Are there geographical and regional differences in *Helicobacter pylori* eradication?

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An important area of controversy in *Helicobacter pylori* eradication is the apparent difference in eradication rates seen in different countries and populations. A recent meta-analysis showed that several factors may affect the outcome of therapy. Individuals residing in northeast Asia had higher eradication rates than those residing in Europe or other areas of Asia. Triple and quadruple drug therapies had significantly higher eradication rates than did dual drug therapies. Treatment regimens that lasted longer than 14 days were better than those that lasted less than seven days, but there was no significant advantage for 10 day therapy over seven day therapy. A number of factors may play a role in determining the regional and geographical differences in *H pylori* eradication therapy. Included in these factors are genetic differences in the metabolism of the proton pump inhibitor, which can alter the availability of antimicrobials in the stomach. Regional differences in antimicrobial resistance also affect the outcome of therapy. Some studies suggest that the degree of gastritis and the nature of the underlying disease may affect the outcome of therapy, but the data are controversial. Understanding the regional and geographical differences in *H pylori* eradication can help physicians select the optimal treatment regimen in different regions.

Key Words: Dyspepsia; Gastritis; *H pylori*; Peptic ulcer disease

Differences in the results of eradication therapy for *Helicobacter pylori* infection in various patient populations may be due to a number of factors. Genetic factors may result in differences in the metabolism and bioavailability of antibiotics. Geographical differences in antimicrobial resistance may affect the results of eradication therapy. The duration of treatment may affect eradication in different patient populations. Patients with certain *H pylori* strains or certain underlying diseases (eg, peptic ulcer disease) may have better eradication rates than patients with nonulcer dyspepsia with conventional regimens for *H pylori* eradication. Each of these is considered in more detail below.

THE EVIDENCE FOR VARIABILITY IN *H PYLORI* ERADICATION RATES

A recent meta-analysis of dual, triple and quadruple therapy regimens to eradicate *H pylori* infection assessed the sources of

Existe-t-il des différences géographiques et régionales dans l'éradication de l'*Helicobacter pylori* ?

La différence apparente dans les taux d'éradication observés selon les pays et les populations demeure un important sujet de controverse dans l'éradication de l'*Helicobacter pylori*. Une méta-analyse récente a démontré que plusieurs facteurs peuvent influencer sur l'issue de la thérapie. Les personnes qui habitent au nord-est de l'Asie présentaient un taux d'éradication plus élevé que celles qui habitent en Europe ou dans d'autres régions d'Asie. Les trithérapies et les quadrithérapies assuraient un taux d'éradication beaucoup plus élevé que les bithérapies. Les schémas thérapeutiques de plus de 14 jours étaient plus efficaces que ceux de moins de sept jours, mais on ne remarquait aucun avantage significatif au traitement de dix jours par rapport à celui de sept jours. Plusieurs facteurs peuvent jouer un rôle dans l'établissement des différences régionales et géographiques du traitement d'éradication du *H pylori*. Parmi ces facteurs, soulignons les différences génétiques du métabolisme de l'inhibiteur de la pompe à protons, qui peut modifier la disponibilité des antimicrobiens de l'estomac. Les différences régionales d'antibiorésistance influent également sur l'issue de la thérapie. Selon certaines études, le degré de gastrite et la nature de la maladie sous-jacente peuvent avoir des répercussions sur l'issue de la thérapie, mais ces données sont controversées. Une meilleure compréhension des différences régionales et géographiques de l'éradication du *H pylori* pourrait aider les médecins à sélectionner le schéma thérapeutique optimal selon les régions.

variation in the results of *H pylori* treatment trials (1). The authors reviewed the English and Spanish language literature and considered studies with subjects older than 18 years and trials with five or more subjects. Cure of *H pylori* infection was defined by the absence of *H pylori* infection on all tests. The authors extracted information about the mean age of the subjects, the number of medications used (two versus three or four), the dose, frequency and duration of treatment and the characteristics of the population being studied, including the geographical location and the prevalence of metronidazole-resistant strains. The study identified 618 antimicrobial treatment groups from 44 countries (western Europe 66%, United States and Canada 11%, Northeast Asia 9%, Australia, New Zealand, Singapore and Malaysia 5%, eastern Europe and the Middle East 4%, South America 3%, Africa 1% and other regions 1%). The results of this analysis showed that triple and quadruple therapies eliminated 33% more *H pylori* infections

