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NSAIDS(Cox-2 inhibitors): A safer approach

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Abstract:*Many investigations have shown that particular cox-2 is valuable for upper and lower git tract, specific cox-2 inhibitors are more viable at that point cox-1 and non-specific cox inhibitors and safe to utilize, additionally successful in counteractive action of tumor used to treat disease however many examinations have demonstrated that treatment with non-particular NSAIDs and particular COX-2 inhibitors is related with an expanded danger of CV (Cardio-vascular) occasions. In any case, a portion of the examination's have demonstrated that cox-2 is not related with CV occasions, its not clear whether the specific cox-2 inhibitors are in charge of CV occasions or not. The connection between COX-2 inhibitors and CV occasions should be tended to further, albeit moral and safe clinical trials are hard to execute practically speaking, a stepwise approach with proper measures is required for its more secure utilize.*

Key words:*Introduction, Selective Cox-2 Inhibitors, Git Benifits, Tumour Prevention, Cv Risk, Preventions, Conclusion*

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I. Introduction

Nonsteroidal anti-inflammatory drugs (**NSAID**s) are class of Drugs that provide analgesic (pain-killing) and antipyretic (fever-reducing) effects and in higher doses, anti-inflammatory effects.[1],[2] First used in 1960, the term served to distance new drugs from steroid-related iatrogenic tragedies.[3] The most prominent members of this group of drugs are aspirin, ibuprofen and naproxen, all available over the counter in most countries.[4]NSAIDs are divided into two sub-classes Non-selective NSAIDs and Selective NSAIDs.

Most of the Non-Selective NSAIDs inhibit the activity of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2)and Selective NSAIDS inhibit the activity of cyclooxygenase-2 (COX-2) also known as Selective COX-2 inhibitors and work by reducing the production of prostaglandins, chemicals that promote inflammation, pain, and fever. It is thought that inhibiting COX-2 leads to the anti-inflammatory, analgesic and antipyretic effects and that those NSAIDs also inhibiting COX-1, particularly aspirin, may cause gastrointestinal bleeding and ulcers due to reduced prostaglandins,[5] also protect the lining of the stomach and intestines from the damaging effects of acid, promote blood clotting by activating platelets, and also affect kidney function and leads to peptic ulcers.[6]

NSAIDs are usually used for the treatment of acute or chronic conditions where pain and inflammation are present.NSAIDs are generally used for the symptomatic relief of the following conditions:[78]

[1]*Bally, M; Dendukuri, N; Rich, B; Nadeau, L; Helin-Salmivaara, A; Garbe, E; Brophy, JM (9 May 2017). "Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data.". BMJ (Clinical research ed.). **357**: j1909.* PMID 28487435.

[2]*Lanas, A; Chan, FK (23 February 2017). "Peptic ulcer disease.". Lancet (London, England).* PMID 28242110

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[6] http://www.rxlist.com/cox-2_inhibitors/drugs-condition.htm

[7]*Simone Rossi, ed. (2006). Australian medicines handbook 2006. Adelaide: Australian Medicines Handbook Pty Ltd.* ISBN 0-9757919-2-3.[page needed]

Osteoarthritis[8],Mild-to-moderate pain due to inflammation and tissue injury[8],Low back pain[8],Inflammatory arthropathies (e.g., ankylosing spondylitis, psoriatic arthritis, reactive arthritis),Headache[8],Migraine[7],Acute gout[7],Dysmenorrhoea (menstrual pain)[7],Metastatic bone pain[7],Postoperative pain[7],Muscle stiffness and pain due to Parkinson's disease[7],Pyrexia (fever)[7],Ileus[7],Renal colic[7],They are also given to neonate infants whose ductus arteriosus is not closed within 24 hours of birth[7]

