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OPTIMAL SELECTION OF PROTON PUMP INHIBITOR TREATMENT FOR PREVENTING AND TREATING NSAID-INDUCED GASTROINTESTINAL HARM

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Abstract:

NSAIDs can lead to gastrointestinal side effects such as dyspepsia, peptic ulcer disease, and severe consequences like hemorrhage or perforation. This gastrointestinal toxicity is a substantial worldwide medical concern. Misoprostol diminishes NSAID-induced mucosal damage; however its efficacy is constrained by low patient tolerance. Antagonists of histamine receptors are useful in treating duodenal ulcers but not stomach ulcers. Proton pump inhibitors (PPIs) such as pantoprazole, omeprazole, and lansoprazole protect high-risk patients from developing gastric and duodenal ulcers and help in the healing of ulcers caused by NSAIDs. Proton pump inhibitors have a favorable safety profile. Proton pump inhibitors such as lansoprazole, omeprazole, pantoprazole, and rabeprazole are utilized for the treatment of acid-related gastrointestinal conditions such as gastro-esophageal reflux and peptic ulcer disease. All four inhibitors have comparable potency and effectiveness, with Rabeprazole demonstrating a quicker onset of acid inhibition but offering modest therapeutic benefit. Esomeprazole, the S-isomer of omeprazole, is more potent but does not offer any therapeutic benefits.

Key Words: proton pump inhibitor, NSAID, ulcer, gastrointestinal

Introduction:

NSAIDs are commonly utilized to offer efficient pain management in chronic arthritic and inflammatory disorders. Approximately 30 million individuals globally use NSAIDs daily, with around 40% of them being over 60 years old.[1,2] NSAIDs have established advantages but come with a risk of gastrointestinal side effects, including dyspepsia, peptic ulcer disease, and severe consequences such hemorrhage or perforation.[3-5] Approximately 50% of NSAID users have gastrointestinal symptoms, although these symptoms are not a dependable indicator of mucosal injury. Asymptomatic endoscopic ulcers have been observed in as many as 40% of individuals who use the medication for an extended period. [1,4,6,7] Severe effects like bleeding or perforation are rare, with an annual occurrence rate of approximately 1.5%. [6,8] The death rate for individuals hospitalized due to NSAID-related bleeding is between 5-10%.[9]

NSAIDs have been linked to harm to the small intestine and colon, leading to consequences such small intestinal rupture, hemorrhage, and strictures. [10,11] An autopsy research found ulcers in the jejunum or ileum in 8.4% of people using NSAIDs or aspirin, compared to 0.6% in control patients. [12]

Video capsule endoscopy, a modern method for better viewing of the gastrointestinal tract, has shown that damage to the small intestine caused by NSAIDs may be more widespread than previously believed.[13] 40 patients with a history of different forms of arthritis participated in a trial involving capsule endoscopy.[14] Half of the patients had used NSAIDs for over 3 months, whereas the other 20 patients were given acetaminophen or no treatment. An evaluation conducted without bias revealed that 58% of NSAID users experienced ulcers or erosions in the small intestine, whereas only 17% of non-users had the same issue. Additionally, 33% of the lesions in the NSAID group were classified as serious, while none were in the control group.
Omeprazole, the first proton pump inhibitor, was launched in 1988. The use of these inhibitors has progressively increased, providing a selection of inhibitors with diverse molecular architectures. Omeprazole's patent lapsed in 2003, leading to the introduction of several generic versions on the market. The discovery of Helicobacter pylori as the infectious agent causing peptic ulcer disease has expanded the uses of proton pump inhibitors. Today, the primary focus of treatment is the complete elimination of microorganisms. Gastro-esophageal reflux disease is now the most common reason for prescribing proton pump inhibitors due to its great prevalence in the population.

Omeprazole was the initial proton pump inhibitor, whereas esomeprazole (S-omeprazole) is the most recent one. Omeprazole is a racemic mixture consisting of the R-isomer and the S-isomer. The isomers undergo metabolism in the liver through two distinct metabolic routes. The S-isomer has a less effective metabolism, leading to higher plasma levels in vivo. The recommended daily dose of the S-isomer is 40 mg, while the recommended daily dose of omeprazole is 20 mg [32]. Is there a significant variation in potency and pharmacological features among different proton pump inhibitors, and if so, do these differences hold therapeutic significance? What dosage is recommended for treating acid-related diseases in a therapeutic setting? We have examined scholarly publications from the PubMed library, which consists of officially recognized medical journals, to address these problems.

