GI café

May 2017 Volume : 10 Issue : 1

SQUARE PHARMACEUTICALS LTD. BANGLADESH

Effectiveness Of Esomeprazole in Gastroesophagealreflux Disease and *Helicobacter pylori* Infection: The Results of a Meta-analysis

Proton pump inhibitors (PPIs) suppress gastric acid secretion by inhibiting hydrogen-potassium adenosine triphosphatase (H+K+ ATPase, also known as proton pump) that transports acid from gastric parietal cells into the gastroesophageal lumen. They are indicated for the treatment of acid-related diseases such as gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD) and *Helicobacter pylori (H. pylori)* eradication in combination with antibiotics. PPIs are one of the most frequently prescribed classes of drug worldwide. In fact, esomeprazole was the top-selling single agent based on non-discounted price in the United States (USD$6 billion) and ranked 4th in the top 20 drug list by sales (USD$7.5 billion) in the global market in 2012. The new generation PPIs including esomeprazole, rabeprazole and dexlansoprazole are designed to have better bioavailability and clinical efficacy than early generation omeprazole. However, evidence comparing efficacy of these drugs with the older generation or between different dosing regimens has been inconsistent in relation to esophagitis healing, symptom resolution and *H. pylori* eradication. Furthermore, 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, consists of a racemic compound of which only the S-enantiomer is active, whereas the R enantiomer is not. Esomeprazole contains only the purified S-enantiomer and has been reported to have improved bioavailability of 68% compared with omeprazole (60%) at 20 mg, dose for dose. This translates into better and longer acid suppression and has been proposed to be the basis for enhanced clinical efficacy. Despite the advantage in bioavailability, comparative studies between esomeprazole and omeprazole have shown conflicting data with some meta-analyses presented a small although significant benefit in esophagitis healing, whereas other studies indicated no significant difference in efficacy. This obviously would have a big impact on cost difference where healthcare delivery system in every country is pressed to adopt new and innovative health technologies in an evidence-based manner, although ensuring that they can be managed within available resources. Therefore, this analysis performed a systematic review and meta-analysis that included the most recent head-to-head trials to determine the efficacy and safety of esomeprazole compared with omeprazole at all doses.

METHODS

Search strategy

A systematic search of PubMed and the Cochrane Library was conducted up to February 2015 to identify relevant trials. The Cochrane Collaboration's sensitivity and precision-maximizing strategy using the following medical subject headings (MeSH), concepts and/or text words in various combinations was applied: gastroesophageal reflux, peptic ulcer, duodenal ulcer, gastric ulcer, *Helicobacter pylori,* omeprazole and esomeprazole. Also searched for were additional trials included in published systematic reviews and bibliographies of all relevant studies.

Study selection and eligibility criteria

Two reviewers (MT and LL) 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. 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 were included. 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.

Outcome assessment

The outcome measures for efficacy were esophagitis healing rate and heartburn resolution rate in patients with GERD, and peptic ulcer healing rate and *H. pylori* eradication rate in patients with peptic ulcer disease. Outcomes derived from intention-to-treat (ITT) analyses were included. For safety, we analysed adverse effects associated with treatments.

Data collection and risk of bias assessment

Data regarding study design, country, patient characteristics, dose and delivery of esomeprazole and omeprazole, duration of treatment, outcomes and funding source were extracted into evidence tables. Risk of bias was assessed for each included study using the Cochrane Collaboration risk of bias tool based on six domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome and selective outcome reporting. Other potential source of bias such as sponsorship of the study was also taken into consideration. Judgment on the risk of bias was made for each domain and categorized as high, low or unclear.

Data analysis

Meta-analyses of outcomes as appropriate by combining trials based on a random effects model in Stata software, version 13.0 (StataCorp LP, College Station, TX, USA) were performed. Outcomes were summarized as relative risks (RR) with 95% confidence intervals (CI). We also calculated number needed to treat (NNT) from risk difference (absolute risk reduction).

Statistical heterogeneity between trials was evaluated using chi-square test at a significance level of $P < 0.1$ and I2 statistic. The value of I2 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. When the P-value for the chi-square test was <0.1 and I2 statistic >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

Search results

468 citations were identified using the search strategy. Of these, excluded 439 after examining the title and abstract including removal of duplicates. Finally 29 articles were retrieved and evaluated in more detail, of which 14 articles were excluded, leaving 15 RCTs that were eligible for inclusion (Fig. 1).

