ORIGINAL RESEARCH ARTICLE

Drug Safety 2001; 24 (8): 625-635
0114-5916/01/0008-0625/$22.00/0

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Safety and Efficacy of Long Term Esomeprazole Therapy in Patients with Healed Erosive Oesophagitis

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Abstract

Objective: To evaluate the safety and tolerability of long term treatment with esomeprazole in patients with healed erosive oesophagitis, and to describe its efficacy in the maintenance of healing.

Design and setting: US multicentre, noncomparative, nonblind study.

Patients and participants: 807 patients with endoscopically confirmed healed erosive oesophagitis.

Methods: Patients received esomeprazole 40mg once daily for up to 12 months. Adverse events and clinical laboratory tests were assessed over the study period. Endoscopy was performed at the final visit of the antecedent healing trials and at months 6 and 12 of the current safety trial; gastric biopsies were obtained at the initial visit of the healing trials and at the end of the safety trial.

Results: 80.9% of patients completed 6 months of treatment; 76.6% completed 12 months of treatment. There were no serious drug-related adverse events. Diarrhoea, abdominal pain, flatulence, and headache were the only treatment-related adverse events reported by >3% of patients. Mean changes in laboratory measures were generally small and not clinically meaningful. Plasma gastrin levels increased, as expected, and reached a plateau after 3 months. No changes in gastric histological scores were noted in the majority of patients. Evaluation of gastric biopsies revealed an overall decline in chronic inflammation and atrophy. Intestinal metaplasia findings remained essentially unchanged. Life table estimates of maintenance of healing were 93.7% [95% confidence interval (CI) 92.0 to 95.5%] at 6 months and 89.4% (95% CI 87.0 to 91.7%) at 12 months.

Conclusions: Daily treatment with esomeprazole 40mg for up to 1 year in patients with healed erosive oesophagitis was generally well tolerated and effective. No safety concerns arose.

Erosive oesophagitis is a chronic disease that tends to relapse rapidly if treatment is stopped after initial healing. Long term acid suppression with proton pump inhibitors (PPIs) is the cornerstone of pharmacotherapy to prevent recurrence.[1,2]

Historically, concerns have been raised about the long term safety of prolonged acid suppression with antisecretory agents. These concerns include enterochromaffin-like (ECL) cell hyperplasia,[3] gastric carcinoids[4-7] and adenocarcinoma attributable to hypergastrinaemia.[8,9] In addition, it has been theorised that vitamin B_{12} and iron deficiency might occur because of malabsorption.[10-12]

However, after more than a decade of experience, no clear association between these events and the use of PPIs has been established. Omeprazole has been associated with few such effects,[13] and no evidence has been documented to suggest that long term antisecretory treatment increases the risk of gastric carcinoids or adenocarcinoma of the stomach or colon.[14,15]

In long term clinical trials with PPIs, the adverse events most commonly reported have been gastrointestinal in nature and include diarrhoea, abdominal pain, nausea and constipation. Headache and dizziness have also been reported in smaller numbers of patients.

Esomeprazole, the (*S*)-isomer of omeprazole, is a new PPI that has been developed for the treatment of acid-related disorders. Comparative pharmacokinetic and pharmacodynamic studies indicate advantages of esomeprazole over other PPIs.[16-18] Esomeprazole has higher systemic bioavailability, produces greater and more prolonged inhibition of gastric acid secretion and less interpatient variability in acid suppression than omeprazole in patients with gastro-oesophageal reflux disease (GORD).[16] At recommended doses, esomeprazole once daily for 4 to 8 weeks provided significantly greater healing than omeprazole once daily across all grades of erosive oesophagitis in 2 acute healing trials.[19,20]

The purpose of this study was to treat a large number of patients for a prolonged period with esomeprazole to further characterise the general safety profile of this new PPI, and to gain insight into the possible occurrence of adverse events with a late onset. A secondary objective was to describe the efficacy of esomeprazole for the maintenance of healed erosive oesophagitis.

