Effects and Prevention of Chronic NSAID Use on the Stomach

Martha K. Braun
Pacific University
Effects and Prevention of Chronic NSAID Use on the Stomach

Abstract
Purpose: As our population continues to age, the prevalence of nonspecific nonsteroidal anti-inflammatory drugs (nsNSAID) and cyclooxygenase-2 (COX-2) inhibitor use increases. Each year approximately 3,200 to >16,500 deaths are attributed to gastrointestinal (GI) toxicity secondary to NSAID use. With the growing concern of the damage these medications can do to the gastric mucosa, the prevention of GI injury is an important clinical issue. The purpose of this review was to determine the current recommendations for prescribing nsNSAID and COX-2 inhibitor drugs in relation to minimizing GI injury.

Methods: An extensive literature review in English was performed searching for articles over the past 10 years using terms related to NSAIDS and GI complications. Articles were rejected if the study was not a randomized controlled trial or retrospective cohort trial; included exclusively children; lasted less than 21 days; or did not measure review outcomes.

Results: NSAID vs COX-2 – Three randomized controlled trials demonstrated the same result: COX-2 selective inhibitors were associated with less significant GI effects than nsNSAIDs alone. However, two out of the three tests came under scrutiny and the results were thought to be biased and not completely reported. COX-2 vs. NSAID plus PPI - Studies found that a COX-2 inhibitor was as effective as an NSAID plus a PPI with respect to the prevention of recurrent bleeding. However, the studies agreed that even though the two methods were as effective, the risk of recurrent bleeding with either treatment was high, suggesting that neither regimen could completely protect patients at high risk from recurrent ulcer complications. COX-2 vs. COX-2 plus PPI – Studies determined that combination treatment was more effective than COX-2 inhibitors alone, for the prevention of ulcer bleeding in patients at high risk. The study defined high risk as patients with a previous history of ulcer bleeding. A limitation noted in a study was the inability to assess the best possible management for patients with high cardiovascular risk and therefore the role of concomitant aspirin in relation to the efficacy of COX-2 inhibitors. NSADI plus PPI vs. COX-s plus PPI – The VENUS and PLUTO studies were conducted at the same time and both concluded that significant reductions in ulcer development were observed for users of both nsNSAIDs and COX-2 inhibitors in combination with a PPI. However, the trial sizes were of significant difference and the percentage of patients in the VENUS study that had a history of ulcer as their sole risk factor was significantly lower than in the PLUTO group.

Conclusion: Many of early studies on COX-2 inhibitors were done by the drug companies themselves, and therefore contained biased information. In the recent years, viable data has emerged to help us make decisions about the proper care for our chronic NSAID-use patients. Upper GI injury while taking aspirin or NSAID’s is typically related to risk factors, dosages and duration spent taking the drug. Therefore, the smaller the dose and the less time spent on the drug will help decrease the risk of developing some sort of GI injury. In the instance where a patient will need to take chronic NSAID therapy, it is recommended a patient with no cardiovascular risks (not taking aspirin) and with no or low risk of GI factors should take an nsNSAID. If a patient with no cardiovascular risks has GI risks then it is recommended they take either a COX2 or an nsNSAID with a PPI. Patients with cardiovascular risks and no GI risk should take nsNSAIDs with a PPI only if GI risks warrant it. A patient with both cardiovascular and GI risks should take a nsNSAID with a PPI.

Degree Type
Capstone Project

This capstone project is available at CommonKnowledge: http://commons.pacificu.edu/pa/184
Degree Name
Master of Science in Physician Assistant Studies

First Advisor
Judy Ortiz, PA-C

Second Advisor
Jonathon W Gietzen MS PA-C

Keywords
nonsteroidal anti-inflammatory drugs, ibuprofen, COX2 inhibitors, cyclooxygenase, omeprazole, misoprostol

Subject Categories
Medicine and Health Sciences

Rights
Terms of use for work posted in CommonKnowledge.

This capstone project is available at CommonKnowledge: http://commons.pacificu.edu/pa/184
Copyright and terms of use

If you have downloaded this document directly from the web or from CommonKnowledge, see the “Rights” section on the previous page for the terms of use.

If you have received this document through an interlibrary loan/document delivery service, the following terms of use apply:

Copyright in this work is held by the author(s). You may download or print any portion of this document for personal use only, or for any use that is allowed by fair use (Title 17, §107 U.S.C.). Except for personal or fair use, you or your borrowing library may not reproduce, remix, republish, post, transmit, or distribute this document, or any portion thereof, without the permission of the copyright owner. [Note: If this document is licensed under a Creative Commons license (see “Rights” on the previous page) which allows broader usage rights, your use is governed by the terms of that license.]

Inquiries regarding further use of these materials should be addressed to: CommonKnowledge Rights, Pacific University Library, 2043 College Way, Forest Grove, OR 97116, (503) 352-7209. Email inquiries may be directed to: copyright@pacificu.edu

This capstone project is available at CommonKnowledge: http://commons.pacificu.edu/pa/184
NOTICE TO READERS

This work is not a peer-reviewed publication. The Master’s Candidate author(s) of this work have made every effort to provide accurate information and to rely on authoritative sources in the completion of this work. However, neither the author(s) nor the faculty advisor(s) warrants the completeness, accuracy or usefulness of the information provided in this work. This work should not be considered authoritative or comprehensive in and of itself and the author(s) and advisor(s) disclaim all responsibility for the results obtained from use of the information contained in this work. Knowledge and practice change constantly, and readers are advised to confirm the information found in this work with other more current and/or comprehensive sources.

The student authors attest that this work is completely their original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.
Effects and Prevention of Chronic NSAID Use on the Stomach

By: Martha K. Braun

A Clinical Research Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University, Forest Grove, OR
For the Masters of Science Degree August 16, 2008

Faculty Advisor: Judy Ortiz, PA-C
Clinical Project Advisor: Jonathon W Gietzen MS PA-C
STATEMENT OF ACCEPTANCE:

This project is hereby accepted as a requirement for completion of the degree of: Masters of Science in Physician Assistant Studies at Pacific University School of Physician Assistant Studies on this day the sixteenth of August, 2008.