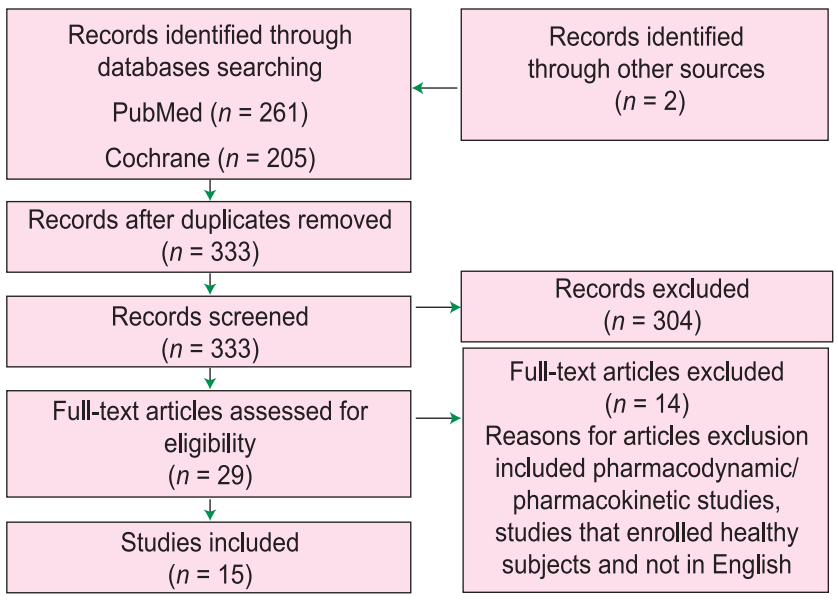

Fig. 1. Study flow diagram illustrating the study selection process.

Study characteristics

Of the 15 studies included, seven studies were related to GERD 1and eight on *H. pylori* infection. The team did not identify 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), whereas the remaining one in patients with endoscopy-negative reflux disease (ENRD). There were 6893 patients included in the GERD trials. The mean age of subjects ranged from 45 to 58 years old. Based on the Los Angeles (LA) classification system that categorized the severity of erosive esophagitis, the proportion of patients with grades A, B, C and D erosive esophagitis were 34%, 39%, 20% and 7%, respectively. Tables 1 and 2 summarized the characteristics and main results of these studies.There were eight studies comparing esomeprazole with omeprazole in combination with standard antibiotics for *H. pylori* treatment. A total of 2598 subjects were included. The mean age of patients ranged from 39 to 59 years old. Three studies compared esomeprazole 40 mg, whereas the other five evaluated esomeprazole 20 mg with omeprazole 20 mg twice daily. Table 3 summarized the characteristics and main results of these studies.

Risk of bias assessment

For the GERD trials, most of them clearly stated the method of randomization, concealment for allocation and blinding of participants. Six trials were funded by manufacturer. For the *H. pylori* trials, majority of them did not provide adequate information on the method used for generating the sequence of randomization, allocation concealment and blinding. Five trials were funded by manufacturer. The risk of bias plots can be found in online.

Esomeprazole versus omeprazole in GERD

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 1.07 (95% CI 1.02 to 1.12) and 1.04 (95% CI 1.01 to 1.08), respectively (Fig. 2).

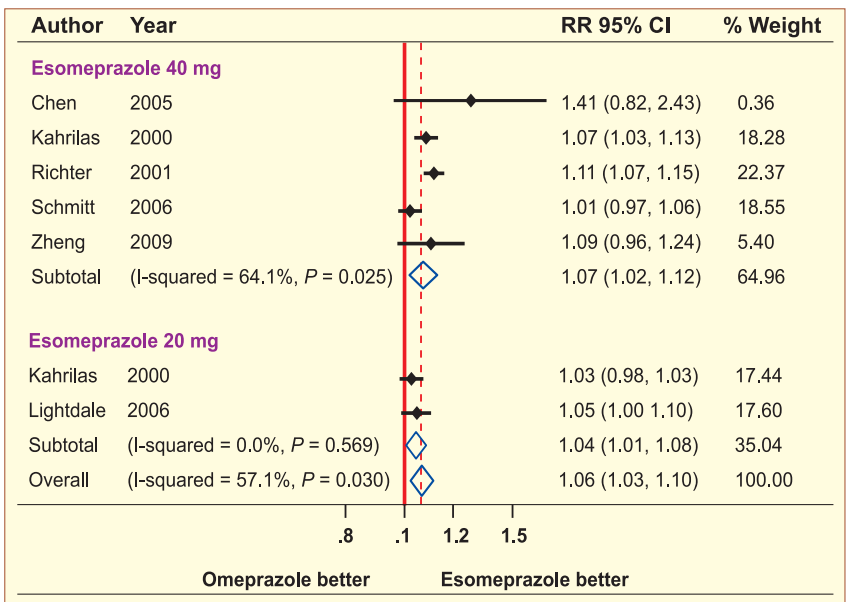

Fig. 2. Forest plot demonstrating the relative risk (RR) with 95% confidence interval (CI) of esophagitis healing rates of esomeprazole 40 mg and 20 mg compared with omeprazole 20 mg once daily at week 8.

