The ideal therapy must be defined in each geographical area: Experience with a quadruple therapy in Spain.

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ABSTRACT

Background

Multiple therapeutic combinations have been tested to determine the optimal regimen/s for Helicobacter pylori eradication, leading to very different results depending on the geographical area. Our goal was to evaluate the efficacy of a "quadruple" therapy with omeprazole, tetracycline, bismuth and metronidazole in our area.

Materials and Methods

We investigate 106 consecutive patients with active peptic ulcer disease, (duodenal, gastric or both) and Helicobacter pylori infection. One-week therapy with omeprazole 20 mgs b.i.d., tetracycline hydrocholoride 500 mgs q.i.d., colloidal bismuth subcitrate 120 mgs q.i.d. and metronidazole 250 mgs t.i.d was prescribed. Between the days 30 and 40 after treatment ended follow-up endoscopy was performed. Eradication was defined as both negative urease test and histology. Between days 90 and 360 a breath test was performed in 100 patients.

Results

91 patients had duodenal ulcer, 12 gastric ulcer, and 3 both. Side effects were observed in 25% of the cases. Eradication was achieved in 87.7% (93/106; CI 79.9-93.3). Healing was obtained in 95.2% (100/105; CI 89.2-98.4); 97.8% (CI 92.4-99.7) in those eradicated and 75% (CI 42.8-94.5) in non-eradicated ($p<0.01$).

C*onclusions*

Quadruple therapy with omeprazole, tetracycline, bismuth subcitrate and metronidazole achieves healing rates up to 95-100%. The 87.7% eradication rate obtained suggests that the regimen we used is a reasonable therapeutic alternative in our area.

INTRODUCTION

Cure of the Helicobacter pylori (*H. pylori*) infection has become the standard therapy of peptic ulcer disease associated to the infection (1,2). Multiple therapeutic combinations have been tested to determine the optimal regimen/s being at the same time simple, effective, well tolerated and with a reasonable cost (3,4,5,6).

Tytgat and coworkers have suggested, according to their own clinical experience, that the efficacy should be the main characteristic when choosing the preferable treatment combination (7). In fact, 7-day quadruple therapy with omeprazole, bismuth subcitrate, tetracycline and metronidazole (OBTM) achieved eradication rates up to 95-100%, with a very low cost, an acceptable rate of side effects, was very well tolerated, with good compliance and, high efficacy even with metronidazole-resistant strains (8,-12).

However, clinical experience reveals that the results achieved in a certain geographical area are not always applicable to other areas. The previous experience with omeprazole plus amoxicillin is particularly revealing. Initial studies, mainly coming from Germany (13), showed eradication rates up to 90% with a very simple and well tolerated regimen. These data were even confirmed in very elegant clinical trials (14). As more experience was gained frustrating results were reported, ranging between 0 and 90 % (15-19). In our area the eradication rate with omeprazole plus amoxicillin is about 30% (20).

With this study we evaluated the effectiveness of a “quadruple” therapy with omeprazole, bismuth subcitrate, tetracycline, and metronidazole (OBTM).

MATERIAL AND METHODS

We planned to include 100 patients with active peptic ulcer in the study. 106 consecutive patients referred to two different centers in the same geographical area (Aragón, Spain) were evaluated. When complete follow-up of 100 patients was achieved inclusion phase was stopped. Afterwards, the six final patients returned to follow-up. Patients were evaluated because of dyspeptic symptoms suggesting peptic ulcer disease. They were four inclusion criteria: a) age between 18 and 75 years, b) active peptic ulcer (duodenal or gastric) diagnosed by endoscopy; c) *H. pylori* infection; and d) informed consent. At first visit, data on demographic characteristics were collected using a standarized form.

Active ulcer was defined endoscopically as a lesion of >5 mm in minor diameter. Routinely we took a biopsy from the minor curvature of the antrum, close to the incisura for an urease test (Jatrox-Test ®). We also took at least four more samples: two from the antrum and two from the body for histological examination. The samples were evaluated systematically with H&E and Giemsa stains. The pathologist graded the presence of Helicobacter-type flora semiquantitatively according to the Sidney protocol (21) as: absent, light, moderate or severe. Between 30 and 40 days after last treatment dose, follow-up endoscopy was performed , with the same set of biopsies as described above. In the cases of gastric ulcer we obtained, also biopsy samples (6-8) were taken from the borders of the lesion to exclude neoplasm.

All the *H. pylori*-positive cases bye histology and a proportion of the negatives were reviewed in an independent and blind way by an external pathologist.

