National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

Comparative study of safety and efficacy of omeprazole, lansoprazole, and rabeprazole in triple therapy for eradication of *Helicobacter pylori* in peptic ulcer patients in Indian population

Padmavathi Devagudi[1], Mabu Shareef S[1], Naser Ashraf Tadvi[2]

[1]Department of Pharmacology, Rajiv Gandhi Institute of Medical Sciences, Kadapa, Andhra Pradesh, India, [2]Department of Basic Medical Sciences, College of Medicine, Majmah University, Kingdom of Saudi Arabia

Correspondence to: Mabu Shareef, E-mail: drsharifshaik@gmail.com

Received: September 05, 2016; **Accepted:** September 30, 2016

ABSTRACT

Background: Triple therapy which includes a proton pump inhibitor (PPI) along with two antimicrobials is routinely used for the eradication of *Helicobacter pylori*. Multiple regimens are reported using different combinations of PPIs and antimicrobials. **Aims and Objectives:** The current study is done to compare the efficacy and safety of three PPIs omeprazole, lansoprazole, and rabeprazole in combination with amoxicillin and tinidazole. **Materials and Methods:** The patients were randomly assigned to receive one of the three regimens including one of the PPI with amoxicillin and tinidazole for 2 weeks followed by respective PPI once daily for 4 weeks. Follow-up visits were done at 2 and 6 weeks of the treatment. Endoscopy was done for any decrease in size of ulcer, rapid urease test, and histopathology for clearance of *H. pylori*. **Results:** There was a significant reduction in the size of ulcer at the end of 2 weeks in all the three groups and total healing of ulcer was observed in rabeprazole group when compared to omeprazole and lansoprazole groups. *H. pylori* eradication as per negative urea breath test was between 85% and 94% and it was highest in rabeprazole group. **Conclusion:** The three drugs were safe and equally effective in eradicating *H. pylori,* but rabeprazole showed earlier symptomatic relief with rapid eradication rate of *H. pylori* in peptic ulcer disease compared to omeprazole and lansoprazole, but it was not statistically significant. Hence, rabeprazole can be recommended to be used in PPI-triple therapy for cure of *H. pylori* infection in Indian population for earlier relief and better cure rates.

KEY WORDS: *Helicobacter pylori*; Peptic Ulcer; Rabeprazole

INTRODUCTION

The recognition of *Helicobacter pylori* to be the main etiological factor in the pathogenesis of duodenal ulcer and non-auto-immune gastritis led to therapeutic strategies targeted to eradicate *H. pylori* to prevent recurrences in peptic ulcer disease.[1] Majority of the patients with duodenal ulcer and non-ulcer dyspepsia are colonized with *H. pylori*.[2] Several studies have shown that eradication of *H. pylori* cures duodenal ulcers and prevent relapse. In addition, there is histological resolution of chronic active gastritis after the eradication of *H. pylori*.[3,4] The National Institute of Health Consensus Conference in 1994 concluded that all patients with peptic ulcer disease whether on the first presentation, recurrence, and those on maintenance therapy for a confirmed ulcer should be cured of their infection using an anti-secretory drug combined with anti *H. pylori* antibiotics.[5,6] According to recent international guidelines, the clinical goals for rapid ulcer healing and prevention of relapse can be accomplished by combination therapy

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2017.7.0926330092016	

National Journal of Physiology, Pharmacy and Pharmacology Online 2016. © 2016 Mabu Shareef et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creative commons.org/licenses/by/4.0/), allowing third partiesto copy and redistribute the materialin any medium or for mat and to remix, transform, and build upon the material for any purpose, even commercially, provided the original work is properly cited and states its license.

consisting of an anti-secretory drug, proton pump inhibitor (PPI) or ranitidine and 2 antimicrobial agents preferably amoxicillin, clarithromycin, or metronidazole,[7] when applying such multi-drug regimens, possible synergy between the agents suggest that pharmacokinetic considerations might help to improve *H. pylori* eradication rates which should be >85-90% on an intention to treat basis.[8]

The results of clinical trials of *H. pylori* eradication regimens have been widely variable, and studies pertaining to efficacy of these regimens in Indian population are less.[9] The different gastric PPIs display similar dose-response relationships with similar potencies and efficacies on a milligram basis, i.e., at the same milligram doses. The different dose recommendations were based on different strategies to balance optimal drug dosage and safety rather than on real differences in milligram related efficacies. Our study, we planned to see whether the difference in pharmacokinetic properties of PPIs shows any difference in the efficacy and safety parameters between treatment with omeprazole, lansoprazole, and rabeprazole in the triple drug regimen for eradication of *H. pylori* infect ion in peptic ulcer patients. In addition, with reports of metronidazole resistance, we have replaced with tinidazole for the evaluation of resistance.

