Does long term therapy with lansoprazole slow progression of oesophageal involvement in systemic sclerosis?

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ABSTRACT

Objectives. *Oesophageal scintigraphy is an effective, non-invasive screening test to detect oesophageal dysmotility and reflux. Our objective was to assess the long term effect of lansoprazole therapy on gastroesophageal dysmotility in systemic sclerosis (SSc).*

Methods. *24 SSc patients were randomised to receive either lansoprazole 30 mg or placebo for 12 months. Gastroesophageal motility was assessed by scintigraphy at baseline, after 6 months and after 12 months. Symptoms were evaluated by self-reported gastrointestinal questionnaire.*

Results. *Of 21 patients starting treatment, 17 (81%) completed the first 6 months and 13 (62%) completed the study. 3 patients from each group were withdrawn due to adverse events. As expected, lansoprazole appeared to decrease frequency of gastroesophageal symptoms in the first 6 months of treatment, but long term benefit was not evident. Scintigraphy showed worsening oesophageal dysmotility in SSc patients irrespective of lansoprazole treatment. In addition, early signs of dysmotility were found in asymptomatic patients. We found no correlation of scintigraphy findings with symptoms of gastroesophageal dysmotility.*

Conclusion. *Although lansoprazole 30 mg daily appears to suppress SSc-related gastroesophageal symptoms in the short term, benefit was not sustained at 12 months, and there was no evidence that progression of gastroesophageal motility was prevented. Scintigraphy findings did not correlate with symptoms of dysphagia.*

Introduction

The gastrointestinal (GI) tract is one of the most frequently affected organs in systemic sclerosis (SSc) (1). The most common problems are oesophageal dysmotility resulting in slower acid clearance, as well as acid reflux causing mucosal injury. It is well known that they are related; however the primary cause of gastroesophageal reflux (GER) is still debated. A previous study showed that 44% of patients suffering from GER had abnormal oesophageal peristalsis and one fifth of patients suffered from severe oesophageal dysmotility (2).

Early recognition of SSc involvement of the GI tract is important to avoid potential life-threatening complications. Previously, scintigraphy was shown to be useful for detection of asymptomatic oesophageal dysfunction in SSc patients (3); however its potential value in monitoring disease progression and treatment response has not been evaluated.

Proton pump inhibitors (PPIs) are generally considered as standard of care for treatment of patients with oesophageal dysfunction in SSc. PPIs are routinely used and they appear to offer excellent and often immediate benefit for symptoms of oesophagitis in SSc. Previous studies showed that lansoprazole provides effective heartburn relief in patients with dyspepsia (5).

The objective of this placebo-controlled, double-blind study was to ascertain whether symptomatic improvement was accompanied by improvement in lack of worsening dysmotility assessed objectively by oesophageal scintigraphy. We compared placebo with lansoprazole 30 mg daily in 24 SSc patients. As expected, an initial symptomatic improvement was observed for most patients. Surprisingly however, no sustained benefit was found in the symptoms, or the oesophageal motility detected by scintigraphy.

Methods

Subjects

Twenty-four SSc patients were enrolled in this prospective, randomised study. To be eligible, patients had to be at least 18 years old, fulfil the American College of Rheumatology (ACR) classification criteria for SSc, and have a grade 0-2 score measured by oesophageal

scintigraphy. Reasons for exclusion from the study included acid suppressive therapy or pro-kinetic treatment within 4 months of entering the study.

Study protocol

The study was a placebo-controlled, double-blind parallel group investigation conducted within the Centre for Rheumatology of the Royal Free Hospital. It was approved by the Royal Free Local Ethics Committee. Patients were randomly allocated to receive either lansoprazole 30 mg or placebo once daily for 12 months. Patients were evaluated at baseline, after 6 months and after 12 months.

Clinical evaluation

At the time of this study there was no validated questionnaire for use in SSc, making it difficult to reliably document patient symptoms. We created a gastrointestinal questionnaire based on previous validated symptom-oriented questionnaires (5-7). This survey elevates 11 gastrointestinal symptoms grouped into four categories: gastroesophageal, small and large bowel, and anorectal symptoms. The test uses a five-graded scale (1 to 5): 'never', 'occasional', 'sometimes', 'frequently' or 'always', in which a higher score means increased frequency of gastrointestinal complaints. Results after 6 and 12 months of treatment were compared with the baseline variables. In addition, all adverse events occurred during the treatment period were recorded by an investigator on the scheduled appointments.

