What do we do about *Helicobacter pylori*?

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CJ Hawkey. What do we do about *Helicobacter pylori*? Can J Gastroenterol 1999;13(2):143-145. *Heliobacter pylori* and nonsteroidal anti-inflammatory drugs (NSAIDs) cause ulcers by different mechanisms. Under some circumstances, patients infected with *H pylori* may be less prone to NSAID-associated ulcers than those who are *H pylori*-negative. Eradication trials have yielded differing results. However, those who have studied patients who have a past history of ulcer disease and are already established on NSAIDs have shown no benefit from *H pylori* eradication.

Key Words: *Acid suppression treatment*, Helicobacter pylori, *Nonsteroidal anti-inflammatory drugs*

Que faire d'*Helicobacter pylori*?

RÉSUMÉ : *Helicobacter pylori* et les anti-inflammatoires non stéroïdiens (AINS) provoquent des ulcères par le biais de mécanismes différents. Dans certains cas, les patients affectés par *H. pylori* sont parfois moins sujets aux ulcères provoqués par les AINS que ceux qui sont *H. pylori*-négatifs. Des essais d'éradication ont donné lieu à des résultats divergents. Par contre, ceux qui ont porté sur des patients qui avaient des antécédents de maladie ulcéreuse et prenaient déjà des AINS n'ont fait état d'aucun avantage lié à l'éradication de *H. pylori*.

Helicobacter pylori and nonsteroidal anti-inflammatory drugs (NSAIDs) have been described as uncomfortable bedfellows (1). This, in part, reflects a view that patients affected by the two factors, known on their own to cause ulcers, seem likely to be at double risk. However, a better description of the relationship may be "a strange affair"!

PATHOGENESIS

Although both NSAIDs and *H pylori* cause peptic ulceration, they do so by different mechanisms. In the case of *H pylori*, inflammatory changes and cytotoxin are probably important (2,3). NSAIDs have a variety of actions, but one commonly thought to be central to their ulcergenic activity is inhibition of prostaglandin synthesis leading to abrogation of prostaglandin-dependent defence mechanisms (4). Thus, ulcers caused by NSAIDs and by *H pylori* are superficially similar end results of fundamentally different pathological processes.

EFFECTS OF *H PYLORI* ON NSAID-ASSOCIATED DISEASE

The effect of *H pylori* on NSAID-associated mucosal injury, ulceration and symptoms has been investigated.

Acute mucosal injury: Most studies have shown no enhancement of acute mucosal injury caused by NSAIDs in subjects who are *H pylori*-positive compared with that in those who are negative (5-9). Where a difference has been shown, it may be attributable to differences in the amount of mucosal injury at baseline, which is higher in *H pylori*-infected individuals.

Ulcers: About as many studies have shown more NSAID-associated ulcers in *H pylori*-infected individuals than in non-infected individuals (10-15) as have shown no difference (16-19). Many of these studies concerned patients presenting for endoscopy. In view of the fact that *H pylori* enhances NSAID-associated dyspepsia (13,20-22), increases in ulcers may have been found spuriously as a result of bias due to increased presentation of *H pylori* individuals.

Dyspepsia: Although evidence regarding the effects of *H pylori* on NSAID-associated dyspepsia is not uniform, a majority of studies have shown that more patients who are *H pylori*-positive get dyspepsia when taking NSAIDs than those who are *H pylori*-negative (13,20-22).

Ulcer complications: There is only one full paper on the effects of *H pylori* on NSAID-associated ulcer complications (23). The study indicates no difference in the rate of presen-

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tation with ulcer bleeding by *H pylori* status in NSAID users. Other studies of perforation have similarly failed to show any significant interaction (24,25). One study, published in abstract form only, has suggested that there may be an enhancement of ulcer bleeding risk but that the magnification factor is less than two (26). If *H pylori* does enhance NSAID-associated bleeding, the effects are relatively small.

H PYLORI ERADICATION IN NSAID USERS

Three studies have investigated directly the effect of *H pylori* eradication in infected individuals who need to take NSAIDs (27-29). Patients enrolled in the first study had had no past history of dyspepsia or ulceration, were not currently taking NSAIDs and had had no more than one-month lifetime exposure to NSAID (27). In this study, use of a bismuth-containing regimen to eradicate *H pylori* was associated with a reduction in the development of gastric ulcers at two months. Notable features of this study were a very high rate of gastric ulceration in the control group and use of bismuth in the eradication regimen, which has potentially cytoprotective actions. It should also be noted that this study did not investigate patients with a past history of ulcers or those already taking NSAIDs. Another study that specifically investigated such patients showed no effect of *H pylori* eradication with a proton pump inhibitor-based regimen when assessed at six months (28). In fact, among patients with ulcers initially, those who received eradication treatment had a reduction in the rate of gastric ulcer healing. A third study compared *H pylori* eradication and prophylaxis with omeprazole as maintenance treatment in patients who had already presented with a bleeding peptic ulcer (29). During the next six months, those receiving omeprazole had 2% recurrence compared with 20% recurrence in those receiving *H pylori* eradication.