Martha K. Braun, PA-S                           Date
Author

Jonathon W Gietzen MS, PA-C                           Date
Clinical Project Coordinator

H. F. Randolph III, PA-C, MPAS                          Date
Program Director
Biography

Martha (Marty) Braun is a native New Mexican where she grew up appreciating the out-of-doors and playing competitive tennis. She got her Bachelor’s degree in Kinesiology from the University of Colorado at Boulder and promptly became a professional ski bum working for Taos Ski Valley as a ski patroller. Through this path she was introduced to the field of emergency medicine and quickly developed a passion for the trade and a possible vision for what she wanted to be when she finally grew up. When the opportunity arose to attend PA school, it was an easy choice to be made. She is married to her wonderful and supportive husband, Kei, for 7 years and they are currently raising two terrific dogs, Chaco age 4 and Rudy age 5. They plan to remain in Taos, close to family and friends, where Marty hopes to find a job at the local hospital in the emergency room. In her free time she is an avid tennis player and skier, but also enjoys spending time with her family, hiking, biking and almost anything else that entails being outdoors.
Acknowledgements

To my Mom, Dad and Sister – thank you for your undying love and support through these past two years. I couldn’t ask for a more supportive and devoted family to help me through all of the ups and downs of PA school. Of course, to my parents, thank you for the generosity of loving my dogs for most of this crazy time. You guys are the best!

To my husband, Kei – thank you for the unwavering support that helped me fulfill this goal. The confidence you have in me to become a PA, was and still is, such an important part of my own belief in myself to realize this dream. Thanks for sticking with me through all of the good and bad times and for keeping the home fires burning. I love you.

To Erin and Megan (my right and left brains) – All of our time spent together studying, having fun and getting to know each other made this experience so much easier. You both have been there every step of the way, knowing and understanding the hardships we all experienced. I am grateful for having met two such incredible women to share such an intense adventure with. I miss you guys already!

To Professor Gietzen – Thank you for your time and devotion you showed us during our time at Pacific. Because of you I believe our class will shine in the professional world. Good luck to you in your new endeavors.

To Professor Ortiz – Thank you for your support as my advisor. I appreciate the honesty and sincerity, but also the light-heartedness you showed all of us. You made it easy to approach you with our issues and looked at them with a fair eye.

To the Faculty and Staff of the PA program – Thank you for all of the time and effort you put forth into making this program a success!

To the Clinical Team – Thank you for all of the hard work you put into making my rotations successful and meaningful so as to help properly prepare me for the “real” world.
Abstract

**Purpose:** As our population continues to age, the prevalence of nonspecific nonsteroidal anti-inflammatory drugs (nsNSAID) and cyclooxygenase-2 (COX-2) inhibitor use increases. Each year approximately 3,200 to >16,500 deaths are attributed to gastrointestinal (GI) toxicity secondary to NSAID use. With the growing concern of the damage these medications can do to the gastric mucosa, the prevention of GI injury is an important clinical issue. The purpose of this review was to determine the current recommendations for prescribing nsNSAID and COX-2 inhibitor drugs in relation to minimizing GI injury. **Methods:** An extensive literature review in English was performed searching for articles over the past 10 years using terms related to NSAIDs and GI complications. Articles were rejected if the study was not a randomized controlled trial or retrospective cohort trial; included exclusively children; lasted less than 21 days; or did not measure review outcomes. **Results:** NSAID vs COX-2 – Three randomized controlled trials demonstrated the same result: COX-2 selective inhibitors were associated with less significant GI effects than nsNSAIDs alone. However, two out of the three tests came under scrutiny and the results were thought to be biased and not completely reported. COX-2 vs. NSAID plus PPI - Studies found that a COX-2 inhibitor was as effective as an NSAID plus a PPI with respect to the prevention of recurrent bleeding. However, the studies agreed that even though the two methods were as effective, the risk of recurrent bleeding with either treatment was high, suggesting that neither regimen could completely protect patients at high risk from recurrent ulcer complications. COX-2 vs. COX-2 plus PPI – Studies determined that combination treatment was more effective than COX-2 inhibitors alone, for the prevention of ulcer bleeding in patients at high risk. The study defined high risk as patients with a previous history of ulcer bleeding. A limitation noted in a study was the inability to assess the best possible management for patients with high cardiovascular risk and therefore the role of concomitant aspirin in relation to the efficacy of COX-2 inhibitors. NSAID plus PPI vs. COX-2 plus PPI – The VENUS and PLUTO studies were conducted at the same time and both concluded that significant reductions in ulcer development were observed for users of both nsNSAIDs and COX-2 inhibitors in combination with a PPI. However, the trial sizes were of significant difference and the percentage of patients in the VENUS study that had a history of ulcer as their sole risk factor was significantly lower than in the PLUTO group. **Conclusion:** Many of early studies on COX-2 inhibitors were done by the drug companies themselves, and therefore contained biased information. In the recent years, viable data has emerged to help us make decisions about the proper care for our chronic NSAID-use patients. Upper GI injury while taking aspirin or NSAID’s is typically related to risk factors, dosages and duration spent taking the drug. Therefore, the smaller the dose and the less time spent on the drug will help decrease the risk of developing some sort of GI injury. In the instance where a patient will need to take chronic NSAID therapy, it is recommended a patient with no cardiovascular risks (not taking aspirin) and with no or low risk of GI factors should take an nsNSAID. If a patient with no cardiovascular risks has GI risks then it is recommended they take either a COX2 or an nsNSAID with a PPI. Patients with cardiovascular risks and no GI risk should take nsNSAIDs with a PPI only if GI risks warrant it. A patient with both cardiovascular and GI risks should take a nsNSAID with a PPI.

**Keywords:** NSAID, nonsteroidal anti-inflammatory drugs, ibuprofen, COX2 inhibitors, cyclooxygenase, peptic ulcer disease, ulcer bleeding, omeprazole, misoprostol, gastrointestinal, upper gastrointestinal and perforated ulcers.
# Table of Contents

Statement of Approval ................................................................. 1
Biography ..................................................................................... 2
Acknowledgements ................................................................. 3
Abstract ....................................................................................... 4
Table of Contents ........................................................................ 5
List of Tables ............................................................................... 6
List of Figures ............................................................................. 6
List of Abbreviations ............................................................... 7
List of Appendices ...................................................................... 8
Introduction and Background .................................................. 9
Methods ................................................................................... 16
Results ..................................................................................... 17
Discussion ................................................................................ 24
Tables ....................................................................................... 28
Figures ..................................................................................... 33
References ............................................................................... 36
Appendix .................................................................................. 40
**List of Tables**

Table I: The Nonsteroidal Anti-Inflammatory Drugs

Table II: Factors Related to Increased Risk of NSAID-Induced GI Complications

Table III: Selected NSAIDS and Other Analgesics: Selectivity for Cyclooxygenase-2 and Potency in Inhibiting Gastric COX Activity

Table IV: Drugs Used In the Treatment of Peptic Ulcer Disease

Table V: Guide to NSAID Therapy

**List of Figures**

Figure I: Prostaglandin and thromboxane synthesis

Figure II: Actions of antiulcer medications

Figure III: Mechanisms by which NSAIDs may induce mucosal injury
List of Abbreviations

COX..........................................................................................................................Cyclo-Oxygenase
GI ......................................................................................................................................Gastro-intestinal
GU ....................................................................................................................................Gastric Ulcer
H$_2$..................................................................................................................................Histamine 2
$H$ pylori..........................................................................................................................Helicobactor pylori
NSAID ..........................................................................................................................Non-Steroidal Anti-Inflammatory
tsNSAID..........................................................non-selective Non-Steroidal Anti-Inflammatory
OTC..............................................................................................................................Over the counter
PPI.................................................................................................................................Proton Pump Inhibitor
PUD ...............................................................................................................................Peptic Ulcer Disease
SR .................................................................................................................................Sustained Release
List of Appendices

Appendix A……Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomized trial.

