Mod Rheumatol (2000) 10:2–7

REVIEW ARTICLE

David Y. Graham

NSAID ulcers: prevalence and prevention

Received: October 9, 1999

Abstract The epidemic of life-threatening complications of nonsteroidal anti-inflammatory drug (NSAID) use has prompted the development of prevention strategies. Recent clinical trials of endoscopic ulcer prevention are critiqued regarding their results in relation to doses and outcome measures as well as *H. pylori* status. Misoprostol is the only agent proven to prevent life-threatening ulcer complication in NSAID users. Proton pump inhibitor therapy was not significantly better than the minimally effective dose of misoprostol for prevention of gastroduodenal ulcers in chronic NSAID users, and was significantly inferior to misoprostol in those with "true" NSAID ulcers (i.e., without complicating *H. pylori* infection). Antisecretory therapy accelerates corpus gastritis in those with *H. pylori* infection, suggesting it is prudent to consider *H. pylori* eradication in those in whom long term co-therapy with anti-secretory therapy is contemplated. *H. pylori* status is a critical variable with regard to endoscopic ulcers in NSAID users. The data suggest that if full-dose misoprostol cannot be given, the combination of an antisecretory drug (e.g., either ranitidine or omeprazole) plus low-dose misoprostol may be better than either alone for the prevention of NSAID ulcer complications. The use of omeprazole alone likely results in a false sense of security.

Key words Misoprostol · Omeprazole · Ulcers · Bleeding · Nonsteroidal anti-inflammatory drug

Introduction

The 20th century saw the introduction of aspirin, which ultimately became a worldwide best seller because for the first time, people almost everywhere had a safe and effective drug that would relieve pain. The success of aspirin encouraged the search for new compounds to achieve the same end. As a result, the second half of the 20th century saw the introduction of a host of new nonsteroidal, anti-inflammatory drugs (NSAIDs). More than 30 million people consume NSAIDs each day worldwide.[1] In 1991, more than 70 million prescriptions for NSAIDs were filled in the United States. The per capita consumption of NSAIDs averaged 278 prescriptions per 1000 population, with ibuprofen and naproxen being prescribed most commonly.[2] The actual use of NSAIDs is higher than the volume of NSAID prescriptions because it also includes over-the-counter use of aspirin or other NSAIDs such as ibuprofen. The number of over-the-counter NSAID tablets sold annually in the USA is estimated as more than 30 000 000 000.[3]

By the 1930s there was concern about the potential for gastrointestinal side-effects associated with aspirin. This concern eventually became the basis for marketing strategies designed to show that new NSAIDs were safer, or better tolerated, than existing NSAIDs or aspirin. Several studies have shown that the risk of developing a serious, life-threatening ulcer complication is in the range 1.2%–2% of a population of NSAID users per year of use.[3,4–6] Recent evidence suggests that 10%–20% of those over age 65 have a current or recent prescription for an NSAID.[7] The increasing evidence for NSAID-induced gastrointestinal complications culminated in 1987 when the United States Food and Drug Administration provided class labeling suggesting that the odds of a serious gastrointestinal event was in the range 2%–4% per year of drug use.

Because this class of drugs provides tremendous benefits, one focus of research has been on how to reduce risk while maintaining benefits. Many of the initial questions have been addressed, such as: What are the best surrogate markers that identify patients at increased risk? Is there a drug class or an individual drug that is safer than another? What are the characteristics that help one identify a safer drug? Can the untoward gastrointestinal events be prevented by the co-administration of anti-secretory therapy such as an

D.Y. Graham (✉)
Rm 3A-320 (111D), Veterans Affairs Medical Center, 2002 Holcombe Blvd., Houston, TX 77030, USA
Tel. +1-713-795-0232; Fax +1-713-790-1040
e-mail: dgraham@bcm.tmc.edu

H_2-receptor antagonist or proton pump inhibitor (PPI)? Can they be prevented by replacement of the prostaglandins whose synthesis is inhibited by the nonsteroidal anti-inflammatory drug?

