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NONSELECTIVE CYCLOOXYGENASE INHIBITION AND GASTROINTESTINAL EFFECTS: A REVIEW OF RECENT CLINICAL OBSERVATIONS

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REVIEW

ABSTRACT. INTRODUCTION. Nonsteroidal anti-inflammatory drugs (NSAIDs) are medications which, besides having pain-relieving (analgesic) effects, have the effect of reducing inflammation. NSAIDs have been associated with adverse gastrointestinal (GI) events such as dyspepsia and upper abdominal pain. OBJECTIVE. The goal of the review is to provide an updated document assessing the risk of GI complications induced by the most commonly used non-selective NSAIDs, by reporting comparative evidence of gastrointestinal toxicity between traditional NSAIDs and cyclooxygenase-2 (COX-2) inhibitors. METHODS. A total of 12 published studies were reviewed and compared on the basis of trial design, inclusion and exclusion factors, treatment regimens, clinical endpoints, outcomes, and date of publication. RESULTS. The clinical endpoints of primary focus were gastric or duodenal perforation, gastric outlet obstruction, upper GI bleeding, and gastric or duodenal ulcers. The studies under review showed that in patients with increased susceptibility to gastrointestinal adverse events, a lower risk of upper gastrointestinal bleeding was observed in users of COX-2 inhibitors compared with users of NSAIDs. CONCLUSION. Studies indicated that COX-2 inhibitors were used more frequently than were traditional NSAIDs in certain groups of patients with varying cardiac or gastrointestinal risk. As further discussions evolve about the safety of COX-2 inhibitors, the same questions will be asked about their alternatives, including NSAIDs and other drugs. In that respect, the management of the GI effects is important.

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BACKGROUND

Nonsteroidal antiinflammatory drugs (NSAIDs) are medications which, as well as having pain-relieving (analgesic) effects, have the effect of reducing inflammation when used over a period of time. NSAIDs have been associated with adverse gastrointestinal (GI) events such as dyspepsia (heartburn, bloating, or belching) and upper abdominal and epigastric pain were identified as the most important GI contributors to reduction in quality of life (QOL) [1]. NSAIDs cause damage in the upper gastrointestinal tract by impairing the ability of the mucosa to resist and respond to injury. Many of these effects of NSAIDs can be attributed to their ability to suppress mucosal prostaglandin synthesis [2]. NSAIDs inhibit cyclooxygenase, the enzyme responsible for conversion of arachidonic acid to prostaglandins [3]. Through their non-specific inhibition of the two cyclooxygenase isoenzymes, both aspirin and conventional NSAIDs induce gastro duodenal damage [4,5].

Selective inhibitors of cyclooxygenase-2 (COX-2) are less likely to disrupt mucosal defense and do not interfere with platelet aggregation. Thus, their use is associated with a reduced incidence of serious GI adverse events; however, a significant risk of such events still persists. COX-2 inhibitors have demonstrated improved GI safety over, traditional NSAIDs [6,7].

Studies included in reviews must explore best level of evidence. Studies conducted by Bollini et al. [8], Hawkey [9], and Gabriel et al. [10] highlighted that most of the meta-analyses focused on cross sectional and retrospective trials, but such designs have been shown to induce overestimated results compared with randomized controlled trials (RCTs) and/or controlled longitudinal cohort studies. RCTs provide a more accurate way to control for confounding factors and bias, and the odds ratios are less conservative estimates than relative risk. The cross sectional and retrospective studies however are more generalizable and not restricted to a specific category of individuals, and thereby favor the external validity. Attempts have been made to characterize the complex time-effect relationship between NSAID intake and GI side effects. The gaps in the available publications reflect the need for further large epidemiological studies examining these important questions. The need for additional research is supported by the widespread use of conventional, non-specific NSAIDs, despite the better GI safety profile of COX-2 inhibitors or the combination of NSAIDs and prostaglandins or proton pump inhibitors [11].

NSAIDs are used to relieve some symptoms caused by arthritis (rheumatism), such as inflammation, swelling, stiffness, and joint pain. Some of these medicines are also used to relieve other kinds of pain or to treat other painful conditions, such as gout attacks, bursitis, tendonitis, sprains, strains, other injuries, or menstrual cramps, Ibuprofen and naproxen are also used to reduce fever. Meclofenamate is also used to reduce the amount of bleeding in some women who have very heavy menstrual periods [2].

According to the trends published in Health United States 2004, for the year 2001-2002 the number of prescription and non prescription NSAIDs recorded were almost 22 per 100 population in men and 32 per 100 population in women for all ages [13]. Since the introduction of COX-2 inhibitors, their use has become widespread. In 2001–02, COX-2 inhibitors accounted for 51 percent of the total NSAID visits among adults age 18 years and over, surpassing traditional NSAIDs. This dramatic growth in COX-2 inhibitors is evident in all adult age groups [13].

