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

Pakozdi A

Wilson H

Black CM

Denton CP

Royal Free and University College Medical School, Center for Rheumatology and Connective Tissue Diseases, Department of Medicine, University College London Hampstead Campus, Hampstead, London, UK

Corresponding Address: Christopher P. Denton

Royal Free & University College Medical School

Centre for Rheumatology

Rowland Hill Street

London NW3 2PF

Tel/Fax: 0 207 794 0432

Email: c.denton@medsch.ucl.ac.uk

Abstract

Objectives. Oesophageal scintigraphy is an effective, non-invasive screening test to detect oesophageal dysmotility and reflux. Our objective was to assess the value of oesophageal scintigraphy in monitoring lansoprazole treatment for systemic sclerosis (SSc)-related gastroesophageal disease.

Methods. 24 SSc patients were randomised to receive either lansoprazole 30 mg or placebo for 12 months. Assessment of gastroesophageal symptoms included a self-reported gastrointestinal symptom questionnaire and oesophageal scintigraphy at baseline, after 6 months and after 12 months.

Results. 21 patients started the treatment, 81% of which completed the first 6 months and 62% completed the entire study. 3 patients from each group were withdrawn due to adverse events. Lansoprazole seemed to decrease frequency of gastroesophageal symptoms in the first 6 months of treatment, however no beneficial effect was observed in the last 6 months. Scintigraphy showed progressing oesophageal dysmotility in SSc patients regardless of lansoprazole treatment. In addition, early signs of dysmotility were found in asymptomatic patients. Further, we found no correlation of scintigraphy findings with symptoms of gastroesophageal dysmotility.

Conclusion. Lansoprazole 30 mg daily initially seemed to suppress SSc-related gastroesophageal symptoms, however beneficial effects were not observed in the long term. The scintigraphy findings did not correlate with symptoms of dysphagia.

Introduction

Systemic sclerosis (SSc) is a chronic connective tissue disorder involving both skin and internal organs. The gastrointestinal (GI) tract is one of the most frequently affected organs, and the oesophagus is particularly involved in 75 to 90% of SSc patients [1]. The most common problems are oesophageal dysmotility resulting in slower acid clearance, as well as acid reflux causing mucosal injury and subsequent motility disorder. 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].

Up to date, there are no validated GI questionnaires focusing on SSc-related symptoms that would reliably assess early GI dysmotility and would monitor treatment efficacy. Nevertheless it is important to early recognize SSc involvement of the GI tract to avoid potential life-threatening complications. Diagnostic procedures used in the investigation of oesophageal involvement include manometry, 24-hour pH monitoring, scintigraphy, electrogastrography, hydrogen breath testing and barium swallowing studies. 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.

The treatment of GER and GI dysmotility is complex and includes behavioural modification, medical therapy and surgical interventions. The medical treatment of

GER aims to reduce gastric acidity using drugs such as proton pump inhibitors [4] [5] [6] and also to enhance motor activity of the smooth muscle cells by prokinetic agents [4] [7]. Previous studies showed that lansoprazole, a proton pump inhibitor, provides effective heartburn relief in patients with dyspepsia [8].

Hence, we now report the results of a single-centre, placebo-controlled, double-blind study using oesophageal scintigraphy to monitor long-term lansoprazole treatment of SSc patients suffering from gastroesophageal involvement.