Causes of peptic ulcer

We now recognize three major categories of causation for chronic ulcer disease: *H. pylori* infection, NSAID use, and pathologic hypersecretory states such as the Zollinger–Ellison syndrome. The NSAID ulcer is becoming the most common ulcer in the USA, and is responsible for much of the current ulcer morbidity and mortality.

What are the best surrogate markers that identify patients at increased risk?

Factors associated with increased risk include advanced age, major co-morbid disease, concurrent steroid use, anti-coagulant use, past history of ulcer, ulcer hemorrhage, or ulcer complications.[5,6,8–11] The risk of bleeding is highest with current use, lower with recent use, and least with past use.[12–15] The risk is higher when two or more NSAIDs are used.[12,16] It is also dose-related.[5,12,13,16–21] It may be higher in the first month of use, but this slight increase is overwhelmed by the continuing risk, which remains at a constant rate thereafter.[13,22]

Is there a drug class, individual drug, or class of drugs that is safer than others?

There is no evidence to suggest that any class of traditional NSAIDs is safer than another.[15,23,24] The route of administration is also not important, as the frequency of ulcers is similar with oral, parenteral, or rectal NSAID administration.[23–27] Prodrugs are no better than conventional NSAIDs, and even administration as enteric coated microbeads does not reduce the frequency of ulcers.[27] It has been known for some time that the acute mucosal damage (or lack of it) seen in short-term endoscopic studies does not provide valid predictive information that could be used to rank NSAIDs in relation to safety, and that in general all NSAIDs appear similar in relation to gastrointestinal complications.[3,23]

The prevailing opinion is that ulcers and ulcer complications are related to the systemic effects of NSAIDs on prostaglandin synthesis by the cyclooxygenase-1 pathway (COX-1). Untoward events are dose-related, and may relate best to the degree of COX-1 inhibition (Fig. 1).[17,28–30]

The recent ability to produce selective COX-2 inhibitors has helped us to understand why some drugs appeared safer than others (e.g., ibuprofen, nabumetone, etodolac). For example, comparative studies have almost invariably reported that ibuprofen is one of the safest NSAIDs.[12,16,31,32] A recent study has shed light on why this occurs, and points out one of the fallacies of doing comparative studies without knowing why a particular drug was chosen. For example, ibuprofen was most likely to be given to patients with mild disease requiring intermittent therapy, whereas patients with serious inflammatory conditions were much more likely to receive a drug with high COX-1 activity such as piroxicam. When patients taking ibuprofen were investigated they were found to be younger, taking fewer other medications, have a lower frequency of arthritis, fewer medical visits, and a more occasional pattern of use than those taking the more traditional anti-inflammatory drugs.[33] These data further confirm the hypothesis that increased COX-1 inhibition equates with increased complications.

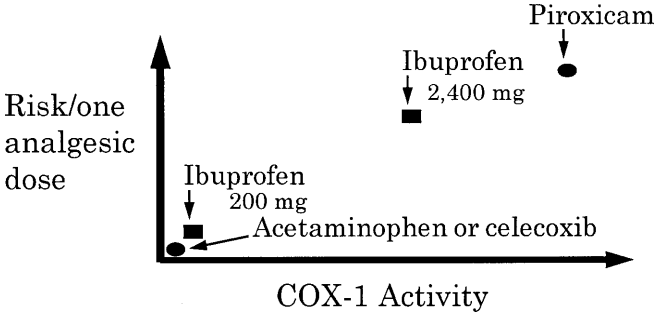

Fig. 1. Illustration of the concept of risk of a major gastrointestinal adverse event in relation to the risk of one analgesic dose. Acetaminophen has no COX-1 or COX-2 activity and can be considered an analgesic. Celecoxib is a selective COX-2 inhibitor with no COX-1 activity. A 200-mg dose of ibuprofen has minimal anti-inflammatory activity but excellent analgesic properties. In contrast, piroxicam has analgesic properties only at high levels of COX-1 inhibition. Increasing the dose of ibuprofen increases its level of COX-1 inhibition and risk without a proportional increase in analgesia

Can gastrointestinal complications be prevented by replacement of the prostaglandins whose synthesis is inhibited by the nonsteroidal anti-inflammatory drug?

