

Non-Steroidal Anti-Inflammatory Drug-Induced Gastroduodenal Toxicity and *Helicobacter pylori*

Joram Wardi MD and Haim Shirin MD

Department of Gastroenterology, Wolfson Medical Center, Holon, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Key words: *Helicobacter pylori*, non-steroidal anti-inflammatory drugs, aspirin

IMAJ 2003;5:195–197

Non-steroidal anti-inflammatory drugs including aspirin are commonly prescribed drugs, especially in the elderly. In the United States, aspirin and other NSAIDs were responsible for 60% of all orally used analgetics in the year 2000. It is well documented that the use of these drugs increases the risk for gastroduodenal toxicity. The expense of hospitalizations for gastrointestinal complications comprised about 66% of the total cost of the NSAIDs used [1]. Concomitant medications that were prescribed to prevent gastroduodenal toxicity added to the cost.

Factors increasing the risk of gastrointestinal toxicity due to NSAIDs include: dose and type of NSAID, history of peptic ulcer, age above 60, concomitant use of anticoagulants, other concurrent illnesses such as ischemic heart disease or diabetes mellitus, and longer duration of NSAID exposure. Two large-scale studies showed that cyclooxygenase-2-selective NSAIDs caused fewer upper gastrointestinal events than the non-selective NSAIDs, although they were not free of these side effects [2,3]. Different approaches have been used to minimize NSAID-related toxicity and adverse events. These include the preferential use of non-NSAID analgesics or COX-2 selective inhibitors, prescribing the lowest effective dose, or use of anti-acid co-therapy in case of non-selective NSAIDs.

From the clinical point of view one of the main questions is whether *Helicobacter pylori*-infected patients receiving NSAIDs or aspirin are prone to increased risk of gastroduodenal pathology. In this scenario, eradication of *H. pylori* in these patients could decrease upper GI side effects, suggesting this approach as an alternative to anti-acid therapy.

Mechanism of damage

NSAIDs inhibit gastric prostaglandin synthesis, which is followed by decreased secretion of mucus and bicarbonate and weakening of the mucosal barriers' ability to resist acid injury. Very low doses of aspirin of even 10 mg/day significantly decreased gastric mucosal prostaglandin levels [4] in healthy volunteers. On the other hand, *H. pylori* stimulates an inflammatory cascade that involves secretion of pro-inflammatory cytokines. In addition, there is increasing evidence that bacterial factors such as proteases, ammonia

production and induction of oxidative stress are also important mechanisms leading to epithelial injury in *H. pylori* gastritis.

In models involving the mouse stomach, *H. pylori* infection and/or NSAID treatment increased both COX-1 and COX-2 protein expression. Compared with controls, *H. pylori* increased gastric prostaglandin E₂ levels, neutrophil activity and the degree of chronic inflammation, whereas indomethacin significantly decreased all these effects. *H. pylori* did not potentiate the effects of NSAID treatment on gastric epithelial inflammation or cell turnover [5]. Studies in humans have shown that gastric tissue mucosal prostaglandin synthesis in *H. pylori*-infected patients is also increased, probably due to an increased expression of COX-2 [6]. Several investigators postulated that the antagonistic effect between NSAID and *H. pylori* may be related to the inhibition of *H. pylori*-induced neutrophil reactive oxygen metabolite production by NSAIDs. However, both NSAIDs and *H. pylori* increase paracellular gastric mucosal permeability and expose the mucosa to acid pepsin and other exogenous factors.

Epithelial cell proliferation and apoptosis

Another important component of the host response to *H. pylori* is a chronic hyperproliferative state, in which there is increased cell turnover and also increased epithelial cell apoptosis. Dysregulation in the balance between hyperproliferative response and apoptosis may ultimately be responsible for the pathologic reaction to *H. pylori*, which may, in some individuals, result in the development of peptic ulcer or even gastric neoplasm.

Data from *in vitro*, animal and human studies have shown that in addition to their central effect of inhibition of COX-1 and COX-2 enzymes, NSAIDs inhibit growth by blocking the cell cycle and inducing epithelial cell apoptosis. It is proposed that the combination of increased apoptosis, delayed ulcer healing and decreased prostaglandin production may be involved in the gastroduodenal damage induced by NSAIDs.

Kim et al. [5] demonstrated that NSAIDs can reverse the increased gastric epithelial cell apoptosis and cell proliferation induced by *H. pylori* in mice. Similar results were reported in humans [7]. However, many other studies have demonstrated opposite data, making the interaction between inflammation, epithelial cell proliferation and apoptosis in the *H. pylori*-infected or NSAID-treated stomach very complicated. We hypothesized that NSAIDs do not exacerbate *H. pylori*-related mucosal damage

NSAID = non-steroidal anti-inflammatory drug
COX = cyclooxygenase
GI = gastrointestinal

because they may directly inhibit the growth of *H. pylori*. Preliminary findings from our study indicate that some NSAIDs such as ibuprofen, indomethacin and the sulindac metabolites, sulindac sulfide and sulfone, have substantial inhibitory and bactericidal activity against *H. pylori* at easily achievable therapeutic levels [8].

