What is the importance of treatment for *Helicobacter pylori* in cases of uncomplicated duodenal ulcers and cases of duodenal ulcers complicated by bleeding?

Javier Leonardo Galindo Pedraza, MD,[1] William Otero Regino, MD,[2] Martín Gómez Zuleta, MD.[3]

[1] Internal Medicine Resident at the Universidad Nacional de Colombia. Bogotá, Colombia
[2] Professor of Medicine in the Gastroenterology Unit of the Universidad Nacional de Colombia. Gastroenterologist at the Hospital El Tunal, Clínica Fundadores. Bogotá, Colombia
[3] Professor of Medicine in the Gastroenterology Unit of the Universidad Nacional de Colombia. Gastroenterologist at the Hospital El Tunal. Bogotá, Colombia

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Abstract

Worldwide *Helicobacter pylori* remains the main etiology for peptic ulcer disease despite progressively decreasing prevalence of the infection. Duodenal ulcers are frequent complications of *H. pylori* infections. Because of the magnitude and consistency of this association, the need for eradication of *Helicobacter pylori* in these cases has been clearly established by the American College of Gastroenterology guidelines and by the Maastricht III consensus. With the eradication treatment healing can be achieved and complications of ulcers such as bleeding can be avoided. It is important to establish an antibiotic treatment appropriate to the population's resistance profile and to confirm eradication of infection in order to eliminate the risk of relapse and complications due to ulcers.

Key words

Helicobacter pylori, duodenal ulcer, bleeding ulcer, verification of eradication.

Helicobacter pylori (H. pylori) infections affect at least 50% of the world's population: more than 80% of the population in developing countries, but only 30 to 40% of the population in the United States (1, 2). H. pylori is involved in the etiologies of gastric cancer (1% to 2% of those infected), gastric MALT (less than 0.1% of those infected) and gastric and duodenal peptic ulcers (1% to 10% of those infected) (2). The risk of suffering from peptic ulcers at some point in life is considered to be 11% to 20% for men and 8% to 11% for women. The annual incidence ranges from 0.03% to 0.19% (3, 4). In many countries H. pylori is the main etiological agent of duodenal ulcers (DU). In Colombia it is present in more than 70% of DU cases, although in other countries such as the US it is present in only 50% of these cases (5). A world-wide consensus now exists on the need to eradicate H. pylori in cases of duodenal ulcers (1-4, 6-12). However, the success of different eradication schemes varies due primarily to the resistance of the microorganisms to different antibiotics (1, 2, 6, 7). The first-line treatment for eradication in Colombia is still not defined owing to the bacteria's profile of resistance to different antimicrobials (13).

CLINICAL CASE

A 68 years old male patient checked in to the emergency room attends urgencies after two occurrences of hematochezia in the previous 12 hours, continuous pain in the upper left quadrant of the abdomen, and nausea without vomiting. Patient had no relevant medical history and was not regularly using any medications.

Vital signs upon admission were BP 86/52, Pulse 102 and Respiratory Rate18. Abdominal examination found no signs of hypoperfusion. Patient was reanimated with isotonic solution until hemodynamic stability was attained. A colonoscopy found residual evidence of bleeding without finding any evidence of bleeding lesions. An upper digestive tract endoscopy showed a bleeding ulcer in the duode-

nal bulb. A urea test was positive. How should this case be handled? Is H. Pylori presence relevant for the treatment?

DISCUSSION

The most important duodenal ulcer etiologies are H. pylori infections and the use of nonsteroidal anti-inflammatory drugs (NSAID) (8). Other duodenal ulcer etiologies include Crohn's disease, Behcet's disease , Zollinger-Ellison syndrome, duodenal neoplasia, intestinal ischemia, amiloidosis, sarcoidosis, eosinophilic gastroenteritis, Henoch-Schonlein purpura and infections by cytomegalovirus, herpes simplex and other types of Helicobacter (8, 9).