It has repeatedly been confirmed that misoprostol co-therapy will reduce the frequency of gastric and duodenal ulcers in NSAID users.[34,35] Misoprostol was also shown to be superior to sucralfate or ranitidine.[36,37] Studies with H_2-receptor antagonists and antacids have found no reduction in risk for patients receiving chronic NSAID therapy, which further supports the conclusions of the various misoprostol trials.[38,39] The recent misoprostol ulcer complication prevention (MUCOSA) study provided the first strong indication that co-therapy with misoprostol would not only reduce the frequency of ulcers in NSAID users, but could also reduce the risk of ulcer complications.[6]

Misoprostol is as effective in suppressing acid as cimetidine; 200 μg misoprostol yields an approximately equivalent suppression as 300 mg cimetidine. One would expect that the beneficial effects of misoprostol in the stomach would also be evident in the duodenum, and this hy-

pothesis has now been proven. Diarrhea, a pharmacologic effect of prostaglandins, has been the side-effect reported most frequently following therapy with misoprostol. Most episodes of diarrhea are not severe and are transient. The frequency of diarrhea can be reduced, and usually prevented, by starting misoprostol at a lower dose (e.g., 100 μg bid or q.i.d.) and gradually increasing the dose.

Can gastrointestinal complications of NSAID therapy be prevented by the co-administration of anti-secretory therapy such as an H_2-receptor antagonist or proton pump inhibitor?

The NSAID ulcer prevention story has been complicated by study design and by the reporting of the data. An ideal study would compare the test agent (e.g., a PPI) with misoprostol and possibly with a placebo, with the primary analysis restricted to true NSAID ulcerations (i.e., *H. pylori*-negative patients). The results of such a study would allow one to put the new drug into perspective, so that the clinician would have a reasonable idea of what to expect. Unfortunately, no such study is available. Direct comparisons of misoprostol with ranitidine have shown misoprostol to be superior (see above).[36] Recent studies have shown that high-dose famotidine[40] was superior to a placebo in preventing NSAID ulcers, but the effect was not impressive (e.g., 26% gastric ulcer recurrence within 26 weeks).[40,41] However, long-term follow up of patients after healing of true NSAID ulcers with famotidine failed to demonstrate a benefit compared to a placebo (i.e., 23.8% recurrence with a placebo vs. 21.4% with famotidine).[42,43] Omeprazole has been compared with misoprostol for both the healing of true NSAID ulcers and the prevention of relapse.[44] The ulcer-healing trial used full-dose misoprostol (800 μg) and two doses of omeprazole (20 and 40 mg). Surprisingly, misoprostol and omeprazole proved equivalent for gastric ulcer healing; there was no added benefit associated with doubling the dose of omeprazole. Direct comparisons with omeprazole showed no dose response for omeprazole as far as ulcer healing was concerned.

Approximately equivalent ulcer prevention was obtained with 20 mg omeprazole as with low-dose misoprostol.[45] That study was continued in order to examine the effect of co-therapy on ulcer relapse. Full-dose omeprazole was continued, but the dose of misoprostol was reduced to the lowest effective dose (400 μg daily) which, incidentally, is less than the average dose used in the large MUCOSA trial which demonstrated the reduction of gastrointestinal complications with NSAID use.[6] Importantly, a large clinical trial compared misoprostol (400, 600, or 800 μg per day) and a placebo for the prevention of ulcers in NSAID users. As shown above, the frequency of gastric ulcer was 8.1%, 3.9%, and 4%, for 400, 600, or 800 μg misoprostol per day, respectively, and 15.7% with a placebo.[46] All the doses of misoprostol were superior to the placebo, and both the 600 and 800 μg per day doses were significantly better than the 400 μg per day dose. The omeprazole vs. misoprostol or vs.

