Enprostil and ranitidine in prevention of duodenal ulcer relapse: one year double blind comparative trial

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Abstract

One hundred and forty two patients with duodenal ulcer who after a short term study had relief of pain and healed ulcers proved endoscopically were allocated at random to double blind maintenance treatment with enprostil (a synthetic dehydroprostaglandin E₂) 35 µg or ranitidine 150 mg at bedtime for up to 12 months. Patients were monitored every third month and examined by endoscopy at three, six, and 12 months, or more often if warranted. The cumulative relapse rates in the enprostil group at three, six, and 12 months were 37% (25/67), 56% (37/66), and 62% (41/66), respectively. The corresponding rates in the ranitidine group were 8% (6/71), 19% (13/69), and 29% (20/69). These differences were highly significant and further enhanced by life table analysis adjusting for withdrawals and by an "intention to treat" analysis in which absence of proof of non-recurrence was counted as failure, more patients in the enprostil group having been withdrawn because of adverse events or recorded as non-compliant with the protocol.

Enprostil 35 µg at bedtime cannot be recommended for preventing relapse of duodenal ulcer. Furthermore, the results challenge the clinical relevance of using so called "cytoprotection" for preventing recurrence.

Introduction

An important challenge in the drug treatment of duodenal ulcer is the prevention of recurrence, which may be associated with pain and complications. Though prolonged use of drugs (maintenance treatment) has still not been proved to reduce the incidence of complications in the long term,¹ several agents have been shown to reduce the incidence of endoscopic relapse.² Nevertheless, even ranitidine 150 mg taken at bedtime fails to prevent recurrence in every third³ or fourth⁴ patient within one year. Synthetic prostaglandin analogues of the E series offer a new approach to the prevention of relapse.⁵ These agents are believed to maintain mucosal integrity by decreasing secretion of gastric acid and in addition by protecting the mucosa, independently of acid inhibition,⁶⁻⁸ by a mechanism termed "cytoprotection."⁹ Enprostil is a synthetic dehydroprostaglandin E₂ which combines antisecretory¹⁰⁻¹³ with cytoprotective properties, such as to protect the antral mucosa against damage by aspirin even at doses below those required for acid inhibition.¹⁴ Hence it might be expected that

enprostil given nightly in an antisecretory dose would prevent recurrence of ulcer. To test this we have carried out a double blind randomised trial of enprostil (35 µg at bedtime) and ranitidine (150 mg at bedtime).

Patients and methods

Patients with endoscopically proved duodenal ulcer (visual loss of substance) included in a short term study comparing enprostil and ranitidine for ulcer healing¹⁵ were considered for this trial within seven days after finishing their study treatment. Criteria for recruitment were that ulcer healing, verified by endoscopy, and pain relief had been obtained. Each patient gave informed consent and the trial was approved by the regional ethics committees.

Patients were reassigned at random (by a computer generated randomisation list stratified for centre in blocks of 20) to double blind maintenance treatment with either one 35 µg capsule of enprostil or one 150 mg tablet of ranitidine at bedtime. Inactive capsules and tablets identical in appearance with the active ones had been prepared so that all patients received the same number of tablets or capsules. Adjuvant antacid (Novaluzid chewing tablets) and paracetamol were supplied for relief of pain, if any. No other antilulcer treatment was permitted. Patients were given diary cards for recording the use of antacids and the intensity of any pain^{15 16} and instructed to attend the clinic if ulcer-like symptoms for three days in any week or haematemesis or melaena occurred.

Patients were seen after three, six, nine, and 12 months for clinical assessment, laboratory screening (haemoglobin and serum creatinine concentrations; alkaline phosphatase, alanine aminotransferase, and lactic acid dehydrogenase activities), and endoscopy. We omitted endoscopy at nine months in patients who were symptom free and had no appreciable decrease in haemoglobin concentration. The main end point was endoscopically proved recurrence of ulcer, and patients completed the study after 12 months, or earlier if recurrence was seen.

Returned tablets and capsules were counted at each visit and patients found later not to have taken the active drug for three days or more per fortnight regarded as ineligible for the "per protocol" analysis (see below).