Oesophageal scintigraphy

Oesophageal scintigraphy was performed using the method developed by Åkesson *et al*. (8). All subjects were examined after overnight fasting at the Nuclear Medicine Department. A semi-solid radioactive meal was prepared by adding ^{99m}Tc tin colloid (Amersham) to 50 ml pineapple purée (HJ Heinz Co. Ltd., Baby Foods, UK) to achieve an activity concentration of 1 MBq/ml. Imaging was performed using a large field-of-view gamma camera (400T Maxicamera, International General Electric Co, UK) fitted with a general purpose collimator and coupled to a dedicated computer (PDP-11, Nuclear Diagnostics, UK). The study was processed using a Gamma-11 software programme (OESOPH version 2.2, Nuclear Diagnostics) designed for the analysis of dynamic swallowing scintigraphy. The parametric images were divided into 5 grades: grade 0 = normal erect and supine scan; grade 1 = normal erect scan, mildly abnormal supine scan; grade 2 = mildly abnormal erect scan, severely abnormal supine scan; grade 3 = moderately abnormal erect scan, severely abnormal supine scan; grade 4 = severely abnormal supine and erect scans (3).

Statistical analysis

Fisher's exact test was used to analyse the statistical association between treatment groups and clinical data. *P*-values less than 0.05 were considered significant. Data are represented as the mean ± standard error of the mean (SEM). Spearman's correlation coefficient was computed to assess the relation between symptom scores and scintigraphy grades.

Results

Patients

Twenty-four patients were randomised in the study. The average age of patients was 55 (range 28-72); among those 21 (87.5%) patients were of Caucasian origin while 3 (12.5%) patients were Asian. 16 patients (67%) were female and 8 (33%) were male. The average duration of the disease at the beginning of the study was 8 years. 19 (79%) SSc patients were diagnosed with the limited and 5 (21%) had the diffuse subset of the disease. 3 patients withdrew before starting the study. Of the 21 subjects who started the study, 1 patient withdrew for personal, non-treatment related reasons, 1 patient was lost to follow-up and 6 patients were withdrawn because of adverse events.

Gastrointestinal symptoms

Patients were evaluated after the first 6 months of the treatment and after 12 months using a patient gastrointestinal symptom questionnaire. The mean pre-treatment values for the clinical symptoms were compared to the values obtained after 6 months and 12 months.

In the first 6 months of the study there was a trend for improvement in gastroesophageal symptoms including heartburn, regurgitation and dysphagia in patients treated with lansoprazole 30 mg (-0.6±0.4, change in average gastroesophageal symptom score compared to baseline, mean ± SEM), while progression was reported by patients taking placebo (0.7±0.5, change in gastroesophageal symptom score compared to baseline, mean ± SEM) (Fig. 1A). However, these changes did not reach statistical significance by Fisher's exact test. Interestingly, regarding bowel symptoms, patients taking lansoprazole reported increased frequency of diarrhoea; however, results were again not statistically significant.

Overall, no significant change in frequency of gastroesophageal symptoms in either of the two groups during the 12-month treatment period compared to baseline (lansoprazole 0.4±0.5, mean ± SEM, placebo 0.2±0.6, change in average score, mean ± SEM) suggesting that lansoprazole 30 mg once daily might not be effective for long-term therapy (Fig. 1B). Our results showed no deterioration in heartburn, but dysphagia occurred more often in the second phase of the study regardless of lansoprazole treatment.

Oesophageal scintigraphy

To detect oesophageal dysmotility and acid reflux, radionuclide oesophageal scintigraphy was performed at baseline, after 6 months and 12 months (Fig. 1C). Regardless of treatment, significant deterioration was seen in the scintigraphy scan results after 12 months of lansoprazole treatment (0.5±0.3 *vs*. 1.1±0.4 and 1.9±0.6; baseline vs. 6-month and 12-month lansoprazole treatment, mean ± SEM). Correlation between dysphagia symptom scores and scintigraphy grades was assessed using Spearman's rank correlation test. We found no correlation between the frequency of dysphagia and the scintigraphy results (Spearman's correlation coefficient 0.31, p=0.2). Interestingly, higher gastroesophageal symptom scores were not necessarily associated with objective scintigraphy findings, while early dysmotility was