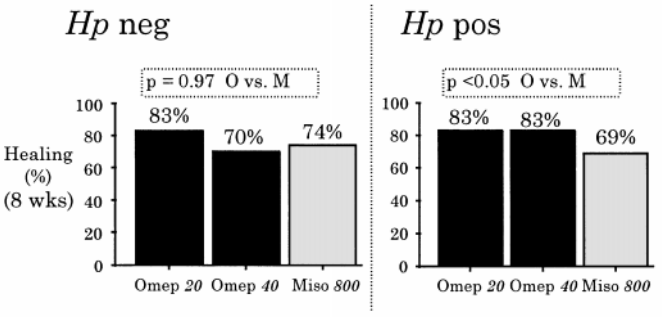

Fig. 2. The lack of a dose response with omeprazole on ulcer healing in NSAID users and the equivalence of misoprostol. Misoprostol was similar to omeprazole in patients with ulcers not complicated by *H. pylori* infection. Data from[45]

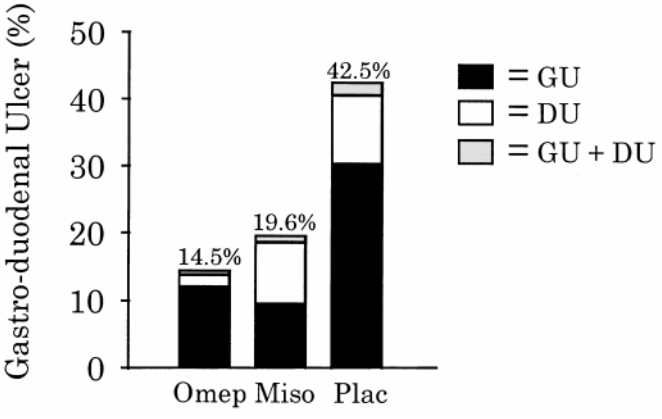

Fig. 3. The effect of 20 mg omeprazole, 400 μg misoprostol, or a placebo on relapse of gastroduodenal ulcers irrespective of *H. pylori* status. There was no significant difference between omeprazole and misoprostol ($P = 0.142$), with both being superior to the placebo. Data from.[45] *GU*, gastric ulcer; *DU*, duodenal ulcer

ranitidine comparisons used either the minimal effective dose of misoprostol (400 μg per day) or a proven ineffective dose of ranitidine (300 mg per day).[44,45] Therefore, these omeprazole comparative studies met one of the criteria Trish Greenhalgh suggested in her "tips for the pharmaceutical industry to present data in the best light" (i.e., "If you must compare it with a competitor, make sure that the latter is given at subtherapeutic doses").[47]

Although omeprazole was better tolerated than misoprostol, the rate of relapse of true NSAID gastric ulcers was essentially identical with omeprazole and the minimally effective dose of misoprostol.[45] Overall, omeprazole was not superior to the minimally effective dose of misoprostol in the prevention of gastroduodenal ulcer relapse (Fig. 2). Possibly unexpectedly, even the highest dose of omeprazole was not superior to the lowest effective dose of misoprostol in the healing of gastric ulcers in uncomplicated (e.g., *H. pylori*-negative) NSAID users (Fig. 3).

In the *H. pylori*-negative patients, low-dose misoprostol was actually superior to omeprazole (recurrence rate 8.2 vs.

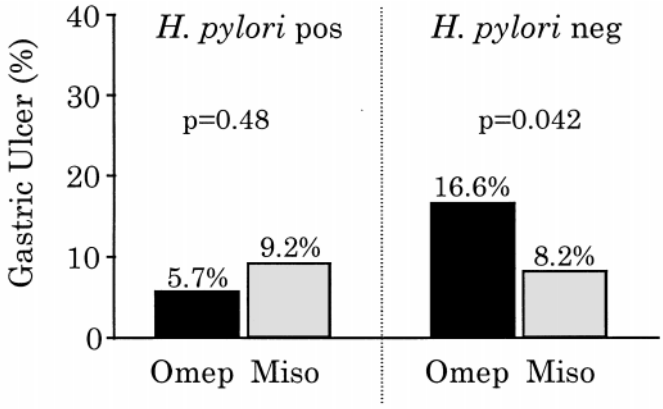

Fig. 4. Comparison of 20 mg omeprazole or 400 μg misoprostol on development of gastric ulcers in chronic NSAID users in relation to *H. pylori* status. Gastric ulcers were significantly less likely with misoprostol in those without complicating *H. pylori* infection. The results were similar to those for omeprazole in patients with *H. pylori* infection. The data regarding *H. pylori* status from[45] were kindly supplied by AstraZeneca, Molndal, Sweden

16.6 for misoprostol vs. omeprazole, respectively) ($P < 0.05$) for the prevention of gastric ulcer relapse, with no significant difference between the drugs with regard to duodenal ulcer relapse[45] (Fig. 4).

