The Relation Between *Helicobacter pylori* and Nonsteroidal Anti-inflammatory Drugs

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Both infection with *Helicobacter pylori* and use of nonsteroidal anti-inflammatory drugs (NSAIDs) can result in gastritis and ulcers. *H. pylori* has been identified as a major etiologic factor in the development of peptic ulcer disease; however, its relationship to NSAID-associated toxicity is less well characterized. Several studies have suggested that NSAID use does not increase susceptibility to *H. pylori*, and the converse has also been suggested, namely, that *H. pylori* does not exacerbate NSAID-associated injury. *H. pylori* itself may stimulate production of gastric prostaglandins, which may have a role in ulcer healing. More carefully controlled studies may be better able to elucidate the individual and synergistic mechanisms involved in ulceration induced by *H. pylori* and NSAIDs. Recent studies have suggested that elimination of *H. pylori* before NSAID treatment decreases ulcer occurrence. Therefore, at this time, eradication of *H. pylori* should be considered only in certain high-risk patients, i.e., those with a history of gastroduodenal ulcers. *Am J Med.* 1998;105(5A):22S–27S.

Gastrointestinal (GI) ulceration and its resulting complications have long been associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs). With an increase in the availability and use of these drugs, NSAID-associated gastropathy has become a significant source of morbidity and mortality, and its treatment has become a major economic concern. In attempts to quantitate and characterize the scale of the problem, many epidemiologic studies have identified factors that increase the risk of these events. In nearly all studies, increasing age has been shown to be a significant risk factor.[1,2] With nearly half of the NSAIDs being prescribed for persons >60 years of age, there is significant risk of toxicity in this population.

Identification of *Helicobacter pylori* as the primary etiologic factor in the development of peptic ulcer disease and the observation that the incidence of *H. pylori* also increases with age[3] have raised the question of a possible synergistic relation between the presence of *H. pylori* infection and NSAID use in the development of gastropathy.

Despite numerous studies, this question has not yet been satisfactorily resolved; a brief survey of the literature will show that the data are not particularly convincing for or against this hypothesis. Since half of all NSAID prescriptions are for a population not only considered at increased risk for NSAID-associated gastropathy but who also have >60% prevalence of *H. pylori*, it is not clear if the individual effects of the 2 variables can in fact be distinguished.

CONFOUNDING FACTORS IN *H. PYLORI*–NSAID STUDIES

When considering the studies that have analyzed the relation between *H. pylori* and NSAID-induced gastropathy, it becomes clear that there are many factors that have not been—and in some cases could not have been—controlled that may significantly affect the outcome.

The use of one particular NSAID may convey a different risk factor than does another NSAID; several studies have determined that the various NSAIDs have different relative risks for GI complications that in some cases may be dose dependent.[4] The toxicity of an NSAID seems to be related to its ability to inhibit cyclo-oxygenase-1 (COX-1) compared with its ability to inhibit cyclo-oxygenase-2 (COX-2), as indicated by the observation that the increase in the relative risk of individual NSAIDs in a

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meta-analysis[4] parallels the increase in potency against COX-1.[5]

In addition, specific host factors, other than age, may contribute to outcome but have not often been considered. An example is the decrease in gastric and duodenal mucosal blood flow that occurs during NSAID use, which may be exacerbated by factors such as smoking and *H. pylori*; these latter factors, however, alter mucosal blood flow in the absence of NSAID use.[6]

For *H. pylori*, specific gene expression results in variability in the pathogenicity of various strains.[7,8] In clinical trials, there is usually no characterization of the strains with respect to this pathogenicity. Consequently, this pathogenic variability can provide an uncontrolled variable when comparing studies, since the prevalence rates of the different strains may vary depending on geographic location.

The accurate determination of the presence of *H. pylori* is critical to the outcome of these studies, yet the choice of diagnostic test can provide an added variable. Currently, there are 3 basic means for determining the presence of *H. pylori*: (1) serologic testing; (2) the urease breath test; and (3) endoscopy with biopsy, utilizing culture, histologic assessment, or a rapid urease test. Evaluation of the biopsy specimen provides the most reliable method, but since it requires an invasive technique, it is used primarily in patients already requiring endoscopy. Serologic testing is widely used, and although it has been shown to be reasonably accurate in predicting the *H. pylori* status of patients who have not been treated for this organism,[9] it may not be as useful a method during or directly after treatment, since the decrease in *H. pylori*–specific immunoglobulin is time dependent over a period as long as 6–12 months.[10,11] Furthermore, both the specificity and the sensitivity varies among the several serologic test systems, with the possibility that the specificity is compromised in the presence of NSAIDs.[12,13] In one study, 23% of the patients who tested positive by serology were shown to be negative by the rapid urease test.[14] The urease breath test, although highly sensitive and specific, requires specialized equipment and is more difficult to perform, and hence is not readily available. A new approach may combine the specificity and sensitivity of the invasive technique with the ease and availability of the serologic method. The polymerase chain reaction (PCR) is a molecular biology technique that can not only detect the presence of *H. pylori* using gastric juice and oral secretions, but should also be able to distinguish between isolates of different pathogenicities.[15,16] However, this assay has not yet become widely used in clinical studies.