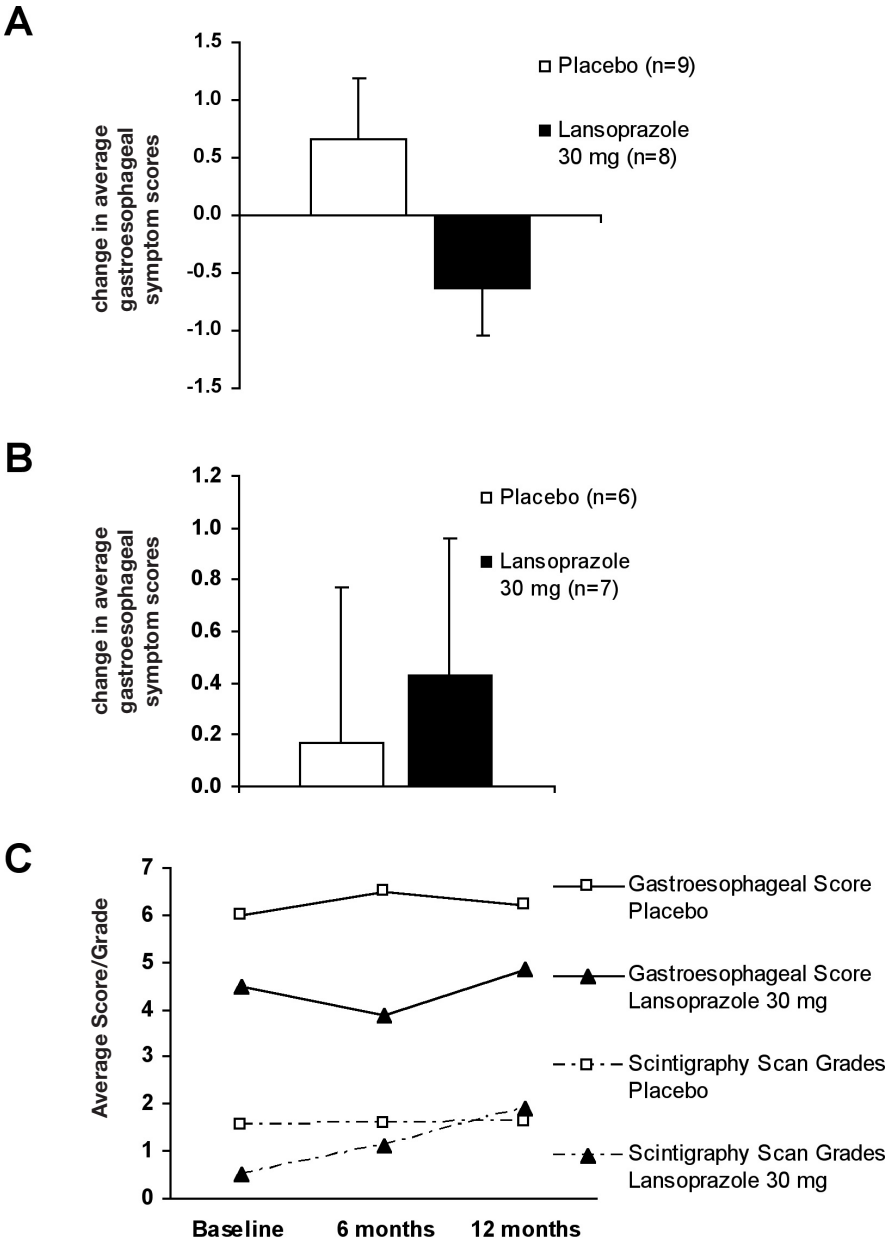

Fig. 1. Gastroesophageal symptom score and scintigraphy findings.
Self-reported gastrointestinal questionnaires were evaluated at baseline, after 6 months and after 12 months. A gastroesophageal symptom score was calculated based on the frequency of heartburn, regurgitation and dysphagia, reported by patients before and after treatment. **A.** After 6 months of treatment, patients receiving lansoprazole had less frequent symptoms, while patients in the placebo group reported more symptoms. **B.** No beneficial effect was seen after 12 months of lansoprazole treatment regarding gastroesophageal symptoms. **C.** Likewise, radionuclide scintigraphy showed progression of oesophageal dysmotility regardless of lansoprazole treatment. n = number of patients.

detected in 2 of three asymptomatic patients. Similarly, using scintigraphy, oesophageal dysmotility was further detected in patients becoming asymptomatic on lansoprazole treatment.

Adverse events

Overall, adverse events were reported in 86% of the patients. Six patients were withdrawn from the study due to adverse events. Among these, 3 were on active treatment and 3 received placebo. In the lansoprazole group, 2 patients suffered from diarrhoea and one from constipation. In the placebo group, reasons for withdrawal included heartburn, vomiting and rash.

Adverse events were more common with lansoprazole than placebo, 6 patients reported either diarrhoea or loose stool and 3 patients had stomach pain while on active treatment. Single adverse events reported with lansoprazole included acne, constipation, heartburn, muscle or joint pain and skin rash. These adverse events were generally mild and required no intervention. All adverse events noted during the study are shown in Table I.