The addition of the irrelevant end point heartburn, which is unrelated to the important outcomes of the study, and its inclusion as a critical component of "success," was largely responsible for omeprazole appearing to be superior to misoprostol.[45] The usefulness of the omeprazole, misoprostol, and ranitidine comparative trials suffered greatly from a choice of comparators that were minimally effective or subtherapeutic, and from using surrogate end points unrelated to the important outcomes as part of the determinants used to define "success."

Overall, one can conclude that PPI therapy is useful in both respects and appears equal to full-dose misoprostol for ulcer healing, and to the lowest effective dose of misoprostol for prevention of NSAID ulcers. It is not known whether the benefits would also translate into a lower rate of ulcer complications, especially since the dose of misoprostol was less than that used in the MUCOSA trial.[6] The cost of co-therapy with a PPI is much greater than with misoprostol, and it would seem prudent to consider PPI therapy as an alternative to misoprostol in patients who are unable to take misoprostol to prevent NSAID ulcers. There appears to be no reason to give more than 20 mg omeprazole, or its equivalent, for this indication.

Is there a role for *H. pylori* eradication in the prevention of NSAID ulcers or ulcer relapse?

H. pylori infection is commonly seen in patients with peptic ulcers caused by nonsteroidal anti-inflammatory drugs, but the pathogenetic role of *H. pylori* in these patients is unclear.[35] There are conflicting data about whether *H. pylori* therapy will reduce the rate of ulcer formation among NSAID users. One study from Hong Kong used 100 randomly assigned eligible patients who were scheduled to receive NSAIDs to receive or not to receive anti-*H. pylori* therapy.[48] Ninety-two patients completed the trial (47 in the naproxen group, 45 in the triple-therapy group). At 8 weeks there were 12 patients (26%) with persistent *H. pylori* infection, but only one patient (3%) with successful *H. pylori* eradication developed ulcers with naproxen ($P = 0.002$), suggesting that eradication of *H. pylori* before NSAID therapy reduces the occurrence of NSAID-induced peptic ulcers. The study was unique in that it evaluated patients who were not regular users of NSAIDs, and more studies of similar design are needed.

Cure of *H. pylori* infection was shown to be associated with a slight delay in gastric ulcer healing using omeprazole in chronic NSAID users.[49] These results can probably be explained by considering what is known of the biology of *H. pylori* infection. Cure of *H. pylori* infection in patients with corpus gastritis both increases acid secretion and makes omeprazole less effective as an acid suppressant.[50–53] One would expect that cure of the *H. pylori* infection would produce a bias against omeprazole by reducing its effectiveness and thus slowing the rate of ulcer healing. Corpus gastritis is associated with multifocal atrophic gastritis, which is associated with a marked increase in the risk of gastric cancer.[52,54] The slight delay in the healing of ulcers in NSAID users should not be interpreted as a reason for not treating the infection. The data do not contradict the guidelines proposed by the NIH consensus panel to treat *H. pylori* infection in all patients with peptic ulcers irrespective of whether the condition was possibly complicated by NSAID use. The *H. pylori* story has continued to be plagued by suggestions based on phenomenology independent of the biology.

Examination of the frequency and type of ulcer recurrence in the placebo group in the large omeprazole NSAID ulcer prevention trial should give some inkling of what differences might be expected in relation to *H. pylori* status. The frequency of gastric ulcer was similar ($P = 0.597$ for *H. pylori*-positive vs. *H. pylori*-negative individuals). In contrast, duodenal ulcer was significantly more frequent in those with *H. pylori* infection (18.5% vs. 4.6% for *H. pylori*-positive vs. *H. pylori*-negative, respectively) ($P = 0.017$). While it is not clear that cure of the infection would lead to such a reduction in the frequency of duodenal ulcer, these results provide additional data supporting eradication of *H. pylori* in NSAID users.