STATISTICS

In planning the trial we estimated that the relapse rate in the ranitidine group would be 35% at 12 months³ and considered that reducing this rate by at least half would be clinically meaningful. We calculated that roughly 160 patients (80 in each group) from among the 180 planned for the healing study would be needed to ensure that the risk of overlooking a reduction from 35% to 15% would be less than 20%.¹⁷ Statistical methods used were Fisher's exact test, the χ^2 test, the Mantel-Haenszel test, and the paired and unpaired *t* tests, as appropriate. Only two tailed tests were used.

Results were subjected to both a "per protocol" analysis (that is, excluding patients non-compliant with the protocol) and an "intention to treat" analysis (that is, including all patients recruited). Per protocol analysis was done (a) by comparing the traditional crude relapse rates and (b) by comparing relapse rates computed by a life table method. The crude relapse rates—that is, the ratio between the number of patients who relapsed and the number recruited, less patients non-compliant with the protocol—were tested by an actuarial extension¹⁸ of the Mantel-Haenszel statistics.¹⁷ The Cutler-Ederer life table method¹⁹ was used to obviate overstatement of the probability of no recurrence in the calculations of crude rates, which assume that patients withdrawn do not experience recurrence. The method adjusts for withdrawals in each period by assuming that the patients were at risk for half that period and that this risk was identical with that of patients in the same treatment group who were not withdrawn. The method entails five steps: (a) subtracting half of the withdrawals from the total number of evaluable patients receiving each treatment in a time interval; (b) calculating

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the proportion of patients with a relapse relative to this number; (c) subtracting this proportion from unity to give the interval specific proportion with no relapse; (d) multiplying this proportion and those for all preceding intervals to produce the cumulative maintenance rate; and (e) subtracting this from unity to give the cumulative relapse rate. The Mantel-Haenszel test¹⁷ was applied to these results. The life table method ignores patients non-compliant with the protocol from the time of non-compliance.

Finally, the Mantel-Haenszel statistics and the actuarial method were applied on an intention to treat basis with estimation of failure (taken as absence of proof of non-recurrence) as the event of interest: (a) the proportion of patients with proved non-recurrence was determined relative to the number at risk; (b) the maintenance rate through the end of a specific interval was the product of this proportion and those for all preceding intervals; (c) for each interval the failure rate was obtained by subtracting the maintenance rate during the interval from unity. The 95% confidence limits for differences in relapse and failure rates between the treatment groups were also calculated.¹⁷

Results

Between September 1984 and September 1985 all 142 of the 180 patients in the short term study¹⁵ who were eligible consented to further study—130 from centre 1 (Odense) and 12 from centre 2 (Bispebjerg). Seventy one were allocated to receive enprostil (65 from centre 1) and 71 to receive ranitidine (65 from centre 1). The treatment groups were well matched for selected patient characteristics (table I).

During the first three months three patients in the enprostil group were withdrawn because of dizziness, diarrhoea, and pain, respectively, and four failed to comply (two had not taken the prescribed amount of medicine, one received ranitidine from his general practitioner, and one emigrated). In the ranitidine group one patient, who suffered epigastric pain, was also withdrawn. Endoscopy showed duodenitis but no ulcer recurrence. During months 4-6 four patients in the enprostil group were withdrawn (because of diarrhoea, fatigue, and (in two cases) epigastric pain without endoscopic evidence of ulcer recurrence) and one stopped taking the capsules. In the ranitidine group two patients were withdrawn because of diarrhoea and epigastric pain (but no ulcer), respectively, and two others were non-compliant (one failed to attend for endoscopy and one stopped the treatment). During months 7-12 one patient in the enprostil group and two in the ranitidine group were withdrawn because of epigastric pain (no ulcer recurrences were found), one patient taking enprostil was withdrawn because of diarrhoea, and one taking ranitidine wished to stop further treatment. Table II summarises outcome in the two treatment groups.

