Infection with Helicobacter pylori and long-term use of non-steroidal antiinflammatory drugs

Včev, Aleksandar; Ivandić, Ante; Včeva, Andrijana; Štimac, Davor; Takač, Boris; Mikolasević, Ivica; Jovanović, Savo; Dmitrović, Branko; Vuković, Dubravka; Egić, Božidar

Source / Izvornik: **Acta medica Croatica : Časopis Akademije medicinskih znanosti Hrvatske, 1998, 52, 27 - 31**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:687407

Acta med. Croatica, 52 (1998) 27–31

Original Scientific Paper

INFECTION WITH *HELICOBACTER PYLORI* AND LONG–TERM USE OF NON–STEROIDAL ANTIINFLAMMATORY DRUGS

ALEKSANDAR VČEV, ANTE IVANDIĆ, ANDRIJANA VČEVA, DAVOR ŠTIMAC, BORIS TAKAČ, IVICA MIKOLAŠEVIĆ[1], SAVO JOVANOVIĆ[1], BRANKO DMITROVIĆ[2], DUBRAVKA VUKOVIĆ[3] and BOŽIDAR EGIĆ[4]

Department of Medicine, Department of Orthopedics[1], Department of Pathology2, Department of Microbiology[3], Osijek University Hospital, Osijek, and Special Hospital for Rheumatic Diseases and Medical Rehabilitation4, Daruvar, Croatia

The use of nonsteriodal anti inflammatory drugs (NSAID) is associated with an increased risk of peptic ulcer and of ulcer complications. However, the relation between *Helicobacter pylori* infection and gastroduodenal damage associated with NSAID use is unclear.

This study investigated the prevalence of *Helicobacter pylori* infection in patients with arthritis (n=85) taking NSAID, trying to find out whether the patients taking NSAID and infected with *H. pylori* were more likely to have dyspepsia, mucosal damage or chronic active gastritis than those without *H. pylori* infection. *H. pylori* was identified by biopsy, rapid urease test and histologic test. Dispeptic symptoms were assessed according to a standardized questionnaire. Gastroduodenal mucosal damage was graded endoscopically (using a modified Lanza scale) and the diagnosis of chronic gastritis was based on the histologic criteria of the Sydney system.

The frequency of *H. pylori* infection was found to increase with age. No statistically significant difference was observed in the presence of damage to gastroduodenal mucosa between the patients with and without *H. pylori* infection. *H. pylori* infection was found to be associated with an increased frequency and severity of dyspeptic symptoms in patients with arthritis taking long–term NSAID. Chronic active gastritis was only present in patients with *H. pylori* infection.

H. pylori infection was shown to be associated with an increased frequency and severity of dyspeptic symptoms in patients with arthritis on long–term NSAID therapy, without causing an increased damage to gastroduodenal mucosa.

Key words: Helicobacter pylory, NSAID

Received for publication June 26, 1997

Correspondence: Aleksandar Včev, MD, PhD
Department of Medicine
Osijek University Hospital
Josipa Huttlera 4
31000 Osijek, Croatia

INTRODUCTION

It is now accepted that *Helicobacter pylori (H. pylori)* causes active gastritis type B[1] and is associated with duodenal and gastric ulcer. The association between *H. pylori* infection and peptic ulcer disease is strongest for the presence of duodenal ulcer[2].

The use of nonsteroidal anti inflammatory drugs (NSAID) is associated with an increased risk of peptic ulcer and ulcer complications[3–5].

However, the relation between *H. pylori* infection and gastroduodenal damage associated with NSAID use is unclear.

In dyspepsia caused by NSAID, there is no correlation between the symptoms and severity of gastroduodenal damage[6, 7]. Upadhyay et al.[8] found an increased prevalence of dyspeptic symptoms in rheumatoid arthritis patients taking NSAID if they had *H. pylori* infection. However, this has not been confirmed by others[9, 10].

