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Review Article

Gastrointestinal and Cardiovascular Risk of Nonsteroidal Anti-inflammatory Drugs

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) confer a gastrointestinal (GI) side effect profile and concerns regarding adverse cardiovascular effects have emerged associated with considerable morbidity and mortality. NSAIDs are highly effective in treating pain and inflammation, but it is well recognized that these agents are associated with substantial gastrointestinal toxicity. Cyclo-oxygenase-2 inhibitors may also reduce the risk for gastrointestinal events, although they may increase cardiovascular adverse events. The selection of an appropriate analgesic or anti-inflammatory agent with or without gastroprotective therapy should be individualized.

Keywords: Nonsteroidal anti-inflammatory drugs (NSAIDS); Cyclo-oxygenase-1(COX-1); Cyclo-oxygenase-2(COX-2).

Introduction

Nonsteroidal anti-inflammatory drugs or NSAIDs are among the most commonly prescribed medications in the world,[1] and are among the most widely used drugs in the world. Every day, more than 30 million people take NSAIDs to relieve pain from headaches, arthritis, and other conditions.[2] Traditional nonselective NSAIDs and cyclooxygenase type 2 selective NSAIDs (COX-2s) are commonly used to treat arthritic and inflammatory conditions, as well as acute and chronic pain. However, nonselective NSAIDs can cause a variety of gastrointestinal (GI) toxicities.[3-12] Endoscopic ulcers occur in as many as 40% of chronic NSAID users,[4] however, it is thought that up to 85% of these ulcers may never reach the stage of clinical significance. Serious NSAID-induced complications such as hemorrhage, perforation, or death occur collectively with an incidence of approximately 2% per year in average-risk NSAID users, and up to 10% per year in high-risk patients.[12] As a class, NSAIDs inhibit synthesis of prostaglandins that sensitize peripheral and central sensory neurons to painful stimuli from arachidonic acid by inhibiting the COX enzyme. NSAIDs that are both COX-1 and COX-2 inhibitors are identified as nonselective, whereas primary COX-2 inhibitors are identified as selective NSAIDs. COX-1 inhibitors include: ibuprofen, naproxen, aspirin, indometacin, ketoprofen, and ketorolac; whereas COX-2 inhibitors include: lumiracoxib, rofecoxib, valdecoxib, etodolac, and celecoxib.[13,14]

In the 1990s, two forms of the COX enzyme were identified. COX-1 creates prostaglandins necessary for platelet aggregation, renal function, and preservation of the gastric mucosa. COX-2, present in many cell types, is induced by inflammatory cytokines and is responsible for proinflammatory responses in pain. The theory underlying the development of the coxibs was that selective COX-2 inhibition would provide analgesia and anti-inflammatory effects without the risks of gastric bleeding associated with COX-1 inhibition.[13-15]

Selective COX-2 inhibitors offer a clear GI safety advantage over nonselective NSAIDs and are better tolerated than the older agents. However, the emergence of data suggesting increased cardiovascular harms with COX-2s and non-naproxen NSAIDs warrants that clinicians keep up with this literature and carefully assess the pros and cons of using a COX-2 on an individual patient basis.[16] Well established limitations of NSAID therapy, include the risk of developing significant injury to the upper Ggastrointestinal (GI) tract.[1,9-11,17,18] The annualized incidence rate of symptomatic GI ulcers and ulcer complications in NSAID users ranges from 2% to 4% (1-2% for ulcer complications alone).[12,19-22]

NSAIDs inhibit cyclooxygenase (COX), the enzyme responsible for the conversion of arachidonic acid to prostaglandins,[23] COX exists in 2 isoforms. COX-1 is a ubiquitous constitutive isozyme producing prostaglandins responsible for homeostatic functions such as maintenance of the GI mucosal integrity. COX-2 is largely a cytokine-induced isozyme producing prostaglandins that mediate pain and inflammation.[24] NSAIDs inhibit both COX-1 and COX-2 to varying degrees.[25,26] Thus, the therapeutic effects of conventional NSAIDs are derived from inhibition of COX-2, while the adverse effects of these agents, particularly in the upper GI tract, arise from inhibition of COX-1 activity.

