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Practice Research

Dyspepsia: incidence of non-ulcer disease in a controlled trial of ranitidine in general practice

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Abstract

Patients who presented to their family doctors with previously uninvestigated dyspepsia of at least two weeks' duration were recruited into a placebo controlled trial of treatment with ranitidine (150 mg twice daily) for six weeks. All patients were examined by endoscopy before treatment, and for those with macroscopical abnormalities the examination was repeated after treatment. Of the 604 patients recruited, 559 had endoscopy, of whom 171 (30%) had no apparent abnormality. Of the 388 patients remaining, one third had two or more lesions. The high incidence of underlying disease was coupled with low accuracy in unaided clinical diagnosis.

After endoscopy 496 patients with persistent symptoms (median duration six to eight weeks) were randomly allocated to treatment and then reviewed every two weeks. Complete remission of symptoms occurred in 76% of patients who were taking ranitidine and in 55% who were taking placebo ($p<0.000004$). Of those with non-ulcer dyspepsia, significantly more became symptom free taking ranitidine compared with placebo ($p<0.002$). Ranitidine healed most duodenal ulcers (80%) and gastric ulcers (90%) within four weeks. Tolerance to ranitidine was good, and the incidence of complaints was similar on placebo.

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Introduction

Family doctors see many patients with dyspepsia for the first time whose symptoms are not entirely typical of peptic ulceration. The short history and relatively mild symptoms may not justify hospital investigations before trying some remedy. Among these patients with dyspepsia are some who have an active gastric or duodenal ulcer, yet their symptoms are indistinguishable from those of patients who have oesophagitis, gastritis, or duodenitis. All these conditions are now regarded as features of acid peptic disease, which may be associated with excessive gastric acidity or reflux. The remaining patients have no disease evident, but their postprandial dyspepsia is similar to that experienced by the others. Non-ulcer dyspepsia may be attributed to emotional stress, but many suspect that acid peptic disease presents a range of clinical features and that early symptoms of dyspepsia may herald the start of the chronic intermittent disease, which may later be recognised as peptic ulceration.

This perception of early acid peptic disease has prompted two ideas. Firstly, some endoscopists believe that family doctors should be encouraged to arrange for endoscopy by providing them with an "open access" service that is run by an endoscopist at a local hospital. Secondly, some gastroenterologists consider that effective treatment to reduce gastric acidity is needed so that any tissue damage is minimised or avoided altogether. The availability of endoscopy and the efficacy and safety of histamine H_2 antagonists have undoubtedly influenced these attitudes. Indeed, these drugs are already being prescribed by family doctors as first treatment without prior investigation.

The purpose of this study was to evaluate the efficacy and safety of ranitidine in an "open access" endoscopy service for family doctors. It would indicate not only what proportion of these patients with dyspepsia had evidence of underlying disease but also the effectiveness of ranitidine in relieving symptoms and in healing ulcers or inflammation in the upper gastrointestinal tract early in the disease. It seemed desirable also to follow up patients for one year after stopping treatment to assess the rate of recurrence.

Patients and methods

A double blind placebo controlled multicentre clinical trial evaluated the efficacy and safety of ranitidine (150 mg twice daily) in managing previously uninvestigated patients with dyspepsia by the assessment of symptoms and endoscopic examination. General practitioners who agreed to participate in the trial liaised with a nearby endoscopy clinic. The trial protocol was approved by the local ethics committee, and informed consent was obtained from the patients. The family doctors performed all assessments other than the endoscopic examinations.

Patients of both sexes were recruited if they presented to their family doctor with dyspepsia of at least two weeks' duration, were aged 18 to 65 years, and were willing and able to participate in the study. Dyspepsia was defined as epigastric or retrosternal pain or discomfort that was usually related to meals. Any patient who had received specific antiulcer treatment, other than antacids for symptomatic use, in the previous four weeks was excluded. Patients who were taking anti-inflammatory drugs, had had surgery to the upper gastrointestinal tract, or had serious systemic illnesses were excluded. Women were excluded if they were pregnant, breast feeding, or likely to conceive during the trial. If the endoscopic examination was delayed for any reason beyond 14 days after the initial presentation or if symptoms of dyspepsia had resolved during the interval before the trial treatment began then the patient was excluded.