Clinical studies

Controversy exists regarding the interaction between *H. pylori* and NSAIDs. The numerous studies conducted so far have been difficult to compare because of the heterogeneity of patient groups, the variable outcome measures, and the different diagnostic tests used for *H. pylori*. In recent years, new studies have emerged supporting the significance of *H. pylori* as an important factor in patients treated with aspirin or NSAIDs. Randomized controlled trials have shown that *H. pylori* increases the risk of ulcer complications, especially in NSAID-naïve patients. It has been shown that the risk of ulcer complications is markedly increased during the first few months of NSAID treatment. This may be due to a subgroup of *H. pylori*-positive patients who are more susceptible to peptic ulcer disease, or to the fact that NSAIDs complicate pre-existing ulcers in these patients.

In patients who take NSAIDs regularly, gastric erosions were found in 50% and ulcers in 15–30% of them when endoscopies were performed. However, clinically important upper GI events occurred in only 3–4.5% of the patients [9]. Low dose aspirin that was administered as vascular prophylaxis to cardiac patients resulted in 4.5% hospitalizations due to upper GI bleeding [10]. In another study, involving patients with transient ischemic attacks treated by aspirin 300 mg or 1,200 mg daily, or placebo, the rates of hospitalizations for upper GI bleeding were 0.9% and 2.1% respectively as compared to 0.2% in the placebo group [11]. In a large case-control study, Lanas et al. [12] concluded that *H. pylori* may be an independent risk factor for upper GI bleeding in low dose aspirin users. Moreover Chan et al. [13] compared eradication of *H. pylori* to omeprazole in patients with a history of upper GI bleeding treated with low dose aspirin. Eradication of *H. pylori* was found to be as effective as omeprazole in preventing recurrent upper GI bleeding. In the same study, eradication therapy was also compared to omeprazole in patients treated with naproxen 500 mg twice daily for musculoskeletal disorders. As expected, in this group omeprazole was significantly more effective than eradication of *H. pylori* for prophylaxis of GI bleeding.

Similar results were reported by others [14], showing no difference in gastric events in rheumatic patients with or without *H. pylori*, when treated with long-term NSAIDs and omeprazole. Conversely, in a recent double-blind study, Chan and co-workers [15] eradicated *H. pylori* before starting diclofenac therapy in 51 arthritis patients. The 6 month probability of ulcers was 12.1% vs. 34.4% in the identical 49 arthritis patients group who received omeprazole with placebo antibiotics.

Owing to the contradictory results of the many studies on the interaction between *H. pylori* and NSAIDs, a large meta-analysis was recently undertaken [16]. Twenty-five studies were included, and in 16 studies with 1,625 patients it was found that

uncomplicated peptic ulcer disease was significantly more common in patients positive for *H. pylori* than in those who were negative. In the presence of *H. pylori* infection, use of NSAIDs increased the risk of peptic ulcer disease 3.5-fold. The risk of a bleeding ulcer was slightly higher if the bacterium was present. The bleeding risk was increased 4.8-fold by NSAIDs alone and 6.1-fold by NSAIDs together with *H. pylori*. The conclusion of this meta-analysis was that a synergistic effect between *H. pylori* and NSAIDs exists, which may increase the risk for developing gastroduodenal lesions [16]. However, this meta-analysis was criticized for selection bias because several large clinical trials were not included.

Future directions

Though NSAIDs and *H. pylori* remain the major risk factors for peptic ulcer disease, the importance of these factors may decrease with time. Although the population worldwide is getting older and consuming more NSAIDs, the use of COX-2-selective NSAIDs, and the decreasing prevalence of *H. pylori* in western countries may alter the etiology and characteristics of peptic ulcer disease in the future.

Conclusion

H. pylori and NSAIDs/aspirin are independent risk factors for peptic ulcer and peptic ulcer bleeding. *H. pylori* may have a synergistic effect, increasing the risk for ulcer-related symptoms or bleeding in patients taking NSAIDs. We do not have sufficient data to suggest that eradication is a prerequisite in patients who are at average risk for GI toxicity and take low dose aspirin. However, *H. pylori* eradication prior to NSAIDs in those patients may reduce the incidence of peptic ulcer and concomitant symptoms.

Patients with ulcers, previous ulcer disease, or an increased risk of bleeding ulcer should be tested and treated for *H. pylori*. *H. pylori* eradication might be a useful strategy for the prevention of ulcer complications in elderly patients taking low dose aspirin – possibly comparable to proton pump inhibitor therapy. However, for patients who receive chronic or prolonged course of NSAIDs, acid suppressants remain the optimal therapy.