Another important variable in endoscopic studies is lack of a standard definition for standard terminology; the distinctions among evaluated criteria such as gastritis, erosions, submucosal hemorrhage, and even ulcers may vary from place to place. In a similar manner, what needs to be determined are appropriate endpoints for studies, i.e., are the studies looking at peptic ulcer disease, gastritis, mucosal hemorrhage, or endoscopic ulcers. An observed interaction between *H. pylori* and NSAIDs may depend on the endpoint chosen and the methodology employed.

With the above caveats in mind, what do the studies actually show?

NSAID USE DOES NOT INCREASE SUSCEPTIBILITY TO *H. PYLORI*

Although mucosal injury, such as occurs with NSAID use, might be expected to result in increased susceptibility to *H. pylori* colonization, several studies have shown that such an interaction does not occur.[17–21] If anything, there appears to be a negative correlation between the use of NSAIDs and the incidence of *H. pylori*. Several studies have determined that there is a lower incidence of *H. pylori* in patients taking NSAIDs.[17,22,23] One study determined that there may even be toxic effects on the *H. pylori*, at least with the use of aspirin.[17] The minimum inhibitory concentration (MIC) for aspirin against *H. pylori* was in the range that is clinically relevant. The MICs for 2 other NSAIDs, diclofenac and ketoprofen, although lower than their peak plasma concentrations, could conceivably be reached in vivo in the milieu of the gastric mucosal surface as the drugs dissociate and become absorbed.

H. PYLORI GASTRITIS AND NSAID-INDUCED GASTRITIS ARE MUTUALLY EXCLUSIVE

Whereas *H. pylori* is associated with a chronic, histologic gastritis,[3] use of NSAIDs gives rise to a reactive or chemical gastritis that is also observed with other drugs or under the condition of bile reflux.[22,24,25] This reactive gastritis may be histologically distinguished from that caused by *H. pylori* by the presence of foveolar hyperplasia and muscle fibers in the lamina propria, as well as edema and vasodilation.[22] In studies involving NSAID users who were also positive for *H. pylori*, it was shown that the 2 types of gastritis can arise from their respective causes independently of the presence of the other cause, that both types result in ulceration, and that there does not appear to be exacerbation of histologic gastritis by NSAIDs.[18,22,24,26]

In what may be a consequence of an observed reduction of incidence of *H. pylori* in NSAID users, some studies have shown a lower incidence of chronic gastritis in NSAID users than in nonusers.[18,23]

H. PYLORI DOES NOT EXACERBATE NSAID-ASSOCIATED MUCOSAL INJURY

Several studies that utilized the Lanza endoscopy scoring system to quantitate mucosal injury as an endpoint de-

termined that the presence of *H. pylori* had no effect on NSAID-associated gastroduodenal mucosal injury or adaptation to such injury. A study by Lanza et al[27] showed that in younger patients (<45 years) with no prior history of peptic ulcer disease, those who were serologically positive for *H. pylori* did not have any greater mucosal injury after 7 days of naproxen or aspirin treatment than did patients who were serologically negative. The concern of this study is that although the risk of NSAID-associated gastropathy is considered to be greatest during early treatment, short-term NSAID studies have been shown to be poor predictors of long-term complications. However, longer studies arrived at conclusions similar to those of the Lanza study.

In several 4-week studies, there was no statistical difference in the degree of gastric mucosal damage between *H. pylori*–positive and *H. pylori*–negative patients taking NSAIDs or placebo.[26,28–30] In one of these studies in which naproxen was used in a healthy patient population whose mean age was 29.6 years and who had no history of peptic ulcer disease, the investigators also determined that there were no significant differences in mucosal blood flow between the *H. pylori*–positive and *H. pylori*–negative groups. They further observed no difference in the degree of gastric mucosal adaptation to naproxen between the groups, as indicated by significant reductions in median damage score in both groups by day 28 compared with day 1.[30]

Similar results were obtained in a 6-month study that compared an asymptomatic patient population >40 years of age who were taking a variety of NSAIDs for rheumatoid arthritis with healthy age-matched controls who were not taking NSAIDs.[20] They found no difference in *H. pylori* prevalence between the 2 study groups, and the presence of *H. pylori* could not be correlated with severity of mucosal injury.

