NSAID Use in Post-Myocardial Infarction Patients

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Objectives

By the end of the presentation, the audience will be able to use the evidence discussed to determine if NSAIDs can safely be used in post-myocardial infarction patients.

Case

- Mr. CP → 45 y.o. male
- Smoker
- PMH: cholecystectomy 1991, HTN (untreated), ↑ cholesterol, sports injury to shoulder several years ago → “flares up” every few months
- Meds on admission:
  - Ø Rx, Ø herbals
  - ibuprofen prn shoulder pain (may use for days to weeks every 2-3 months)
- Presents to hospital with inferior STEMI → angiogram shows diffuse CAD (med tx; Ø PCI)

Pharmacotherapeutic question

- In someone who has had an MI, is it safe to use ibuprofen regularly?

Case

- Discharge medications include:
  - ASA 81mg daily
  - Clopidogrel 75mg daily x 30d
  - Metoprolol 50mg BID
  - Ramipril 5mg daily
  - Atorvastatin 80mg
- While doing discharge medication reconciliation, I was reminded of his regular ibuprofen use
- Considering his diseases and drugs, can Mr. CP safely take ibuprofen as needed?

Cyclooxygenase

- Part of prostaglandin synthase → enzyme converting arachidonic acid into prostanoids (ie/ prostacyclin, thromboxane A₂)
- COX-1 and COX-2 isoforms
  - Inhibition of COX-1 linked to antiplatelet effects and GI toxicity
  - Inhibition of COX-2 implicated in ameliorating inflammation
Cyclooxygenase inhibitors

- 3 types:
  - Acetylsalicylic acid → irreversibly acetylates COX
  - Non-selective COX inhibitors (ie/ indomethacin, ibuprofen, naproxen) → competitively inhibit COX
  - COX-2 selective inhibitors (ie/ “coxibs”)

NSAIDs

- Abundant use in many populations
- To reduce fever, treat pain, reduce inflammation
  - Osteoarthritis, rheumatoid arthritis, dysmenorrhea, headache, sports injuries, dental pain, etc
- Easy to acquire (ie/ OTC ibuprofen)

Side effects of NSAIDs

- Dyspepsia → GI ulceration and perforation
- Nephrotoxicity
- Worsening hypertension and CHF
- Cardiovascular toxicity

CV toxicity – remember Vioxx®??

- COX-2 inhibitors developed and prescribed widely due to their possible decreased risk of GI toxicity/bleeding
- VIGOR trial – comparison of upper GI toxicity of rofecoxib 50mg daily vs naproxen 500mg BID in RA patients; no ASA allowed
- Less upper GI events with rofecoxib, but increased rate of MI (RR=4.5) → high rate in people at highest risk ie/ people who should have been on ASA

Vioxx® continued

- Merck’s APPROVe trial → rofecoxib 25mg daily vs placebo for colonic polyps
- ASA used if indicated
- ↑ incidence of MI and stroke (RR = 1.92)


- CV risks of coxibs
- Clinical studies indicate long-term use of coxibs ↑ CV events (MI, stroke)
- Limited available evidence suggests CV risk with traditional NSAIDs as well; degree of risk differs among agents
- Monographs for all NSAIDs should be revised to describe available data or lack of data on CV toxicity


Health Canada Summary

- Rofecoxib has strong evidence of CV toxicity (ie/ 3 year APPROVe trial; risk became apparent at 18 months) → removed from market September 2004
- Valdecoxib (Bextra®) – no studies longer than 1 year, however short term use in CABG patients showed increased MI and CVA; reports of serious skin reactions → removed from market April 2005
- Meloxicam available – lack of evidence for CV risk (no studies > 1 year); labelling changes

Health Canada Summary

- Evidence of risk for celecoxib not consistent; data from APC trial (cancer prevention, n=2035) indicates that high doses and long-term use ↑ CV risk
- Remains on market given:
  - CV risks appear to be lower than with rofecoxib
  - No evidence for greater risk vs traditional NSAIDs
  - Revised labelling indicating possible risks
  - GI harm appears to be less than most NSAIDs
  - Removal from market would limit NSAID options


MEDAL – November 2006

- CV outcomes with etoricoxib and diclofenac in patients with OA and RA
- Other studies have reported CV adverse events, but none have had the primary aim of assessing relative CV risk vs traditional NSAIDs
- Randomly assigned etoricoxib 60-90mg/d vs diclofenac 150mg/d
- 34 701 patients


MEDAL continued

- Aim to estimate RR of thrombotic CV events with etoricoxib vs diclofenac using a non-inferior trial design
- Broad population, including people with CV risk factors
  - Patients with hx of MI, CABG, or PCI more than 6 months preceding enrolment could participate
- Average treatment duration 18 months
MEDAL outcomes and concerns