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than did dual therapies. The treatment effect increased with longer treatment duration. The efficacy of metronidazole-containing regimens decreased by 0.5% for every 1% increase in the prevalence of metronidazole resistance. Clarithromycin-based triple therapies containing either amoxicillin or metronidazole were more effective in northeast Asia (effect size 10%) than in other regions of the world (1).

When regimens of fewer than seven days in duration were compared with those of 14 days or longer, eradication rates were 33% greater (95% CI 25% to 42%) with nitroimidazole-based regimens administered for 14 days or longer and 29% greater (95% CI 12% to 45%) for non-nitroimidazole-based regimens (1). Short (7-day) treatment regimens were very effective in northeast Asia (Japan, Korea and Taiwan), with eradication rates exceeding 90%. In the United States the most effective therapies were proton pump inhibitors (PPIs) given with amoxicillin and clarithromycin for at least one week. A two week combination of metronidazole, bismuth and tetracycline combined with a PPI was effective in North America in populations with low rates of nitroimidazole resistance. Regimens containing metronidazole, clarithromycin and a PPI were less effective in North America than in Europe or Asia, even when populations with similar rates of metronidazole resistance were compared. Limited data were available in developing countries outside Asia, but they suggest that eradication rates were lower than in other areas. For example, in Brazil, which has high metronidazole resistance rates, eradication rates of 68% were seen with two week triple therapies containing metronidazole (1). Study size influenced the results of eradication in the meta-analysis with only one regimen: the combination of metronidazole, amoxicillin and a PPI. Eradication rates were 75% (95% CI 62% to 84%) for studies with a sample size of 25, but only 59% (95% CI 57% to 61%) with the studies of larger size. These data suggest a significant bias with small studies of this regimen (1).

POSSIBLE EXPLANATIONS FOR VARIABILITY

There are several possible explanations for the variability seen with the different eradication treatment regimens. The principal causes are listed below and discussed individually.

Genetic differences in the metabolism of drugs

The triple therapy regimens currently used for *H pylori* eradication use PPIs as an adjunct to the antimicrobials in the regimen. PPIs have complex effects on antibiotic concentrations, which are summarized in Table 1. The interaction of PPIs and clarithromycin on the hepatic cytochrome P450 (CYP) pathway can result in increased serum concentrations of clarithromycin or of the PPI (2). PPIs alter the transport of antibiotics into the stomach; an increase is seen in amoxicillin transport while metronidazole transport decreases (3,4). A reduction in the volume of gastric secretion increases the concentration of antibiotics in the gastric juice, and a change in the thickness and viscosity of the gastric mucus layer can change the delivery of the antibiotics to the bacteria (5). Many PPIs used in clinical practice are metabolized by the CYP system in the liver, and genetic polymorphisms of the CYP 2C19 can affect *H pylori* eradication. Poor metabolic activity is genetically determined and results in high plasma concentrations of PPIs and a prolonged PPI effect. Poor metabolizers were found in 3% to 5% of populations of European descent; prevalence rates

TABLE 1

The effect of proton pump inhibitors (PPIs) on antibiotic delivery in the gastric mucus layer

- PPI and clarithromycin interaction at hepatic cytochrome p450 3A4 can increase serum clarithromycin levels
- Increased secretion of amoxicillin into the gastric lumen when a PPI is coadministered
- Decrease in gastric volume caused by PPIs increases antibiotic concentrations in gastric juice
- Decreased viscosity of gastric juice induced by PPIs increases the permeability of antibiotics into the gastric mucus

of 18% to 23% have been described in China, Vietnam, Thailand and Japan (6). Individuals who are poor PPI metabolizers should exhibit more profound effects of the PPI therapy on antibiotic concentrations in the stomach. Clinical studies have shown that patients who are poor metabolizers have significantly better eradication rates than those who are rapid metabolizers, presumably due to the increased effects on gastric concentrations of antibiotics (7). Patients who were homozygous poor metabolizers had significantly higher eradication rates (98%, 95% CI 86% to 100%) with proton pump inhibitor triple therapy than those who were homozygous extensive metabolizers (73%, 95% CI 64% to 82%), suggesting that inherited differences in CYP function can have a profound effect on eradication (7).