Patients and Methods

Study Design and Patient Selection

This nonblind, noncomparative, 12-month trial was conducted at 111 centres in the US. Patients were eligible for enrollment if they had participated in one of two 8-week healing studies, had healed erosive oesophagitis (no erosions present at final oesophagogastroduodenoscopy of healing trial) after 4 or 8 weeks of treatment with esomeprazole 40mg, esomeprazole 20mg or omeprazole 20mg once daily, and were negative for *Helicobacter pylori* by histology (confirmation was part of the biopsy evaluation of samples taken during the antecedent healing trials). Those testing positive for *H. pylori* were excluded to eliminate a potentially confounding factor in the efficacy analysis of these trials. Study medication received in the healing trials was not unblinded as a requirement for eligibility for the safety trial. Laboratory data from the final visit of the healing studies served as baseline data for this extension study. The baseline biopsies for patients enrolled into this study were performed upon entry into the healing studies (prior to PPI treatment). The baseline *H. pylori* status for this study was also performed at entry into the healing studies (based on negative serology and subsequent histology results). All patients provided written informed consent prior to being enrolled. This study was conducted in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practices regulations and guidance issued by the US Food and Drug Administration. Institutional review board approval was obtained at each study site.

Patients were not eligible for inclusion in this study if they had evidence of Zollinger-Ellison syndrome, primary motility disorders, oesophageal stricture, inflammatory bowel disease, evidence of

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upper gastrointestinal malignancy, macroscopic Barrett's oesophagus, severe concomitant disease, or if they were pregnant or lactating. Patients requiring continuous concurrent therapy within 1 week of the baseline visit with nonsteroidal anti-inflammatory drugs, prokinetic agents, anticholinergics or salicylates (>165 mg/day) were excluded from the study. Additionally, patients who had received either PPI therapy (other than the study medication provided in the healing studies) within 28 days of the baseline visit or a histamine H_2 receptor antagonist on a daily basis (occasional use was permitted) during the 2 weeks prior to baseline endoscopy were excluded. H_2 antagonist use was not allowed during this safety assessment study. Patients were also excluded if they had known hypersensitivity to any component of esomeprazole. Those with acute hypersensitivity reactions to esomeprazole in the healing trials would have been identified prior to trial entry.

Patients took esomeprazole 40mg orally in the morning before breakfast. Compliance was assessed through unused capsule count. Since this was a noncomparative study, no randomisation, stratification, or blinding procedures were used.

Adverse Event Assessments

Defining the safety and tolerability of esomeprazole was the primary study objective. Adverse events were recorded at each visit after entry, either when reported spontaneously by patients or in response to an open question. The investigator was asked to report any clinically significant physical or laboratory changes as adverse events. The percentage of patients who reported an adverse event was summarised for the entire study period.

An adverse event was defined as any unfavorable and unintended change in the structure, function or chemistry of the body temporally associated with any use of the study drug whether or not considered related to the use of the study drug. A serious adverse event was defined as an adverse event that resulted in death, permanent or substantial disability, or inpatient hospitalisation (or prolongation of hospitalisation), was immediately life threatening or resulted in a congenital anomaly, was a cancer, was the result of an overdose (>100% of daily dose, whether accidental or intentional), or required medical or surgical intervention to prevent permanent impairment or damage. The safety and tolerability summaries included all patients who received at least 1 dose of study drug. Investigators assessed whether each adverse event was caused by the study drug and classified the relationship to the study drug as probable, possible or unlikely. They also rated the severity of each adverse event as mild, moderate or severe.

Analysis of adverse events, including incidence rates for adverse events by body system and preferred term, was performed over the entire 12-month study period. Preferred terms encompassing 31 system organ classes were used to describe adverse events reported by patients. Standard terminology for the classification of adverse events was based on a modified version of the World Health Organization (WHO) Adverse Reaction Terminology (WHOART) developed by the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden.