MATERIALS AND METHODS

The present study is a randomized, prospective, and comparative study conducted after approval from Institutional Ethics Committee. The total number of patients were randomly divided into three groups with 15 patients in each group. Patients were included after endoscopically proven peptic ulcer with a size >2.5 mm in size and with evidence of *H. pylori* infection by histopathology and rapid urease test.[6] Patients on antiulcer drugs in preceding 4 weeks except antacids, on nonsteroidal antiinflammatory drugs, and corticosteroids, with coexisting gastric carcinoma, pyloric stenosis, active upper gastrointestinal (GI) hemorrhage, cirrhosis, renal disorders or any other severe organ disease, chronic alcoholics, hypersensitivity to study drugs, pregnant, or lactating mothers were excluded from the study. Written informed consent was obtained from every patient. Patients unwilling to participate were excluded from the study.

Upper GI endoscopy was done to note the site, number, and size of the ulcers, and four biopsy samples one each from body and the fundus and two samples from antrum of the stomach were taken. The three samples were checked for the evidence of *H. pylori*, by rapid urease test, and one sample from the antrum was collected in 10% neutral formalin and was sent for histopathological examination.[9] The patients were randomly assigned to receive one of the three regimens including PPI with amoxicillin and tinidazole, i.e., omeprazole 20 mg bid, amoxicillin 500 mg tds and tinidazole 500 mg bid (OAT regimen); lansoprazole 30 mg bid, amoxicillin 500 mg tds, and tinidazole 500 mg bid (LAT regimen); rabeprazole 20 mg, amoxicillin 500 mg tds., and tinidazole 500 mg bid (RAT regimen). The patients received one of the three triple drug regimens for 2 weeks followed by respective PPI twice daily for 4 weeks.

Follow-up visits were done at 2 and 6 weeks of the treatment. At every follow-up visit, specific dyspeptic symptoms were recorded on 3-point scale (epigastric pain, heartburn, anorexia, nausea, and vomiting) graded as 0-absent, 1-mild, 2-moderate, and 3-severe. Endoscopy was done for any decrease in size of ulcer, rapid urease test, and histopathology for the clearance of *H. pylori*. Patients were reviewed regarding adverse effects and compliance at every visit till the end of the therapy. Statistical analysis was performed using analysis of variance and Fisher exact test and level of significance was kept at $P < 0.05$. The response rate was assessed by the eradication of *H. pylori* associated with healing of ulcers, resolution of antral gastritis, and a significant fall in the rate of ulcer relapse in >4 weeks of treatment.

RESULTS

A total of 90 adult subjects of either sex were enrolled in the study. The mean age was 50.9 ± 1.76, and there was male preponderance in all the groups. The baseline observations of ulcer size, symptoms of nausea, heartburn, vomiting, and anorexia were recorded. The enrolled patients had single to multiple ulcers. Percentage reduction in the size of ulcer at the end of 2 weeks was 83, 88, and 90 with omeprazole, lansoprazole, and rabeprazole, respectively. At the end of 6 weeks, total healing of ulcer was observed in rabeprazole group when compared to omeprazole and lansoprazole groups. The baseline histopathology for *H. pylori* was positive in 94%, 96% and 96% of patients in omeprazole, lansoprazole, and rabeprazole groups, respectively. Histopathological resolution at the end of 2 weeks was 59%, 66%, and 75% with omeprazole, lansoprazole, and rabeprazole, respectively. At the end of 6 weeks, total histological resolution was observed in rabeprazole group when compared to omeprazole and lansoprazole groups (Tables 1-5).

At the baseline, the rapid urease test was positive in all the three groups. 54%, 62%, and 75% of the patients had negative rapid urease test ($P < 0.001$) after 2 weeks of treatment which was significant. Patients in all the three groups had significant reduction in symptoms at the end of 2 weeks, and highest was in the rabeprazole group. 73% of patients were relieved of epigastric pain at the end of 2 weeks in rabeprazole group in comparison to 48% and 65% in omeprazole and lansoprazole groups, respectively. In addition, 78% patients had better appetite at the end of 2 weeks in rabeprazole group in comparison to 54% and 64% in omeprazole and lansoprazole groups, respectively.

