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The role of acid suppression in patients with endoscopy-negative reflux disease: the effect of treatment with esomeprazole or omeprazole

D. ARMSTRONG*, N. J. TALLEY†, K. LAURITSEN‡, B. MOUM§, T. LIND¶, H. TUNTURI-HIHNALA**, T. VENABLES††, J. GREEN‡‡, M. A. BIGARD§§, J. MÖSSNER¶¶ & O. JUNGHARD¶

**McMaster University Medical Centre, Ontario, Canada; †Mayo Clinic College of Medicine, Rochester, MN, USA and Department of Medicine, University of Sydney; ‡Odense University Hospital, Odense, Denmark; §Östfold Central Hospital, Fredrikstad, Norway; ¶AstraZeneca Research and Development, Mölndal, Sweden; **Seinäjoki Central Hospital, Seinäjoki, Finland; ††Calverton Practice, Nottingham, UK; ‡‡North Staffordshire Hospital Centre, Stoke-on-Trent, UK; §§Hospitalier Universitaire de Nancy, Nancy, France; ¶¶Universität Leipzig, Medizinische Klinik II, Leipzig, Germany*

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SUMMARY

Background: Patients with endoscopy-negative reflux disease have reflux symptoms, mainly heartburn, but not mucosal breaks characteristic of erosive oesophagitis. Standard-dose proton pump inhibitors can provide symptom relief in endoscopy-negative reflux disease but the effect of greater acid suppression has not been studied.

Aim: To test the hypothesis that esomeprazole produces heartburn resolution in a greater proportion of patients with ENRD than omeprazole.

Methods: Three multi-centre randomized, controlled, double-blind, 4-week acute treatment studies were conducted in endoscopy-negative reflux disease patients. In study A ($n = 1282$), patients received either esomeprazole 40 mg, esomeprazole 20 mg or omeprazole 20 mg daily; in studies B ($n = 693$) and C ($n = 670$) patients received either esomeprazole 40 mg or omeprazole 20 mg (B), and esomeprazole 20 mg or omeprazole 20 mg (C), respectively.

Results: Resolution of heartburn at 4 weeks (no heartburn symptoms during the last 7 days) was achieved in similar proportions of patients in each treatment arm in study A (esomeprazole 40 mg, 56.7%; esomeprazole 20 mg, 60.5%; omeprazole 20 mg, 58.1%), study B (esomeprazole 40 mg, 70.3%; omeprazole 20 mg, 67.9%) and study C (esomeprazole 20 mg, 61.9%; omeprazole 20 mg, 59.6%). There were no significant differences between treatment groups within each study.

Conclusions: More than 60% of endoscopy-negative reflux disease patients reported heartburn resolution but, after 4 weeks of therapy, these proportions did not differ significantly between treatments.

INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is defined in the Genval reflux disease workshop report as including all individuals who are exposed to the risk of physical complications from gastro-oesophageal reflux, or who experience clinically significant impairment of health-related well-being (quality of life) because of reflux-related symptoms.[1] Endoscopy-negative reflux disease (ENRD) is defined as GERD in individuals who do not have either Barrett's oesophagus or definite endoscopic oesophageal 'mucosal breaks' (oesophageal mucosal erosion or ulceration).[1–3]

Endoscopy-negative reflux disease occurs in 40–60% of patients with reflux disease, with patients experien-

Correspondence to: Prof N. J. Talley, Mayo Medical School, Center for Enteric Neurosciences and Translational Epidemiological Research (CENTER), Charlton 8-127, Mayo Clinic, 200 First Street, Rochester, MN, USA.
E-mail: talley.nicholas@mayo.edu, njtalley@charter.net, talley@pnc.com.au.

cing reflux symptoms which are comparable in severity and duration to those experienced by patients with erosive oesophagitis.[4] Health-related quality of life is also impaired equally in both groups of patients.[5] The cardinal symptom of GERD is heartburn and, although this is the basis for the diagnosis of ENRD,[1] it may be accompanied by a number of other symptoms including regurgitation, nausea, epigastric pain, chest pain or other extra-oesophageal complications.

