How can the current strategies for Helicobacter pylori eradication therapy be improved?

Alex Ford MBChB MRCP, Paul Moayyedi MBChB BSc MRCP PhD

BACKGROUND: The use of Helicobacter pylori eradication therapy is advocated in an increasing variety of situations. It is therefore important to optimise current strategies to eradicate H pylori infection.

OBJECTIVES: To define the optimum dosage, drugs and duration of proton pump inhibitor (PPI) triple therapy.

METHODS: A review of the literature was performed to identify randomized controlled trials and systematic reviews addressing these issues.

RESULTS: In PPI, amoxicillin and clarithromycin (PAC) based regimens, twice daily PPI gave optimal eradication rates (relative risk reduction [RRR] compared with once daily = 7% 95% CI 2% to 12%), but in PPI, clarithromycin and metronidazole (PCM) based regimens there was no difference (RRR = 2% 95% CI –7% to 10%). Omeprazole and lansoprazole-containing triple therapies achieved similar eradication rates, but rabeprazole appeared superior to omeprazole (RRR = 8% 95% CI 2% to 14%). The optimum clarithromycin dose in a PAC regimen was 500 mg twice daily (RRR = 11% 95% CI 3% to 18%), but 250 mg twice daily in a PCM regimen (RRR = 2% 95% CI 4% to 7%). Eradication rates were lower with a seven day regimen compared with fourteen (RRR = 12% 95% CI 7% to 17%). Overall there was no difference between a PAC and a PCM regimen (RRR = 0% 95% CI –3% to 3%).

CONCLUSIONS: PAC and PCM regimens are equally effective if used optimally, though PCM is cheaper. The eradication regimen and its duration should be tailored according to the clinical situation.

Key Words: Clarithromycin; Eradication; Helicobacter pylori; Meta-analysis; Proton pump inhibitor

Eradiation therapy for Helicobacter pylori infection has become an important weapon in the clinician’s armoury against dyspepsia. The European Helicobacter pylori Study Group (EHPSG) suggests that H pylori eradication is strongly recommended for patients with peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, atrophic gastritis, postgastric cancer resection, patients with a first-degree relative with gastric cancer and as part of a test and treat strategy (1). The Maastricht 2-2000 consensus also suggested H pylori eradication is advisable for patients with nonulcer dyspepsia, long term acid suppression and before nonsteroidal anti-inflammatory drug therapy (1). With such a variety of indications, it is important to optimise current strategies to eradicate H pylori infection.

Trials indicate that clarithromycin-based proton pump inhibitor (PPI) triple therapies are the most effective regimens for the treatment of H pylori infection (2,3). A systematic review (4) reported that ranitidine bismuth citrate triple therapy regimens are as effective as their PPI counterparts in eradicating H pylori, but because PPI-based triple therapies are more widely used they are the focus of the present review. The aims of the present paper are to address the optimum doses of the drugs used in PPI-based clarithromycin triple therapies to reach conclusions as to the optimal regimens. Strategies that could improve on these therapies using existing antibiotics will also be explored.

OPTIMUM DOSE AND DURATION OF PPI IN CLARITHROMYCIN-BASED THERAPY

Optimum dose of PPI

The dose of PPI required in amoxycillin dual therapy is important, with increasing acid suppression leading to greater efficacy (5). A review and meta-analysis of the literature was performed to evaluate whether the dose of PPI was also important in clarithromycin-
Improving current strategies for *H pylori* eradication

### Optimum PPI

A meta-analysis of 10 RCTs performed in 2001 (20), evaluating a total of 1348 patients, showed that there was no significant difference between omeprazole and lansoprazole-containing triple therapies of seven days or more.

However, five RCTs (16,21-24) evaluating 934 patients were found that compared the equivalent doses of rabeprazole and omeprazole in PAC regimens. Meta-analysis of these trials suggests that rabeprazole is superior to omeprazole (RRR 11%, 95% CI 3% to 18%; NNT 11, 95% CI 9 to 65) (Figure 3). With regard to the use of rabeprazole in PAC regimens, there was only one trial comparing it to an omeprazole-containing regimen, and that trial showed no significant difference between the two regimens (22). There was insufficient evidence to allow any comparison between pantoprazole and the other PPIs to be made.