The aims of this study were, firstly to determine the prevalence of *H. pylori* infection in patients with arthritis receiving NSAID; and secondly, to determine whether the patients on NSAID treatment and with *H. pylori* infection are more likely to develop dyspepsia and mucosal damage than those not infected with *H. pylori*.

PATIENTS AND METHODS

The study included 85 patients on long–term (more than 8 months) NSAID treatment (39 with rheumatoid arthrits, 28 with osteoarthritis, and 18 with ankylosing spondylitis; M: F 27: 48; mean age 54, range 23–80 years).

An informed consent was obtained from each patient. Patients who were receiving steroids, gold, penicillamine sulfasalazine, or other slow–acting antirheumatic drugs, were excluded from the study. None of the study patients was receiving H_2 antagonists, proton pump inhibitors, or any mucosal protective drug during the study period.

During examination, the clinician, pathologist and endoscopist were blinded for the results of their work.

Dyspeptic symptoms were assessed according to a scoring system similar to that of Upadhyay[8] (Table 1) during a 3–week period, before the endoscopic examination, while the patients were receiving their routine NSAID treatment.

Esophagogastroduodenoscopy was performed after an overnight fast, and the gastric and duodenal appearance was assessed according to a modified Lanza scale[11] (Table 2). Three biopsy specimens were taken from the antrum (within 4 cm from the pylorus) and three from the corpus. Four specimens were submitted for histologic examination and two for the biopsy urease test[12–14]. The endoscopes

Table 1.

Dysepsia scoring system: abdominal pain, abdominal bloating, nausea, vomiting and heartburn were each scored according to the chart below. In addition, the use of antacids was scored according to the frequency alone

	Score			
	1	2	3	4
Timing	Short period	< 2 hours	> 2 hour	
Frequency	Occasional	Some days	Most days	Every day

As an example, a patient who had abdominal pain on most of days (score 3) lasting for less than two hours but for more than a short period (score 2) would score a total of 5 for this symptom. The total score was the sum of these for each individual symptom.

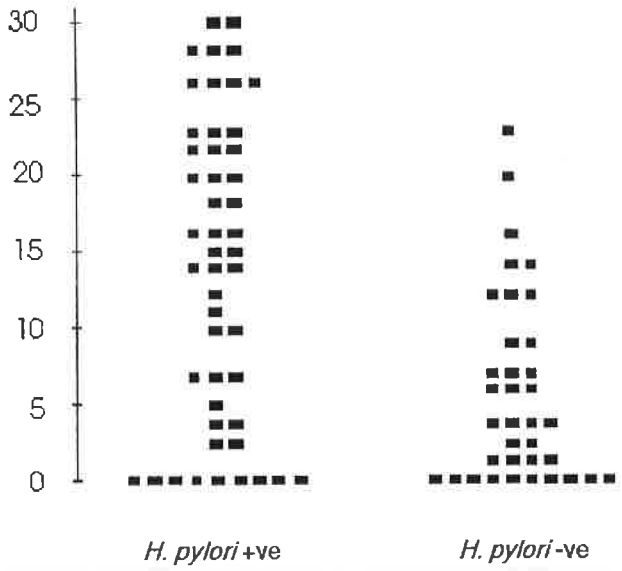

Fig. 1. *Dyspeptic symptoms score was increased ($p < 0.05$) in H. pylori+ve patients.*

Table 2.

Modified Lanza system for scoring mucosal damage in the stomach and duodenum

Grade	Endoscopic appearance
0	No evidence of erosions or submucosal hemorrhage
1	Single erosion or submucosal hemorrhage
2a	More that one but not numerous erosions or submucosal hemorrhages
3	Numerous areas of erosions or submucosal hemorrhages
4	Invasive ulcer or large areas of erosions or submucosal hemorrhage with active bleeding

(Olympus GIF Q 10) and bioptic pincer (Olympus FBO 24–K) were sterilized with 2% glutaraldehyde between examinations. The biopsies were fixed in formalin, oriented and embedded in paraffin. Sections 3 μm thick were stained with hematoxylin and eosin for histologic evaluation, and with May–Grünwald Giemsa for identification of *H. pylori*. The diagnosis of chronic gastritis was based on the histologic criteria proposed in the Sydney system[15]

Table 3.

