Aliment pharmacol Ther 1997: 11: 541–546.

Lansoprazole 30 mg daily versus ranitidine 150 mg b.d. in the treatment of acid-related dyspepsia in general practice

R. H. JONES & G. BAXTER*
*Department of General Practice, UMDS (Guy's and St Thomas's), London, UK; and *Wyeth Laboratories, Taplow, UK*

Accepted for publication 29 January 1997

SUMMARY

Aim: To compare lansoprazole 30 mg daily with ranitidine 150 mg b.d. in the treatment of acid-related dyspepsia in general practice.
Methods: In a double-blind, parallel group, randomized, multicentre study conducted in 32 general practices in the UK, 213 patients were randomized to receive lansoprazole 30 mg daily, and 219 to receive ranitidine 150 mg b.d., for 4 weeks. All patients had experienced symptoms of reflux-like or ulcer-like dyspepsia on at least 4 of the 7 days prior to the study; 75% had experienced dyspepsia in the past, and 74 of the lansoprazole patients and 77 of the ranitidine patients had documented histories of acid-related disorders, investigated by either radiology or endoscopy.
Results: After 2 weeks 55% of the lansoprazole patients and 33% of the ranitidine group were symptom-free ($P = 0.001$, $\chi^2 = 7.12$) with corresponding 4-week figures of 69% and 44%, respectively ($P = 0.001$, $\chi^2 = 18.03$). Similar figures were found at both 2 and 4 weeks for daytime and night-time heartburn and epigastric pain scores; in the lansoprazole group, at 4 weeks, 80% of patients were free of daytime heartburn and 81% of night-time epigastric pain, compared with 55% ($P = 0.001$, $\chi^2 = 15.44$) and 65% ($P = 0.01$, $\chi^2 = 6.10$) in the ranitidine group.
Conclusion: Superior symptom relief for patients presenting with ulcer-like and reflux-like symptoms in general practice is provided by lansoprazole 30 mg daily compared with ranitidine 150 mg twice daily.

INTRODUCTION

Dyspepsia, defined as upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting or other symptoms considered referable to the upper alimentary tract, is a common problem. The 6-month community prevalence of dyspepsia is in the region of 40%,[1] and dyspepsia accounts for 4–5% of consultations in general practice.[2] Although dyspepsia may signal the presence of a range of underlying disorders, the majority of patients presenting in general practice do not have serious disease; open-access endoscopy services report frequencies of peptic ulcer and moderate to severe gastro-oesophageal reflux disease in the region of 10%, and less than 2% of patients will turn out to have a malignant cause for their symptoms. Up to half of examinations will be entirely normal.[3,4]

These observations form the basis for a range of management strategies adopted to deal with dyspepsia. Patients with alarm symptoms (pain on swallowing, difficulty swallowing, anaemia, evidence of bleeding, weight loss, etc.) and those over the age of 45 years with new dyspeptic symptoms require relatively urgent referral or investigation. In those under the age of 45 years, in an attempt to avoid over-use of endoscopy services, short-term empirical antisecretory therapy is frequently used and subsequent management determined on the basis of response to that treatment.[5] There is research evidence to support this approach, which is likely to be at least as cost-effective and clinically effective as early endoscopy followed by appropriately

Correspondence to: Prof. R. Jones, Wolfson Professor of General Practice, UMDS (Guy's and St Thomas's), 5 Lambeth Walk, London SE11 6SP, UK

chosen drug therapy.[6,7] In both situations, however, patients whose symptoms recur or fail to respond to therapy require further investigation or referral.

In the treatment of peptic ulcer disease and gastro-oesophageal reflux disease (GERD), the proton pump inhibitor lansoprazole has been shown to be superior to ranitidine and the other H_2-receptor antagonists in the relief of symptoms.[8,9] However, no comparison has been made in the relief of dyspeptic symptoms in unselected patients presenting in general practice with undiagnosed acid-related dyspepsia.

