Therapy and Prevention of Gastric Ulcer

Cornelis B.H.W. Lamers, Izák Biemond, Ad A.M. Masclee, and Roeland A. Veenendaal

Department of Gastroenterology-Hepatology, University Hospital, Leiden, The Netherlands

(Received March 8, 1996; returned for revision October 8, 1996; accepted February 8, 1997)

After establishing the benign nature of a gastric ulcer, the treatment is primarily medical. This medical therapy is aimed to alleviate symptoms, to heal the ulcer and to prevent relapses. Based on the history of non-steroidal anti-inflammatory drugs (NSAIDs) and the Helicobacter pylori-status, gastric ulcer patients can be divided into four categories (1) H. pylori positive plus NSAID-use, (2) H. pylori positive without NSAID use, (3) NSAID use with negative H. pylori-status, (4) Negative H. pylori-status and no NSAID use.

Patients taking NSAIDs should stop this therapy if possible. Patients with gastric H. pylori infection should be treated by a regimen of a proton pump inhibitor with at least two appropriate antibiotics. This treatment will result in early alleviation of symptoms, rapid healing of the ulcer and prophylaxis of ulcer relapse. In patients with gastric ulcer who cannot stop NSAIDs, maintenance therapy with prostaglandins or potent antisecretory drugs should be considered. The few patients with gastric ulcer who do not take NSAIDs and do not have gastric H. pylori infection should be treated by antisecretory drugs, and they should be carefully followed endoscopically to exclude malignant (carcinoma, lymphoma) or non-peptic (Crohn’s disease) disease. All patients with gastric ulcer should be re-endoscoped to verify complete ulcer healing. Surgery may be considered in gastric ulcer patients with complications, in those with severe dysplasia of the gastric mucosa, and in those who are not able or willing to take the medication.

INTRODUCTION

Histamine-2 receptor antagonists (H2RAs) have been the mainstay of treatment of gastric ulcer for many years [1]. These compounds have proved to be more effective than antacids without relevant side-effects. H2RAs not only accelerate healing of gastric ulcer but also prevent recurrences when used as prophylactic maintenance therapy [1, 2]. However, an analysis from Scandinavia showed that even between 1980 and 1990, about one-third of gastric ulcer patients were burdened by their disease [3]. Recent developments have challenged the primacy of H2RA in the treatment of peptic lesions. First, the development of proton pump inhibitors with potent and long-acting antisecretory effects has led to higher healing rates than those obtained with H2RAs [4, 5]. Second, the discovery of the role of Helicobacter pylori infection has warranted antimicrobial therapy as the logical approach to gastric ulcer disease [6, 7]. Third, there is increasing interest in the importance of non-steroidal anti-inflammatory drugs (NSAIDs) in the pathogenesis of gastric ulcer and in the possibility of prevention with prostaglandin analogues [8, 9, 10].

Not only antisecretory drugs but also compounds that do not interfere with gastric acid secretion have been shown to accelerate gastric ulcer healing when compared with placebo treatment [11]. These so-called gastric protective agents comprise carbenoxolone,

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\(a\) To whom all correspondence should be addressed: Prof. Dr. C.B.H.W. Lamers, Dept. Gastroenterology and Hepatology, Building 1, C4-P15 University Hospital, Leiden P.O. Box 9600 2300 RC Leiden, The Netherlands. Tel: 31-71-5263507; Fax: 31-71-5248115.

\(b\) Abbreviations: H2RA, histamine-2 receptor antagonist; NSAIDs, non-steroidal anti-inflammatory drugs.
sucralfate, colloidal bismuth compounds and prostaglandin analogues. Furthermore, pro-
kinetics such as cisapride have been studied in the therapy of gastric ulcer [12]. However,
none of these drugs is superior to H₂RAs in healing gastric ulcer and alleviating its symp-
toms [13].

ANTISECRETORY THERAPY IN GASTRIC ULCER

Meta-analysis of various antisecretory therapies for gastric ulcer has shown that there
are three primary determinants of gastric ulcer healing: (1) the duration of treatment, (2)
the degree of acid suppression and (3) the duration of acid suppression over the 24-hour
period [14]. The duration of treatment appears to be the most important single determi-
nant of gastric ulcer healing. Maintaining the gastric pH above 3 for 18 hours daily pre-
dicts healing in 100 percent of gastric ulcers at eight weeks, while such a degree of acid
suppression will heal all duodenal ulcers within four weeks [1, 14]. Thus, gastric ulcers
require longer antisecretory therapy than duodenal ulcers.

