Back to Bengay??*

The evidence for the good and the bad in COX 2 specific inhibitors

Lin Brown, MD

Dartmouth Medical School

*Shamelessly taken from Dr. Brooks

What I plan to cover

- The evidence for reduction in meaningful GI events with Cox 2 inhibitors
- The evidence for increased risk of thrombotic events, primarily cardiac, with Cox 2 inhibitors.
- The evidence for the addition of ASA to traditional NSAIDs and its negative effect on cardioprotection.
- What to do with this flood of information.

What Cox 2 inhibitors do that nonselective Cox 2 do not

- Both inhibit cyclooxygenase that converts arachadonic acid to PGs but the nonselective NSAID target both Cox 1 and 2 isoforms of the enzyme and cox 2 effects only one isoform induced by inflammation and cell proliferation but also present constitutively in endothelium, kidney, brain and ovaries.
- NSAIDs target cox 1 and 2 to different degrees and can be compared by the IC50 cox-2/IC50cox-1 ratio with drugs with a ratio below 1 being very cox 2 selective. This system ranks drugs from a very cox 1 drug like sulindac (37) to rofecoxib at 0.001.

Cox 2 history

- The isoforms of cyclooxygenase were first described in 1989 and confirmed in 1991. Celecoxib and rofecoxib were approved in 1999.
- Theoretically these agents could be predicted to increase clotting because cox 1 is present on platelets and cox 2 on endothelial cells. Inhibiting the antithrombotic endothelial product prostacyclin and not the platelet associated thromboxane could upset this balance although the system has many redundancies that could reduce this negative effect.

Was this concern born out?

- Reviews of the newly released Cox 2 inhibitors do not mention thrombosis as a significant concern.
- **Feldman Ann Intern Med 2000;132:134-143**
- **Wernick Ann Intern Med 2000;132:125-133**
- **Bulletin of rheumatic diseases 1999; 48:no. 2**
- But some experts cited the theoretical risk in case reports.
- Then came the VIGOR and CLASS studies in 2000.
- These established quite solidly that there were fewer clinically relevent GI events in patients on these agents.

VIGOR study

- 8000 patients with RA not on ASA randomized to receive naproxen or rofecoxib (1000mg and 50 mg per day)
- 2.1/100pt years c/w 4.5/100pt years for a RR of .5 (CI .3-.6) p<.001 for symptomatic ulcers
- .6 vs 1.4 for a RR of .4 (.2-.8) p=0.005 for complicated ulcer events NNT 41
- **Bombardier NEJM 2000;343:1520-1528**

CLASS

- 8000 younger patients, 27% with RA; 57% completion rate at 6 months comparing 400mg per day celecoxib to other NSAIDs. ASA was allowed.
- OVERALL 2.08 vs 3.54 for symptomatic ulcers (p=.02) and .76 vs 1.45 for complicated ulcers (p=.02)
- The RR of .59 for symptomatic ulcers with CI of .38-.94

CLASS continued

- Only in the non-aspirin group did the decrease in ulcer rate reach statistical significance.
- In fact in the ASA group the rate was 4.7 vs 6.0 for symptomatic ulcers and 2.0 vs 2.12 for complicated ulcers neither sig different from NSAIDS.
- *So, the addition of ASA for cardioprotection abolished the gastroprotection of the selective cox 2 inhibitors.
- **Silverstein JAMA 2000;284:1247-1255**

BUT

- Clearly noted in the VIGOR abstract was the acknowledgment that the myocardial infarction rate was different between the two drugs:
- .4 vs .1 (CI of .1-.7) with no p value given.
- No increase in MI risk was found in the CLASS study.

The accusations begin...

