Heartburn treatment in primary care: randomised, double blind study for 8 weeks

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The sample size calculation, flow of participants through the trial, members of the Norwegian Heartburn Study Group, and participating gastroenterologists appear on the BMJ's website

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Abstract

Objective To compare the effects and tolerability of omeprazole and cisapride with that of placebo for control of heartburn in primary care patients.
Design Randomised, double blind, placebo controlled study.
Setting 65 primary care practices in Norway.
Participants 483 untreated patients with complaints of heartburn ≥3 days a week, with at most grade 1 reflux oesophagitis.
Interventions Omeprazole 20 mg once daily, cisapride 20 mg twice daily, or placebo for 8 weeks.
Main outcome measures Adequate control of heartburn, defined as ≤1 day of the past 7 days with no more than mild heartburn, after 4 weeks of treatment.
Results In the all patients treated analysis, adequate control of heartburn was achieved in 71% of patients taking omeprazole, 22% taking cisapride, and 18% taking placebo after 4 weeks of treatment (omeprazole *v* cisapride and placebo, $P < 0.0001$; cisapride *v* placebo, non-significant). Results were comparable in patients with or without reflux oesophagitis. In patients treated with omeprazole only, symptom control was achieved significantly more often in patients positive for *Helicobacter pylori*. Antacid use was 2-3 times greater in patients taking cisapride or placebo than in those taking omeprazole. Relief of non-reflux symptoms did not significantly differ between the three groups. Significantly more patients taking cisapride reported adverse events than those taking omeprazole or placebo.
Conclusions Omeprazole 20 mg once daily was highly effective in relieving heartburn whereas cisapride 20 mg twice daily was not significantly more effective than placebo.

Introduction

Heartburn is the most typical symptom of gastro-oesophageal reflux disease and a common complaint in the general population.[1 2] Most patients with heartburn are treated in primary care and are not extensively investigated. Severity of symptoms, frequency of abnormal endoscopic findings, and effect of treatment in such patients is not well known. Omeprazole was effective in primary care patients with symptomatic gastro-oesophageal reflux disease in previous studies.[3 4] A prokinetic agent such as cisapride could represent an alternative approach to treatment, as dyspeptic symptoms and motility abnormalities are common in patients with gastro-oesophageal reflux disease.[5] We compared omeprazole and cisapride for the treatment of heartburn in a primary care population.

Participants and methods

Protocol

Investigators were primary care physicians, in 10 networks of 2-8 physicians each, liaising with the local endoscopy unit and pharmacy. We enrolled patients aged between 18 and 80 who had had heartburn as a predominant upper gastrointestinal symptom for ≥3 months and which had been present for ≥3 days a week, in a 14 days run-in period, during which endoscopy was performed. The patients gave their written consent to participate. We excluded patients who had had severe oesophagitis (grade 2-3), Barrett's oesophagus, peptic ulcer disease, gallstone disease, oesophagogastric surgery, or evidence of these at endoscopy. Other reasons for exclusion were intake of prokinetic or antisecretory drugs or antibiotics less than 2 weeks before endoscopy, misuse of alcohol or drugs, the need for an interpreter, or concomitant disease making assessment of symptoms difficult. Participants were to visit their physician after 2 weeks (range 11-17 days), 4 weeks (range 25-31 days), and 8 weeks (50-62 days) of treatment.

Investigations

Reflux oesophagitis was classified according to the Berstad[6] and Los Angeles[7] systems, and a meeting was held to optimise consensus. Barrett's oesophagus was defined as intestinal metaplasia extending for more than 3 cm into the oesophagus. Gastric *Helicobacter pylori* infection was diagnosed with a rapid urease test (Helicobacter Urease Test, Astra, Germany), read after 24 hours. In three networks, consecutive patients had 24 hour intraoesophageal pH-metry as previously described,[8] after stopping treatment for more than 1 week. These results were not shown to the investigators or patients.

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Interventions

Patients received either one capsule of omeprazole 20 mg (Astra Hässle, Mölndal, Sweden) and two tablets of placebo before breakfast and supper (omeprazole group), one capsule of placebo before breakfast and two tablets of cisapride 10 mg (Janssen Pharmaceutica, Beerse, Belgium) before breakfast and supper (cisapride group), or placebo for both (placebo group). Calcium carbonate antacid tablets (Titralac Nycomed, Oslo, Norway) with a buffering capacity of 7 mmol per tablet were provided for use only when heartburn occurred.