Non-Steroidal Anti-inflammatory Drug-Related Gastrointestinal Damage:
Identifying people at elevated risk is crucial because not all individuals using NSAIDs experience gastroduodenal injury, and predicting it based on symptoms is difficult. Factors associated with an increased risk of NSAID-related gastrointestinal complications include a history of gastroduodenal ulcer or hemorrhage, age 65 or older, prolonged use of high-dose NSAIDs, using multiple NSAIDs, taking corticosteroids or anticoagulants simultaneously, and having serious conditions

like cardiovascular disease, renal or hepatic impairment, diabetes, or hypertension. [1,15] (Table 1)

Table 1. Risk factors for development of non-steroidal anti-inflammatory drug (NSAID)-related gastroduodenal damage (1)

Definite risk factors	Possible risk factors
Advanced age	Concomitant *Helicobacter pylori* infection
History of ulcer	Smoking
High doses of NSAIDs	Alcohol use
Multiple NSAIDs	
Concomitant use of corticosteroids	
Concomitant use of anticoagulants	
Comorbid diseases	

The correlation between Helicobacter pylori infection and NSAID use in the formation of peptic ulcers is still a topic of discussion.(Table 1) Studies have suggested several theories on the relationship between H. pylori infection and NSAIDs in terms of ulcer risk and mucosal damage. Current research indicates that H. pylori infection[16,17] and NSAID use are separate but combined risk factors for gastroduodenal ulcer formation[18-21}. Reducing or eliminating the risk associated with NSAID use should be prioritized over the risk of gastrointestinal complications from H. pylori infection due to the increased association of NSAIDs with such difficulties.

Gastrointestinal toxicity is caused by the inhibition of cyclo-oxygenase type-1 (COX-1), which leads to a decrease in the production of protective compounds such prostaglandin E2 and prostacyclin. Newer highly selective COX-2 inhibitors induce less gastrointestinal harm compared to NSAIDs, which inhibit both COX-2 and COX-1. Goldstein et al. conducted a double-blind placebo-controlled trial where three groups of healthy patients were treated with celecoxib, naproxen with omeprazole, or placebo for 2 weeks. Video capsule endoscopy revealed a greater occurrence of small intestinal mucosal lesions with naproxen plus omeprazole (55%) compared to celecoxib (16%, $p < 0.001$) and placebo (7%, $p < 0.001$). The safety of COX-2 inhibitors has been questioned due to the discontinuation of rofecoxib in September 2004, as it was linked to a higher risk of heart attack, stroke, and sudden death.[23,25,26] Recent data indicates that celecoxib and valdecoxib may be associated with cardiovascular side effects at high doses compared to placebo, but not when compared to non-selective NSAIDs.[27-29]

