CLINICAL TRIAL

Improved symptom relief and duodenal ulcer healing with lansoprazole, a new proton pump inhibitor, compared with ranitidine

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Abstract

The purpose of this study was to compare duodenal ulcer healing, symptom relief, and safety of lansoprazole (a new proton pump inhibitor) given at doses of 30 mg and 60 mg, in the morning with ranitidine 300 mg at bedtime. Two hundred and eighty nine patients were enrolled over a 20 month period in a double blind randomised parallel group comparative study set in outpatient endoscopy units of six United Kingdom medical centres. Patients were randomised to receive lansoprazole 30 mg in the morning (n=95), 60 mg in the morning (n=96), or ranitidine 300 mg at bedtime (n=98) for four weeks. Efficacy was assessed by gastroscopy at study entry and after two and four weeks of treatment. Symptom relief was monitored by patient diaries and physician review at two and four weeks. Both doses of lansoprazole resulted in significantly greater ulcer healing than ranitidine after two and four weeks. Respective healing rates on lansoprazole 30 mg, 60 mg, and ranitidine 300 mg were 78%, 80%, and 60% after two weeks and 93%, 97%, and 81% after four weeks. Patients on lansoprazole 30 mg ($p=0.002$) and lansoprazole 60 mg ($p=0.026$) also recorded greater relief of night time pain in the diary cards during the first seven days of treatment than those on ranitidine. Patients on lansoprazole 60 mg reported significantly better pain relief at their two week visit compared with those receiving ranitidine ($p=0.007$). There were no differences between treatment groups in the occurrence or pattern of adverse drug reactions during the trial. It is concluded that for patients with duodenal ulcer, lansoprazole 30 mg or 60 mg is associated with faster ulcer healing and better symptom relief than ranitidine 300 mg at bedtime. There were no significant differences between lansoprazole 30 mg and 60 mg. These data indicate that lansoprazole should be used at a once daily dose of 30 mg for the treatment of duodenal ulcer.

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The efficacy of inhibitors of gastric acid secretion in healing duodenal ulcers has been repeatedly confirmed during the past 18 years. More recent-

ly the discovery of substituted benzimidazoles, which inhibit the (H^+ , K^+) ATPase (proton pump) of the parietal cell¹ has led to the development of compounds that can profoundly inhibit gastric acid production. Lansoprazole is a novel member of this new generation of acid inhibiting drugs, the proton pump inhibitors. It selectively inhibits the proton pump in vitro^{2,3} and in vivo.⁴ Human clinical pharmacology studies have shown profound and prolonged suppression of 24 hour intragastric acidity with single 15 or 30 mg doses of lansoprazole, which increased with repeated doses.^{5,6} In addition a single 60 mg dose produced almost total inhibition of 24 hour gastric acidity as well as inhibiting pentagastrin stimulated acid secretion by 92%.⁶ Early clinical studies with lansoprazole showed a dose related increase in duodenal ulcer healing rates at daily doses of 7.5 mg, 15 mg and 30 mg.⁷ We, therefore, compared lansoprazole at single daily doses of 30 mg and 60 mg in the morning with ranitidine 300 mg at bedtime for four weeks in the treatment of patients with duodenal ulcer, to investigate whether these doses of lansoprazole were superior to ranitidine and determine which was optimal. Efficacy was assessed by endoscopic evidence of healing and by symptomatic relief. Safety was monitored in terms of clinical adverse events as well as biochemical and haematological screening.

Methods

STUDY DESIGN

The study was a double blind, randomised, parallel group comparison of lansoprazole 30 mg, lansoprazole 60 mg both in the morning and ranitidine 300 mg at bedtime conducted at six hospitals in Nottingham, Rotherham, Glasgow, and Dundee, United Kingdom.

PATIENT SELECTION

Patients between the ages of 18 and 75 (inclusive), with duodenal ulcer(s) proved by endoscopy greater than 3 mm but not more than 2.5 cm in diameter were eligible if they had not received therapeutic doses of ulcer treatment in the previous six days or bismuth within the previous three months. Standard exclusion

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criteria were used, the principal ones being concomitant reflux oesophagitis, oesophageal stricture, Barrett's oesophagus, gastric ulceration, upper gastrointestinal bleeding, gastrointestinal malignancy, previous gastric surgery, inflammatory bowel disease, or any serious cardiac, renal or hepatic disorders. Women of child bearing potential could be enrolled provided they were practising effective contraception. Patients taking steroids or anti-coagulants were excluded.