Discussion

Since PPI's are generally considered to be standard treatment for oesophageal symptoms of scleroderma, it is surprising that sustained benefit was not apparent at the dose used in this trial. There are several possible explanations.

First, it is possible that lansoprazole at a dose of 30 mg once daily may be ineffective in long-term maintenance therapy. It is currently common practice to increase the daily dose to 60mg or even 90mg to gain better symptom control, and sometimes other acid suppressive medication such as H2-receptor antagonists are added. Thus the 30mg dose evaluated in this study may have been inadequate to give long-term benefit.

Secondly, although PPI therapy is generally considered the best treatment for patients with dyspepsia, it may not be effective in the long term. Unfortunately, most studies demonstrate short-term efficacy of PPIs in SSc-related gastroesophageal problems, but the long-term efficacy of these drugs are not well known. Previously, a randomised, double-blind, placebo-controlled study showed that short-term lansoprazole treatment (8 weeks) significantly reduced the frequency of upper abdominal discomfort in patients suffering from functional dyspepsia (4). Interestingly, a similar study of lansoprazole failed to improve global dyspeptic symptoms of patients after 12 weeks of treatment (9).

Thirdly, our findings may reflect the methodological limitations of the study. For example, the number of patients completing the study was small raising the possibility of a false negative result. In addition there is likely to have been case selection bias excluding patients with severe symptoms. Another possibility is that cases were switched to active treatment after withdrawing from the trial and this may have influenced

Table I. Adverse events reported during the trial.

	Placebo	Active treatment
Number of patients, n	10	11
Acne, n (%)	-	1 (9)
Constipation, n (%)	-	1 (9)
Diarrhoea, n (%)	1 (10)	4 (36)
Heartburn, n (%)	2 (20)	1 (9)
Loose stool, n (%)	-	2 (18)
Muscle pain, n (%)	-	1 (9)
Nausea and vomiting, n (%)	2 (20)	-
Oesophagus pain, n (%)	1 (10)	-
Pain in left hip, n (%)	-	1 (9)
Rash, n (%)	1 (10)	1 (9)
Stomach pain, n (%)	-	3 (27)

the 6-month time point that was analysed according to intention to treat.

Finally, the lack of validated SSc-related gastrointestinal symptom questionnaire may also contribute to the absence of correlation. It is possible that a larger study would obtain more definitive results, but this would be challenging because PPIs are now used widely as standard treatment in SSc therefore recruitment into a placebo controlled trial would be difficult. Thus we consider our study to be of substantial value despite the limitations outlined above.

Previous studies showed that oesophageal scintigraphy is a safe and non-invasive method with a high sensitivity to detect gastroesophageal dysmotility (3) (10). The clinical assessment of motility abnormalities does not seem to be reliable as oesophageal scintigraphy detects early oesophageal dysfunction in asymptomatic patients (3). In our study, we investigated whether radionuclide scintigraphy is a useful method to monitor changes in oesophageal dysmotility over 12 months in SSc patients treated with lansoprazole or placebo. The gastroesophageal symptom scores for heartburn, regurgitation and dysphagia, suggested that lansoprazole tended to decrease frequency of gastroesophageal symptoms in the first 6 months but failed to demonstrate efficacy in the last 6 months of the trial. Patients receiving lansoprazole showed no change in heartburn symptoms in the second phase of the study, while dysphagia occurred slightly, but not significantly, more often. Overall, the two groups did not differ significantly after either 6 or 12 months of treatment, which is likely to be due to small patient numbers in both groups.

In this study we observed worsening oesophageal dysmotility irrespective of lansoprazole treatment. In addition, Spearman's rank correlation test did not reveal correlation between treatment groups and dysphagia symptom scores. Our results are in an agreement with previous reports (3), in which the absence of oesophageal symptoms did not exclude oesophageal involvement showed by scintigraphy. In conclusion, scintigraphy does not seem to be useful to assess the treatment efficacy of PPIs, nevertheless it appears to have a role in detection of early disease. Further, our results suggest that scintigraphy may be useful in monitoring oesophageal dysfunction in initially symptomatic SSc patients asymptomatic on acid suppressive treatment.

In summary, whilst lansoprazole 30 mg daily may initially decrease gastroesophageal reflux symptoms in SSc patients; no beneficial effects were observed long term. Similarly, radionuclide scintigraphy showed deterioration of oesophageal dysmotility regardless of treatment. No relationship was found between symptoms of oesophageal dysfunction and oesophageal scintigraphy findings. Our recommendation is that higher than standard doses of PPIs may be required to control symptoms of this common complication of SSc.

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