Antibiotics, commonly amoxicillin, tetracycline, metronidazole and clarithromycin, are presently used in combination with anti-ulcer agents such as omeprazole, colloidal bismuth subcitrate, and sucralfate to treat Helicobacter pylori infection in patients with peptic ulcer, and compelling evidence has accumulated that eradication of the organism prevents duodenal ulcer relapse. The latest combination (MACH I) involved omeprazole, amoxicillin or metronidazole, and clarithromycin and claimed 90-96 percent success in H. pylori eradication. While the eradication rates of the bacteria are usually between 60-80 percent, the healing rates of duodenal ulcer using these regimens have been remarkably high, often over 90 percent, even with regimens that do not contain proton-pump inhibitors. Antibiotics alone, such as furazolidone and metronidazole, have been reported to heal peptic ulcer with various successes. In a recent double-blind placebo-controlled study, we showed that antibiotics alone, in the form of metronidazole, amoxicillin and clarithromycin, effectively healed 92.5 percent of patients with duodenal ulcer, and that the healing was largely accountable by clearance of H. pylori. Thus, the present day evidence indicates that both healing and prevention of relapse of peptic ulcer can be achieved by treatment of H. pylori. Metronidazole resistance is emerging rapidly, especially in Asia, and is likely to affect eradication success. At this point in time, the best regimen for peptic ulcer associated with H. pylori includes the use of a proton-pump inhibitor plus two antibiotics for one to two weeks.

INTRODUCTION

The observation that treatment of Helicobacter pylori infection of the stomach prevents the relapse of duodenal ulcer [1, 2, 3] and gastric ulcer [4] forms the first clue that the organism has an etiological role in these conditions and the platform for the advocate to eradicate the organism in patients with peptic ulcer. A regimen containing colloidal bismuth subcitrate, which is a gastroprotective ulcer-healing agent, and two antibiotics, metronidazole and amoxicillin or tetracycline became the classical triple therapy [5], and achieved an eradication rate (i.e., negative test for H. pylori at least four weeks after antibacterial treatment) of about 80 percent in most reported series. Side effects were common, and were mostly ascribed, and rightly so, to the antibiotics employed (Table 1).

There has been a massive proliferation of H. pylori related therapeutic trials in recent years, and close to 500 have been reported. A major problem with these trials has been a distinct lack of a controlled design except in about two dozens of them.

OMEPRAZOLE-BASED ERADICATION REGIMENs

It was observed that omeprazole, a proton-pump inhibitor, reduced the density of H. pylori and improved the antral gastritis associated with duodenal ulcer [6]. The significant rise in gastric pH has been considered to be responsible for the antibacterial action,
and for the enhancement of the action of certain antibiotics. The initial enthusiasm was focused on dual therapy, namely omeprazole plus one antibiotic, usually amoxycillin, The reported eradication rates, however, varied from 0 percent to 90 percent [7]. It would appear from a recent meta-analysis [8] that with dual therapy using amoxycillin, a higher eradication rate was achieved using omeprazole 20 mg twice daily (83 percent) than when it was used in a single daily dose of 40 mg (58 percent). Combination with clarithromycin appeared promising [9, 10], with an eradication rate of around 80 percent, but whether this new enthusiasm will be sustained requires further controlled studies.

Dual therapy has largely been superceded by triple therapy because the latest triple regimens have consistently achieved over 90 percent eradication rates [11, 12, 13, 14]. It would also appear that omeprazole-based triple therapy for one week was as good as the same therapy for two weeks [12, 13, 14] (Table 2). The latest trial involving 787 patients was reported in Germany and showed that omeprazole, metronidazole and clarithromycin for one week was successful in 90-95 percent, and that omeprazole, amoxycillin and clarithromycin for one week was successful in 84-96 percent [15].

**SUCRALFATE-BASED ERADICATION REGIMENS**

Improvement of duodenal-ulcer associated antral gastritis has also been observed with sucralfate, which was able to reduce the density of *H. pylori* [16] and interfere with

### Table 1. Side effects of classical triple therapy (colloidal bismuth subcitrate, metronidazole, amoxycillin/tetracycline).

| Side effect                | Frequency |
|----------------------------|-----------|
| Nausea                     | 20 percent|
| Esophageal burn             | 15 percent|
| Foul taste                 | 15 percent|
| Diarrhea                   | 10 percent|
| Vomiting                   | 7.5 percent|
| Rash                       | 5 percent |
| Dizziness                  | 2 percent |
| Pseudomembranous colitis   | 1 percent |