Appendix B.......Prevention of Ulcers by Esomeprazole in At-Risk Patients Using Non-Selective NSAIDs and COX-2 Inhibitors

Appendix C……The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review.

Appendix D……Guidelines for the appropriate use of non-steroidal anti-inflammatory drugs, cyclo-oxygenase-2-specific inhibitors and proton pump inhibitors in patients requiring chronic anti-inflammatory therapy
EFFECTS AND PREVENTION OF CHRONIC NSAID USE ON THE STOMACH

INTRODUCTION

Each year approximately 30 billion over-the-counter (OTC), nonsteroidal anti-inflammatory (NSAID) tablets are sold and 60 million prescriptions are written for NSAIDs, of which 3.6 times more are written for elderly patients than for younger patients. In fact, after the introduction of COX-2 inhibitors in the year 2000, the number of prescriptions written for NSAIDs was >111 million at a cost of $4.8 billion. Currently in the United States there are at least 20 types of NSAID’s available by prescription and/or OTC and more in other parts of the world (Table I).

An NSAID is defined as a drug that has “analgesic, anti-inflammatory, and antipyretic actions”. It is used to treat “acute and chronic pain, including the pain of injuries, arthritis, and dysmenorrhea; to reduce inflammation; and to prevent complications in serious illness, such as sepsis”. This versatility of NSAID’s has led to an increased popularity of the drug. Unfortunately, aspirin and other NSAID’s can injure the gastric and duodenal mucosa, leading to considerable morbidity and mortality. In fact, patients who take NSAID’s have a 4 to 7-fold increased risk of developing a type of gastric injury. These gastric injuries can range from nausea and dyspepsia to serious gastrointestinal (GI) complications such as peptic ulcerations complicated by bleeding or perforation. The risk of developing a GI complication is not the same for all patients, the risk of bleeding increases with the presence of risk factors (see Table II). It has been estimated that GI toxicity related to NSAID use in the US population is attributable to approximately “3200 to >16,500 deaths annually”. Therefore, the prevention of GI injury due to NSAID use is an important clinical issue.
The purpose of this review was to determine the current recommendations for the prescribing of NSAID’s and the prevention of concurrent GI damage with NSAID use. As stated above, the prevalence of aspirin and NSAID use in the United States alone is significant and as the population continues to age will become more so in the upcoming future, therefore being able to prevent gastric injury is imperative.

BACKGROUND

History of NSAIDs

The first original NSAID was discovered in 1763, called sodium salicylate and was used in various impure forms as an antipyretic and as an analgesic. Even back then there were gastrointestinal side effects associated with the use of acetylsalicylic acid (ASA) which in turn led to the evolution over a period of time of over “20 different drugs, from six major classes determined by their chemical structures, available for use in the United States” (Table 1). Many of these drugs were developed also in hopes to increase patient’s compliance with their medication adherence by decreasing the absolute number of pills and frequency of which they are taking them each day. Other purposes were to reduce the toxicity of the drug and to increase the anti-inflammatory effect.

Mechanism of Action of NSAID’s

The primary effect of NSAID’s is to inhibit cyclooxygenase. Cyclooxygenase is one of several enzymes (COX1, COX2, etc) that make prostaglandins from arachidonic acids. They play a central role in inflammatory diseases, blood clotting, pain and cellular proliferation. By inhibiting cyclooxygenase, NSAIDs prevent arachidonic acid
from producing prostaglandins which are important mediators in the inflammatory process\textsuperscript{7} (see Figure I). However, prostaglandins also play a role in the protection of the gastric and duodenal mucosal lining from luminal acid-pepsin\textsuperscript{4}. The extent of the cyclooxygenase inhibition varies from NSAID to NSAID which may be why different patients react differently to the same medication whether it be the effectiveness of the drug or the extent of side effects the drug may have on the patient.

Cyclooxygenase is expressed as a least two different enzymes, COX1 and COX2. They are 50-60\% homologous and are coded on different chromosomes. COX1 has a fairly steady rate of expression in most cells of the body and is stimulated by hormones or growth factors. In contrast, COX2 is usually undetectable in most tissues but is expressed in cells only when bacterial polysaccharides, pro-inflammatory cytokines such as TNFa or IL-1b, or growth factors induce its expression\textsuperscript{4}.

Typically in healthy gastric and duodenal mucosa, COX1 is used to produce its mucosal protective prostaglandins. The mechanism of action in many NSAID’s is to block the COX1 and COX2 pathways more or less equally (are non-selective) and therefore can cause suppression in the production of the prostaglandin that is protective of the gastric mucosa. This can lead to the injury of the gastric mucosa which can have considerable morbidity and mortality secondary to gastric ulcer disease. Other types of NSAID’s that selectively inhibit the COX2 pathway have less of an impact on the suppression of gastric prostaglandin synthesis and therefore less gastric mucosal injuries are incurred\textsuperscript{4}. Table III lists the selectivity for COX-2 for select NSAIDs.
Mechanism of Action for Cox-2 Inhibitors

In contrast with non-selective NSAID’s, COX-2 inhibitors “inhibit prostaglandin synthesis by decreasing the activity of the enzyme, cyclooxygenase-2, which results in decreased formation of prostaglandin precursors”\(^9\). By inhibiting the COX-2 pathway, instead of the COX-1 pathway, COX-2 inhibitors have an advantage by showing a lower risk for the development of GI bleeding\(^{10}\). However, all NSAIDs have some inhibitory effects on COX-1 and COX-2 activities, so that none is absolutely selective for COX-2\(^{11}\).

Mechanism of Action for Drugs that Treat PUD

There are numerous drugs available today in the United States that are used for treatment and maintenance therapy of peptic ulcer, treatment of gastroesophageal reflux disease, and management of dyspepsia\(^{12}\) (see Table IV). Of these drugs three classes have been studied in the prevention or recurrence of PUD with chronic NSAID or COX-2 usage.

