheum*. 1997;40(9)(suppl):S93.
[2]Data on file, G.D. Searle & Co.

NSAID-Induced GI Ulcer Bleeding

Consequence of Two Processes

Process	COX Isoform	Consequence
1) Prostaglandin inhibition in GI Tract	COX-1	Endoscopic Ulceration
2) Thromboxane inhibition in Platelet	COX-1	Bleeding Tendency
	=	Bleeding Ulcer

• COX-1 sparing NSAIDs have decreased effects on GI tract & platelets

COX-1 Sparing NSAIDs

Celecoxib

Rofecoxib

Meloxicam*

* at a dose of 7.5 mg

CLASS Study

- 7982 patients :72% OA; 28% RA
- Celecoxib 400 mg bid vs. Diclofenac 75mg bid or Ibuprofen 800 mg tid
- Low dose aspirin allowed
  - 21% of patients
- Pre-defined endpoint criteria
  - Complicated UGI events
  - Above + symptomatic ulcers

Silverstein, JAMA 2000;284:1247

CLASS Study: Validity

- Randomized — Yes
- Allocation concealed — Yes
- Double blinded — Yes
- Complete follow-up? — No
- Intention to treat analysis: — Yes

CLASS Study: Results

End Point*	NSAID (n=3987)	Celecoxib (n=3995)	RRR
Complicated UGI Events	1.4%	0.8% (p=0.09)	43%
Above + Sxic Ulcers	3.5%	2.1% (p=0.03)	40%

*Event rate per 100 pt years

Silverstein, JAMA 2000;284:1247

The Effect of ASA on UGI Events with Celecoxib

In patients taking low-dose aspirin, there were no significant differences in UGI events between patients taking non-selective NSAIDs and celecoxib:

Complicated Events = 2.1% vs. 2.0% (p=.92)

Above + Sxic Ulcers = 6.0% vs. 4.7% (p=.49)

CLASS Study: Results in patients not taking low-dose ASA

End Point*	NSAID (n=3987)	Celecoxib (n=3995)	RRR
Complicated UGI Events	1.3%	0.4% (p=0.04)	69%
Above + Sxic Ulcers	2.9%	1.4% (p=0.02)	52%

* Event rate per 100 pt years

Silverstein, JAMA 2000;284:1247

CLASS Study: UGI ADVERSE EVENTS

	Celecoxib (N=3995)	Diclofenac (N=1999)	Ibuprofen (N=1988)
Dyspepsia	16.5%	19.5%*	16.5%
Abdominal Pain	11.6%	18.4%*	11.2%
Nausea	8.2%	12.1%*	9.0%

* p 0.05 vs celecoxib

CLASS Study: MORTALITY AND CARDIOVASCULAR EVENTS

	Celecoxib (N=3995)	Diclofenac (N=1999)	Ibuprofen (N=1988)
All Deaths	0.6%	0.6%	0.7%
CV Deaths	0.3%	0.4%	0.5%
MIs	0.5%	0.3%	0.5%
CVAs	0.2%*	0.5%	0.5%

* p 0.05 vs ibuprofen

VIGOR Study

- 8,076 patients with RA
- Rofecoxib 50 mg QD vs. Naproxen 500 mg BID
- Low-Dose ASA not permitted
- Pre-defined endpoint criteria
  - Complicated UGI events + Sxic ulcer
  - Complicated UGI events

Bombardier, N Engl J Med 2000;343:1520

VIGOR Study: Validity

- Randomized — Yes
- Allocation concealed — Yes
- Double blinded — Yes
- Complete follow-up? — No
- Intention to treat analysis: — Yes

VIGOR Study: Results

End Point*	Naproxen (n=4029)	Rofecoxib (n=4047)	RRR
Complicated UGI Events	1.4%	0.6% (p=0.005)	57%
Above + Sxic Ulcers	4.5%	2.1% (p<0.001)	53%

*Event rate per 100 pt. years

Bombardier, N Engl J Med 2000;343:1520

VIGOR Study: Top 5 Adverse Events Leading To Discontinuation

	Rofecoxib (N=4047)	Naproxen (N=4029)
Dyspepsia	1.1%	1.4%
Abd. Pain	0.7%	1.2%*
Epi Discomf	0.6%	1.3%*
Nausea	0.8%	0.8%
Heartburn	0.7%	0.7%
Any of 5 sxs	3.7%	5.3%*