This study compares the safety and efficacy of lansoprazole 30 mg daily with ranitidine 150 mg b.d. in the relief of dyspeptic symptoms in patients presenting in general practice with ulcer-like and reflux-like dyspepsia.

METHODS

This was a Phase III, double-blind, randomized, parallel group, multicentre study, conducted in 32 general practices in the UK. Participating general practitioners were members of the Primary Care Society for Gastroenterology.

Patients

Patients with symptoms of reflux-like or ulcer-like dyspepsia were included in the study if they were aged between 18 and 80 years (patients aged 45 years or over were not entered until the possibility of gastro-oesophageal cancer had been considered and excluded), and had either (i) ulcer-like (episodic epigastric pain) or reflux-like (heartburn) dyspeptic symptoms persistently during the 2 weeks before entry to the study but no previous confirmed history of GERD or peptic ulcer; or (ii) a documented history of GERD or peptic ulcer and who had experienced similar symptoms over the 2 weeks prior to the study, considered to be indicative of a symptomatic relapse. In both cases, symptoms were required to be of at least mild severity (occasional pain) and to have been present on at least 4 of the 7 days prior to the study.

Patients were excluded from the study if any of the following criteria were met: symptoms suggestive of disordered gut motility (diffuse pain during the day, hunger with premature satiety, epigastric fullness, nausea and vomiting); patients with symptoms suggestive of irritable bowel syndrome (significantly abnormal bowel habit, constipation requiring treatment, lower abdominal pain, diffuse abdominal pain); a history of previous biliary tract disease; patients taking antisecretory therapy within 1 month of study entry; patients taking corticosteroids, anticoagulants, phenytoin or non-steroidal anti-inflammatory drugs; and any patient suspected of having underlying malignant disease. Exclusions also included patients who had previous gastric surgery, a history of alcoholism or drug abuse, symptoms of upper gastrointestinal haemorrhage, serious or uncontrolled concomitant illness, patients who were pregnant or lactating, night-shift workers and women taking the oral contraceptive pill who were not prepared to use an additional non-hormonal method of contraception during the trial.

Sample size

The number of patients required for the study was based on the assumption that, at 2 weeks, the percentage of patients with complete symptom relief would be 65% for the lansoprazole arm and 50% for the ranitidine arm. This required 340 evaluable patients in order to show at least a 15% difference with a power of 80% at the 5% level of significance (two-tailed); to allow for 25% of the patients being ineligible or unevaluable, a total population of 428 patients (214 per arm) was estimated to be required.

Treatment

Patients were randomly allocated to one of the following treatment regimens from a computer-generated randomization list stratified by centre in blocks of four patients; treatment consisted either of lansoprazole 30 mg o.m. + placebo nocte or ranitidine 150 mg o.m. + ranitidine 150 mg nocte, for 4 weeks. Identical capsules were taken in the morning before breakfast and at bedtime. A box of 48 antacid tablets was provided for symptom relief.

Outcome measures

At the baseline visit an information sheet was provided and written informed consent obtained. As well as recording demographic and medical baseline data, the physician assessed the patient's primary symptoms over the week prior to study entry, in terms of day- and night-time symptoms of heartburn and epigastric pain,

in accordance with the following categorical scale: None—no pain; Mild—occasional pain that does not significantly affect sleep/normal activities; Moderate–frequent pain or pain that affects sleep/normal activities; Severe—constant pain. Secondary symptoms associated with dyspepsia were also recorded. Patients were then provided with a diary card on which to record day- and night-time symptoms of heartburn and epigastric pain using a visual analogue scale with a 10 cm range from no pain to worst pain ever.

At a second visit, 2 weeks later, primary and secondary symptoms were again assessed by the physician, changes in concomitant medication and adverse events were recorded and a capsule and antacid count was undertaken. Patients' diary cards were collected and checked.

At a third visit, 2 weeks later, similar assessments were made so that physician and patient evaluations of symptoms over the preceding weeks were obtained, and all medication not consumed was returned to the investigator.