\(H_2\) receptor antagonists block the actions of histamine at all \(H_2\) receptors (see Figure II). However, their chief use is to inhibit gastric acid secretion induced by histamine or gastrin being particularly effective against nocturnal acid secretion. The four drugs used in the United States (see Table IV) potently inhibit basal, food-stimulated and nocturnal secretion of gastric acid after a single dose\(^{13}\). All four of these agents have been effective in promoting healing of gastric ulcers, though recurrence is common after treatment is stopped (60-100% per year)\(^{13}\).

Proton pump inhibitors (PPI’s) bind to the proton pump of the parietal cell (see Figure II), thereby suppressing secretion of hydrogen ions into the gastric lumen\(^{13}\). At
standard doses, all PPI’s inhibit both basal and stimulated gastric acid secretion more than ninety percent. Since PPI’s arrival on the market, they have proven to be superior over H₂ antagonists for suppressing acid production and healing peptic ulcers. However, a study has shown that ‘long-term PPI therapy, particularly at high doses, is associated with an increased risk of hip fracture’.

Prostaglandin E₂, produced by the gastric mucosa, inhibits secretion of hydrochloric acid and stimulates secretion of mucus and bicarbonate, a cytoprotective effect. Non-selective NSAID’s inhibit the production of prostaglandins and therefore their protectiveness over the gastric mucosa which can lead to peptic ulcers. Misoprostol is a stable analog of prostaglandin E₁ and has been approved for the prevention of gastric ulcers induced by NSAID’s. However, Misoprostol has been shown to cause abortion premature birth and birth defects, therefore should be avoided with women who are pregnant or are of child-bearing potential. Other serious side-effects of Misoprostol are hypertension, myocardial infarctions and arrhythmias, so when considering a gastric protective measure for a patient with cardiovascular concerns this drug should be avoided.

In comparison of the three types of treatments, studies have shown “standard doses of H₂-receptor antagonists were effective at reducing the risk of endoscopic duodenal ulcers (RR=0.36; 95% CI: 0.18-0.74) but not gastric ulcers (RR=0.73; 95% CI:0.50-1.09). Both double dose H₂RAs and PPIs were effective at reducing the risk of endoscopic duodenal and gastric ulcers (RR=0.44; 95% CI: 0.26-0.74 and RR=0.40;95% CI:0.32-0.51 respectively for gastric ulcer), and were better tolerated than misoprostol.”
**Peptic Ulcer Disease**

Peptic ulcer disease encompasses both gastric and duodenal ulcers. Ulcers are defined as breaks in the mucosal surface >5 mm in size, with depth to the submucosa. Gastric ulcers (GU) tend to appear later in life, with peak incidence around the sixth decade. Most benign GU’s are located distal to the junction between the antrum and the acid secretory mucosa. The majority of GU's can be attributed to either *H. pylori* or NSAID-induced mucosal damage with other causes associated with genetic predisposition, psychological stress, cigarette smoking and diet.

Prostaglandins play an important role in maintaining gastroduodenal mucosal integrity and repair. Therefore, interruption of prostaglandin synthesis which occurs with NSAID use can impair mucosal defense and repair, leading to mucosal injury. Figure III demonstrates how systematically administered NSAIDs may lead to mucosal injury.

Clinical manifestations of PUD include abdominal pain and epigastric pain with about 10% of patients presenting without symptoms. It is important to do a thorough history and physical exam with patients thought to have PUD. Abdominal pain is common to many GI disorders and therefore has a poor predictive value of the presence of GU’s. Epigastric pain can be described as a burning or gnawing discomfort or as an ill-defined, aching sensation or hunger pain. The typical pain pattern associated with GU’s is associated with the ingestion of food. Nausea and weight loss may also be associated with a GU. The list of GI and non-GI disorders that can mimic ulceration of the stomach is long and includes proximal GI tumors, gastroesophageal reflux (GERD), vascular disease, biliary colic, chronic pancreatitis and gastroduodenal Crohn’s disease.
The extent of ulcer complications may be determined by a description of symptoms or an increase in ulcer complications may be indicated by a new onset of symptoms or a change in frequency of symptoms. Ulcer complication can be indicated by onset of associated symptoms such as nausea and/or vomiting. A penetrating ulcer may be described as dyspepsia that has become constant, is no longer relieved by food or antacids, or radiates to the back. A perforation may be indicated by sudden, severe, generalized abdominal pain. A patient experiencing gastric outlet obstruction will present with pain worsening with meals, nausea and vomiting of undigested food. A bleeding ulcer will present with tarry stools or coffee ground emesis.

Upon physical exam the most frequent finding is epigastric tenderness in patients with GU’s. A patient with tachycardia or orthostasis may be dehydrated from vomiting or active GI blood loss. A severely tender, board-like abdomen suggests a perforation.

GI bleeding is the most common complication observed with PUD. It occurs in approximately 15% of patients and more often in individuals over 60 years of age. The higher incidence in the elderly is likely due to their increased NSAID use.

Perforation is the second most common ulcer-related complication. The incidence rate has been reported in as many as 6-7% of PUD patients, with the incidence in perforation in the elderly increasing secondary to the increased use of NSAID’s.

Gastric outlet obstruction is the least common complication of PUD with the occurrence being approximately 1-2% of patients. Obstruction may be secondary to ulcer-related inflammation and edema in the peripyloric region which often resolves after the ulcer has healed. Another possible obstruction occurs secondary to scar formation in
the peripyloric area which is resolved with an endoscopic balloon dilation or surgical intervention.

Diagnostic studies are often used to establish the presence of an ulcer due to the multiple disease processes that can mimic PUD. Documentation of an ulcer requires either a barium study or an endoscopic procedure. However, for patients who are otherwise healthy and less than 45 years of age, empirical therapy is appropriate before proceeding with an endoscopic evaluation.

Barium studies of the proximal GI tract are still commonly used as a first test for documenting an ulcer. Typically a benign GU ulcer will appear as a “discrete crater with radiating mucosal folds originating from the ulcer margin.” Ulcers greater than 3 cm or those associated with a mass are often malignant in nature. Because “8% of GU’s that appear to be benign by barium studies are in fact malignant, a barium study that shows a GU most be followed up by endoscopy and biopsy.”

Endoscopy provides the most sensitive and specific approach for examining the upper GI tract. It allows for direct visualization, photographic documentation of the mucosal defect and for biopsy to rule out malignancy or H. pylori. Endoscopy also helps in identifying lesions too small to be detected by barium studies and to determine whether an ulcer is a source of blood loss.

