Lansoprazole for persistent throat symptoms in secondary care: the TOPPITS RCT

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Scientific summary

The TOPPITS RCT

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Scientific summary

Background

Persistent throat symptoms, such as globus pharyngeus, catarrh, throat clearing and recurrent hoarseness, are among the commonest reasons for attendance at secondary care throat or voice clinics. There is a growing trend to treat throat symptom patients with proton pump inhibitors to suppress stomach acid, in the belief that acid refluxing into the throat leads to the symptoms. However, most controlled studies fail to demonstrate a significant benefit of proton pump inhibitors over placebo. In addition, patient views on proton pump inhibitor use vary widely.

Objectives

Primary objective

To compare the symptomatic response in patients with persistent throat symptoms at the end of 16 weeks' therapy with lansoprazole versus placebo.

Secondary objectives

- To explore recruitment feasibility using an internal pilot.
- To compare the symptom response at 12 months with that at 16 weeks.
- To assess potential outcome predictors, namely the Reflux Symptom Index, the Comprehensive Reflux Symptom Score, the Reflux Finding Score laryngoscopic evaluation, age, sex, smoking and body mass index.
- To assess side effects, treatment compliance and use of self-pay medications.
- To compare changes in disease-specific quality of life as assessed by the Laryngopharyngeal Reflux – Health Related Quality of Life.

Methods

Setting and conduct

This multicentre trial was conducted at eight UK NHS sites, recruiting participants from 28 April 2014 to 28 February 2017. The trial received a favourable ethics opinion from the National Research Ethics Service Committee North East – Tyne and Wear South (reference: 13/NE/0336) on 2 December 2013 and a Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency on 12 February 2014. A trial-specific website (www.TOPPITS.co.uk) was designed.

Trial design

This was a multicentre, Phase III, randomised, double-blind, placebo-controlled trial, with an internal feasibility pilot, carried out in secondary care. Patients with persistent throat symptoms were identified and recruited from NHS ear, nose and throat clinics. This was a pragmatic trial designed to mirror current NHS clinical practice. Participants were randomised in a double-blind fashion between two treatment groups in a 1 : 1 ratio, stratified by centre and baseline severity [on the basis of the Reflux Symptom Index score omitting item 9 ('Heart burn, chest pain, indigestion, or stomach acid coming up'), hereinafter referred to as Reflux Symptom Index minus the heartburn/dyspepsia item (range 0–40)]. The 'mild' cohort had Reflux Symptom Index minus the heartburn/dyspepsia item scores of 10–20 (inclusive) and the 'severe' cohort had scores of > 20.

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Inclusion criteria

- Referred with a history of throat symptoms (globus pharyngeus, hoarseness, throat clearing, throat discomfort, choking spasms, excess mucus/postnasal drip, otherwise unexplained night-time cough or choking) that had been persistent for at least 6 weeks.
- Score of ≥ 10 on the non-heartburn items of the Reflux Symptom Index.

Exclusion criteria

- Reflux Symptom Index minus the heartburn/dyspepsia item score of < 10.
- Unwilling to undergo flexible endoscopy.
- Aged < 18 years.
- Endoscopic evidence of specific laryngopharyngeal pathology that would ordinarily be treated by surgical intervention or be investigated by specific investigations.
- Performing voice users.
- Pregnancy.
- Currently on acid suppressants, acid neutralisers and alginates and unwilling to discontinue use for (1) a 4-week pre-study washout period in the case of proton pump inhibitor usage or (2) a 24-hour period for alginate or acid neutraliser.

Randomisation

A blocked allocation (permuted random blocks of variable length) system was used to allocate participants in a 1 : 1 ratio, stratified by centre and baseline severity (Reflux Symptom Index minus the heartburn/dyspepsia item score: group 1, ≤ 20; group 2, > 20).

Interventions

The active intervention was a 16-week course of a 30-mg twice-daily dose of the proton pump inhibitor lansoprazole. The control group received a 16-week course of twice-daily matched placebo.

Outcomes

Primary outcome

The primary outcome measure was the symptomatic response measured using the Reflux Symptom Index in patients with persistent throat symptoms at the end of 16 weeks' therapy with lansoprazole versus placebo. The Reflux Symptom Index score is calculated from a nine-item, self-administered questionnaire scored on a Likert scale with each item score ranging from 0 to 5, giving a total score range of 0–45. A higher score indicates more severe symptoms.