The importance of the degree and duration of suppression of gastric acid has been
clinically demonstrated in several studies comparing proton pump inhibitors with H₂RAs.
In a large multicentral study of 602 patients with gastric ulcer, both omeprazole 20 mg
every morning and omeprazole 40 mg every morning induced significantly higher healing
rates at four weeks (69 percent and 80 percent ) and eight weeks (89 percent and 96 per-
cent) than ranitidine 150 mg twice daily (59 percent and 85 percent at four and eight
weeks) [15]. Similar high healing rates were obtained with other proton pump inhibitors.
With lansoprazole in doses of 15, 30 and 60 mg every morning, healing rates of gastric
ulcer were 65 percent, 58 percent and 53 percent at four weeks and 92 percent, 97 percent
and 93 percent at eight weeks, respectively [16]. The overall healing rates of gastric ulcer
with pantoprazole were 84 percent and 97 percent at four and eight weeks, respectively
[5]. When compared to H₂RAs, proton pump inhibitors tend to give slightly faster symp-
tom relief but the difference only rarely achieves statistical significance [5, 15].

Antisecretory agents are also efficacious in the prophylaxis of gastric ulcer. This pre-
ventive effect has mainly been studied using maintenance therapy with ranitidine. In a re-
respective study on patients taking 150 or 300 mg/day ranitidine as maintenance treatment
for gastric ulcer prophylaxis, the cumulative remission rates were 97 percent after one
year, 94 percent after two years, 90 percent after three years, 79 percent after four and five
years [2]. However, since the recognition of the important role of H. pylori eradication in
prevention of peptic ulcer, maintenance therapy for the prevention of gastric ulcer is like-
ly to be replaced by H. pylori eradication regimens in the near future.

HELICOBACTER PYLORI ERADICATION IN GASTRIC ULCER

Prevalence of H. pylori in gastric ulcer

It has been known for long time that gastric ulcer is often accompanied by chronic
gastritis. Prostaglandin deficiency secondary to this gastritis may contribute to the devel-
opment of gastric ulcer despite the absence of gastric acid hypersecretion in this condition
[17]. In fact, most patients with benign gastric ulcer have normal or low gastric acid secre-
tion. Gastric H. pylori infection may play a crucial role in the pathogenesis of the chron-
ic inflammation of the gastric mucosa often found in gastric ulcer patients [18]. In the past
10 years, a large number of studies have been performed to determine the prevalence of
H. pylori infection in gastric ulcer disease. In an analysis of 25 studies comprising 1395
patients with gastric ulcer, the prevalences of H. pylori ranged from 44 to 100 percent with
an average of 84 percent [19]. In four of the studies, which comprised a total of 235
patients, the prevalence of H. pylori positivity in gastric ulcer was even 100 percent . The
failure to find H. pylori positivity in all gastric patients may be related to the inclusion of
gastric ulcer due to NSAIDs or malignancy or to the low sensitivity of the biopsy test for *H. pylori* [19].