TREATMENT

Patients were stratified for smoking habits before randomisation (in blocks of three at each centre) to receive lansoprazole 30 mg or 60 mg in the morning or ranitidine 300 mg at bedtime. Drugs and placebo were provided as white, hard gelatin capsules in blister packs to maintain blinding. Patients took two capsules in the morning half an hour before food and two capsules at night before retiring. Patients received treatment for 28 (+ or minus three days) regardless of healing state (see below). Maalox tablets were provided for additional symptom relief as required.

EVALUATIONS

Patients were entered into the study within seven days of an endoscopy showing active duodenal ulceration. Duodenal ulcer was defined as a break in the mucosa distal to the opening of the pylorus with excavation and slough at the base. Healing was monitored by repeat endoscopy performed after 14 (+ or minus three days) of treatment, and (in those unhealed at 14 days) after 28 (+ or minus three days).

The occurrence of pain, nausea, and vomiting (occasional, daily, continual) over the previous week were assessed by the investigator at each visit. In addition, patients recorded day and night time pain (none, mild, moderate, severe) and antacid consumption on a daily diary card. Compliance was monitored by capsule count at each visit. Safety evaluation was based upon adverse event monitoring as well as physical examination, urinalysis, blood count, urea and electrolytes, liver function tests, uric acid, calcium and phosphate estimations.

STATISTICAL METHODS

The primary end point was cumulative ulcer healing in evaluable patients (all those having an endoscopy at a particular visit). This can be regarded as a pragmatic approach.⁸ In addition a secondary 'per protocol' analysis was performed, in those patients who met the eligibility criteria (patient selection) and evaluability criteria (repeat endoscopy within three days of specified time having taken 75% of treatment) as specified in the protocol. Healing rates at weeks 2 and 4 were compared across treatment groups using a $3 \times 2 \chi^2$. If this was at or near the 5% significance value, pairwise comparisons between groups were made using the χ^2 test (with continuity correction) or Fisher's exact test, and 95% confidence intervals were constructed for each pairwise difference.⁹ Multivariate logistic

TABLE I Demography of patients studied

	Lansoprazole 30 mg	Lansoprazole 60 mg	Ranitidine 300 mg
No of patients	95	96	98
M/F	71/24	65/31	68/30
Mean age (SD)	43 (14)	46 (16)	48 (13)
Smokers (%)	57	67	63
Drinkers (%)	73	69	60
Receiving NSAIDs (%)	2	5	7
New patient (%)	42	59	53
Relapsed (%)	57	40	47
Refractory (%)	1	1	0
History (%)			
<1 year	15	25	22
1-5 years	44	32	38
>5 years	41	41	40

NSAIDs = non-steroidal anti-inflammatory drugs.

regression analysis¹⁰ was used to assess the influence of prognostic factors and to justify the pooling of response data across trial centres (centre/treatment interaction). The Kruskal-Wallis test was used to compare the frequency of pain and antacid use, and adverse events. Analysis of variance was used to assess changes in laboratory values. All calculations were performed using the SAS package.^{11 12}

Sample size was calculated assuming a healing rate of 65% with ranitidine at week 2. With 95 patients in each treatment group, a 20% improvement with either lansoprazole group could be detected with a power of 80% at a two sided significance value of 5%.¹³

Results

Two hundred and eighty nine patients were enrolled into the study over a period of 20 months. One hundred and eighty were smokers and 109 were non or former smokers. Table I shows the distribution of patient characteristics across the three treatment groups. Age, sex, smoking, and alcohol use seem to be relatively well balanced across the treatment groups. Any effect these factors may have had on healing rates were examined using logistic regression analysis.

ULCER HEALING

The primary analysis showed a statistically significant difference across treatment groups both at week 2 ($p=0.005$) and week 4 ($p=0.001$). Pairwise comparisons showed that the superiority of healing rates with both doses

TABLE II Healing rates in evaluable patients

	Lansoprazole 30 mg	Lansoprazole 60 mg	Ranitidine 300 mg
No of patients	95	96	98
Week 2: No of patients healed (%)	65/83 (78.3)	67/84 (79.8)	52/87 (59.8)
% Difference (95% CI) compared with ranitidine*	18.5 (4.9, 32.1)	20.0 (6.6, 33.4)	—
Week 4: No of patients healed (%)	81/87 (93.1)	87/90 (96.7)	75/92 (81.5)
% Difference (95% CI) compared with ranitidine*	11.6 (2.0, 21.2)	15.2 (6.5, 24.0)	—

*Difference lansoprazole 30 mg v lansoprazole 60 mg (95% CI): week 2: -1.5% ($-13.8, 10.8$); week 4: -3.6% ($-10.1, 2.9$).