Secondary outcome measures

- Reflux Symptom Index changes at 12 months after randomisation.
- Reflux Symptom Index minus the heartburn/dyspepsia item.
- Comprehensive Reflux Symptom Score total and subscales (oesophageal, upper airway and pharyngeal).
- Quality of life measured using the Laryngopharyngeal Reflux – Health Related Quality of Life total score and subscales.
- Laryngeal mucosal changes recorded by Reflux Finding Score total (range 0–29), scored by an independent observer.
- The ability of the Reflux Finding Score and patient characteristics (age, sex, smoking status and body mass index) to predict any observed responses.
- Side effects, adverse events and serious adverse events.
- Use of over-the-counter medication.
- Participant-reported satisfaction with the trial using a five-point overall satisfaction scale.
- Participant accuracy in determining which treatment they had received.

Sample size

A mean difference of 3 points in the Reflux Symptom Index score at 16 weeks was agreed to be a clinically relevant target. A mean difference of 3.1 points with an assumed standard deviation of 7.7 equates to a standardised mean effect size of 0.4 (upper bound of small effect, lower bound of medium effect). A total of 332 participants (166 in each group of the study) were required, to provide 266 participants (133 in each group) completing the trial intervention, to detect a standardised mean effect size of 0.4 with 90% power and a 5% significance level allowing for 20% loss to follow-up. There were no planned formal interim analyses or stopping rules.

Statistical methods

Descriptive statistics were used to summarise patient characteristics, treatment compliance, Reflux Symptom Index and other secondary measures. For the primary outcome measure, an unadjusted univariate analysis of the 16-week Reflux Symptom Index was carried out. The primary analysis was a multivariable analysis using the analysis of covariance and multilevel mixed-effect linear regression to compare the Reflux Symptom Index at 16 weeks while adjusting for potential confounders, specifically stratification factors at randomisation.

The primary hypothesis tested was H_0: the mean Reflux Symptom Index at 16 weeks in the lansoprazole group is equal to the mean Reflux Symptom Index at 16 weeks in the placebo group after adjustment for baseline stratification factors. Secondary analyses of the primary outcome measure considered adjustment for important clinical and demographic baseline factors, specifically sex, age, body mass index, smoking status, alcohol consumption, baseline laryngeal appearance scores by the Reflux Finding Score, Comprehensive Reflux Symptom Score total and subscales and categories of symptoms. Three models were derived for each outcome:

- model 1 – adjusted for stratification factors at randomisation [recruiting centre (as a random effect) and baseline severity as defined by the binary Reflux Symptom Index minus the heartburn/dyspepsia item cut-off value of 20 (as a fixed effect)]
- model 2 – adjusted for baseline severity with Reflux Symptom Index minus the heartburn/dyspepsia item utilised better as a continuous measure
- model 3 – adjusted for baseline severity (Reflux Symptom Index minus the heartburn/dyspepsia item as a continuous measure) and other important clinical and demographic baseline factors, specifically age, sex, smoking status and body mass index.

Continuous covariates were investigated for non-linear relationships with outcomes using first-order fractional polynomial transformations, which were retained if they substantially improved the model fit based on the Akaike information criterion. The optimal model was derived using a forward selection method with comparison of –2log-likelihood for variable inclusion. Analyses were conducted at a two-sided 5% level of significance throughout. The impact of removing any covariates from the final model was assessed in order to derive the most parsimonious model.

The analysis of secondary outcomes followed a broadly similar strategy for questionnaire scores. Safety data were not subject to statistical comparison. Analyses were carried out on a complete-case basis. Missing data were described. The use of multiple imputation techniques was considered for the primary outcome and covariate data if data were missing for participants completing the study to a sufficient extent (> 10%) and deemed missing at random. No formal interim analyses were planned. A statistical analysis plan was in place prior to any comparative analyses and was approved by the external oversight committees. Primary statistical analyses were based on a compliant intention-to-treat group of participants who attended their 16-week follow-up visit between 14 and 20 weeks, with sensitivity analyses on a pragmatic intention-to-treat group including all 16-week follow-up assessments. Data were analysed using the statistical software package Stata® version 14 (StataCorp LP, College Station, TX, USA).