Endoscopic mucosal damage scores for 36 patients with arthritis without Helicobacter pylori infection and for 49 patients with arthritis and Helicobacter pylori infection

Ulcer	Duodenum						Stomach					
Group	0	1	2a	2b	3	4	0	1	2a	2b	3	4
(*H. pylori*–ve)												
None	20	3	4	2	0	0	14	3	5	3	1	1
Duodenal	0	0	0	0	0	5	1	2	2	1	0	0
Gastric	2	0	0	0	0	0	0	1	0	0	0	2
(*H. pylori*+ve)												
None	24	3	5	3	2	0	19	4	5	4	3	1
Duodenal	1	0	0	0	0	7	3	2	2	2	0	0
Gastric	3	1	0	0	0	0	1	1	0	0	0	2

Morphologic evidence of *H. pylori* infection was determined by the presence of typical curved bacilli, approximately 1 to 3 μm long and 0.5 μm wide, lining the surface epithelium or penetrating the mucous layer (particularly in the gastric pits).

A patient was considered *H. pylori* positive (+ve) if *H. pylori* was identified on histologic examination and if the biopsy rapid urease test was positive. All patients found to be *H. pylori* positive by the rapid urease test were confirmed by histology (in other words, the rapid urease test produced no false positives).

Statistics. The Mann–Whitney U test was used for unpaired, and Wilcoxon signed rank test for paired comparisons, with a p value of less than 0.05 considered significant.

RESULTS

In 85 patients with arthritis on long–term NSAID therapy, the frequency of *H. pylori* infection was 57.6% (49/85).

The frequency of *H. pylori* infection in the patients on long–term NSAID therapy increased with age from 35% in the 21–30 age group to 73% in 61–70 age group.

Dyspeptic symptoms were more severe in the *H. pylori* +ve than in *H pylori* –ve patients with arthritis ($p<0.05$) (Fig. 1).

In 85 patients with arthritis, duodenal ulcer was found in 12 (14. 1%) patients, seven of them with *H. pylori* infection. Gastric ulcer was found in four (4.7%) patients, two of them with *H. pylori* infection. Sixty–nine (81.2%) patients were free from ulcer, 40 of them with *H. pylori* infection.

Table 3 shows endoscopic score of mucosal damage to gastroduodenum in the patients with or without *H. pylori* infection. There was no statistically significant difference in mucosal damage to gastroduodenum between the patients with and without *H. pylori* infection.

Chronic active gastritis was found in all the 49 *H. pylori* +ve patients. In the group of patients without *H. pylori* infection, 16 patients had normal histologic findings and 20 had chronic inactive gastritis.

DISCUSSION

In this study, the overall prevalence of *H. pylori* infection in the patients with arthritis (57.6%) was similar to that expected for a population with a mean age of 54[10, 16] suggesting that NSAID ingestion and arthritis do not affect the risk and natural course of *H. pylori* infection. However, two studies[17, 18] have reported a reduced prevalence of *H. pylori* infection in those taking NSAID. Other studies[8, 10, 11, 19] reported on the prevalence of *H. pylori* infection in NSAID users to be similar to that in the general population.

In this study, showed an increased frequency and severity of dyspeptic symptoms in the patients with arthritis on long–term NSAID therapy, if they had *H. pylori* infection. Similar results have been reported from two other studies[8, 11]. In contrast, some studies found the prevalence of *H. pylori* infection in patients taking NSAID to be similar in dyspeptic and asymptotic subjects[9], and with no correlation between dyspeptic symptoms and the presence of *H. pylori* infection[10]. Jones and et al.[19] found that rheumatoid arthritis patients taking NSAID who were *H. pylori* +ve were more likely to have a history of peptic ulcer disease, and had more severe dyspeptic symptoms leading to multiple NSAID intolerance.