Nevertheless, reports of cardiovascular adverse reactions began to emerge in 2000-03, [9]and subsequent placebo controlled trials showed that COX 2 inhibitors were associated with an increased risk of atherothrombotic vascular events.[10]However, meta-analyses of randomised trials and observational studies have since shown that the higher cardiovascular risk is not restricted to COX 2 inhibitors, but also applies to some traditional NSAIDs[11]

In particular, NSAID use has been found to be associated with an increased risk of heart failure in several randomised clinical trials[12] and observational studies.[13]A large meta-analysis of over 600 randomised trials showed that COX 2 inhibitors and high doses of traditional NSAIDs (that is, diclofenac, ibuprofen, and naproxen) increased the risk of hospital admission for heart failure from 1.9-fold to 2.5-fold compared with placebo.In the light of this evidence, current guidelines limit the use of NSAIDs in patients predisposed to heart failure, with a full contraindication for patients with diagnosed heart failure.[14]

Nevertheless, there is still limited information on the risk of heart failure associated with the use of individual NSAIDs (both COX 2 inhibitors and traditional NSAIDs) in clinical practice, and especially on their dose-response associations. Therefore, heart failure was included as an outcome of interest in the overall cardiovascular and gastrointestinal risk evaluation of individual NSAIDs within the Safety of Non-Steroidal Anti-Inflammatory (SOS) Project, a multinational project funded by the European Commission under the seventh Framework Programme. A large, common protocol, nested case-control study based on electronic healthcare databases from four European countries was carried out

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OpenUrlAbstract/FREE Full Text

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Selective COX-2 inhibitors

COX-2 inhibitors are a subclass of nonsteroidal anti-inflammatory drugs that directly targets cyclooxygenase-2, COX-2, an enzyme responsible for inflammation and pain. Targeting selectivity for COX-2 reduces the risk of peptic ulceration, and is the main feature of celecoxib, rofecoxib and other members of this drug class.[15] Some COX-2 inhibitors are used in a single dose to treat pain after surgery.

[16]Etoricoxib appears as good as if not better than other pain medications. [17]Celecoxib appears to be about as useful as ibuprofen.[18] COX-2 appears to be related to cancers and abnormal growths in the intestinal tract. COX inhibitors have been shown to reduce the occurrence of cancers and pre-cancerous growths. The National Cancer Institute has done some studies on COX-2 and cancer.[19]The FDA has approved Celebrex for treatment of familial adenomatous polyposis (FAP).[20]COX-2 inhibitors are currently being studied in breast cancer and[21] appear to be beneficial.[22]COX-2 inhibitors have been found to be effective in suppressing inflammatory neurodegenerative pathways in mental illness, with beneficial results in trials for major depressive disorder as well as schizophrenia.

The biology and efficacy of COX-2 inhibitors

[23]The primary property of this class of drugs is the inhibition of cyclooxygenase (COX). -2 enzymes use arachidonic acid to generate the same product, prostaglandin H2 (PGH2). A number of enzymes further modify this product to generate bioactive lipids (prostanoids), including prostacyclin, thromboxane A2, and prostaglandins D2,E 2, and F2, which influence immune, cardiovascular, GI, renovascular, pulmonary, central nervous system, and reproductive function The COX-2 inhibitors vary in their selectivity for the COX-2 versus the COX-1 enzyme The differences in the biological effects of COX inhibitors are a consequence of the degree of selectivity for COX-2 versus COX-1 and tissue-specific variations in the distribution of COX and related enzymes that convert prostaglandin H2 into specific prostanoids.

Selective COX-2 inhibitors (valdecoxib, rofecoxib, celecoxib, and others yet in development) were developed to minimize GI toxicity because of the relative paucity of COX-2 expression in the GI tract and the relative abundance of COX-2 expression in inflamed and painful tissues. selective inhibition of COX-2 could produce a relative reduction in endothelial production of prostacyclin, but leave the platelet production of TXA2 intact. It has been speculated that this imbalance of haemostaticprostanoids may increase the risk for cardiovascular event.