TABLE III Healing rates in per protocol analysis

	Lansoprazole 30 mg	Lansoprazole 60 mg	Ranitidine 300 mg
Week 2: No of patients healed (%)	43/55 (78.2)	44/55 (80.0)	29/53 (54.7)
% Difference (95% CI) compared with ranitidine	23.5 (6.2, 40.8)	25.3 (8.2, 42.4)	—
Week 4: No of patients healed (%)	52/56 (92.9)	58/59 (98.3)	43/53 (81.1)
% Difference compared with ranitidine	8.8 (-0.7, 24.3)	17.2 (6.2, 28.2)	—

of lansoprazole compared with ranitidine were statistically significant at both week 2 and week 4 (Table II). There was no difference between the response rates in the two lansoprazole groups at either time point. The per protocol analysis supported this result (Table III). The difference between lansoprazole 30 mg or 60 mg and ranitidine remained statistically significant at week 2 in this group. There was no difference between the two lansoprazole groups (difference -1.8%, 95% confidence intervals -17.0, 13.4).

Smoking and drinking habits, sex, number of lesions, and treatment were included as possible factors affecting healing at the two week assessment in the multivariate analysis (the analysis was not performed at four weeks as the proportion of patients healed was high, 80–90%). The

Figure 1: Effect of smoking on ulcer healing shown by drug treatment.

Figure 2: Effect of drug treatments on the number of patients reporting no symptoms in the seven days before clinic visit. L30=lansoprazole 30 mg, L60=lansoprazole 60 mg, RAN=ranitidine.

number of patients receiving non-steroidal anti-inflammatory drugs in each group was too small to include in the model. Although the study was stratified for smoking habits as a possible prognostic factor this was not confirmed in this study. This was probably due to similar healing rates for smokers and non former smokers receiving either dose of lansoprazole (Fig 1).

The analysis showed a difference in healing rates across centres in the per protocol analysis but not the evaluable patient group. All treatments were equally affected, however, (treatment/centre interactions not significant, $p=0.51$) so that the odds ratios for lansoprazole *v* ranitidine adjusted for centre effect was consistent with the unadjusted odds ratio (lansoprazole 30 mg 2.43 (adjusted) *v* 2.45 (unadjusted); lansoprazole 60 mg 2.65 *v* 2.61). It is therefore justified to pool data across centres.

PAIN RELIEF

After two weeks of treatment there was a statistically significant difference between the treatment groups ($p=0.027$) in the reduction of the percentage of patients reporting themselves to have experienced pain in the previous week. Pairwise comparisons showed this to be due to a significantly greater improvement in patients receiving lansoprazole 60 mg compared with those receiving ranitidine ($p=0.007$). There was no difference between the two lansoprazole groups ($p=0.19$). There was no difference across the treatment groups after four weeks of treatment ($p=0.24$). Figure 2 shows the proportion of patients pain free at each time point.

PATIENT DIARY ASSESSMENTS

Patient diary records also showed improved symptom relief. Lansoprazole was associated with a significantly greater reduction of night time pain after seven days of treatment compared with ranitidine (Fig 3, $p=0.002$ for lansoprazole 30 mg *v* ranitidine, $p=0.026$ for lansoprazole 60 mg *v* ranitidine). There was no difference between the two lansoprazole groups ($p=0.12$). Differences in the extent of improvement in

Figure 3: Effect of drug treatments on symptoms recorded in the diary card.

daytime pain did not reach statistical significance ($p=0.37$).

ANTACID USE

The degree of pain relief was reflected in the consumption of antacids. There was a statistically significant ($p=0.018$) difference between the three treatment groups in the proportion of days on which antacids were taken. Patients receiving lansoprazole 30 mg took antacids on 12.7% (median) of days. Those on lansoprazole 60 mg took them on 15.7% of days, and those on ranitidine 25.5% of days. Pairwise comparisons showed the difference between those receiving lansoprazole 30 mg and those receiving ranitidine 300 mg was significant ($p=0.005$), while that between those receiving lansoprazole 60 mg and those receiving ranitidine approached statistical significance ($p=0.06$). There was no difference between the two lansoprazole groups ($p=0.973$).