Laboratory Assessments

Samples for clinical laboratory tests were obtained by standardised techniques and, with the exception of pregnancy testing, were assessed by a central laboratory. Haematology (haemoglobin, total white blood cell count and platelet count), urinalysis (protein, glucose, white blood cell count and red blood cell count using dipstick testing), standard serum chemistry and specific serum chemistry [creatinine, uric acid, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), sodium, potassium, vitamin B_{12}, iron, gastrin and, for women of child-bearing potential, human chorionic gonadotropin (β-hCG)] were collected on fasting patients at baseline (final visit of the healing trial) and at months 1, 3, 6, 9 and 12 (or the final visit). Vital signs were recorded at each visit and a physical examination was done at the baseline, month 6 and month 12 visits.

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Gastric biopsy samples were obtained according to a standardised procedure at the start of the healing studies and the final visit of this safety study. Two biopsies were obtained from the antrum and 4 from the corpus. Biopsy samples were evaluated by 2 independent pathologists for 3 characteristics of gastritis (chronic inflammation, atrophy, and intestinal metaplasia) using the updated Sydney system of classification.[21] This system is based on the Sydney system of classification[22] and combines topographical, morphological and aetiological information with a visual analogue scale (0 = none, 1 = mild, 2 = moderate and 3 = severe) to enhance interobserver reproducibility. All corporal biopsy samples obtained from the present study were evaluated for ECL cell hyperplasia using the 8-point ECL cell classification scale [where 0 = normal and 7 = invasive neoplasm (invasive carcinoid); table I].[23,24]

Summaries of gastritis ratings (chronic inflammation, atrophy and intestinal metaplasia) for data obtained at initial and final biopsies were compared for antral and corporal sites. Frequencies of ECL cell ratings from the initial and final biopsies were evaluated, as were frequencies of patients who had normal or an increase (worsening) in ECL cell rating. All patients with moderate or severe atrophy or intestinal metaplasia at any location had their biopsies evaluated for atrophic gastritis. Patients with atrophy or intestinal metaplasia ratings of none or mild were assumed to be negative for atrophic gastritis.

Table I. Enterochromaffin-like cell classification scale[23,24]

Rating	Definition
0	Normal
1	Simple (diffuse) hyperplasia
2	Linear or chain forming hyperplasia
3	Micronodular hyperplasia
4	Adenomatoid hyperplasia
5	Dysplastic changes (precarcinoid)
6	Intramucosal carcinoid
7	Invasive carcinoid

Efficacy Assessments

Evaluating the maintenance of healing of erosive oesophagitis was a secondary objective of this study. An endoscopic evaluation of the oesophagus, stomach and duodenum, including evaluation of erosive oesophagitis using the Los Angeles (LA) classification,[25] was performed at months 6 and 12 to evaluate maintenance of healing of erosive oesophagitis through to month 12. Endoscopy results from the final visits of the healing studies were used as the baseline confirmation of healing in this maintenance study. If esophageal mucosal breaks were present (LA classification grade of A, B, C or D), the patient was considered to have relapsed. The LA classification was chosen because it offers a high degree of interobserver reliability among experienced endoscopists.[26-29]

Because the primary aim of this study was to assess the safety and tolerability of esomeprazole, patients who had oesophageal mucosal breaks (LA classification grade A, B, C or D) at the 6-month endoscopy were continued in the study at the investigators' discretion. Maintenance of healing status at month 12 was summarised for subgroups of patients based on gender, age group (<65 years, ≥65 years), race and initial severity of erosive oesophagitis by LA classification grade at entry into the healing studies. The efficacy summaries included all patients enrolled in the study [intention-to-treat (ITT) population].

Statistical Analysis

The analysis of tolerability and safety included all patients who received at least 1 dose of study treatment, whereas the efficacy population included all patients enrolled in the study (ITT population).

No inferential statistics were planned or performed for the safety analysis, since this was a non-comparative trial. All summary tables and descriptive statistics (number, mean and standard deviation) were generated using the SAS® system. Adverse events were summarised by using descriptive statistics for each event. Laboratory test results were

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also summarised using descriptive statistics for each test by visit, and for the change from baseline in each test by visit, as well as across all visits. Vital signs were summarised by visit and across all visits using descriptive statistics.