Each patient was allocated to six weeks' treatment with ranitidine 150 mg twice daily or matching placebo. Each pack of tablets carried a code number, and general practitioners dispensed treatment in ascending number order. Treatment had been equally and randomly allocated by computer within each block of six consecutive numbers. Patients were also provided with Rennie Digestif tablets (chalk 680 mg, light magnesium carbonate 80 mg, peppermint oil 1 mg) to be taken as required. Compliance with treatment was checked by counting tablets every two weeks.

At two week intervals patients were seen by their family doctor for assessment of symptoms and physical examination and to check smoking and drinking habits. Patients also returned their daily diary of symptoms and antacid consumption and completed questionnaires asking about their experience of 32 different adverse events. Any new sign or symptom which developed during treatment was also reported as an adverse event. The doctors completed a questionnaire a year later which documented investigations done and treatment prescribed for dyspepsia during the previous 12 months for each patient. The base line endoscopic examination was repeated four weeks after the start of treatment if an ulcer was detected or after six weeks if other disease was present.

Efficacy was assessed by differences in the response to symptoms between the patients treated with ranitidine and those treated with placebo overall and also within each diagnostic subgroup. Ulcer healing rates for both treatments were also compared. Tolerance to treatment was evaluated by the adverse events that were spontaneously reported and by those recorded in the questionnaires. The latter allowed the incidence of each event to be calculated at every visit, and then by means of transition tables the number of patients changing category—for example, better, same, worse—between visits was calculated. All statistical tests of significance were χ^2 with Yates's correction, but Fisher's exact test was applied in the analysis of the small group of patients with gastric ulcers.

Results

Patients—After a 12 month pilot study the trial began in May 1982, and the last patient completed treatment in February 1984. A total of 604 patients was recruited by 106 general practitioners in the United Kingdom, who collaborated with 35 endoscopists (three quarters of patients were examined by 12 endoscopists). Of the 604 patients, 23 failed to attend for endoscopic examination and in 22 patients endoscopy was performed more than 14 days after their provisional registration into the trial. Of the remaining 559 patients, 496 finally entered the trial: nine had been withdrawn by the endoscopist (one gastric carcinoma, three benign tumours, two atrophic gastritis, one bleeding ulcer, one further investigation, one error) and another 54 had been excluded(18 were asymptomatic after endoscopy, 22 violated the protocol, 14 defaulted). The demographic characteristics of the final 496 patients were similar in the ranitidine and placebo groups. In the ranitidine group (243 patients) there were 137 men and 106 women, mean ages 42 (range 18-65) and 43 (range 19-65) years respectively. In the placebo group (253 patients) there were 146 men and 107 women, mean ages 40 (range 18-65) and 42 (range 19-65) years respectively.

Disease characteristics—The duration of presenting symptoms exceeded 99 weeks in seven patients treated with ranitidine and in eight patients treated with placebo. Of the remainder, the median and mean (SD) durations of presenting symptoms were six weeks and 13·1 (17·5) weeks respectively for the patients treated with ranitidine and eight weeks and 13·7 (16·5) weeks respectively for those allocated to placebo treatment. Roughly 80% of patients had experienced symptoms of dyspepsia before the presenting episode, and 60% of these first had dyspepsia more than a year before. Some (12%) had their first dyspeptic episode within two to 12 weeks of consulting their doctor. Three quarters of patients had taken antacids before entering the trial, and 70% of all patients gained relief that way. All such features of dyspeptic history were equally represented in both treatment groups.

Initial endoscopic findings—Out of 559 patients who had a valid endoscopic examination, no abnormality was found in 171 (30%). The remainder had macroscopical evidence of disease. Of the 388 patients with abnormalities on endoscopy, about one third had two or more discrete features of disease—for example, oesophagitis and gastric ulcer (table I): Oesophagitis was the commonest finding on endoscopy, followed by duodenal ulcer (table II). Gastric ulcer was found in a few patients, and the macroscopical appearances of inflammation in the stomach or duodenum ("gastritis" or "duodenitis") were the main findings in 103 patients (18%).