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, fulfill 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 at the Department of Rheumatology of the Royal Free Hospital. It was approved by the Royal Free Local Ethics Committee. The aim of this study was to assess the value of oesophageal scintigraphy in long-term follow-up of lansoprazole treatment in patients with GER secondary to SSc. 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. Currently there is no validated questionnaire for use in SSc and it is therefore very difficult to reliably document patient symptoms. We created a gastrointestinal questionnaire based on previous validated symptom-oriented questionnaires. 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. [9]. All subjects were examined after overnight fasting at the Nuclear Medicine Department. A semisolid 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 camera head was oriented vertically and the patients seated erect on a stool with his/her back to the camera in 35^{o} left posterior oblique projection. The camera was set to acquire a dynamic study in 64 x 64 matrix comprising 0.5 s frames for 30 s followed by 15 s frames for the succeeding 5-10 min. A practice run preceded the study. Then the radioactive meal was placed in the mouth of the patient, who refrained from swallowing until prompted. The computer was activated for study acquisition. After 10 s the patient was asked to perform a single swallow and abstain from further swallowing for the duration of the acquisition period. After completion of the study, the patient was given a drink of water to remove any residual activity in the oesophagus. This was confirmed by visual assessment on the persistent oscilloscope of the gamma camera. The procedure was then repeated with the patient lying supine on the imaging table with the camera underneath.

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; 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 reason, 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, in terms of gastroesophageal symptoms including heartburn, regurgitation and dysphagia, decreased symptom frequency was observed 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) (Figure 1A). However, due to the small patient number in each group, Fisher's exact test did not

reveal significant difference in the symptoms between treatment groups. Interestingly, regarding bowel symptoms, patients taking lansoprazole reported increased frequency of diarrhoea; however, results were again not statistically significant.

Overall, no significant improvement or deterioration in the frequency of gastroesophageal symptoms occurred 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 maintenance therapy (Figure 1B). Our results showed no deterioration concerning heartburn, while 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 scintigraphy was performed at baseline, after 6 months and 12 months (Figure 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 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, one or several adverse events were reported for 86% of the patients. Six patients were withdrawn from the study due to adverse events. Among these six patients, 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 withdrawn included heartburn, vomiting and skin rash.

Overall, 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 1.

Discussion

The oesophagus is the most frequently involved organ in SSc. Nearly 90% of SSc patients suffer from oesophageal dysfunction [1]. The most common symptoms are dysphagia and dyspepsia. In GER, dysfunction of the lower oesophageal sphincter allows the retrograde movement of gastric contents into the oesophagus resulting in mucosal injury.

The most useful diagnostic tools to assess oesophageal dysmotility include manometry, scintigraphy and barium swallowing studies. 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 oesophageal dysmotility in SSc patients treated with lansoprazole. 24 patients were randomised to receive either lansoprazole 30 mg or placebo for 12 months. Patients were assessed at baseline, after 6 months and after 12 months using a self-reported gastrointestinal symptom questionnaire and radionuclide scintigraphy was also then performed. Regarding gastroesophageal symptom scores that include heartburn, regurgitation and dysphagia, we found 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. Part of the explanation for the failure to demonstrate good symptom control is that lansoprazole 30 mg once daily may not be efficient in long-term maintenance therapy. In this case, it is therefore possible to achieve efficient symptom control by increasing the dose or adding pro-kinetic agents to the treatment. Proton pump inhibitor therapy is generally considered the best treatment for patients with dyspepsia, however studies show controversial results. Unfortunately, most studies demonstrate short-term efficacy of proton pump inhibitors 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 [8]. Interestingly, a similar study of lansoprazole failed to improve global dyspeptic symptoms of patients after a 12 weeks of treatment [11]. Lastly, the lack of validated SSc-related gastrointestinal symptom questionnaire may also contribute to the absence of correlation.

Concerning scintigraphy findings, we found progressing oesophageal dysmotility in our patients commenced on 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 proton pump inhibitors, nevertheless it is highly efficient and therefore important in detection of early

diseases. Further, our results suggest that scintigraphy may be useful in monitoring oesophageal dysfunction in asymptomatic SSc patients even though they are successfully commenced on acid suppressive treatment.

The most common adverse events occurred during lansoprazole treatment were diarrhoea (36%) as well as the presence of loose stool (18%). Diarrhoea led to discontinuation of treatment in the case of two patients. In contrast to other proton pump inhibitors, lansoprazole was previously reported to induce microscopic colitis in a few cases [12] where profuse and watery diarrhoea was described and substitution of lansoprazole with an alternative proton-pump inhibitor completely resolved it.