The recent controversy surrounding COX-2 inhibitor use and its association with cardiovascular risks [14], is calling for alternative therapies including NSAIDs, and emphasizes the need for an update on the current evidence on NSAIDs and their risk profiles.

The goal of the review is to provide an updated document accurately assessing the risk of GI complications induced by the most commonly used non-selective NSAIDs by reporting comparative evidence of gastrointestinal toxicity between traditional NSAIDs and COX-2 inhibitors.

LITERATURE SEARCH AND INCLUSION CRITERIA

We aimed to identify all relevant randomized clinical trials, meta-analysis, cross-sectional analysis, case-control, and cohort studies that compared the prevalence of GI toxicities resulting from the use of traditional NSAIDs vs. COX-2 inhibitors. We searched Medline to collect literature that was published between October 2003 and November 2004. First we combined a search for articles that included the MeSH term "cyclooxygenase inhibitors," focused primarily on the following subheadings: adverse effects, analysis, poisoning, contraindications, diagnostic use, therapeutic use, economics, and toxicity. Next we performed a search for all articles that contained the prefix "gastr" to extract all studies on gastrological topics. We then combined our results from using "cyclooxygenase inhibitors" and "gastr" to limit our results to articles that dealt primarily with both cyclooxygenase inhibitors and gastrological topics. Finally, we limited our yielded results to human studies that were written in English and published between the years 2003 and 2004. The literature search was focused on the current years to summarize the updates pertaining to NSAID use and gastrointestinal toxicity. Landmark studies such as the CLASS and VIGOR trials have been included in the review.

The 148 results obtained from the literature search were filtered based on titles and abstracts. We selected ten articles based on comparative analysis between at least one traditional NSAID and one COX-2 inhibitor in regards to gastro toxicity. The CLASS and VIGOR trials were also included in our meta-analysis due to their landmark status as two of the largest, high impact studies that compared gastro toxicity (and other clinical endpoints) between traditional NSAIDs and COX-2 inhibitors.

The twelve total articles were organized based on trial design, inclusion and exclusion factors, treatment regimens, clinical endpoints, outcomes, and date of publication. Gastric or duodenal perforation, gastric outlet obstruction, upper GI bleeding, and gastric or duodenal ulcers were considered the primary endpoints of gastro toxicity in most of these studies. Secondary endpoints included but were not limited to GI and coronary heart disease (CHD) risk factors, hospitalization rate for MI and heart failure, heartburn, dyspepsia, abdominal pain, nausea, and vomiting. Eight of the twelve studies were double-blind randomized clinical trials. Most of the articles studied rofecoxib and celecoxib as COX-2 inhibitors, and ibuprofen and naproxen as traditional NSAIDs.

REVIEW OF RESULTS

The patient population in the articles under review ranged from N = 121 to N = 190,409. The time intervals that were studied in our articles were between 4 weeks and 90 months.

A study by Ofman et al. [15] evaluated the utilization of NSAIDs and antisecretory agents. Commercial claims and encounters database, and the medicare supplemental and coordination of benefits (COB) Database were used. The study included patients aged 18 years or older who had continuous enrollment in calendar years 1998 to 2001 and drug coverage for their entire enrollment period. Evidence of antisecretory drug use was defined primarily by the use of proton pump inhibitors, but also included the use of histamine H2-receptor antagonists and misoprostol. Prophylactic proton pump inhibitor use was defined by prescription of a proton pump inhibitor within 15 days of the index prescription if the patients had no diagnosis of ulcer or gastrointestinal hemorrhage within the 90 days before the index prescription. For each treatment group, they evaluated medical utilization, including outpatient visits, hospitalizations, and emergency department visits, in the pre- and post-periods. The study found that COX-2 inhibitors were used more frequently than were traditional NSAIDs in certain groups of patients with varying cardiac or gastrointestinal risk, but did not find that their use resulted in reductions in clinical events, cotherapy with proton pump inhibitors, or costs.

Kivitz et al. [16] focused on the efficacy and safety of rofecoxib 12.5 mg versus nabumetone 1,000 mg in patients with osteoarthritis of the knee.

A 6-week, randomized, parallel-group, double-blind was conducted comparing rofecoxib 12.5 mg once a day (n5424), nabumetone 1,000 mg once a day (n5410), or placebo (n5208). Rofecoxib 12.5 mg daily demonstrated better efficacy over 6 weeks of treatment and quicker onset of OA efficacy over the first 6 days than nabumetone 1,000 mg daily. Both therapies were generally well tolerated.