For patients with erosive oesophagitis, proton pump inhibitors (PPIs) are superior to histamine H_2-receptor antagonists (H_2-RAs) and other therapies for healing and symptom relief.[6] More recently, studies have demonstrated that esomeprazole produces higher rates of healing and heartburn relief in patients with erosive oesophagitis than omeprazole[7, 8] or lansoprazole.[9] Acid suppression therapy with a PPI has also been shown to produce symptom relief in a greater proportion of patients suffering from either ENRD or GERD than therapy with an H_2-RA, prokinetic or placebo.[10–15] However, a lower rate of symptom resolution has been described in ENRD patients compared to patients with erosive disease[12, 13, 16] possibly indicating that patients with ENRD are a more heterogeneous population than patients with erosive disease.

Prior to the present studies, there have been no controlled trials comparing esomeprazole with omeprazole for the acute management of ENRD. However, the results of pharmacokinetic studies indicate that esomeprazole, 40 mg once daily, produces more prolonged acid suppression than esomeprazole, 20 mg once daily, and that in turn, the lower dose of esomeprazole also produces greater acid suppression than omeprazole, 20 mg once daily.[17] The aim of the present studies was, therefore, to test the hypothesis that the greater acid suppression produced by esomeprazole would produce heartburn relief in a greater proportion of patients than omeprazole after 4 weeks of therapy. The three studies to be reported were comparable in design and hence the data are presented together.

METHODS

Study design and patient selection

Three multinational (10 countries), multicentre, double-blind, randomized, parallel-group studies (studies A, B and C) were carried out to compare the effect of once daily oral dosing of esomeprazole 40 mg, esomeprazole 20 mg or omeprazole 20 mg in symptomatic patients with ENRD. All patients who had experienced heartburn (defined as a burning feeling, rising from the stomach or lower part of the chest up towards the neck) as their main symptom for 6 months or longer, and for 4 days or more during the last week before the start of each study, and who had a normal endoscopy were included.

The studies were of identical design and each provided a 4-week treatment period. Patients in study A received either esomeprazole 40 mg, esomeprazole 20 mg or omeprazole 20 mg. Patients in study B received esomeprazole 40 mg or omeprazole 20 mg and patients in study C received esomeprazole 20 mg or omeprazole 20 mg. All medication was taken once daily in the morning.

Treatment began on day 0 (visit 1), with a baseline endoscopy within 14 days prior to visit 1, and ended on day 28 ± 4 (visit 3). Patients also attended the study centre for assessment on day 14 ± 2 (visit 2). At visit 1, the patients' medical and surgical history was taken. A physical examination and routine laboratory safety tests were performed at visits 1 and 3. Testing for the presence of *Helicobacter pylori* with a ^{13}C-urea breath test (UBT) was performed in all patients before the start of treatment; patients and investigators remained unaware of the results of the UBT until after completion of the study.

Efficacy assessments

The primary efficacy end-point was complete resolution of heartburn, assessed retrospectively by the investigator, and defined as no days with heartburn episodes during the last 7 days before visit 3. The secondary efficacy end-points were complete resolution of heartburn at visit 2, adequate control of heartburn (defined as no more than 1 day of mild heartburn during the last 7 days before visit 3), relief of other reflux and gastrointestinal (GI) symptoms and relief of heartburn as assessed by patient diary.

At each visit, the frequency and severity of heartburn were assessed by the investigator. Frequency was recorded as the number of days with heartburn during the last 7 days (scale of 0–7 days) and symptom severity was classified, on a 4-point scale, as none, mild (awareness of symptoms, but easily tolerated), moderate (discomfort sufficient to cause interference with normal activities), or severe (incapacitating with inability to perform normal activities). The severity of other reflux symptoms (regurgitation, dysphagia) and GI symptoms

(epigastric pain, nausea) during the last 7 days was assessed by standard questioning by the investigator and classified in the same way as heartburn. Patients assessed the most severe night-time and daytime heartburn episode each day throughout the study and recorded it on a diary card. In addition, an overall treatment evaluation (OTE) was assessed: patients rated whether they were better, the same or worse compared with baseline and the degree of change was rated using a 7-graded Likert scale.

Each study was conducted in accordance with the Declaration of Helsinki and was consistent with Good Clinical Practice. Signed informed consent was obtained from all patients before conducting any specific procedures in all of the studies.