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) (Fig. 3).

The results were robust to sensitivity analysis by excluding the study with high risk of performance and detection bias. Heterogeneity was observed in the analyses of esomeprazole 40 mg at week 8 (I2 = 64%, P = 0.025) and week 4 (I2 = 75%, P = 0.018). The meta-regression analysis revealed that the efficacy of esomeprazole versus omeprazole became less pronounced as the proportion of patients with LA grades C and D increased.

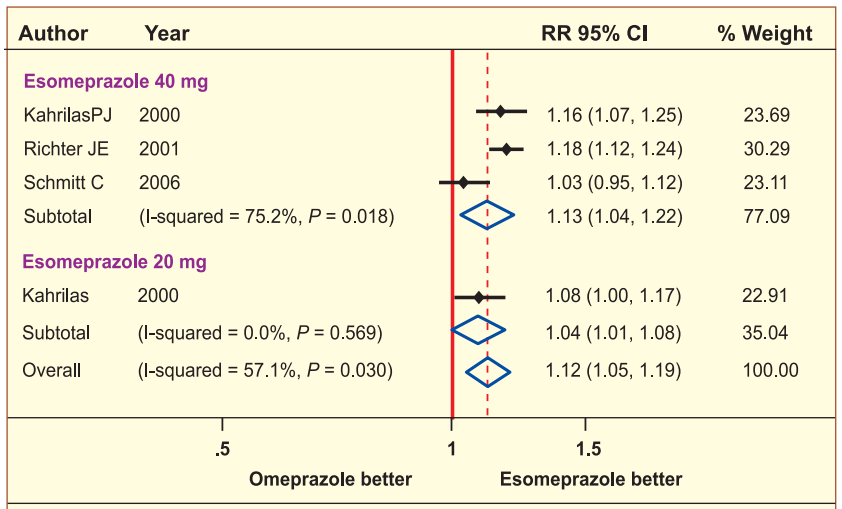

Fig. 3. Forest plot demonstrating the relative risk (RR) with 95% confidence interval (CI) of esophagitis healing rates of esomeprazole 40 mg and 20 mg compared with omeprazole 20 mg once daily at week 4.

Therefore, the statistical heterogeneity could be attributed to the different distribution of patients with specified baseline disease severity according to LA grades across the included studies. This relationship was, however, not statistically significant (P = 0.053 at week 8 and P = 0.216 at week 4). A subgroup analysis by ethnicity showed that esomeprazole 40 mg was not statistically better than omeprazole 20 mg at week 8 (RR=1.11; 95% CI 0.95 to 1.30) among the participants in eastern Asia.

Heartburn resolution rates

Three of the RE studies reported the proportion of patients with heartburn resolution at week 4. 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 ENRD16 was included. 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.

Esomeprazole versus omeprazole in *H. pylori* The treatments in all the eight included studies were the standard 7-day triple-therapy regimen with the co-administered antibiotics being eithe amoxicillin and clarithromycin or metronidazole and clarithromycin. In three studies, omeprazole was continued for another 3 weeks as maintenance monotherapy versus placebo in esomeprazole treatment arm. The primary endpoint of these studies was the *H. pylori* eradication rate at 4–8 weeks as assessed by histology and urea breath test.

Table 1. Characteristics and main results of studies evaluatingendoscopically confirmed reflux esophagitis