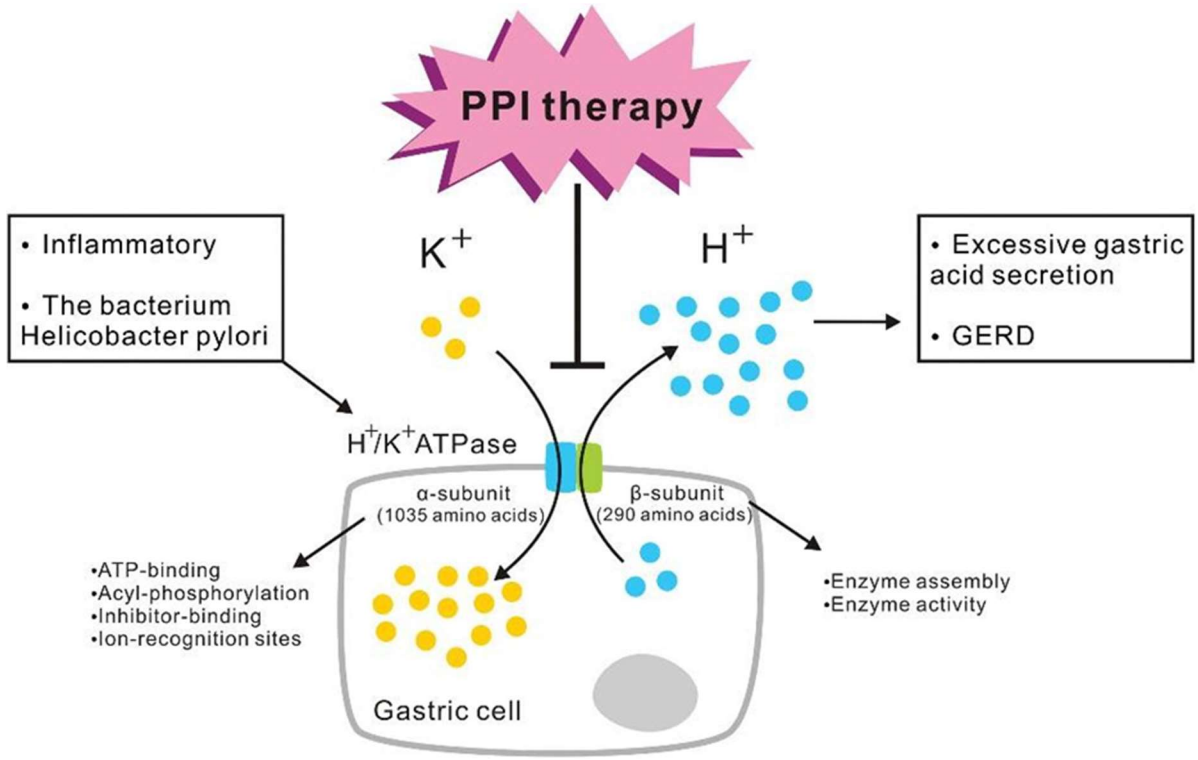
Low-dose aspirin is commonly recommended as a preventive measure for older individuals with heart conditions who may also be using NSAIDs for joint pain. It is crucial to establish if combining low-dose aspirin with NSAIDs raises the risk of gastroduodenal problems. A study

found that using low-dose aspirin by itself raises the likelihood of upper gastrointestinal bleeding in a dose-dependent way, with a fourfold higher risk at a dosage of 300 mg/day.

A study found that individuals receiving naproxen and aspirin had a higher incidence of gastroduodenal ulcer (27%) compared to those on celecoxib plus aspirin (19%, $p = 0.016$) or placebo plus aspirin (8%, $p < 0.001$). While the likelihood of severe gastrointestinal issues in individuals using low-dose aspirin by itself is minimal, it is advisable to consider gastroprotection for people who are also using low-dose aspirin along with NSAIDs for an extended period.[30,31]

Drug target: The enzyme H+,K+-ATPase:

Proton pump inhibitors are benzimidazoles with alkaline characteristics that serve as precursors of thiophilic sulphenamides. The change is influenced by pH and takes place inside the parietal cell. The sulphenamide is attached through covalent bonds to hydrogen sulphide residues of the H+,K+-ATPase molecule located on the luminal side of the canaliculi in the parietal cell. The binding occurs rapidly at pH 1 [33]. Omeprazole has a comparable inhibitory impact on the H+,K+-ATPase for both the S- and R-isomers. Both isomers are activated in a pH-dependent manner and converted into a cyclic sulphenamide, whose action is not influenced by its optical configuration [34]. A greater pKa of the precursor results in a faster conversion from an inactive molecule to an active molecule, specifically the sulphenamide.



A molecular diagram illustrating the structure of the enzyme H+,K+-ATPase. The enzyme is composed of 1034 amino acid residues distributed over two subunits. When H+-ions are released, a phosphate group is moved from ATP in the cytoplasm to aspartic acid in the enzyme's active

site, resulting in the creation of a phosphorus intermediate. This intermediate releases hydrogen ions at the luminal side of the enzyme. The catalytic α-subunit facilitates the exchange of H+ and K+ ions and is a big protein consisting of 10 domains that span the cell membrane. Proton pump

inhibitors (PPIs) attach to the enzyme section situated on the outer luminal membrane of the canaliculi, preventing phosphorylation and exchange of H+- and K+-ions. The β-subunit traverses the cell membrane at a single location. The β-subunit's extracellular domain is extensively glucosylated near the α-subunit. The role of the β-subunit has not been determined. significance set at a p-value of less than 0.05.