It is now clear that long-term use of anti-secretory therapy may have untoward effects on the gastric mucosa in *H. pylori*-infected individuals. There are now sufficient data to support the hypothesis that chronic therapy with PPIs or H_2-receptor antagonists is associated with a rapid worsening of the degree of corpus gastritis in patients having *H. pylori* infection therapy.[55–60] While the full implications of these observations remain unclear, acceleration of corpus gastritis may hasten the development of the gastric cancer phenotype of gastritis, and should be avoided if possible. If

chronic anti-secretory therapy is contemplated in *H. pylori*-infected NSAID users, it may be prudent to consider eradication therapy.

Cyclooxygenase-1 or cyclooxygenase-2 inhibition

Selective COX-2 inhibitors have now been released, and clinical experience with them will surely prove whether they live up to their promise. The available clinical data are consistent with the hypothesis that this new class of drugs will live up to the promise of providing anti-inflammatory and analgesic activity with markedly less gastrointestinal toxicity. A selective COX-2 inhibitor is one that has no measurable COX-1 activity at full therapeutic anti-inflammatory doses. There are a number of drugs that have greater COX-2 than COX-1 inhibition, but they exhibit significant COX-1 inhibition when used at therapeutic doses. In many areas of the world these drugs are represented as COX-2 inhibitors. This form of marketing has defined a new class of drugs with "preferential COX-2 selectivity," which I call "COX-2 impostors."[61] If the truly selective COX-2 inhibitors live up to their promise, I predict that we will rapidly see a marked reduction in the use of traditional NSAIDs and a marked reduction in the number of patients experiencing major NSAID-induced gastrointestinal complications.

Acknowledgments The author thanks Jorgen Naesdal, AstraZeneca, Molndal, Sweden, for providing data from the the ASTRONAUT and OMMIUM ulcer prevention trials in relation to *H. pylori* status.[44,45]

