

and mometasone, respectively, for attending several conferences and has acted as a consultant to GSK and Altana. His department has received research funds for clinical trials from AZ, GSK, Novartis, and Merck; SFW has received fees for speaking, chairing, or advising from GSK, AZ, SP, and Aventis; IF has received research funding and committee honorariums from GSK and a committee honorarium and speaking fee from AZ.

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Empirical prescribing for dyspepsia: randomised controlled trial of test and treat versus omeprazole treatment

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Abstract

Objective To compare the efficacy of a “*Helicobacter pylori* test and treat” strategy with that of an empirical trial of omeprazole in the non-endoscopic management by empirical prescribing of young patients with dyspepsia.

Design Randomised controlled trial.

Setting Hospital gastroenterology unit.

Participants 219 patients under 45 years old presenting with dyspepsia without alarm symptoms.

Intervention Patients received treatment with omeprazole 20 mg (group A) or with a urea breath test followed by an eradication treatment in case of *H pylori* infection or omeprazole alone in non-infected patients (group B). Lack of improvement or recurrence of symptoms prompted endoscopy.

Main outcome measures Improvement in symptoms assessed by a dyspepsia severity score every two months; use of medical resources (endoscopic workload and medical consultation); clinical outcome.

Results 96/109 (88%) patients in group A and 61/110 (55%) in group B ($P < 0.0001$) had endoscopy: in 19 patients in group A and 32 in group B (20/67 infected and 12/43 non-infected) because of no improvement; in 77 further patients in group A and 29 in group B (7 infected and 22 non-infected) because of recurrence of symptoms during follow up. Endoscopy showed peptic ulcers only in group A; oesophagitis occurred significantly more often in group B than in group A. About 80% of examinations

were normal in both groups, but nine duodenal scars occurred in group A.

Conclusions Eradication treatment allows resolution of symptoms in a large number of patients with dyspepsia and reduces the endoscopic workload. After a trial of omeprazole, symptoms recur in nearly every patient. Such treatment is also likely to mask an appreciable number of peptic ulcers and cases of oesophagitis.

Introduction

Dyspepsia is a common condition in the general population of industrialised countries. The increasing cost of treatments for dyspepsia has led to a search for safe and cost-effective management strategies. Agreement exists that patients older than 45 with dyspeptic symptoms and patients with alarm symptoms should undergo endoscopy. To reduce endoscopic workload empirical treatment with proton pump inhibitors has been proposed for young patients.¹⁻⁴ In industrialised countries people under the age of 45 who are not taking non-steroidal anti-inflammatory drugs are unlikely to be affected by serious gastroduodenal disease if they have a negative *H pylori* test. On the basis of these observations, the European *H pylori* Study Group advised that young dyspeptic patients without alarm symptoms and found to be infected by means of non-invasive tests should receive empirical eradication treatment without endoscopy.³

To date, no published prospective fully randomised trials have compared the efficacy of the “test and treat” strategy with that of empirical treatment with a proton pump inhibitor in a clinical setting as an initial management strategy for dyspeptic patients. We aimed to conduct such a trial.

Methods

We studied outpatients with symptoms of dyspepsia referred by their general practitioners to our department over a two year period. We included young adults (18-45 years of age) presenting with uninvestigated upper abdominal symptoms. Exclusion criteria were age less than 18 years, alarm symptoms, symptoms of gastro-oesophageal reflux disease, regular use of non-steroidal anti-inflammatory drugs, previous surgery to the upper gastrointestinal tract, pregnancy, and treatment with antibiotics, proton pump inhibitors, or H₂ antagonists in the previous four weeks.