Another study that did not specifically state a time frame but indicated long-term exposure to NSAIDs reported a significantly lower percentage of patients with gastric hemorrhages and a quantifiably lower percentage with gastric mucosal erosions in *H. pylori*–positive NSAID users (32% and 34%, respectively) than in *H. pylori*–negative NSAID users (61% and 57%, respectively).[19]

Two recent studies on the enhancement of ulcer healing by the proton pump inhibitor omeprazole suggest that the presence of *H. pylori* is a positive prognostic factor for ulcer healing.[31,32] In both studies, the success rate of omeprazole, as well as of ranitidine in one of the studies, was greater in *H. pylori*–positive patients than in *H. pylori*–negative patients; the presence of *H. pylori* was assessed by the rapid urease test.

Although it is unlikely that *H. pylori* conveys protection against NSAID injury, these data may point to a possible explanation for the reported lack of significant synergism between NSAIDs and *H. pylori*: *H. pylori* induces an increase in mucosal prostaglandins.[26,33]

The studies discussed above contrast with 2 studies that indicated an exacerbation of NSAID toxicity in the presence of *H. pylori*.[21,34] However, one of these studies suggested that the additive effect between *H. pylori* and NSAIDs may occur in cases in which the NSAID is one that already has an increased risk of gastric toxicity.[21] The other study was a prospective study that included groups of patients already presenting with moderate-to-severe mucosal injury, including bleeding,[34] and this preselection may thus present a built-in sampling bias.

H. PYLORI AND NSAIDs ARE BOTH ASSOCIATED WITH ULCEROGENESIS

Numerous studies have determined that both *H. pylori* and NSAIDs are independent risk factors for the development of ulcers. However, similar to what has been observed for gastric mucosal injury, there are currently no convincing studies suggesting that these factors are additive or synergistic when endoscopically detected ulcers are used as an endpoint.

In a prospective study by Kim and Graham,[35] there was no significant difference between the percentage of *H. pylori*–positive long-term NSAID users who developed gastroduodenal ulcers (50%) and the percentage of *H. pylori*–negative long-term NSAID users who developed ulcers (50%). Although serology was the method of *H. pylori* analysis, if anything the use of this method might actually have overestimated the *H. pylori*–positive population.

Two studies did report a higher incidence of gastric or duodenal ulcers in *H. pylori*–positive NSAID users than in *H. pylori*–negative users.[36,37] The findings from these studies only support the idea that *H. pylori* is a risk factor for ulcers; the studies should not suggest any additive or synergistic relation, since control groups of non-NSAID users were not included. The same conclusion was reached by Greenberg[38] in a prospective, nested, case-controlled study of patients taking acetylsalicylic acid. He found that *H. pylori* was a risk factor for ulceration in patients taking aspirin or placebo.

The only recent study that shows a positive correlation between *H. pylori* and increased risk of NSAID-induced ulcers is based on eradication of *H. pylori* using triple therapy: bismuth subcitrate, tetracycline, and metronidazole.[39] In this study, 26% of the patients on naproxen who were also *H. pylori* positive developed ulcers, compared with only 3% of the patients in whom *H. pylori* was successfully eradicated before NSAID therapy. The uncertainty in this study deals with the use of bismuth, which can accumulate in the GI system and has other effects on the GI mucosa, including stimulation of prostaglandin synthesis that can be maintained during and beyond the

duration of treatment.[40] (Cf. *H. pylori* eradication may be of benefit in NSAID users, this article.)

H. PYLORI AND NSAIDs BOTH ARE RISK FACTORS FOR ULCER COMPLICATIONS

Ulcer complications, especially bleeding, are the major cause of morbidity and mortality in patients with peptic ulcer disease. Several studies have addressed the question of whether *H. pylori*, NSAIDs, or the combination presents a greater risk for upper GI bleeds. Although most of these studies did show that *H. pylori* and NSAIDs are risk factors for upper GI bleeding, there is still no consensus on whether *H. pylori* exacerbates NSAID-associated bleeds. Most studies have shown that *H. pylori* and NSAIDs are independent risk factors that do not seem to have an additive or synergistic effect[14,41,42]; several studies have suggested that NSAIDs themselves are the primary risk factor.[14,41,43] Al-Assi et al[43] recently suggested that NSAID use may in fact exacerbate *H. pylori*–induced ulcers and their complications. This suggestion is based on data obtained during the Misoprostol Ulcer Complication Outcomes Safety Assessment (MUCOSA) study, which showed that a prior history of peptic ulcer disease and/or gastrointestinal bleeding was a primary risk factor for NSAID-associated bleeds, although *H. pylori* itself was not studied as a potentially confounding factor.[44,45]