### Table 2. One-week triple therapies with omeprazole.

| Author     | Medications* | n    | Eradication rates     |
|------------|--------------|------|-----------------------|
| Bazzoli    | omeprazole 20 mg qd metronidazole 500 mg bid clarithromycin 250 mg bid | 59   | 93 percent (55/59)    |
| Labenz     | omeprazole 20 mg qd metronidazole 400 mg bid clarithromycin 250 mg bid | 40   | 95 percent (38/40)    |
| Jaup       | omeprazole 20 mg bid metronidazole 500 mg bid clarithromycin 250 mg bid | 112  | 93 percent (104/112)  |
| Moayyedi   | omeprazole 20 mg bid metronidazole 500 mg bid clarithromycin 250 mg bid | 47   | 94 percent (44/47)    |

* qd: daily; bid: twice daily
the colonization of the organism to the gastric epithelium [17]. Dual therapy with sucralfate and amoxycillin achieved an eradication rate of 40 percent [18], which was similar to those observed in dual therapy using bismuth compounds. A total of six studies have examined triple therapy using sucralfate (usually 4 g daily in divided doses) with two other antibiotics, and the eradication rates achieved were about 80 percent, ranging from 59 percent to 100 percent [19, 20, 21, 22, 23, 24]. The healing rates of duodenal ulcer reported in these studies are generally over 90 percent. In one comparative study, the four-week healing rates as shown by endoscopy were not distinguishable from those of omeprazole combined with two antibiotics [20]. The results showed that the 4-week healing rates of the two regimens were both over 90 percent and that the *H. pylori* eradication rates were 87 percent and 86 percent respectively. The high 4-week healing rate with the sucralfate combination is surprising, since the use of sucralfate alone has not been shown in the past to achieve a 4-week healing rate of over 90 percent. In fact, a recent review showed that the mean healing rate of duodenal ulcer with sucralfate was 79 percent [25]. While this apparent improvement in healing rate needs to be confirmed by controlled studies, it is of interest to note that another anti-ulcer agent, ranitidine, has been shown when combined with colloidal bismuth, metronidazole and tetracycline to have superior duodenal ulcer healing rate to ranitidine alone [26]. These results seem to suggest that eradication of *H. pylori* lead to additional healing.

**DO ANTIBIOTICS DESIGNED TO ERADICATE H. PYLORI HEAL ULCERS?**

It should be noted that even before the *H. pylori* era, the use of antibiotics including metronidazole [27] and furazolidone [28] had been reported to have various successes in the healing of peptic ulcer. A recent double-blind placebo-controlled study [29] on 97 patients with duodenal ulcer in Hong Kong attempted to answer this fundamental question, and showed that two weeks of metronidazole, amoxycillin and clarithromycin healed 92.5 percent of the patients at four weeks versus 36.6 percent in those treated with placebo. These results constituted the strongest evidence to this date that *H. pylori* infection is aetiologically related to duodenal ulceration.

While this explanation is most likely true, the results also suggest that antibiotics may possess ulcer-healing properties per se. Indeed, intragastric instillation of amoxycillin suspension and solution, as well as injection of amoxycillin by the intraperitoneal route, significantly protected gastric mucosal damage by absolute ethanol in rats in a dosedependent manner [30]. This protection was lost when the animals were pretreated with indomethacin, suggesting that the cytoprotection by amoxycillin was through the release of prostaglandins. Gastric mucosal blood flow as measured by laser doppler flowmetry and acid secretion were unaffected by amoxycillin, so that these mechanisms were unlikely to be responsible for the cytoprotection. Similarly metronidazole, given either per oral or intraperitoneally, dose-dependently prevented 40 percent ethanol-induced gastric mucosal damage in the rat [31]. The protection was due to a direct vascular and glandular cytoprotective property, and was neither through prostaglandin synthesis nor the improvement of gastric mucosal blood flow. Oral clarithromycin, on the other hand, did not protect ethanol-induced gastric mucosal damage in the rat, but it prevented indomethacin-induced damage in the animal [32]. We conclude from these studies that certain antibiotics possess cytoprotective properties.

**CONCLUSIONS**

The concept has emerged to treat peptic ulcer as an infection and to control its symptoms with acid-reducing agents such as antacids, H2-receptor antagonists, and proton pump inhibitors. The best available regimen is now close to ideal, and is able to eradicate *H. pylori* infection in one week with few reported side-effects. While at the present time
proton-pump inhibitors assume conveniently the antibacterial and anti-symptom role, other players such as ranitidine bismuth citrate will come into the scene.

Acknowledgement: This work was supported by Hong Kong Research Grant Council (RGC 344/041/0001), and Peptic Ulcer Research Fund (311/041/0372) of the University of Hong Kong.

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