Bias et al. [17] assessed the gastrointestinal tolerability of the LOX/COX Inhibitor, Licofelone, in healthy volunteers. A controlled double blind RCT was conducted where volunteers received licofelone 200 mg b.i.d., licofelone 400 mg b.i.d., naproxen 500 mg b.i.d., or placebo. Tolerability was assessed by pastor/duodenoscopy following 4 weeks of treatment. Laboratory parameters and the incidence of ulcers and adverse events were recorded. The results from this trial indicate that licofelone has a potential gastrointestinal safety advantage over conventional NSAID therapy, as licofelone was associated with significantly superior gastric tolerability and a lower incidence of ulcers compared with naproxen in healthy volunteers.

Lisse et al. [18] compared the gastrointestinal tolerability, and effectiveness of rofecoxib versus naproxen in the treatment of osteoarthritis. A double blind RCT was conducted comparing rofecoxib, 25 mg/d, naproxen, and 500 mg twice daily. Use of routine medications, including aspirin, was permitted. In patients with osteoarthritis treated for 12 weeks, rofecoxib, 25 mg/d, was as effective as naproxen, 500 mg twice daily, but had statistically significantly superior GI tolerability and led to less use of concomitant GI medications. Benefits of rofecoxib in subgroup analyses were consistent with findings in the overall sample.

A prospective, double blind, randomized controlled trial by Silverstein et al. [19] evaluated the gastrointestinal toxicity with celecoxib vs non specific NSAIDs for osteoarthritis and rheumatoid arthritis. Patients were randomly assigned to receive celecoxib, 400 mg twice per day (2 and 4 times the maximum RA and OA dosages, respectively; n = 3987); ibuprofen, 800 mg 3 times per day (n = 1985); or diclofenac, 75 mg t.i.d. (N = 1996). Symptomatic ulcers consisted of cases that did not meet the definition of an ulcer complication but did have endoscopic or x-ray evidence of a gastric or duodenal ulcer as judged by the committee. All patients with symptomatic ulcers or ulcer complications were withdrawn from the study and included in the analysis as having had a study end point. The study suggested that fewer celecoxib-treated patients than NSAID-treated patients experienced chronic GI blood loss, GI intolerance, hepatotoxicity, or renal toxicity. Celecoxib, at dosages greater than those indicated clinically, was associated with a lower incidence of symptomatic ulcers and ulcer complications combined, as well as other clinically important toxic effects, compared with NSAIDs at standard dosages. The decrease in upper GI toxicity was strongest among patients not taking aspirin concomitantly.

Bombardier et al. [20] compared upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. A double blind randomized controlled trial included patients with rheumatoid arthritis who were at least 50 years old (or at least 40 years old and receiving long-term glucocorticoid therapy) and who were expected to require NSAIDs for at least one year. Three to 14 days after discontinuing NSAIDs, eligible patients were randomly assigned to receive either 50 mg of rofecoxib once daily or 500 mg of naproxen t.i.d. After randomization, the patients returned to the clinic at six weeks and at four months and every four months thereafter until the end of the study. Patients were contacted by telephone at week 10 and every four months thereafter. Compliance was assessed by pill counts at clinic visits and by questioning of patients during the scheduled telephone calls. Serum was obtained from all patients for Helicobacter pylori testing. The study concluded that in patients with rheumatoid arthritis, treatment with rofecoxib is associated with significantly fewer clinically important upper gastrointestinal events than treatment with naproxen.

A recent retrospective, observational study by Goldstein et al. [21] focused on the incidence of outpatient physician claims for upper gastrointestinal symptoms among new users of celecoxib, ibuprofen, and naproxen in an insured population. Incidence and risk of outpatient medical claims for

UGI symptoms among new users of celecoxib versus ibuprofen, and naproxen were determined using person-time analysis. Celecoxib use was associated with a significantly decreased risk of outpatient physician claims for UGI symptoms compared with commonly used prescription nonspecific nonsteroidal anti-inflammatory drugs.

A case–control study by Norgard et al. [22] assessed risk of upper gastrointestinal bleeding in high-risk patients, with previous gastrointestinal diseases. The study identified incident cases with upper gastrointestinal bleeding and randomly selected controls, respectively. All cases and controls had previous gastrointestinal diseases. Data on drug exposure were obtained from the countywide Prescription Database to examine the risk of upper gastrointestinal bleeding in high-risk patients who filled prescriptions for COX-2 inhibitors or other non-steroidal anti-inflammatory drugs. The study showed that in patients with increased susceptibility to gastrointestinal adverse events, a lower risk of upper gastrointestinal bleeding was observed in users of COX- 2 inhibitors compared with users of other non-aspirin, non-steroidal anti-inflammatory drugs.