Regional differences in antimicrobial resistance rates

Antimicrobial resistance has a profound effect on the outcome of eradication therapy. Eradication rates fall significantly when metronidazole or clarithromycin resistance is present and one of these agents is part of the regimen. There are wide geographical variations in the prevalence of resistant strains of *H pylori*; these reflect the use of metronidazole and clarithromycin for other diseases in the populations. A large meta-analysis from the United States (8) evaluated 3624 patients and found that clarithromycin resistance was seen in 10.1% of the patients, and metronidazole resistance was seen in 37%. Significant regional differences were also found within the United States. Clarithromycin resistance was more prevalent in the Mid- and North-atlantic states than in the Mid-western states. Older women tended to have higher prevalences of clarithromycin resistance. With metronidazole resistance, the geographical distribution was somewhat different. Individuals of Asian origin and residents of the southeastern United States had higher rates of metronidazole resistance, and the rates were highest in young women. These data suggest that patterns of immigration, ethnic origin and prior antibiotic use can substantially influence the outcome of therapy.

Underlying disease state

It has been suggested that *H pylori* eradication rates are lower in nonulcer dyspepsia than in peptic ulcer disease. Differences in the eradication rates have been attributed to the degree or pattern of gastritis seen in these patients. Gisbert et al (9) studied 298 patients with peptic ulcer disease and 183 patients with nonulcer dyspepsia who were treated with a multitude of regimens. Eradication rates were

73% (95% CI 64% to 82%) in the nonulcer dyspepsia group and 89% (95% CI 86% to 93%; $P < 0.05$) in the peptic ulcer group. This study was not designed to address the question of the differences in eradication rates specifically, but rather, consisted of a post hoc reanalysis of patients enrolled in a number of *H pylori* eradication trials of varying durations (five to seven days). A recent prospective, controlled trial (10) that studied 400 patients with endoscopically documented peptic ulcer disease and 403 patients with nonulcer dyspepsia showed similar eradication rates in both treatment groups. The best data suggest that eradication success probably does not depend on the underlying disease.

Duration of therapy

An important area of controversy is the duration of therapy. Some studies performed in the United States have raised questions concerning the efficacy of seven day triple therapy (PPI with amoxicillin and clarithromycin). Laine et al (11) compared seven, 10 and 14 day therapy and found that the eradication rate was lower in patients given seven day therapy than in those given 14 day therapy; however, the results were not statistically significant. Another small, uncontrolled study (12) showed poor eradication with seven day triple therapy, but only 31 patients were enrolled in this trial. Despite the limitations of these studies, current United States guidelines recommend 10 or 14 day

therapy, and some actively discourage seven day therapy (13,14). A recent study (15) compared three, seven and 10 day triple therapy (rabeprazole with amoxicillin and clarithromycin) in an American population and found no difference in the eradication rates with the duration of the treatment regimen. A meta-analysis of treatment trials suggests that treating for 14 days or longer may be significantly better than treatment regimens that are shorter than seven days in duration (effect size 33%, 95% CI 25% to 42%) (1). Seven and 10 day regimens were not significantly different than 14 day regimens (effect size 5.9%, 95% CI 0.9% to 11%) (1).

CONCLUSIONS

There are genetic and geographical differences in eradication rates for *H pylori* infection. Some of these differences are real and significant, but others have been overemphasized based on relatively poor data and do not stand up to rigorous analysis. There are good data to support the notion that poor drug metabolizers fare better with PPI therapy, and that these patients are more likely to be found in Asian populations rather than in white populations of European extraction. Well-performed studies suggest that seven day eradication therapy is just as effective as 10 day therapy in the United States, and that eradication success does not depend on the underlying disease (ulcer versus nonulcer dyspepsia).

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