Ulcer relapse—Cumulative relapse rates were significantly higher in the enprostil group than in the ranitidine group at any point in the study (table III) regardless of the method of analysis (crude rates and life table method). In both treatment groups relapse rates were higher among smokers, but not significantly so (table IV). The ulcer relapse was asymptomatic in 15% (6/41) of patients taking enprostil and in 10% (2/20) taking ranitidine ($p>0.05$). In

TABLE III—Ulcer relapse rates in two treatment groups calculated by two methods of "per protocol" analysis (that is, excluding patients non-compliant with protocol). Figures are percentages

Analysis method	Cumulative relapse rates	Enprostil group	Ranitidine group	Difference*	p Value†
Crude relapse rate‡	3 Months	37	8	29 (15 to 43)	<0.0001
	6 Months	56	19	37 (22 to 52)	
	12 Months	62	29	33 (17 to 49)	
Life table method§	3 Months	40	9	31 (17 to 45)	<0.00001
	6 Months	63	20	43 (28 to 58)	
	12 Months	71	31	40 (24 to 56)	

*Values in parentheses are 95% confidence intervals for differences.

†Mantel-Haenszel test.

‡Calculated as ratio between number of patients who relapsed and number recruited less patients non-compliant with protocol (table II).

§Cutler-Ederer method; adjusts for withdrawals but not for patients non-compliant with protocol beyond time of non-compliance.

TABLE IV—Ulcer relapse rates after 12 months according to smoking

	Smokers		Non-smokers		p Value
	No	%	No	%	
Enprostil group	34/52	65	7/14	50	NS*
Ranitidine group	16/48	33	4/21	19	NS*

*Fisher's exact test ($p>0.05$).

TABLE V—Failure rates in two treatment groups calculated by "intention to treat" analysis (that is, including all patients recruited, counting absence of proof of non-recurrence as failure). Figures are percentages

Cumulative failure rate	Enprostil group	Ranitidine group	Difference*	p Value†
3 Months	45	10	35 (21 to 49)	<0.000001
6 Months	69	25	44 (29 to 59)	
12 Months	77	39	38 (23 to 53)	

*Values in parentheses are 95% confidence intervals for differences.

†Mantel-Haenszel test.

six cases (five taking enprostil) the recurrent ulcer was prepyloric. For the intention to treat cohort the differences in cumulative rates of failure (that is, no proved non-recurrence) were even further enhanced (table V), more patients having been withdrawn from the enprostil group.

Use of antacids—The use of adjuvant antacids differed between the two treatment groups, including the subgroups who did not have a relapse. In the enprostil group 16 patients completed the 12 month study without relapse. Seven patients had not used antacids, two had used antacids in a single (three month) period, and seven had used antacids more regularly. Corresponding figures in the ranitidine group were 27 of 43, 10 of 43, and six of 43, respectively ($\chi^2=6.1$, $df=2$, $p<0.05$).

Unexpected symptoms and laboratory findings—Diarrhoea (that is, increased stool frequency or loose stools, or both) was reported by a further two patients (in addition to those mentioned above) taking enprostil, and two taking ranitidine reported transient headache. The paired t test showed a small but significant increase in haemoglobin concentration in the ranitidine group after the trial. No other trends in laboratory values were found in either study group. In several cases a single value fell outside the reference range for the laboratory concerned, but such abnormalities occurred at random in both treatment groups.

TABLE I—Characteristics of patients in two treatment groups

	Enprostil group (n=71)	Ranitidine group (n=71)	p Value
Sex ratio M:F	44:27	46:25	NS*
Mean age in years (range)	54.7 (22-78)	54.6 (23-78)	NS†
Mean duration of history in years (range)	13.3 (0-55)	12.4 (0-45)	NS†
No with previous ulcer bleeding or perforation	19	20	NS*
No of smokers	55	50	NS*
No healed with enprostil: ranitidine	30:41	32:39	NS*
No treated for 2, 4, and 6 weeks in short term study	29, 27, 15	28, 28, 15	NS‡

*Fisher's exact test ($p>0.05$).

†Two sample t test ($p>0.05$).

‡ χ^2 Test ($p>0.05$).