The principle endpoints for the study were the investigator's assessment of primary symptom severity at baseline, 2 and 4 weeks, the patient's assessment of symptom severity recorded on a daily basis and the number of antacid tablets consumed during treatment.

The statistical analysis was performed using the statistical package SAS release 6.10; all tests were two-sided and significance was assessed at the 5% level.

RESULTS

A total of 450 patients from 32 general practices in the UK were enrolled during a 17-month period. Twenty of the 32 centres enrolled at least eight patients, and the number of patients enrolled ranged from 1 to 41. A total of 213 eligible patients were randomized to receive lansoprazole and 219 to receive ranitidine; at week 2, 171 in each group were both eligible and evaluable, and at the third visit at week 4, 137 lansoprazole and 146 ranitidine patients were suitable for the per protocol evaluation. The main reasons for patients becoming non-evaluable were that scheduled visits to investigators were missed (26 lansoprazole patients and 27 ranitidine patients), and the most common reason for withdrawal was the occurrence of adverse events (12 lansoprazole patients and 14 ranitidine patients). Non-compliance rates were otherwise low.

The demographic characteristics of patients in the lansoprazole and ranitidine groups were comparable; there were 89 (52%) men and 82 (48%) women in the lansoprazole group compared with 81 (47%) men and 90 (53%) women in the ranitidine group. The median age of the lansoprazole patients was 53.5 years and of the ranitidine patients 52.9 years. There were, similarly, no significant differences with respect to height or weight.

There were 47 smokers (28%) in the lansoprazole group compared with 53 (31%) in the ranitidine group, and alcohol consumption was similar in both groups. The distribution of symptoms in the study groups was also similar; 43 (25%) of the lansoprazole group had ulcer-like symptoms, 104 (61%) reflux-like symptoms and 24 (14%) both symptoms, compared with 26%, 57% and 17%, respectively, in the ranitidine group. Three-quarters of the patients in the study had a previous history of dyspepsia and their median duration of dyspepsia was 6 years in the lansoprazole group and 5 years in the ranitidine group ($P = 0.69$, Wilcoxon test).

Similar numbers of patients had documented histories of acid-related disease; 12 patients in the lansoprazole group and 15 in the ranitidine group had histories, for example, of duodenal ulcers, and 27 in the lansoprazole group and 31 in the ranitidine group a history of GERD. Overall, 74 of the lansoprazole patients and 77 of the ranitidine patients had documented histories of acid-related disorders investigated by either radiology or endoscopy. The median duration of the current episode of dyspepsia was 2 months, and 60% of the lansoprazole patients and 52% of the ranitidine patients had taken treatment for dyspepsia in the 4 weeks prior to entry.

At baseline, similar numbers of patients had mild, moderate and severe symptoms of dyspepsia, as indicated in Figure 1. After 2 and 4 weeks of treatment significantly more patients were symptom-free in the lansoprazole treatment group compared to the ranitidine treatment group (Figure 1), with 2-week figures of 55% for lansoprazole and 33% for ranitidine ($P = 0.001$, $\chi^2 = 17.12$) and 4-week figures of 69% and 44%, respectively ($P = 0.001, \chi^2 = 18.03$).

Forty-six per cent of lansoprazole patients experienced an improvement of at least two grades in the severity of their overall primary dyspepsia symptoms (i.e. from Severe to Mild/None or from Moderate to None) during the first 2 weeks of treatment, compared with 33% of ranitidine-treated patients. At the end of the 4-week