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Results

A total of 346 participants, out of 1427 initially screened for eligibility, were recruited and randomised; 172 were randomised to the lansoprazole group and 174 were randomised to the placebo group. Of those randomised to lansoprazole, 101 were female (59%) and 71 were male (41%), with a mean age of 53.5 (standard deviation 13.3) years. In the placebo group, there were 95 (55%) females and 79 (45%) males, with a mean age of 50.8 (standard deviation 13.9) years. The mean overall body mass index was 28.1 kg/m^2 (standard deviation 5.6 kg/m^2, range 11.3–56.9 kg/m^2). A total of 184 (53%) participants in both groups had mild Reflux Symptom Index minus the heartburn/dyspepsia item scores at baseline, and 162 (47%) reported severe scores. Overall, there were 125 participant withdrawals and losses to follow-up. A total of 267 (77%) participants completed the primary outcome measure at 16 weeks as the 'pragmatic intention-to-treat group' (127 in the lansoprazole group and 140 in the placebo group) according to the sample size; 220 participants completed the primary outcome measure within the 14- to 20-week window as the 'compliant intention-to-treat group' (102 in the lansoprazole group and 118 in the placebo group).

Primary outcome measure

For the primary compliant intention-to-treat group, the mean Reflux Symptom Index in the lansoprazole group at baseline was 22.0 (95% confidence interval 20.4 to 23.6), reducing to 17.4 (95% confidence interval 15.5 to 19.4) after 16 weeks of treatment. The mean Reflux Symptom Index in the placebo group at baseline was 21.7 (95% confidence interval 20.5 to 23.0), reducing to 15.6 (95% confidence interval 13.8 to 17.3) after 16 weeks of treatment. The lansoprazole group had a mean 16-week score that was 1.8 points higher than that in the placebo group (t-score = 1.402, $p = 0.162$).

There was no statistically significant difference between the randomised groups (lansoprazole vs. placebo) when adjusted for site and baseline binary Reflux Symptom Index minus the heartburn/dyspepsia item ($p = 0.096$). The estimated difference between randomised groups when accounting for site and baseline severity indicated that participants receiving lansoprazole had Reflux Symptom Index scores at 16 weeks that were 1.9 points higher (worse) than those of the placebo group (95% confidence interval –0.3 to 4.2; $p = 0.096$). Participants in the severe symptom stratum at baseline had Reflux Symptom Index scores at 16 weeks that were 8 points higher (worse) than the mild stratum. Results were similar in the sensitivity analysis conducted in the pragmatic intention-to-treat group.

Reflux Symptom Index score omitting item 9

A secondary analysis of the primary outcome based on the Reflux Symptom Index minus the heartburn/dyspepsia item score showed that the lansoprazole group had a mean 16-week score that was 2.4 points higher than that of the placebo group: 16.3 (95% confidence interval 14.5 to 18.1) versus 13.9 (95% confidence interval 12.2 to 15.5), respectively ($t = 1.945$, $p = 0.053$). When adjusted for site and continuous baseline severity Reflux Symptom Index minus the heartburn/dyspepsia item, the placebo group again showed a greater reduction in symptoms, estimating that lansoprazole participants had Reflux Symptom Index minus the heartburn/dyspepsia item scores at 16 weeks that were 2.0 points higher (worse) than placebo participants (95% confidence interval 0.0 to 4.0; $p = 0.049$).

Secondary outcome measures

Reflux Symptom Index changes at 12 months after randomisation

The mean Reflux Symptom Index in the lansoprazole group at 12 months was 16.0 (95% confidence interval 13.6 to 18.4); in the placebo group, it was 13.6 (95% confidence interval 11.7 to 15.5). There was no statistically significant difference between lansoprazole and placebo when adjusted for site and baseline continuous Reflux Symptom Index minus the heartburn/dyspepsia item. The estimated difference between the groups is that lansoprazole participants have Reflux Symptom Index scores at 12 months 1.7 points higher (worse) than placebo (95% confidence interval –0.7 to 4.1; $p = 0.157$). Results were similar in the sensitivity analysis conducted in the pragmatic intention-to-treat group.

