
COX-2 SPECIFIC INHIBITORS (COXIBS) CRISIS

Abbas Ali Mansour

DM, FICMS, Board Certificate Internal Medicine, Department of Medicine, Basrah Military Hospital, Basrah; IRAQ.

Summary

Nonsteroidal anti-inflammatory drugs (NSAIDs) represent the most frequently prescribed medicine in the world. Their main disadvantages were related to their effect on the gut and kidney. Since the early 80s of the last century, drugs manufacturers try to discover a NSAIDs which does not affect the gut and kidney. The gut toxicity may be decrease by concomitant use of antisecretory agents, but this increase their cost and decrease the compliance. The fully selective cyclooxygenase inhibitors has been introduced recently as an alternative to old generation NSAIDs. Unfortunately subsequent long-term evaluation produced disappointing results, and opened the door for a lot of discussion and controversies.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are in use for more 3500 year since dried myrtle leaves (contain salicylates) used to relieve pain by ancient Egypt¹. They are use by 30 million persons daily (more than 60 million prescriptions per year in USA, each year) and represent the most frequently prescribed medicines in the world, and its more used in elderly.

More than 3 decades ago, its was discovered that NSAIDs act by inhibiting the enzyme cyclo-oxygenase (COX)^{2,3}.

Mechanism of action

By 1991, it has been discovered that COX, an enzyme which induced the synthesis of prostaglandin (PG) that mediate inflammation and blocked by NSAIDs, is of two isoforms (type) of COX, COX-1 and COX-2⁴. COX-1 is described as a "housekeeping" enzyme, (preserve diverse homeostasis) regulating normal cellular processes (such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney tubular function, where they diminished renal vascular resistance and enhance organ perfusion (redistributing blood flow from the renal cortex to the juxtamedullary region), and is stimulated by hormones or growth factors. Its necessary for the cellular integrity. COX-2 is usually undetectable in most tissues; its expression is increased during

Correspondence to:
Dr. Abbas Ali Mansour
Department of Medicine, Basrah Military
Hospital, Basrah; IRAQ.

states of inflammation or, experimentally, in response to mitogenic stimuli. It's an inducible enzyme that produces large amounts of prostanoids involved in pain and inflammatory responses; like PG E₂ which is chemotactic for neutrophils, and PGI₂ which mediates vascular permeability, facilitating extravasations of leucocytes². So theoretically speaking if we can block the COX-2 enzyme alone without affecting COX-1, we are going to relieve pain and inflammation without producing the side effects of non-selective NSAIDs.

Since the early 80s of the last century, drug manufacturers try to discover new NSAIDs, which does not affect the gut and kidney; meanwhile the mechanism of toxicities of classical NSAIDs were studied in detail.

GIT side effects

The common side effects are on the gastrointestinal tract (GIT) like bleeding, erosion, non-ulcer dyspepsia, perforation, or obstruction of the stomach, duodenum and to less extent in the esophagus and bowel. Approximately 1 to 2 percent of patients taking NSAIDs will develop serious GIT toxicity, this has resulted in 100,000 to 400,000 hospitalizations per year in the United States at a cost of over 2 billion dollars⁵⁻⁷. Up to 35% of peptic ulcer complications are due to NSAIDs use^{1,8}. The prevalence of NSAIDs-induced peptic ulcer ranges from 9% to 22%. Such complications are more common in the elderly and those with comorbidities. Each year 7600 excess premature deaths occur due to NSAIDs-induced GIT toxicity and 60%-100% of patients on NSAIDs therapy for 1-2 weeks, develop submucosal hemorrhage, erythema, superficial erosions, and increase fecal blood loss. On chronic use 5%-30% of patients develop gastric, antral or duodenal ulcer. The ratio of gastric ulcer to duodenal ulcer is 3:2^{1,8}. No evidence that enteric-coated preparation, the intra-

venous or rectal route will decrease the GIT side effect of NSAIDs¹.

Risk factors for NSAIDs-induced GIT toxicity⁹.