DISCUSSION

Pharmacological suppression of gastric acid secretion is traditionally the most rational approach to heal ulcers successfully. It was reported that suppression of acid secretion with antimicrobials produces very high cure rates rather than antimicrobials alone. Treatment with only anti-secretory drugs alone also showed relapse after withdrawal of treatment. Eradication of *H. pylori* by antimicrobial therapy in patients with duodenal and gastric ulcer has reduced the relapse rates. The preferred therapeutic regimen nowadays is triple drug therapy including two antibiotics and a PPI and is the most successful in eradicating *H. pylori*.[10] The regimens such as PPIs in combination with two antibiotics such as clarithromycin, amoxicillin, and metronidazole or tinidazole are advocated as 7-14 day regimen.[11] Addition of PPI in triple drug regimen leads to eradication rate of 97%.[12] Many different therapeutic regimens with various combinations have been reported making it difficult to make optimal choice of drugs, dosage, and duration of treatment and hence the current study to evaluate difference in efficacy of three PPIs in Indian population.

PPI's have a synergistic effect with several antibiotics by raising pH, by increasing chemical stability and making it optimal for the activity of other drugs. Lansoprazole exerted antibacterial activity *in vitro*, which is selective for *H. pylori*.[13] Gatta et al. proved that omeprazole has antimicrobial activity apart from inhibiting the urease activity of *H. pylori*.[14] Many studies have used omeprazole as the part of the regimen in the eradication of *H. pylori*. Use of omeprazole 20 mg twice daily, metronidazole 400 mg twice daily, clarithromycin 250 mg twice daily for 1 week produced *H. pylori* eradication rates of 77-88%.[15] Bell et al. used a 2 week regimen of omeprazole, ampicillin, and metronidazole and reported *H. pylori* eradication rate of 96.4% in metronidazole-sensitive cases and of 75% in metronidazole resistance cases 10. Hence, the overall eradication rate of *H. pylori* with omeprazole varied from 77% to 97% from the previous studies.

Table 1: Demographic profile

Parameter	Group A	Group B	Group C
Age (years)	52.6.±1.3	50.5±2.1	49.6±1.9
Male/female	11/4	10/5	12/3

Table 2: Percentage reduction in ulcer size at 2 and 6 weeks

Ulcer size	Baseline 0 weeks	% Reduction in size 2 weeks	% Reduction in size 6 weeks
Group OAT	8.6±1.7	83	91
Group LAT	8.9±1.4	88	95
Group RAT	8.1±1.9	90	100

Values expressed as mean±SEM and $P<0.05$. OAT: Omeprazole, amoxycillin and tinidazole, LAT: Lansaprazole, amoxycillin and tinidazole, RAT: Rabeprazole, amoxycillin and tinidazole

In our study, we got 54%, 62%, 75% eradication rate with omeprazole, lansoprazole, and rabeprazole after 2 weeks of treatment. It was less compared to the previous data. It may be because of the use of highly effective clarithromycin in the regimen used in the previous studies.[16] In our study, 94% eradication rate was obtained after 6 weeks of treatment with rabeprazole containing regimen. Eradication rates in various studies from West ranged from 80% to 90%. In the present study, we observed that triple drug therapy was highly effective in eradicating *H. pylori* infection in all the three groups. The percentage of eradication rate in our study was comparable with the previous studies conducted using PPIs with clarithromycin and amoxicillin which was about 94%.

The previous studies reported improvement in frequency and severity of epigastric pain in 80-82% of patients and heartburn in 63% of patients. In our study, the complete relief of epigastric pain varied from 48% to 73% which was less than the data obtained elsewhere. It may be because of small sample size. Relief from epigastric pain in rabeprazole group was 78% with rabeprazole in our study, which was comparable to the previous data. Before treatment most common symptom was epigastric pain (86%), followed by dyspepsia (80%) and then nausea (73%). Meta-analysis of published clinical studies showed that 71% of patients treated with the omeprazole 20 mg daily had complete relief of symptoms within 2 weeks.