All proton pump inhibitors have a similar mechanism of action. Their binding occurs at a specific and shared location on the α-subunit of the proton pump, namely at cysteine 813 located on the luminal loop between transmembrane domains 5 and 6. Pantoprazole binds to cysteine 822, while omeprazole binds to cysteine 892. Lansoprazole and rabeprazole interact with cysteine 892 and cysteine 321 at other binding sites [35].

All proton pump inhibitors generate active sulphenamides at an equivalent speed under pH 1 conditions. Therefore, their maximum ability to reduce secretion and strength in a living organism are alike as long as the molecules have identical pharmacokinetic characteristics. Omeprazole and pantoprazole have comparable antisecretory abilities in animal studies [36]. Pantoprazole and rabeprazole have significantly different pKa values and activation rates, but they both achieve the same level of gastric acid inhibition with similar ID50 values. This similarity is also observed with lansoprazole, omeprazole, and esomeprazole, despite their slightly varying pKa values [37] (fig. 2). Proton pump inhibitors are activated rapidly, with a doubling time of 1-5 minutes, in contrast to a half-life of approximately 60 minutes in the bloodstream [38]. The efficacy of each medicine is determined by the level of available precursor, plasma AUC, and activation time at pH 1. Because all proton pump inhibitors remain in the plasma for a longer duration than necessary to inhibit the enzyme H+,K+-ATPase, any little variations in the time it takes for the inhibitors to become active in an acidic environment are insignificant.

Optimal dosing of proton pump inhibitors for treating acute and maintaining acid-related illnesses:

Research on gastro-esophageal reflux illness shows that treatment with 40 mg of omeprazole results in a higher healing rate compared to 20 mg. Esomeprazole 40 mg has approximately 15% higher healing rates in gastro-esophageal reflux illness compared to omeprazole 20 mg [39]. Studies have revealed that pantoprazole's healing rates in gastro-esophageal reflux disease vary depending on the dosage, with 10, 20, and 40 mg daily being effective [40]. Lansoprazole shows similar dose-response patterns in terms of effectiveness at 15 and 30 mg [41]. In conclusion, the recommended dosage of any proton pump inhibitor for treating gastro-esophageal reflux disease is 30–40 mg per day.

The most effective dosage for quick symptom relief and improved healing rate in treating peptic ulcer disease appears to be 40 mg daily of omeprazole and pantoprazole. Lansoprazole has not been studied at this specific dosage, although research suggests that a 60 mg dosage is more beneficial than lesser dosages based on intragastric 24-hour pH measurements [42]. The pharmacodynamic profile of lansoprazole appears to be similar to that of other proton pump inhibitors. Rabeprazole 20 mg and omeprazole 20 mg have similar effectiveness in inhibiting acid secretion for peptic ulcer and reflux disease [43]. Rabeprazole has a unique characteristic where acid inhibition begins more quickly compared to omeprazole, with noticeable effects as early as the first day of treatment [44]. This effect may be due to the elevated pKa of rabeprazole.

For maintenance treatment of gastro-esophageal reflux disease, a dosage of 15 mg lansoprazole, or alternatively 20 mg omeprazole or pantoprazole, is deemed enough. However, studies suggest that a dose as low as 10 mg may also be useful [45]. Esomeprazole at a daily dose of 20 mg provides a dependable maintenance treatment, resulting in maintained healing of 93.2% over a 6-month period [46]. Research on pantoprazole indicates comparable outcomes with doses of 20 mg and 40 mg [47] An appropriate daily dose of 20 mg is recommended for esomeprazole, omeprazole, and pantoprazole, while a 15-mg dose is considered effective for lansoprazole in the maintenance therapy of gastro-esophageal reflux disease.