TABLE I—*Distribution of disease in 559 patients*

	Patients with finding alone or in combination	
	No	(%)
Duodenal ulcer	97	(17)
Duodenal ulcer with deformed duodenal cap	35	(6)
Duodenal erosion	30	(5)
Gastric ulcer	32*	(6)
Gastric erosions	31	(6)
Oesophagitis	164	(29)
Oesophageal ulcer	11	(2)
Hiatus hernia	84	(15)
Hiatus hernia with oesophagitis	45	(8)
Gastritis (macroscopical appearance)	90	(16)
Duodenitis (macroscopical appearance)	117	(21)
Deformed duodenal cap	54	(10)
Gastric carcinoma	1	(0·2)
Benign neoplasm	4	(0·7)

* Histological examination showed gastric ulcer was malignant in one patient.

TABLE II—*Main diagnosis on endoscopic examination (n = 559)*

	Patients with this finding as main diagnosis	
	No	(%)
Duodenal ulcer	93	(17)
Gastric ulcer	28*	(5)
Gastric and duodenal ulcer	4	(0·7)
Oesophagitis without duodenal or gastric ulcer	132†	(23·6)
Hiatus hernia only	16	(3)
Gastritis (macroscopical appearance, without peptic ulcer or oesophagitis)	51	(9)
Duodenitis (macroscopical appearance, without peptic ulcer or oesophagitis)	35	(6)
Deformed duodenal cap only	3	(0·5)
Mixed mucosal disease	17	(3)
Gastric carcinoma	1‡	(0·2)
Benign neoplasm	4	(0·7)
Bile reflux only	4	(0·7)
No abnormality	171	(30·6)

* Histological examination showed gastric ulcer to be malignant in one patient.
† One patient with mild oesophagitis and severe gastritis had carcinoma of the head of the pancreas.
‡ True incidence of malignant disorders: three (0·5%).

Symptoms and endoscopic findings—A detailed examination of the symptoms and sites of pain that patients reported to their general practitioners at the first attendance showed no characteristic history or patterns of distribution that could be accurately related to underlying disease (table III). For example, retrosternal pain and the association of symptoms with posture were more commonly reported by patients with oesophagitis than by those with ulcers, but they were also experienced by a similar proportion of patients with neither ulcers nor oesophagitis. Symptoms disturbed sleep for more patients with duodenal ulcers than for those with gastric ulcers, and more patients with gastric ulcers found that their symptoms were made worse by eating.

Risk factors—At the first attendance 48% of all patients in the ranitidine group had smoked in the previous two weeks and 42% in the placebo group. Eleven per cent of the ranitidine group were heavier smokers (an average of more than 20 cigarettes a day over the previous two weeks) as were 13% of

the placebo group. The proportion of smokers was higher in patients with duodenal ulcers (65% in the ranitidine group and 73% in the placebo group). At the first attendance 52% of patients in both treatment groups had consumed alcohol in the previous two weeks. The proportion of heavier drinkers (an average daily consumption over the previous two weeks equivalent to three pints of beer or six single measures of spirits) was 5% in the ranitidine group and 8% in the placebo group. There was no statistically significant difference in drinking and smoking habits between the two groups and no clear cut trends found during the trial from checking on habits every two weeks.

Accuracy of clinical diagnosis—Before the endoscopic examination general practitioners made a clinical diagnosis based on history and examination, which was then correlated with the findings at endoscopy (table IV). Duodenal ulceration was diagnosed most accurately: of the 93 patients with endoscopic evidence, 51 (55%) had been diagnosed clinically and 62 (67%) diagnosed with duodenal or peptic ulceration. One hundred and ninety one patients, however, were considered clinically to have a duodenal ulcer compared with 93 on endoscopy, and a similar ratio was found between a clinical diagnosis of gastric, duodenal, or peptic ulceration (319 patients) and endoscopic evidence of gastric or duodenal ulcers (125). Of those patients with no evidence of peptic ulceration or oesophagitis (302), over half (164) were given a clinical diagnosis of gastric, duodenal, or peptic ulceration.