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BENEFIT OF COX-2 INHIBITORS IN UPPER GASTROINTESTINAL TRACT

[24]It has been reported by an epidemiological survey that people reported git ulcers and lesions after regular consumption of NSAIDs.Mostcommoncause of ulcers is irritation of the stomach arising from regular use of non-steroidal anti-inflammatory drugs, or NSAIDs

COX-2 inhibitors may impair the healing of existing upper GI lesions, comparing twice daily dosing of celecoxib with placebo and with three conventional NSAIDs -- naproxen, diclofenac, and ibuprofen - administered 2-3 times daily. They found that the celecoxib patients and those taking a placebo had similar results, with the majority exhibiting improvement in symptoms according to the index of gastric mucosal change (and about 10% showed worsening). Fewer of those patients taking the conventional NSAIDs showed improvement, while 33% had worsening of symptoms recorded using the same index. This prompted the researchers to conclude that COX-2 inhibitors do not delay or impair healing of upper gastrointestinal lesions.

Twonew studies of COX-2 inhibitors were reported by researchers from three institutions, the University of Illinois at Chicago, Duke University, and the University of Washington School of Medicine, conducting their research under a grant from G.D. Searle & Co. One used blinded evaluations by an external independent review committee to evaluate upper gastrointestinal events in 5,155 patients taking celecoxib over a period of up to two years. Forty-seven percent of the patients used celecoxib for more than one year, and researchers reported an annualized incidence of upper GI side effects of 0.18%, which compares quite favourably to historical rates of complication in the range of 1.3% to 1.9% annualized incidence in patients using conventional NSAIDs.

BENEFITS OF COX-2 INHIBITOR IN LOWER GI TRACT

[25]With recent improved technology such as capsule endoscopyand colonoscopy, there is emerging evidence that traditional non-selective NSAIDs cause lower GI injuries. In western countries,60% of patients prescribed with NSAIDs for a long term develop injuries of the small intestine14) with 75 % of these patients manifesting mucosal ulcers of the lower GI tract including colon15,16). NSAIDs induced colitis is often detected in theterminal ileum and reveals various types of mucosal damagesuch as redness, erosion, small ulcer, ring ulcer and haemorrhagic ULCER.

Celecoxib is associated with less/minimal lower gi tract infection by developing small bowel mucosal breaks than naproxen plus omeprazole. This means that PPI(proton pump inhibitors) do not inhibit the development of small bowel mucosal breaks induced by NSAIDs. Thus selective cox-2 inhibitors may have some significant effect in decreasing the lower git tract problems.

The Efficacy of Selective COX-2 inhibitors on tumour prevention

[26]COX-2 is regulated in various cancers such as breast and gastric cancer. COX-2 activity is very low in normal state, but is induced by several stimuli such as cytokines and mitogens, and participates in the processes of cancer cell proliferation and differentiation. Epidemiologic studies have demonstrated that NSAIDs and Aspirin reduce the the incidence of colorectal carcinoma. A recent study with 2,446,431 person years of follow up of 82,911 women and 47,363 men suggested that regular use of aspirin reduces the risk of colorectal cancers that overexpress COX-2 but not the risk of colorectal cancers with weak or absent expressions of COX-2. In such patients Selective COX-2 inhibitor Celecoxib 400mg is given twice-daily which leads to decreased colorectal cancers, use of celecoxib for upto three years can reduce the risk, but is not given to general population because of increase in frequency of CV events.