Proton pump inhibitors used to prevent ulcers caused by nonsteroidal anti-inflammatory drugs:

Patients who are at a high risk of gastrointestinal injury from NSAIDs should be evaluated for prophylactic treatment with a gastroprotective medication. [1,15] Long-term prophylaxis with the prostaglandin analogue misoprostol is known to prevent NSAID-induced stomach and duodenal ulcers and decrease the chances of severe consequences like hemorrhage[6,45,46]. Patients' adherence is hindered by side symptoms, including diarrhea and stomach cramps. H2-receptor antagonists like ranitidine and famotidine provide some protection against duodenal ulcers when taking NSAIDs but do not offer considerable protection against stomach ulcers, which are more common in this group. [46-51] An enhanced preventive therapy is needed for individuals who need to use NSAIDs long-term and are therefore susceptible to gastrointestinal adverse effects.

Proton pump inhibitors (PPIs) like pantoprazole, omeprazole, and lansoprazole are being recognized as useful and well-tolerated medications that safeguard the stomach and duodenum when using NSAIDs. PPIs decrease stomach acid production by blocking the proton pumps in activated gastric parietal cells.[52] PPIs have shown success in treating acid-related illnesses, suggesting they could be beneficial in avoiding and mending stomach and duodenal ulcers resulting from NSAID exposure. A study in healthy individuals demonstrated that even a small number of aspirin taken briefly can lead to substantial harm to the stomach. However, when pantoprazole is given alongside, it provides defense against this harm.[53] The expected gastroprotective action of pantoprazole is likely to result in clinical benefits by minimizing NSAID-induced damage in long-term users of this medication class.

Conclusion:

Proton pump inhibitors are utilized at different standard doses to reduce acid secretion in both acute and maintenance therapy for acid-related conditions. The proton pump inhibitors lansoprazole, omeprazole, pantoprazole, and rabeprazole exhibit comparable anti-secretory potency per milligram. Rabeprazole demonstrates a somewhat quicker onset of acid inhibition compared to other medications. Esomeprazole exhibits a higher acid inhibitory potency compared to other proton pump inhibitors. The practical benefit of these discoveries appears minimal, and there is a dearth of research showing their therapeutic significance. Administering 40 mg of proton pump inhibitors daily inhibits H+,K+-ATPase at the upper end of the dose-response curve, indicating that variations in acid inhibitory effects among various inhibitors are typically minimal and challenging to discern.

An ideal dosage of 30–40 mg of proton pump inhibitors is recommended for treating active ulcer disease and moderate to severe gastro-oesophageal reflux disease based on the available data. To eradicate Helicobacter pylori, a two-dose program of proton pump inhibitor along with antibiotics is necessary. For mild symptomatic gastro-oesophageal reflux disease, or for maintenance treatment after healing erosive oesophagitis, a daily dose of 15–20 mg is considered enough. The recommended doses of proton pump inhibitors are based on their potency and effectiveness, rather than only their milligram strength. All proton pump inhibitors exhibit comparable potency.

Patented proton pump inhibitors are currently in competition with generic versions on a global scale. Competition for market shares will lead to lower prices. The primary objective from a clinical perspective should be to define criteria for selecting the correct medication and determining the suitable dosage. All proton pump inhibitors in the therapeutic environment exhibit equivalent potency and possess identical ability to suppress acid secretion. The clinician must determine the level of acid suppression to target in each patient, using their understanding of the disease's characteristics and seriousness. Optimal outcomes can be achieved by using any proton pump inhibitor after the appropriate dosage is determined for the individual patient.

The increasing issue of gastrointestinal toxicity associated with NSAID medication use is a concern. As the older population continues to increase, physicians are expected to see more individuals on NSAIDs, putting them at risk of developing ulcers and related complications. Extensive clinical trials have consistently shown that Proton Pump Inhibitors (PPIs) are more effective and more tolerated than H2-receptor antagonists and prostaglandin analogues in preventing and treating drug-induced gastrointestinal damage in patients who need ongoing NSAID treatment. Current treatment guidelines suggest using a preventive PPI in patients taking NSAIDs who have risk factors linked to more frequent or severe gastrointestinal complications. These risk factors include patients with prior ulcers, the elderly, individuals taking steroids or anticoagulants at the same time, and those with cardiovascular disease for whom bleeding poses a specific risk. Proton pump inhibitors (PPIs) are recommended as the preferred treatment for healing and preventing the recurrence of ulcers in patients who are on long-term NSAID medication. Additional research is required to validate the finding that PPIs can also decrease the

likelihood of bleeding and perforation in long-term NSAID users. Due to the infrequency of these issues, extensive studies would be necessary to identify any impact of the treatment.