Response of symptoms—Table V shows that for complete remission of symptoms there was a highly significant difference between the percentage of patients who had taken ranitidine and that of patients who had taken placebo. Those with duodenal ulcers showed a significant response to ranitidine, and all those without gastric or duodenal ulcers or oesophagitis had significant relief of symptoms with ranitidine. In patients with gastric or duodenal ulcers the diary cards showed a rapid response of symptoms from ranitidine, especially pain relief, in the first two weeks, and a definite reduction in consumption of antacids from the first day.

Repeat endoscopy—After four weeks of treatment 90% of patients with gastric or duodenal ulcers returned for a repeat endoscopic examination. Significantly more patients with duodenal ulcer who took ranitidine healed than those who took placebo (80% *v* 46%; $p<0·01$) and similarly with gastric ulcers (91% *v* 47%; $p<0·05$). Only 60% of patients with evidence of oesophagitis on the first endoscopic examination attended for a repeat endoscopy after four to six weeks of treatment, and at this stage no significant difference in complete healing was seen between the patients in the two treatment groups.

ADVERSE EVENTS

At five attendances (two before treatment and three during treatment) patients completed questionnaires about 32 symptoms that are sometimes experienced as the side effects of drugs. No significant differences were found in the proportion of patients in each treatment group who experienced each of these symptoms with the exception of headaches. Significantly more

TABLE III—*Symptoms before treatment*

		Before endoscopy				After endoscopy					
		Percentage of patients who experienced pain at each site				Percentage of patients who experienced each factor in association with dyspepsia					
Endoscopic diagnosis	No	Retrosternum	Epigastrium	Left hypochondrium	No	Associated with bending/stooping	Relieved by antacid	Brought on by eating	Relieved by eating	Sleep disturbed
Oesophagitis alone	97	32	76	21	95	46	69	68	24	62
Duodenal ulcer	99	19	89	20	94	21	78	40	50	72
Gastric ulcer	32	16	75	41	30	17	80	50	40	63
All except ulcers or oesophagitis	336	34	91	20	251	44	68	61	25	57

TABLE IV—*Comparison of endoscopic findings with clinical diagnosis for 559 patients for whom no more than 14 days elapsed between clinical diagnosis and endoscopy*

	No of patients given each clinical diagnosis before endoscopic examination								
Main finding on endoscopy	Gastric ulcer	Duodenal ulcer	Peptic ulcer	Oesophagitis	Gastritis or duodenitis	Dyspepsia	Hiatus hernia	Other	Accurate diagnoses
Gastric ulcer (n = 28)	8	6	4	4	4	1		1*	29% gastric ulcer
Duodenal ulcer (n = 93)	13	51	11	3	12	1	2		43% gastric or peptic ulcer 55% duodenal ulcer
Duodenal and gastric ulcer (n = 4)		3	1						67% duodenal or peptic ulcer
Oesophagitis (without ulcer) (n = 132)	16	29	13	34	23	3	14		26% oesophagitis 36% oesophagitis or hiatus hernia
All except gastric or duodenal ulcers or oesophagitis (n = 302)	31	102	31	43	50	19	25	1	
Total No	68	191	60	84	89	24	41	2	

TABLE V—*Outcome of treatment after six weeks for patients in each treatment group*

Endoscopic diagnosis (treatment group)	No treated	No who defaulted	No who withdrew	Final No evaluated	Free of symptoms No (%)	χ^2 test with Yates's correction
All patients						
Ranitidine	243	13	9	221	169 (76)	21·46, $p<0·000004$
Placebo	253	17	13	223	123 (55)	
Duodenal ulcer*						
Ranitidine	48	1	0	47	38 (81)	9·97, $p<0·002$
Placebo	45	3	1	41	19 (46)	
Gastric ulcer*						
Ranitidine	13	0	1	12	9 (75)	$p>0·2$
Placebo	17	1	0	16	7 (44)	(Fisher's exact test)
No abnormality						
Ranitidine	70	3	4	63	51 (81)	2·81, $p>0·09$
Placebo	74	5	7	62	41 (66)	
All patients without ulcers or oesophagitis (non-ulcer dyspepsia)						
Ranitidine	115	7	5	103	82 (80)	9·62, $p<0·002$
Placebo	136	8	10	118	70 (59)	

* Including four patients with both duodenal and gastric ulcers.

patients in the placebo group experienced headaches before treatment, and this difference persisted until the sixth week of treatment.