TABLE II—Patient outcome distributed by treatment group

	Enprostil group				Ranitidine group			
	Entry	1-3 Months	4-6 Months	7-12 Months	Entry	1-3 Months	4-6 Months	7-12 Months
No recruited	71				71			
No withdrawn		3	4	2		1	2	3
No non-compliant with protocol		4	1	0		0	2	0
No with endoscopic relapse		25	12	4		6	7	7

Discussion

These findings show that ranitidine 150 mg at bedtime is superior to enprostil 35 µg at bedtime in preventing relapse of duodenal ulcer. The extreme differences in relapse rates were surprising because enprostil 35 µg has been claimed to have antisecretory effects comparable¹⁰ or superior¹¹ to those of cimetidine 600 mg. Relapse rates in the ranitidine group were comparable with rates reported in other recent trials.³⁻⁴ By contrast, the relapse rates in the enprostil group were of the same magnitude as those described after placebo² and similar to rates found in our population after treatment for duodenal ulcer healing.²⁰⁻²¹ Hence enprostil, which is also inferior to ranitidine for duodenal ulcer healing,¹⁵⁻²² cannot be recommended for the prevention of ulcer relapse.

The dose of enprostil used in this study inhibits acid secretion, and the therapeutic benefit, if any, is explicable by this effect rather than by any mythical "cytoprotection" which may be achieved at lower doses.¹⁴ These results and our previous findings in studies on duodenal ulcer healing¹⁵ and duodenal ulcer haemorrhage²³ question the clinical relevance of promoting cytoprotective properties of prostaglandin analogues for duodenal ulcer treatment.

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SHORT REPORTS

Irritable bowel syndrome as a cause of chronic pain in women attending a gynaecology clinic

Chronic lower abdominal pain and pelvic pain is a common problem in gynaecological practice. Most of these women undergo diagnostic laparoscopy, which shows a normal pelvis in up to 90% of cases.¹ Despite the lack of a definite abnormality further gynaecological procedures are often undertaken, which may include surgery.

The irritable bowel syndrome is common and a recognised cause of chronic pain. It is associated with many non-colonic features, including dyspareunia,² and is more prevalent in young women.³ A diagnosis of the irritable bowel syndrome is made on the history alone, and, although results of special investigations are by definition negative, the diagnosis should not simply be one of exclusion.⁴

The purpose of this study was to see whether patients attending a gynaecological clinic with chronic pain might be suffering from the irritable bowel syndrome by taking a detailed history using Manning's questionnaire, which has been shown to identify successfully such patients.⁴

Patients, methods, and results

Fifty patients with chronic abdominal pain who had been shown to have no pelvic disease at laparoscopy were studied at their follow up visit. The women were aged between 18 and 35 and had had symptoms for at least three months. Each patient was asked the questions listed in the table and then examined for the physical signs. The table shows the number of positive responses to each question.

At least 26 patients admitted to looser stools at the onset of pain, pain eased by defecation, distension, mucus per rectum, hard pellet stools, or dyspareunia. Similarly, 38 patients had a tender, palpable colon and 36 rectal tenderness per vagina. Thirty patients had at least three symptoms associated with the irritable

bowel syndrome and these patients were very likely to have the disorder. A further eight patients had two symptoms of the irritable bowel syndrome. Only three patients had none of these symptoms.

Incidence in 50 patients of symptoms and signs commonly present in the irritable bowel syndrome

	No of patients
Looser stools at onset of pain	26
More frequent bowel movement at onset of pain	21
Pain eased after bowel movement (often)	32
Visible distension	31
Feeling of distension	42
Mucus per rectum	29
Feeling of incomplete emptying	15
Hard pellet stools	33
Dyspareunia	41
Rectal tenderness per vagina	36
Tender, palpable colon	38

Comment

The questionnaire has been shown to identify successfully those patients with the irritable bowel syndrome.⁴ Dyspareunia is not one of Manning's symptoms but has been shown to be associated with the syndrome.² It is another manifestation of a tender colon. Similarly, a tender colon and rectal tenderness are associated with the syndrome.⁵ The combination of chronic pain and three symptoms of the irritable bowel syndrome supported the diagnosis in 30 (60%) of the patients in this study. A further eight patients may have been suffering from the condition with two symptoms. As the irritable bowel syndrome may be present without an abnormal bowel habit³ the diagnosis was not excluded in the other 12 patients. The presence of