Risk factors for NSAIDs related complications

A number of factors have been identified that increase the risk of NSAID associated upper gastrointestinal complications, including ulcers.[27] Use of multiple NSAIDs (including OTC NSAIDs and aspirin) and high dosages of medication increase risk. Interestingly,

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the greatest relative risk for gastrointestinal complications exists during the first month of treatment. Other important risk factors include prior ulcer complications, advanced age, and concomitant corticosteroid or anticoagulant use. The severity of rheumatoid arthritis may appear to increase risk independently for adverse gastrointestinal events. In contrast, dyspepsia and other upper gastrointestinal symptoms do not predict the development of upper gastrointestinal events.[28]

Gastrointestinal risk

The use of NSAIDs is associated with various gastrointestinal side effects. Minor side effects such as nausea, dyspepsia, anorexia, abdominal pain, flatulence, and diarrhea may affect 10% to 60% of patients.[29-31] Symptomatic ulcers and potentially life-threatening ulcer complications such as upper gastrointestinal bleeding, perforation, and gastric outlet obstruction are reported in 2% to 4% of patients who take NSAIDs for a year.[21,32,33] The chance of hospitalization or death from a gastrointestinal adverse event is 1.3% to 1.6% per year in patients with rheumatoid arthritis.[6] Life-threatening events such as perforation or serious hemorrhage from NSAID-induced ulcers, which often develop with little or no warning are a real problem because of the many patients at risk.[34-36] NSAIDs increase the risk of serious upper gastrointestinal disease (NSAID-induced gastropathy), including peptic ulcers, perforations, and upper gastrointestinal hemorrhages.[1,37] Endoscopic studies indicate that 20-30% of regular NSAID users develop ulcers.[28,38-41] NSAID-induced gastric negative impacts may result from the damage in prostaglandin synthesis, and various studies have demonstrated that prostaglandins may be important in mucosal Protection.[23,42,43]

Cardiovascular risk

In the last decade, there have been increased concerns regarding the cardiovascular safety profile of NSAIDs. These concerns have primarily been related to results from studies demonstrating increased cardiovascular risk with cyclooxygenase-2 (COX-2) inhibitors. Recently, there has been accumulating evidence from several large observational studies and meta-analyses that nonselective NSAIDs are also associated with increased cardiovascular risk. The main action of NSAIDs is inhibition of the COX enzyme that facilitates synthesis of prostaglandins from arachidonic acid. The prostaglandins are mediators of several physiological functions, including inflammation, thrombosis, body salt and water homeostasis, blood pressure, and gastric protection.[44]

The vascular effect of NSAIDs is mainly mediated by two products of COX prostaglandin synthesis: thromboxane A2 (TXA2), a vasoconstrictor and potent stimulator of platelet aggregation modulated by the COX-1 isoform, and prostaglandin I2 (PGI2), a potent vasodilator and inhibitor of platelet function predominantly regulated by the COX-2 isoform. TXA2 increases renal salt and fluid retention, increases blood pressure, and enhances myocardial and vascular remodeling, whereas PGI2 facilitates renal salt and fluid excretion and lowers systemic blood pressure. Equilibrium between TXA2 and PGI2 exists in the healthy vascular system, and it has been proposed that NSAIDs, in varying degrees, tip the TXA2/PGI2 balance, thereby increasing cardiovascular risk.[44] Although studies have demonstrated increased cardiovascular risk with COX-2 inhibitors,[45-48] nonselective NSAIDs with high COX-2 inhibition (e.g., diclofenac) seem to have higher cardiovascular risk, whereas nonselective NSAIDs with high COX-1 inhibition (e.g., naproxen, aspirin, ibuprofen) seem to have higher gastrointestinal risk.[44]

Several studies have demonstrated that in persons with established cardiovascular disease or increased cardiovascular risk, NSAIDs are even more harmful with regards to cardiovascular adverse events.[49-52] NSAIDs increase both systolic and diastolic blood pressure, and this can precipitate congestive cardiac failure and myocardial infarction,[53,54] and a recent database analysis of 9218 cases of first-ever diagnosis of myocardial infarction (MI) suggested an increased risk of MI with current use of rofecoxib, diclofenac, and ibuprofen, but not with naproxen.[55]