Study	Treatment arms	*N*	LA grades of RE (%) (A. B. C. D)	Healing rate (week 4) by ITT *n/N* (%) I *p* value	Healing rate (week 8) by ITT *n/N* (%) I *p* value	Heartburn resolution *n/N* (%) I *p* value
Chen 2005[17]	E 40 mg QD	25	60, 28, 8, 4	Not reported	16 / 25 64 I p > 0.05	Not reported
	O 20 mg QD	23	48,30,9, 13	Not reported	10 / 22 45.5	Not reported
Kahrilas 2000[19]	E 20 mg QD	656	33, 42, 18, 7	436 / 656 66.5 I *p* > 0.05	550 / 656 83.8 I *p* > 0.05	382 / 626 52.4 I *p* > 0.05
	E 40 mg QD	654	36, 39, 18, 7	465 / 654 71.1 I *p* > 0.05	572 / 654 87.5 I *p* > 0.05	402 / 621 63.7 I *p* > 0.05
	O 20 mg QD	650	31, 41, 21, 7	399 / 650 61.4	529 / 650 81.4	357 / 624 57.2
Lightdale 2006[19]	E 20 mg QD	588	38, 35, 21, 6	Not reported	508 / 587 86.5 I *p* > 0.05	356 / 588[a] 60.5 I *p* > 0.05
	O 20 mg QD	588	36, 38, 17, 9	Not reported	484 / 588 82.3	355 / 587[a] 60.5
Rechter 2001[22]	E 40 mg QD	1216	35, 39, 21, 5	955 / 1216 78.6 I *p* > 0.05	1093 / 1216 89.9 I *p* > 0.05	831 / 1216 68.3 I *p* > 0.05
	O 20 mg QD	1209	32, 41, 20, 7	805 / 1209 66.6	978 / 1209 80.9	702 / 1209 58.1
Schmitt 2006[23]	E 40 mg QD	576	32, 35, 25, 8	393 / 576 68.2 I *p* > 0.05	501 / 576 86.9 I *p* > 0.05	374 / 576 64.9 I *p* > 0.05
	O 20 mg QD	572	33, 37, 22, 8	379 / 572 66.3	491 / 572 85.8	361 / 572 63.1
Zheng 2009[29]	E 40 mg QD	68	30, 38, 29, 3	Not reported	62 / 68 91.2 I *p* > 0.05	Not reported
	O 20 mg QD	68	30, 38, 29, 3	Not reported	57 / 68 / 572 83.8	Not reported

E, esomeprazole; O, omeprazole; QD, once daily; LA, Los Angeles grading system; RE, reflux esophagitis; ITT, intention-to-treat.aHeartburn resolution was measured at week 8.

Table 2. Characteristics and main results of study evaluating endoscopy-negative reflux disease.

Heterogeneity was observed in the analysis of esomeprazole 40 mg dose (I2 = 53%, P = 0.12). However, meta-regression analysis could not be performed due to insufficient number of studies.

The results were robust to analysis taking into account the different antimicrobial agents (amoxicillin versus metronidazole). The results of subgroup analysis based on studies that included 3-week omeprazole maintenance therapy and ethnicity were as follows: esomeprazole 20 mg was superior to omeprazole 20 mg when there was no omeprazole maintenance therapy (RR=1.10; 95% CI 1.01 to 1.20) and the treatment difference between esomeprazole 40 mg and omeprazole 20 mg was insignificant among participants from the Eastern Asia (RR=1.09; 95% CI 0.98 to 1.20).

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

E, esomeprazole; O, omeprazole; QD, once daily.

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Safety

The data on adverse effects in all the included studies comprising 9200 patients were pooled. The safety profiles of esomeprazole and omeprazole were generally similar. The pooled estimates of the treatment-associated adverse effects for esomeprazole versus omeprazole were abdominal pain (3.2% vs 2.9%), diarrhea (3.1% vs 3.0%), flatulence (3.2% vs 3.8%) and headache (6.6% vs 5.6%). Meta-analyses of these adverse effects did not reveal any statistically significant differences between esomeprazole and omeprazole.

Reference : Journal of clinical pharmacy and therapeutics 40.4 (2015): 368-375.

Congratulations!

The Winners of GI café Quiz Competition

(November 2016 Volume : 9 Issue : 2)

Dr. Bikash Chandra Nag
MD, FCPS
Prime Diagnostic Centre
Barisal

Dr. Mst. Mosfika Kowsari (Lisa)
MBBS, FCPS (Gynae & Obs.)
Adhunik Sadar Hospital
Chapai Nawabganj, Rajshahi

Dr. Jahedul Islam
MBBS, FCPS
Noakhali Sadar Hospital
Maizdee

Dr. Md. Ferdous
MBBS, FCPS
Metro Plus Diagnostic
Barisal

Dr. Rezaul Karim Mir
MBBS, FCPS
250 Bed Sadar Hospital
Moulvibazar

Editorial Note:

Dear Doctor, It's our immense pleasure to inform you that we have published the first issue, 2017 of *GI Café*. In this issue we try to focus on Effectiveness of esomeprazole in *gastroesophageal reflux disease* and *Helicobacter pylori* infection: The results of a Meta-analysis. Your comments and suggestions will enrich our upcoming issues. Please participate in quiz competition and win prizes.

Executive Editor:
Sarder Fahim Hossain
M. Pharm
Cell: 01755631864
e-mail: fahim.hossain@squaregroup.com