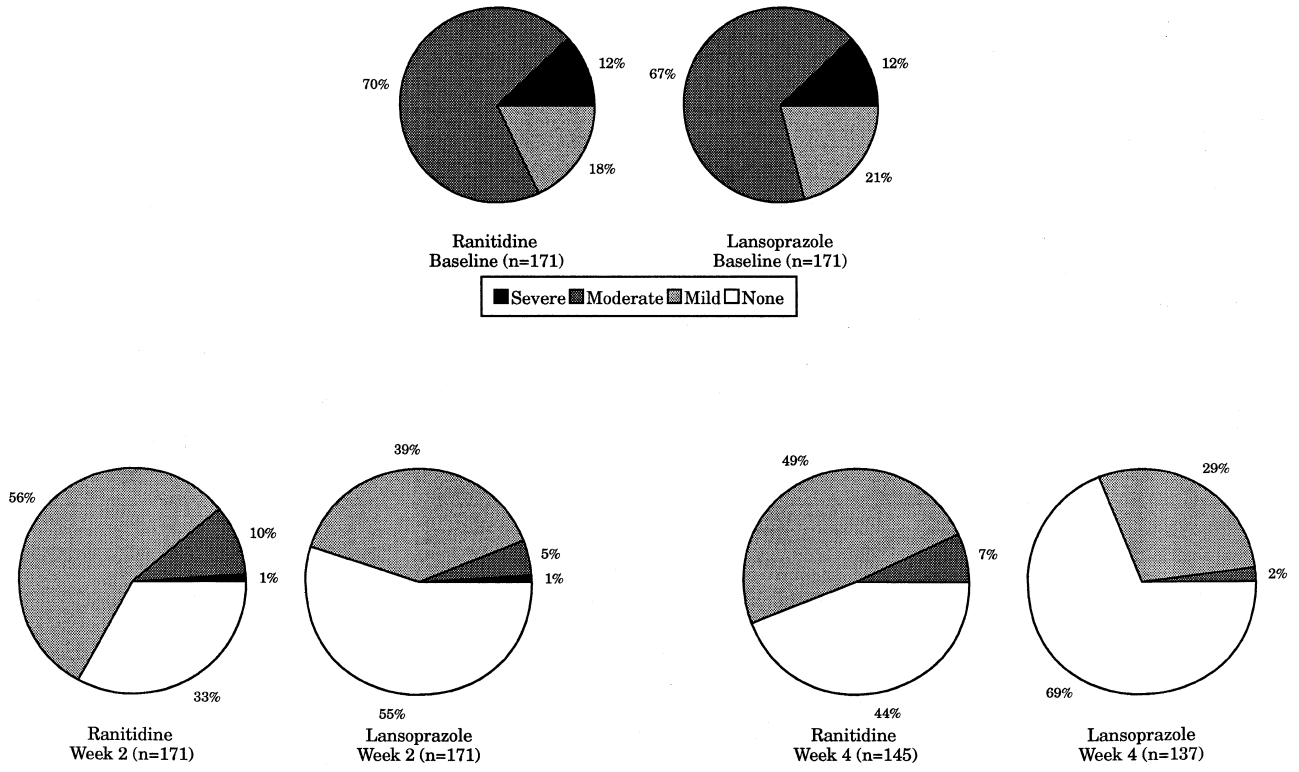

Figure 1. Overall primary symptoms: changes in symptom severity from baseline.

treatment period the proportion of patients experiencing a similarly marked improvement in overall primary symptoms increased to 59% of lansoprazole patients and 41% of ranitidine patients. Significantly larger improvements in the severity of overall primary symptoms were observed in the lansoprazole group at both 2 weeks ($P = 0.009$) and 4 weeks ($P = 0.004$) compared with the ranitidine group (Figure 1).

After 2 and 4 weeks of treatment, significantly more patients were free from symptoms of daytime heartburn in the lansoprazole treatment group compared to the ranitidine treatment group (Figure 2a), with figures at 2 weeks of 66% and 49%, respectively ($P = 0.006$, $\chi^2 = 7.52$), and at 4 weeks of 80% and 55%, respectively ($P = 0.001$, $\chi^2 = 15.44$). Night-time heartburn scores were also improved significantly in the lansoprazole group compared to the ranitidine group (Figure 2b); at week 2 the percentage of symptom-free patients in the lansoprazole group was 69% compared with 52% in the ranitidine group ($P = 0.005$, $\chi^2 = 7.74$), and at 4 weeks the figures were 83% and 64%, respectively ($P = 0.003$, $\chi^2 = 9.11$).