Four clinical trials (APC, VIGOR, APPROVe, and TARGET) were instrumental in uncovering evidence of cardiovascular risk. The APC Trial (Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention) focused on the prevention of colorectal adenomas. In this trial, 2,035 patients with a history of colorectal neoplasia were randomized to receive a placebo or 1 of 2 doses of celecoxib (200 or 400 mg) twice daily. After 2.8 to 3.1 years of follow-up, the Independent Data Safety Monitoring Board concluded that exposure to celecoxib placed patients at significant risk for a cardiovascular event.[45]

The VIGOR Trial (The Vioxx Gastrointestinal Outcome Study) compared rofecoxib 50 mg/d with naproxen 1,000 mg/d in patients with rheumatoid arthritis. Aspirin use was not permitted. Trial outcomes suggested that whether the patient was eligible for aspirin or not, Vioxx was associated with significant risk of a thrombotic cardiovascular event.[56,57]

The APPROVE Trial (Atheromatous Polyp Prevention on Vioxx Trial) compared rofecoxib 25 mg/d with placebo in patients with a history of colorectal adenomas. Again, rofecoxib was associated with a significant risk of a cardiovascular event (relative risk: 1.92; 95% confidence interval: 1.19Y3.11; p=0.008).[58] In September 2004, Merck, the manufacturer of rofecoxib (Vioxx), voluntarily withdrew the drug from the market based on the interim analysis of the APPROVE Trial results. Based on increasing reports of thrombotic events associated with rofecoxib, celecoxib, and valdecoxib, the Food and Drug Administration (FDA) issued a health advisory on December 23, 2004, concerning the use of all COXIBs. Then, in February 2005, the FDA convened an advisory committee to review the emerging evidence. The committee recommended that celecoxib and valdecoxib may remain on the market with black box warnings regarding the cardiovascular risks.[59-61]

The TARGET Trial (Therapeutic Arthritis Research and Gastrointestinal Event Trial) compared lumiracoxib 400 mg

once a day with naproxen 500 mg twice a day or ibuprofen 800 mg 3 times a day for a year in 18,325 patients. Randomization was stratified for aspirin use and age. Primary end points were nonfatal and silent MI, stroke, and death. One hundred and nine cardiovascular events occurred, 59 in the lumiracoxib group and 50 in the ibuprofen group. The primary end point did not differ between lumiracoxib, ibuprofen, or naproxen, irrespective of aspirin use. Investigators concluded that lumiracoxib was an appropriate treatment for osteoarthritis in patients at high risk of a cardiovascular event and taking low-dose aspirin. However, in the absence of a placebo group, the conclusion that lumiracoxib is as "safe" as ibuprofen is tenuous because the data also suggests that all 3 drugs are associated with increased risk of a cardiovascular event.[13,62]

Finally, in April 7, 2005, the FDA requested Pfizer to voluntarily withdraw valdecoxib from the market, and Pfizer did so. The FDA allowed celecoxib to remain on the market and requested the labeling of celecoxib and 18 other nonselective NSAIDs to describe the increased risk of a cardiovascular event. In addition, the FDA directed that all NSAID prescriptions must include medication information guide for patients.[13,63]

Mechanism of NSAIDs-Ulcer

NSAIDs work by blocking cyclooxygenase (COX) enzymes and inhibiting the synthesis of prostaglandins throughout the body which cause inflammation and pain. However, the non-selective inhibition of COX enzymes and subsequent inhibition of systemic prostaglandin synthesis leads to an impairment of the mucosa of the stomach and the upper gastrointestinal (GI) tract. Impaired mucosa creates susceptibility to serious GI complications such as bleeding, ulceration and perforation, often without warning to the patient.[64] It is well known that the inhibition potencies of non-steroidal anti-inflammatory drugs (NSAIDs) on cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes are different. It is believed that while inhibition of COX- 1 by NSAIDs causes side effects as a result of reduced prostaglandin (PG) synthesis, inhibition of COX-2 is related to their anti-inflammatory effect.[65]