Comprehensive Reflux Symptom Score total and subscales (oesophageal, upper airway and pharyngeal)

The total Comprehensive Reflux Symptom Score was 50.3 (95% confidence interval 44.9 to 55.7) at baseline in the lansoprazole group, reducing to 38.9 (95% confidence interval 33.4 to 44.3) at 16 weeks and 36.6 (95% confidence interval 29.8 to 43.5) at 12 months. In the placebo group, the total Comprehensive Reflux Symptom Score was 51.1 (95% confidence interval 46.4 to 55.8) at baseline, 34.7 (95% confidence interval 29.6 to 39.9) at 16 weeks and 31.8 (95% confidence interval 26.6 to 36.9) at 12 months.

The relationship between the Reflux Symptom Index at baseline and total Comprehensive Reflux Symptom Score at baseline for the compliant intention-to-treat group demonstrates a linear relationship, suggesting that an increased Comprehensive Reflux Symptom Score is associated with an increased Reflux Symptom Index score. Baseline Comprehensive Reflux Symptom Score total and subscales appear to be significant predictors of the primary outcome (Reflux Symptom Index at 16 weeks). The Comprehensive Reflux Symptom Score upper airway covariate explains more variability in the Reflux Symptom Index score at 16 weeks than the total Comprehensive Reflux Symptom Score does but, nevertheless, performs less well than Reflux Symptom Index minus the heartburn/dyspepsia item.

Quality of life: change in Laryngopharyngeal Reflux – Health Related Quality of Life total score and subscales at 16 weeks and 12 months

The overall Laryngopharyngeal Reflux – Health Related Quality of Life mean score (adjusted scale 0–100) was 28.9 (95% confidence interval 24.5 to 33.3) at baseline in the lansoprazole group, reducing to 20.5 (95% confidence interval 16.1 to 25.0) at 16 weeks and 18.8 (95% confidence interval 13.7 to 23.8) at 12 months. In the placebo group, the total Laryngopharyngeal Reflux – Health Related Quality of Life mean score was 26.5 (95% confidence interval 22.5 to 30.5) at baseline, 17.1 (95% confidence interval 13.3 to 21.0) at 16 weeks and 13.9 (95% confidence interval 10.0 to 17.8) at 12 months.

Laryngeal mucosal changes recorded by Reflux Finding Score total (range 0–29), scored by an independent observer

Reflux Finding Scores were available for 256 participants included in the trial. Within the compliant intention-to-treat group, 80% of participants in the lansoprazole group and 72% of participants in the placebo group had Reflux Finding Scores at baseline. The mean Reflux Finding Scores were 9.7 (standard deviation 4.1) in the lansoprazole group and 9.2 (standard deviation 3.8) in the placebo group. The baseline Reflux Finding Score was not significantly related to the Reflux Symptom Index score at 16 weeks.

The ability of Reflux Finding Score and patient characteristics (age, sex, smoking status and body mass index) to predict any observed responses

None of the patient baseline characteristics or the baseline Reflux Finding Score was found to be univariate predictors of Reflux Symptom Index at 16 weeks (see *Appendix 8*, *Tables 11* and *57*, for baseline Reflux Finding Scores).

Side effects, adverse events and serious adverse events

There were 112 reported adverse events in 74 unique participants. Six were classed as 'probably related' to the lansoprazole treatment (one severe event and five moderate events). There were no such events in the placebo group.

Participant-reported satisfaction with the trial using a five-point overall satisfaction scale

At 12 months' follow-up, 213 out of 346 (62%) participants answered the satisfaction question, of whom 115 (54%) were very satisfied, 59 (28%) were satisfied, 29 (14%) were neither satisfied nor dissatisfied, five (2%) were dissatisfied and five (2%) were very dissatisfied.

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Participant accuracy in determining which treatment they had received

Forty-two per cent of the lansoprazole group and 56% of the placebo group correctly identified the treatment they had received at the end of the study period.

Conclusions

Twice-daily lansoprazole was not shown to offer any symptomatic benefit over matched placebo to patients with chronic throat symptoms. The severity of presenting symptoms dictated the level of symptoms following treatment. Therefore, the evidence from this trial does not support the common practice of prescribing proton pump inhibitors to this patient population.

Trial registration

This trial is registered as ISRCTN38578686 and EudraCT number 2013-004249-17.

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