From these data, it can be concluded that outcome may vary according to the patient group studied. It is possible that, in patients with a 'virgin' mucosa, *H pylori* eradication may protect against ulceration, but whether it does so for longer than two months requires further study. Among patients with previous or current ulcer disease, *H pylori* eradication by itself does nothing beneficial and appears to impair the effects of ulcer healing drugs.

EFFECT OF *H PYLORI* STATUS ON THE EFFECTIVENESS OF ACID-SUPPRESSING TREATMENT

Concepts regarding the effect of *H pylori* status on the effectiveness of acid-supressing treatment are supported by large studies of patients treated with omeprazole, ranitidine or misoprostol for healing and maintenance of NSAID-associated ulcers (30,31). In these studies, patients consistently had faster ulcer healing and reduced tendency to relapse while taking acid-suppressing drugs if they were *H pylori*-positive compared with if they were negative. Among those treated with misoprostol, the differences were not significant, and, if anything, the trends were in the opposite direction.

MECHANISMS

It is well know that a higher pH is achieved in patients treated with omeprazole or ranitidine if they are *H pylori*-positive rather than -negative (32,33). This may well explain the better outcome in such individuals. Another factor that may operated to enhance the effectiveness of acid-suppressing drugs and partially protect patients not taking acid-suppressing drugs relates to the ability of *H pylori* to enhance prostaglandin synthesis in NSAID users (13).

CONCLUSIONS

The idea that *H pylori* protects against the effects of NSAIDs is not as counterintuitive as it may at first seem. In practical terms, fracture of the favourable relationship between *H pylori* and NSAIDs in patients requiring acid-suppressive treatment for protection might be regarded as a crime of passion!

REFERENCES

1. Taha AS, Russell RI. *Helicobacter pylori* and non-steroidal anti-inflammatory drugs: uncomfortable partners in peptic ulcer disease. Gut 1993;34:580-3.
2. Peek RM Jr, Blaser MJ. Pathophysiology of *Helicobacter pylori*-induced gastritis and peptic ulcer disease. Am J Med 1997;102:200-7.
3. Atherton JC. *H pylori* virulence factors. Br Med Bull 1998;54:105-20.
4. Wallace JL, Bell CJ. Gastroduodenal mucosal defense. Curr Opin Gastroenterol 1996;12:503-11.
5. Hawkey CJ. Are NSAIDs and *Helicobacter pylori* separate risk factors? In: RH Hunt, GNJ Tytgat, eds. *Helicobacter pylori*: Basic Mechanisms to Clinical Cure, 1996: The Proceedings of a Symposium/Organised by Axcan Pharma, Held in Ottawa, June 10-12, 1996. Boston: Kluwer Academic Publishers, 1996:312-23.
6. Lanza RL, Evans DG, Graham DY. Effect of *Helicobacter pylori* infection on the severity of gastroduodenal mucosal injury after acute administration of naproxen or aspirin to normal volunteers. Am J Gastroenterol 1991;86:735-7.
7. Laine L, Cominelli, Sloane R, Casini-Raggi V, Marin-Sorensen M, Weinstein WM. Interaction of NSAIDs and *Helicobacter pylori* on gastrointestinal injury and prostaglandins production: a controlled double-blind trial. Aliment Pharmacol Ther 1995;9:127-35.
8. Thillainayagam AV, Tabaqchali S, Warrington SJ, Farthing MJG. Interrelationships between Helicobacter infection, nonsteroidal antiinflammatory drugs and gastroduodenal disease. A prospective study in healthy volunteers. Dig Dis Sci 1994;39:1085-9.
9. Goggin PM, Collins DA, Juzrawi RP, et al. *Helicobacter pylori* infection and its effect on symptoms and non-steroidal anti-inflammatory drug induced gastrointestinal damage in patients with rheumatoid arthritis. Gut 1993;34:1677-80.
10. Graham DY, Lidsky MD, Cox AM, et al. Long term nonsteroidal antiinflammatory drug use and *Helicobacter pylori* infection. Gastroenterology 1991;100:1653-7.
11. Martin DF, Montgomery E, Dobek AS, Patrissi GA, Puera DA. *Campylobacter pylori*, NSAIDs, and smoking – risk factors for peptic ulcer disease. Am J Gastroenterol 1989;84:1268-72.
12. Shallcross TM, Heatley RV. Effect of non-steroidal anti-inflammatory drugs on dyspeptic symptoms. BMJ 1990;300:368-9.
13. Hudson N, Balsitis M, Filipowicz B, Hawkey CJ. Effect of *Helicobacter pylori* colonisation on gastric mucosal eicosanoid synthesis in patients taking non steriodal anti-inflammatory drugs. Gut 1993;34:748-51.
14. Janssen M, Dijkmans BAC, Lamers CBHW, Zwinderman AH, Vandenbroucke JP. A gastroscopic study of the predictive value of risk factors for non-steroidal anti-inflammatory drug-associated ulcer disease in rheumatoid arthritis patients. Br J Rheumatol 1994;33:449-54.
15. Taha AS, Dahill S, Sturrock RD, Lee FD, Russell RI. Predicting NSAID related ulcers – assessment of clinical and pathological risk factors and importance of differences in NSAID. Gut 1994;35:891-5.
16. Caselli M, Pazzi P, LaCorte Raleott A, Trevisani L, Stabellini G. Campylobacter-like organisms, nonsteroidal anti-inflammatory drugs and gastric lesions in patients with rheumatoid arthritis. Digestion 1989;44:101-4.