Mamdani et al. [23] evaluated the gastrointestinal bleeding after the introduction of COX-2 inhibitors, conducting a population based cross sectional time series analysis. The study's time frame was divided into 15 intervals of six months from September 1, 1994 to February 28, 2002. As supplementary analyses, they examined changes in the use of gastroprotective agents, oral corticosteroids, prescription aspirin, and warfarin, since these factors may be strongly related to upper gastrointestinal hemorrhage. They used time series analysis involving autoregressive integrated moving average models to evaluate changes over time. The study concluded that a rise in NSAID use was accompanied by a 10% increase in hospitalization rates for upper gastrointestinal hemorrhage. However, they could not evaluate whether the potential improvement in population level pain relief offsets the increase in hospitalizations for upper gastrointestinal hemorrhage.

Schnitzer et al. [24] compared lumiracoxib with naproxen and ibuprofen in the reduction of ulcer complications. The study incorporated a 52-week, international, multi-center, randomized investigation using parallel group methodology and a double-dummy technique. Men and women aged 50 years or older with a clinical diagnosis of osteoarthritis of the hip, knee, or hand who fulfilled American College of Rheumatology preliminary classification criteria 25–27 or osteoarthritis of the cervical or lumbar spine (confirmed by radiography, with absence of radicular symptoms) were enrolled. They randomly allocated patients treatment with lumiracoxib 400 mg once daily (two or four times the recommended chronic dose for osteoarthritis), naproxen 500 mg twice daily (maximum therapeutic dose), or ibuprofen 800 mg t.i.d. (maximum therapeutic dose) for 52 weeks. The primary endpoint of TARGET was difference in time-to-event distribution of definite or probable upper gastrointestinal ulcer complications (clinically significant bleeding, perforation, or obstruction from erosive or ulcer disease). Lumiracoxib showed a three to four-fold reduction in ulcer complications compared with NSAIDs without an increase in the rate of serious cardiovascular events, suggesting that lumiracoxib is an appropriate treatment for patients with osteoarthritis.

Pavelka et al. [25] compared valdecoxib and diclofenac in the management of rheumatoid arthritis with a lower incidence of gastroduodenal ulcers. Patients, at least 18 yr old, who had been diagnosed with adult-onset RA of at least 6 months' duration satisfying the American College of Rheumatology criteria, and who required continuous treatment with anti-inflammatory drugs to control arthritis symptoms, were eligible for entry into the study. At baseline, patients were required to have a Functional Capacity Classification of I–III and a Global Assessment of Arthritis rated as fair, poor or very poor. Acetylsalicylic acid (ASA) 325 mg/day was allowed if the dosing regimen was stable for at least 30 days prior to the first dose of study medication. They evaluated the arthritis efficacy and GI safety of valdecoxib 20 and 40 mg q.d. compared with diclofenac 75 mg SR b.i.d. in treating the signs and symptoms of RA. Efficacy and safety assessments were performed at baseline and at

TABLE1. DESCRIPTION OF STUDIES DOCUMENTING GI RISK FROM NSAIDS

AUTHOR / YEAR	STUDY DESIGN	TREATED DISORDER (# OF PATIENTS)	INTERVENTION / EXPERIMENTAL CASE #.	COMPARISON/ CONTROL CASE #	DURATION	ENDPOINTS
SILVERSTEIN, ET AL. (2000)	Double-blind RCT	OA or RA (N = 7968)	Celecoxib 800 mg (N = 3987)	Ibuprofen 2400 mg (N = 1985); Diclofenac 150 mg (N = 1996)	6 months recorded	Gastric or duodenal perforation, gastric outlet obstruction, upper GI bleeding.
BOMBARDIER, ET AL. (2000)	Double-blind RCT	RA (N = 8076)	Rofecoxib 50 mg (N = 4047)	Naproxen 1000 mg (N = 4029)	9 months	Gastroduodenal perforation or obstruction, upper GI bleeding, symptomatic gastroduodenal ulcers.
MAMDANI, ET AL. (2004)	Cross sectional time series analysis	>1.3 million in database considered	COX-2 inhibitors	Non-selective NSAIDs	90 months	Hospitalization Rate for upper GI bleeding. Hospitalization rate for MI and heart failure.
SCHNITZER, ET AL. (2004)	Double-blind RCT	OA (N = 18,325)	Lumiracoxib 400 mg (N = 9156)	Naproxen 1000 mg (N = 4754); Ibuprofen 2400 mg (N = 4415)	52 weeks	Time-to-event distribution of clinically significant bleeding, perforation, or obstruction from
OFMAN, ET AL. (2004)	Retrospective, observational cohort	N = 106,564	COX-2 inhibitors without prior NSAID use (N = 36,472); COX-2 inhibitors with prior NSAID use (N = 32,992)	Nonselective NSAIDs (N = 37,100)	48 months	GI and CHD risk factors based on ICD-9-CM codes. Use of proton-pump inhibitors, H2-receptor antagonists, and misoprostol.
PAVELKA, ET AL. (2003)	Double-blind RCT	RA (N = 722)	Valdecoxib 20 mg (N = 246) Valdecoxib 40 mg (N = 237)	Diclofenac 150 mg SR (N = 239)	26 weeks	Patient's Assessment of Arthritis Pain. Health Assessment Questionnaire. GI erosions and ulcers. Adverse Effects.
NORGARD, ET AL. (2004)	Case-control	N = 3686	Upper GI bleeding with previous GI disease (N = 780)	No upper GI bleeding with previous GI disease (N = 2906)	36 months	Prescriptions for rofecoxib, celecoxib, and non-aspirin NSAIDs within 30 days of the date of diagnosis of upper gastrointestinal bleeding.