References

1. Baum C, Kennedy DL, Forbes MB. Utilization of nonsteroidal antiinflammatory drugs. Arthritis Rheum 1985;28:686–92.
2. Anti-arthritic medication usage: United States, 1991. Stat Bull Metrop Insur Co. 1992;73:25–34.
3. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med 1999;340: 1888–99.
4. Fries JF. NSAID gastropathy: the second most deadly rheumatic disease? Epidemiology and risk appraisal. J Rheumatol Suppl 1991;28:6–10.
5. Fries JF. Assessing and understanding patient risk. Scand J Rheumatol Suppl 1992;92:21–4.
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 randomized, double-blind, placebo-controlled trial. Ann Intern Med 1995;123:241–9.
7. Griffin MR. Epidemiology of nonsteroidal anti-inflammatory drug-associated gastrointestinal injury. Am J Med 1998;104:23S–29S.
8. Agrawal N. Risk factors for gastrointestinal ulcers caused by nonsteroidal anti-inflammatory drugs (NSAIDs) [published erratum appears in J Fam Pract 1991 Jul;33(1):16]. J Fam Pract 1991;32:619–24.
9. Fries JF, Williams CA, Bloch DA, et al. Nonsteroidal anti-inflammatory drug-associated gastropathy: incidence and risk factor models. Am J Med 1991;91:213–22.
10. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. Ann Intern Med 1991; 115:787–96.
11. Shorr RI, Ray WA, Daugherty JR, et al. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. Arch Intern Med 1993;153:1665–70.
12. Garcia Rodriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs [published erratum appears in Lancet 1994 Apr 23;343(8904):1048]. Lancet 1994;343:769–72.
13. Griffin MR, Piper JM, Daugherty JR, et al. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. Ann Intern Med 1991;114:257–63.
14. Garcia Rodriguez LA, Walker AM, Perez Gutthann S. Nonsteroidal antiinflammatory drugs and gastrointestinal hospitalizations in Saskatchewan: a cohort study. Epidemiology 1992;3:337–42.
15. Lanza LL, Walker AM, Bortnichak EA, et al. Peptic ulcer and gastrointestinal hemorrhage associated with nonsteroidal anti-inflammatory drug use in patients younger than 65 years. A large health maintenance organization cohort study. Arch Intern Med 1995;155:1371–7.
16. Henry D, Lim LL, Garcia Rodriguez LA, et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. BMJ 1996;312:1563–6.
17. Graham DY, Smith JL. Aspirin and the stomach. Ann Intern Med 1986;104:390–8.
18. Hochain P, Berkelmans I, Czernichow P, et al. Which patients taking non-aspirin non-steroidal anti-inflammatory drugs bleed? A case-control study. Eur J Gastroenterol Hepatol 1995;7:419–26.
19. Simon LS, Goodman T. NSAID-induced gastrointestinal toxicity. Bull Rheum Dis 1995;44:1–5.
20. Langman MJ, Weil J, Wainwright P, et al. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs [published erratum appears in Lancet 1994 May 21;343(8908):1302]. Lancet 1994;343:1075–8.
21. Roderick PJ, Wilkes HC, Meade TW. The gastrointestinal toxicity of aspirin: an overview of randomised controlled trials. Br J Clin Pharmacol 1993;35:219–26.
22. Smalley WE, Ray WA, Daugherty JR, et al. Nonsteroidal anti-inflammatory drugs and the incidence of hospitalizations for peptic ulcer disease in elderly persons. Am J Epidemiol 1995;141:539–45.
23. Graham DY. Prevention of gastroduodenal injury induced by chronic nonsteroidal antiinflammatory drug therapy. Gastroenterology 1989;96:675–81.
24. Nobunga M, Graham DY, Saito T, et al. NSAID-induced gastrointestinal damage and its management. J Rheumatol (Ryumachika) 1993;9:279–92.
25. Graham DY, Smith JL. Effects of aspirin and an aspirin–acetaminophen combination on the gastric mucosa in normal subjects. A double-blind endoscopic study. Gastroenterology 1985;88: 1922–5.
26. Swift GL, Arnold J, Williams GT, et al. A comparison of upper gastrointestinal mucosal damage by standard and delayed-release indomethacin. Aliment Pharmacol Ther 1992;6:717–25.
27. Collins AJ, Davies J, Dixon AS. A prospective endoscopic study of the effect of Orudis and Oruvail on the upper gastrointestinal tract, in patients with osteoarthritis. Br J Rheumatol 1988;27:106–109.
28. Graham DY. Clinical aspects of the protective effects of prostaglandins on non-steroidal anti-inflammatory drug-associated mucosal injury. In: Domschke W, Dannann HG, Peskar BM, et al. editors. Prostaglandins and leukotrienes in gastrointestinal diseases. Berlin: Springer-Verlag; 1988. p. 161–7.
29. Cooper SA. New peripherally acting oral analgesic agents. Annu Rev Pharmacol Toxicol 1983;23:617–47.
30. Brogden RN, Heel RC, Speight TM, et al. Piroxicam: a review of its pharmacological properties and therapeutic efficacy. Drugs 1981;22:165–87.
31. Trewin VF, Lawrence CJ, Rae SA, et al. Development and use of a gastropathy index for ranking the safety of non-steroidal anti-inflammatory drugs in the elderly. J Clin Pharm Ther 1994;19:209–14.
32. Henry D, Dobson A, Turner C. Variability in the risk of major gastrointestinal complications from nonaspirin nonsteroidal anti-inflammatory drugs. Gastroenterology 1993;105:1078–88.