Statistical analysis

All efficacy variables were analysed using the intention-to-treat (ITT) populations, which included all randomized patients who took at least one dose of study drug and had post-randomization data.

The Mantel–Haenszel chi-square test, stratified for country, was used to analyse the primary efficacy end-point of complete resolution of heartburn at 4 weeks, and the secondary efficacy end-points of resolution of heartburn at 2 weeks and adequate control of heartburn at 4 weeks. The Mantel–Haenszel chi-square test stratified according to baseline scores was used to analyse the relief of reflux symptoms, and the relief from other GI symptoms were documented in frequency tables. Diary card data were analysed using one-way ANOVA for percentage of heartburn-free days and nights; the time to first resolution of heartburn (defined as the first day with no heartburn) and the time to first sustained resolution (defined as the first period of 7 consecutive days with no heartburn) were derived from these data and analysed by a log-rank test. The Mann–Whitney test was used to analyse the OTE data.

RESULTS

Demographic data show that, with respect to age, gender, *H. pylori* status and history of episodes of heartburn, there were no important differences between the matched treatment groups within each study (Table 1).

The primary outcome, complete resolution of heartburn at 4 weeks, was comparable for all treatment arms within in each of the studies (Table 2). In addition, resolution of heartburn at 2 weeks was comparable in all treatment arms within each study. However, in all studies, the proportions of patients with resolution of heartburn increased by 15%–30% between weeks 2 and 4 (Table 2).

When evaluating adequate control, in study A, 60.5%, 66.0% and 63.1% of patients in the esomeprazole 40 mg, esomeprazole 20 mg and omeprazole 20 mg groups, respectively, reported adequate control of heartburn. In study B, 73.5% of patients in the esomeprazole 40 mg group and 72.8% in the omeprazole 20 mg group had adequate control of heartburn. In study C, the proportions of patients were 67.9% in the esomeprazole 20 mg group and 65.3% in the omeprazole 20 mg group.

In all three studies, high proportions of patients treated with either esomeprazole or omeprazole had no regurgitation and no dysphagia at 4 weeks. In study A, significantly more patients in the esomeprazole 20 mg group had complete relief from regurgitation at 2 weeks compared with patients in the omeprazole 20 mg group (Figure 1), but the proportions of patients with relief from regurgitation at 4 weeks, and dysphagia at 2 and 4 weeks, were comparable between groups. Similarly, in studies B and C, the proportions of patients with relief from regurgitation and dysphagia were over 80% for all treatments at 2 and 4 weeks, with no significant differences detected between treatment groups in either study.

In study A, patient diary cards indicated that the proportion of patients reporting periods without daytime or night-time heartburn was higher for esomeprazole 20 mg, whereas no differences were detected between treatment groups in the other two studies (Table 3). The median number of days to the first period of 7 consecutive days or nights without heartburn was similar across the studies and treatments.

The OTE assessment (Figure 2) revealed that at least 79.5–89% of patients reported feeling better at 4 weeks and this proportion was similar in magnitude across all treatment groups.

Overall, esomeprazole, 40 mg and 20 mg, and omeprazole 20 mg were well-tolerated and the proportions of patients experiencing adverse events were similar between treatment groups during the study period.

DISCUSSION

Gastro-oesophageal reflux disease has been defined by impairment of health-related quality of life because of reflux-related symptoms, such as heartburn and by the risk of physical complications from gastro-oesophageal

Table 1. Baseline demographic and clinical characteristics of the intention-to-treat (ITT) study population in studies A, B and C

