Failure of *Helicobacter pylori* eradication: is poor compliance the main cause?

Joël WERMEILLE (1), Michael CUNNINGHAM (2), Jean-Pierre DEREDING (2), Laurent GIRARD (2), Rémy BAUMANN (2), Georges ZELGER (3), Pierre BURI (4), Jean-Michel METRY (5), Radan SITAVANC (6), Landri GALLAZ (7), Hans MERKI (8), Norman GODIN (2)


**SUMMARY**

Objective — The aim of the study was to evaluate whether poor compliance can be considered as the main cause of the low *Helicobacter pylori* (H. pylori) eradication rate observed in an ambulatory population.

Methods — Seventy-eight patients with non-ulcer dyspepsia or gastroduodenal ulcer in whom H. pylori infection was confirmed by urease Cl-test and histology or bacterial culture, received a 1-week triple therapy comprising lansoprazole 30 mg b.d., amoxicillin 1000 mg b.d. and clarithromycin 500 mg b.d. Compliance was assessed using MEMS® containers (Medication Event Monitoring System) which recorded time of medicines consumption.

Results — The overall H. pylori eradication rate was 65.4% (95% CI: 54.8-76.0%) (intention to treat). Sixty-nine subjects (88.5%) consumed greater than 85% of doses and were considered as “good compliers”. The major reason listed by the nine remaining patients for stopping treatment prematurely was side effects. In the population categorised as “good compliers”, H. pylori eradication rate was 69.6% (95% CI: 58.7-80.5%) (per protocol) indicating that compliance could not be considered as the sole reason for treatment failure. Bacterial culture in a subset of 30 patients further showed a H. pylori eradication rate of 73.9% (95% CI: 55.7-92.1%) in “good compliers” with a clarithromycin-sensitive H. pylori strain. On multivariate analysis, H. pylori eradication was inversely associated with poor compliance (P = 0.029). Presence of a gastroduodenal ulcer, age, gender and smoking habit did not differ significantly between the eradicated and noneradicated groups.

Conclusion — Although poor compliance and bacterial resistance were important factors in determining treatment success in our population, they could only explain 40% of failures suggesting that other factors must be involved.


The importance of *Helicobacter pylori* (H. pylori) infection in the pathogenesis of different gastroduodenal diseases is now clearly established. Treatments that can cure the infection in approximately 90% of the patients are now available, as shown by several large clinical studies [1-5]. However, in Geneva (Switzerland), eradication rates observed by gastroenterologists in primary care are estimated to be 70%, as reported in a few French, Italian and Spanish clinical studies [6-9]. Compliance has been shown to be one of the most important factors in determining the treatment success [10-13]. Previous studies assessing compliance with H. pylori eradication regimens have used indirect methods such as pill count or patient interview, techniques listed amongst the least reliable evaluation strategies [4-6, 10-15]. Advances in computer technology have made it possible to incorporate a concealed microprocessor in the cap of normal-sized medicine bottle, recording the date and time the container is opened and assuming a presumptive dose on each occasion. Nowadays, these computerised compliance monitors represent the most reliable of the indirect methods for assessing compliance [14-20]. Additionally, they are easier to use and provide supplementary data on the time of medicine consumption than other methods, such as the measurement of the medication level in the blood [14-17].

The aim of our study was to evaluate compliance as a potential factor responsible for the lower H. pylori eradication rates observed in our ambulatory population by using a computerised compliance monitor (MEMS®: Medication Event Monitoring System, Aardex Ltd, Zug, Switzerland).

**Materials and methods**

**Patients and diagnosis**

Ambulatory patients selected for the study had an endoscopically proven diagnosis of a gastroduodenal ulcer or gastritis with nonulcer dyspepsia, and unequivocal evidence of *H. pylori* infection assessed by rapid urease test [21, 22] from two biopsies (one from the antrum and the other from the corpus). Three quarters of the subjects also had confirmation of *H. pylori* infection by histology or bacterial culture. Exclusion criteria were: (i) patients younger than 20 years old, (ii) history of allergy to any of the medicines used in the study, (iii) major organic, systemic, metabolic or psychiatric diseases, (iv) pregnancy, (v) treatment with antibiotics within the 2 weeks before study entry.
More than 90% of the patients included in the study were receiving an eradication treatment of H. pylori for the first time and less than 10% had taken a proton pump inhibitor during the week before the therapy. The study was approved by the local ethics committee for clinical research in private practice and all patients gave written informed consent. Endoscopy was performed with Olympus (GF-XQ10), Pentax (EG-2901) and Fujinon (EG-200) gastrosopes. Endoscopes and biopsy equipment were disinfected between the procedures with 2% glutaraldehyde, according to standard procedures.

