

**DYSPEPSIA MANAGEMENT****Use of antisecretory agents as a trial of therapy****M B Fennerty***Gut* 2002;**50**(Suppl IV):iv63–iv66

Dyspepsia is a common clinical condition, and its diagnostic evaluation and treatment result in the expenditure of enormous healthcare resources each year. Studies indicate that the omeprazole test is the most sensitive and cost effective test for diagnosing gastro-oesophageal reflux disease (GORD) in patients with extra-oesophageal or more "classic" symptoms suggestive of GORD. Studies also indicate that a therapeutic trial of omeprazole in patients with dyspepsia results in greater symptom improvement and lower costs than treatment with less potent acid suppression.

**SUMMARY**

Dyspepsia is a common clinical condition, and its diagnosis and treatment result in the expenditure of enormous healthcare resources. Empirical therapies are often used in the evaluation and management of diseases, and the possibility was therefore raised that such therapy could be used in the management of dyspepsia. In patients with "atypical" symptoms of gastro-oesophageal reflux disease (GORD), a trial of antisecretory therapy was found to have both therapeutic and diagnostic value. It was also shown that more profound antisecretory activity (that is, with a proton pump inhibitor) was better at establishing this symptomatic relationship. In this patient group, the "omeprazole test" had a diagnostic sensitivity and specificity of 80% and resulted in a cost saving of over US\$500 per patient compared with more traditional diagnostic tools. In patients with more "typical" GORD symptoms, a positive omeprazole test was shown to confirm the diagnosis with a high degree of accuracy, resulting in a cost saving of US\$347 per patient. Given the accuracy and cost effectiveness of a trial of proton pump inhibitor therapy in patients with suspected GORD, it is logical to assume that similar results could be attained in patients with dyspepsia. Data from studies strongly suggest that omeprazole results in the identification of patients with acid sensitive dyspepsia (arising from GORD, peptic ulcer disease, or ulcer-like functional dyspepsia), and is not only more effective than H<sub>2</sub> receptor antagonists in relieving the symptoms of dyspepsia but also leads to improvement in quality of life and decreased healthcare costs.

**INTRODUCTION**

Dyspepsia is a common clinical condition, with an annual prevalence of 25–40% in Western societies.<sup>1</sup> It is probably the most common gastrointestinal symptom encountered by primary care

physicians, accounting for 2–4% of office visits. Furthermore, the symptoms of dyspepsia, as well as the causative clinical conditions (GORD, peptic ulcer disease, functional dyspepsia, etc.), are managed mainly by primary care physicians. The diagnostic evaluation and treatment of dyspepsia result in the expenditure of enormous healthcare resources each year (more than US\$1.5 billion in the USA alone).

The diagnostic evaluation of a patient with dyspepsia often necessitates referral to a subspecialist, for example a gastroenterologist, who performs tests such as endoscopy or ambulatory pH monitoring to achieve a precise diagnosis. In many cases, what is not appreciated by either the referring physician or the gastroenterologist is that these tests are largely insensitive and non-specific for dyspepsia associated disease. For instance, the sensitivity of endoscopy in diagnosing GORD is less than 50% and the sensitivity of ambulatory pH monitoring in diagnosing GORD is, at best, only 85%. Neither endoscopy nor ambulatory pH monitoring detect underlying motility disorders, and antibody tests for *Helicobacter pylori* are non-specific as many patients without disease or symptoms related to *H pylori* infection will test positive for this common bacterium.

Empirical therapies (versus diagnostic testing) are often used by primary care physicians in the evaluation and management of many disease states. It is therefore logical that empirical trials of therapy could be used by physicians in the management of the dyspepsia symptom complex. This philosophy was validated to some extent by the 1985 recommendation of the American College of Physicians to utilise a trial of antisecretory therapy in patients presenting with dyspepsia.<sup>2</sup> Rationales for using antisecretory agents as a trial of therapy in patients presenting with dyspepsia include: it is a primary care physician based "procedure"; it is non-invasive and relatively inexpensive; and preliminary studies indicate that an empirical trial of a high dose proton pump inhibitor has better sensitivity and specificity than traditional methods of diagnosing dyspeptic related gastrointestinal disease such as endoscopy and/or ambulatory pH monitoring.