It has been demonstrated in one study that rabeprazole had higher eradication rate than omeprazole as well as with potent and rapid acid suppression.[16] In our study, we have noted that rabeprazole, amoxicillin, and clarithromycin were the most effective regimen which showed faster eradication rate and rapid acid suppression. There was

Table 3: Patients relieved of symptoms at the end of 2 weeks

Parameter	Epigastric pain		Heart burn		Anorexia	
	Baseline	2 weeks	Baseline	2 weeks	Baseline	2 weeks
Group OAT	92	48	100	66	86	54
Group LAT	98	65	100	64	94	64
Group RAT	94	73	100	84	92	78

All values expressed in %. And $P<0.05$. OAT: Omeprazole, amoxycillin and tinidazole, LAT: Lansaprazole, amoxycillin and tinidazole, RAT: Rabeprazole, amoxycillin and tinidazole

Table 4: Histopathological resolution

Parameter	Histopathology (positive status)		
	Baseline	2 weeks	6 weeks
Group OAT	94	38	8
Group LAT	96	32	10
Group RAT	96	24	5

All values expressed in %. And $P<0.05$. OAT: Omeprazole, amoxycillin and tinidazole, LAT: Lansaprazole, amoxycillin and tinidazole, RAT: Rabeprazole, amoxycillin and tinidazole

Table 5: Rapid urease test

Parameter	Rapid urease test (positive status)				
	Baseline	2 weeks	% Reduction	6 weeks	% Reduction
Group OAT	100	46	54	15	85
Group LAT	100	38	62	10	90
Group RAT	100	25	75	6	94

All values expressed in %. And $P<0.05$. OAT: Omeprazole, amoxycillin and tinidazole, LAT: Lansaprazole, amoxycillin and tinidazole, RAT: Rabeprazole, amoxycillin and tinidazole

also complete healing of ulcer in rabeprazole group after 6 weeks of therapy when compared to omeprazole and lansoprazole treated groups, therefore showing faster healing rate. The gastric ulcer study by Dekkers et al. also supports our study where they produced inconsistent results since rabeprazole was superior to omeprazole in gastric ulcer patients only with regard to symptom relief but as potent as omeprazole with respect to healing rates.[17] No major adverse events were seen in 88% of the study population. Chronic use of PPIs carries the risk of hip fractures, infection with Clostridium difficle, community-acquired pneumonia, exposure in elderly population was also found to be associated with hyperparathyroidism.[18] The most common adverse effects reported include diarrhea, taste disturbance, and skin rash. However, there are no cases withdrawn during treatment as no adverse events were reported.

Based on pharmacodynamic properties, all PPIs share the same mode of action by inhibiting gastric proton pump. Metabolized in liver. Their potency depends on the serum AUC of the free prodrug and its chemical activation and half-life at pH 1 relative to its serum elimination half-life. Therefore, the available PPIs display the same potency and efficacy. *In vitro* and *in vivo* data on the efficacy of omeprazole, lansoprazole, and rabeprazole indicate antiurease activity and antimicrobial effect against *H. pylori*.[19,20] These effects have been shown to be highest with rabeprazole followed by lansoprazole and omeprazole. The higher efficacy of rabeprazole may be due to more effective acid suppression than omeprazole and lansoprazole. Further, the action of rabeprazole is known to be less affected by genetic polymorphism compared to omeprazole. Rabeprazole may have less potential for drug interaction than omeprazole which may make it useful in the elderly and others in multiple drug therapy.[21]

On the basis of their identical pharmacodynamic and similar pharmacokinetic properties (minor differences in bioavailability and nonlinearity in the disposition of omeprazole), all presently marked PPIs can be used interchangeably. In regard to the interaction potential of various PPI's, omeprazole might be regarded as slightly less favorable than the other PPIs whereas several studies showed significant difference in pharmacokinetic characteristics among different PPIs.[8]

CONCLUSION

Efficacy of the therapeutic regimen may vary according to patient population or geographical region. In our study, all the triple drug regimens were safe and almost equally effective in eradicating *H. pylori* but rabeprazole showed earlier symptomatic relief with rapid eradication rate of *H. pylori* in peptic ulcer disease. All the three groups showed significant reduction in histopathology status and rapid urease test with good eradication rates after 6 weeks. However, rabeprazole group showed earlier and better reduction rates compared to omeprazole and lansoprazole, but it was not statistically significant. Hence, rabeprazole can be recommended to be used in PPI-triple therapy for cure of *H. pylori* infection in Indian population for earlier relief and better cure rates.