	Esomeprazole 40 mg	Esomeprazole 20 mg	Omeprazole 20 mg
Study A (Canada, England, Ireland,)			
N	425	423	434
Male, *n* (%)	183 (43.1)	183 (43.3)	187 (43.1)
Female, *n* (%)	242 (56.9)	240 (56.7)	247 (56.9)
Mean age, years (range)	48.4 (19–79)	48.0 (18–80)	48.3 (19–78)
History of episodes of heartburn[a]			
6 to < 12 months	56	65	50
1–5 years	178	148	183
> 5 years	191	209	201
Helicobacter pylori status (negative/positive/unknown)	290/125/10	262/147/14	292/127/15
Study B (France, Germany, Switzerland)			
N	347	NA	346
Male, *n* (%)	154 (44.4)	NA	156 (45.1)
Female, *n* (%)	193 (55.6)	NA	190 (54.9)
Mean age, years (range)	50.6 (21–77)	NA	50.0 (19–83)
History of episodes of heartburn			
6 to < 12 months	83	NA	75
1–5 years	129	NA	149
> 5 years	135	NA	122
Helicobacter pylori status (negative/positive/unknown)	208/128/11	NA	216/127/3
Study C (Denmark, Finland, Norway, Sweden)			
N	NA	336	334
Male, *n* (%)	NA	175 (52.1)	168 (50.3)
Female, *n* (%)	NA	161 (47.9)	166 (49.7)
Mean age, years (range)	NA	48.5 (19–79)	48.5 (20–79)
History of episodes of heartburn[b]	NA		
6 to < 12 months	NA	29	37
1–5 years	NA	100	94
> 5 years	NA	207	202
Helicobacter pylori status (negative/positive/unknown)	NA	226/108/2	237/93/4

NA = Not applicable.
[a] One patient in the esomeprazole 20 mg group had a history of heartburn of < 6 months duration.
[b] One patient in the omeprazole 20 mg group had a history of heartburn of < 6 months duration.

Table 2. Percentage of patients with complete resolution of heartburn at 14 and 28 days in studies A, B and C

Study/treatment	Percentage of patients with resolution of heartburn at 14 days (95% CI)	Percentage of patients with resolution of heartburn at 28 days (95% CI)
Study A		
Esomeprazole 40 mg ($n = 425$)	34.6 (30.1–39.3)	56.7 (51.8–61.5)
Esomeprazole 20 mg ($n = 423$)	39.7 (35.0–44.6)	60.5 (51.8–61.5)
Omeprazole 20 mg ($n = 434$)	37.6 (33.0–42.3)	58.1 (53.3–62.8)
Study B		
Esomeprazole 40 mg ($n = 347$)	41.2 (36.0–46.6)	70.3 (65.2–75.1)
Omeprazole 20 mg ($n = 346$)	42.5 (37.2–47.9)	67.9 (62.7–72.8)
Study C		
Esomeprazole 20 mg ($n = 336$)	41.4 (36.1–46.8)	61.9 (56.5–67.1)
Omeprazole 20 mg ($n = 334$)	44.3 (38.9–49.8)	59.6 (54.1–64.9)

reflux.[1] The occurrence of heartburn, on ≥ 2 days a week, is considered to indicate a high likelihood of GERD[1], and, in the absence of endoscopic findings such as Barrett's oesophagus or endoscopic oesophageal 'mucosal breaks', patients with heartburn are considered to have ENRD.