Progressive diminution in the frequency of the peptic ulcers, as well as modification of the prevalence of its different etiologies, has been documented for all populations (4). At present, H. pylori infections are present in more than 80% of the world's complicated and uncomplicated cases of duodenal ulcers. Nevertheless, the frequency of ulcers due to consumption of NSAIDs and other factors other than the two main causes is increasing daily (8). The number of ulcers secondary to H. pylori has decreased both in areas with high rates of infection and in areas of low rates of infection. In the latter areas this is especially true among the youngest members of these populations (7, 10, 11). These changes in epidemiology are probably related to decreasing rates of childhood H. pylori infections, increasing use of eradication treatments, better formulations of proton pump inhibitors (PPIs) and to increased NSAIDs consumption (10, 11).

H. pylori infections are more frequently the cause of duodenal ulcers than they are of gastric ulcers. Duodenal ulcers secondary to H. pylori are associated with increased acid secretion due to greater gastrin production induced by H. pylori in the antral region (7, 12). This acid secretion leads to gastric metaplasia of the duodenal mucosa which is most frequently colonized by very virulent H. pylori strains that carry the CagA, Cow and dupA genes (12, 14, 15).

Peptic ulcers secondary to the chronic use of NSAIDs develop in up to 25% of the users of these medicines. Annually 1% to 4% of these patients develop peptic ulcers. Of these, 2% to 4% present complications of bleeding or perforation (3, 16). Ulcers appear more frequently among patients who use NSAIDs at high doses for prolonged periods, among older patients, and among patients with concomitant use of corticoids or anticoagulants (16).

Within the current changing epidemiological trend up to 40% of current cases of peptic ulcers are not associated with H. pylori or NSAIDs. These cases tend to appear in older populations, have greater recurrence rates, and more frequently result in complications and death (7, 8). Ulcers which appear not to be associated with H. pylori and NSAIDs are always endoscopically suspicious when there are multiple, recurring distal bulb lesions (9). In fact some of the ulcers classified in this group are due to unreported use of NSAIDs by patients, while others are cases associated with cases of H. pylori infections undetected due to limitations of diagnostic tests, especially among patients with concomitant use of PPIs (8). Colonization of H. pylori isolated to the duodenum has also been postulated as a reason H. Pylori positive patients test false (17).

In Colombia a recent study described the epidemiology of duodenal ulcers (5). Using direct diagnosis methods, H. pylori were identified as a cause in 73% of the duodenal ulcers. SNAIDs were documented as the exclusive cause of ulcers in 11.5% of the patients, but were also used by 29.8% of the patients with H. pylori infections. 14.4% of the cases corresponded to ulcers which were negative for both H. pylori and NSAIDs use.

ERADICATION OF *H. PYLORI* INFECTIONS IN DUODENAL ULCER

Treating H. pylori has direct repercussions for treatment of peptic ulcers. Consequently the diagnosis of a peptic ulcer mandates eradication (1, 2). In a review by Cochrane that evaluated the utility of eradication of peptic ulcers secondary to H. pylori. Eradication of the bacteria consistently favored healing of duodenal ulcers. The relative risk (RR) compared to antisecretory treatment was 0.66 (CI 95% 0.58-0.76), and was 0.37 (CI 95% 0.26-0.53) compared to placebos (18).

Elimination of H. pylori infection also leads to fewer incidences of relapses than does treatment with PPIs alone. Consequently, for ulcers secondary to H. pylori infections, there is no need to continue treatment with PPIs after the elimination of the infection has been verified (19, 20). Gastric ulcer remission occurs in 97.1% of the patients who have successfully had the bacteria eradicated, while it occurs in only 60.9% of the patients who have not had the bacteria eradicated. For duodenal ulcers, remission is obtained in 98% the patients who have had the bacteria eliminated, as opposed to 57.5% of those who have not (NNT= 4). These findings are independent of NSAID use (21). Cochrane's systematic review found no significant differences in the prevention of recurrence between eradication treatment and maintenance of antisecretory therapy (RR 0.73 CI 95% 0.42-1.25) (18). In patients who have H. pylori eradicated, the annual recurrence rate for duodenal ulcers is of 1.5% (21, 22). In these cases recurrence is generally due to reinfection by the bacteria. This occurs most frequently in underdeveloped countries where there is an annual reinfection rate of around 13% (23-25). Considering the benefits of H. pylori eradication, and the

fact that negative diagnostic tests do not absolutely exclude infection, some authors suggest empirical treatment for the infection whether or not diagnostic confirmation has been made (8). A cost effectiveness study performed in Spain suggests that the empirical approach should be adapted (26). Nevertheless, at present confirmation of the infection with a high performance test is considered necessary, especially because of the epidemiologic utility of determining H. pylori as an etiologic agent and to prevent development of antibiotic resistance (13, 27).