Of the antisecretory agents available (H<sub>2</sub> receptor antagonists and proton pump inhibitors), what is the rationale for using a proton pump inhibitor based trial of therapy? In patients with dyspepsia, 15–20% are found to have oesophagitis when investigated with endoscopy. However, fewer than 50% of patients with GORD have oesophagitis, indicating that as much as 30–40%

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**Abbreviations:** GORD, gastro-oesophageal reflux disease.

of dyspepsia is related to GORD. Thus many, if not most, patients (30–40%) with dyspepsia may have GORD as a cause of their symptoms, and the antisecretory agent and dose used need to ensure normalisation of intra-oesophageal pH exposure in order to maximise the accuracy of a diagnostic trial of therapy. H<sub>2</sub> receptor antagonists are largely ineffective in this regard as they fail to control meal stimulated gastric acid secretion. A single daily standard dose of a proton pump inhibitor results in a gastric pH greater than 4 for about 67% of the time, allowing for the possibility of some intra-oesophageal acid exposure. Therefore, higher and more frequent doses of a proton pump inhibitor may be necessary to ensure adequate suppression of intragastric acidity and normalisation of intra-oesophageal pH exposure.<sup>3</sup> Thus if antisecretory agents are to be used as a trial of therapy, higher and/or more frequent doses would appear to be a prudent approach.

### TRIALS OF THERAPY IN PATIENTS WITH EXTRA-OESOPHAGEAL SYMPTOMS OF GORD

It was initially appreciated that many patients with chest pain had concomitant symptoms of GORD and it was hypothesised that in patients without evidence of coronary disease perhaps GORD was the causative factor for their chest pain. This led to trials of therapy using antisecretory agents to assess their ability to control symptoms as well as diagnose GORD. Singh *et al* identified 20 patients with chest pain and acid reflux who had a positive symptom index on ambulatory pH monitoring.<sup>4</sup> These patients then underwent eight weeks of intensive antireflux therapy with high dose H<sub>2</sub> receptor antagonists or a proton pump inhibitor. Of the 18 evaluable patients, 13 became either asymptomatic or improved by at least 75%, suggesting that a trial of antisecretory therapy could indicate whether these symptoms were related to GORD. Subsequently, Stahl *et al* examined the effect of ranitidine 150 mg three or four times daily on mean symptom score of what was perceived to be GORD associated chest pain.<sup>5</sup> Thirteen patients were treated for eight weeks and the mean symptom score decreased from 2.87 to 0.86, indicating that GORD was the underlying cause of their symptoms. Achem *et al* compared omeprazole 20 mg twice daily for eight weeks with placebo for symptom improvement in patients with GORD associated non-cardiac chest pain confirmed by ambulatory pH monitoring.<sup>6</sup> Of 36 patients, 81% treated with twice daily omeprazole had overall improvement in their symptoms compared with only 6% of those treated with twice daily placebo ( $p=0.001$ ). These studies indicated that a trial of antisecretory therapy was effective in improving extra-oesophageal symptoms associated with GORD and was diagnostic of the presence of GORD. Thus a trial of therapy in this setting has both therapeutic and diagnostic value. Also evident from these studies was the fact that more profound antisecretory activity (that is, with proton pump inhibitors) was better at establishing this symptomatic relationship.

Fass *et al* attempted to validate the diagnostic utility of a trial of high dose proton pump inhibitor (“the omeprazole test”) in patients with chest pain who were suspected of having GORD.<sup>7</sup> Patients underwent an intensive diagnostic evaluation with endoscopy and ambulatory pH monitoring prior to the study to establish the presence or absence of GORD. They then received omeprazole 40 mg in the morning and 20 mg in the evening, or placebo for seven days using a double blind, placebo controlled, crossover design with a washout phase. In patients with GORD, 78% had either resolution or more than 50% improvement in their symptoms with the omeprazole test. In patients without GORD, 14% achieved a symptomatic response with the omeprazole test. Thus the omeprazole test demonstrated a sensitivity and specificity of approximately 80% in identifying GORD in patients presenting with atypical symptoms. Moreover, this empirical trial of therapy resulted in

a cost saving of over US\$500 per patient compared with a conventional diagnostic strategy of endoscopy and/or ambulatory pH monitoring. This cost saving was realised by a decrease in the number of diagnostic studies required, from 1960 per 1000 patients in the conventional arm to 800 per 1000 patients in the omeprazole test arm. This study validated the use of a trial of therapy and indicated that the use of a high dose proton pump inhibitor ensured diagnostic accuracy in patients presenting with symptoms that may be related to GORD.

