www.nature.com/clinicalpractice/gasthep

How effective are quadruple therapies as first-line *H. pylori* eradication therapies?

Original article Fischbach LA *et al.* (2004) Meta-analysis: the efficacy, adverse events, and adherence related to first-line anti-Helicobacter pylori quadruple therapies. *Aliment Pharmacol Ther* **20:** 1071–1082

SYNOPSIS

KEYWORDS *Helicobacter pylori*, eradication therapy, first-line therapy, quadruple therapy, triple therapy

BACKGROUND

First-line triple therapies for the eradication of *Helicobacter pylori* infection are becoming less effective owing to a rise in clarithromycin and metronidazole resistance. The use of quadruple therapy has been suggested as an effective alternative first-line therapy; however, concerns regarding patient compliance and an increased incidence of adverse events have discouraged its use in clinical practice.

OBJECTIVE

To determine the safety, patient adherence and efficacy of first-line quadruple therapies and compare their efficacy with that of first-line triple therapies.

DESIGN AND INTERVENTION

Ninety-eight studies (7,151 patients) were identified as suitable for this meta-analysis. Eligible studies included at least one treatment arm with adult patients who tested positive for *H. pylori* infection and who had received quadruple therapy as a first-line treatment. These studies also indicated the percentage of patients in whom *H. pylori* was eradicated, and included the name, dosage, frequency and duration of all drugs used in quadruple therapy regimens. Duplicate and pediatric studies as well as studies with insufficient treatment information were excluded. Rates of efficacy for quadruple therapies (and sources of heterogeneity between efficacy rates), data regarding study quality, adverse events and patient adherence were all entered into a database. Meta-regression models were used to evaluate sources of variation in efficacy of first-line therapies. Each *H. pylori* eradication regimen was analyzed using a number of statistical tests.

OUTCOME MEASURES

The primary outcome measure was the number of patients who successfully eradicated *H. pylori* as a result of quadruple therapy. Secondary outcome measures included adverse effects, patient adherence and the identification of factors that caused variation in treatment efficacy among eradication regimens.

RESULTS

Quadruple therapy combining metronidazole, tetracycline, a gastric acid inhibitor and a bismuth compound (GBMT) was the most commonly used quadruple regimen (3,991 [56%] of 7151 patients). The inclusion of omeprazole as part of the quadruple therapy regimen was shown to improve treatment efficacy by 6%. A 10–14-day GBMT regimen including omeprazole eradicated *H. pylori* in >85% of patients, even in areas of high metronidazole resistance. The most effective drug dosage of GBMT was 1,000 mg tetracycline and metronidazole and 20 mg omeprazole twice-daily. Metronidazole resistance was the most significant indicator of variation in treatment efficacy between triple and quadruple regimens. Meta-regression analysis revealed GBMT was 11% (95% CI 4–17, $P=0.002$) more effective in areas with high metronidazole resistance than triple therapy. Quadruple therapy was more effective in the Netherlands, Hong Kong and Australia. Quadruple therapy eradicated *H. pylori* in 90–100% of patients with clarithromycin-resistant *H. pylori* infection, compared with 25–61% ($P<0.001$) of patients who received triple therapy. Adverse events and patient adherence were similar for both quadruple and triple regimens.

CONCLUSION

Quadruple therapy combining a proton-pump inhibitor, a bismuth compound, metronidazole and tetracycline should be considered for use as a first-line therapy for *H. pylori* infection.

COMMENTARY

Thomas J Borody

Early eradication therapies for *H. pylori* infection used bismuth compounds alone, which lacked efficacy unless combined with antibiotics. High cure rates have been achieved by classic triple therapy of bismuth, metronidazole and tetracycline in metronidazole after 7 days of treatment, although 14 days were required to substantially eradicate resistant strains.[1] By contrast, quadruple therapy, with a proton pump inhibitor (PPI) plus bismuth, metronidazole and tetracycline, was effective in reducing dyspeptic symptoms, had fewer adverse effects, had a higher cure rate in sensitive and resistant *H. pylori* strains, and can be used for a shorter treatment period than a triple therapy of bismuth, metrondiazole and tetracycline alone.[2] Quadruple therapy was first accepted as first-line treatment by Canadian Guidelines, but other guidelines have suggested that it should be used as a 'rescue' therapy only after failure of triple therapy.[3] Meanwhile, the efficacy of 1-week triple therapies with a PPI plus two antibiotics (i.e. clarithromycin and metronidazole or clarithromycin and amoxicillin), has fallen as a result of rising resistance to clarithromycin. It has therefore been suggested that quadruple therapy supplant current first-line clarithromycin-based triple therapies for the eradication of *H. pylori* infection. The perception that the dosing complexity and side effects of quadruple therapy could lead to noncompliance has restricted this idea gaining wide acceptance, except in the US. Quadruple therapy had an efficacy similar to (although slightly higher than) triple therapy in a meta-analysis of randomized trials for the eradication of *H. pylori* infection.[4]