Treatment against H. pylori presents difficulties due to the development of resistance to the more frequently used antibiotics in eradication therapies. Globally the effectiveness of triple therapy using amoxicillin, clarithromycin and PPIs is less than 80% (6). Therefore certain alternatives have been included, such as sequential, concomitant therapies and therapies with levofloxacin (27). The international consensus suggests first line treatment with high doses of PPIs plus amoxicillin and clarithromycin or metronidazole whenever resistance to clarithromycin does not exceed 20% and resistance to metronidazole does not exceed 40% (6). In Colombia resistance to clarithromycin is between 17.7% and 21.7% (27, 28) and resistance to metronidazole is between 72% and 81% (13, 28-30). Considering the recommendations of Maastricht III (6), these antibiotics should not be used as first line triple therapies here in Colombia.

BLEEDING PEPTIC ULCERS

Complications occur in 25% of peptic ulcer patients. They include bleeding, perforation and scarring with secondary obstructions. Of these, bleeding ulcers are most frequent: they occur in 15% of all cases and have a mortality rate of around 10% (3). 80% of these deaths result from causes other than bleeding (multiple organ failure, pulmonary complications and terminal tumors among others). The other 20% are due to hemorrhaging (31). Bleeding is a complication which often recurs. It is described in up to 50% of all patients within 10 years if eradication treatment has not been performed (32).

Initial treatment for a bleeding peptic ulcer is hemodynamic resuscitation. This is followed by high doses of PPIs and, when indicated, by diagnostic and therapeutic high digestive endoscopy (33-36). The first objective of hemodynamic stabilization is to restore lost volume through the use of crystalloid solutions. In addition, red blood cell transfusions may be needed to restore the oxygen transportation capacity of the blood (7 mg/dL of hemoglobin or less) (34). The use of PPIs prior to endoscopy is recommended for all patients because it significantly reduces the severity of bleeding and the necessity of endoscopic therapy. Even so, it only reduces the risk of rebleeding modestly, and it does not reduce the risk of mortality (34,35). Early endoscopy (within 24 hours) is fundamental and is recommended for the majority of patients (33-36). The objectives of endoscopy are to determine the etiology and location of the bleeding, and then to control it. Endoscopy has been shown to effectively reduce mortality, rebleeding and the necessity of surgery (37). Digestive endoscopy allows identification of etiology and location of bleeding of 95% of these patients, although only 25% require endoscopic hemostasis (35). Another objective of early endoscopy is to stratify the risk to the patient (33-36). At present there are a number of endoscopic methods for hemostasis. These include sclerosants, vasoconstricting substances (adrenalin), procoagulants, thermal methods and mechanical devices (33-36). The use of adrenalin (dilution 1:10.000) as a vasoconstrictor has been demonstrated to be effective in stopping the bleeding of a majority of patients. Nevertheless, when used alone, it is less effective at preventing rebleeding. Consequently, the present standard is to combine use of adrenalin with a second hemostatic method (dual method). These include injection therapy using absolute alcohol, thrombin, or fibrin sealant; thermal contact methods and clips (33-36). Cochrane´s systematic review found that the use of two hemostatic methods allows for a reduction in the recurrence of hemorrhaging from 18.8% to 10.4% (NNT= 11), a reduction in the requirement for emergency surgery from 10.8% to 7.1% (NNT= 27) and a reduction in mortality from 5% to 2.5% (NNT= 40) (36). Second look endoscopy is not recommended at present (33-35). High doses of intravenous PPIs during the first 72 hours after endoscopic hemostasis greatly diminish rebleeding, surgery and mortality (38).