17. Taha AS, Nakshabendi I, Lee FD, Sturrock RD, Russell RI. Chemical gastritis and *Helicobacter pylori* related gastritis in patients receiving non-steroidal anti-inflammatory drugs: comparison and correlation with peptic ulceration. J Clin Pathol 1992;45:135-9.
18. Safe AF, Warren B, Corfield A, et al. *Helicobactor pylori* infection in elderly people: correlation between histology and serology. Age Ageing 1993;22:215-20.
19. Kim JG, Graham DY. *Helicobacter pylori* infection and development of gastric or duodenal ulcer in arthritic patients receiving chronic NSAID therapy. Am J Gastroenterol 1994;89:203-7.
20. Upadhyay R, Howatson A, McKinlay A, Danesh BJZ, Sturrock RD, Russell RI. *Campylobacter pylori* associated gastritis in patients with rheumatoid arthritis taking nonsteriodal anti-inflammatory drugs. Br J Rheumatol 1988;27:113-6.
21. Doube A, Morris A. Nonsteroidal anti-inflammatory drug-induced dyspepsia – is *Campylobacter pyloridis* implicated? Br J Rheumatol 1988;27:110-2.
22. Jones STM, Clague RB, Eldridge J, Jones DM. Serological evidence of infection with *Helicobacter pylori* may produce gastrointestinal intolerance to non-steroidal anti-inflammatory drug (NSAID) treatment in rheumatoid arthritis. Br J Rheumatol 1991;30:16-20.
23. Cullen DJE, Hawkey GM, Greenwood DC, et al. Peptic ulcer bleeding in the elderly: relative roles of *Helicobacter pylori* and non-steroidal anti-inflammatory drugs. Gut 1997;41:459-62.
24. Reinbach DH, Cruickshank G, McColl KEL. Acute perforated duodenal ulcer is not associated with *Helicobactor pylori* infection. Gut 1993;34:1344-7.
25. Debongnie J-C, Wibin E, Timmermans M, Mairess J, Dekonick X. Are perforated gastroduodenal ulcers related to *Helicobactor pylori* infection? Acta Gastroenterol Belg 1995;58:208-12.
26. Aalykke C, Lauritsen JM, Hallas J, Reinholdt S, Krogfelt K, Lauritsen K. *Helicobactor pylori* – a risk factor in NSAID-related bleeding peptic ulcer: a prospective case control study. Gastroenterology 1997;122:A51. (Abst)
27. Chan FKL, Sung JJY, Chung SCS, et al. Randomised eradication of *Helicobacter pylori* before non-steroidal anti-inflammatory drug therapy to prevent peptic ulcers. Lancet 1997;350:975-9.
28. Hawkey CJ, Tullasay Z, Szczepanski L, et al. Randomised controlled trial of *Helicobacter pylori* eradication in patients taking non-steroidal anti-inflammatory drugs: HELP NSAIDs study. Helicobacter Eradication for Lesion Prevention. Lancet 1998;352:1016-21.
29. Chan FKL, Sung JY, Suen R, et al. Eradication of *H pylori* versus maintenance acid suppression to prevent recurrent ulcer haemorrhage in high risk NSAID users. A prospective randomised study. Gastroenterology 1998;114:A87. (Abst)
30. Yeomans ND, Tulassay Z, Juhasz L, et al. A comparison of omeprazole and ranitidine for treating and preventing 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.
31. 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.
32. 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.
33. Labenz J, Tillenburg B, Peitz U, et al. Effect of curing *Helicobacter pylori* infection on intragastric acidity during treatment with ranitidine in patients with duodenal ulcer. Gut 1997;41:33-6.