Outcome measures

The primary efficacy variable was adequate control of heartburn, defined as ≤1 day with no more than mild heartburn in the 7 days before the 4 week visit. Heartburn was defined as burning substernal discomfort with no radiating component and described with common words. Secondary efficacy variables were antacid consumption, severity and number of days with heartburn in the 7 days before each visit, as well as severity of regurgitation, belching, dysphagia, abdominal pain or discomfort, epigastric pain or discomfort, bloating, nausea, and vomiting. Each symptom was graded as either 1 (mild; awareness of symptom but easily tolerated), 2 (moderate; interference with normal activities), or 3 (severe; inability to perform normal activities). Adverse events were defined as unintended unfavourable symptoms or deterioration of existing illness, as well as deterioration in clinical tests, whether considered treatment related or not.

Statistics

We performed an "all patients treated" analysis, including all randomised patients who took at least one dose of study drug. A χ^2 test was used for comparison of the main efficacy variables and adverse events. Concomitant gastrointestinal symptoms and use of antacids were compared using the Kruskal-Wallis non-parametric test.

Assignment

Randomisation was done in blocks of eight for each network. The randomisation list was computer generated, and all packing of study drugs was done in one pharmaceutical laboratory to ensure that patients and investigators were blinded to study assignment.

Masking

Study drugs were double blinded using a double dummy technique. Drugs were dispensed and collected by the network pharmacy. Randomisation lists for emergency use were kept at the pharmacies, at the research coordination office, and at the research laboratory of the sponsor, but the code was not broken until the database had been formally closed.

Results

Participant flow and follow up

Overall, 573 patients (16 did not show up for endoscopy and three were excluded owing to the procedure being contraindicated) had a complete endoscopy, and 68 patients were excluded owing to endoscopic findings—reflux oesophagitis grade 2 (38 patients) or grade 3 (2), suspected Barrett's oesophagus (7), prior or current peptic ulcer disease (20), and suspected gastric tumour (1). Twenty one patients could not be randomised for other reasons—heartburn for less than 3 days a week (14 patients), use of a prohibited drug during the run-in period (4), and other (3). Table 1 lists the personal and endoscopic details of all 483 patients. Overall, 51% of participants had reflux oesophagitis Berstad grade 1, and 49% had no oesophagitis. The results of intraoesophageal pH monitoring for 24 hours were abnormal in 105/121 patients (87%). No significant differences in baseline characteristics or compliance with drugs were found between treatment groups or between patients with or without oesophagitis.

Table 1 Personal and endoscopic details of patients treated in each study arm. Values are percentages unless stated otherwise

Variable	Placebo (n=159)	Cisapride (n=163)	Omeprazole (n=161)
Male	50	50	57
Median age (years)	49.6	47.2	49.0
Median weight (kg)	76	78	77
Helicobacter pylori	39	37	32
Hiatal hernia	33	39	39
Berstad classification of reflux oesophagitis:			
No oesophagitis	52	43	52
Grade 1	48	57	48
Los Angeles classification of reflux oesophagitis:			
No oesophagitis	50	42	49
Grade A	24	33	26
Grade B	26	26	26
Severity of heartburn 7 days before randomisation:			
Mild	21	22	20
Moderate	64	72	68
Severe	15	6	12
Mean No of days with heartburn before randomisation	5.5	5.4	5.7
Patients with heartburn all 7 days before randomisation	47	45	54

Analysis

Adequate control of heartburn was achieved after 4 weeks in 71% of patients taking omeprazole, 22% taking cisapride, and 18% taking placebo; a statistically significant difference in favour of omeprazole (*v* cisapride and placebo, $P<0.0001$; cisapride *v* placebo, non-significant). Table 2 shows the results after 2 and 8 weeks. Results were similar after 4 weeks in patients with or without reflux oesophagitis (omeprazole 72% *v* 71%; cisapride 20% *v* 23%; placebo 10% *v* 24%). Patients taking omeprazole who were positive for *H pylori* achieved adequate control of heartburn more often than patients who were negative for *H pylori* (86% *v* 65%, $P<0.02$). Severity of heartburn and mean number of days with heartburn (table 3) decreased more in patients taking omeprazole than in those taking placebo or cisapride ($P<0.0001$).

