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Original Research Article

Esomeprazole versus omeprazole for the eradication of *Helicobacter pylori* infection

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ABSTRACT

Background: Proton pump inhibitors (PPIs) are one of the most commonly used classes of drugs. Though, the quantum clinical benefit of newer and more expensive PPIs over the older generation PPIs residues undefined. The present meta-analysis ought to assess the safety and clinical profiles of esomeprazole versus omeprazole at pharmacologically equivalent doses in healing gastroesophageal reflux disease (GERD), peptic ulcer disease and eradicating *Helicobacter pylori* infection.
Methods: PubMed and the Cochrane Library were searched for randomized controlled trials comparing esomeprazole with omeprazole at all doses up to July 2017. Meta-analysis was conducted using a random effects model, and heterogeneity in the estimated effects was investigated using meta-regression.
Results: Eleven trials were included and none of which compared esomeprazole with omeprazole in peptic ulcer disease. In gastroesophageal reflux disease, esomeprazole 40 mg (relative risk (RR) = 1.11; 95% confidence interval (CI) 1.14 to 1.23) and 20 mg (RR=1.08; 95% CI 1.02 to 1.12) significantly improved esophagitis healing when compared with omeprazole 20 mg at week 8. In *H. pylori* eradication, there was no difference in the treatment effects between esomeprazole 20 mg and omeprazole 20 mg (RR = 1.05;95% CI 1.01 to 1.11).
Conclusions: Esomeprazole established better esophagitis healing rate in patients with GERD than omeprazole at week 8. Though, this clinical advantage reduced when both drugs were given at the same doses at week 4. Superiority of esomeprazole was not perceived in the *H. pylori* eradication rates.

Keywords: Proton pump inhibitors, Esomeprazole, *Helicobacter pylori*, Omeprazole

INTRODUCTION

Proton pump inhibitors (PPIs) suppress gastric acid secretion by inhibiting hydrogen-potassium adenosine triphosphatase that transports acid from gastric parietal cells into the gastroesophageal lumen. They are specified for the treatment of acid-related diseases, for example, peptic ulcer disease (PUD), gastroesophageal reflux

disease (GERD) and *Helicobacter pylori* (*H. pylori*) eradication in combination with antibiotics. PPIs are one of the most commonly prescribed classes of drug. The new generation PPIs containing esomeprazole, dexlansoprazole and rabeprazole are intended to have better clinical efficacy and bioavailability than early generation omeprazole.[1]

Though, indication comparing efficacy of these drugs with the older generation or between different dosing regimens has been varying with regard to symptom resolution, esophagitis healing, and *H. pylori* eradication. Moreover, many of these trials were commissioned by pharmaceutical company and had compared doses of PPIs licensed by the United States Food and Drug Administration rather than pharmacologically equivalent doses that are used in the real world. Omeprazole, the first in PPI drug class, contains a racemic compound of which only the S-enantiomer is active, while the R enantiomer is not. Esomeprazole contains only the purified S-enantiomer and has been reported to have enhanced bioavailability of 68% compared with omeprazole (60%) at 20 mg, dose for dose.[2] This explains better and longer acid suppression and has been suggested to be the basis for improved clinical efficacy.[3] Regardless of the advantage in bioavailability, comparative studies between omeprazole and esomeprazole have displayed conflicting data with some meta-analyses presented a small while significant advantage in esophagitis healing, while other studies indicated no significant difference in effectiveness.[4,5]

This clearly would have a big influence on cost difference where healthcare delivery system in every country is pressed to adopt innovative and new health technologies in an evidence-based manner, while making sure that they can be managed within obtainable resources. It similarly requests the question whether certain acid-related disease groups would benefit particularly from the benefit of esomeprazole and explain its high cost. Thus, we performed a meta-analysis that comprised the most recent head-to-head trials to determine the efficacy and safety of omeprazole compared with esomeprazole at all doses.

METHODS

Search strategy

A systematic search of PubMed and the Cochrane Library was conducted up to July 2017 to recognize relevant trials. We also searched for additional trials included in published systematic reviews and bibliographies of all relevant studies.

Study selection and eligibility criteria

Two reviewers screened abstracts according to predefined study inclusion criteria. Full text articles (published in English) were retrieved and reviewed if a decision on inclusion could not be made solely based on the abstract. Any disagreements were resolved by consensus between the two reviewers. We included head-to-head randomized controlled trials (RCTs) which compared oral esomeprazole with oral omeprazole, in any dose, in the management of GERD or peptic ulcer disease. The study participants were adults aged 18 years and above who had GERD, peptic ulcer disease or *H. pylori* infection. The outcomes of interest included resolution of GERD-related symptoms, esophagitis healing, peptic ulcer healing, H. pylori eradication, quality of life and adverse effects. Studies that involved specific patient groups (e.g. elderly), reported only intragastric acidity or pH measurement, and of which the PPIs were used as prophylaxis for NSAID-induced ulcers were excluded.