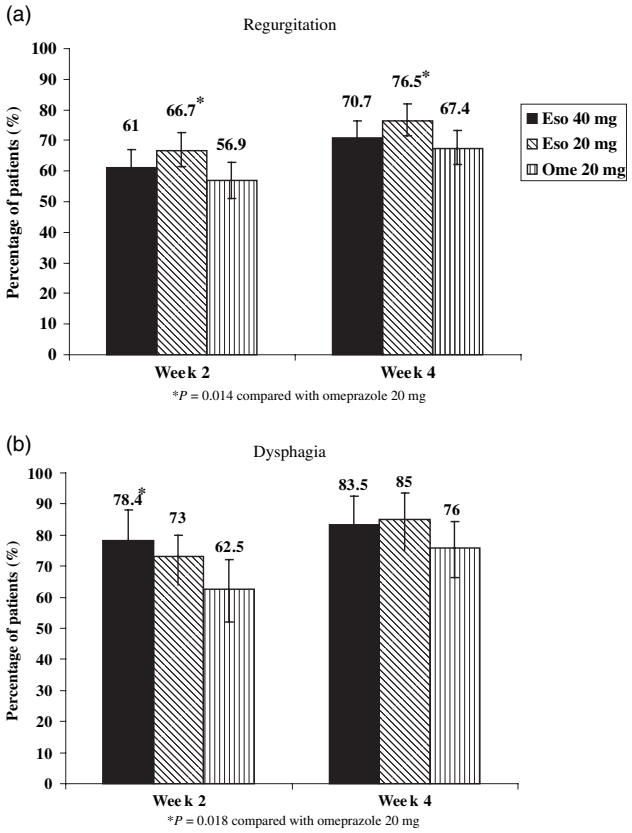

Figure 1. Percentage of patients in study A with complete resolution of regurgitation or dysphagia at week 2 and week 4 who presented with at least mild regurgitation or dysphagia at baseline (regurgitation, $n = 287$, 285 and 288; dysphagia, $n = 97$, 100, 96 for Eso 40, Eso 20 and Ome 20 respectively) [intention-to-treat (ITT) population, error bars depict 95% exact confidence intervals].

Resolution of heartburn frequently accompanies healing of erosive oesophagitis but oesophageal erosions are not the sole cause of reflux symptoms because they occur in patients who do not have typical reflux symptoms.[18] Furthermore, typical reflux symptoms occur in patients in the absence of endoscopic abnormalities. While it is generally considered that ENRD is part of the spectrum of GERD, true, acid-related ENRD is probably a subset of a more heterogeneous condition – endoscopy-negative heartburn – that may include patients with acid-unrelated heartburn. As a result, endoscopy negative heartburn and ENRD are difficult to diagnose and study because there are no conclusive diagnostic criteria for either condition. Nonetheless, they are common and important conditions; data from a number of studies now indicate that ENRD and erosive oesophagitis have similar effects on health-related quality of life[5] and that the duration, nature and severity of reflux symptoms are similar in both conditions.

Although there may be multiple causes of symptoms in patients with endoscopy-negative heartburn (non-acid reflux, oesophageal acid sensitivity, generalized oesophageal hypersensitivity,[19–21] oesophageal dysmotility or even extra-oesophageal conditions such as stress, anxiety and depression[22, 23]), the studies reported here were conducted in patients with presumed ENRD. This was to test the hypothesis that more effective acid suppression achieved by esomeprazole would resolve symptoms in a greater proportion of patients than a standard dose of a comparator PPI, omeprazole. The studies were predicated on previous reports that

Table 3. Freedom from heartburn during daytime and night-time periods as recorded in patients' diaries in studies A, B and C

	Daytime periods		Night-time periods	
Study/treatment	Mean percentage of periods during which patients recorded no heartburn	Median time (days) to onset of seven consecutive periods during which patients recorded no heartburn	Mean percentage of periods during which patients recorded no heartburn	Median time (days) to onset of seven consecutive periods during which patients recorded no heartburn
Study A				
Esomeprazole 40 mg ($n = 425$)	62.2	11	70.2	7
Esomeprazole 20 mg ($n = 423$)	66.5	9	74.7	7
Omeprazole 20 mg ($n = 434$)	63.4	12	72.6	7
Study B				
Esomeprazole 40 mg ($n = 347$)	63.5	11	72.5	7
Omeprazole 20 mg ($n = 346$)	63.5	11	71.5	7
Study C				
Esomeprazole 20 mg ($n = 336$)	60.7	11	71.4	7
Omeprazole 20 mg ($n = 334$)	61.3	11	73.5	6

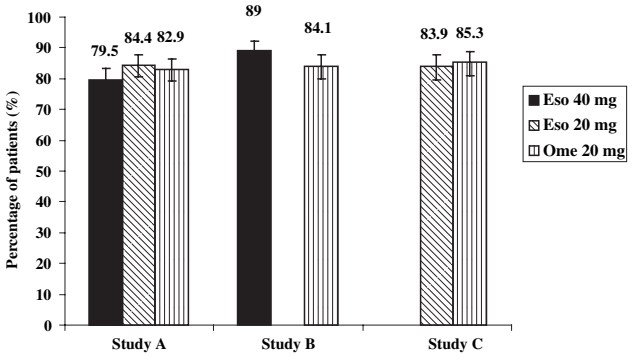

Figure 2. Percentage of patients feeling better as assessed by OTE at 4 weeks in studies A, B and C. The OTE scale consists of seven levels for worse ('a very great deal worse' through 'almost the same hardly worse at all'), 'about the same' and seven levels for better ('almost the same, hardly better at all' through 'a very great deal better'). A cut of above 'about the same' is used for the definition 'feeling better'. [Intention-to-treat (IIT) population, error bars depict 95% exact confidence intervals].