The present role of surgery in treating complicated duodenal ulcers with bleeding is as a rescue therapy after the failure of endoscopic procedures. An alternative is embolization through angiography (33). Infection by H. pylori is less prevalent in cases of complicated ulcers than in cases of ulcers without complications. Approximately of 60% to 70% of patients with complicated ulcers have H. pylori infections. This could be due to diminished sensitivity of direct testing in the presence of bleeding (8). Despite the apparently less important relation of the infection to complicated ulcers, it has been demonstrated that complicated ulcers also benefit from eradication therapy (39). Cochrane's review evaluated the utility of eradication treatment in recurrences of bleeding and found that the risk of rebleeding among patients with duodenal ulcers decreased from 20% to 2.9% (NNT= 7, and RR of 0.22 (CI 95% 0.12-0.40). When the effectiveness in prevention of bleeding of maintenance administration of PPIs is compared the effectiveness of eradication of H. pylori, we find an association that eradication treatment reduces risk 0.05%

(NNT= 20) more than PPI treatment while the relative risk is 0.27 (CI 95% 0.09-0.77) (32).

WHY VERIFY ERADICATION?

The importance of determining the eradication of H. pylori infection is justified by the need for epidemiologic evaluation of therapeutic failure, by prevention of associated resistance, by the need for restoration of a second line procedure to guarantee the eradication, by the need to avoid complications from the infection. Eradication must be verified after the treatment of duodenal ulcers since the success of the treatment is directly associated with elimination of H. pylori.

To diagnose whether H. pylori infection persists subsequent to treatment we have direct (invasive) tests and noninvasive tests. The Maastricht III consensus (6) suggests verification of eradication four weeks after treatment with noninvasive tests. The only exception to this recommendation is when direct evaluation by endoscopy is indicated. In cases of duodenal ulcers, which general have benign etiologies, it is not necessary to perform a direct evaluation. Noninvasive tests for H. pylori diagnosis include the urea breath test (UBT), assessment of fecal antigens and immunological tests. Of these tests we use only UBTs and fecal antigen tests for confirmation of eradication since immunological tests tend to remain positive for years (6).

UBTs reveal the presence of H. pylori based on the capacity of the bacteria to unfold urea which results in the production of ammonium and CO_2. The test detects CO_2 formed from the C13 and C14 isotopes in urea ingested by the patient. Post-treatment detection of the infection has a sensitivity of 96% (CI 95% 93-98%) with a specificity of 99% (95% CI: 98% to 99%) (39). Although the UBT is considered to be the gold standard for evaluating eradication, its cost is high for use in routine evaluations of eradication. Consequently the American guide recommends selective verification for patients with dyspepsia and MALT and for those who have undergone resections for early gastric cancer and peptic ulcers (1). Its use for patients with peptic ulcers is recommended only for determination of eradication for those whose ulcers have complications (41).

Fecal antigen testing is a diagnostic alternative which is less expensive and has greater availability (6). Tests available in this market include Premier™ Platinum HpSA® (polyclonal antibodies by ELISA), IDEIA™ Hp StAR™ (monoclonal antibodies by ELISA) and ImmunoCard STAT! HpSA (immunoassay fast test by immunochromatography). Of these tests the ones based on monoclonal antibodies yield better results for evaluation of treatment against H. pylori (41, 42). The IDEIA™ Hp StAR™ test reaches a sensitivity between 87% and 100% with a specificities of 95% to100%, whereas the Premier™ Platinum HpSA® and ImmunoCard STAT! HpSA tests have sensitivities between 75% and 94% with specificities of 91% to 100% (40, 42-44). The usefulness of these tests can be affected by poor sample processing, concomitant use of PPIs or by the presence of gastrointestinal bleeding (44).

CONCLUSSIONS

Infection by H. pylori has a close relation with the development of complicated and uncomplicated duodenal ulcers and is the main etiology of this condition. The literature demonstrates the importance of treating this infection for healing ulcers as well as for preventing their recurrence. Thus, eradication treatment is a fundamental pillar of therapeutic success.

The profile of resistance of the bacterium in our population makes establishment of therapies that will eradicate this infection an urgent necessity. The verification of the eradication is a practice that must be implemented to guarantee the recovery of tissue and to prevent complications from duodenal ulcers when the presence of H. pylori persists. Because of the cost of urea breath tests, determination using fecal antigen testing is a useful alternative here in Colombia.

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