SAFETY

A total of 91 clinical adverse events was reported (32 on lansoprazole 30 mg, 31 on lansoprazole

60 mg, 28 on ranitidine). Thirty five were regarded as possibly, probably or definitely drug related. Ten of these occurred on lansoprazole 30 mg, 13 on lansoprazole 60 mg, 12 on ranitidine. Table IV shows the most frequently reported events (regardless of drug relation – that is, all events). Statistical testing was performed taking into account severity (mild, moderate, severe) as well as incidence of each event. There was no statistically significant difference between the three treatment groups in the incidence/severity of any adverse event. Likewise no differences were apparent across treatment groups when only drug related events were considered (no statistical comparison was made as the numbers were too small).

LABORATORY CHANGES

Changes in haematology and serum biochemistry values after four weeks of treatment were small and not of any clinical relevance. Statistically significant differences between the treatment groups were noted for chloride (increase in patients receiving ranitidine after four but not two weeks) and sodium (increase in patients receiving lansoprazole after two but not four weeks) but the changes were small and of no clinical relevance and are likely to be a chance finding because of the number of statistical comparisons made.³⁶

There were 15 individual instances of abnormal laboratory values regarded as clinically significant by the investigator, of which nine were regarded as possibly (8) or probably (1) drug related (2 on lansoprazole 30 mg, 2 on lansoprazole 60 mg, 5 on ranitidine). Table IV gives details of these instances.

Discussion

Our data show that both doses of lansoprazole are superior to ranitidine in healing duodenal ulcers both in terms of the rate of healing and in the proportion of patients healed after a standard four week course of treatment (93–97% *v* 81%). Roughly as many patients are healed after two weeks of lansoprazole (78–80%) as after four weeks of ranitidine (81%), emphasising that ulcer healing is achievable with shorter courses of treatment than with the H_2 receptor antagonists. It is also interesting to note that the healing rates were similar in smokers and non-smokers in patients receiving lansoprazole. This could be a result of lansoprazole achieving more effective acid inhibition.

Acid suppression may also account for the improved symptom relief with lansoprazole that accompanied the accelerated ulcer healing. This symptomatic improvement was achieved with a concomitant decrease in antacid consumption in patients receiving lansoprazole as a further indicator of the effectiveness of symptom relief. Diary card symptoms were analysed in terms of changes in the number of days or nights in which pain was experienced. Lansoprazole was superior to ranitidine for night time pain during the first seven days but thereafter the rate of change levelled off with most patients being asymptomatic, particularly on lansoprazole.

TABLE IV Most frequently reported adverse events

	Lansoprazole 30 mg	Lansoprazole 60 mg	Ranitidine 300 mg
Pain	1	3	0
Dizziness	1	1	2
Headache	2	2	3
Constipation	2	2	0
Diarrhoea	2	1	4
Nausea	2	0	3
Depression	0	3	1
Rhinitis	3	2	1
Laboratory changes	↑ γ -glutamyl- transferase (1) ↑ mean cell volume (1)	↑ γ -glutamyl- transferase (1) ↑ uric acid (1)	↓ leucocytes (1) ↓ platelets (1) ↓ alkaline phosphatase (1) ↓ alanine transaminase (1) abnormal liver function tests (1)

Likewise, a higher number of patients taking lansoprazole were free of daytime pain but a higher proportion of those on lansoprazole 60 mg had been symptom free before treatment and differences between drugs in the changes in diary card symptoms did not achieve statistical significance.

Assessment of safety and adverse drug reactions show that lansoprazole combines high efficacy with apparent absence of any serious side effects. The incidence and severity of adverse events in patients receiving lansoprazole at either dose did not differ from those of patients receiving ranitidine. There were no unusual adverse events associated with the use of lansoprazole. Detailed analysis of laboratory parameters showed no clinically significant changes in those measured.

Healing rates in our study are similar to those previously reported in dose ranging placebo controlled comparisons.^{7,14} These studies have suggested dose dependence up to 30 mg and that this dose seems to be superior at two weeks to ranitidine 300 mg⁷ and famotidine 40 mg.¹³ In our studies there were no significant differences between the two doses of lansoprazole in either efficacy or safety. Response rates and symptom relief seemed to be slightly higher with the 60 mg than the 30 mg dose, but the difference was minimal and never statistically significant. An effective dose, therefore, seems to be 30 mg per day for rapid symptom relief and ulcer healing, without significant adverse events.

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