Clinical trials have not shown any notable or consistent variations among Proton Pump Inhibitors (PPIs) in terms of clinical or endoscopic outcomes. All medications in the PPI class seem to have similar clinical effects when compared milligram for milligram (64). Pantoprazole stands apart from other medications in its class due to its low likelihood of causing pharmacokinetic drug interactions. Pantoprazole is a good option for senior individuals who often take many medications simultaneously. Pantoprazole is very effective and safe, with minimal risk of drug interactions, making it a favorable choice for preventing and treating NSAID-induced gastrointestinal issues.

References

1. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. N Engl J Med 1999; 340: 1888–99.
2. Lee M, Feldman M. The aging stomach: implications for NSAID gastropathy. Gut 1997; 41: 425–6.
3. Smalley WE, Griffin MR, Fought RL, Ray WA. Excess costs from gastrointestinal disease associated with nonsteroidal anti-inflammatory drugs. J Gen Intern Med 1996; 11: 461–9.
4. Stalnikowicz R, Rachmilewitz D. NSAID-induced gastroduodenal damage: is prevention needed? A review and metaanalysis. J Clin Gastroenterol 1993; 17: 238–43.
5. Fries JF, Miller SR, Spitz PW et al. Identification of patients at risk for gastropathy associated with NSAID use. J Rheumatol 1990; 20: 12–9.
6. Silverstein FE, Graham DY, Senior JR et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: a randomised, double-blind, placebo-controlled trial. Ann Intern Med 1995; 123: 241–9.
7. Singh G, Ramey DR, Morfeld D et al. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis: a prospective observational cohort study. Arch Intern Med 1996; 156: 1530–6.
8. Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. Arch Intern Med 2000; 160: 2093–9.
9. Armstrong CP, Blower AL. Non-steroidal anti-inflammatory drugs and life threatening complications of peptic ulceration. Gut 1987; 28: 527–32.
10. Smale S, Tibble J, Sigthorsson G, Bjarnason I. Epidemiology and differential diagnosis of NSAID-induced injury to the mucosa of the small intestine. Best Pract Res Clin Gastroenterol 2001; 15: 723–38.
11. Schneider AR, Benz C, Riemann JF. Adverse effects of non-steroidal anti-inflammatory drugs on the small and large bowel. Endoscopy 1999; 31: 761–7.
12. Allison MC, Howatson AG, Torrance CJ et al. Gastrointestinal damage associated with the use of non-steroidal anti-inflammatory drugs. N Engl J Med 1992; 327: 749–54.

13. Chutkan R, Toubia N. Effect of nonsteroidal anti-inflammatory drugs on the gastrointestinal tract: diagnosis by wireless capsule endoscopy. Gastrointest Endosc Clin N Am 2004; 14: 67–85.
14. Graham DY, Opekun AR, Willingham FF, Qureshi WA. Visible small-intestinal mucosal injury in chronic NSAID users. Clin Gastroenterol Hepatol 2005; 3: 55–9.
15. Lanza FL. A guideline for the treatment and prevention of NSAID-induced ulcers. Am J Gastroenterol 1998; 93: 2037–46.
16. Chan FKL, To KF, Wu JCY et al. Eradication of Helicobacter pylori and risk of peptic ulcers in patients starting long-term treatment with non-steroidal anti-inflammatory drugs: a randomised trial. Lancet 2002; 359: 9–13.
17. Bianchi Porro G, Parente F, Imbesi V et al. Role of Helicobacter pylori in ulcer healing and recurrence of gastric and duodenal ulcers in long-term NSAID users: response to omeprazole dual therapy. Gut 1996; 39: 22–6.
18. Lai KC, Lau CS, Ip WY et al. Effect of treatment of Helicobacter pylori on the prevention of gastroduodenal ulcers in patients receiving long-term NSAIDs: a double-blind, placebo-controlled trial. Aliment Pharmacol Ther 2003; 17: 799–805.
19. Bannwarth B, Dorval E, Caekaert A, Barthelemy P. Influence of Helicobacter pylori eradication therapy on the occurrence of gastrointestinal events in patients treated with conventional nonsteroidal antiinflammatory drugs combined with omeprazole. J Rheumatol 2002; 29: 1975–80.
20. Huang JQ, Sridhar S, Hunt RH. Role of Helicobacter pylori infection and non-steroidal anti- inflammatory drugs in peptic ulcer disease: a meta-analysis. Lancet 2002; 359: 14–22.
21. Hawkey CJ, Tulassay Z, Szczepanski L et al. Randomised controlled trial of Helicobacter pylori eradication in patients on non-steroidal anti-inflammatory drugs: HELP NSAIDs study. Lancet 1998; 352: 1016–21.
22. Micklewright R, Lane S, Linley W et al. Review article: NSAIDs, gastroprotection and cyclo-oxygenase-II-selective inhibitors. Aliment Pharmacol Ther 2003; 17: 321–32.
23. Bombardier C, Laine L, Reicin A et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000; 343: 1520–8.
24. Goldstein JL, Eisen GM, Lewis B et al. Video capsule endoscopy to prospectively assess small bowel injury with celecoxib, naproxen plus omeprazole and placebo. Clin Gastroenterol Hepatol 2005; 3: 133–41.
25. Solomon DH, Schneeweiss S, Glynn RJ et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation 2004; 109: 2068–73.
26. Juni P, Nartey L, Reichenbach S et al. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Lancet 2004; 364: 2021–9.
27. Porter V. NSAIDs still under surveillance – celecoxib, valdecoxib and naproxen have been added to the list of suspects. Medscape Cardiol 2005; 9 (1). Retrieved from http://www.medscape.com/viewarticle/496951?rss.