**METHODS**

An extensive literature review in English was performed searching for articles over the past 10 years using the following search terms, but not limited to: NSAID, nonsteroidal anti-inflammatory drugs, ibuprofen, COX2 inhibitors, cyclooxygenase,
peptic ulcer disease, ulcer bleeding, omeprazole, misoprostol, gastrointestinal, upper gastrointestinal and perforated ulcers. Articles were rejected if the study was not a randomized controlled trial or retrospective cohort trial; included exclusively children; lasted less than 21 days; or did not measure review outcomes. Data sources included OVID-Medline, PubMed, UpToDate, Taber’s Cyclopedic Medical Dictionary, Epocrates, Minneapolis VA Medical Center Research Library and University of New Mexico Health and Sciences Library.

RESULTS

Five GI Protective Strategies

In 2004, the British Medical Journal published a study regarding “The Effectiveness of Five Strategies for the Prevention of Gastrointestinal Toxicity Induced by Non-Steroidal Anti-Inflammatory Drugs: Systematic Review” (see Appendix A). The five strategies included “H₂ receptor antagonists plus nsNSAIDs, PPI’s plus nsNSAIDs, misoprostol plus nsNSAIDs, COX-2 selective NSAIDs and COX-2 specific NSAIDs” (see Appendix A). The review looked at only randomized controlled trials that assessed gastroprotective strategies versus placebo. The results when comparing gastroprotective strategies versus placebo were as follows: “no evidence of effectiveness of H₂ receptor antagonists; proton pump inhibitors may reduce the risk of symptomatic ulcers (relative risk 0.09, 95% confidence interval 0.02 to 0.47); misoprostol reduces the risk of serious gastrointestinal complications (0.57, 0.36 to 0.91) and symptomatic ulcers (0.36, 0.20 to 0.67); COX-2 selectives reduce the risk of symptomatic ulcers (0.41, 0.26 to 0.65) and COX-2 specifics reduce the risk of symptomatic ulcers (0.49, 0.38 to 0.62) and possibly
serious gastrointestinal complications (0.55, 0.38 to 0.80)”\(^{18}\). Overall the review concluded that “misoprostol, COX-2 specific and selective NSAIDs, and probably proton pump inhibitors significantly reduce the risk of symptomatic ulcers, and misoprostol and probably COX-2 specifics significantly reduce the risk of serious gastrointestinal complications, but data is low”\(^{18}\).

**NSAID VS. COX-2**

When researching the comparison of NSAIDs to COX-2 selective inhibitors, three randomized controlled trials demonstrated the same result: COX-2 selective inhibitors are associated with less significant GI effects than nsNSAIDs alone. In 2000, JAMA published the *Celecoxib Long-Term Arthritis Safety Study* (CLASS) which set out to determine “whether celecoxib, a COX 2-specific inhibitor was associated with a lower incidence of significant upper GI toxic effects and other adverse effects compared with conventional NSAIDs”\(^{19}\). Patients were randomly assigned to receive either “celecoxib, 400mg twice daily (2 to 4 times the maximum rheumatoid arthritis and osteoarthritis dosages, respectively), ibuprofen, 800mg three times daily or diclofenac, 75mg twice daily”\(^{19}\). Results from this study showed that for all patients, the “incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs. NSAIDs were 0.76% vs. 1.45% (\(P=\cdot09\)) and 2.08% vs. 3.54% (\(P=.02\)) respectively”\(^{19}\). Overall the study concluded that 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”\(^{19}\). However, the results of this study came under
scrutiny. It was stated that “the CLASS study was not designed to compare the efficacy of the drugs, and the choice of dosing regimens was based on an analysis of prescription patterns, rather than evidence of similar efficacy.”20. The patient population was not equal as well, with their being more patients with osteoarthritis than rheumatoid arthritis and more being female19. Also, the trial did not take into account patients already at risk for PUD, therefore naturally leading to a higher rate of PUD despite the medication they were given. In addition, only the first six months of data from this trial was published, though the trial ended at 13 months20. Another possibility for inaccurate results was that patients were allowed, if needed, to take aspirin, up to 325mg daily. This trial received its funding from Pharmacia, the maker of the drug celecoxib, thereby possibly allowing for the industry bias in the published results.

In the New England Journal of Medicine in the same year another large trial, VIOXX Gastrointestinal Outcomes Research (VIGOR), was published comparing upper GI toxicity of NSAIDs vs. COX 2-selective inhibitors, specifically rofecoxib (Vioxx) and naproxen, in patients with rheumatoid arthritis21. Patient’s were randomly assigned to receive either 50mg of rofecoxib daily or 500mg of naproxen twice daily21. Results of the VIGOR trial demonstrated “2.1 confirmed gastrointestinal events per 100 patient-years occurred with rofecoxib, as compared with 4.5 per 100 patient-years with naproxen”21. In conclusion, the study demonstrated “treatment with rofecoxib, a selective inhibitor of cyclooxygenase-2, is associated with significantly fewer clinically important upper gastrointestinal events than treatment with naproxen, a non-selective inhibitor.”21. However, the VIGOR trial also revealed a link to an increased risk of myocardial infarctions with the use of rofecoxib with the rates of myocardial infarctions
in the naproxen group being 0.1% and in the rofecoxib group being 0.4%\textsuperscript{21}. The trial attributed this significance to the high rate of myocardial infarctions occurring in the population with the highest risk of myocardial infarctions, whom low dose aspirin was indicated. Since this trial was published, rofecoxib and other COX2 selective inhibitors were taken off of the market due to the cardiovascular side effects. This trial received funding from Merck and many of the participating authors had ties to the company at time of the trial, thereby leading to probable industry bias towards rofecoxib.

In 1999 the Lancet published a study titled “Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomized double-blind comparison”\textsuperscript{22}. Patients were “randomly assigned celecoxib, 200mg twice daily or diclofenac SR 75mg twice daily for 24 weeks”\textsuperscript{22}. Findings stated that “gastroduodenal ulcers were detected endoscopically in 15% of patients treated with diclofenac and in 4% of patients in the celecoxib group (\( P<0.001 \))\textsuperscript{22}, thereby leading to the conclusion that celecoxib “had a lower frequency of upper gastrointestinal ulceration”\textsuperscript{22} than diclofenac. Conversely, this study was supported by G D Searle and Co., the company that makes celecoxib. Though their data appears straight forward, some of the data may have had a different outcome if patients positive for \textit{H. pylori} and patients with a history of GI complications were excluded from this trial.