There were also significant differences in the response of daytime epigastric pain (Figure 2c), with a significant difference at 2 weeks (61% of patients symptom-free on lansoprazole compared with 45% on ranitidine, $P = 0.007$, $\chi^2 = 7.16$), and a borderline significant difference at 4 weeks, with corresponding figures of 72% and 60% ($P = 0.06$, $\chi^2 = 3.40$). There were also differences in the response of night-time epigastric pain to the two drugs (Figure 2d); at 2 weeks 68% of lansoprazole patients were symptom-free compared with 50% of the ranitidine patients ($P = 0.004$, $\chi^2 = 8.45$) with corresponding figures at 4 weeks of 81% and 65% ($P = 0.01$, $\chi^2 = 6.10$).

With the exception of night-time heartburn, the significant differences between the two treatment groups obtained from the 'per protocol' analysis described above were also observed in the 'intention-to-treat' analysis consisting of the 211 lansoprazole patients and 206 ranitidine patients who received at least one dose of the study medication and who had efficacy data for at least one post-baseline visit.

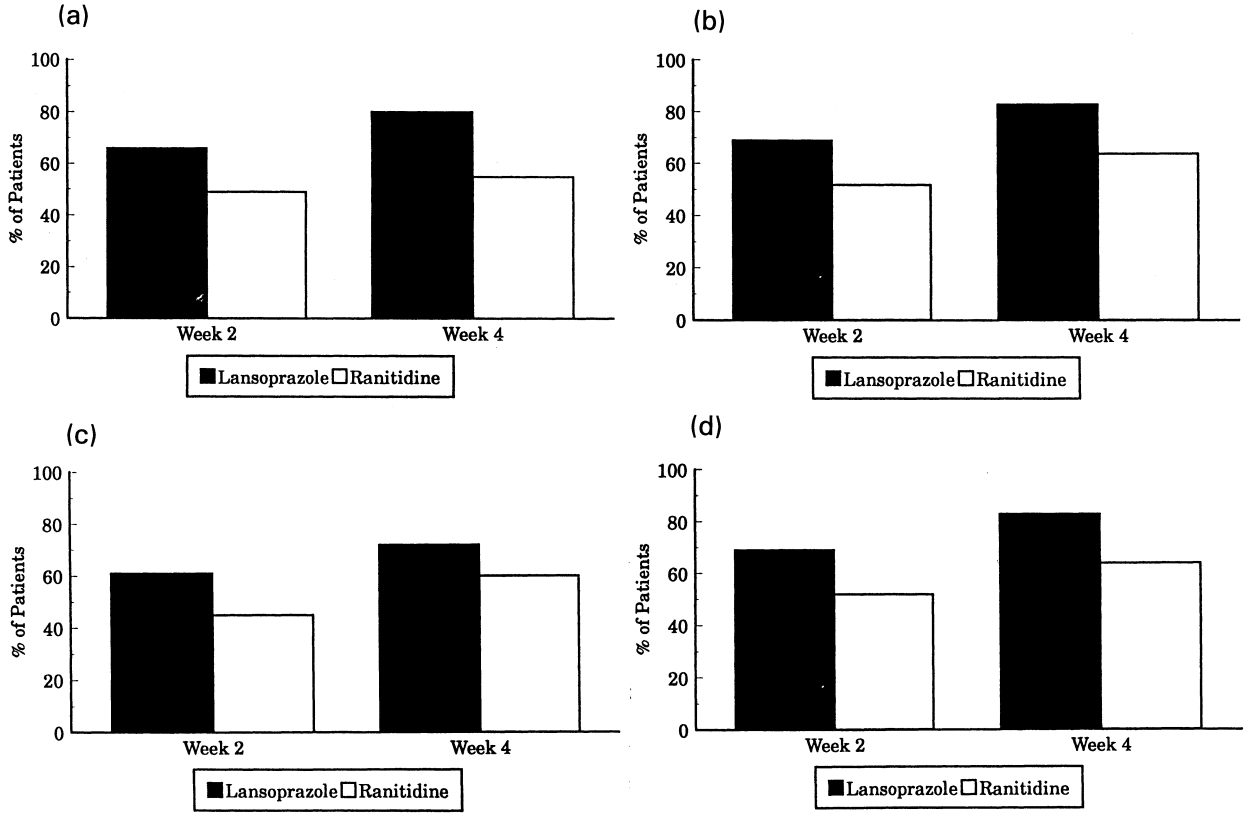

Figure 2. Symptom-free patients at 2 and 4 weeks: (a) daytime heartburn; (b) night-time heartburn; (c) daytime epigastric pain; and (d) night-time epigastric pain.

These overall improvements were reflected in subgroup analyses of patients with predominantly ulcer-like or predominantly reflux-like symptoms, where the superiority of lansoprazole 30 mg daily over ranitidine 150 mg b.d. was sustained. These findings were also reflected in the differences in antacid consumption between the two groups; between baseline and the first visit, almost twice as many antacid tablets were consumed by the ranitidine group (17.5 vs. 9.5, $P = 0.0001$), and during weeks 3 and 4 a mean of 6.5 antacid tablets were consumed in the lansoprazole group compared with 12.9 in the ranitidine group ($P = 0.0001$).

Both drugs were well tolerated, almost all adverse events were minor. Fifty-nine events in the lansoprazole group and 63 in the ranitidine group where considered by the investigators to have a possible or probably causal relationship with the study drug. Gastrointestinal, nervous system and respiratory events accounted for three-quarters of all adverse events reported. The number, type, frequency and severity of adverse events was similar between the two groups. There were four serious adverse events, two in each group, of which only one (headache, nausea, dizziness and urticarial rash in a patient receiving lansoprazole) was thought to have a possible relationship with the study drug.

DISCUSSION