Recent findings of Kim and Graham[20] show that *H. pylori* infection does not increase the risk of duodenal ulcer in patients with arthritis and long–term NSAID treatment. In our study, duodenal ulcer was more common in the *H. pylori* +ve patients who were on long–term NSAID treatment. It remains unclear whether most NSAID–associated duodenal ulcers are *H. pylori* associated ulcers, NSAID–exacerbated *H. pylori*–associated ulcers, or NSAID induced ulcers. The known age–related increase in *H. pylori* infection[21] coupled with the relatively older population characteristic of patients with chronic arthritis ensures that, by chance, a large number of them will both receive NSAIDs and have *H. pylori* infection.

Goggin and et al.[11] found that there was a trend toward a greater increase in the endoscopic score of gastroduodenal damage in *H. pylori* –ve subjects, but the differences were not statistically significant. In this study, there was no significant difference in the endoscopic score of damage between the patients on NSAID treatment who were *H. pylori* +ve and those *H. pylori* –ve. In a serologic study, healthy volunteers received NSAID for seven days, but no difference was found in the endoscopic score of damage between the subjects who were *H. pylori* +ve and those who were *H. pylori* –ve[22]. Two studies[10, 23] found that *H. pylori* +ve patients taking NSAID had less gastric hemorrhages. In the latter study[23] the presence of neutrophils on gastric cytology was presumably related to *H. pylori* infection. In contrast, Heresbach et al.[24] found an increased prevalence of *H. pylori* infection in patients taking NSAID if gastropathy was present.

In this study, all patients with *H. pylori* infection had chronic active gastritis Twenty (55.6%) patients without *H. pylori* infection had chronic inactive gastritis and 16 (44.4%) had normal histologic finding[5]. These results suggested that NSAID were not the cause of histologic gastritis. In the studies by Metzger et al.[25], and Goggan and et al.[11] the histologic gastritis score was found to be unchanged after the tratment with NSAID. In contrast, Taha et al.[26] report that the percentage of patients with severe gastritis increased from 5% to 78% after one–month treatment with naproxen or etodolac, and NSAIDs have been suggested as the cause of active chronic gastritis. This discrepancy between the findings of

Taha et al. findings and previously mentioned findings is difficult to explain.

In conclusion we showed that *H. pylori* infection was associated with an increased frequency and severity of dyspeptic symptoms in the patients with arthritis on long–term NSAID therapy without causing an increased damage to gastroduodenal mucosa.

R E F E R E N C E S

1. Rauws EA, Langerberg W, Zanen HC, Tytgat GN. *Campylobacter pyloridis* associated chronic active antral gastritis. A prospective study of its prevalence and the effects of antibacterial and antiulcer treatment. Gastroenterology 1988; 94: 33–40.

2. Graham DY. *Campylobacter pylori* and peptic ulcer disease. Gastroenterology 1989; 96(Suppl): 615–625.

3. Armstrong CP, Blower AL. Non–steroidal anti–inflammatory drugs and life threatening complications of peptic ulceration. Gut 1987; 28: 527–532.

4. Graham DY. Prevention of gastroduodenal injury induced by chronic nonsteroidal antiinflammatory drug therapy. Gastroenterology 1989; 96 (Suppl): 675–681.

5. Somasundaram S, Hayllar H, Rafi S, Wrigglesworth JM, Macpherson AJS, Bjarnason J. The biochemical basis of non–steroidal antiinflammatory drug induced damage to the gastrointestinal tract: a review and a hypothesis. Scand J Gastroenterol 1995; 30: 289–299.