References

1. Rahme E, Joseph L, Kong SX, Watson KJ, LeLorier J. Gastrointestinal health care resource use and costs associated with nonsteroidal antiinflammatory drugs versus acetaminophen: retrospective cohort study of an elderly population. *Arthritis Rheum* 2000;43:917–24.
2. 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.
3. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs. non-steroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial: Celecoxib Long-Term Arthritis Safety Study. *JAMA* 2000;284:1247–55.
4. Cryer B, Feldman M. Effects of very low dose daily, long-term aspirin therapy on gastric, duodenal and rectal prostaglandin levels and on mucosal injury in healthy humans. *Gastroenterology* 1999;117:17–25.
5. Kim TI, Lee YC, Lee KH, et al. Effects of nonsteroidal anti-inflammatory drugs on *Helicobacter pylori* infected gastric mucosa of mice: apoptosis cell proliferation, and inflammatory activity. *Infect Immun* 2001;69:5056–63.

6. Fu S, Ramanujam KS, Wong A, et al. Increased expression and cellular localization of inducible nitric oxide synthase and cyclooxygenase 2 in *Helicobacter pylori* gastritis. *Gastroenterology* 1999;116:1319–29.
7. Zhu GH, Yang XL, Lai KC, et al. Nonsteroidal anti-inflammatory drugs could reverse *Helicobacter pylori*-induced apoptosis and proliferation in gastric epithelial cells. *Dig Dis Sci* 1998;43:1957–63.
8. Shirin H, Moss SF, Kancherla S, et al. Ability of NSAIDs to suppress *Helicobacter pylori* growth in vitro [Abstract]. *Gastroenterology* 2001;120:A589.
9. Laine L. Approaches to non-steroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology* 2001;120:594–606.
10. Serrano P, Lanas A, Arroyo MT, Ferreira JJ. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. *Aliment Pharmacol Ther* 2002;16:1945–53.
11. Slattery J, Warlow CP, Shorrock CJ, Lamgman MJS. Risks of gastrointestinal bleeding during secondary prevention of vascular events with aspirin: analysis of gastrointestinal bleeding during the UK-TIA trial. *Gut* 1995;37:509–11.
12. Lanas A, Fuentes J, Benito R, Serrano P, Bajador E, Sainz R. *Helicobacter pylori* increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. *Aliment Pharmacol Ther* 2002;16:779–86.
13. Chan FK, Chung SC, Suen BY, et al. Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *N Engl J Med* 2001;344:967–73.
14. 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 anti-inflammatory drugs combined with omeprazole. *J Rheumatol* 2002;29:1975–80.
15. Chan FKL, TO KF, Justin CY, et al. Eradication of *Helicobacter pylori* and risk of peptic ulcers in patients starting long-term treatment with non-steroidal anti-inflammatory drugs: a randomized trial. *Lancet* 2002;359:9–13.
16. Huang J, 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.

Correspondence: Dr. H. Shirin, Dept. of Gastroenterology, Wolfson Medical Center, Holon 58100, Israel.
 Phone: (972-3) 502-8499
 Fax: (972-3) 503-5111
 email: shirin@wolfson.health.gov.il

I am the chip on my own shoulder

Wayne Sleep (1948-), British dancer and choreographer

Capsule

A lack of taste

In 1931, *Science* published the finding that many individuals are unable to taste phenylthiocarbamide. Now, Kim et al. have determined the molecular basis of this trait using single-nucleotide polymorphisms to identify a gene associated with taste insensitivity; it encodes a member of the TAS2R bitter taste

receptor family. The combination of three polymorphisms within inherited units in the population gives rise to the breadth of variation in tasting ability.

Science 2003;299:1221

Capsule

Blocking MS

In multiple sclerosis (MS), lymphocytes and monocytes gain access to the central nervous system by breaking through the blood-brain barrier at sites of inflammation. The trans-endothelial migration and activation of these immune cells depends on the cell surface integrin alpha4beta1/VLA-4. Administration of antibodies against four integrins suppresses disease progression in a mouse model of MS. Miller et al. (*N Engl J Med* 2003;348:15) have extended this promising finding by treating patients suffering from relapsing MS with a humanized monoclonal antibody against four integrins, called natalizumab. In a small, placebo-controlled study, patients treated with this integrin antagonist for 6 months showed a 90% reduction in brain lesion formation and progression. In an

independent study, Cannella et al. (*J Neurosci Res* 2003;71:407) tested a synthetic small-molecule antagonist of VLA-4 called TBC 3486 in the mouse model of MS. Mice given this compound before disease onset showed delayed and reduced demyelination and production of pro-inflammatory cytokines. Even when treatment was terminated, disease severity was reduced for several weeks. However, the drug had little effect when given during the chronic phase of the disease, suggesting that once inflammation and lesions are established, other adhesion molecules may be involved in disease progression. Thus, immune cells bearing the four integrins are likely to be important in MS pathogenesis, and selective inhibition of four integrins may be effective in the clinic.