- Prior history of a gastrointestinal event (ulcer, hemorrhage).
- Age >60.
- High dosage of NSAIDs.
- Concurrent use of glucocorticoids.
- Concurrent use of anticoagulants.

The role of *Helicobacter pylori* infection in NSAIDs-induced gastritis or ulcer formation is unsettled¹⁰.

How to avoid NSAIDs induced GIT toxicity?

Concomitant use of antisecretory drugs may be useful to prevent the GIT toxicity. H₂ antagonists for prophylaxis cannot be relied upon, since tolerance to pH control occurs after long-term therapy with these drugs, but high doses of famotidine (40 mg BID) may decrease the rate of recurrence of NSAID-induced ulcer disease¹¹.

Studies proved that concomitant use of prostaglandin analogue like misoprostol in high dose (200 µg three to four times daily) may decrease the GIT toxicity if used concomitantly with NSAIDs, with reduction in the rate of gastric or duodenal ulcer and their complications¹². Such combination proved later to be expensive and there were a lot of GIT side effects like abdominal pain and diarrhea produced by misoprostol, that made the compliance poor. More patients receiving misoprostol than placebo withdraw from the studies during the first month, primarily because of diarrhea and abdominal discomfort. To be useful misoprostol should begin in dose 200-µg four-time daily¹³. For patients taking non-selective NSAIDs, only misoprostol has received FDA approval for prophylaxis against NSAIDs-induced ulcer disease and its complications. In comparison, omeprazole and

high-dose H₂ antagonists have not yet been approved for this purpose. Which one to choose omeprazol 20mg/day, lansoprazol 15-30 mg/day or misoprostol 200 QID? Its unsolved issue till now, but the side effect profile and compliance is in favor of proton pump inhibitors (PPI)^{6,14}. Although the concomitant use of NSAIDs with omeprazol may interfere with NSAIDs absorption (NSAIDs are acidic and their absorption needs acid media) and consequently their actions^{8,15}. Combination of misoprostol with non-selective NSAIDs in the same pill is another useful way to prevent ulcer and improve compliance¹⁶.

Other side effects

The second important toxicity is their effect on the kidney¹⁷. Their antiplatelet effect is minor unless there is platelets dysfunction. The incidence of asthma and nasal polyposis is rare⁷.

Because of complicated prophylaxis programs and their high cost, scientist try to made new discovery to avoid the side effects of these most commonly used drugs.

Pre COX-2 era

At this point the era of COX-2 specific NSAIDs started with the introduction of drugs that have mild selectivity. Some older NSAIDs are also relatively selective for the COX-2 receptor at low doses like the Nabumetone, Etodolac and Meloxicam¹⁸. All principally inhibits the activity of COX-2 at low doses, while it has more effects upon COX-1 at higher doses. In general, these agents have similar effects when used clinically as the other NSAIDs and they add nothing to avoid NSAIDs side effects¹⁹.

COX-2 ERA

This stimulates the release of fully COX-2 specific drugs, the Celecoxib, Rofecoxib, Valdecoxib, and Etoricoxib or some times called Coxibs²⁰. They are as effective as other NSAIDs for relief of

symptoms of osteoarthritis and rheumatoid arthritis²¹.

The manufacturer's of these drugs funded a lot of research on the theory of COX-2 selective NSAIDs^{22,23}, until the FDA approved Celecoxib in USA, few years ago as a gold standard COX-2 specific with less gut and renal toxicity.

Subsequent evaluation of such and long term follow up of patients proved the story is not that easy and the side effect profile after 6 months use of these medications, may be the same to that of other non-selective NSAIDs. After 6 months the ulcer complication occurs only in the users of Celecoxib compared with placebo.²⁴ Unfortunately this new finding did not appear in the same journal that publish the class²² study, which was the first optimistic randomized trial. To complicate the story more, studies proved that COX-2 is useful enzyme for ulcer healing^{25,26}. This could lead to a long term increase of ulcer related complications that occur without warning symptoms.²⁷ Although retardation of ulcer healing is non-specific to Coxibs, and seen also with non-selective NSAIDs⁶. Beside that all NSAIDs will mask ulcer pain. Therefore, in theory the rate of ulcer formation after a while may be even is higher in those using these COX-2 specific inhibitors.