Seventy six adverse events were spontaneously reported to have occurred in 61 patients who received ranitidine and 77 adverse events in 67 patients who received placebo. Of these patients, four who were taking ranitidine and eight who were taking placebo were withdrawn because of suspected adverse events related to treatment. Of the four patients treated with ranitidine, two had diarrhoea before ranitidine treatment started, which became worse during treatment. A third patient was withdrawn after a single episode of abdominal pain, weakness, and anxiety after taking ranitidine for four weeks. The fourth patient had sore eyes during the first week of treatment, stopped ranitidine for four days, then resumed treatment to the end of six weeks without recurrence. Of the eight patients treated with placebo, three had nausea or vomiting, one had diarrhoea after a single dose, one had loss of taste on the first day of treatment which persisted for 17 days, one had headaches that started two hours after each dose for two weeks of treatment, one experienced chest pain, paraesthesiae, and unsteadiness on the second and fourth days of treatment, and the eighth patient developed an urticarial rash after 14 days of treatment but had also received trimethoprim for a urinary tract infection.

ANNUAL REVIEW

Of the 496 patients who were randomised to treatment, 361 (73%) were reviewed 12 months later. General practitioners completed a questionnaire at interview for 246 patients and from case records for the remainder. Six of these patients had been hospitalised in this period (four taking ranitidine, two taking placebo). Four of these patients (two taking ranitidine, two taking placebo) with no abnormalities on endoscopy underwent further investigations for recurrent symptoms and had cholecystectomies. The third patient taking ranitidine was a 64 year old man who had recurrence of symptoms one month after his duodenal ulcer had healed. Further investigations showed a bronchial carcinoma. His duodenal ulcer perforated five months after the trial, and he died after the operation. A fourth patient from the ranitidine group whose duodenal ulcer had healed during the trial had a gastric ulcer when symptoms recurred eight months later.

One patient in each treatment group reported having had headaches during the follow up year, which they believed to be due to the trial treatment. The patient who had taken ranitidine had had migraine headaches during treatment which continued for four to six weeks after treatment with no further recurrence. The patient who had taken placebo had headaches in the follow up period which the doctor thought were due to stress.

The patients who had taken placebo who returned for annual review were mainly placebo responders. Those patients who had failed to respond to trial treatment were subsequently treated by their doctors. The remaining patients may have been exposed to a variety of treatments during this follow up period. For these reasons valid comparisons between the two treatment groups could not be made. Roughly 50-60% of patients reviewed, however, had had a recurrence of symptoms at some time during the 12 months after treatment.

Discussion

Endoscopic examination of 559 patients with dyspepsia who consulted their family doctors showed that 70% had abnormalities that might be considered to be consistent with acid peptic disease. About one third of these had the macroscopical appearances of more than one abnormality in the upper gastrointestinal tract. None had been investigated before, although their presenting symptoms had lasted more than three months on average. Most (80%) had had dyspepsia before and many of these (60%) for over a year, so endoscopy was clearly justified, although most would not have had it done if they had not presented to their doctor during the trial period. The three patients with malignancies were over 40 years of age, and although diagnosis was made early, they died within two to 14 months of presentation.

The incidence of non-ulcer dyspepsia in the findings from 14 studies reported in the last 40 years has been reviewed.[1] These groups of patients may not be identical and diagnostic methods have gradually improved, but even so the proportion of patients with no abnormalities has remained between 30% and 50%. Endoscopy has increased the accuracy of diagnosis, and in the results of studies reported since 1975 the mean proportion of patients with no evident abnormality is 34%, which is consistent with our finding (30%).[2-7] Some might argue that the macroscopical diagnosis of "gastritis" or "duodenitis" is too subjective, and accordingly these should not be classified as definite abnormal findings. If so, the proportion of patients in this study with definite lesions would be 50%, which still accords with other studies.