Data analysis

We performed meta-analyses of outcomes as appropriate by combining trials based on a random effects model in Stata software, version 13.0. Outcomes were summarized as relative risks (RR) with 95% confidence intervals (CI). We also calculated number needed to treat (NNT) from risk difference. Statistical heterogeneity between trials was evaluated using chi-square test at a significance level of $p<0.1$ and I^2 statistic. The value of I^2 statistic ranges from 0% to 100%, with 0% representing no observed heterogeneity and larger values indicating increasing heterogeneity. A value of I2 below 25% was chosen to represent low heterogeneity.[6] When the P value for the chi-square test was 25%, the heterogeneity would be considered important and meta-regression would be carried out to investigate the heterogeneity where possible. Sensitivity analysis or subgroup analysis was performed to test the robustness of the results and account for any differences in the study level characteristics such as ethnicity, antibiotic regimen and maintenance therapy in *H. pylori* eradication.

RESULTS

We recognized 468 citations using the search strategy. Of these, we excluded 347 after examining the title and abstract including removal of duplicates. We retrieved and evaluated 23 articles in more detail, of which 12 articles were excluded, leaving 11 RCTs that were eligible for inclusion (Figure 1).[7-17]

Of the 11 studies included, five studies were related to GERD and six on *H. pylori* infection.[7-17] We did not classify any studies that directly compared esomeprazole and omeprazole in peptic ulcer disease. Six of the GERD studies were conducted in patients with endoscopically confirmed reflux esophagitis (RE), while the remaining one in patients with endoscopy-negative reflux disease (ENRD).[7-11,17] Tables 1 and 3 summarized the characteristics and main results of these studies. There were five studies comparing esomeprazole with omeprazole in combination with standard antibiotics for

H. pylori treatment.[7-11] Table 2 summarized the characteristics and main results of these studies.

The primary outcomes of the studies evaluating RE were the proportion of patients who achieved endoscopically confirmed healing and the proportion who achieved complete resolution of GERD-related symptoms at week 8. Secondary outcomes included esophagitis healing and symptom relief at week 4. The primary endpoint of the study evaluating ENRD was the proportion of patients with complete resolution of heartburn as defined by no heartburn episodes during the previous seven consecutive days. In all of these studies, symptom relief was assessed subjectively by investigator or patients.

Esophagitis healing rates: We meta-analysed the esophagitis healing rates at week 4 and week 8. The RRs for esomeprazole 40 mg and 20 mg compared with omeprazole 20 mg at week 8 were 1.11 (95% CI 1.14 to 1.23) and 1.08 (95% CI 1.02 to 1.12), respectively. The calculated risk differences were 6% and 3.3%, which corresponded to NNT of 17 and 30, respectively. At week 4, the RR of esomeprazole 40 mg versus omeprazole 20 mg was 1.13 (95% CI 1.04 to 1.22) and the corresponding NNT was 12. There was no significant difference between esomeprazole 20 mg versus omeprazole 20 mg (based on one study) (Table 4).

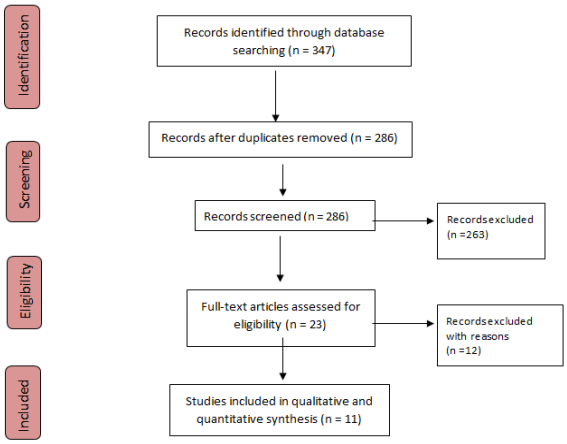

Figure 1: Flow diagram showing the selection criteria of assessed studies.

Table 1: Characteristics and main results of studies evaluating endoscopically confirmed reflux esophagitis.