- Results:
  - Event rates 1.24/100 patient years with etoricoxib and 1.30/100 patient years with diclofenac (HR 0.95; 95% CI, 0.81-1.11)
  - CV events in patients on etoricoxib similar to diclofenac; later in presentation, we’ll see why this is not great news
- Do not know absolute risk increase of either agent since no placebo group
- More CHF, HTN with etoricoxib
- More GI and hepatic adverse events with diclofenac

COX-2 meta-analysis

- 2006: 138 RCTs (COX-2 vs placebo and COX-2 vs traditional NSAIDS)
- Effects of COX-2 inhibitors and traditional NSAIDS on risk of serious vascular events (=MI, stroke, or CV death)
- COX-2 vs placebo:
  - 42% relative increase in incidence of serious vascular events (primarily MI)
  - event rates small in both groups (1.2%/yr vs 0.9%/yr = 3 excess events/1000 people treated in a year)

COX-2 systematic review

- Review of 23 observational studies (case-control, cohort)
- Compared CV events with COX-2’s, NSAID use, or both with non-use/remote use as reference exposure
  - Rofecoxib ≤ 25mg/d: RR = 1.33 (95%CI 1.0-1.79)
  - Rofecoxib > 25mg/d: RR = 2.19 (95%CI 1.64-2.91)
  - Celecoxib RR = 1.06 (95% CI 0.91-1.23)
- Early risk associated with rofecoxib (within 30 days)

Are all COX-2’s the same?

- Meta-analysis and systematic review not in complete agreement
- ‘State-of-the-art’ paper → although ↑ CV events with coxibs suggesting class effect, numerous studies indicating different degrees of risk associated with different coxibs
- No head-to-head comparisons

Why do coxibs increase CV toxicity?

- Possible mechanism
  - TxA2 and PGI2 in vasculature → balance of vasoconstriction, platelet activation vs vasodilation and platelet inhibition
  - TxA2 important in development of acute arterial thrombosis (use ASA to block synthesis; ↓ MI)
  - PGI2 ↑ during episodes of unstable angina (ie/ COX-2 upregulated for protection)
  - If PGI2 synthesis is blocked by COX-2 inhibitors, may tip equilibrium into prothrombotic state

Zarraga IGE and Schwarz ER. Coxibs and Heart Disease: What have we learned and what else do we need to know? J.Am. Coll. Cardiol. 2007;49:1-14.

Safety of non-selective NSAIDs

- If the COX-2-selective inhibitors are unsafe due to the mechanism indicated, then non-selective COX inhibitors should be safe.

- Why do the STEMI guidelines specifically ask us to avoid ibuprofen?

**Remember the question:**

- The case of Mr. CP:
  - In someone who has had an MI, is it safe to use ibuprofen regularly?

**Ibuprofen statement in guidelines**

- Based on 3 studies:
  - 2001 (Catella-Lawson)
  - 2003 (MacDonald)
  - 2003 (Kurth)

**Catella-Lawson article**

- Structural basis of inhibition of COX-1 in platelets by both ASA and NSAIDs had been elucidated → both binding sites within the core of the enzyme

- Concerned about competitive interactions between ASA and NSAIDs since patients with arthritis and vascular disease may receive both

  - if NSAIDs compete with ASA and prevent binding, may ↓ cardioprotection since platelet function only impaired by NSAIDs for a portion of dosing interval (reversible binding)

Catella-Lawson

- Measured serum thromboxane B2 levels (an index of COX-1 activity in platelets) and platelet aggregation in platelet-rich plasma ex vivo

Results:

- Ibuprofen given before ASA or given TID antagonized the irreversible platelet inhibition induced by ASA
- Rofecoxib, acetaminophen and diclofenac had no effect

Conclusions:

- Treatment with ibuprofen in patients with ↑ CV risk may limit the cardioprotective effects of ASA

MacDonald (2003)

- Postulated that patients with known CV disease who take low-dose ASA and ibuprofen might have ↑ risk of CV mortality
- Accessed UK database retrospectively → selected patients diagnosed with MI, angina, stroke or TIA, and peripheral vascular disease
- 4 groups: discharged home on ASA, ASA + ibuprofen, ASA + diclofenac, ASA + other NSAID

Results

- Outcomes: all-cause mortality and CV mortality

ASA + ibuprofen (mean dose 1210mg/d) vs ASA alone: HR = 1.93 (95% CI 1.30-2.87)
- A statistically and clinically significant increased risk of mortality in users of ASA/ibuprofen vs ASA alone

No increase noted in other groups

- Lends support to hypothesis that ibuprofen combined with ASA given for secondary prevention may be deleterious (antagonism of cardioprotective effects of ASA

Kurth (2003)

- 5 year randomized, DB, PC trial
- 22,071 apparently healthy US male MDs
- 325mg ASA on alternate days vs placebo
- 139 MIs (ASA group) vs 239 MIs (placebo)
- Prospective observational data on use of NSAIDs (subgroup analysis of Physicians’ Health Study)

