

## Efficacy of ilaprazole in the treatment of duodenal ulcers: A meta-analysis

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### Abstract

**AIM:** To compare the efficacy and tolerance of ilaprazole compared with other proton pump inhibitors (PPIs) in the treatment of duodenal ulcer.

**METHODS:** An electronic database search of Medline, Embase, the Cochrane controlled trials register, Web of Science, PubMed, and the Chinese Biomedical Literature Database (updated to July 2013), and manual searches were conducted. A meta-analysis of randomized controlled trials comparing the efficacy and tolerance of ilaprazole and other PPIs in the treatment of duodenal ulcers was performed.

**RESULTS:** Five articles involving 1481 patients were included. The meta-analysis showed no difference in the 4-wk healing rate between ilaprazole and other PPIs [89.7% vs 87.0%; relative risk (RR) = 1.02; 95%CI: 0.98-1.06;  $Z = 1.00$ ;  $P = 0.32$ ]. The results did not change in the sensitivity analyses. The meta-analysis indicated that the adverse effect rate in the ilaprazole group was lower than that in the control group, but the

difference was not significant (9.7% vs 13.0%; RR = 0.81; 95%CI: 0.60-1.07;  $Z = 1.47$ ;  $P = 0.14$ ).

**CONCLUSION:** Ilaprazole is a highly effective and safe PPI in the treatment of duodenal ulcers. Ilaprazole can be recommended as a therapy for acid-related disorders, especially in Asian populations.

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**Key words:** Ilaprazole; Proton pump inhibitor; Duodenal ulcer; Meta-analysis

**Core tip:** Ilaprazole, a proton pump inhibitor (PPI), is a newly developed medicine in the management of acid-related disorders. This meta-analysis showed that ilaprazole was a highly effective and safe PPI compared with other PPIs in the treatment of duodenal ulcer. Ilaprazole can be recommended as a therapy for acid-related disorders, especially in Asian populations.

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### INTRODUCTION

Duodenal ulcer (DU) is a very common digestive disease with a high incidence all over the world<sup>[1-4]</sup>. As the first proton pump inhibitor (PPI), omeprazole has been used therapeutically for many years, and shown great efficacy in treating peptic ulcers<sup>[5-7]</sup>. Currently, research is focused on more effective PPIs with a lower dose and comparative safety<sup>[8-11]</sup>.

Ilaprazole (also known as IY-81149), the latest pro-

ton pump inhibitor (PPI), has been less well reported in clinical practice, as a newly developed medicine in the management of acid related disorders<sup>[12,13]</sup>. Ilaprazole is synthesized by Il-Yang (South Korea) and presently developed by Livzon Pharmaceutical Group Inc. (China), and has been approved by the State Food and Drug Administration of China (license ID: CN 1121714A) with a recommended dose of 10 mg/d for peptic ulcers. The mechanism of ilaprazole's action to suppress gastric acid secretion is almost the same as omeprazole, in which the protonated substituted benzimidazoles suppress gastric acid secretion through inhibition of the  $H^+/K^+-ATPase$  at the secretory surfaces of gastric parietal cells<sup>[14,15]</sup>.

Preclinical research found that ilaprazole had a more prolonged half-life and higher suppression of gastric acid secretion in a dose-dependent manner, and similar safety compared with omeprazole. A comparative pharmacodynamic study on patients with gastroesophageal reflux disease reported that ilaprazole, at a dose of 5 mg, provided gastric pH control comparable with the use of 20 mg omeprazole, and at doses of 10 and 20 mg it was found to have a more powerful and longer-lasting acid-suppressant effect than omeprazole at a dose 20 mg<sup>[16]</sup>.

There have been several clinical trials comparing ilaprazole and other PPIs in the treatment of duodenal ulcer, which showed that ilaprazole had a high 4-wk healing rate<sup>[17-19]</sup>. The aim of the present study was to conduct a pooled meta-analysis of randomized controlled trials (RCT) comparing the efficacy and tolerance of ilaprazole with other PPIs in the treatment of duodenal ulcers.

## MATERIALS AND METHODS

### Literature search

Relevant studies were identified and selected by searching the databases, Medline (1990 to July 2013), Embase (1990 to July 2012), Cochrane controlled trials register (Cochrane Library Issue 2, 2013), Web of Science (1990 to July 2013), PubMed (updated to July 2013) and Chinese Biomedical Literature Database (1989 to July 2013) under the search term "ilaprazole". We also performed a full manual search from the bibliographies of each peer-reviewed paper selected. No language or date limitations were imposed. Furthermore, there was no limitation in publication form.