Study	Year	Treatment arms	N	Healing rate (week 4) by ITT (%)	Healing rate (week 8) by ITT (%)	Heartburn resolution (week 4) (%)	P value
Schmitt[7]	2006	E 40 mg QD	576	68.2%	86.9	64.9	p>0.05
		O 20 mg QD	572	66.3%	85.8	63.1	
Zheng[8]	2009	E 40 mg QD	68	Not reported	91.2	Not reported	p>0.05
		O 20 mg QD	68	Not reported	83.8	Not reported	
Richter[9]	2001	E 40 mg QD	1216	78.6%	89.9	68.3	p<0 05
		O 20 mg QD	1209	66.6%	80.9	58.1	
Lightdale[10]	2006	E 40 mg QD	588	Not reported	86.5	60.5	p>0.05
		O 20 mg QD	588	Not reported	82.3	60.5	
Kahrilas[11]	2000	E 20 mg QD	656	66.5%	83.8	52.4	p>0.05
		E 40 mg QD	654	71.1%	87.5	63.7	p<0 05
		O 20 mg QD	650	61.4%	81.4	57.2	

Table 2: Characteristics and main results of studies evaluating *H. pylori* infection.

Study	Year	Treatment arms	Antibiotics	Treatment duration	Eradication rates by ITT (%)
Veldhuyzen[12]	2003	E 20 mg BID	Metronidazole 500 mg BID Clarithromycin 500 mg BID	7 days+3 weeks maintenance	75.8
		O 20 mg BID			72.5
Subei[13]	2007	E 20 mg BID	Amoxicillin 1 g BID Clarithromycin 500 mg BID	7 days+3 weeks maintenance	74.7
		O 20 mg BID			78.7
Sheu[14]	2005	E 40 mg BID	Amoxicillin 1 g BID Clarithromycin 500 mg BID	7 days	86,00
		O 20 mg BID			79,00
Choi[15]	2007	E 40 mg BID	Amoxicillin 1 g BID Clarithromycin 500 mg BID	7 days	70.3
		O 20 mg BID			65,00
Anagnostopoulos[16]	2004	E 40 mg QD	Amoxicillin 1 g BID Clarithromycin 500 mg BID	7 days	81,00
		E 40 mg BID			96.2
		O 20 mg BID			71,00

Table 3: Characteristics and main results of study evaluating endoscopy-negative reflux disease.

Study	Year	Treatment arms	N	Percentage of patients with heartburn resolution at week 4 (95% CI)
Armstrong[17] (study A)	2004	E 40 mg QD	425	56.7 (52–62)
		E 20 mg QD	423	60.5 (52–62)
		O 20 mg QD	434	58.1 (53–63)
Armstrong[17] (study B)	2004	E 40 mg QD	347	70.3 (65–75)
		O 20 mg QD	346	67.9 (63–73)
Armstrong[17] (study C)	2004	E 20 mg QD	336	61.9 (57–67)
		O 20 mg QD	334	59.6 (54–65)

Table 4: Forest plot demonstrating the relative risk (RR) with 95% confidence interval (CI) of esophagitis healing rates of esomeprazole 40 mg and 20 mg compared with omeprazole 20 mg once daily at week 4.

Study	Year	RR (95% CI)	Weight (%)
Esomeprazole 40 mg			
Kahrilas	2000	1.16 (1.07, 1.25)	23.69
Richter	2001	1.18 (1.12, 1.24)	30.29
Schmitt	2006	1.03 (0.95, 1.12)	23.11
Subtotal (I-squared=75.2%, p=0.018)		1.13 (1.04, 1.22)	77.09
Esomeprazole 20 mg			
Kahrilas	2000	1.08 (1.00, 1.17)	22.91
Subtotal (I-squared=NA%, p=NA.)		1.08 (1.00, 1.17)	22.91
Overall (I-squared=68%, p=0.025)		1.12 (1.05, 1.19)	100.0

Esophagitis healing rates: We meta-analysed the esophagitis healing rates at week 4 and week 8. The RRs for esomeprazole 40 mg and 20 mg compared with omeprazole 20 mg at week 8 were 1.11 (95% CI 1.14 to 1.23) and 1.08 (95% CI 1.02 to 1.12), respectively. The calculated risk differences were 6% and 3.3%, which corresponded to NNT of 17 and 30, respectively. At week 4, the RR of esomeprazole 40 mg versus omeprazole 20 mg was 1.13 (95% CI 1.04 to 1.22) and the corresponding NNT was 12. There was no significant difference between esomeprazole 20 mg versus omeprazole 20 mg (based on one study) (Table 4).

Three of the RE studies reported the proportion of patients with heartburn resolution at week 4.[7,9,11] The heartburn resolution rate ranged from 64% to 68% for patients on esomeprazole 40 mg and 57% to 63% for those on omeprazole 20 mg. Meta-analysis for the rate of heartburn resolution was not performed given that the definition of this endpoint differed among the studies. Only one study evaluating ENRD was included.[17] In this study, esomeprazole 40 mg and 20 mg were compared with omeprazole 20 mg once daily for 4 weeks in symptomatic patients with ENRD. There was no significant difference in the proportion of patients who achieved heartburn resolution among the groups.