Forty seven patients were prematurely withdrawn (see website). Thirty four patients with adequate control of heartburn at the 4 week visit reported not to have adequate control of heartburn at the 8 week visit—placebo 11 (33%), cisapride 12 (35%), and omeprazole 11 (12%)—significantly less often in the omeprazole group ($P<0.001$). Median antacid

Table 2 Percentage of patients achieving adequate control of heartburn in each treatment arm during week before 2, 4, and 8 week visits

Visit	Placebo (n=159)	Cisapride (n=163)	Omeprazole (n=161)	P value*
2 weeks	15	21	59	<0.0001
4 weeks (95% CI)	18 (12.0 to 24.4)	22 (15.4 to 28.6)	71 (63.8 to 78.4)	<0.0001
8 weeks	30	40	76	<0.0001

Six patients who were prematurely withdrawn but reported adequate control of heartburn are included: omeprazole (3), cisapride (2), placebo (1).
*Omeprazole *v* cisapride or placebo.

Table 3 Proportion of patients achieving adequate control of heartburn, mean number of days per week with heartburn after 2, 4, and 8 weeks of treatment, and median number of antacid tablets consumed

Variable	Placebo (n=159)	Cisapride (n=163)	Omeprazole (n=161)	P value†
Patients (%) achieving adequate control of heartburn*				
2 weeks	15	21	59	
4 weeks	18	22	71	<0.0001
8 weeks	30	40	76	
Mean No of days per week with heartburn				
Baseline	5.5	5.4	5.7	
2 weeks	4.3	3.6	1.8	<0.001
4 weeks	3.9	3.4	1.2	
8 weeks	3.5	3.0	1.0	
Median No of antacid tablets consumed				
Weeks 1-2	13	9	2	
Weeks 3-4	10	8	0	<0.0001
Weeks 5-8	17	12	0	

*No more than mild heartburn for ⩽1 day per week.
†Omeprazole *v* cisapride or placebo.

consumption (table 3) was significantly lower at all times in patients taking omeprazole (*v* cisapride and placebo, $P < 0.0001$).

Other gastrointestinal symptoms

Severity score of regurgitation, belching, epigastric pain or discomfort, abdominal pain or discomfort, bloating, dysphagia, and nausea improved significantly in all three groups after 4 and 8 weeks of treatment. No differences were found between cisapride and placebo, whereas the improvement with omeprazole was significantly greater than with cisapride and placebo in regurgitation ($P < 0.001$ after 4 and 8 weeks), belching ($P = 0.001$ after 4 and 8 weeks), and epigastric pain or discomfort ($P = 0.005$ after 4 weeks).

Adverse events

Adverse events were reported in significantly more patients receiving cisapride than either omeprazole ($P = 0.024$) or placebo ($P = 0.004$) after 4 weeks. The gastrointestinal and central nervous systems were most commonly affected. Five serious adverse events were reported (placebo, 1 adverse event; cisapride, 3; and omeprazole, 1), but the causal relation with study drug was scored as unlikely by the investigators.

Discussion

Patient population

In young individuals with typical heartburn and absence of alarm symptoms such as dysphagia and weight loss, most authorities agree that treatment on the basis of symptom evaluation and treatment response is justified.[9] In the primary care setting in particular, measures that may reduce the need for drug treatment include advice on diet, stopping smoking, and raising the head end of the bed.[9] In our experience these measures are often inadequate particularly in patients with frequent and bothersome symptoms. Heartburn was present every day in about 50% of our patients and interferred with daily activities in more than 75%. The great majority also had other associated gastrointestinal symptoms. Frequency and severity of symptoms were similar in patients with and without oesophagitis. To what extent these patients could be successfully managed by non-drug measures is unknown.

Only a minority of our patients had other gastrointestinal disease or complicated gastro-oesophageal reflux disease that would require a different treatment stategy from omeprazole once daily. Barrett's oesophagus was found in 1% of our patients, which was less than expected.[10 11] Our study thus confirmed that most patients with heartburn have either no or only low grade oesophagitis.