To summarize our findings, lansoprazole 30 mg daily seemed to initially decrease GER symptoms in SSc patients; however no beneficial effects were observed after 12 months of treatment. Similarly, radionuclide scintigraphy showed deterioration of oesophageal dysmotility regardless of treatment.

Acknowledgements

The authors declare that they have no competing financial interests.

References

1. Clements PJ, Becvar R, Drosos AA, Ghattas L, Gabrielli A: Assessment of gastrointestinal involvement. *Clin Exp Rheumatol* 2003, 21(3 Suppl 29):S15-18.
2. Diener U, Patti MG, Molena D, Fisichella PM, Way LW: Esophageal dysmotility and gastroesophageal reflux disease. *J Gastrointest Surg* 2001, 5(3):260-265.
3. Kaye SA, Siraj QH, Agnew J, Hilson A, Black CM: Detection of early asymptomatic esophageal dysfunction in systemic sclerosis using a new scintigraphic grading method. *J Rheumatol* 1996, 23(2):297-301.
4. Lock G, Holstege A, Lang B, Scholmerich J: Gastrointestinal manifestations of progressive systemic sclerosis. *Am J Gastroenterol* 1997, 92(5):763-771.
5. Herrick AL: Development of agents for the treatment of systemic sclerosis. *Expert Opin Investig Drugs* 2001, 10(7):1255-1264.
6. Shoenut JP, Wieler JA, Micflikier AB: The extent and pattern of gastro-oesophageal reflux in patients with scleroderma oesophagus: the effect of low-dose omeprazole. *Aliment Pharmacol Ther* 1993, 7(5):509-513.
7. Sjogren RW: Gastrointestinal motility disorders in scleroderma. *Arthritis Rheum* 1994, 37(9):1265-1282.
8. Peura DA, Kovacs TO, Metz DC, Siepman N, Pilmer BL, Talley NJ: Lansoprazole in the treatment of functional dyspepsia: two double-blind, randomized, placebo-controlled trials. *Am J Med* 2004, 116(11):740-748.

9. Akesson A, Gustafson T, Wollheim F, Brismar J: Esophageal dysfunction and radionuclide transit in progressive systemic sclerosis. *Scand J Rheumatol* 1987, 16(4):291-299.

10. Bestetti A, Carola F, Conciato L, Marasini B, Tarolo GL: Esophageal scintigraphy with a semisolid meal to evaluate esophageal dysmotility in systemic sclerosis and Raynaud's phenomenon. *J Nucl Med* 1999, 40(1):77-84.

11. Leung WK, Wu JC, Chan FK, Fung SS, Wong VW, Hui AJ, Hung LC, Sung JJ: Initial treatment with lansoprazole in young dyspeptic patients with negative urea breath test result: a randomized controlled trial with 12-month follow-up. *Am J Gastroenterol* 2007, 102(7):1483-1488.

12. Chande N, Driman DK: Microscopic colitis associated with lansoprazole: report of two cases and a review of the literature. *Scand J Gastroenterol* 2007, 42(4):530-533.

