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COX-2 SPECIFIC INHIBITORS (COXIBS) CRISIS

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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 antisecretery 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.Unfortunaltly subsequent long-term evaluation produced disappointing results, and opened tne 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 Egypt[1]. 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].

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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 isofroms (type) of COX, COX-1 and COX-2[4]. 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 juxtmedullary 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

states of inflammation or, experimentally, in response to mitogenic stimuli. Its an inducible enzyme that produce large mount of prostanoids involved in pain and inflammatory responses; like PG E_2 which is chemotactic for neutrophils, and PGI_2 which mediate vascular permeability, facilitating extravasations of leucocytes[2]. So theoretically speaking if we can block the COX-2 enzyme alone with out affecting COX-1, we are going to relive pain and inflammation with out producing the side effects of non- selective NSAIDS.

Since the early 80s of the last century, drugs 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 detailed.

GIT side effects

The common side effects are on 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 dollars[5-7]. Up to 35% of peptic ulcer complications are due to NSAIDs use[1,8]. The prevalence NSAIDs induced peptic ulcer ranges from 9% to 22%. Such complications are more common in the elderly and those with comorbidties. Each year 7600 excess premature death occurs due to NSAIDs induced GIT toxicity and 60%-100% of patients on NSAIDs therapy for 1-2 week, 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 intravenous or rectal route will decrease the GIT side effect of NSAIDs[1].

Risk factors for NSAIDs induced GIT toxicity[9].

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

The role of Helicobacter pylori infection in NSAIDs-induced gastritis or ulcer formation is unsettled[10].

How to avoid NSAIDs induced GIT toxicity?

Concomitant use of antisecreatory 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 disease [11].

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 complications .[12] 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 daily[13]. 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 choice 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 complianc[16].

Other side effects

The second important toxicity is their effect on the kidney[17]. Their antiplatelet effect is minor unless there is platelets dysfunction. The incidence of asthma and nasal polyposis is rare[7].

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 Meloxicam[18]. 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 effects[19].

COX-2 ERA

This stimulates the release of fully COX-2 specific drugs, the Celecoxib, Rofecoxib, Valdecoxib, and Etoricoxib or some times called Coxibs [20]. They are as effective as other NSAIDs for relief of symptoms of osteoarthritis and rheumatoid arthritis[21].

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 class[22] 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 NSAIDs[6]. Beside that all NASADs 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 necrosis[28-30]. 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 A_2 (TXA_2) and endothelial-derived prostacycline (PGI_2) 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 PGI_2 synthesis but not platelet TXA_2 synthesis may lead to increased risk of thrombosis[28].

Their role in prevention of cancer of colon is the same as non-selective one[33].

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-simplification[28]. 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 2001[36].

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 syndrome[38]. 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.

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Editorial Comment

We do appreciate the material in he 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 inhabitor on fracture healing [3,4], so many published articles emphasis the inhabitory 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 interfere with the production of prostaglandin which plays a vital rule 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 produce effect on bone growth [3]. So better avoid using it in children and adolescent.

So the ideal pain killer for fracture pain is pure analgesic like, acetaminophene, tramadol, caffeine of glifenon, because it carries no antiinflammatory 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 remind 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."

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