### Study selection criteria

The selection criteria for inclusion in the meta-analysis were: (1) RCT comparing ilaprazole 10 mg/d and other PPIs in the treatment of duodenal ulcers; (2) duodenal ulcers must have been diagnosed by upper gastrointestinal endoscopy; (3) the patients should not receive other medical therapies before the trial, except the standard triple therapy for *Helicobacter pylori* (*H. pylori*) eradication; and (4) the duration of the trials should be 4 wk, and ulcer healing was also assessed by endoscopy after 4 wk of therapy. The decision to include or exclude any trial was made by 2 researchers separately. The 2 lists were com-

pared and discrepancies were resolved.

### Data extraction

Data were independently abstracted from each trial by 2 researchers, and disagreement was resolved by consensus. Data were extracted with a pre-designed review form. Data to be extracted were as follows: study design, number of patients in each treatment arm, duration of treatment, drug regimen, percentage of adverse effects, and quality score.

### Quality of methodology

The methodological quality of studies included in the meta-analysis was scored with the Jadad composite scale (including items of randomization, double-blinding, and description of withdrawal/dropouts)<sup>[20,21]</sup>. This is a 5-point quality scale, with low quality studies having a score of  $\leq 2$  and high quality studies a score of  $\geq 3$ <sup>[21,22]</sup>. Methodological quality assessment was independently performed by 2 of the present authors. Each study was given an overall quality score based on the above criteria, which was then used to rank studies.

### Statistical analysis

The meta-analysis was performed using the Mantel-Haenszel method (fixed effects model) or the DerSimonian and Laird method (random effects model) with Review Manager Software (RevMan 5.1, Cochrane Collaboration, Oxford, England). The relative risk (RR) for each clinical event was presented with 95% confidence interval (CI). Heterogeneity was tested using the  $\chi^2$  test (with  $P \leq 0.05$  indicating significant heterogeneity) and  $I^2$  test (25%, 50%, and 75%, represent low, moderate, and high heterogeneity, respectively). The RR for each clinical event was pooled with the fixed effects model, and if the  $\chi^2$  test and  $I^2$  test for heterogeneity were significant, the analysis was also done with random effects model.

## RESULTS

### Description of selected studies

The search strategy generated 32 studies. From these, we identified 5 trials involving 1481 patients comparing ilaprazole with other PPIs in the treatment of duodenal ulcer, which fulfilled the criteria for the meta-analysis. Four papers were published as peer-reviewed articles, and one as a meeting abstract<sup>[18]</sup>. Four were published in English and the other was published in Chinese<sup>[19]</sup>. The baseline characteristics of the 5 articles are listed in Table 1. All the trials were based on intention-to-treat analysis. All trials were of high quality except one<sup>[18]</sup> (Table 1). The results of the 5 trials are shown in Table 2<sup>[17-19,23,24]</sup>.

### Meta-analysis

We first compared ilaprazole at the standard dose 10 mg/d with other PPIs on the 4-wk healing rate and rate of adverse effects (Figure 1). There was no statistical heterogeneity in the 4-wk healing rate among the 5 trials and

**Table 1** Baseline characteristics of trials included in the meta-analysis

Ref.	Language	Publication type	Time	Patients (n)	Duration (wk)	Jadad score
Ho <i>et al</i> <sup>[17]</sup> , 2009	English	Full text	2002-2004	202	4	5
Zhou <i>et al</i> <sup>[19]</sup> , 2009	Chinese	Full text	2005-2006	510	4	5
Song <i>et al</i> <sup>[18]</sup> , 2010	English	Abstract	Not reported	156	4	2
Wang <i>et al</i> <sup>[23]</sup> , 2011	English	Full text	2004-2005	117	4	5
Wang <i>et al</i> <sup>[24]</sup> , 2012	English	Full text	2005-2006	496	4	5

**Table 2** Results of the randomized controlled trials with intention-to-treat analysis

Ref.	Regimen	4-wk healing rate	Rate of adverse effects
Ho <i>et al</i> <sup>[17]</sup> , 2009	I 10 mg/d	78.6% (77/98)	23.5% (23/98)
	O 20 mg/d	78.8% (82/104)	22.1% (23/104)
Zhou <i>et al</i> <sup>[19]</sup> , 2009	I 10 mg/d	90.3% (307/340)	8.2% (28/340)
	O 20 mg/d	87.6% (149/170)	11.2% (19/170)
Song <i>et al</i> <sup>[18]</sup> , 2010	I 10 mg/d	85.9% (67/78)	6.4% (5/78)
	E 40 mg/d	87.2% (68/78)	7.5% (6/78)
Wang <i>et al</i> <sup>[23]</sup> , 2011	I 10 mg/d	93.1% (54/58)	6.9% (4/58)
	O 20 mg/d	89.8% (53/59)	13.6% (8/59)
Wang <i>et al</i> <sup>[24]</sup> , 2012	I 10 mg/d	95.0% (307/331)	8.5% (28/331)
	O 20 mg/d	90.0% (149/165)	11.6% (19/165)