**COX-2 vs. NSAID + PPI**

An article was published in the New England Journal of Medicine in 2002 regarding a study titled “Celecoxib versus Diclofenac and Omeprazole in Reducing the Risk of Recurrent Ulcer Bleeding in Patients with Arthritis”\textsuperscript{23}. In this study patients were
randomly assigned to either receive “celecoxib, 200mg twice daily plus omeprazole placebo daily or 75mg of extended-release diclofenac twice daily plus 20mg of omeprazole daily for six months”\textsuperscript{23}. “A committee identified 16 cases of recurrent ulcer bleeding, 7 in the celecoxib group and 9 in the diclofenac-plus-omeprazole group”\textsuperscript{23}. Overall, the “probability of recurrent bleeding was 4.9% in the celecoxib group and 6.4% in the diclofenac-plus-omeprazole group, with the difference between the two groups not being significant ($P=0.60$ by the log-rank test)”\textsuperscript{23}. The study also calculated the probability for recurrent bleeding in patients not taking concomitant aspirin as being 4.5% in the celecoxib group and 5.6% in the combination therapy group\textsuperscript{23}. The study concluded that “the treatment with celecoxib (alone) was as effective as treatment with diclofenac plus omeprazole, with respect to the prevention of recurrent bleeding”\textsuperscript{23}. However, the study warns that even though the two methods were as effective, the risk of recurrent bleeding with either treatment was high, suggesting that neither regimen could completely protect patients at high risk from recurrent ulcer complications\textsuperscript{23}. An important note about this study was that two of the co-authors received consulting fees from drug companies; One from Novartis the maker of Voltaren XR (diclofenac) and the other from Pfizer the current manufacturer of celecoxib. However, in regards to the former author, the study was performed prior to the merger between Pfizer and Pharmacia in 2003. During this study Pharmacia manufactured celecoxib. In spite of this, the article appeared to present its data clearly and fairly and also recognized the limitations of the study.

Another similar study was published in 2005 in The American Journal of Medicine, titled “Celecoxib compared with lansoprazole and naproxen to prevent
gastrointestinal ulcer complications”\textsuperscript{24} For this study patient’s were “randomly assigned to treatment with celecoxib 200mg daily alone or naproxen 750mg daily and lansoprazole 30mg daily for 24 weeks”\textsuperscript{24}. At 24 weeks “4 patients (3.7%, 95% confidence interval (CI) 0.0%-7.3%) in the celecoxib group, compared with 7 patients (6.3%, 95% CI 1.6%-11.1%) in the naproxen and lansoprazole group, developed recurrent ulcer complications (absolute difference -2.6%, 95% CI for the difference -9.1% - 3.7%)”\textsuperscript{24}. The study concluded that in patients with a history of nsNSAID-related complicated peptic ulcers, celecoxib alone was statistically as effective as the co-therapy of naproxen and lansoprazole in the prevention of recurrent ulcer complications\textsuperscript{24} As in the previous study, it was found the two therapies were as effective in reducing ulcer complication recurrence, yet they were still associated with a significant proportion of ulcer complication recurrences (4%-6\%)\textsuperscript{24}. This was found to occur especially in the population of patients 65 years of age and older\textsuperscript{24}. This study was not funded by a pharmaceutical company, though since it was not a placebo-controlled study, there may still have been a possible bias.

**COX-2 vs. COX-2 plus PPI**

In 2007, The Lancet published a study titled “Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomized trial”\textsuperscript{25} (see Appendix B). The study defined “very high risk” as patients with a previous history of ulcer bleeding\textsuperscript{25}. Patients participating in this study were all given celecoxib 200mg twice daily, then half were randomly assigned to receive either 20mg of esomeprazole twice daily or to receive
a placebo for 12 months. Of 21 suspected serious GI events, 12 cases were identified as recurrent ulcer bleeding, all being from the celecoxib only group\textsuperscript{25}. The study stated its findings as “combination treatment was more effective then celecoxib alone for prevention of ulcer bleeding in patients at high risk”\textsuperscript{25}. This study appeared to present its data clearly, without bias and did well to recognize the limitations of the study itself. They noted the design was not able to assess the best possible management for patients with high cardiovascular risk and therefore the role of concomitant aspirin in relation to the efficacy of COX-2 inhibitors. Though this study was not sponsored by a pharmaceutical company, some of the authors had received grant support from different drug companies associated with the study drugs, though it is unclear if it was to aid in this research.

**nsNSAID plus PPI vs. COX-2 plus PPI**

In 2006, a study was published in the American Journal of Gastroenterology titled “*Prevention of ulcers by esomeprazole in at-risk patients using non-selective NSAIDs and COX-2 inhibitors*”\textsuperscript{26} (See Appendix C). Two similar studies, titled *The Verification of Esomeprazole for NSAID Ulcers and Symptoms (VENUS)* and the *Prevention of Latent Ulceration treatment Options (PLUTO)*, were performed at the same time with patients requiring daily NSAIDs, including COX-2 inhibitors\textsuperscript{26}. They were randomly assigned to be given either esomeprazole (20 or 40mg) or placebo, daily for 6 months\textsuperscript{26}. In the VENUS study the proportion of “patients who developed ulcers over 6 months was 20.4% on placebo, 5.3% on esomeprazole 20mg ($P<0.001$) and 4.7% on esomeprazole 40mg ($P<0.0001$)\textsuperscript{26}. In the PLUTO study, “the values were 12.3% on placebo, 5.2%
with esomeprazole 20mg ($P=0.018$) and 4.4% with esomeprazole 40mg ($P=0.007$). Overall “significant reductions were observed for users of both non-selective NSAIDs and COX-2 inhibitors”\textsuperscript{26}, leading to a conclusion that “for at-risk patients, esomeprazole was effective in preventing ulcers in long-term users of NSAIDs, including COX-2 inhibitors”\textsuperscript{26}. The two studies used similar protocols, except for minor local variations. However, some differences noted between the two groups may have led to limitations of this study. One difference was the number of participants in each study. The VENUS study had 844 patients all from the United States and the PLUTO study had 585 patients from 11 different countries, including the United States\textsuperscript{26}. Comparison of the two groups may have been skewed due to multiple variables. Another possible source of a limitation could have been that 10% of the VENUS population had a history of ulcers as their sole risk versus being \textgreater 60 years of age, whereas 25% of the PLUTO population had ulcers as their sole risk\textsuperscript{26}, possibly leading to the higher percentage of recurrent ulcers in the PLUTO group. It was also noted that AstraZeneca, the manufacturer of esomeprazole, provided the research grant and financial assistance for the VENUS and PLUTO studies.