We assessed symptoms at baseline,⁵ and randomly assigned patients to either empirical treatment with omeprazole 20 mg/day for four weeks (group A) or a ¹³C-urea breath test for *H pylori* (group B). Patients whose *H pylori* test showed no infection received four weeks' treatment with omeprazole 20 mg/day. Infected patients received one week of triple eradication treatment (omeprazole 20 mg, clarithromycin 500 mg, and tinidazole 500 mg, all twice daily). We tested for *H pylori* again at the four week review and gave a further course of treatment if the test was positive. Patients who had improved symptoms at the four week visit entered the follow up phase. If symptoms had not improved we offered endoscopy, which we performed at least two weeks after the visit in order to reduce the rate of false negative *H pylori* test results.

An investigator who was blinded to group assignment followed up participants every two months for one year or when symptoms recurred. We defined a relapse as the recurrence of symptoms as judged by the patient on a four point Likert-type scale (no symptoms, improvement in symptoms, no change, worse symptoms). This was the primary endpoint of the trial. We offered endoscopy to patients who relapsed.

Statistical analysis

We assessed the rate of patients undergoing endoscopy as well as the time to first relapse. We analysed the data by using life table methods and compared the remission curves of the two groups by using the log rank test. We used the Mann-Whitney U test to

Table 1 Baseline characteristics of the study groups

	Group A—proton pump inhibitor alone (n=109)	Group B—eradication of <i>Helicobacter pylori</i> (n=110)
Mean (range) age (years)	38 (19-45)	38.9 (18-44)
Sex (male/female)	61/48	59/51
Smokers (No (%))	44 (40)	45 (41)
Alcohol drinkers (excess intake)	0	0
Mean (95% CI; range) symptom scores at baseline	4.7 (4.45 to 4.95; 1-7)	4.6 (4.36 to 4.83; 2-7)

compare symptom scores between the groups and the χ^2 test to compare categorical variables. All analyses were intention to treat.

Results

Between November 1998 and November 2000 we randomised 109 patients to treatment with a proton pump inhibitor (group A) and 110 to a urea breath test (group B). Sixty seven (61%) patients in group B tested positive for *H pylori* and received eradication treatment. The other 43 had a negative result and received omeprazole. Baseline characteristics of the two groups were similar (table 1). The *H pylori* infection was eradicated in 63 patients in group B after the first treatment (eradication rate 94%) and in four patients after second line treatment. All patients identified for follow up were successfully reassessed.

Clinical efficacy and endoscopic assessment—Ninety (83%, 95% confidence interval 74% to 89%) patients in group A and 78 (71%, 61% to 79%) in group B described improvement in symptoms at the four week visit (P=0.05) and entered the follow up. Overall, 96 patients (88%, 0.8 to 0.93) in group A and 61 (55%, 46% to 65%) patients in group B had an endoscopy during the study (P<0.0001). Table 2 shows the diagnoses found by endoscopy in the patients in the two groups. No peptic ulcer occurred in group B; the prevalences of hiatus hernia and oesophagitis were significantly higher in the patients in group B who had an endoscopy. Interestingly, among the patients who did not show active lesions at endoscopy, nine (9%) in group A and none in group B showed a scar in the duodenal bulb (P<0.05).

Symptom assessment—The dyspepsia score was significantly better in the proton pump inhibitor group than in the test and treat group at the first follow up visit but became significantly worse at six and 12 months (fig 1).

Relapses between 0 and 12 months—The proportion of days (number of days per patient) without

Table 2 Diagnoses by upper gastrointestinal endoscopy in each of the two study groups. Values are numbers (percentages) unless stated otherwise

Diagnosis*	Group A—proton pump inhibitor alone		Group B—eradication of <i>Helicobacter pylori</i>		P value
	Total	<i>H pylori</i> positive	Total	<i>H pylori</i> positive	
Patients who had endoscopy	96	60 (63)	61	0	
Duodenal ulcer	15 (16)	13 (87)	0	0	<0.001
Gastric ulcer	1 (1)	1 (100)	0	0	NS
Oesophagitis	4 (4)	2 (50)	9 (15)	0	0.03
Normal	76 (79)	44 (58)	52 (86)	0	NS
Hernia	25 (26)	14 (56)	26 (43)	0	0.03
Duodenal scar	9 (9)	9 (100)	0	0	0.01

NS—not significant

*More than one diagnosis is possible; endoscopies showing hiatus hernia or scar without other lesions were considered to be normal.