Results of intervention

Omeprazole 20 mg once daily gave adequate control of heartburn rapidly and in most patients continued to do so for the treatment period of 8 weeks. Adequate control of heartburn was achieved in 71% of patients after 4 weeks, comparable to results in other studies.[4] Some previous studies have shown less effect of omeprazole in patients without reflux oesophagitis,[4] but this was not the case in our study. Patients with gastro-oesophageal reflux disease but no reflux oesophagitis may be abnormally sensitive to acid, and our findings question the belief that these patients have milder disease. Some patients had adequate control of heartburn after 4 weeks of treatment but not after 8 weeks, but the stability of symptom control was significantly better with omeprazole.

Other recent studies have also focused on patients with dyspepsia and heartburn in primary care, and results of treatment. In an international multicentre trial, patients with reflux symptoms diagnosed with a questionnaire randomly received omeprazole 10 mg or 20 mg daily for 4 weeks. Omeprazole significantly reduced symptoms of gastro-oesophageal reflux, and 73% of patients taking 20 mg obtained sufficient control of upper gastrointestinal symptoms including heartburn.[4] In another study, patients with heartburn as the predominant symptom were randomised to omeprazole 20 mg or 10 mg once daily or ranitidine 150 mg twice daily, and adequate relief of heartburn was achieved in 61%, 49%, and 40% respectively after 4 weeks.[3]

Omeprazole and cisapride have previously been compared in only one study. That study, partly conducted in specialist care, showed that omeprazole 10 mg or 20 mg daily was significantly more effective than cisapride 10 mg four times daily after 4 and 8 weeks.[12] Adequate control of heartburn with omeprazole 20 mg daily (65% after 4 weeks) was comparable to our findings, whereas cisapride showed a better effect than we observed (41%). The lack of a placebo group in that study, however, makes comparisons difficult.

Cisapride is anticipated to improve non-reflux symptoms such as bloating, epigastric pain, abdominal pain, and nausea better than placebo, but this was not our finding. These symptoms improved in all

Key messages

- In primary care patients, heartburn is commonly treated empirically
- Most randomised clinical trials of treatment for heartburn have been conducted in specialist care, and documentation for empirical treatment is limited
- Omeprazole was significantly more effective than cisapride or placebo in controlling heartburn and other symptoms of gastro-oesophageal reflux after 2, 4, and 8 weeks, whereas cisapride did not differ significantly from placebo
- Omeprazole should be considered as a first choice for empirical treatment of heartburn in primary care

treatment groups with no significant differences between them and seemed to parallel relief of heartburn.

Early short term studies with cisapride reported symptom relief and healing of oesophagitis comparable to H_2 receptor antagonists, but symptom relief was slower.[13 14] Later short term studies showed only minor improvement in heartburn and endoscopic variables.[15 16] A recent US multicentre study of 398 patients with mild to moderate gastro-oesophageal reflux disease showed a statistically significant reduction in reflux symptoms compared with placebo, but changes were moderate, and few patients had adequate control of heartburn as we defined it.[17] The high frequency of gastrointestinal adverse events with cisapride in that and our study has also been reported previously.[8 17]

Cisapride has been shown to increase the lower oesophageal sphincter resting pressure[18 19] and to improve gastric emptying in patients with gastro-oesophageal reflux disease.[20] The main motility disturbances in gastro-oesophageal reflux disease, however, are ineffective oesophageal motility[21] and increased frequency of transient lower oesophageal sphincter relaxations resulting in acid reflux,[22] abnormalities that are not improved by cisapride.[23 24] Low lower oesophageal sphincter pressure and delayed gastric emptying may be uncommon in primary care patients.

Implications for practice

We have shown that primary care patients with heartburn as their predominant symptom of gastro-oesophageal reflux disease can be safely and very effectively treated with omeprazole 20 mg once daily. The effects of treatment with cisapride 20 mg twice daily were not significantly different from placebo, but significantly more patients reported adverse events during treatment with cisapride. Omeprazole should be considered as a first choice when treating patients with heartburn in primary care.

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Contributors: All authors were members of the steering committee and contributed actively to the protocol, data analyses, and interpretation of data. JGH was mainly responsible for the study design, was chairman on the committee, and had prime responsibility for writing the manuscript. AH initiated the study, was mainly responsible for the study at Astra Norge, and contributed actively to the manuscript. PHM and POW recruited and followed up the patients. PM was responsible for statistical analyses. JGH and AB will act as guarantors for the paper.

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Competing interests: AH, PM, and TB were employed by Astra Norge. JGH and AB have accepted fees from Astra Norge and Janssen Cilag for speaking. TS has accepted fees from Astra Norge for organising education.

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