Life-table estimates were used to determine the maintenance of healing rate through to months 6 and 12, which accounted for patients whose erosive oesophagitis recurred before month 12 or who otherwise did not remain in the study through to month 12. Although patients who had recurrence of erosive oesophagitis at month 6 could continue in the study, calculations of maintenance of healing rates considered these patients as recurred from month 6, even if their erosive oesophagitis was again healed at month 12.

Results

Patient Characteristics

A total of 808 patients were enrolled in this trial and thus eligible for the ITT analyses. One patient withdrew from the study before taking a single dose of study medication and was therefore excluded from the safety and tolerability analyses. Of the 807 patients who received study medication, 653 patients (80.9%) completed 6 months of treatment and 618 patients (76.6%) completed 12 months of treatment and had an endoscopy performed at month 12. Patient demographics and baseline characteristics are summarised in table II. Most patients were male, Caucasian, *H. pylori*-negative and had experienced GORD symptoms for more than 1 year. 30% of all patients were classified as LA grade C or grade D at initial screening of the healing studies. Patients found to be *H. pylori*-positive were not eligible for inclusion in the healing or safety studies. However, 16 patients (2.0%) who were *H. pylori*-negative by serology at the start of the healing trials were included in the safety trial and were subsequently determined to be *H. pylori*-positive when analysis of the biopsy samples taken at the initial endoscopy trials was completed. Data from these patients were included in this study and their data are included in all summaries of both efficacy and safety.

Table II. Patient demographics (n = 808)

Characteristic	Value [n (%)]
Male gender	503 (62.3%)
Age	
range (y)	18-81
mean [y (SD)]	46.7 (13.5)
<65	714 (88.4%)
Race	
Caucasian	763 (94.4%)
Black	27 (3.3%)
Asian	5 (0.6%)
other	13 (1.6%)
GORD history[a]	
<1 year	40 (5.0%)
1-5 years	342 (42.3%)
>5 years	426 (52.7%)
***Helicobacter pylori* status (by histology)**[a]	
missing	1 (0.1%)
negative	791 (97.9%)
positive	16 (2.0%)
Los Angeles classification[a]	
grade A	275 (34.0%)
grade B	291 (36.0%)
grade C	185 (22.9%)
grade D	57 (7.1%)

a At baseline of the antecedent healing studies.

GORD = gastro-oesophageal reflux disease; **SD** = standard deviation.

Safety and Tolerability

Clinical Adverse Events

A total of 44 patients (5.5%) reported serious adverse events, none of which was judged by the investigator to be treatment-related. The most frequently reported serious adverse event was overdose (reported by 9 patients); on no occasion were any symptoms related to the overdose reported. There was 1 fatality in this study (pancreatic cancer), which occurred 77 days after the patient withdrew from the study. Adenocarcinoma was diagnosed in this patient on day 121 of maintenance treatment with esomeprazole (the patient had previously received esomeprazole 20mg once daily for 32 days in the healing study). However, the

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Table III. Adverse events reported in ≥5% of 807 patients treated with esomeprazole 40mg once daily for up to 1 year irrespective of causal link to treatment

Adverse event	Incidence (% of patients)
Respiratory infection	13.0
Headache	10.3
Sinusitis	9.8
Diarrhoea	9.4
Abdominal pain	9.3
Accident or injury	7.2
Gastritis[a]	6.8
Nausea	6.1
Back pain	5.9

a Based on visual observation at endoscopy evaluation.

investigator considered the causality unlikely to be related to the study medication.

The most frequently reported adverse events, occurring in at least 5% of patients during the 12-month study period, are shown in table III. The most frequently reported adverse events occurring after 6 and 12 months of treatment were similar to those reported after 1 month of treatment in this study. The only treatment-related adverse events occurring in more than 3% of patients were diarrhoea, abdominal pain, flatulence and headache.