The effects of COX-2 inhibition on renal function are similar to those observed with non-selective NSAIDs such as precipitation of hemodynamically-mediated acute renal failure, peripheral edema, hypertension, acute interstitial nephritis, nephrotic syndrome, and papillary necrosis²⁸⁻³⁰. And selective COX-2 inhibitors also should be avoided in patients with chronic renal insufficiency, severe heart disease, volume depletion, and/or hepatic failure^{31,32}.

Furthermore platelet-induced thromboxane A₂ (TXA₂) and endothelial-derived prostacycline (PGI₂) maintain normal blood flow and modulate thrombogenic

responses to injury. COX-2 seems to play a pivotal role in the production of endothelial prostacycline. A balancing of prothrombotic and antithrombotic effects can be proposed during NSAID administration as they inhibit both COX-1 and COX-2. Inhibiting endothelial PGI₂ synthesis but not platelet TXA₂ synthesis may lead to increased risk of thrombosis²⁸.

Their role in prevention of cancer of colon is the same as non-selective one³³.

Recent meta-analysis indicated a potential unexpected substantial excess of serious cardiovascular events with Coxibs^{34,35}.

From the above data and evolving knowledge of the activities of COX-1 and COX-2 has indicated that the original paradigm was an over-simplification²⁸. And the evidence reviewed so far does not support the view of COX selectivity.

This unfortunate news end long period of controversy and discussion on COX-2 selectivity and open the future for lot of questions. Like why these new drugs sold by billions of dollars over short period of time? This unjustified early conclusion lead to increase in the sales of Celecoxib from \$ 2623 million in 2000 to \$ 3114 million in 2001³⁶.

Who is responsible on such bias in medical research with misleading and disappointing results? Who mislead the people over long period with expensive drugs? The lessons also is that one should not put much weight on studies funded by manufactures of drugs and,

any new drug should not approved unless studies proved its safety over years rather than months.³⁷

Publishing and distributing over-optimistic short term data using post hoc changes to the protocol, while omitting disappointing long term data of trials, which involved large numbers of volunteers, is misleading. Lobbying from the pharmaceutical industry may be the cause of such bias like what happen with alosetron in irritable bowel syndrome³⁸. An "industry independent," individual patient data meta-analysis of all large scale, long term trials of selective COX 2 inhibitors must be performed to include both published and unpublished data.

These disappointing results open the way for new discoveries for drugs which can relive arthritis with little side effects like: NO-NSAIDs, through which nitric oxide incorporated with NSAIDs, Switterinoic NSAIDs, R-Enantiomers of NSAIDs and dual COX-2 with 5-lipoxygenase (LOX) inhibitors^{6,28}.

Recommendation

Until new drugs appear that proved safe and effective after long term follow up in randomized trials, one should use the old generations of NSAIDs, and use common sense recommendation, which includes avoiding these drugs in high risk group especially elderly and the use of concomitant PPI or misoprostol to decrease their side effect on the gut, and awaiting critical appraisal of selective COX-2 inhibitors.

References

1. Raskin JB. Gastrointestinal effect of nonsteroidal anti-inflammatory therapy. *Am J Med* 1999;106(5B):3S-12S.
2. Lipsy PE. COX-2 specific inhibitors: basic science and clinical implications. *Am J Med* 1999; 106(5B): 1S-2S.
3. Vane JR. Inhibition of prostaglandin synthesis as a mechanisms of action for the aspirin - like drugs. *Nature* 1971; 231:232.
4. Seibert K, Masferrer JL, Fu JY, Honda A, Raz A, Needleman P. The biochemical and pharmacologic manipulation of cellular cyclooxygenase (COX) activity. *Adv Prostaglandin Thromboxane Leukot Res* 1991;21:45-51.
5. Smalley WE, Griffin MR. The risks and costs of upper