REFERENCES

1. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet. 1984;1(8390):1311-5.
2. Parsonnet J. *Helicobacter pylori*: The size of the problem. Gut. 1998;43 Suppl 1:S6-9.
3. Qureshi WA, Graham DY. Diagnosis and management of *Helicobacter pylori* infection. Clin Cornerstone.

1999;1(5):18-28.
4. Nousheen, Tadvi NA, Shareef SM. Use of proton pump inhibitors in general practice: Is it rationale? Int J Med Res Health Sci. 2014;3(1):37-42.
5. Misiewicz JJ, Harris AW, Bardhan KD, Levi S, O'Morain C, Cooper BT, et al. One week triple therapy for *Helicobacter pylori*: A multicentre comparative study. Lansoprazole helicobacter study group. Gut. 1997;41(6):735-9.
6. Ghazzawi IM, Obeidat WA, Zuriekat FA. Triple therapy with pantoprazole, clarithromycin and amoxicillin for eradication in patients with *Helicobacter pylori* positive duodenal ulcers. Saudi Med J. 2004;25(8):1006-9.
7. Suerbaum S, Michetti P. *Helicobacter pylori* infection. N Engl J Med. 2002;347:1175-86.
8. Klotz U. Pharmacokinetic considerations in the eradication of *Helicobacter pylori*. Clin Pharmacokinet. 2000;38(3):243-70.
9. Dayal VM, Kumar P, Kamal J, Shahi SK, Agrawal BK. Triple-drug therapy of *Helicobacter pylori* infection in duodenal ulcer disease. Indian J Gastroenterol. 1997;16(2):46-8.
10. Kate V, Ananthakrishnan N. Treatment of *Helicobacter pylori* infection- A review. Indian J Pharmacol. 2001;33:410-6.
11. Bell GD, Powell KU, Burridge SM, Bowden AN, Rameh B, Bolton G, et al. *Helicobacter pylori* eradication. Efficacy and side effects of a combination of omeprazole, amoxicillin and metronidazole compared with four alternate regimens. Q J Med. 1993;86(11):734-50.
12. De Boer WA, Driessen W, Tytghat GN. *Helicobacter pylori* infection. Lancet. 1995;345:817-20.
13. Figura N, Crabtree JE, Dattilo M. *In vitro* activity of lansoprazole against *Helicobacter pylori*. J Antimicrob Chemother. 1997;39:585-90.
14. Gatta L, Perna F, Figura N, Ricci C, Holton J, D'Anna L, et al. Antimicrobial activity of esomeprazole versus omeprazole against *Helicobacter pylori*. J Antimicrob Chemother. 2003;51:439-42.
15. Van der Hulst RW, Tytgat GN. *Helicobacter pylori* and peptic ulcer disease. Scand J Gastroenterol. 1995;332:139-42.
16. Miwa H, Ohkura R, Murai T, Sato K, Nagahara A, Hirai S, et al. Impact of rabeprazole, a new proton pump inhibitor, in triple therapy for *Helicobacter pylori* infection - comparision with omeprazole and lansoprazole. Aliment pharmacol Ther. 1999;13(6):741-6.
17. Dekkers CP, Beker JA, Thjodleifsson B, Gabryelewicz A, Bell NE, Humphries TJ. Comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of active gastric ulcer - A European multicentre study. The European rabeprazole study group. Aliment Pharmacol Ther. 1998;2(8):789-95.
18. Tadvi NA, Hussain S, Ghaffar UB. Benefits versus risks of proton pump inhibitors: Are we opening the can of worms. Int J Med Res Health Sci. 2016;5(1):91.
19. Kromer W, Horbach S, Luhmann R. Relative efficacies of gastric proton pump inhibitors: Their clinical and pharmacological basis. Pharmacology. 1999;59(2):57-77.
20. Stedman CA, Barela ML. Review article: Comparison of the pharmacokinetics, acid suppression and efficacy of proton pump inhibitors. Aliment Pharmacol Ther. 2000;14(8):963-78.
21. Carswell CI, Goa KL. Rabeprazole: An update of its use in acid related disorders. Drugs. 2001;61(15):2327-56.

How to cite this article: Devagudi P, Shareef M, Tadvi NA. Comparative study of safety and efficacy of omeprazole, lansoprazole, and rabeprazole in triple therapy for eradication of *Helicobacter pylori* in peptic ulcer patients in Indian population. Natl J Physiol Pharm Pharmacol 2017;7(3):250-254.

Source of Support: Nil, **Conflict of Interest:** None declared.