33. LeLorier J. Patterns of prescription of nonsteroidal antiinflammatory drugs and gastroprotective agents. J Rheumatol Suppl 1995;43:26–7.
34. Agrawal NM, Aziz K. Prevention of gastrointestinal complications associated with nonsteroidal antiinflammatory drugs. J Rheumatol Suppl 1998;51:17–20.
35. Graham DY. Nonsteroidal anti-inflammatory drugs, *Helicobacter pylori*, and ulcers: where we stand. Am J Gastroenterol 1996;91: 2080–6.
36. Raskin JB, White RH, Jaszewski R, et al. Misoprostol and ranitidine in the prevention of NSAID-induced ulcers: a prospective, double-blind, multicenter study. Am J Gastroenterol 1996;91: 223–7.
37. Agrawal NM, Roth S, Graham DY, et al. Misoprostol compared with sucralfate in the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcer. A randomized, controlled trial. Ann Intern Med 1991;115:195–200.
38. 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.
39. Gunshefski L, Flancbaum L, Brolin RE, et al. Changing patterns in perforated peptic ulcer disease. Am Surg 1990;56:270–4.
40. Taha AS, Hudson N, Hawkey CJ, et al. Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs. N Engl J Med 1996;334:1435–9.
41. Hudson N, Taha AS, Russell RI, et al. Famotidine for healing and maintenance in nonsteroidal anti-inflammatory drug-associated gastroduodenal ulceration. Gastroenterology 1997;112:1817–22.
42. NSAIDs and peptic ulcers [letter]. BMJ 1990;300:814–16.
43. Graham DY. High-dose famotidine for prevention of NSAID ulcers? Gastroenterology 1997;112:2143–5.
44. Yeomans ND, Tulassay Z, Juhasz L, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. Acid suppression trial: ranitidine versus omeprazole for NSAID-associated ulcer treatment (ASTRONAUT) study group. N Engl J Med 1998;338:719–26.
45. Hawkey CJ, Karrasch JA, Szczepanski L, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. Omeprazole versus misoprostol for NSAID-induced ulcer management (OMNIUM) study group. N Engl J Med 1998;338:727–34.
46. 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.
47. Greenhalgh T. How to read a paper. The basics of evidence-based medicine London: BMJ Publishing Group; 1997.
48. Chan FK, Sung JJ, Chung SC, et al. Randomised trial of eradication of *Helicobacter pylori* before non-steroidal anti-inflammatory drug therapy to prevent peptic ulcers. Lancet 1997;350:975–9.
49. 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. Helicobacter eradication for lesion prevention. Lancet 1998;352: 1016–21.
50. Gutierrez O, Melo M, Segura AM, et al. Cure of *Helicobacter pylori* infection improves gastric acid secretion in patients with corpus gastritis. Scand J Gastroenterol 1997;32:664–8.
51. El-Omar EM, Oien K, El-Nujumi A, et al. *Helicobacter pylori* infection and chronic gastric acid hyposecretion. Gastroenterology 1997;113:15–24.
52. Miehlke S, Hackelsberger A, Meining A, et al. Severe expression of corpus gastritis is characteristic in gastric cancer patients infected with *Helicobacter pylori*. Br J Cancer 1998;78:263–6.
53. Labenz J, Tillenburg B, Peitz U, et al. *Helicobacter pylori* augments the pH-increasing effect of omeprazole in patients with duodenal ulcer. Gastroenterology 1996;110:725–32.
54. Sipponen P, Stolte M. Clinical impact of routine biopsies of the gastric antrum and body. Endoscopy 1997;29:671–8.
55. Stolte M, Bethke B. Elimination of *Helicobacter pylori* under treatment with omeprazole. Z Gastroenterol 1990;28:271–4.
56. Klinkenberg-Knol EC, Festen HP, Jansen JB, et al. Long-term treatment with omeprazole for refractory reflux esophagitis: efficacy and safety. Ann Intern Med 1994;121:161–7.
57. Lamberts R, Creutzfeldt W, Struber HG, et al. Long-term omeprazole therapy in peptic ulcer disease: gastrin, endocrine cell growth, and gastritis. Gastroenterology 1993;104:1356–70.
58. Meining A, Kiel G, Stolte M. Changes in *Helicobacter pylori*-induced gastritis in the antrum and corpus during and after 12 months of treatment with ranitidine and lansoprazole in patients with duodenal ulcer disease. Aliment Pharmacol Ther 1998;12: 735–40.
59. Meining A, Bosseckert H, Caspary WF, et al. H_2-receptor antagonists and antacids have an aggravating effect on *Helicobacter pylori* gastritis in duodenal ulcer patients. Aliment Pharmacol Ther 1997;11:729–34.
60. Kuipers EJ, Lundell L, Klinkenberg-Knol EC, et al. Atrophic gastritis and *Helicobacter pylori* infection in patients with reflux esophagitis treated with omeprazole or fundoplication. N Engl J Med 1996;334:1018–22.
61. Hawkey C, Kahan A, Steinbruck K, et al. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. International MELISSA study group. meloxicam large-scale international study safety assessment. Br J Rheumatol 1998;37:937–45.