TABLE1. DESCRIPTION OF STUDIES DOCUMENTING GI RISK FROM NSAIDS (CONTINUED)

AUTHOR / YEAR	STUDY DESIGN	TREATED DISORDER (# OF PATIENTS)	INTERVENTION / EXPERIMENTAL CASE #.	COMPARISON/ CONTROL CASE #	DURA-TION	ENDPOINTS
GOLDSTEIN, ET AL. (2003)	Retrospective, observational cohort	N = 190,409	Celecoxib (N = 68,939)	Ibuprofen (N = 71,456) Naproxen (N = 50,014)	25 months	Outpatient physician claim for dyspepsia, abdominal pain, nausea/vomiting. Any "UGI symptoms" consisting of outpatient dyspepsia, abdominal pain, nausea, or dyspepsia, outpatient gastritits and duodenitis with hemorrhage, unspecified functional disorder of the stomach, or heartburn.
KIVITZ, ET AL. (2004)	Double-blind RCT	RA (N = 893)	Lumiracoxib 400 mg (N = 227) Lumiracoxib 800 mg (N = 227)	Ibuprofen 2400 mg (N = 216) Celecoxib 400 mg (N = 223)	13 weeks	Cumulative incidence of endoscopically detected gastro-duodenal ulcers. Incidence of larger ulcers (those ≥5 mm in diameter). Joint pain intensity assessment using a 5-point Likert categorical scale. Categorical global assessment of disease activity. Number of swollen joints. Number of tender joints.
KIVITZ, ET AL. (2004)	Double-blind RCT	OA (N = 1042)	Rofecoxib 12.5 mg (N = 5424)	nabumetone 1000 mg (N = 5410) Placebo (N = 5208)	6 weeks	Patient global assessment of response to therapy pain walking on a flat surface, IGART, withdrawals due to lack of efficacy, and quality of life as assessed using the SF-36. Analysis of adverse events for physical examinations and laboratory tests or spontaneously reported by the patient.
LISSE, ET AL. (2003)	Double-blind RCT	OA (N = 5557)	Rofecoxib 25 mg (N = 2785)	Naproxen 1000 mg (N = 2772)	12 weeks	Discontinuation due to GI adverse events and use of concomitant medication to treat GI symptoms. Efficacy was determined by patient-reported global assessment of disease status and the Australian/Canadian Osteoarthritis Hand Index, and discontinuations due to lack of efficacy.
BIAS, ET AL. (2004)	Double-blind RCT	N = 121	Licofelone 400 mg (N = 30); Licofelone 800 mg (N = 30)	Naproxen 1000 mg (N = 30) Placebo (N = 31)	4 weeks	Individual and combined gastric and duodenal mucosa Lanza scores and the incidence of gastric or duodenal ulcers.

weeks 2, 6, 8, 12, 18 and 26 or at early termination. All patients underwent an endoscopic examination of the mucosa of the stomach and duodenum at week 26 or at early termination. The endoscopy was performed no more than 2 days after the last dose of study medication. The study concluded that single daily doses of valdecoxib 20 and 40 mg provided efficacy comparable to that of diclofenac, with a superior upper GI safety profile in the long-term treatment of RA patients.

Kivitz et al. [26] evaluated reduced incidence of gastroduodenal ulcers associated with lumiracoxib compared with ibuprofen in patients with rheumatoid arthritis. A total of 893 patients with rheumatoid arthritis were randomized to lumiracoxib 400 mg once daily, lumiracoxib 800 mg once daily, ibuprofen 800 mg three times daily or celecoxib 200 mg twice daily for 13 weeks, in a double blind randomized controlled clinical trial. Lumiracoxib demonstrated gastroduodenal safety superior to ibuprofen and similar to celecoxib in patients with rheumatoid arthritis.

The summary of the reviewed articles has been presented in a tabular format in TABLE1.

DISCUSSION

In making treatment decisions, physicians and health workers must take into account relevant RCTs and systematic reviews. There is a concern among clinicians that external validity is often poor, particularly in pharmaceutical industry trials, a perception that has led to under use of effective treatments. [27] Lack of external validity is the most frequent criticism by clinicians of the RCTs. This criticism does not invalidate the results of the trials but emphasizes the importance of patient preference, placebo effects, and the doctor-patient relationship outside trials.