**DISCUSSION**

**Overall Conclusions and Recommendations**

Many of the early studies comparing nsNSAIDs to COX-2 inhibitors when COX-2 inhibitors first appeared on the market found COX-2 inhibitors to be statistically superior to nsNSAIDs in preventing PUD. However, it was determined that many of these studies published biased results or were not forth coming in all of the results due to the fact the trials were funded by the drug companies of the specific study drug. In
recent years additional studies have been published with higher validity demonstrating the combination of an nsNSAID with a PPI is as effective in gastroprotection as a COX-2 inhibitor alone\(^\text{24}\) and the combination of a COX-2 inhibitor with a PPI is more effective in gastroprotection than a COX-2 inhibitor alone\(^\text{25}\). With the recent removal from the market of many COX-2 inhibitors because of increased cardiovascular risks, many patients and practitioners have valid concerns about taking and prescribing COX-2 inhibitors, though still are concerned with prevention of PUD in patients in need of chronic NSAID use. Consequently, over the past few years recommendations have been put forth to aide in this decision making process (see Table V).

An article titled “The relative efficacies of gastroprotective strategies in chronic users of nonsteroidal anti-inflammatory drugs” published in Gastroenterology (2008) proposed recommendations as follows: In high-risk patients requiring chronic NSAID use, a COX-2 inhibitor plus a PPI is suggested\(^\text{27}\). For those patients whom a COX-2 inhibitor is contraindicated because of either cardiac disease or the cost of both medications is prohibitive, either the combination of a nsNSAID plus misoprostol plus a PPI or the combination of nsNSAID plus a PPI or low dose misoprostol is their recommendation\(^\text{27}\).

In 2004, Alimentary Pharmacology and Therapeutics, published an article titled “Guidelines for the appropriate use of non-steroidal anti-inflammatory drugs, cyclo-oxygenase-2-specific inhibitors and proton pump inhibitors in patients requiring chronic anti-inflammatory therapy”\(^\text{28}\) (See Appendix E). These guidelines are as follows: “the use of an NSAID alone is appropriate for those aged <65 years, and the use of an NSAID plus proton pump inhibitor or cyclo-oxygenase-2-selective inhibitor plus proton pump
inhibitor is not appropriate”28. “For patients aged >65 and at low risk, an NSAID or
cyclo-oxygenase-2-selective inhibitor alone was rated as ‘uncertain’28.” For patients with
a previous GI event or who concurrently received aspirin, an NSAID alone was rated as
not appropriate28, and either “a cyclo-oxygenase-2-selective inhibitor or an NSAID +
proton pump inhibitor was rated as ‘appropriate’”28. “Finally, for patients with a
previous gastrointestinal event and on aspirin, an NSAID or cyclo-oxygenase-2-selective
inhibitor in conjunction with a proton pump inhibitor was rated as ‘appropriate’”28.

LIMITATIONS OF STUDY

There are many studies that have looked at the efficacy of NSAID’s and COX-2
inhibitors whether alone or with combination therapy of a PPI. However, chronic PPI
usage has been linked to complications such as “community acquired pneumonia, C-dif
associated diarrhea and hip fractures”27. There currently is no research detailing the
risk/benefit ratio of chronic PPI usage29. To tie into this research it may be of value to
study H₂ receptor antagonists vs. PPI’s as there is very little research and no recent
research comparing the two in their efficacy to decrease PUD while taking NSAIDs.

The research provided does not take into account patient compliance associated
with the number of pills they have to take29. It may be beneficial to assess compliance in
patients by treating with one combination NSAID/PPI pill versus separately prescribed
mediations.
CONCLUSIONS

NSAIDs are among the most widely used drugs and their usage will continue to increase as our population continues to age. Therefore, it is imperative to be aware of the side effects these drugs can have on a person and how to prevent them from occurring. The recommendations presented above are a step in this direction. Of course these are only guidelines and are here to assist in the process of balancing the risks and benefits, and the cost of medications. As always “regulatory advice and good clinical practice are to use anti-inflammatory drugs at the lowest effective dose and for the shortest possible time.”

Table I

<table>
<thead>
<tr>
<th>The nonsteroidal anti-inflammatory drugs</th>
<th>NSAID</th>
<th>Trade name</th>
<th>Usual dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxylic acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (acetylsalicylic acid)</td>
<td>Multiple</td>
<td>2.4-6 g/24h in 4-5 divided doses</td>
<td></td>
</tr>
<tr>
<td>Buffered aspirin</td>
<td>Multiple</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td>Enteric-coated salicylates</td>
<td>Multiple</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td>Salsalate</td>
<td>Disalcid</td>
<td>1.5-3.0 g/24h BID</td>
<td></td>
</tr>
<tr>
<td>Diflunisal</td>
<td>Dolobid</td>
<td>0.5-1.5 g/24h BID</td>
<td></td>
</tr>
<tr>
<td>Choline magnesium trisalicylate</td>
<td>Trilisate</td>
<td>1.5-3 g/24h BID-TID</td>
<td></td>
</tr>
<tr>
<td>Propionic acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Motrin, Rufen, OTC</td>
<td>OTC:200-400 mg QID; Rx: 400-800 mg; max 3200 mg/24h</td>
<td></td>
</tr>
<tr>
<td>Naproxen; Enteric</td>
<td>Naprosyn, Anaprox, OTC: Alleve</td>
<td>250, 375, 500 mg BID; 225 mg BID</td>
<td></td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>Nalfon</td>
<td>300-600 mg QID</td>
<td></td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Orudis; Oruvail</td>
<td>75 mg TID; q day</td>
<td></td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>Ansaid</td>
<td>100 mg BID-TID</td>
<td></td>
</tr>
<tr>
<td>Oxaprozin</td>
<td>Daypro</td>
<td>600 mg; 2 tabs per day</td>
<td></td>
</tr>
<tr>
<td>Acetic acid derivatives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Indocin, Indocin SR</td>
<td>25, 50 mg TID-QID; SR:75 mg BID; rarely &gt;150 mg/24h</td>
<td></td>
</tr>
<tr>
<td>Tolmetin</td>
<td>Tolectin</td>
<td>400, 600, 800 mg; 800 to 2400 mg/24h</td>
<td></td>
</tr>
<tr>
<td>Sulindac</td>
<td>Clinoril</td>
<td>150, 200 mg BID; some increase to TID</td>
<td></td>
</tr>
<tr>
<td>Drug Name</td>
<td>Brand Name</td>
<td>Dosage</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>------------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>Diclofenac (plus misoprostol)</td>
<td>Voltaren; Cataflam; (Arthrotec)</td>
<td>50, 75 mg BID (50 mg BID)</td>
<td></td>
</tr>
<tr>
<td>Etodolac</td>
<td>Lodine</td>
<td>200, 300 mg BID-QID; max:1200 mg/24h</td>
<td></td>
</tr>
<tr>
<td>Fenamates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meclofenamate</td>
<td>Meclomen</td>
<td>50-100 mg TID-QID</td>
<td></td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>Ponstel</td>
<td>250 mg QID</td>
<td></td>
</tr>
<tr>
<td>Enolic acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Feldene</td>
<td>10, 20 mg q day</td>
<td></td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>Butazolidin</td>
<td>100 mg TID up to 600 mg/24h</td>
<td></td>
</tr>
<tr>
<td>Naphthylkanones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nabumetone</td>
<td>Relafen</td>
<td>500 mg BID up to 1500 mg/24h</td>
<td></td>
</tr>
<tr>
<td>Selective COX-2 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Celebrex</td>
<td>100, 200 mg a day</td>
<td></td>
</tr>
</tbody>
</table>