### Optimum dose of clarithromycin

The question of the optimum dose of clarithromycin has already been the subject of a systematic review published in 1999 (25). At that time, there were four trials, evaluating a total of 385 patients, comparing clarithromycin 250 mg with clarithromycin 500 mg in a PAC regimen. Meta-analysis suggested that the higher dose of clarithromycin was optimal (RRR 11%, 95% CI 3% to 18%; NNT 11, 95% CI 9 to 65) (20). There were also four trials, evaluating a total of 642 patients, comparing 250 mg with 500 mg of clarithromycin in a PAC regimen. Doubling the dose of clarithromycin had no statistically significant effect on eradication rates (RRR 2%; 95% CI –7% to 4%) (20). There were also four trials, evaluating a total of 1348 patients, comparing clarithromycin 250 mg with clarithromycin 500 mg in a PAC regimen. Meta-analysis of these trials suggests that clarithromycin 250 mg is optimal (RRR 11%, 95% CI 3% to 18%; NNT 11, 95% CI 9 to 65) (20). There were also four trials, evaluating a total of 642 patients, comparing 250 mg with 500 mg of clarithromycin in a PAC regimen. Doubling the dose of clarithromycin had no statistically significant effect on eradication rates (RRR 2%; 95% CI –7% to 4%) (20). There were also four trials, evaluating a total of 1348 patients, comparing clarithromycin 250 mg with clarithromycin 500 mg in a PAC regimen. Meta-analysis of these trials suggests that clarithromycin 250 mg is optimal (RRR 11%, 95% CI 3% to 18%; NNT 11, 95% CI 9 to 65) (20). There were also four trials, evaluating a total of 642 patients, comparing 250 mg with 500 mg of clarithromycin in a PAC regimen. Doubling the dose of clarithromycin had no statistically significant effect on eradication rates (RRR 2%; 95% CI –7% to 4%) (20). There were also four trials, evaluating a total of 1348 patients, comparing clarithromycin 250 mg with clarithromycin 500 mg in a PAC regimen. Meta-analysis of these trials suggests that clarithromycin 250 mg is optimal (RRR 11%, 95% CI 3% to 18%; NNT 11, 95% CI 9 to 65) (20). There were also four trials, evaluating a total of 642 patients, comparing 250 mg with 500 mg of clarithromycin in a PAC regimen. Doubling the dose of clarithromycin had no statistically significant effect on eradication rates (RRR 2%; 95% CI –7% to 4%) (20).

### Optimum regimen

The data suggest that the optimum PAC regimen is one that contains a PPI, clarithromycin 500 mg and amoxicillin 1 g, all given twice daily, whereas the optimum PCM regimen is PPI
A previous systematic review and meta-analysis (49) was updated and reanalyzed to examine the question of optimum duration of treatment. There were six RCTs (7,21,50-52) evaluating 1992 patients that compared seven and 10 days of clarithromycin-based PPI triple therapy. There was a statistically nonsignificant trend for a reduction in H. pylori cure for seven-day compared with 10-day therapy (RRR 4%; 95% CI −2% to 10%) (Figure 6). Twelve trials (43,51,52,54-60) evaluating 1592 patients that compared seven- with 14-day PPI triple therapy were also identified. Seven days of therapy was significantly less likely to cure H. pylori infection (RRR 12%, 95% CI 7% to 17%; NNT 12, 95% CI 9 to 21) (Figure 7). These data combine PAC and PCM regimens, but the longer duration therapy was still significantly more effective when these two regimens were considered separately. Present evidence, therefore, suggests that increasing the length of therapy to two weeks will improve eradication rates.

New approaches using existing antibiotics
A recent trial performed in Italy (61) compared a novel 10-day eradication regimen, in the form of five days of rabeprazole 20 mg and amosxycillin 1 g twice daily followed by five days of rabeprazole 20 mg, clarithromycin 500 mg and tinidazole 500 mg twice daily, with a standard seven-day PAC regimen in 1099 H pylori-positive patients. H pylori was eradicated in 378 of 399 patients (95%) allocated to the 10-day therapy compared with 301 of 397 patients (76%) given seven days of PAC. This is an interesting finding, but the regimen also needs to be compared with a standard PPI regimen and further trials are needed to ensure that these results can be replicated in other centres.
The optimum H pylori eradication regimen is still the subject of intensive research, with the results of many RCTs being published each year. The Cochrane collaboration (62) is conducting a systematic review that will hopefully give definitive answers as to the most effective therapy. This publication is eagerly awaited but until then a picture appears to be emerging. PAC and PCM are equally effective but the latter requires a lower dose of PPI and clarithromycin. PCM is, therefore, less expensive than PAC and is the most cost effective option. However, the EHPSG guidelines prefer the combination of PAC to be used as first-line treatment (1). The reason for this is that if PAC fails, the second-line treatment of quadruple therapy with PPI, bismuth, metronidazole and tetracycline involves treatment of the patient with antibiotics that they have not previously received. The overall success rate for this strategy could theoretically be as high as 98% (63), whereas if PCM fails as first-line treatment the second-line approach would be PPI and amoxycillin dual therapy, giving an overall theoretical eradication rate of 95% (20).

There can be no generic recommendation for an eradication regimen that should be applied to all cases of H pylori infection. Each clinical situation should be considered separately and, using the information available, the best decision for the treatment of that patient should be made. In a ‘test and treat’ strategy for the management of dyspepsia and when H pylori eradication is being used to treat nonulcer dyspepsia, PCM should be used. This is because the gains from H pylori eradication are relatively small (64) and, therefore, the cheapest strategy will be the most cost effective (20). In other cases such as peptic ulcer disease and MALT lymphoma, where the evidence suggests that eradication carries a more definite advantage, PAC should be used, and may be more effective if the duration of therapy is 14 days and the possibility that rabeprazole may be more effective in this regimen deserves further consideration.

REFERENCES


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