The accuracy with which family doctors evaluated dyspepsia was approximately 50% in this trial, which agrees with that in other studies.[8,9] Attempts have been made to identify patients with dyspepsia who have serious underlying disease by discriminant analysis of case histories using scoring systems[10,11] or computers.[12] These results show, as we have shown, that it is difficult not only to make an accurate diagnosis but also to recognise which dyspeptic patients have underlying disease from symptoms alone.

The high incidence and multiplicity of disease in patients with dyspepsia who are seen in general practice and the inaccuracy of clinical diagnosis supports hospital investigation—probably earlier than symptoms alone might suggest. The following guidelines are suggested to family doctors: treat patients with dyspepsia without investigation if it is their first episode; if they relapse arrange for endoscopy and other tests as appropriate; those aged over 40 may have a malignancy, and it may be prudent to investigate them at the outset.

Antacids are widely used as the first treatment for symptoms of dyspepsia and had been beneficial for almost three quarters of the patients who entered this study. It is not surprising, therefore, that ranitidine, with its 24 hour control of gastric secretion, was better than placebo in producing relief of symptoms in a variety of dyspeptic conditions. Treatment for six weeks with ranitidine produced complete remission of symptoms in about 80% of patients with non-ulcer dyspepsia, as well as healing up to 90% of ulcers, which is appreciably better than antacid therapy. Ranitidine treatment was shown to be safe.

If non-ulcer dyspepsia heralds the beginning of acid peptic disease, as many believe, it may be preferable to try to limit the extent and degree of mucosal damage. The disease seen in patients in this study might be regarded in the long term as unacceptable when we have the means to detect and treat it early.

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References

1 Thompson WG. Nonulcer dyspepsia. *Can Med Assoc J* 1984;130:561-9.
2 Mollmann KM, Bonnevie O, Gudthead Hover E, Wulff HR. A diagnostic study of patients with upper abdominal pain. *Scand J Gastroenterol* 1975;10:805-9.
3 Oddsson E, Bieder V, Thorgeirsson T, *et al*. A prospective comparative study of clinical and histological characteristics in Icelandic and Danish patients with gastric ulcer, duodenal ulcer, and X-ray negative dyspepsia. I. Design and clinical features. *Scand J Gastroenterol* 1977;12:689-94.
4 Horrocks JC, De Dombal FT. Clinical presentation of patients with 'dyspepsia'. Detailed symptomatic study of 360 patients. *Gut* 1978;19:19-26.
5 Bevan AK, La Brooy S, Mawhirter JJ. Evaluation of one-year endoscopic clinic for patients with dyspepsia. *Br Med J* 1979;i:1387-9.
6 Gear MWL, Barnes RJ. Endoscopic studies of dyspepsia in a general practice. *Br Med J* 1980;280:1136-7.
7 Priebe WM, DeCosta LR, Beck IT. Is epigastric tenderness a sign of peptic ulcer disease? *Gastroenterology* 1982;82:16-9.
8 Horrocks JC, De Dombal FT. Computer aided diagnosis of dyspepsia. *American Journal of Digestive Diseases* 1975;20:397-406.
9 Ross P, Dutton AM. Computer analysis of symptom complexes in patients having upper gastrointestinal examinations. *American Journal of Digestive Diseases* 1972;17:248-54.
10 Mann J, Holdstock G, Harman M, Machin D, Lorkey CA. Scoring system to improve cost effectiveness of open access endoscopy. *Br Med J* 1983;287:937-40.
11 Cross GP, Card WI, Bourke AD, *et al*. Ulcer like dyspepsia. *Scand J Gastroenterol* 1982;79(suppl):9-15.
12 Davenport PM, Morgan AG, Daruhoorgah A, De Dombal FT. Can preliminary screening of dyspeptic patients allow more effective use of investigational techniques? *Br Med J* 1985;290:217-20.

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