I: Ilaprazole; O: Omeprazole; E: Esomeprazole.

the fixed effects model was used ( $\chi^2 = 0.62$ ;  $P = 0.96$ ;  $I^2 = 0\%$ ). The meta-analysis showed no difference between the ilaprazole and other PPIs in 4-wk healing rate (89.7% *vs* 87.0%; RR = 1.02; 95%CI: 0.98-1.06;  $Z = 1.00$ ;  $P = 0.32$ ). Regarding adverse effects, there was no statistical heterogeneity found by the  $\chi^2$  test ( $\chi^2 = 1.96$ ;  $P = 0.74$ ) or  $I^2$  test ( $I^2 = 0\%$ ), and the fixed effects model was used. The meta-analysis indicated that the rate of adverse effects in the ilaprazole group was lower than that in the control group, but the difference was not significant (9.7% *vs* 13.0%; RR = 0.81; 95%CI: 0.60-1.07;  $Z = 1.47$ ;  $P = 0.14$ ).

### Sensitivity analysis

The funnel plots for the 4-wk healing rate comparing ilaprazole at a dose of 10 mg/d with other PPIs showed some asymmetry, suggesting the possibility of publication bias (Figure 2). Thus, we further performed a sensitivity analysis to assess the stability and reliability of the results of the primary meta-analysis (Table 3). The sensitivity analysis only included the 4 trials of high quality (Jaded score  $\geq 3$ ). The analysis indicated no difference in the 4-wk healing rate between 10 mg/d ilaprazole and other PPIs (RR = 1.02; 95%CI: 0.98-1.07;  $Z = 1.16$ ;  $P = 0.25$ ).

Four trials were published in English and the other was published in Chinese. A further sensitivity analysis was made only including the studies published in the English. The analysis revealed no difference between the 10 mg/d ilaprazole and other PPIs in the trials published in English (RR = 1.01; 95%CI: 0.97-1.07;  $Z = 0.61$ ;  $P = 0.54$ ).

A final sensitivity analysis was performed only including trials using omeprazole as control. The analysis indicated no difference between the ilaprazole at a dose of

10 mg/d and omeprazole (RR = 1.02; 95%CI: 0.98-1.07;  $Z = 1.16$ ;  $P = 0.25$ ).

## DISCUSSION

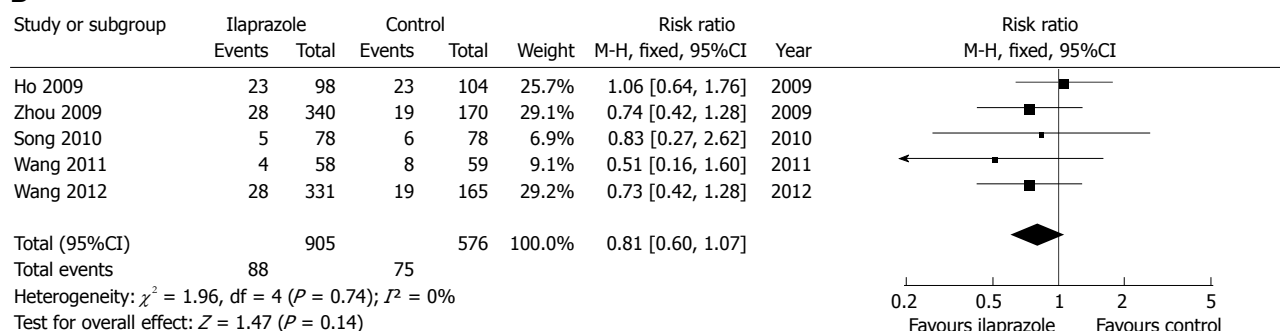
PPIs are highly effective medications widely used in the management of peptic diseases including gastric and duodenal ulcers, gastroesophageal reflux disease and Zollinger-Ellison syndrome<sup>[25]</sup>. Many new therapeutic drugs with similar structures and better therapeutic outcomes have been developed since omeprazole first entered the market, including rabeprazole, pantoprazole, lansoprazole, esomeprazole, and the new molecule we studied in this analysis, ilaprazole. Because ilaprazole was currently only approved in a number of Asian countries, the clinical studies on ilaprazole were not regularly reported in international journals, and most were conducted in China and published in Chinese. Thus, this study aimed to perform a systematic review and meta-analysis on the effect of ilaprazole on the healing of duodenal ulcers.