61 patients (7.6%) discontinued study treatment because of adverse events. The adverse events most frequently associated with treatment discontinuation were nausea, abdominal pain and flatulence. With the exception of discontinuation because of gastrointestinal disturbances (21 patients), there was no apparent pattern observed among the adverse events resulting in treatment discontinuation. In 6 patients treatment was discontinued because of laboratory changes; 5 patients had an increased ALT value and 1 had a decreased white blood cell count. All 5 patients who discontinued treatment because of increased ALT values had increased values at study entry. The 1 patient who discontinued treatment because of low white blood cell count (recorded by investigator as possibly related to treatment) was subsequently diagnosed with leukaemia (not considered to be treatment-related) based on a bone marrow biopsy.

There was 1 report of angioedema and 2 reports of urticaria, all of which resolved during continued treatment with esomeprazole 40mg. One patient had hepatitis A, 1 had hepatitis C and 1 had primary biliary cirrhosis, none of which was attributed to the study drug. Rash/erythematous rash was reported in 20 patients during the course of the trial; the rash resolved in 18 patients despite continuing treatment, and study drug was discontinued in 2 patients.

Clinical Laboratory Observations

Most of the mean changes in laboratory measurements were small and not clinically meaningful (table IV). The largest mean maximum increases were seen in alkaline phosphatase, ALT, and AST levels (increases of 7 to 11 U/L or 15 to 38% from baseline); these changes were not consistent over the course of the study and were attributable to large changes in a small number of patients rather than a population-wide trend. No clinically meaningful mean changes from baseline to last measurement were noted for serum iron or vitamin B_{12} lev-

Table IV. Mean change from baseline in clinical laboratory measurements at 1, 6, and 12 months after start of treatment with esomeprazole 40mg once daily

Measurement and unit	Mean baseline value[a]	Mean change from baseline (number of patients with complete data)		
		month 1	month 6	month 12
Alkaline phosphatase (U/L)	71.63	3.00 (760)	3.03 (701)	1.61 (594)
ALT (SGPT) [U/L]	29.68	2.31 (760)	–0.45 (658)	–1.29 (594)
AST (SGOT) [U/L]	22.91	0.45 (760)	–0.11 (658)	–0.47 (594)
Serum iron (μg/dl)	87.98	–2.51 (724)	–1.95 (671)	0.08 (604)
Serum vitamin B_{12} (ng/L)	462.64	–0.94 (751)	–13.03 (653)	–10.02 (588)
Serum gastrin (ng/L)	77.34	44.90 (711)	21.59 (624)	39.41 (562)
Haemoglobin (g/dl)	14.24	0.22 (749)	–0.14 (646)	0.01 (584)

a Final visit of the antecedent healing trials.

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Table V. Individual laboratory findings outside predefined limits in 807 patients receiving esomeprazole 40mg once daily for 12 months

Measurement	Predefined limit	Number of patients outside limit		
		at any time point during the study	at baseline[a]	at final visit
ALT (SGPT)	>144 U/L	16	7	9
AST (SGOT)	>126 U/L	11	3	6
Serum iron	<25 μg/dl	27	2	12
Serum vitamin B_{12}	<160 ng/L	19	1	8
Haemoglobin	<9.5 g/dl (females) or <11.5 g/dl (males)	11	5	8

a Final visit of the antecedent healing trials.

els. Over the entire study period, individual laboratory tests showed that ALT, AST, haemoglobin, serum vitamin B_{12} and alkaline phosphatase levels or white blood cell counts shifted from within to outside the normal range in 3 to 15% of all patients; 2 to 10% of all patients had values outside the normal range at baseline. However, because these values represent values recorded for each patient across ≤5 separate measurements taken during the 1-year treatment period, changes may be attributable to normal intrapatient variation. At 12 months, only 1.5 to 2.3% of patients had a shift in serum iron, serum vitamin B_{12} or haemoglobin levels or white blood cell count to below normal.

Only 6 patients (5 with increased ALT values and 1 with a decreased white blood cell count) discontinued treatment because of a potentially clinically significant laboratory change. All 5 patients with high ALT values had potentially clinically significant ALT values at baseline.