- gastrointestinal disease attributable to NSAIDs. *Gastroenterol Clin North Am* 1996; 25:373.
6. Hawkey CJ. Nonsteroidal anti-inflammatory drug gastropathy. *Gastroenterology* 2000; 119:521-535.
 7. Amadio P Jr, Cummings DM, Amadio P. Nonsteroidal anti-inflammatory drugs. Tailoring therapy to achieve results and avoid toxicity. *Postgrad Med* 1993; 93:73-6,79-81,85-88.
 8. Guarner F. Prescribing nonsteroidal anti-inflammatory drugs together with antisecretory agents is safe but may be useless. *Gastroenterology* 1996;111:1145-1146.
 9. Simon LS, Hatoum TH, Bittman RM, et al. Risk factors for serious nonsteroidal-induced gastrointestinal complications: Regression analysis of the MUCOSA trial. *Fam Med* 1996; 28:202.
 10. Kim, JG, Graham, DY. Misoprostol Study Group. *Helicobacter pylori* infection and development of gastric or duodenal ulcer in arthritis patients receiving chronic NSAID therapy. *Am J Gastroenterol* 1994; 89:203.
 11. Taha AS, Hudson NH, Hawkey CJ, et al. Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs. *N Engl J Med* 1996; 334:1435-1439.
 12. Lanza FL. A guideline for the treatment and prevention of NSAID-induced ulcers. Members of the Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. *Am J Gastroenterol* 1998; 93:2037.
 13. Oddsson E, Gudjonsson H, Thjodleifsson B. Protective effect of omeprazole or ranitidine against naproxen induced damage to the human gastroduodenal mucosa. *Scand J Gastroenterol* 1990; 13(Suppl 176): 25.
 14. Graham DY, Agrawal NM, Campbell DR, et al. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs. *Arch Intern Med.* 2002; 162: 169-175.
 15. Fernández FJ. Might proton pump inhibitors prevent the antiplatelet effects of low- or very low-dose aspirin? *Arch Int Med* 2002; 162 : 2248.
 16. Pincus T, Koch GG, Sokka T, et al. A randomized, double-blind, crossover clinical trial of diclofenac plus misoprostol versus acetaminophen in patients with osteoarthritis of the hip or knee. *Arthritis Rheum.* 2001; 44: 1587-1598.
 17. Patrono C, Dunn MJ. The clinical significance of inhibition of renal prostaglandin synthesis. *Kidney Int* 1987; 32:1.
 18. Patrignani P, Panara MR, Greco A, et al. Biochemical and pharmacological characterization of the cyclooxygenase activity of human blood prostaglandin endoperoxide synthases. *J Pharmacol Exp Ther* 1994; 271:1705-1712.
 19. Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. *Am J Med* 1998; 104:413-421 .
 20. Percival RD, Brideau C, Charleson S, et al. Etoricoxib (MK-0663): pre-clinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. *J Pharmacol Exp Therapeutics* 2001; 296: 558-566.
 21. Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. *BMJ* 2002; 325: 619
 22. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000; 284: 1247-1255
 23. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* 2000; 343: 1520-1528 .
 24. Peter Jüni, Anne WS Rutjes, Paul A Dieppe, Are selective COX 2 inhibitors superior to traditional nonsteroidal anti-inflammatory drugs? *BMJ* 2002;324:1287-1288.
 25. Mizuno H, Sakamoto C, Matsuda K, et al. Inhibition of cyclooxygenase 2 in gastric mucosal lesions and its inhibition by the specific antagonist delays healing in mice. *Gastroenterology* 1997; 112: 387-397.
 26. US Food and Drug Administration. Transcript of the arthritis advisory committee. www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t1.rtf (Accessed 10 Dec.2001.)
 27. Berg Hrachovec J, Mora M. Reporting of 6-month vs 12-month data in a clinical trial of celecoxib. *JAMA* 2001; 286: 2398.
 28. Gambaro G. Strategies to safely interfere with prostanoid activity while avoiding adverse renal effects: could COX-2 and COX-LOX dual inhibition be the answer? *Nephrol Dial Transplant* 2002 ; 17: 1159-1162 .
 29. Gause A. Progress in the