Only one study has so far suggested that *H. pylori* increases the risk for NSAID-induced bleeding. This study compared the presence of *H. pylori*, assayed by serology or the urease breath test, in NSAID patients with, and in those without, bleeding peptic ulcers and determined that the presence of *H. pylori* is associated with a 2-fold increase in risk for bleeding peptic ulcer among NSAID users.[46]

H. PYLORI IS ASSOCIATED WITH INCREASED MUCOSAL PROSTAGLANDIN PRODUCTION

As previously mentioned, the incidence of NSAID-associated gastric mucosa injury appears to be lower in the presence of *H. pylori*. The apparent association between *H. pylori* and increased levels of mucosal prostaglandin production may provide a possible explanation, since prostaglandins are important mediators of mucosal protection and ulcer healing.

Although an early study[47] found a correlation between increased prostaglandin levels and gastritis regardless of *H. pylori* status, more recent studies have determined that higher prostaglandin production occurs in *H. pylori*–positive patients.[26,33] Furthermore, the decrease in mucosal prostaglandin production associated with some NSAIDs, such as naproxen,[26,47,48] is ameliorated by the presence of *H. pylori*[26,33]; i.e., the level of prostaglandin synthesis in NSAID users who are histologically positive for *H. pylori* is approximately equivalent to that of control subjects.

H. PYLORI ERADICATION MAY BE OF BENEFIT IN NSAID USERS

Two studies have addressed the question of whether *H. pylori* eradication is beneficial to NSAID users. Bianchi Porro et al[49] used the combination of amoxicillin and omeprazole in long-term NSAID users with *H. pylori* and determined that the presence of *H. pylori* did not significantly affect the rate of ulcer healing. However, in the 6-month follow-up after cessation of omeprazole therapy and after ulcer healing, there was a quantitatively higher rate (not significant) of ulcer recurrence in an *H. pylori*–positive group (46%) compared with the *H. pylori*–negative (27%) or *H. pylori*–eradicated (31%) groups. These data not only suggest that a combination of *H. pylori* and NSAIDs may be more damaging to the gastric mucosa than NSAIDs alone, but also indirectly suggest that *H. pylori* eradication may be of benefit in patients requiring NSAIDs.

The second study, by Chan et al,[39] found that eradication of *H. pylori* using a triple therapy (bismuth subcitrate, tetracycline, and metronidazole) before NSAID administration significantly decreased the occurrence of NSAID-associated ulcers. In this study, 12 of 47 *H. pylori*–positive patients (26%) developed gastric and/or duodenal ulcers after 8 weeks of naproxen administration. This was significantly ($p = 0.01$) greater than the 7% of patients (3 of 45) who developed NSAID-associated ulcers in the *H. pylori*–eradication group. The difference becomes even more significant ($p = 0.002$) if it is considered that 2 of the 3 ulcers in the eradication group were in patients in whom eradication therapy failed; the overall percentage of successful eradication was 89%. However, as stated previously, the use of bismuth in this study may provide an additional uncontrolled protective factor.

It is important to note that neither of these studies indicate any adverse effects of eradicating *H. pylori*, and indeed, there may be benefits. However, it has been suggested that *H. pylori* may be an innocent bystander to NSAID-induced injury,[50] and if this proves to be the case, eradication may not necessarily predict a better outcome during NSAID use.

SUMMARY

Although broad generalizations may be possible regarding the effects of both *H. pylori* and NSAIDs on the upper GI tract, the available data do not unequivocally suggest an interaction between these 2 ulcerogenic agents or suggest specific mechanisms of protection or pathogenesis. What needs to be obtained is a consensus on the specific questions to be addressed and on the specific studies, i.e., endpoints, patient populations, and appropriate meth-

odology, that should be initiated to more clearly determine the relationship between these 2 agents of GI pathogenesis.

However, given that the eradication of *H. pylori* before initiation of NSAID therapy *may* be beneficial, it may be prudent to consider such a course, as recommended in the NIH consensus report,[51] in patients determined to be at high risk for a complication of NSAID use, i.e., those patients with a history of gastroduodenal ulcers.

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