Figure legend

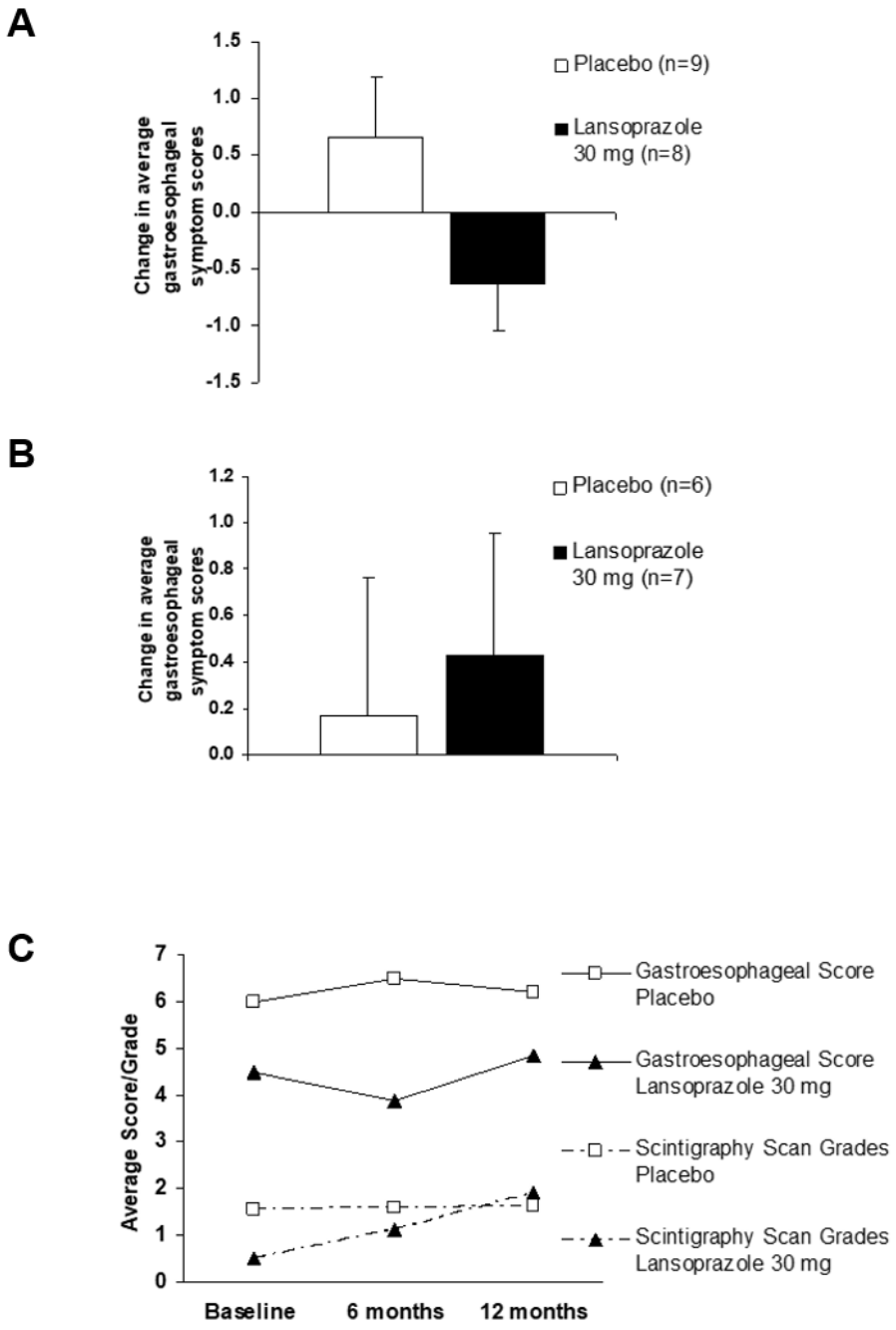
Figure 1 Gastroesophageal symptom score and scintigraphy findings

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 treatment regarding gastroesophageal symptoms. **C.** Likewise, radionuclide scintigraphy showed progression of oesophageal dysmotility regardless of lansoprazole treatment (*$p < 0.05$). n = number of patients.

Table 1. 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)**

Figure 1


A
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
Change in average gastroesophageal symptom scores
Placebo (n=9)
Lansoprazole 30 mg (n=8)
B
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Change in average gastroesophageal symptom scores
Placebo (n=6)
Lansoprazole 30 mg (n=7)
C
7
6
5
4
3
2
1
0
Average Score/Grade
Baseline
6 months
12 months
Gastroesophageal Score Placebo
Gastroesophageal Score Lansoprazole 30 mg
Scintigraphy Scan Grades Placebo
Scintigraphy Scan Grades Lansoprazole 30 mg