omeprazole, 20 mg daily, produces symptom relief in a greater proportion of ENRD patients than omeprazole, 10 mg daily.[10, 24] Indeed, many reports have examined acid suppression as a tool to indicate that symptoms are acid related.[25–28] Pharmacodynamic studies have shown that esomeprazole produces greater acid suppression than omeprazole, lansoprazole, and all other PPIs[17, 29, 30] and subsequent clinical studies in reflux oesophagitis patients have shown greater rates of oesophagitis healing and symptom resolution with esomeprazole than with omeprazole[7,8] or lansoprazole.[9] Since healing of erosive oesophagitis and symptom resolution are related directly to the degree of acid suppression produced by therapy,[31] it was hypothesized that more effective acid suppression with esomeprazole relative to omeprazole would lead to superior symptom resolution in ENRD patients.

In the three separate studies reported here, esomeprazole, 40 and 20 mg once daily, and omeprazole, 20 mg once daily, all achieved high rates of symptom resolution leading to complete freedom from heartburn after 4 weeks in 56.7–70.3% of ENRD patients. However, there were no significant differences in symptom resolution rates between omeprazole and either dose of esomeprazole in any of the studies. Furthermore, the rates of symptom resolution were comparable for esomeprazole, 40 and 20 mg once daily, in the study in which both doses were included.

While ENRD patients may be less likely to achieve complete symptom resolution than erosive oesophagitis patients,[12–14,16] there is, nonetheless, evidence of a dose–response effect at lower levels of acid suppression.[10, 24] However, the expected increase in symptom relief at the higher levels of acid suppression achieved by esomeprazole[17, 25] was not confirmed.

Other studies have also failed to demonstrate differences between different PPI doses for symptom relief in ENRD. In one study, complete symptom relief at 4 weeks was achieved in 28.3%, 29.3% and 3.4% of ENRD patients with rabeprazole 20 mg daily, rabeprazole 10 mg daily and placebo, respectively.[32] Similarly, in another study, symptom relief at 4 and 8 weeks was no greater for ENRD patients receiving lansoprazole 30 mg daily than it was for those receiving lansoprazole 15 mg daily, although both doses were superior to placebo.[33] In a study comparing lansoprazole 15 and 30 mg with ranitidine 150 mg daily there was no significant difference after 8 weeks for either of the lansoprazole doses compared to ranitidine with respect to the symptom index or the health-related quality of life dimensions.[34]

One possible explanation is that ENRD patients have a milder form of GERD than do erosive oesophagitis patients. In general, ENRD patients have reduced oesophageal acid exposure compared with erosive oesophagitis patients[35–37] and it has also been reported that greater baseline oesophageal acid exposure is associated with a greater symptomatic response to PPI therapy in ENRD.[10] Furthermore, severe oesophagitis (LA grades 'C' and 'D') is associated with greater oesophageal acid exposure.[38] More effective acid suppression with esomeprazole 40 mg provides a greater increase in healing rates and symptom improvement following therapy.[7–9]

Some patients with heartburn and presumed ENRD may not have acid-related symptoms. Despite this, many ENRD patients do respond symptomatically to acid suppressive therapy and the overall symptom response rates in these three esomeprazole studies were, in fact, somewhat higher than those observed in previous ENRD studies.[10–14] In the absence of other explanations, we would, therefore, hypothesize that the majority of ENRD patients have acid-related symptoms, which respond well to acid suppressive therapy, but that some patients who are thought to have ENRD actually have symptoms that are not acid-related.

In conclusion, the results of these three large studies indicate that the majority of patients with endoscopy-negative heartburn or reflux-like symptoms and presumed ENRD respond to acid suppression in 4 weeks

even using a stringent end-point, namely complete symptom resolution. Importantly, the response rates were higher than that observed previously in patients with ENRD, supporting the clinical strategy of instituting a PPI for reflux symptoms in settings where ENRD is common. Since the majority of patients receiving acid suppressive therapy are in fact uninvestigated, future studies should address the problem of identifying those patients with ENRD who do not have acid-related symptoms, with the aim of identifying features which will enable clinicians to predict who will benefit from acid suppressive therapy.

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