6. Farah D, Sturrock RD, Russel RI. Peptic ulcer in rheumatoid arthritis. Ann Rheum Dis 1988; 47: 478–480.

7. Lanza FL. A review of gastric ulcer and gastroduodenal injury in normal volunteers receiving aspirin and other nonsteroidal antiinflammatory drugs. Scand J Gastroenterol 1989; 163 (Suppl): 24–31.

8. Upadhyay R, Howatson A., Mc Kinlay A, Danesh BJ, Sturrock RD, Russel RI. *Campylobacter pylori* associated gastritis in patients with rheumatoid arthritis taking nonsteroidal antiinflammatory drugs. Br J Rheumatol 1988; 27: 113–116.

9. Doube A, Morris A. Nonsteroidal antiinflammatory drug induced dyspepsia — is *Campylobacter pyloridis* implicated? Br J Rheumatol 1988; 27: 110–112.

10. Graham DY, Lidsky MD, Cox AM, Evans DJJr, Evans DG, Alpert L et al. Long–term nonsteroidal antiinflammatory drug use and *Helicobacter pylori* infection. Gastroenterology 1991; 100: 1653–1657.

11. Goggin PM, Collins DA, Jazrawi RP, Jackson PA, Corbishley CM, Bourke BE, Northfield TC. Prevalence of *Helicobacter pylori* infection and its effect on symptoms and nonsteroidal antiinflammatory drug induced gastrointestinal damage in patients with rheumatoid arthritis. Gut 1993; 34: 1677–1680.

12. Marshall BJ, Warren JR, Francis GJ, Langton SR. Rapid urease test in the management of *Campylobacter pyloridis* associated gastritis. Am J Gastroenterol 1987; 82: 200–210.

13. Szeto ML, Pounder RE, Hamilton DS, Dhilton AP. Rapid urease test provides specific identification of *Campylobacter pylori* in antral mucosal biopsies. Postgrad Med J 1988; 64: 935–936.

14. Morris A, Ali MR, Brown P, Lane M, Patton K. *Campylobacter pylori* infection in biopsy specimens of gastric antrum: laboratory diagnosis and estimation of sampling error. J Clin Pathol 1989; 42: 727–732.

15. Misiewcs JJ, Tytgat GNj, Goodwin CS et al. The Sydney system: a new classification of gastritis. World Congress of Gastroenterology. Working Party Reports. Sydney: Blackwell Sci Publ, 1990; 1–10.

16. Wyant JI, Rathbone BJ. The role of serology in the diagnosis of *Campylobacter pylori* infection. Scand J Gastroenterol 1989, 24 (Suppl 160). 27–34.

17. Iglehart IW, Edlow DW, Mills Lj, Morrison SA, Hochberg MC. The presence of *Campylobacter pylori* in nonsteroidal antiinflammatory drug associated gastritis. J Rheumatol 1989; 16: 599–603.

18. Caselli M, Pazzi P, La Corte R, Aleotti A, Trevisani L, Stabellini G. *Campylobacter*–like organisms, nonsteroidal antiinflammatory drugs and gastric lesions in patients with rheumatoid arthritis. Digestion 1989; 44: 101–104.

19. Jones ST, Clague RB, Eldridge J, Jones DM. Serological evidence of infection with *Helicobacter pylori* may predict gastrointestinal intolerance to nonsteroidal antiinflammatory drug (NSAID) treatment in rheumatoid arthritis. Br J Rheumatol 1991: 30: 16–20.

20. Kim JG, Graham DY. *Helicobacter pylori* infection and development of gastric or duodenal ulcer in arthritic patients receiving chronic NSAID therapy. The Misoprostol Study Group. Am J Gastroenterol 1994; 89: 203–207.

21. Graham DY, Adam E, Klein PD et al. Epidemiology of *Campylobacter pylori*. Gastroentrol Clin Biol 1989; 13: 848–88B.

22. Lanza FL, Evans DG, Graham DY. Effect of *Helicobacter pylori* infection on the severity of gastroduodenal mucosal injury after the acute administration of naproxen or aspirin to normal volunteers. Am J Gastroenterol 1991; 86: 735–737.