The eradication rate related with esomeprazole (regardless of dose) ranged from 70% to 96%, whereas that for omeprazole ranged from 65% to 88%. The RRs for esomeprazole 40 mg and 20 mg compared with omeprazole 20 mg twice daily were 1.21 (95% CI 1.13 to 1.29) and 1.05 (95% CI 1.01 to 1.11), respectively. Heterogeneity was observed in the analysis of esomeprazole 40 mg dose (I^2=49%, p=0.13). However, meta-regression analysis could not be performed due to insufficient number of studies.

DISCUSSION

The present meta-analyses clarifies that esomeprazole 40 mg and 20 mg were statistically more effective than omeprazole 20 mg once daily for esophagitis healing at 8 weeks in patients with GERD. Though, the difference was marginal, with the lower bound of CI approaching 1.0. The corresponding NNT was also not promising. According to a Cochrane systematic review that compared PPIs with H2-receptor antagonists and placebo in the treatment of esophagitis, PPI was associated with a NNT of three and two, respectively.[18,19] Esomeprazole 20 mg did not significantly improve the esophagitis healing at week 4. This recommended that esomeprazole would have limited clinical benefit over omeprazole if the duration of PPI treatment was 4 weeks.

When used in combination with antibiotics for *H. pylori* eradication, a statistically significant difference was perceived between esomeprazole 40 mg and omeprazole 20 mg, however, the present analysis was allied with significant heterogeneity and a lower bound CI approaching 1.0. There was no significant difference in efficacy between esomeprazole 20 mg and omeprazole 20 mg. Given that esomeprazole is the active isomer, it is expected that esomeprazole would achieve more potent

antisecretory activity than omeprazole on milligram basis and result in better efficacy. Though, our analysis showed that the efficacy of esomeprazole and omeprazole did not differ significantly in achieving *H. pylori* eradication when combined with antimicrobial agents (amoxicillin and clarithromycin or clarithromycin and metronidazole) as a standard triple therapy. This was probable as a result of the fact that the extent of bacterial susceptibility to antimicrobial agents contributes to the *H. pylori* eradication and that the necessary level of acid inhibition for *H. pylori* eradication within a standard triple therapy could be achieved with either omeprazole or esomeprazole. It was notable that omeprazole 20 mg was inferior to esomeprazole 20 mg in the absence of omeprazole maintenance therapy. However, these outcomes were derived from the meta-analysis of only two studies. The rate of adverse effects was commonly greater in studies on GERD than *H. pylori* eradication, which implied that the treatment duration correlated to incidence of adverse effects. Treatment with esomeprazole was related with higher rates of adverse effects such as abdominal pain and headache than omeprazole. Nevertheless, the difference did not reach statistical significance. Generally, both drugs demonstrated similar safety profiles.

The present meta-analyses distinguished itself from previous reviews by comprising most recent comparative trials of esomeprazole and omeprazole. Majority of the previous systematic reviews comparing PPIs in the management of GERD were supported by industry.[20,21] These studies assessed the effects of esomeprazole 40 mg versus other PPIs and reported that esomeprazole was superior in healing esophagitis. Furthermore, the treatment difference between esomeprazole at 20 mg and other PPIs was not investigated. In the present meta-analyses study, a rigorous and systematic search strategy was applied, which provides more robust results. To provide a realistic comparison given that esomeprazole is the active enantiomer of omeprazole, which is akin to omeprazole at double dose, we evaluated the effectiveness of esomeprazole versus omeprazole on pharmacologically comparable doses. As esomeprazole is the active enantiomer of omeprazole, it would be more rational to compare omeprazole 40 mg with esomeprazole 20 mg. Though, there were no available clinical studies that compared omeprazole 40 mg with esomeprazole. A potential research area would be to compare the effectiveness of omeprazole 40 mg with esomeprazole in treating gastroesophageal reflux disease.

CONCLUSION

Esomeprazole provided a statistically significant but marginal degree of improvement in esophagitis healing when compared with omeprazole. Though, this clinical benefit in patients with gastroesophageal reflux disease reduced when the treatment duration was within 4 weeks. There was no difference in the *H. pylori* eradication rates when esomeprazole and omeprazole were given at the same doses. Based on our analysis, it is practical to consider other factors such as the cost of treatment, severity of esophagitis, bacterial susceptibility to antimicrobial agents and variation in CYP2C19 genotype when prescribing these agents to patients with GERD or *H. pylori* infection.

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