For the purposes of the study we have considered two possibilities:

a) *H. pylori* infection: positive rapid urease test read at 60 minutes *and* histological evidence of the infection.

b) *H. pylori* eradication if at the second endoscopy (performed at least 30 days after the last dose of treatment); both: urease testing (read at 24 hours) and histology (at least 4 biopsy samples, two from the antrum and two from the gastric body) were negative for *H. pylori*.

Pregnant patients, women in fertile age if they did not receive appropriate contraception (defined as oral contraceptive or IUD), patients allergic to one of the drugs to be used in the treatment, or those requiring concomitant treatment with aspirin or NSAIDs were excluded. Patients who had received any anti-*H. pylori* treatment in the last six months, proton pump inhibitors (PPIs), bismuth, or any antibiotic within the 30 days prior to endoscopy, were also excluded .

The following 1-week regimen was prescribed for all 106 patients: omeprazole (Mopral ®)20 mgs b.i.d., tetracycline hydrocholoride 500 mgs (Ambramicina 500 ®) q.i.d., colloidal bismuth subcitrate 120 mgs q.i.d. (Helol or Gastrodenol ®); and metronidazole 250 mgs t.i.d. (Flagyl ®). No other ulcer healing drug was allowed until surveillance. The drugs were prescribed as it is usually done in clinical practice. Patients were informed in detail about the necessity of the treatment and the importance of the compliance to achieve eradication. Verbal explanations and printed instructions were given to the patients to take the drugs.

All the patients were clinically evaluated when finishing the treatment (day 8). At this visit, compliance and side effects were evaluated. To assess compliance, patients filled out a standard questionnaire. We also asked the patients to retrieve the remaining tablets to be counted. Patients were asked about side effects. The first question was the generic one; have you noticed any new symptoms this week?, later a questionnaire on specific possible more frequent secondary effects was made.

Between the days 30 and 40 after treatment ended (day 38 to 48) a second endoscopy was performed, and patients were re-interviewed.

Between 90 and 360 days after finishing the treatment, a breath test with ^{13}C-urea was performed following the European standard protocol in 100 (94,33) of patients (22).

. All values with $p<0.05$ were considered to be statistically significant. Data were included into a data base and results are expressed as means +/-SEM and with a confidence interval of 95%. Confidence intervals were calculate with Epiinfo software (v. 6.04). Healing rates were compared using the χ^2 test with Yates correction

RESULTS

All patients who satisfied the entry criteria agreed to participate. The age of the included patients was of 45,8 years + 2,48 (mean+/-SEM); the rest of the characteristics appear summarized in the table (table 1). 91 patients had duodenal ulcer, 12 gastric ulcer, and 3 simultaneously duodenal and gastric ulcer. All the patients completed treatment and follow-up endoscopy. The compliance was >80% in all the cases. Side effects were reported by 25% of the patients but considered mild by the investigators. All finished the treatment.

According to the preset approach, the intention-to-treatment analysis (it considers not eradicated the patient with pyloric stenosis at the second endoscopy, patient in whom the *H. pylori* status was not evaluated.) showed an eradiation rate of 87.7 % (93/106; CI 79.9-93.3). In the per-protocol analysis (*H. pylori* eradication in the 105 patients in whom the protocol was completed) the cure rate was 88.5 % (93/105; CI 80.9-94). In the 12 patients non-eradicated both, the urease test and histology were positive and all confirmed by the independent pathologist.

Demographic data and endoscopic diagnosis for all patients included in the study are listed in table 2. There were no significant demographic or diagnostic differences between the group of eradicated and non-eradicated patients.

In 100 patients we also performed a breath test. This test confirmed the positivity in 11 out of the 12 non-eradicated cases. The remaining case was reevaluated blindly by a third independent pathologist, who confirmed the infection, with the presence of abundant *H. pylori*. Therefore, it was considered a false negative breath test.

The Breath test was negative in 87 cases. Two of the negative cases on histology and urease test showed a positive breath. In both cases the test was performed more than 180 days after the endoscopy (280 days and 1 year after the inclusion) so reinfection can not be excluded as an explanation of the discrepancy.

Healing was observed in 100/105 patients (95.2%; CI 89.2-98.4). The ulcer had healed in 91 of the 93 (97,8%; CI 92.4-99.7) eradicated patients, and in 9 of the 12 non-eradicated (75%; CI 42.8-94.5) ($p<0.01$). In the table, results are given by subgroups according to the lesion type (table 3).