Risk of developing complication with NSAIDs

The use of NSAIDs is associated with a 3- to 4-fold increase of UGIC, whereas the corresponding increase with selective inhibitors of cyclooxygenase-2(COX-2) is between 2- and 3-fold. Concomitant medication with aspirin clearly cancels out the superior upper gastrointestinal complications (UGIC) safety profile of (COX-2) compared with NSAIDs. Also, the risk of UGIC is clearly determined by the daily dose of the individual agent, and results indicate that intrinsic pharmacokinetic (e.g., half-life) and pharmacodynamic (e.g., COX-2 selectivity) features of the individual NA-NSAID have an independent measurable clinical impact on the risk of UGIC.[66]

Individuals with advanced age, alcohol intake, selective serotonin reuptake inhibitors, corticosteroid, and use of antithrombotic drugs, anticoagulants and a history of complicated peptic ulcer disease have a much higher baseline risk of UGIB and the greatest absolute risk when taking NSAIDs. The overall 4-fold increased risk associated with current NSAID use is maintained with treatment and decreases once treatment is stopped. The increased risk is common to all studied NSAIDs and is dose dependent, and consequently speaks forcefully in favor of a class effect. Whenever possible, NSAID therapy should be stopped, or lower effective NSAID doses should be administered in clinical practice to reduce the morbidity associated with all traditional NSAIDs.[44,67-69]

Gastroprotective Therapy

Various agents have been used in attempts to reduce the incidence of NSAID-induced gastrointestinal lesions. In one endoscopic study, cimetidine at a dose of 300 mg four times a day showed no benefit in healing NSAID-related lesions compared with placebo, and 400 mg at bedtime provided no benefit in preventing these lesions compared with placebo.[70] Antacids (magnesium-aluminum hydroxide, 10 to 20 mL as needed to a dose as high as 60 mL daily) and sucralfate have recently been reported to reduce dyspeptic symptoms in arthritic patients receiving NSAIDs in whom gastropathic lesions (but not ulcers) were shown endoscopically.[71,72] The surface-active antiulcer drug sucralfate was ineffective in preventing ulcers in persons receiving NSAIDs,[73,74] and the histamine-2-receptor antagonist ranitidine did not prevent gastric ulcers but did reduce the frequency of duodenal ulcers.[75,76] Several clinical trials have shown that the incidence of endoscopically visible erosions and ulcers associated with NSAID use can be reduced by cotherapy with the synthetic prostaglandin misoprostol.[77-81] Misoprostol administration significantly reduces the incidence of NSAID-induced, serious upper gastrointestinal complications, including perforation, obstruction, and bleeding, in older patients with rheumatoid arthritis.[12]

The synthetic prostaglandin misoprostol reduces ulcer complications in NSAID users by 40%,[12] but is poorly tolerated and now infrequently used. The histamine- 2 receptor antagonists (in doses twice those recommended for ulcer healing) and the proton pump inhibitors are well-tolerated medications that reduce the occurrence of NSAID-associated peptic ulcers identified by endoscopic examination by 60%–80%.[82]

A prospective study that compared NSAIDs alone with NSAIDs plus misoprostol reported that 0.95% of patients with rheumatoid arthritis who were taking an NSAID alone had upper gastrointestinal complications over a period of six months, with a relative reduction in the risk of such complications with combination treatment of 40% during this period.[12] At present, there are two primary strategies to reduce the gastrointestinal risk: use of a coxib or concurrent use of medications that protect the gut from the adverse effects of NSAIDs (gastroprotective co-therapy).[83-85] Coxibs confer a 40-60% lower risk of ulcer complications than the NSAIDs,[32,56,86] but also can cause serious

cardiovascular disease.[45,56,58,87]

The clinical trials of proton pump inhibitors and double-dose histamine-2 receptor antagonists had endoscopic lesions as an end point,[88-90] therefore it remains uncertain whether or not these agents prevent the clinically relevant ulcer complications. Despite the lack of data, expert bodies have recommended the use of gastroprotective cotherapy for high-risk NSAID users.[83-85]