The current standard dose of ilaprazole recommended for the management of peptic diseases is 10 mg/d. The meta-analysis showed no difference between 10 mg/d ilaprazole and other PPIs with standard or higher doses. In addition, the sensitivity analyses also confirmed the results of the primary meta-analysis. The meta-analyses documented that ilaprazole was a highly effective PPI compared with other PPIs.

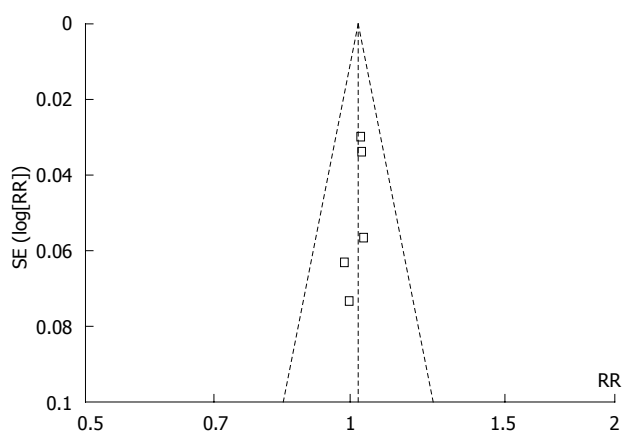
Ilaprazole shows major suppression of gastric acid secretion. As an inhibitor of acid output, ilaprazole is more powerful than omeprazole. An experimental study in a surgically-induced rat reflux esophagitis model showed that ilaprazole had a much lower ED<sub>50</sub> than omeprazole<sup>[26]</sup>. Ilaprazole at a dose of 5 mg provided gastric pH control comparable with 20 mg omeprazole<sup>[16]</sup>.

As for the safety and tolerability profile, the meta-analysis on adverse effects also revealed fewer adverse effects in the ilaprazole group, though the difference was not significant. Wang *et al*<sup>[23]</sup> reported that ilaprazole at a dose of 5, 10, or 20 mg/d is comparable to 20 mg/d omeprazole. Considering the rate of adverse effects of PPIs is low, and the adverse effects are usually mild, we may conclude that ilaprazole is a safe drug with minor adverse effects.

There were several limitations in this study. First, the low quality of 2 individual trials was a major limitation. Second, due to the fact that ilaprazole is only approved in Asian countries, the trials included in this study all come from Asian countries, and thus further trials are needed

**A****B**

**Figure 1 Meta-analysis chart.** A: Meta-analysis of 4-wk healing rate comparing ilaprazole at 10 mg/d with other proton pump inhibitors (PPIs); B: Meta-analysis of adverse effects comparing 10 mg/d ilaprazole with other PPIs.



**Figure 2 Funnel plot of the included trials comparing 10 mg/d ilaprazole with other proton pump inhibitors.**

in Western populations. Third, there were few trials comparing ilaprazole at a dose of 5 mg/d with other PPIs.

In conclusion, ilaprazole is a highly effective and safe PPI in the treatment of duodenal ulcers. Ilaprazole can be recommended as a therapy for acid-related disorders, especially in Asian populations.

## COMMENTS

### Background

Ilaprazole, the latest proton pump inhibitor (PPI), is a newly developed medicine in the management of acid related disorders.

### Research frontiers

There have been several clinical trials comparing ilaprazole and other PPIs in

**Table 3 Sensitivity analysis of the included trials**

Analysis	n	RR (95%CI)	P value
High quality studies	4	1.02 (0.98–1.07)	0.25
English studies	4	1.02 (0.97–1.07)	0.54
Studies using omeprazole as control	4	1.02 (0.98–1.07)	0.25

RR: Relative risk.

the treatment of duodenal ulcers which showed that ilaprazole had a high 4-wk healing rate.

### Innovations and breakthroughs

The authors conducted a meta-analysis of randomized controlled trials comparing the efficacy and tolerance of ilaprazole with other PPIs in the treatment of duodenal ulcer.

### Applications

Ilaprazole is a highly effective and safe PPI in the treatment of duodenal ulcer. Ilaprazole can be recommended as a therapy for acid-related disorders, especially in Asian populations.

### Peer review

This study evaluated the efficacy and tolerance of ilaprazole with other PPIs in the treatment of duodenal ulcer by conducting a meta-analysis. The findings are useful in the management of duodenal ulcer.

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