- treatment of rheumatic disease. *Nephrol Dial Transplant* 2003;18: 13-16 .
- 30.Swan SK, Rudy DW, Lasseter KC, et al.Effect of Cyclooxygenase-2 Inhibition on Renal Function in Elderly Persons Receiving a Low-Salt Diet. *Ann Intern Med.* 2000; 133:1-9.
- 31.Dunn MJ. Are COX-2 selective inhibitors nephrotoxic? *Am J Kidney Dis* 2000; 35:976.
- 32.Komhoff M, Wang JL, Cheng HF, et al. Cyclooxygenase -2- selective inhibitors impair glomerulogenesis and renal cortical development. *Kidney Int* 2000; 57:414.
- 33.Tsujii M, Kawano S, Du Bois RN. Cyclooxygenase-2 expression in human colon cancer cells increases metastatic potential. *Proc Natl Acad Sci U S A* 1997; 94: 3336-3340.
- 34.Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001; 286: 954 – 959.
- 35.Budenholzer BR. Rofecoxib did not provide unequivocal benefit over traditional non-steroidal agents [electronic response to Jiini et al. Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs? *BMJ* 2002. bmj.com/cgi/eletters/324/7349/1287#22965 (accessed 2 Sep 2002).
- 36.Pharmacia earnings releases. Peapack, NJ, Pharmacia Corporation 2002. www.pharmacia.com/investor/earnings.asp
- 37.Jones R. Efficacy and safety of COX 2 inhibitors. *BMJ* 2002;325:607-608.
- 38.Lièvre M. Alosetron for irritable bowel syndrome. *BMJ* 2002; 325:555-556.

Editorial Comment

We do appreciate the material in the article, certainly it is very useful, and stressing on many vital and practical points. But the author did not mention the negative effect to Cox-2 inhibitor on fracture healing^{3,4}, so many published articles emphasize the inhibitory effect of Cox-2 on fracture healing process, though this effect was abolished after stopping Cox-2 inhibitor, so it is advisable not to use Cox-2 inhibitor as analgesia for fracture pain because it interferes with the production of prostaglandin which plays a vital role in fracture healing process. However, this effect of Cox-2 inhibitor can also be produced by indomethacin, Diclofenac, Piroxicam and Ibuprofen but not by Aspirin^{1,2,3,4,5}.

Cox-2 inhibitor also produces effect on bone growth³. So better avoid using it in children and adolescents.

So the ideal pain killer for fracture pain is pure analgesic like, acetaminophene,

tramadol, caffeine or glifonon, because it carries no anti-inflammatory effect.

The safety of Cox2 inhibitor during pregnancy is not yet favoured, by any scientific article so better avoid using it during pregnancy. Mixing Cox2 inhibitor with other nonsteroidal anti-inflammatory particularly if given through the same route is also unsafe.

The story of Cox, crisis reminds us of an old saying by Sir Robert Hutchinson, 1871-1960:

*“From inability to leave well alone;
From too much zeal for what is new and
contempt for what is old;
From putting knowledge before wisdom,
science before art, cleverness before
common sense;
From treating patients as cases; and
From making the cure of a disease more
grievous than its endurance,
God Lord, deliver us.”*

References

1. Beck A, Krischak G, Sorg T, et al. Influence of diclofenac (group of nonsteroidal anti inflammatory drugs) on fracture healing. Arch orthop Trauma Surg 2003; June 13.
2. Reuben SS. Consideration in the use of Cox2 inhibitor. Anaesthesia and Analgesia 2001; 93: 798-804.
3. Sara Sellis. Cox2 inhibitors may interfere with bone growth, healing. Stanford report, 2002, Nov. 20, Internet.
4. Thomas A. Einhorn. Use of Cox-2 inhibitor in patients with fractures. The American Academy of Orthopaedic Surgeons 2002; 50(2).
5. Walter A. Hoeman. Ibufrofen and fracture healing (Internet) <http://www.ppc.com/lists>.