In a cohort study by Ray WA et al. the results showed that the use of an NSAID in conjunction with a proton pump inhibitor had a gastrointestinal safety advantage over NSAID use alone comparable to that of a coxib, with respective reductions in the risk of peptic ulcer hospitalizations of 54% and 40%.[91] This is similar to the 40-60% reduction in ulcer complications reported from the pivotal coxib trials.[32,56,86]

Höer et al. found that concomitant prescribing of a proton pump inhibitor with diclofenac reduced the odds ratio of an ulcer hospitalization from 2.4 to 1.3.[92] García-Rodríguez et al. reported that coxibs conferred a lower risk of serious upper gastrointestinal complications than did NSAIDs, but the addition of gastroprotective cotherapy reduced the risk associated with NSAIDs by nearly 40%.[93] Lanas et al. noted that among current users of NSAIDs, concurrent use of histamine-2 receptor antagonists or proton pump inhibitors was associated with a 35% and 67% reduction in the risk of hospitalization for upper gastrointestinal bleeding.[94] Prophylaxis with a proton-pump inhibitor (PPI),[95-97] or substitution of NSAIDs with a selective inhibitor of cyclo-oxygenase-2 (COX 2) reduces the risk of ulcer complications.[56,86,98]

In a randomized trial of patients who had had previous NSAID-induced ulcer bleeding, the COX 2 inhibitor celecoxib was shown to be as effective as a combination of the NSAID diclofenac and the PPI omeprazole for prevention of recurrent ulcer bleeding. However, about 5% of patients in either treatment group still had recurrent bleeding within six months.[99] The rate of recurrent endoscopic or complicated ulcers was unacceptably high with either treatment in patients with previous ulcer bleeding; one study reported that the 6-month incidence of recurrent endoscopic ulcers was 18.7% with a COX 2 inhibitor and 25.6% with NSAIDs and a PPI.[100] In another study, the 6-month incidence of recurrent complicated ulcers was 3.7% with celecoxib and 6.3% with NSAIDs and a PPI.[101] Thus, neither a COX 2 inhibitor nor non-selective NSAIDs plus a PPI seem to be effective when used as a stand-alone strategy in patients at very high gastrointestinal risk.[102,103] Might a COX 2 inhibitor combined with a PPI provide the best protection in patients at very high gastrointestinal risk?[104] A 6-month endoscopic study showed that PPIs reduced the rate of ulcers in long-term users of NSAIDs, including a subgroup of patients given COX 2 inhibitors.[105,106]

Prevention of NSAIDs associated Ulcer Symptoms

Non-aspirin users alone demonstrated that celecoxib was associated with a significantly lower incidence of symptomatic ulcers and/or ulcer complications compared with NSAIDs. The rate of ulcer complications in non-aspirin users taking celecoxib (0.44%) is similar to the background rate of ulcer complications observed in patients not taking NSAIDs or aspirin in the general population (0.1% - 0.4%).[11,19,20,107-111]

Finally, the integrated body of data demonstrating that aspirin use concomitantly with a coxib creates ulceration at a rate similar to that of a dual inhibitor, clinical decision making should mandate additional strategies to reduce the risk in the relevant patients. Furthermore, since aspirin use should be a marker of cardiovascular risk, the use of coxibs in such patients should be a concern not only from the GI, but the cardiovascular perspective as well.[112]

Conclusion

Patients should be educated about the gastrointestinal and cardiovascular risks associated with NSAIDs and the potential for undesirable interactions among these medications. The cyclooxygenase-2-selective inhibitor resulted in significantly fewer clinically important upper gastrointestinal events than did treatment with nonselective NSAIDs. Nonselective NSAIDs with proton pump inhibitor have presented a gastrointestinal safety advantage over NSAIDs use alone compared to COXIBs. The cyclooxygenase-2 inhibitors did not convey a significant increase in myocardial infarctions, stroke, cardiovascular death, or other thrombotic cardiovascular adverse events when compared with non-steroidal anti-inflammatory drugs.

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