23. Wood PH, Harvey–Smith EA, Dixon AJ. Salicylates and gastrointestinal bleeding–acetylsalicylic acid and aspirin derivates. BMJ 1962; 1: 669–675.

24. Heresbach D, Raoul JL, Bretagne JF et al. *Helicobacter pylori* — a risk and severity factor of nonsteroidal antiinflammatory drug induced gastropathy. Gut 1992; 33: 1608–1611.

25. Metzger WH, Mc Adam L, Bluestone R, Guth PH. Acute gastric mucosa injury during continuous or interrupted aspirin ingestion in humans. Am J Dig Dis 1976; 21: 963–968.

26. Taha AS, Mc Laughlin S, Hollandd PJ, Kelly RW, Sturrock RD, Russel RI. Effects on gastric and duodenal mucosal prostaglandins of repeated intake of therapeutic doses of naproxen and etodolac in rheumatoid arthritis. Ann Rheum Dis 1990; 49: 354–358.

A. Včev, A. Ivandić, A. Včeva, D. Štimac, B.Takač, I. Mikolašević, S. Jovanović, B. Dmitrović, D. Vuković, B. Egić. Infection with *Helicobacter pylori* and Long–term Use of Non–steroidal Antiinflammatory Drugs. Acta med. Croat. Vol. 52 (1998) No. 1, pp 27–31

S A Ž E T A K

INFEKCIJA *HELICOBACTER PYLORI* I DUGOTRAJNA UPORABA NESTEROIDNIH ANTIREUMATIKA

A. VČEV, A. IVANDIĆ, A. VČEVA, D. ŠTIMAC, B. TAKAČ, I. MIKOLAŠEVIĆ[1], S. JOVANOVIĆ[2], B. DMITROVIĆ[2], D. VUKOVIĆ[3] i B. EGIĆ[4]

Interna klinika, Klinika za ortopediju[1], Zavod za patologiju[2], Zavod za mikrobjologiju[3] Kliničke bolnice u Osijeku i Specijalna bolnica za reumatske bolesti i medicinsku rehabilitaciju[4] u Daruvaru, Hrvatska

Uporaba nesteroidnih antireumatika (NSAR) udružena je s porastom rizika od peptičkih ulceracija i komplikacija istih. Međutim, odnos između infekcije *Helicobacter pylori* i gastroduodenalnog oštećenja uzrokovanog NSAR–om nije jasna.

Autori su istraživali prevalenciju infekcije *Helicobacter pylori* u bolesnika s artritisom (n=85) na dugotrajnoj terapiji NSAR, te razliku u sklonosti razvoja dispepsije, mukoznog oštećenja i kroničnog aktivnog gastritisa u bolesnika s infekcijom *H. pylori* i bez infekcije *H. pylori*. *Helicobacter pylori* identificiran je pomoću brzog bioptičkog ureaza testa i histološkog ispitivanja. Dispeptički simptomi ustanovljeni su prema standardiziranom upitniku. Gastroduodenalno mukozno oštećenje stupnjevano je endoskopski (prema modificiranoj Lanza skali), a dijagnoza kroničnog gastritisa temeljena je na histološkim kriterijima propisanim u Sydney sustavu. Učestalost *H. pylori* raste s bolesnikovim godinama. Nije bilo statistički značajnih razlika u mukoznom oštećenju gastroduodenuma u bolesnika s i bez *H. pylori*. Kronični aktivni gastritis imali su samo (svi) bolesnici s *H. pylori* infekcijom. Infekcija *H. pylori* udružena je s porastom učestalosti i jačine dispeptičkih simptoma u bolesnika s artritisom na dugotrajnoj NSAR terapiji.

***Ključne riječi*: *Helicobacter pylori*, nesteroidni antireumatici**