**Gastric ulcer healing in *H. pylori*-positive patients**

Several therapeutic regimens have been developed to eradicate *H. pylori* from the stomach. The optimal regimen will result in rapid gastric ulcer healing, fast pain relief and prevention of ulcer recurrences. The *H. pylori* status does not seem to influence the healing rate of gastric ulcer when treated with H2RAs. After 12 weeks of therapy with 800 mg/day cimetidine, 67 of 77 *H. pylori*-positive (87 percent) and 16 of 18 *H. pylori*-negative (89 percent) gastric ulcers were healed [20]. However, *H. pylori* eradication appears to accelerate gastric ulcer healing. Labenz et al. treated a total of 83 patients presenting with *H. pylori*-positive gastric ulcer with omeprazole and antibiotics [21]. At endoscopy after six weeks, gastric ulcer healing was higher in the patients in whom *H. pylori* was eradicated (85 percent) than in those with persistent *H. pylori* infection (60 percent). Similar results were obtained by Seppälä et al. who treated 210 gastric ulcer patients with either colloidal bismuth subcitrate, or bismuth plus metronidazole or ranitidine [22]. At re-endoscopy after 12 weeks, 32 of 35 (91 percent) of *H. pylori*-negative compared to 130 of 175 (74 percent) of *H. pylori*-positive patients had their gastric ulcer healed. Sung et al. compared triple therapy consisting of bismuth subcitrate, tetracycline and metronidazole with omeprazole in patients with *H. pylori* positive gastric ulcer [23]. Endoscopy at five weeks showed complete healing of the ulcers in 84 percent on triple therapy and 73 percent on omeprazole. However, the patients treated by omeprazole had experienced less days with pain than the patients treated by triple therapy both in the first week (1.9 ± 2.6 vs. 3.6 ± 3.0; p < .005) and in week two through five (4.4 ± 8.7 vs 7.6 ± 9.5; p = .09) [23]. Thus, the combination of a proton pump inhibitor and at least two antibiotics seems presently to be the preferred therapy for *H. pylori* positive gastric ulcer, since this regimen is likely to result in early pain relief and successful *H. pylori* eradication.

**Prevention of *H. pylori*-positive gastric ulcers**

As mentioned earlier, maintenance therapy with ranitidine prevents relapse of gastric ulcer in the majority of patients [2]. In an open study with 150 or 300 mg/day ranitidine, the proportion of patients remaining free from symptomatic recurrence was 97 percent after one year and 79 percent after five years [2]. However, in a placebo-controlled study on 12-month maintenance therapy with 150 mg ranitidine at night, only 64 percent of those on ranitidine and 24 percent of those on placebo were free from gastric ulcer relapse [24]. Thus, despite maintenance therapy with ranitidine, about one-third of the patients had symptomatic or asymptomatic recurrences of gastric ulcer within one year. The recognition of the association of *H. pylori* infection with gastritis and peptic ulcer has prompted several studies to be performed in order to determine whether *H. pylori* eradication prevents relapse of gastric ulcer. Although the follow-up period was usually limited to one year at the most, several studies have confirmed the importance of *H. pylori* eradication therapy for prevention of gastric ulcer relapse. Graham et al. studied 15 patients with gastric ulcer treated with ranitidine plus triple therapy (bismuth subsalicylate, tetracycline and metronidazole) and 11 gastric ulcer patients treated with ranitidine alone [25]. The life table probability of ulcer recurrence one year after ulcer healing was significantly lower in the patients who had received ranitidine plus triple therapy (13 percent) than in those who had been treated by ranitidine alone (74 percent). Similar results were obtained by Sung et al. who compared triple therapy (bismuth subcitrate, tetracycline and metronidazole) with omeprazole [23]. One year after treatment, recurrent gastric ulcers were detected in one of 22 (5 percent) patients in the triple therapy group and 12 of 23 (52 percent) patients in the omeprazole group. Bayerdörffer et al. treated a total of 102 gastric ulcer patients with
either triple therapy (bismuth subsalicylate, amoxicillin and tinidazole) or omeprazole [26]. The 12-month gastric ulcer relapse rate was 51 percent in the patients who had received omeprazole compared to three percent in those who had been treated by triple therapy. In all of the above-mentioned studies, there was a striking relation between \textit{H. pylori} eradication and absence of gastric ulcer recurrence. This relationship was confirmed by studies in which gastric ulcer patients treated by \textit{H. pylori} eradication therapy regimens were divided into those with successful \textit{H. pylori} eradication and those in whom the \textit{H. pylori} eradication regimen had failed. Labenz et al. reported a one-year gastric ulcer recurrence rate of 58 percent (10/18) in patients with \textit{H. pylori} persistence compared to three percent (1/32) in patients in whom \textit{H. pylori} was eradicated from the stomach [21]. Similar results were reported by Seppälä et al. who reported a one-year recurrence rate of 47 percent (60/128) and seven percent (2/29) in gastric ulcer patients after failed and successful \textit{H. pylori} eradication, respectively [22].

**NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND GASTRIC ULCER**

NSAIDs are generally accepted to play a pathogenetic role in the development of gastric ulcer in patients taking such drugs. These ulcers are suggested to be secondary to the NSAID-induced reduction of gastric prostaglandins resulting in an impaired mucosal barrier against aggressive luminal factors, such as acid or pepsin. Interestingly, gastric ulcer may also occur during NSAID-use in patients with achlorhydria due to gastric atrophy [27]. This finding may be important in understanding the limited role of antisecretory drugs in NSAID-related gastric ulcer [28]. The contribution of \textit{H. pylori} infection to the pathogenesis of gastric ulcer in patients taking NSAIDs is a matter of debate.

In an endoscopic study of patients with rheumatoid arthritis, five of 81 [29] were found to have a gastric ulcer. In the patients who were seropositive for \textit{H. pylori} the gastric ulcer rate was five percent (3/55) compared to eight percent (2/26) in \textit{H. pylori} seronegative patients with rheumatoid arthritis. Thus, gastric ulcer may occur in both \textit{H. pylori}-positive and \textit{H. pylori}-negative patients with rheumatoid arthritis. It has, however, been claimed that NSAIDs induce gastric ulcer mainly in \textit{H. pylori} carriers. In patients with a history of NSAID use, \textit{H. pylori} positivity was found in 21 of 27 (78 percent) gastric ulcer patients compared to 13 of 38 (34 percent) patients without an ulcer [30]. Furthermore, a recent study in healthy volunteers showed that severe gastric damage induced by NSAIDs was associated with \textit{H. pylori} infection [31].

Since the ulcerogenic effect of NSAIDs has been well established, this therapy should be discontinued in any patient with a gastric ulcer who is taking such drugs. Continuing NSAID therapy is reported to lower the ulcer healing effect of antisecretory drugs. For example, 32 percent and 53 percent of NSAID-users compared to 59 percent and 85 percent of patients not taking NSAIDs had their gastric ulcer healed with 150 mg twice daily ranitidine at four and eight weeks, respectively [15]. However, the percentage of healed gastric ulcer with 40 mg/day omeprazole in patients receiving concurrent treatment with NSAIDs (81 percent at four weeks and 95 percent at eight weeks) was not different from that in patients who did not take NSAIDs (80 percent at four weeks and 96 percent at eight weeks) [15]. Thus, in patients who need continuous NSAID-therapy, powerful acid inhibitory therapy is required to heal gastric ulcer. It has not yet been established whether \textit{H. pylori} eradication therapy accelerates gastric ulcer healing during continuous NSAID therapy. Clinically it is very difficult to determine whether a gastric ulcer in an \textit{H. pylori}-positive patient with a history of NSAID use is related to the NSAID use, to the \textit{H. pylori}-associated gastritis or to the combination of both factors. Since \textit{H. pylori} eradication therapy largely prevents gastric ulcer recurrences, it seems logical to apply this therapy also to \textit{H. pylori} positive gastric ulcer patients with chronic NSAID use.
However, the prophylactic effect of *H. pylori* eradication therapy in patients on continuing NSAID treatment has yet to be determined.

*H. pylori*-negative patients on chronic NSAID therapy who have a history of NSAID-induced gastric ulcer are candidates for long-term prophylactic therapy. The efficacy of acid inhibitory therapy in the prevention of gastric ulcer in patients taking NSAIDs is limited. Preliminary studies suggest that powerful acid inhibitory therapy with high-dose H₂RAs or proton pump inhibitors may be beneficial in such patients [32, 33]. Another approach is the long-term administration of prostaglandin analogues. Several studies have shown that the prostaglandin analogue misoprostol lowers the relapse rate of gastric ulcer in patients on chronic NSAID-therapy [8-10, 34]. However, side-effects (abdominal cramps, diarrhea) occur rather frequently and may hamper the application of this class of compounds.

**CONCLUSION**

The recent appreciation of the importance of *H. pylori* infection and of NSAID use has changed the medical management of patients with a gastric ulcer. By far the majority of patients will be effectively managed by one of the modalities of drug therapy. Surgery is to be restricted to gastric ulcer patients with complications, severe dysplasia and those who are not able or willing to take the medication.

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