### TRIALS OF THERAPY IN PATIENTS WITH SUSPECTED GORD

The symptom of “heartburn” is not discriminatory in identifying a patient with GORD. Thus there may be a place for a therapeutic trial of an antisecretory agent even in patients with more “typical” but non-diagnostic symptoms of GORD. Schindlbeck *et al* evaluated the accuracy of seven days of antisecretory therapy in identifying patients with GORD.<sup>8</sup> Utilising ambulatory pH monitoring as the gold standard for GORD, 33 patients were then treated with omeprazole 40 mg twice daily, omeprazole 40 mg once daily, or ranitidine 150 mg twice daily. All therapies demonstrated a significant improvement in the symptom severity score. The sensitivity of omeprazole 40 mg twice daily was 83% compared with 27% for omeprazole 40 mg once daily. Thus a twice daily dose of the proton pump inhibitor was significantly more sensitive than a single daily dose, despite the latter being classed as a high dose. Schenk *et al* showed similar results using omeprazole compared with placebo in identifying patients with suspected GORD.<sup>9</sup> Ambulatory pH monitoring was also used as the gold standard of GORD in this study, and either omeprazole 40 mg once daily or placebo was given for 14 days. In this study, the sensitivity of omeprazole was 68%, with a specificity of 63%. However, omeprazole was used only in a single daily dose (see above), possibly limiting its sensitivity, as inhibition of oesophageal acid exposure at this dose may be incomplete.

Building on their prior study of the omeprazole test (omeprazole 40 mg in the morning and 20 mg in the evening for seven days), Fass *et al* studied the sensitivity, specificity, and economic impact of utilising the omeprazole test as a trial of therapy in patients with symptoms suggestive of GORD.<sup>10</sup> Forty three patients with typical GORD symptoms were evaluated by endoscopy and ambulatory pH monitoring and were then randomised in a crossover, blinded trial. In this study, the sensitivity of the omeprazole test was 80%, with a specificity of 57% and a positive predictive value of 90%. The omeprazole test resulted in a cost saving of US\$347 per patient, and an overall decrease in the use of endoscopy and ambulatory pH monitoring of 64% and 53%, respectively.

These data indicate that in patients suspected of having GORD, a positive omeprazole test confirms the diagnosis with a high degree of accuracy. As with any patient identified as having GORD, the appropriate therapeutic strategy should then be to establish the lowest effective dose of an antisecretory agent that maintains the patient in remission. In patients with symptoms suggestive of GORD but with a negative omeprazole test, GORD is a very unlikely diagnosis. Other causes of dyspepsia resulting in GORD-like symptoms should be investigated. Consideration of other empirical trials of therapy, including testing for and treating *H pylori* infection or the use of prokinetics, should be considered in this clinical situation. These data also suggest that the omeprazole test should be further evaluated to find the optimal dose and duration for a trial of therapy. The data indicate that twice daily dosing is superior but the optimal dose and duration have yet to be determined. Validation of the assessment of response in this clinical situation will also be necessary.

### TRIALS OF THERAPY IN PATIENTS WITH DYSPEPSIA

Given the accuracy and cost effectiveness of a trial of proton pump inhibitor therapy in patients with suspected GORD, as

discussed above, it is logical to assume that similar results could also be attained in the dyspeptic patient. In these patients, GORD can be found with a frequency of 15–50%. However, it is likely that GORD has been under estimated in previous studies of dyspepsia as only a minority of patients with GORD have oesophagitis. Therefore, many patients classified as having functional dyspepsia, on the basis of a negative endoscopy, may still have GORD that is unrecognised. In patients with GORD who present with symptoms of dyspepsia, it is logical to assume that the response to a trial of an antisecretory agent should be similar to that seen in patients with more typical symptoms of GORD.

The PILOT study by Lauritsen *et al* in 197 patients with functional dyspepsia demonstrated that twice daily omeprazole resolved symptoms in 31% of patients compared with 16% of those given placebo ( $p < 0.05$ ).<sup>11</sup> When a response was defined as an overall treatment effect that was “better” (versus worse or about the same on the McMaster questionnaire used to evaluate symptoms<sup>12</sup>), 54% of patients receiving twice daily omeprazole had symptom response compared with 33% of patients receiving placebo. This study confirmed that many patients with functional dyspepsia respond to acid suppression.