The articles under review predominantly looked at comparison of the NSAIDs and the COX-2 inhibitors and compared the two with regards to the gastroprotective capability.The clinical endpoints of primary focus were gastric or duodenal perforation, gastric outlet obstruction, upper GI bleeding, and gastric or duodenal ulcers. The studies under review showed that in patients with increased susceptibility to gastrointestinal adverse events, a lower risk of upper gastrointestinal bleeding was observed in users of COX-2 inhibitors compared with users of other non-aspirin, non-steroidal anti-inflammatory drugs. The common COX-2 inhibitors used were celecoxib, rofecoxib, and valdecoxib. The studies also indicated that COX-2 inhibitors were used more frequently than were traditional NSAIDs in certain groups of patients with varying cardiac or gastrointestinal risk

Upper gastrointestinal bleeding is a potentially fatal condition at times due to loss of large volumes of blood. GI bleeds attributable to NSAID use account for 103,000 hospitalizations and 16,500 deaths each year [28,29]. NSAIDs are widely used; over 100 million prescriptions for NSAIDs are written annually in the United States [30,31]. All patients taking NSAIDs have an increased risk of developing GI complications. The literature identifies a number of predisposing risks. The most important include a history of ulcer or GI complications, and older age, history of peptic ulcers, alcohol, steroids [32,33]. Concurrent illness has also been reported to increase the risk of GI events [32]. All non selective NSAIDs are associated with an increased risk of GI events. The confidence intervals for the individual NSAID risks overlap, and hence it is difficult to rank the risks attributable to specific NSAIDs. In addition, there are significant economic implications to the GI events associated with NSAIDs. For example, the GI medications accounted for most of the GI related costs in a study conducted on rheumatoid and osteoarthritis patients at a Massachusetts health maintenance organization setting [34].

The interventions focusing on reduction in non selective NSAIDs related upper gastrointestinal diseases include educational methods aimed at reducing prescribing, co-prescription of mucosal protective drugs, and the use of paracetamol as an alternative analgesic [35,36].

A study by Henry et al. [37] which summarized the adjusted relative risks seen with the different non selective NSAIDs with regards to gastrointestinal events. The meta-analysis showed that

differences existed between the NSAID drugs. The study suggested that ibuprofen, was associated with the lowest relative risk of severe gastrointestinal toxicity of the 12 NSAIDs compared followed by diclofenac. The highest risk was associated with ketoprofen, tolmentin, and azapropazone [37]. The study also looked at the risk associated with dose. A pool of 5 studies provided data on relative risk stratified by does of individual drugs. The meta-analysis yielded positive dose-response relations for ibuprofen, naproxen, and indomethacin [37].

The nuisance symptoms such as heartburn, nausea, and abdominal pain do impact the quality of life of the patient and hence is an important consideration. Dyspepsia (heartburn, bloating, or belching) and upper abdominal/epigastric pain were identified as the most important GI contributors to reduction in QOL, and the simultaneous presence of both these symptoms was associated with lower QOL [38]. Dyspepsia and upper abdominal/epigastric pain are more strongly related to QOL measures than other GI symptoms, and are common among arthritis patients. A meta-analysis to evaluate the quality of life effects was conducted on a group of eight randomized, double blind, trials of rofecoxib. The side effects in the rofecoxib group were significantly lower than the nonselective NSAIDs (ibuprofen, diclofenac, or nabumetone) [39].

Selective COX-2 inhibitors have been the drug of choice comparing their gastrointestinal safety profile to the NSAIDs. With the recent concerns relating to the association of COX-2 inhibitors with cardiovascular events the decision making on the part of the clinician has been complicated. The Graham study had recommended that COX-2 use is associated with a higher cardiovascular risk whereas the study by Shaya et al. found no increased risk cardiovascular events between COX-2 inhibitors and non-naproxen NSAIDs [40]. With more information needed on the risk/benefit of the COX-2 inhibitors, NSAIDs will regain its dominance in the fight against pain. The management of the gastrointestinal effects will be of prime importance.

REFERENCES

[1] WATSON, DJ, HARPER SE, ZHAO PL, QUAN H, BOLOGNESE JA AND SIMON TJ [2000] Gastrointestinal tolerability of the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib compared with nonselective COX-1 and COX-2 inhibitors in osteoarthritis. Arch Intern Med 160: 2998-3003.

[2] PERINI R, FIORUCCI S AND WALLACE JL [2004] Mechanisms of nonsteroidal anti-inflammatory drug-induced gastrointestinal injury and repair: a window of opportunity for cyclooxygenase-inhibiting nitric oxide donors. Can J Gastroenterol 18: 229-236.

[3] VANE JR [1971] Inhibition of prostaglandin synthesis as a mechanism of action for the aspirin-like drugs. Nat New Biol 231: 235-239.