- Much commentary ensued after these publications and vioxx was withdrawn in Sept 2004. However, there was an FDA change in labeling information in 2002.
- The final straw was the APPROVe study of 2600 pts without cardiac hx who were randomized to rofecoxib vs placebo in the treatment of polyps after colon cancer. The study was stopped due to increased cardiac risk: 3.5% vs 1.9% $p<0.001$ **Topol NEJM 2004;351:1707-1709**
- There are also concerns about the interpretation of the celecoxib studies, concerns about the FDA waiting too long and not mandidating the appropriate trials on cardiac risk in the coxibs..

What is the extent of the concern

- Was naprosyn cardioprotective? No and concerns have been raised about increased cardiovascular risk with Aleve in a study of Alzheimers disease.
- Is this a class effect? Possibly even probably, with Bextra having the most concern. The data has been sliced and diced many ways. There is concern about valdecoxib more than lumiracoxib or celecoxib.
- Was the risk greater than the benefit? A judgement call.

- **Mukherjee JAMA 2001;286:954-959**
- **Boers Lancet 2001;357:1222-1223**
- **Strand A&R 2002;47:349-355**
- **Wayne Lancet 2002;360:1071-1073**
- **White Amer J Cardio 2003;92:411-418**
- **Solomon Circulation 2004;109:2068-2073**

Overall risk and benefit

- In the MUCOSA trial of misoprostel and NSAID induced ulcers in RA patients the rate of complicated GI ulcers was 1% (over 6 months) in placebo and .6% with misoprostel, a significant reduction.
- So, comparing a 2% per year rate of bad GI outcomes to a rate of .7% for MI with rofecoxib you might choose ??
- **Bombardier A&R 1998;41:16-25**
- **Mukherjee JAMA 2001;286:954--959**

Alternative strategies to gastro and cardio protection

- Give a cox 2 with ASA… but negates the gastro protection
- Give a nonselective cox and add gastroprotection with misoprostol or omeprazol since data on both these agents with NSAIDs reduced risk in a range similar to the cox 2 (.4-.5 RR reduction).
- NSAIDs however, cannot substitute for ASA in cardioprotection

Furthermore

- But treatment with ASA and another NSAID may negate the cardioprotection of ASA!
- Ibuprofen with ASA (tid dosing or within 2 hours of ASA in a single dose) competes with ASAs effect on Cox 1. This has not been shown for either celecoxib or for diclofenac. Other NSAIDs have not been studied.

- **Catella-Lawson NEJM 2001;345:1807-1817**
- **Kurth Circulation 2003;108:1191-1195**
- **Medical letter 2004; 46:61-62**

We have a dilemma

- NSAIDs cause GI toxicity
- Cox 2 inhibitors avoid that but result in increased risk of myocardial infarction
- Other gastroprotection can be used with equal success - misoprostel and omeprazol
- But nonselective NSAIDs are not cardioprotective
- So ASA must be added
- And some NSAIDs interfer with ASA cardioprotection

The perfect pill

- Part NSAID (diclofenac), 81mg ASA, misoprostol and a statin for good measure.

What do the experts say?

- ACR has put out many press releases stating that the data is evolving and to use judgement of the risk of GI or cardiac events in making a decision for the individual pt. The ACR believes that the risk with celecoxib and othe NSAIDs is not different from placebo but that Bextra and Vioxx pose significant risk. Renal effects and exaccerbation of CHF is present with all agents.
- **www.rheumatology.org**

What do I do

- Appreciate that the overall risk is low for any of these events in the individual patient.
- Take into account co-morbidity including preexisting heart disease, hypertension, CHF and prior GI bleeding.
- Elderly patients with RA and prior GI events are the best candidates for gastroprotection but are also the best candidates for cardiac disease.

What do I do

- Recall nonacetylated salicylates - trilisate and salsalate - do not interfer with either cox 1 or 2 and could be reasonable anti-inflammatory substitutions.
- ASA could be used at therapeutic levels with misoprostol or omeprazole.
- Acetominophen or tramadol could be used for OA.
- Overall it is a discussion between you and the pt of the perceived risks and benefits - isn't it always?

Now what do you do?