Helicobacter pylori and NSAIDs

Erik Rauws

Helicobacter pylori and NSAIDs are both capable of inducing gastroduodenal mucosal injury. *H. pylori* induces gastritis by an inflammatory mucosal reaction and subsequent cascade of inflammatory cytokines. NSAIDs apart from local effects cause mucosal injury mainly by decreasing the endogenous prostaglandin synthesis. These two mechanisms causing mucosal damage, might interact producing either an increased or decreased risk for injury. It also might be possible that *H. pylori* organism oppose some of the toxic effects of NSAIDs and enhance the effectiveness of antisecretory drugs in healing ulcers and in preventing ulcer relapse while taking NSAIDs.[1]

Early uncontrolled studies showed a decreased prevalence of ulcer disease in *H. pylori*-positive NSAID users versus *H. pylori*-negatives. Since then, several prevalence studies have been performed, but sofa data are conflicting whether there is a relationship between *H. pylori* infection and NSAID usage.[2-4] In similar, but incidence studies performed in healthy volunteers taking NSAID for 7-28 days, no increase in incidence in gastroduodenal mucosal lesions was observed in *H. pylori*-positive individuals.[5-7] This finding might be explained by the fact that *H. pylori*-gastritis increases the gastric mucosal PG synthesis, which might be protective against subsequent NSAID-induced mucosal injury. The available incidence data obtained from chronic NSAID users are also conflicting. Kim et al[8] endoscoped 181 chronic arthritic patients and followed them up for 3 months while taking NSAIDs continuously. *H. pylori* was more prevalent in patients who developed a gastric ulcer (p=0.06), whereas 36% of the patients who developed a

duodenal ulcer were *H. pylori*-positive and 53% were *H. pylori*-negative (p=0.36). In contrast however, Taha et al[9] reported more ulcers in *H. pylori*-positive patients (40%) versus 15% in *H. pylori*-negatives (p=<0.05), during 6 months NSAID therapy. There is no explanation for these conflicting results, but one can conclude that if there is an increased risk for ulceration in *H. pylori*-positives while taking NSAIDs, the effect must be modest.

What is needed are prospective trials testing the hypothesis that eradication of *H. pylori* reduces or prevents ulceration. Bianchi Porro[10] evaluated 70 arthritic patients taking NSAID-maintenance therapy who presented with an *H. pylori*-positive endoscopically confirmed ulcer. The 6-month ulcer incidence after *H. pylori*-treatment was 46% in those who remained *H. pylori*-positive compared to 31% in those who became *H. pylori*-negative (N.S.). Chan et al[11] randomized *H. pylori*-positive patients without ulcer history to naprosyne (8 weeks) or bismuth-based triple therapy followed by naprosyne (8 weeks). In this study the ulcer incidence was only 3% in those who became *H. pylori*-negative versus 26% in those who got naprosyne only (p=0.002). On the other hand, a larger multi-centre double-blind study including 285 patients with an ulcer history on NSAIDs has shown that ulcer healing was retarded in whom *H. pylori* had been eradicated, and that eradication of *H. pylori* did not improve the overall outcome over 6 months of follow-up (45% ulcer/symptom recurrence in *H. pylori*-eradicated patients, versus 49% in the control group.[12]

What hardly has been studied in chronic NSAID users in the impact or effect of *H. pylori* and NSAIDs in the development of complicated ulcer disease, being the most important outcome from both a morbidity and economic standpoint. Several studies have shown that the risk of complicated ulcers in NSAID users is increased in patients with a prior history of ulcer disease. Patients with prior history of ulcers who have not been taken NSAIDs are presumed to have had *H. pylori*-associated ulcers, possibly indicating that NSAID use in these patients increases the risk for complications. These facts might explain why individuals with preexisting *H. pylori*-ulcers given NSAID, relapse with new ulcers in the first months after starting NSAID usage. However, Lanas et al[13], in a case-controlled study of gastrointestinal perforation revealed a strong association with NSAID use (p<0.0001), but not with *H. pylori* infection. Furthermore Pilotto et al[14] reported from a case-controlled study of 146 NSAID users that bleeding was associated with NSAID usage (53% versus 19%, p<0.0001), but was inversely correlated with *H. pylori*, as 48% of the bleeders were *H. pylori*-positive, while 73% of the ulcer controls were *H. pylori*-positive (p=0.004). Aalykke et al[15] performed a case controlled study of current users of NSAIDs (including acetylsalicylic acid) admitted because of bleeding peptic ulcer with NSAID-users without bleeding as con-

trols. They reported that NSAID-users infected with *H. pylori* have an almost twofold increased risk of bleeding peptic ulcer compared with NSAID users without *H. pylori*.

Concluding remarks

- Chronic use of NSAIDs may increase the risk of complicated ulcer disease in those with an history of *H. pylori*-ulcer.
- NSAID use might induce complications (bleeding; perforation) in patient with a concurrent *H. pylori* ulcer.
- It appears that *H. pylori*-positives without prior (*H. pylori*-associated) ulcer disease may have a lower risk of ulceration and bleeding while taking NSAIDs.

Medical Advises for Routine Clinical Practice

- There are no data to support testing for *H. pylori* and eradicate the organism in all who are put on NSAIDs.
- In patient who develop an ulcer while taking NSAIDs, "testing and treating" *H. pylori* is indicated.
- In patients with a documented ulcer in the history, *H. pylori*-positives should be treated before starting or while already on NSAIDs.

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