In ASA group:

- NSAID use <60d/yr: RR of MI = 1.21 (95% CI, 0.78 – 1.87)
- NSAID use ≥ 60d/yr ("regular use"): RR of MI = 2.86 (95% CI, 1.25 – 6.56)

Conclusions: regular but not intermittent use of NSAIDs inhibits clinical benefits of ASA

Limitations of ibuprofen information

- Theory makes sense, but evidence to support it is weak
- MacDonald: retrospective, unclear if patients took prescribed NSAIDs as directed, and no adjustments for severity of CV disease, doses of individual NSAIDs, smoking or BMI
- Kurth: observational (bias and confounding possible), post-hoc
  - MDs using NSAIDs regularly also had greater BMI, more arthritis, DM, and HTN, and were more likely to be smokers
  - No information on brand or dose of NSAIDs
  - Few events for comparison in exposed groups

Meta-analysis (Kearney) information on ibuprofen

- Effects of COX-2 inhibitors and traditional NSAIDS on risk of serious vascular events (=MI, stroke, or CV death)
- For CV effects of traditional NSAIDs, used mostly indirect methods to compare NSAIDs to placebo (in pain trials of NSAIDs, no placebo control)
- Statistical methods indicated that high-dose ibuprofen (800mg TID) increased risk of vascular events (RR=1.51, 95% CI 0.96-2.37)
- Unable to assess differing CV effects among ASA users and non-users

Systematic review (McGettigan)

- Review of 23 observational studies (case-control, cohort)
- Compared CV events with COX-2’s, NSAID use, or both with non-use/remote use as reference exposure
- CV events no different when ibuprofen compared to placebo (RR=1.07, 95% CI 0.97-1.18)
- RR’s close to 1 in users and non-users of ASA

What to do for Mr. CP?

- Ibuprofen should not be used; even if evidence is not strong, it’s what we have → do no harm (and guidelines are explicit)
- Based on previous discussion, COX-2 inhibitors do not seem like a good idea
- How about acetaminophen 1g q6h prn??

Outstanding questions

- What about other non-selective NSAIDs?

Kearney meta-analysis

- High-dose regimens of ibuprofen and diclofenac (75mg BID) associated with a moderate increase in the risk of vascular events
  - Ibuprofen RR=1.51 (95% CI 0.96-2.37)
  - Diclofenac rate ratio for vascular events = 1.63 (95% CI, 1.12-2.37)
- High-dose naproxen (500mg BID) NOT associated with an excess of CV events → RR=0.92 (0.67-1.26)
- ??? – no increased risk with naproxen since sustained inhibition of COX-1? (t1/2=14h, BID dosing)
McGettigan Systematic Review

- Diclofenac RR = 1.40 (1.16-1.70)
- Other traditional NSAIDs had RRs close to 1
  - Naproxen 0.97 (0.87-1.07)
  - Piroxicam 1.06 (0.70-1.59)
  - Ibuprofen 1.07 (0.97-1.18)

Summary

- COX-2 inhibitors appear to have an increased risk of CV events (ie/ 3 excess events in 1000 people treated; may be higher in high risk groups)
- Ibuprofen may or may not increase risk; some evidence to support it, a sensible theory, and a guideline statement
- Diclofenac may increase risk
- Naproxen appears not to...

Study limitations

- BMJ meta-analysis
  - Relatively small number of events available for analysis; limits assessment of hazards of various agents
  - Timing of hazard
  - Tabular summaries of data
  - Attention limited to CV hazards
- Systematic review of observational studies
  - Most information from databases; exposure?
  - Self-prescription possible
  - CV risk information was not complete in all studies (ie/ smoking, HTN, hyperlipidemia)
  - Differing baseline ages and risks
  - Many of pooled RR estimates are close to null

So can I safely use NSAIDs in people at risk of MI?

- No clear answer!
- Some of the data is conflicting, but there appears to be an increase in this rare but serious event
- Must consider risks and benefits
  - What are CV risks? Immediately post-MI vs no risk factors for CAD
  - Non-NSAID options for pain
  - Subjective report of efficacy
  - Risk of other adverse events ie/ GI bleeding

Suggestions

- In patients with high risk of CV events (ie/ post-MI, post-CABG, multiple risk factors), prudent to avoid
- If an NSAID must be used, evidence indicates naproxen may be safest choice
  - If at risk for GI bleed, can we use a ulcer prophylaxis and naproxen?
- If patient needs COX-2 inhibitor, may be willing to accept increased risk
- Dose/duration issue not clear; seems prudent to use lowest dose for shortest period of time possible

Pharmaceutical care

- Involve the patient in the decision → explain possible risks and benefits and choose together

Questions?