**Table II**

**Factors related to increased risk of NSAID-induced GI complications**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2.74</td>
<td>2.54-2.97</td>
</tr>
<tr>
<td>Age (&gt;60)</td>
<td>5.52</td>
<td>4.63-6.60</td>
</tr>
<tr>
<td>Prior GI event</td>
<td>4.76</td>
<td>4.05-5.59</td>
</tr>
<tr>
<td>High dosage (&gt;2 X normal)</td>
<td>10.1</td>
<td>4.6-22.0</td>
</tr>
<tr>
<td>Concurrent corticosteroids</td>
<td>4.4</td>
<td>2.0-9.7</td>
</tr>
<tr>
<td>Concurrent anticoagulants</td>
<td>12.7</td>
<td>6.3-25.7</td>
</tr>
</tbody>
</table>

**Table III**

*Selected NSAIDs and other analgesics: selectivity for cyclooxygenase-2 and potency in inhibiting gastric COX activity*

<table>
<thead>
<tr>
<th></th>
<th>COX-2 selectivity*</th>
<th>Gastric IC **</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salicylates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (acetylsalicylic acid)</td>
<td>0.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Salsalate (salicylsalicylic acid)</td>
<td>2.8</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>4.0</td>
<td>&gt;100</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>0.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>0.6</td>
<td>0.70</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>0.7</td>
<td>0.85</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1.0</td>
<td>0.52</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>1.3</td>
<td>0.87</td>
</tr>
<tr>
<td>Ketoralac</td>
<td>1.5</td>
<td>0.33</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>1.6</td>
<td>0.48</td>
</tr>
<tr>
<td>Etodolac</td>
<td>7.9</td>
<td>3.20</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>9.2</td>
<td>11.14</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>12.1</td>
<td>0.70</td>
</tr>
<tr>
<td>Nimesulide (not available in US)</td>
<td>58.3</td>
<td>1.49</td>
</tr>
</tbody>
</table>

* In whole blood assays in man. A number ≤ 1 indicates COX non-selectivity while numbers much >1 indicate COX-2 selectivity. Values for nabumetone are for its active metabolite, 6-MNA. Value for salsalate is a minimum, since this drug did not inhibit COX-2 in whole blood at any concentration tested.  
** Concentration of drug in µM that inhibits human gastric mucosal COX activity by 50% and thus gastric mucosal PG production by 50%. The lower the IC50, the more potent the inhibition of gastric COX activity for a given drug.  
**Table IV**

**Drugs Used In The Treatment of Peptic Ulcer Disease**

<table>
<thead>
<tr>
<th>Drug Type/Mechanism</th>
<th>Examples</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acid-suppressing drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antacids</td>
<td>Mylanta, Maalox, Tums,</td>
<td>100-140 meq/L 1 and 3 h after meals and hs</td>
</tr>
<tr>
<td></td>
<td>Gaviscon</td>
<td></td>
</tr>
<tr>
<td><strong>H$_2$ receptor antagonists</strong></td>
<td>Cimetidine</td>
<td>400 mg bid</td>
</tr>
<tr>
<td></td>
<td>Ranitidine</td>
<td>300 mg hs</td>
</tr>
<tr>
<td></td>
<td>Famotidine</td>
<td>40 mg hs</td>
</tr>
<tr>
<td></td>
<td>Nizatidine</td>
<td>300 mg hs</td>
</tr>
<tr>
<td><strong>Proton pump inhibitors</strong></td>
<td>Omeprazole</td>
<td>20 mg/d</td>
</tr>
<tr>
<td></td>
<td>Lansoprazole</td>
<td>30 mg/d</td>
</tr>
<tr>
<td></td>
<td>Rabeprazole</td>
<td>20 mg/d</td>
</tr>
<tr>
<td></td>
<td>Pantoprazole</td>
<td>40 mg/d</td>
</tr>
<tr>
<td></td>
<td>Esomeprazole</td>
<td>20 mg/d</td>
</tr>
<tr>
<td><strong>Mucosal protective agents</strong></td>
<td>Sucralfate</td>
<td>1 g qid</td>
</tr>
<tr>
<td>Sucralfate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostaglandin analogue</td>
<td>Misoprostol</td>
<td>200 µg qid</td>
</tr>
<tr>
<td>Bismuth-containing compounds</td>
<td>Bismuth subsalicylate (BSS)</td>
<td></td>
</tr>
<tr>
<td>No/Low NSAID GI Risk</td>
<td>NSAID GI Risk</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>No CV risk (no Traditional NSAID aspirin)</td>
<td>Coxib or Traditional NSAID + PPI Consider non-NSAID therapy</td>
<td></td>
</tr>
<tr>
<td>CV risk (consider aspirin)</td>
<td>Traditional NSAID + PPI if GI risk warrants gastroprotection A gastroprotective agent must be added if a traditional NSAID is prescribed</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** NSAID, nonsteroidal anti-inflammatory drug; GI, gastrointestinal; CV, cardiovascular; PPI, proton pump inhibitor.

**Source:** Adapted from AM Fendrick: Am J Manag Care 10:740, 2004.
Figure I

Prostaglandin and thromboxane synthesis

Schematic representation of the steps involved in synthesis of prostaglandin E2 (PGE2) and prostacyclin (PGI2). Characteristics and distribution of the cyclooxygenase (COX) enzymes 1 and 2 are also shown. TXA2, thromboxane A2.
H2 receptor antagonists (H2RAs) inhibit acid secretion by blocking histamine H2 receptors on the parietal cell. The proton pump inhibitors (eg, omeprazole, lansoprazole, and pantoprazole) effectively block acid secretion by irreversibly binding to and inhibiting the hydrogen- potassium ATPase pump that resides on the luminal surface of the parietal cell membrane. The mechanism involved in antacid healing of peptic ulcers may include neutralizing gastric acid, but probably also includes a number of other factors.
Figure III
Mechanisms by which NSAIDs may induce mucosal injury.

References