[4] HENRY D, LIM LL, GARCIA RODRIGUEZ LA, PEREZ GUTTHANN S, CARSON JL, GRIFFIN M, SAVAGE R, LOGAN R, MORIDE Y, HAWKEY C, HILL S AND FRIES JT [1996] Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. BMJ 312: 1563-1566.

[5] TRAMER MR, MOORE RA, REYNOLDS DJ AND MCQUAY HJ [2000] Quantitative estimation of rare adverse events which follow a biological progression:a new model applied to chronic NSAID use. Pain 85:169-182.

[6] BOMBARDIER C, LAINE L, REICIN A, SHAPIRO D, BURGOS-VARGAS R, DAVIS B, DAY R, FERRAZ MB, HAWKEY CJ, HOCHBERG MC, KVIEN TK, SCHNITZER TJ AND VIGOR STUDY GROUP [2000] Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 343: 1520-1528.

[7] SILVERSTEIN FE, FAICH G, GOLDSTEIN JL, SIMON LS, PINCUS T, WHELTON A, MAKUCH R, EISEN G, AGRAWAL NM, STENSON WF, BURR AM, ZHAO WW, KENT JD, LEFKOWITH JB, VERBURG KM AND GEIS GS [2000] Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for oscteoarthritis and rheumatoid arthritis. The CLASS study: A randomized controlled trial. JAMA 284: 1347-1255.

[8] BOLLINI P, RODRIGUEZ LA, GUTTHANN SP AND WALKER AM [1992] The impact of research quality and study design on epidemiologic estimates of the effect of nonsteroidal anti-inflammatory drugs on upper gastrointestinal tract disease. Arch Intern Med 152: 1289-1295.

[9] HAWKEY CJ [2002] NSAIDs toxicity: where are we and how do we go forward? J Rheumatol 29: 650-651.

[10] GABRIEL SE, JAAKKIMAINEN L AND BOMBARDIER C [1991] Risk of serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. Ann Intern Med 115: 787-795.

[11] MAMDANI M, ROCHON PA, JUURLINK DN, KOPP A, ANDERSON GM, NAGLIE G, AUSTIN PC AND LAUPACIS A [2002] Observational study of upper gastrointestinal haemorrhage in elderly patients given selective cyclo-

oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs. BMJ 325: 624–627.

[12] http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202743.html

[13] http://www.cdc.gov/nchs/data/hus/hus04.pdf

[14] MEMORANDUM FROM DAVID J. GRAHAM, MD, MPH, associate director for Science, office of Drug Safety to Paul Seligman, MD, MPH, acting Director, Office of Drug Safety entitled, "Risk of acute myocardial infarction and sudden cardiac death in patients treated with COX-2 selective and Non-Selective NSAIDs," September 30, 2004.

[15] OFMAN JJ, BADAMGARAV E, HENNING JM, KNIGHT K AND LAINE L [2004] UTILIZATION of nonsteroidal anti-inflammatory drugs and antisecretory agents: A managed care claims analysis. Am J Med 116: 835-842.

[16] KIVITZ AJ, NAYIAGER S, SCHIMANSKY T, GIMONA A, THURSTON HJ AND HAWKEY C [2004] Reduced incidence of gastroduodenal ulcers associated with lumiracoxib compared with ibuprofen in patients with rheumatoid arthritis. Alimentary Pharmacol Ther 19: 1189-1198.

[17] BIAS P, BUCHNER A, KLESSER B AND LAUFER S [2004] The Gastrointestinal tolerability of the LOX/COX inhibitor, licofelone, is similar to placebo and superior to naproxen therapy in healthy volunteers: Results from a randomized, controlled trial. Am J Gastroenterol 99: 611-618.

[18] LISSE JR, PERLMAN M, JOHANSSON G, SHOEMAKER JR, SCHECHTMAN J, SKALKY CS, DIXON ME, POLIS AB, MOLLEN AJ, GEBA GP AND ADVANTAGE STUDY GROUP [2003] Gastrointestinal tolerability and effectiveness of rofecoxib versus naproxen in the treatment of osteoarthritis: A randomized, controlled trial. Annals Intern Med 139: 539-546.

[19] = REFERENCE NO. 7.

[20] = REFERENCE NO. 6.

[21] GOLDSTEIN JL, ZHAO SZ, BURKE TA, PALMER R, VON ALLMEN H AND HENDERSON SC [2003] Incidence of outpatient physician claims for upper gastrointestinal symptoms among new users of celecoxib, ibuprofen, and naproxen in an insured population in the United States. Am J Gastroenterol 98: 2627-2634.