28. National Cancer Institute. Press release: NIH halts use of COX-2 inhibitor in large cancer prevention trial. 17 December 2004 Retrieved from http://www.nci.nih.gov/newscenter/pressreleases/APCtrialCOX2.
29. Ray WA, Griffin MR, Stein CM. Cardiovascular toxicity of valdecoxib. N Engl J Med 2004; 351: 2767.
30. Weil J, Colin-Jones D, Langman M et al. Prophylactic aspirin and risk of peptic ulcer bleeding. BMJ 1995; 310: 827–30.
31. Goldstein JL, Gibofsky A, Fort JG. Incidence of endoscopic gastroduodenal ulcers in subjects on 325 mg qd of aspirin for cardiovascular prophylaxis with placebo, a COX-2 specific inhibitor, or a nonspecific NSAID: results from a randomized, double-blind, controlled trial [Poster LB14/523]. Presented at the American College of Rheumatology Annual Meeting, Orlando, USA, 23–28 October 2003.
32. Thitiphuree, S. & N. J. Talley: Esomeprazole, a new proton pump inhibitor: pharmacological characteristics and clinical efficacy. Int. J. Clin. Pract. 2000, 54, 537–541.
33. Sachs, G., J. Shin, C. Briving, B. Wallmark & S. Hersey: The pharmacology of the gastric acid pump: the H+,K+ ATPase. Annu. Rev. Pharmacol. Toxicol. 1995, 35, 277–305.
34. Erlandsson, P., R. Isaksson, P. Lorentzon & P. Lindberg: Resolution of the enantiomers of omeprazole and some of its analogues by liquid chromatography on a trisphenylcarbamoylcellulose-based stationary phase. The effect of the enantiomers of omeprazole on gastric glands. J. Chromatogr. 1990, 532, 305–319.
35. Besancon, M., A. Simon, G. Sachs & J. Shin: Sites of reaction of the gastric H, K-ATPase with extracytoplasmic thiol reagents. J. Biol. Chem. 1997, 272, 22438–22446.
36. Kromer, W., S. Horbach & R. Lühmann: Relative efficacies of gastrin proton pump imhibitors: Their clinical and pharmacological basis. Pharmacology 1999, 59, 57–77.
37. Kromer, W., U. Krüger, R. Huber, M. Hartmann & V. W. Steinijans: Differences in pH-dependent activation rates of substituted benzimidazoles and biological in vitro correlates. Pharmacology 1998, 56, 57–70.
38. Yasuda, S., A. Ohnishi, T. Ogawa, Y. Tomono, J. Hasegawa, H. Nakai, Y. Shimamura & N. Morishita: Pharmacokinetic properties of E3810, a new proton pump inhibitor, in healthy male volunteers. Int. J. Clin. Pharmacol. Therap. 1994, 32, 466–473.
39. Kahrilas, P. J., G. W. Falk, D. A. Johnson, C. Schmitt, D. W. Collins, J. Whipple, D. D'Amico, B. Hamelin & B. Joelsson: Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. Aliment. Pharmacol. Therap. 2000, 14, 1249–1258.
40. Bochenek, W., D. Miska & M. Beg: Efficacy of pantoprazole in reflux erosive esophagitis (EE) is dose related. Digestion 1998, 59 (suppl. 3), 601.
41. Earnest, D. L., E. Dorsch, J. Jones, D. E. Jennings & P. A. Greski-Rose: A placebo-controlled dose-ranging study of lansoprazole in the management of reflux esophagitis. Amer. J. Gastroenterol. 1998, 93, 238–243.