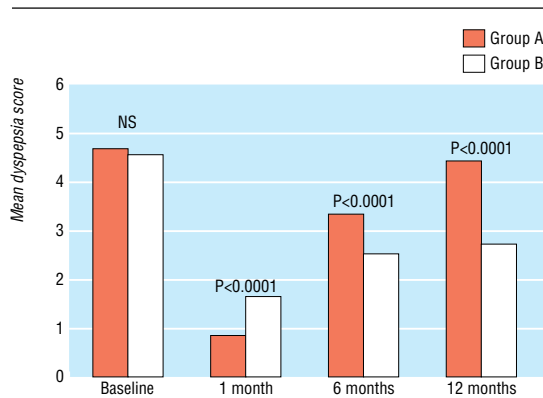


Fig 1 Mean dyspepsia scores over the various time points of the study in patients undergoing empirical treatment with omeprazole (group A) and a “test and treat” strategy (group B). Group B includes both patients who received eradication treatment for *Helicobacter pylori* infection and those who tested negative for the infection and received four weeks’ treatment with omeprazole. (Data are expressed as mean and standard deviation; NS=not significant)

symptoms was significantly higher in the test and treat group than in the proton pump inhibitor group (mean 231.5 (95% confidence interval 205.7 to 257.2) v 139.3 (117.9 to 160.7); P<0.001), even including in the first group the *H pylori* negative patients who received omeprazole (fig 2).

Adherence to treatment and adverse events—No patient was withdrawn as a result of poor adherence to drugs or because of adverse events. Thirty six (33%) patients in the omeprazole group and 40 (36%) in the test and treat group reported at least one adverse event. Nausea, taste perversion, diarrhoea, and headache were the most common events reported.

Discussion

The test and treat strategy is as efficient and safe as endoscopy in the management of patients with dyspepsia.^{6,7} Conversely, the cost effective use of endoscopy is

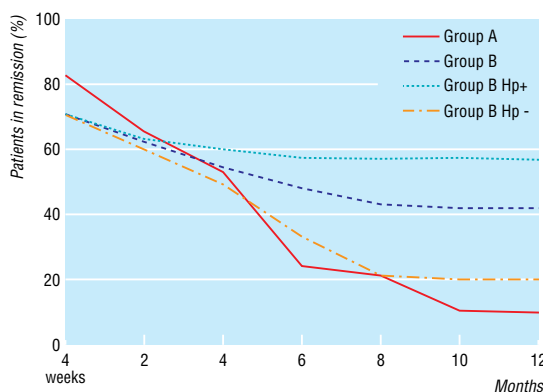


Fig 2 Symptom remission curves from 0 to 12 months of follow up. At the first visit for assessment, four weeks after the beginning of the treatment (time 0), 90/109 (83%) patients in the omeprazole group (group A) and 78/110 (70.9%) in the “test and treat” group (group B) were in remission. The curves for patients undergoing *Helicobacter* eradication treatment (Group B HP+, 47/67 in remission) and those who tested negative for *H pylori* infection (Group B HP-, 31/43 in remission) and received omeprazole treatment are also shown

hotly debated.^{2,8-12} Our study was not designed to estimate the cost effectiveness of the management strategies. In a public health perspective good clinical judgment, the patient’s wishes, and the availability of resources will influence the choice of strategy. However, if we choose to offer an empirical treatment the test and treat strategy should be the preferred option.

A main concern regarding the empirical treatment of dyspepsia is the possibility of missing gastric cancer. No gastric cancer was diagnosed or missed in our study. Although a delay in diagnosis of a few weeks does not affect the likelihood of cure of gastric cancer, a shorter empirical treatment is likely to represent a better option. After discontinuation of treatment in our study, symptoms recurred earlier in the patients who received eradication treatment than in those treated with proton pump inhibitor.