*P<0.05

VIGOR Study: MORTALITY AND CARDIOVASCULAR EVENTS

	Rofecoxib (N=4047)	Naproxen (N=4029)
All Deaths	0.5%	0.5%
CV Deaths	0.2%	0.2%
MIs	0.4%	0.1%*
CVAs	0.2%	0.2%

*P<0.05

SUMMARY: VIGOR And CLASS Studies

Annualized Results With No Aspirin Use
COX-1 Sparing vs. Traditional NSAIDs

- Complicated UGI Events
  - RRR: 57 - 69%
  - NNT: 111-125
- Complicated UGI Events + Sxic Ulcers
  - RRR: 53%
  - NNT: 42 - 67

COX-1 SPARING AGENTS: SUMMARY

- Significant decrease in UGI events
- Slight decrease in UGI symptoms
- Lack of a COX-1 effect excludes these agents as a means of decreasing cardiovascular events

Questions of Interest

- What is the risk of GI complications with NSAIDs?
- What is the evidence that these GI complications can be decreased?
  - Misoprostol
  - PPIs
  - Cox-1 sparing NSAIDs
- In whom should these agents be used?

ARR and NNT for Varying Baseline Risks of UGI Complications

Assume RRR = 50%

Base Risk	.002	.005	.01	.05	.10	.20
ARR	.001	.0025	.005	.025	.05	.10
NNT	1000	400	200	40	20	10

Recommendations:
Low-risk Patients

- If cost is no object, COX-1 sparing agents can be used at any time
- Patients at low baseline risk can use non-selective NSAIDs +/- low dose ASA

Recommendations:
High Risk Patients

- NSAIDs: Use COX-1 sparing NSAID +/- PPI or misoprostol

Recommendations:
High Risk Patients

- NSAIDs: Use COX-1 sparing NSAID +/- PPI or misoprostol
- LD-ASA: Use LD-ASA +/- PPI or misoprostol

Cardiovascular Prophylaxis: The Future

- In rats. NSAID-induced gastric damage requires inhibition of BOTH COX-1 and COX-2 (Wallace et al)
- A pure COX-1 inhibitor may be a safer agent for cardiovascular prophylaxis than low-dose ASA. which inhibits both COX-1 and COX-2

Recommendations: High Risk Patients

- NSAIDs: Use COX-1 sparing NSAID +/- PPI or misoprostol
- LD-ASA: Use LD-ASA +/- PPI or misoprostol
- NSAIDs + LD-ASA: Use either COX-1 sparing or non-selective NSAID + LD-ASA + PPI or misoprostol

Ibuprofen Antagonizes The Irreversible Anti-Platelet Effect of Aspirin

- Healthy volunteers treated with:
  (1)ASA 2hr before ibuprofen
  (2)Ibuprofen 2hr before ASA
  (3)ASA 2hr before rofecoxib
  (4)Rofecoxib 2hr before ASA
- Platelet aggregation and serum TxB2 were inhibited 24hr after dosing in each group except Group 2

Catella-Lawson et al Arthritis Rheum 2000;43(suppl):S1392

Case Scenario

- 75 y/o man presents to you with recurring osteoarthritis in his knees and hips despite acetaminophen
- Past history includes an NSAID-associated bleeding gastric ulcer 18 months previously
- Patient has also started taking 81 mg ASA per day for CV prophylaxis

Questions

- In an elderly patient with a past history of bleeding peptic ulcer, and who is taking low-dose ASA, what is the risk of an NSAID-associated side effect?

The exact relative risk is not known, but must be considered very high.

Case Scenario

What should you prescribe?

COX-1 sparing NSAID/LD-ASA

plus

misoprostol

or

PPI

Summary

- The risk of NSAID-associated UGI complications is ~0.5%/yr in patients with no risk factors
- The risk of NSAID-associated UGI complications increases substantially with factors such as age and prior ulcer

Note: It has been suggested that OTC NSAIDs pose a greater risk than some drugs recently recalled by the FDA

Summary

- Cox-1 sparing NSAIDs decrease UGI events by ~50% compared to non-selective NSAIDs
- Misoprostol and perhaps PPIs also decrease UGI events by ~50%
- Head-to-head studies of COX-1 sparing NSAID vs Non-selective NSAID + PPI or misoprostol have not been reported

Summary

- The use of low-dose ASA may abrogate the beneficial effects of Cox-1 sparing NSAIDs; consideration should be given to using misoprostol or PPIs in such patients
- Non-selective NSAIDs taken beforeASA may prevent irreversible platelet inhibition

References

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