CARDIOVASCUAR RISK ASSOCIATED WITH COX-2

[27]Though NSAIDs are associated with cv risk as they tend to associate with thromboembolism in body. Cox-2 is associated with induced thromboembolism, it suppresses the production of prostacyclin but not thromboxane. Selective cox-2 inhibition may potentiate the cardiovascular events in patients.[28] In September

[24]https://www.jstage.jst.go.jp/article/inflammregen/27/6/27_6_552/_pdf

[25]https://www.jstage.jst.go.jp/article/inflammregen/27/6/27_6_552/_pdf
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[27] https://www.jstage.jst.go.jp/article/inflammregen/27/6/27_6_552/_pdf
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https://www.researchgate.net/profile/Alan_Daugherty/publication/7952852_The_Use_of_Nonsteroidal_Anti-Inflammatory_Drugs_NSAIDs_A_Science_Advisory_From_the_American_Heart_Association/links/004635240788ae27f8000000/The-Use-of-Nonsteroidal-Anti-Inflammatory-Drugs-NSAIDs-A-Science-Advisory-From-the-American-Heart-Association.pdf?origin=publication_detail
published on-April 5 , 2005

2004, Merck announced a voluntary worldwide withdrawal of Vioxx (rofecoxib) because of an increased risk of heart attack and stroke. the National Institutes of Health announced that the ADAPT (Alzheimer's Disease Anti-inflammatory Prevention Trial) showed an increase in the risk of cardiovascular events in patients given naproxen but not in those given celecoxib; the trial was halted.

There was a 1% composite cardiovascular end point of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or nonfatal heart failure in the placebo group, compared with a 2.3% composite cardiovascular end point in patients receiving a total dose of 400 mg per day celecoxib and a 3.4% composite cardiovascular end point in those taking 800 mg celecoxib per day.14 The APPROVe trial included patients with a history of colorectal adenomas who received long-term rofecoxib or placebo. An increased risk of thrombotic events was observed in the treatment group after 18 months of treatment (0.78 events/100 patient-years versus 1.5 events/100 patient-years in the rofecoxib group).6 Finally, a study in post-CABG patients compared valdecoxib/parecoxib with placebo and found that cardiovascular events were more frequent in the treatment group (2.0% versus 0.5% for the placebo group). these evidences indicates that selective COX-2 inhibitors have important adverse cardiovascular effects including increased risk for myocardial infarction, stroke, heart failure, and hypertension.

[29]one study explored the effects of dosage and regimen in a pooled analysis of six randomised placebo controlled trials of celecoxib and found that lower dosages and once daily regimens that avoided continuous interference of the drug with prostaglandin metabolism were associated with lower relative risks for the cardiovascular composite outcome than higher dosages and twice daily regimens and they found no clear relation between specificity of cyclo-oxygenase-2 inhibitors and risk of cardiovascular events.

A stepwise approach is suggested, beginning with the agents that have the lowest associated cardiovascular risk and moving to the agents with higher risk if treatment failure occurs. Patients beginning NSAID therapy should start with a nonselective NSAID, such as ibuprofen or naproxen. However, the literature suggests naproxen as the nonselective NSAID of choice for these patients. If pain control is not established with nonselective NSAIDs, the next trial should be with an agent that is semiselective for COX-2, such as meloxicam or diclofenac.

Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) concluded that ibuprofen was shown to negate the cardioprotective effects of aspirinAlthough no cardiovascular interaction has been seen with concomitant use of celecoxib and aspirin, administration of aspirin with a selective COX-2 inhibitor may negate the gastroprotective effects of selective COX-2 inhibition.

Prevention

[30]At the end of 2004, the FDA issued a Public Health Advisory summarizing the agency's recent recommendations concerning the use of the nonsteroidal anti-inflammatory drug products (NSAIDs) Vioxx, Bextra, Celebrex, and naproxen.1 Quoting from the Public Health Advisory:

1. Patients who are at a high risk of gastrointestinal (GI)bleeding,haveahistoryofintolerancetonon-selective NSAIDs, or are not doing well on non-selective NSAIDs may be appropriate candidates for COX-2 selective agents.
2. In December 2004, the FDA issued the following advisory for physicians for prescribing COX-2 inhibitors, naproxen, and other types of NSAIDs to their patients:6
3. Physicians should closely evaluate each patient's risk for cardiovascular events (such as heart attack and stroke) when making decisions about using NSAIDs and COX-2 inhibitor drugs.6
4. Some patients with a high risk of gastrointestinal problems, who have a history of intolerance to non-selective NSAIDs (e.g. NSAIDs other than COX-2 inhibitors), or who have not had good results with non-selective NSAIDs may be the most appropriate patients to continue using COX-2 inhibitors Celebrex or Bextra.6
5. Patients should be well-advised to follow label directions for over-the-counter pain medications and NSAIDs (e.g. Aleve or brands of ibuprofen), being sure not to use longer than 10 days in a row without

[29] http://www.bmj.com/content/342/bmj.c7086

BMJ 2011; 342 doi: https://doi.org/10.1136/bmj.c7086 (Published 11 January 2011) Cite this as: BMJ 2011;342:c7086

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consulting a physician. Patients should also be sure not to take a higher dosage of Aleve or other NSAIDs than what is recommended on the label.6 In a separate statement, the FDA also recommended that patients taking Celebrex should take the lowest effective dose in order to avoid overuse.

6. Patients who are allergic to sulfonamide-type drugs and sulfa should not take Celebrex or Bextra. Patients who have had asthma, hives, or other allergic reactions from other types of NSAIDs or aspirin also avoid COX-2 inhibitors.
7. Patients who have serious coronary artery disease or who have had coronary artery bypass graft surgery (CABG) should not take COX-2 inhibitors.
8. A rare side effect of COX-2 inhibitors is stomach problems. The risk increases with a longer duration of taking the drugs, as well as with daily use of alcohol or excessive alcohol consumption.
9. Also rare, but serious, are the known side effects of heart attacks, serious allergic reactions, kidney problems and liver problems.

routinely by their physician to check for early signs of kidney damage.

[31]When should patients stop taking NSAIDs immediately?

Patients taking Bextra, Celebrex, or other NSAIDs should stop taking the drugs immediately and call their physician if they experience any of the following warning signs of ulcers:

a burning pain in the stomach

black bowel movements that look like tar

vomit that looks like blood or coffee grounds7

Bextra poses a risk of serious (and potentially fatal) skin reactions, including Steven-Johnson Syndrome and toxic epidermal necrolysis. Use of Bextra should be discontinued immediately if the patient develops any of the following symptoms:

a skin rash

mouth sores

any other signs of an allergic reaction5

The most important guideline for safe use of NSAIDs like Celebrex, Bextra and naproxen (e.g. Aleve) is for patients to remain under constant supervision by their physicians and to follow all label directions. Patients should talk to their physicians about any questions or concerns they have and should be aware of their individual risk factors in relation to new study findings.

As new information arises, patients can stay updated by visiting the FDA's Center for Drug Evaluation and Research informational webpage at www.fda.gov or by calling (888) INFO-FDA. Patients can also visit the official websites for the companies manufacturing individual drugs.

II. Conclusion

Many studies have demonstrated that selective cox-2 is beneficial for upper and lower git tract, selective cox-2 inhibitors are more effective then cox-1 and non-selective cox inhibitors and safe to use, also effective in prevention of tumour used to treat cancer but many studies have showed that treatment with non-selective NSAIDs as well as selective COX-2 inhibitors is associated with an increased risk of CV (Cardio-vascular) events. But some of the research's have shown that cox-2 is not associated with CV events, its not clear whether the selective cox-2 inhibitors are responsible for CV events or not. The relationship between COX-2 inhibitors and CV events needs to be addressed further, although ethical and safe clinical trials are difficult to implement in practice, a stepwise approach with appropriate measures is required for its safer use. Moreover, COX-2 inhibitors having advantages with regard to GI tract events are safer than traditional non-selective NSAIDs. Taken together, it is very important for daily clinical work to determine the best use of the advantages of NSAIDs with a particular attention paid to patients with elevated CV and or GI risk.

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