As expected, the mean serum gastrin level increased as compared with baseline (the final visit of the healing trials) and generally reached a plateau after 3 months of treatment. Patients enrolled in this safety study had been treated with esomeprazole (40 or 20 mg) or omeprazole (20mg) once daily in the antecedent healing trials, so the baseline gastrin value in this study constitutes a mean value from patients who had been receiving any of these treatments. Mean serum gastrin values fluctuated greatly over the course of this study. Increases in mean serum gastrin level during treatment with esomeprazole 40mg ranged from a low of 21.6 ng/L, which occurred at month 6, to a high of 80.9 ng/L, which occurred at month 9 (not the final visit). A considerable intraindividual variation was also observed during this 12-month safety trial.

A small number of patients had individual laboratory findings that were potentially clinically meaningful (above or below predefined values) at some time point after baseline (defined as the final visit of the preceding healing trial) [see table V]. Of those with abnormal values at any time point, about half had an abnormal value at the final measurement, and many of those with abnormal findings at the final measurement also had abnormal findings at initial evaluation.

Histopathology

About 20% of patients had a missing biopsy sample (136 samples from the baseline or final visit) because of problems with evaluating the tissue sample (e.g. inadequate biopsy sample size) or because the procedure was not done. Therefore, baseline and final visit samples from the antrum of 657 patients and from the corpus of 661 patients were evaluated. The effect of long term treatment with esomeprazole on the gastric mucosa will be published in detail in the future (only an abstract is currently published[30]). The major trends are presented here.

Enterochromaffin Cells

Eleven patients had non-normal ECL cell findings at initial biopsy (start of the healing trial). Final biopsies of these 11 patients were either normal (n = 9) or missing (n = 2). 42 patients had non-normal ECL cell findings at the final visit; 38 of these patients had normal ratings at baseline and 4 lacked baseline values. Among the non-normal findings, 39 patients had simple hyperplasia, 2 had linear

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hyperplasia and 1 had micronodular hyperplasia. None of the patients with an increased (worsening) score had non-normal findings rated higher than 3 (micronodular hyperplasia) on the 7-point rating scale. No patient was found to have ECL cell dysplasia or intramucosal/invasive neoplasm.

Gastritis Ratings

Gastric biopsy evaluation showed an overall decline in chronic inflammation and atrophy in the antrum and corpus, whereas intestinal metaplasia findings remained essentially unchanged. Less than 3.5% of patients showed an increase in inflammation. A total of 25 biopsies in 19 patients had ratings of moderate or severe atrophy or intestinal metaplasia at any location, making them eligible for evaluation for the presence of atrophic gastritis. Two patients (0.1%) were found to have atrophic gastritis; 1 of these patients had atrophic gastritis at both the baseline and final biopsy. Both patients were *H. pylori* negative.

No differences were seen in the subgroup of 16 patients who were *H. pylori*-positive at baseline biopsy versus the study group as a whole. No patients who were *H. pylori*-negative at baseline were *H. pylori*-positive at their final biopsy.

Efficacy

Life-table estimates of maintenance of healing of erosive oesophagitis indicated that 93.7% of patients maintained healing at month 6 and 89.4% of patients maintained their healed status at month 12 (table VI). In addition, 22 of 27 patients (81.5%) who demonstrated a relapse of erosive oesophagitis at month 6 continued with therapy and were healed at 12 months. No clinically relevant differences in the number of patients who maintained healing of erosive oesophagitis were observed when gender, age, race or initial LA classification grade was considered. Daily treatment with esomeprazole 40mg once daily for up to 1 year therefore appears to be effective in maintenance of healing in patients with previously healed erosive oesophagitis irrespective of baseline characteristics, consistent with observations from controlled studies.[31,32]

Table VI. Life table estimates of maintained healing of erosive oesophagitis with esomeprazole 40mg once daily (n = 808; intention-to-treat population)