Treatment

All patients received a 1-week triple therapy comprising lansoprazole 30 mg, amoxycillin 1000 mg and clarithromycin 500 mg, all twice daily with food [1, 3]. Patients with gastroduodenal ulcer additionally received a 3-week treatment of lansoprazole 30 mg per day, following completion of the eradication regimen.

Assessment of eradication and side effects

Assessment of H. pylori eradication was performed by 13C-urea breath test four to eight weeks after completion of the treatment (positive = excess ≥ 13C ≥ 0.5%, specificity ≥ 95 to 100%) [22, 23]. All patients were seen or contacted by phone, 1 to 7 days after the end of the therapy and interviewed about possible side effects.

Assessment of patient compliance

Each patient received 3 MEMS boxes, containing a 7-day supply of each medication. Written information provided with the MEMS boxes instructed the patient to (i) take each medicine twice daily, allowing approximately 12 hours between each dose, (ii) return the empty container on completion of the course.

Compliance was defined as the percentage of doses taken (as assessed by the number of container openings) during the 8 days (192 h) following the first dose. Arbitrarily, patients were considered to be "good compliers" if they had taken at least 12 out of 14 doses of each medication (compliance ≥ 85%) during the assessed time period, as reported in some large clinical studies [4].

Assessment of H. pylori sensitivity

Culture was performed in the last 30 patients because a planned interim analysis showed a lower eradication rate than expected in the patients considered as "good compliers".

One to two antral biopsies were taken for bacterial culture and transported at room temperature in a specific medium (Portagarm pylori®; BioMerieux SA, Marcy-l’Etoile, France). The same day the samples were inoculated on Columbia agar plates containing 10% horse plasma (Gelose pylori®, BioMerieux) and incubated for 3-9 days at 35-37°C in a microaerophilic atmosphere (5% O2, 10% CO2, 85% N2) and 100% relative humidity. H. pylori was identified by colony morphology and positive biochemical reaction for catalase, urease and oxidase. The minimum inhibitory concentrations (MICs) of amoxicillin and clarithromycin were determined using the E-test method (AB Biodisk, Solna, Sweden) according to the manufacturers instructions, on Muller-Hinton agar containing 5% sheep blood. The breakpoint MICs used to define antibiotic resistance were chosen according to the available data published in the literature: 2mg/L for amoxycillin [24] and 1 mg/L for clarithromycin [25].

Statistical method

Both an intention-to-treat (ITT) and a per-protocol (PP) analysis were performed. Patients were included in the ITT analysis if they were positive for H. pylori infection in the rapid urease test and if they had agreed to be involved in the study. Patients who had taken less than 85% of the prescribed eradication treatment were not included in the PP analysis.

A multivariate analysis was performed to assess potential association between success of the treatment and compliance, gender, age, gas-

Fig. 1 – Distribution of the patients according to treatment compliance and H. pylori eradication rates. Days of Rx: Number of treatment days correctly followed. Compliance (%): Percentage of prescribed doses taken.

Results

Seventy eight patients (38 women, 40 men) were included in the study between July 1997 and May 1999. The mean age was 44 years with a range of 20-77 years. Fifty eight patients had nonulcer dyspepsia, 14 duodenal ulcer and 6 gastric ulcer. Fourteen subjects were smokers (≥ 10 cigarettes per day). Twenty four patients (31%) took 1-5 medicines for chronic disease management in addition to the eradication treatment. No patient was lost during the follow up period.

Overall (ITT analysis), H. pylori eradication treatment was successful in 51 of 78 patients (65.4%, 95% CI: 54.8-76.0%). Sixty-nine patients (88.5%) were “good compliers” and less than 10% of them had taken 1-2 doses at an interval greater than 15 hours or smaller than 9 hours. Nine patients (11.5%) demonstrated compliance lower than 85% (figure 1)). Six stopped their treatment prematurely because of side effects (nausea, vomiting, stomatitis and epigastric pain) and three missed doses of their medicines. H. pylori eradication rate was 69.6% (95% CI: 58.7-80.5%) (48 of 69 patients) in the population categorised as “good compliers” (PP analysis) and only 33.3% (3 of 9) in subjects having taken less than 85% of the prescribed medicines. On multivariate analysis, H. pylori eradication was inversely associated with poor compliance (P = 0.029). Presence of a gastroduodenal ulcer, age, gender and smoking habit did not significantly affect eradication rate.