42. Seensalu, R., M. Iwarzon, I. Janczewska, B. Hammarlund, A. Oksanen & M. Sagar: Dose-response comparison of lansoprazole and omeprazole on 24-hour gastric acidity and plasma gastrin in healthy volunteers. Gastroenterology 1995, 108 (suppl.), A215.
43. Dekkers, C. P. M., J. A. Beker, B. Thjodleifsson, A. Gabryelewicz, N. E. Bell, T. J. Humphries & E. R. S. Group: Double-blind, placebo-controlled comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of erosive or ulcerative gastro-osesofageal reflux disease. Aliment. Pharmacol. Therap. 1999, 13, 49–57.
44. Williams, M. P., J. Secombe, M. I. Hamilton & R. E. Pounder: A placebo-controlled trial to assess the effects of 8 days of dosing with rabeprazole versus omeprazole on 24-h intragastric acidity and plasma gastrin concentrations in young healthy male subjects. Aliment. Pharmacol. Therap. 1998, 12, 1079–1089.
45. Graham DY, Agrawal NM, Campbell DR et al. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: results of a double-blind randomized, multicenter, active- and placebo-controlled study of misoprostol vs lansoprazole. Arch Intern Med 2002; 162: 169–75.
46. Chan FK, Sung JJ, Ching JY et al. Randomized trial of low-dose misoprostol and naproxen vs nabumetone to prevent recurrent upper gastrointestinal hemorrhage in users of non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther 2001; 15: 19–24.
47. Hawkey CJ, Karrasch JA, Szczepanski L et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. N Engl J Med 1998; 338: 727–34.
48. Agrawal NM, Van KE, Erhardt LJ, Geis GS. Misoprostol co-administered with diclofenac for prevention of gastroduodenal ulcers. A one-year study. Dig Dis Sci 1995; 40: 1125–31.
49. Raskin JB, White RH, Jackson JE et al. Misoprostol dosage in the prevention of nonsteroidal anti-inflammatory drug-induced gastric and duodenal ulcers: a comparison of three regimens. Ann Intern Med 1995; 123: 344–50.
50. Rostom A, Dube C, Wells G et al. Prevention of NSAID-induced gastroduodenal ulcers (Cochrane Review). In: The Cochrane Library Issue 2. Oxford: Update Software, 2003.
51. Taha AS, Hudson N, Hawkey CJ et al. Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal anti-inflammatory drugs. N Engl J Med 1996; 334: 1435–9.
52. Simon B, Muller P. Nizatidine in therapy and prevention of non-steroidal anti-inflammatory drug-induced gastroduodenal ulcer in rheumatic patients. Scand J Gastroenterol 1994; 206: 25–8.
53. Levine LR, Cloud ML, Enas NH. Nizatidine prevents peptic ulceration in high-risk patients taking nonsteroidal anti-inflammatory drugs. Arch Intern Med 1993; 153: 2449–54.
54. Swift GL, Heneghan M, Williams GT et al. Effect of ranitidine on gastroduodenal mucosal damage in patients on long-term non-steroidal anti-inflammatory drugs. Digestion 1989; 44: 86–94.

55. Ehsanullah RSB, Page MC, Tildesley G et al. Prevention of gastroduodenal damage induced by non-steroidal anti-inflammatory drugs: controlled trial of ranitidine. BMJ 1988; 297: 1017– 21.