This study demonstrates that superior symptom relief for patients presenting with ulcer-like and reflux-like symptoms in general practice is afforded by lansoprazole 30 mg daily compared with ranitidine 150 mg twice daily. A significantly greater proportion of patients receiving lansoprazole were free from heartburn and epigastric pain, the primary symptoms of dyspepsia, at both 2 and 4 weeks after treatment, and this was accompanied by greater control of daytime and night-time dyspeptic symptoms. The superior symptom relief afforded by lansoprazole was accompanied by lower

antacid consumption and an incidence rate of side-effects comparable with other studies involving both drugs.[10] These results indicate that lansoprazole is a potentially useful and effective agent in the initial treatment of patients presenting in general practice with dyspeptic symptoms. In patients with a documented history of an acid-related disorder, including gastro-oesophageal reflux disease and peptic ulcer, lansoprazole 30 mg daily offers a useful alternative to the H_2-receptor antagonists as an initial treatment for symptom relapse. In patients without a positive history, and in whom empirical antisecretory therapy is an appropriate initial strategy, lansoprazole, once again, offers superior symptom relief and a more effective basis for a 'therapeutic trial' on which to base subsequent management decisions.

It is, however, important that patients presenting with dyspepsia in general practice are 'triaged' so that serious disease is identified as soon as possible. Patients with alarm symptoms and those over the age of 45 years with dyspeptic symptoms require more urgent attention, and are not suitable for empirical antisecretory therapy in the absence of a firm diagnosis.

Management strategies for dyspepsia now have to include the role of *Helicobacter pylori* in duodenal ulcer disease. At present we do not have the evidence on which to base clinical or health economic decisions about choosing between a Helicobacter-testing strategy and an empirical antisecretory strategy. Evidence exists to suggest that both of these may be appropriate, and the place of an individual management strategy may relate as much to the characteristics of the health-care system in which it is used as to the costs and effects of the tests and therapeutic agents used in it.[6,7,11,12] In the absence of clear guidance on this important topic, antisecretory therapy remains an important component of general practitioners' management strategies and lansoprazole 30 mg daily clearly offers advantages over previously available therapy for this purpose.