The test and treat strategy was superior to empirical treatment with omeprazole in our study population, but this advantage might be less evident in populations with a lower prevalence of *H pylori* infection. A recent study shows that treatment with a proton pump inhibitor becomes less costly than the test and treat strategy when the prevalence of *H pylori* is lower than 20%.¹³ The prevalence of *H pylori* infection in our study was about 60%, but we excluded patients with reflux symptoms, who have a lower prevalence of infection.¹⁴ Including patients with reflux symptoms, the prevalence of infection in our dyspepsia population would be 55%,¹⁵ similar to the value of 55.2% reported in a large meta-analysis.¹⁶

Although our study took place in a hospital clinic, we consider the results to be applicable to primary care patients. As a reference centre for dyspepsia, we invited primary care doctors to refer their uninvestigated patients to us, so our patients are likely to be similar to

What is already known on this topic

Dyspeptic patients aged under 45 without alarm symptoms are unlikely to have a malignancy

An empirical prescribing approach has been recommended as a way to reduce endoscopic workload

The “test for *Helicobacter pylori* and treat” strategy and acid suppressing drugs have both been recommended for uninvestigated dyspepsia, but no randomised controlled trials have compared the two approaches

What this study adds

Treatment to eradicate *H pylori* allows the resolution of symptoms in a large number of dyspeptic patients and reduces the endoscopic workload

Treatment with omeprazole is likely to mask an appreciable number of peptic ulcers and cases of oesophagitis

The *H pylori* test and treat strategy should be the preferred approach to dyspepsia, if we choose to perform an empirical treatment.

those seen in the primary care setting. We believe, however, that our findings would need to be assessed in the primary care setting before implementation is considered.

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Evaluation of suicide rates in rural India using verbal autopsies, 1994-9

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Suicide rates have increased in many developing countries.¹ But the reported rates are misleading because population counts are unreliable, and identifying suicides is problematic because of inefficient civil registration systems, non-reporting of deaths, variable standards in certifying death, and suicide's legal and social consequences.

Suicide rates were between 8.1 and 58.3/100 000 population for different parts of India.² Police records, which under-report, were used to calculate these rates.

We used verbal autopsies in the 85 villages of the Kaniyambadi region of southern India (area 127 km²; population 108 873 in 1999) to calculate mean age and sex specific suicide rates for the period 1994-9.

Methods and results

A community health worker (a resident of the village), health aide, community nurse, and doctor reached a consensus on the cause of death. The community health worker, health aide, and nurse independently visited the home of the deceased and collected information from relatives and neighbours of the deceased, traditional healers, and village leaders. These health professionals discussed the circumstances of the death with the doctor. The doctor independently collected information from the different sources in the village in case of any doubts about cause of death.³ The system was evaluated by independent interviewers in

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Age and sex specific suicide rates in the Kaniyambadi region of southern India, 1994-9

	Age* (years)						
	15-24	25-34	35-44	45-54	55-64	65-74	≥75
Men:							
No of suicides	58	63	62	58	37	31	22
Person years	60 192	55 710	40 980	29 777	22 412	13 073	6 725
Age specific suicide rate†	96	113	151	195	165	237	327
Women:							
No of suicides	102	64	29	21	17	25	20
Person years	62 085	55 044	38 403	31 044	23 042	14 721	7 041
Age specific suicide rate†	164	116	76	68	74	170	284
Total:							
No of suicides	160	127	91	79	54	56	42
Person years	122 277	110 754	79 383	60 821	45 454	27 794	13 766
Age specific suicide rate†	131	115	115	130	119	201	305

*There were no suicides among people younger than 15 years.

†Age specific suicide rate=(No of suicides for an age group×100 000)/(Total person years in that age group).