Adverse events were reported by 67% of the patients, but were usually mild (table I). All tested strains at culture were sensitive to amoxycillin, 4 (1.3%) were resistant to clarithromycin (MICs > 1mg/L). Further analysis in this subset of patients showed an overall H. pylori eradication rate of 66.7% (95% CI: 49.9-83.7%) (20 of 30 patients), which was comparable to overall eradication rate. “Good compliers” with a clarithromycin-sensitive H. pylori strain demonstrated an eradication rate of 73.9% (95% CI: 55.7-92.1%) (17 of 23 patients). The presence of clarithromycin resistant strains was associated with a low
Table I. – Side effects associated with H. pylori eradication treatment.

<table>
<thead>
<tr>
<th>Severity of side effects*</th>
<th>Incidence of side effects according to patient judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade a (base stools, metallic taste, stomatitis, nausea, fatigue)</td>
<td>50% (39 patients)</td>
</tr>
<tr>
<td>Grade b (diarrhoea, stomatitis, fatigue)</td>
<td>9% (7 patients)</td>
</tr>
<tr>
<td>Grade c (epigastric pain, stomatitis, nausea, vomiting, fatigue)</td>
<td>8% (6 patients)</td>
</tr>
<tr>
<td>No side effects</td>
<td>33% (26 patients)</td>
</tr>
</tbody>
</table>

*Severity of side effects:
- Grade a: Slight discomfort, not interfering with daily activities
- Grade b: Moderate side effects, interfering partially with daily activities
- Grade c: Side effects severe enough to lead the patient to stop his therapy

eradication rate (25%), although not significantly because of the limited number of patients.

Compliance was inversely associated with severe (grade c) side effects (P < 0.001). Gender, age, gastroduodenal disease and the number of additional medicines for chronic disease management did not differ significantly between “good compliers” and patients having taken less than 85% of the prescribed medicines.

Discussion

Compliance depends on factors which are subjective (personality of the patient, illness symptoms) as well as objective, such as the number of daily doses, the occurrence of side effects and length of treatment. In our study, overall compliance was good, with poor compliance being clearly associated with side effects considered by the patients important enough to stop treatment. Three arguments could explain the good compliance observed in the group of patients without severe (grade c) side effects: (i) the treatment was short and relatively simple, (ii) less than a third of the subjects were taking medicines in addition to H. pylori treatment, (iii) patients involved in compliance clinical studies may be more conscientious in their medicines consumption and better informed by the physician about the importance of treatment and the possible risk of side effects. Lee et al observed that patients in an “enhanced compliance program” were more prone to take their medication (67% of the control group versus 89% of the “enhanced compliance program” group; P < 0.01) [26]. Published studies which have assessed compliance with 1 week proton pump inhibitor triple therapy [4-6, 12, 13] used relatively unreliable strategies. It is therefore difficult to compare results since our method was more accurate in determining “poor compliers”.

In large clinical studies [1-5] using the proton pump inhibitor triple therapy, the rate of side effects is disparate, ranging from 10 to 60% according to the trial. In our study, side effects were reported by 67% of the patients. This high rate can be explained to some extent by the method of interview: usual adverse events of triple therapy were suggested to the patients. This emphasises the importance of the methodology adopted in data collection of side effects. Most of the adverse events were mild and only 17% of the patients reported a disruption to their daily activities. About 8% of the patients discontinued their treatment because of side effects, which was higher than previous reported studies [1-5, 9]. The setting of the study may explain this result, as in an ambulatory context, patients are more liable to stop their treatment when experiencing adverse events.

In our study, poor compliance was clearly associated with low eradication rate (P = 0.029). However, this factor cannot be considered as the sole reason for treatment failure, as even within the population classified as “good compliers”, our eradication rate of approximately 70% was lower than those reported in large clinical trials [1-5]. Bacterial resistance also cannot explain most treatment failures because the sub-group (n=30) of clarithromycin-sensitive patients had a similarly low eradication rate of 73.9%.

In conclusion, although poor compliance and bacterial resistance were important factors, they could only explain 40% of treatment failures in our ambulatory population, suggesting that other factors were involved. Additional studies are required to further investigate the reasons for treatment failure associated with 1-week H. pylori eradication treatment comprising a proton pump inhibitor and 2 antibiotics.

ACKNOWLEDGMENTS - The authors thank Mr H. Patthey and Mr H. Messmer for medical monitoring, and Mr B. Grab for statistical assistance and critical review of the manuscript. Financial support was received from Grientschul Pharma SA, Takeda Pharma Division, Mülheid, Switzerland. Clarithromycin was received from Abbott AG, Cham, Switzerland.

REFERENCES