DISCUSSION

This study wasis neither blind nor randomised, but was prospective, and included a large number of patients (>100), reproduced the real clinical circumstances, and used several methods to validate *H. pylori* status.

Our results contrast with those described previously by DeBoer and other authors (8-12). We did not achieve 90% eradication rate. These results would question the proposal of Tytgat (7) that recommended this regimen as the reference one, at least in our geographical area. However, before accepting our results we must consider the possible causes of the (relatively) low efficacy of this combination.

First, it is well known that the efficacy mainly depends on compliance (23). DeBoer recommends several steps to improve it (24). Our patients received detailed verbal information as well as a written guide of the treatment. All patient returned to the clinical follow-up and accepted a second endoscopy. Based on self-reporting and remaining pills, the compliance was up to 80% in all the cases and >95% in the majority. No patient abandoned treatment due to side effects. All these data endorse the reasoning of DeBoer (24) that this therapy is well tolerated, but lack of compliance seems an unlikely explanation of the relatively low eradication rate.

A second explanation could be high metronidazole resistance rate, or an insufficient dosage of the drug. We do not know the exact resistance rate to imidazoles in our work area. Rates between 30 and 50% have been reported in close areas (25). Preliminary data reported from our region is about 46% (Ducóns JA: personal communication). Therefore it is possible, that many of our patients were infected by resistant strains to the imidazoles. However, DeBoer has suggested that the quadruple therapy is very effective even with metronidazole-resistant strains, (8) proposing it as reasonable alternative in areas of high resistance. Moreover, triple therapy can be very effective in spite of metronidazole resistance (26).

Although additional studies are needed, it doesn't seem that the resistance rate to metronidazole explains the lack of effectiveness satisfactorily, at least as unique factor (27).

The dose of metronidazole we used was 250 mg tid versus the 500 tid dose used by DeBoer et al. Althought there are several studies with low dose of metronidazole that report eradication rates similar to another studies using higher doses (28-31), it is clear that dose can make a difference, particularly considering that metronidazole is critical to the efficacy of bismuth-based triple therapies (32). We are now studying the effect of the same combination with the dose of metronidazole used by DeBoer.

The duration of therapy can also be important. A pooled analysis of the literature reveals that the combination of bismuth, tetracycline and metronidazole obtains eradication rates between 77 and 81%. However if the duration is below 14 days, eradication rates are 71 to 79% (33). Therefore is possible that to prolong therapy to 10 or 14 days could improve our results. However, DeBoer has reported excellent eradication rates with a duration of seven and even only four days (34). The addition of proton pump inhibitors at high doses could explain the efficacy of shorter therapies.

It might be possible that we overestimated the Helicobacter presence after therapy and that false positive histology could explain low eradication rates. However, all *H. pylori*-positive cases were confirmed independently by an external (and blinded to clinical data) pathologist, who also confirmed the negativity of 30 negative samples. In addition 11 out of 12 *H. pylori*-positive cases have been confirmed by a positive 13C urea breath test.

Our data confirm, that a regimen lasting only a week achieves complete ulcer healing and eradication rates close to 90% and was well tolerated. This fact, together with a with a very low probability of complications during the period without treatment makes this regimen a reasonable therapeutic alternative. However, this regimen has some disadvantages, especially the great number of pills (35). It seems rather unreasonable to request a patient to take 15 pills a day, if the same efficacy can be reached with a much simpler regimen (36).

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TABLES

Table 1: Characteristics of the patients included in the study.

	DUODENAL ULCER	GASTRIC ULCER	GASTRIC AND DUODENAL ULCER
SEX: male/female	71/20	8/4	2/1
Smokers	37	6	2

Table 2: Demographic data and endoscopic diagnosis and status *H. pylori*.

	Eradicated	Non-eradicated	Statistics ($p<0.05$)
Mean age(range)	46	42.25	n.s.
Sex (Male/Female)	71/22	9/3	n.s.
Smoker (%)	38	33	n.s.
Diagnosis			
DU	82	9	
GU	10	2	n.s.
DU+GU	2	1	

Table 3: Results distributed by subgroups of lesions.

		Healed	Non-Healed	Total
Duodenal Ulcer	Eradicated	79	2	81
	Non-eradicated	6	3	9
Gastric Ulcer	Eradicated	10		10
	Non-eradicated	2		2
Duodenal Ulcer + Gastric Ulcer	Eradicated	2		2
	Non-eradicated	1		1

TABLE LEGENDS

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