Fischbach *et al.* have conducted a comprehensive meta-analysis of quadruple therapy versus triple therapy for *H. pylori* infection using a 'meta-epidemiological' approach. Like other meta-analyses, the Fischbach *et al.* study has limitations, including a lack of information on the potential determinants influencing treatment outcomes (e.g. adverse effects, compliance, diagnosis, antibiotic resistance, patient subgroups), and the small sample size of the study groups. Fischbach *et al.* found that quadruple therapy (with omeprazole) was highly effective even in the presence of metronidazole resistance. Efficacy was heterogeneous across treatment arms, with geographical location, metronidazole resistance, duration, omeprazole use and sample size being important predictors. There was greater efficacy in countries such as Australia, Hong Kong and the Netherlands, probably owing to low metronidazole resistance.

Metronidazole resistance reduced efficacy by 9% whereas omeprazole use increased efficacy by 6%, suggesting that these factors have little influence on the efficacy of quadruple therapy. By contrast, the Fischbach *et al.* meta-analysis revealed that clarithromycin resistance alone accounted for 67% of the variation in treatment efficacy when quadruple therapy was compared in six studies assessing triple therapy of a PPI, clarithromycin and amoxicillin. In three studies, therapies based on a PPI plus bismuth, metronidazole and tetracycline were significantly more effective than PPI plus clarithromycin and amoxicillin in the presence of clarithromycin resistance, suggesting that clarithromycin resistance has little impact on the efficacy of quadruple therapy.

Although the use of quadruple therapy has been associated with adverse effects and noncompliance, Fischbach *et al.* found that these were similar for quadruple therapy and triple therapy in 10 controlled trials. The analysis also showed that the average cost of a 10-day treatment with quadruple therapy is similar to a 7-day triple therapy, but that the cost varies from country to country. Thus, in the absence of other effective first-line therapies, the evidence presented in this meta-analysis is clear enough to recommend a combination of a PPI, bismuth, metronidazole and tetracycline as a first-line treatment for *H. pylori* infection,[5] especially in areas where current therapy is performing poorly because of rising resistance to clarithromycin.

References

1 Borody TJ *et al.* (1987) Symptoms improve after the eradication of gastric Campylobacter pyloridis. *Med J Aust* **148:** 450–451
2 de Boer W *et al.* (1995) Effect of acid suppression on efficacy of treatment for Helicobacter pylori infection. *Lancet* **345:** 817–820
3 Malfertheiner P *et al.* (2002) Current concepts in the management of Helicobacter pylori infection—the Maastricht 2-2000 Consensus Report. *Aliment Pharmacol Ther* **16:** 167–180
4 Gene E *et al.* (2003) Triple vs. quadruple therapy for treating Helicobacter pylori infection: a meta-analysis. *Aliment Pharmacol Ther* **17:** 1137–1143
5 Borody TJ (2000) Quadruple should be first-line therapy for Helicobacter pylori infection. In *Helicobacter pylori: Basic Mechanisms to Clinical Cure*, 629–633 Boston: Kluwer Academic Publishers

Thomas J Borody is Director of the Centre for Digestive Diseases, Sydney, Australia.

Acknowledgments
The synopsis was written by Rachel Jones, Associate Editor, Nature Clinical Practice.

Competing interests
The author declared he has no competing interests.

Correspondence
144 Great North Road
Five Dock
NSW 2046
Australia
tborody@zip.com.au

Received 2 February 2005
Accepted 15 March 2005
www.nature.com/clinicalpractice
doi:10.1038/ncpgasthep0137

PRACTICE POINT
Quadruple therapy should be used as a first-line treatment for *H. pylori* infection