[22] NORGARD B, PEDERSEN L, JOHNSEN SP, TARONE RE, MCLAUGHLIN JK, FRIIS S AND SORENSEN HT [2004] COX-2-selective inhibitors and the risk of upper gastrointestinal bleeding in high-risk patients with previous gastrointestinal diseases: a population-based case-control study. Alimentary Pharmacol Ther 19: 817-825.

[23] MAMDANI M, JUURLINK DN, KOPP A, NAGLIE G, AUSTIN PC AND LAUPACIS A [2004] Gastrointestinal bleeding after the introduction of COX-2 inhibitors: ecological study. BMJ 328: 1415-1416.

[24] SCHNITZER TJ, BURMESTER GR, MYSLER E, HOCHBERG MC, DOHERTY M, EHRSAM E, GITTON X, KRAMMER G, MELLEIN B, MATCHABA P, GIMONA A, HAWKEY CJ AND TARGET STUDY GROUP [2004] Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. Lancet 364(9435): 665-674.

[25] PAVELKA K, RECKER DP AND VERBURG KM [2003] Valdecoxib is as effective as diclofenac in the management of rheumatoid arthritis with a lower incidence of gastroduodenal ulcers: results of a 26-week trial. Rheumatology 42: 1207-1215.

[26] KIVITZ AJ, GREENWALD MW, COHEN SB, POLIS AB, NAJARIAN DK, DIXON ME, MOIDEL RA, GREEN JA, BARAF HS, PETRUSCHKE RA, MATSUMOTO AK, GEBA GP AND PROTOCOL 085 STUDY INVESTIGATORS [2004] Efficacy and safety of rofecoxib 12.5 mg versus nabumetone 1,000 mg in patients with osteoarthritis of the knee: a randomized controlled trial. J Am Geriatrics Soc 52: 666-674.

[27] ROTHWELL PM [2005] Treating individuals 1: External validity of randomized controlled trials: "To whom do the results of the trials apply?" Lancet: 365: 82-93.

[28] SINGH G AND ROSEN RAMEY D [1998] NSAID induced gastrointestinal complications: The ARAMIS perspective — 1997. Arthritis, rheumatism, and aging medical information system. J Rheumatol Suppl. 51: 8-16.

[29] WOLFE MM, LICHTENSTEIN DR AND SINGH G [1999] Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med 340: 1888-1899.

[30] LAINE L, MARIN-SORENSEN M AND WEINSTEIN WM [1992] Nonsteroidal anti-inflammatory drug-associated gastric ulcers do not require Helicobacter pylori for their development. Am J Gastroenterol 87: 1398–1402.

[31] GABRIEL SE, JAAKKIMAINEN L AND BOMBARDIER C [1991] Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. Ann InternMed.; 115: 787–796.

[32] LAINE L [2001] Approaches to NSAID use in the high-risk patient. Gastroenterology 120 594–606.

[33] FRIES JF, WILLIAMS CA, BLOCH DA AND MICHEL BA [1991] Nonsteroidal anti-inflammatory drug-associated gastropathy: incidence and risk factor models. Am J Med 91: 213-222.

[34] LANES SF, LANZA LL, RADENSKY PW, YOOD RA, MEENAN RF, WALKER AM AND DREYER NA [1997] Resource utilization and cost of care for rheumatoid arthritis in a managed care setting. The importance of drug and surgery costs. Arthritis Rheum 40: 1475–1481.

[35] SILVERSTEIN FE, GRAHAM DY, SENIOR JR, DAVIES HW, STRUTHERS BJ, BITTMAN RM AND GEIS GS [1995] Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving non-steroidal anti-inflammatory drugs. Ann Intern Med123: 241-249.

[36] BRADLEY JD, BRANDT KD, KATZ BP, KALASINSKI LA AND RYAN SI [1991] Comparison of an anti-

inflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. N Engl J Med 325: 87-91.

[37] HENRY D, LIM LL, GARCIA RODRIGUEZ LA, PEREZ GUTTHANN S, CARSON JL, GRIFFIN M, SAVAGE R, LOGAN R, MORIDE Y, HAWKEY C, HILL S AND FRIES JT [1996] Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. BMJ 312(7046): 1563-1566.

[38] WOLFE F, KONG SX AND WATSON DJ [2000] Gastrointestinal symptoms and health related quality of life in patients with arthritis. J Rheumatol 27: 1373-1378.

[39] WATSON, DJ, HARPER SE, ZHAO PL, QUAN H, BOLOGNESE JA AND SIMON TJ [2000] Gastrointestinal tolerability of the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib compared with nonselective COX-1 and COX-2 inhibitors in osteoarthritis. Arch Intern Med 160: 2998-3003.

[40] SHAYA FT, BLUME SW, BLANCHETTE CM, WEIR MR AND MULLINS CD [2005] Selective cyclooxygenase-2 inhibition and cardiovascular effects: An observational study of a Medicaid population. Arch Intern Med 165: 181-186.

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