Talley *et al* studied 1248 patients with functional dyspepsia and assessed their therapeutic response to 20 mg omeprazole, 10 mg omeprazole, or placebo.<sup>13</sup> Overall, complete symptom relief was seen in 38% of patients receiving omeprazole 20 mg once daily, in 36% of patients receiving omeprazole 10 mg once daily, and in 28% of those receiving placebo ( $p = 0.002$  and  $p = 0.02$ , respectively). In these patients with functional dyspepsia that was subclassified based on the predominant symptom, symptom response was seen in 40%, 35%, and 27%, respectively ( $p = 0.006$  for omeprazole 20 mg once daily versus placebo, and  $p = 0.08$  for omeprazole 10 mg once daily versus placebo) of the subgroup of patients with ulcer-like dyspepsia whereas in those with reflux-like dyspepsia, symptom relief was seen in 54%, 45%, and 23%, respectively ( $p = 0.002$  for omeprazole 20 mg once daily versus placebo, and  $p = 0.02$  for omeprazole 10 mg once daily versus placebo). However, in patients with dysmotility-like dyspepsia, there was no significant difference between omeprazole 20 mg once daily, omeprazole 10 mg once daily, and placebo in providing symptom relief. These data strongly suggest that in GORD patients presenting with dyspepsia, a trial of therapy with a highly effective antisecretory agent such as omeprazole results in accurate identification of those with acid sensitive dyspepsia (that is, arising from either GORD or peptic ulcer disease). Whether higher or more frequent dosing of omeprazole would be even more effective is currently unknown.

Similar to that demonstrated in patients with GORD associated non-cardiac chest pain, a trial of omeprazole has also been shown to be superior to H<sub>2</sub> receptor antagonists or the combination of antacids and H<sub>2</sub> receptor antagonists in alleviating symptoms in dyspeptic patients. Blum *et al* evaluated two doses of omeprazole, ranitidine, and placebo in symptom response in 801 patients with functional dyspepsia.<sup>14</sup> Omeprazole 20 mg once daily resulted in a 35% symptom response rate compared with 28% in those receiving omeprazole 10 mg once daily, 26% in those receiving ranitidine 150 mg twice daily, and 17% in those receiving placebo. Again, a hierarchy of therapeutic response was demonstrated which was related to the efficacy of gastric acid inhibition. In a similar study, Mason *et al* compared omeprazole with an antacid-alginate and H<sub>2</sub> receptor antagonist combination in 725 patients presenting with dyspepsia in a general practice setting.<sup>15</sup> There was a significant difference between the therapeutic response in patients receiving omeprazole compared with those receiving the antacid-alginate and H<sub>2</sub> receptor antagonist combination (61% versus 40%, respectively;  $p < 0.0001$ ).

Similarly, Meineche-Schmidt and Krag studied 1017 patients with dyspepsia in general practice; the percentage of patients with total symptom relief was 47–50% in those receiving ome-

prazole 20 mg once daily compared with 33% in those receiving cimetidine 400 mg twice daily, and 35% in those receiving placebo.<sup>16</sup> In this study, not only was the proton pump inhibitor shown to be significantly more effective than the H<sub>2</sub> receptor antagonist and placebo in producing symptom relief (omeprazole versus cimetidine,  $p = 0.004$ ; omeprazole versus placebo,  $p = 0.001$ ) but there was no difference in symptom relief between the H<sub>2</sub> receptor antagonist and the placebo arms of the study. In a subsequent study in 559 patients with functional dyspepsia, the effects of symptom resolution on quality of life and healthcare costs were evaluated.<sup>17</sup> There were significantly fewer office visits and days requiring medical therapy in patients rendered symptom free compared with those with continued dyspeptic symptoms.

What remains to be resolved is whether a therapeutic response to omeprazole in the dyspeptic patient represents a patient with GORD, a patient with peptic ulcer disease, or a patient with functional dyspepsia and an acid sensitive stomach that is responding to a proton pump inhibitor. Further clinical studies are necessary to resolve this conundrum, but nevertheless a therapeutic trial with a high dose and highly effective antisecretory agent (that is, omeprazole) has therapeutic and diagnostic value.

## CONCLUSION

These studies indicate that the omeprazole test is the most sensitive and cost effective test for diagnosing GORD in patients with extra-oesophageal or more “classic” symptoms suggestive of GORD. These studies also indicate that a therapeutic trial of omeprazole in patients with dyspepsia results in greater symptom improvement and lower costs than treatment with less potent acid suppression. What remains unresolved is the efficacy of a trial of omeprazole compared with anti-*H pylori* therapy or other trials of therapy in dyspeptic patients, or whether a clinical response in this situation is diagnostic of GORD. Appropriately designed clinical trials using validated instruments measuring response are necessary to determine the role of a trial of proton pump inhibitor therapy, as well as the optimal dose of proton pump inhibitor, in the treatment of patients presenting with dyspepsia.

Conflict of interest: This symposium was sponsored by AstraZeneca, makers of omeprazole. The author of this paper has received sponsorship for travel and an honorarium from AstraZeneca.

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## Use of antisecretory agents as a trial of therapy

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*Gut* 2002 50: iv63-iv66  
doi: 10.1136/gut.50.suppl\_4.iv63

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