Time (months)	Maintained healing rate (%)	95% Confidence interval (%)
6	93.7	92.0 to 95.5
12	89.4	87.0 to 91.7

Discussion

This clinical trial demonstrates that long term treatment with esomeprazole 40mg is well tolerated in a large number of patients for up to 1 year. No serious adverse events or deaths related to esomeprazole were reported in the 807 patients treated in the current study. Changes in serum transaminase, white blood cell counts, haemoglobin, and serum vitamin B_{12} levels were seen in only a small number of patients and did not contribute to a pattern that signaled a safety concern. Overall, the adverse event profile of esomeprazole was similar to that previously reported for other PPIs[1,33,34] and did not differ from that reported in shorter 8- to 26-week trials of the drug.[19,20,31,32]

As with antisecretory therapy in general, acid suppression with esomeprazole resulted in increases in serum gastrin level. However, changes showed considerable intra- and interpatient variability over the study.

Historically, concerns have been raised regarding the safety of long term therapy with PPIs, especially with regard to the effects of prolonged acid suppression, which was thought to lead to hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids. The magnitude of hypergastrinaemia associated with the administration of PPIs is comparable to that observed after vagotomy and is much lower than that observed in patients with pernicious anaemia.[35] All current evidence suggests that the increases in serum gastrin level observed during PPI therapy are expected as a physiological response to acid inhibition and appear to be clinically unimportant.[14,35-37] In the current study, increases in serum gastrin level were seen as expected and reached a

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plateau after 3 months of therapy with esomeprazole 40mg.

Although proliferation of gastric ECL cells may occur as a result of increases in serum gastrin level, this is not thought to be clinically significant even during long term therapy with PPIs.[36,37] A recent literature review found no evidence that long term acid suppression with PPIs induced ECL cell neoplastic changes, although gastric ECL cell hyperplasia has been reported. There is no documentation of gastric cancer or multifocal atrophic gastritis that has led to gastric adenocarcinoma as a result of chronic PPI therapy.[15] There is, however, no doubt that some stimulation of ECL cells does occur as a result of acid suppression, as reflected in increased levels of chromogranin A in patients treated with omeprazole.[38] In the present study, changes in gastric ECL cells were hyperplastic only and were observed in the minority of patients. No patient developed ECL cell dysplasia or carcinoids and there were no clinically meaningful changes in gastritis ratings. There were no cases of treatment-emergent gastric intestinal metaplasia, dysplasia or adenocarcinoma. One case of atrophic gastritis emerged during the 12-month study period; there was insufficient data available on this patient to draw conclusions regarding the relationship of the atrophic gastritis to the study drug.

It has been proposed that diminished serum iron and serum vitamin B_{12} absorption can occur as a result of acid inhibition during long term treatment with PPIs. These reductions in absorption do not appear to be of clinical importance, since deficiency states are rarely reported and those that are reported have an uncertain relationship with acid-suppressive therapy.[36,39] Although diminished serum vitamin B_{12} levels have been reported in a small minority of patients receiving long term continuous PPI therapy, most of these patients maintained levels that were considered within normal limits.[11,12,40,41] Furthermore, in patients with GORD who were randomised to continuous treatment with omeprazole or anti-reflux surgery, no difference was observed in vitamin B_{12} values during a 5-year study period.[42] As the body stores considerable amounts of vitamin B_{12}, deficiency would not be expected to appear in a 12-month trial and is unlikely to occur during long term PPI treatment.

Conclusion

The data in the current trial demonstrate that long term acid suppression with esomeprazole 40mg once daily was well tolerated and effective for maintaining healing of erosive oesophagitis, and that no issues relating to the safety of the drug were detected. The adverse event profile of esomeprazole is similar to that previously reported for omeprazole.

Acknowledgements

Both Paul N. Maton and Nimish B. Vakil have acted as consultants to AstraZeneca. This manuscript was prepared with the assistance of Eileen Gallagher and resources from AstraZeneca.

An abstract of this study was presented at Digestive Disease Week 2000 in San Diego, CA, May 21-24.

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