ACKNOWLEDGEMENTS

The authors wish to thank the following general practitioner investigators who participated in this study: Dr C.L. Anand, Glasgow; Dr C. Barret, Rutherglen; Dr R.G. Bowen, Cardiff; Dr L. Braidwood, Doncaster; Dr M.C. Brown, West Loughton, Dr C. Charlwood, Tunbridge Wells; Dr P.T. Chue Hong, Kinghorn; Dr M.R.B. Cottrill, Leigh; Dr F.R. Cranfield, St Dials; Dr B.A. Hamilton, Stanstead; Dr T.D. Hennessy, Heswall; Dr G.A.C. Hosie, Glasgow; Dr M. Hossain, London; Dr I.C. Kemp, Reading; Dr L. King, Wakefield; Dr A.G. Lane, Cardiff; Dr D. F. McCann, Parkstone; Dr G.S. McGregor, Bishop Auckland; Dr J.A. Millar-Craig, Derby; Dr D.E. Murfin, Ammanford; Dr J.M. Price, Chichester; Dr E. Raubitschek, Addingham; Dr N.J. Riddell, Reading; Dr J.D.V. Roberts, Paignton; Dr B. Rosenberg, Preswich; Dr G.P. Rubin, Thornaby; Dr K. Sher, Leicester; Dr R. Spence, Bristol; Dr C. Temple, Leith; Dr P.G. Williams, Luton; Dr D. Withnall, Colchester; and Dr A.J. Wright, Bolton.

Our grateful thanks to Gareth Lewis, Wendy Underwood and Diane Piper for their assistance with the conduct and statistical analysis of the study.

The study was supported by Wyeth Laboratories.

REFERENCES

1 Jones R, Lydeard S. Prevalence of symptoms of dyspepsia in the community. Br Med J 1989; 298: 30–2.
2 Jones R. ed. Gastrointestinal Problems in General Practice. Oxford: Oxford University Press, 1993.
3 Jones R. Upper gastrointestinal endoscopy—a view from general practice. J R Coll Gen Pract 1986; 36: 8–6.
4 Hungin APS, Thomas PR, Bramble MG, *et al*. What happens to patients following open access gastroscopy? An outcome study from general practice. Br J Gen Pract 1994; 388: 519–21.
5 British Society of Gastroenterology. Provision of Gastrointestinal Endoscopy and Related Services for a District General Hospital. London: British Society of Gastroenterology, 1990.
6 Goulston KH, Dent OF, Mant A, *et al*. The use of H_2 receptor antagonists in patients with dyspepsia and heartburn: a cost comparison. Med J Aust 1991; 155: 20–6.
7 Bytzer P, Hausen JM, Schaffalitzky de Muckadell OB. Empirical H_2 blocker therapy or prompt endoscopy in the management of dyspepsia. Lancet 1994; 343: 811–6.
8 Bardhan KD. The role of proton pump inhibitors in the treatment of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 1995; 9(Suppl 1): 15–25.
9 Hawkey CJ, Long RG, Bardhan KD, *et al*. Improving symptom relief and duodenal ulcer healing with lansoprazole, a new proton pump inhibitor, compared with ranitidine. Gut 1993; 34: 1458–62.
10 Smallwood RA, Berlin RG, Catagnoir N, *et al*. Safety of acid-suppressing drugs. Dig Dis Sci 1995; 40(Suppl 2): 63–80.
11 Patel P, Khulusi S, Mendall MA, *et al*. Prospective screening of dyspeptic patients by *Helicobacter pylori* serology. Lancet 1995; 346: 1315–8.
12 Silverstein MD, Petterson T, Talley NJ. Initial endoscopy or empirical therapy with or without testing for Helicobacter for dyspepsia: a decision analysis. Gastroenterology 1996; 110: 72–83.