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META-ANALYSIS

Efficacy of mosapride plus proton pump inhibitors for treatment of gastroesophageal reflux disease: A systematic review

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Abstract

AIM: To assess the potential benefits of mosapride plus proton pump inhibitors (PPIs) in the treatment of gastroesophageal reflux disease.

METHODS: A literature search was performed through MEDLINE, EMBASE, and the ISI Web of Knowledge. The clinical trials that compared the benefit of mosapride plus PPI treatment with that of PPI monotherapy were analyzed. The rate of responders was evaluated by the pooled relative risk (PRR) and improvement in symptom scores was assessed by single effect size of a standardized mean, while Hedges'g was used as the effect size. Pooled effect sizes with 95%CIs were calculated using a fixed-effects model. Between-study heterogeneity was assessed using Q test and I^2 analyses. In addition, studies that assessed the additional efficacy of mosapride in PPI-resistant patients were also reviewed.

RESULTS: This systematic review included information on a total of 587 patients based on 7 trials. Four trials compared the efficacy of combination therapy of mosapride plus a PPI with that of PPI monotherapy. The statistical analysis for the effect of additional mosapride showed equivocal results (PRR = 1.132; 95%CI: 0.934-1.372; P = 0.205; Hedges'g = 0.24; 95%CI: 0.03-0.46; P = 0.023). No heterogeneity and publication bias were found among the studies. Three open-labeled trials assessed the additional efficacy of mosapride in PPI-resistant patients. However, since these trials did not set the control group, the results may be considerably biased.

CONCLUSION: Mosapride combined therapy is not more effective than PPI alone as first-line therapy. Whether it is effective in PPI-resistant patients needs to be determined.

Key words: Mosapride; Proton pump inhibitor; Gastroesophageal reflux disease; Systematic review; Combined therapy

Core tip: Prokinetic agents have been widely used to relieve the gastroesophageal reflux disease (GERD) symptoms, and mosapride is a selective 5-HT$_4$ receptor agonist that can be safely used. We conducted a systematic review and meta-analysis to assess the potential benefits of the addition of mosapride to proton pump inhibitors (PPIs) in the treatment of GERD. Based on this research, mosapride combined therapy seems to be not more effective than PPI alone as first-line therapy. Whether it is effective in PPI-resistant patients needs to be determined.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) encompasses a spectrum of clinical presentations in which gastric content refluxes into the esophagus leading to symptoms with or without visible damage to the esophageal mucosa. It is the most common gastrointestinal diagnosis recorded during visits to outpatient clinics[1]. Population-based studies suggest that GERD is a common condition with a prevalence of 10%-20% in Western Europe, while in Asia it is lower, less than 5%[2,3]. Traditionally, the treatment for GERD should be focused on symptom control, and abundant data from randomized trials show benefits of inhibiting gastric acid secretion in patients with GERD. Treatment with proton pump inhibitors (PPIs) heals reflux esophagitis in 83% of patients with comparable symptom relief, an outcome that is superior to treatment with histamine 2-receptor antagonists[4].

However, GERD patients present with a wide range of symptom severity and frequency, sometimes do not respond to PPI therapy. Several mechanisms have been proposed for the pathogenesis of refractory GERD, including weakly acidic reflux, visceral hypersensitivity and delayed gastric emptying[5].

An Asia-Pacific consensus on the management of GERD showed that the use of prokinetic agents either as monotherapy or adjunctive therapy to PPIs may have a role in the treatment of GERD in Asia[6]. Prokinetic agents like cisapride, which act on the 5-hydroxytryptamine (5-HT)$_1$-receptor, have been found to be associated with potentially fatal heart rhythm abnormalities. However, mosapride, a selective 5-HT$_4$ receptor agonist, is an alternative prokinetic agent that can be safely used in patients with upper gastrointestinal disorders[7-9], while stimulating gastrointestinal motility and gastric emptying[10-12]. Many studies have shown that mosapride can reduce acid reflux episodes and esophageal clearance of refluxate, theoretically, suggesting potential efficacy in the treatment of GERD[13,14]. In a randomized trial, mosapride combined with PPIs achieved a better therapeutic effect than use of a PPI alone[15]. However, another clinical trial showed the additional effect of mosapride was limited[16].

In this study, our aim was to clarify the data on the treatment of GERD by systematically reviewing the literatures on the efficacy of mosapride plus PPIs with regard to initial symptom relief. The additional treatment effect of mosapride in PPI-resistant GERD patients was also assessed.

MATERIALS AND METHODS

Study retrieval and selection

The present meta-analysis follows the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA[17]. We performed a literature search using the following databases: MEDLINE, EMBASE and the ISI Web of Knowledge. The search pool was enlarged by references found in these initial articles. Three authors (Liu Q, Feng CC and Wang EM) independently searched from the beginning of indexing for each database to May 10th, 2013, using the key terms ("gastroesophageal reflux disease" or "reflux esophagitis" or "non-erosive reflux disease") and ("mosapride" or "mosapride citrate" or "prokinetic" or "prokinetics"). Only the articles written in English were included.

Three authors (Liu Q, Feng CC and Wang EM) independently evaluated all of the retrieved studies according to pre-specified selection criteria. Discrepancies between the three investigators were resolved by discussion. Studies were included based on the following criteria: (1) published as original articles; (2) investigations of adults; (3) clinical trials that evaluated the efficacy of mosapride. Studies were excluded if they had the following features: (1) without specific description for the diagnosis of GERD; (2) reported duplicated results that have been published in other articles as repeated data; (3) other primarily identifiable causes of GERD symptoms such as esophageal neoplasm and esophageal stricture; (4) use of mosapride was not designed as an additional drug in combination with a PPI; and (5) included participants who were taking medications that could have complicated interpretation of results.

Data extraction and analysis

The following data were abstracted from each article: the author(s), publication year, country, study design, numbers of enrolled patients, age, gender distribution and body mass index of the subjects, definition of GERD, treatment dose and duration, effects of treatment. Data extraction was performed independently by two reviewers (Liu Q and Feng CC). We validated a priority of data from intention-to-treat (ITT) analysis other than per-protocol (PP) analysis when the data obtained from two approaches were both available in certain studies.

Subsequently, we arranged the clinical trials using thematic analysis. The overarching categories included the controlled trials showing parallel comparisons between efficacy of mosapride and PPI group with that of PPI alone group, and open trials to assess the additional efficacy of mosapride to PPI-resistant patients.

Using the data from the controlled trials in which treatment efficacy was evaluated by comparing the rate of responders and improvement in symptom scores in a group receiving mosapride plus a PPI with those in patients receiving PPI alone, we assessed the drug effect based on the pooled relative risk (PRR) and single effect

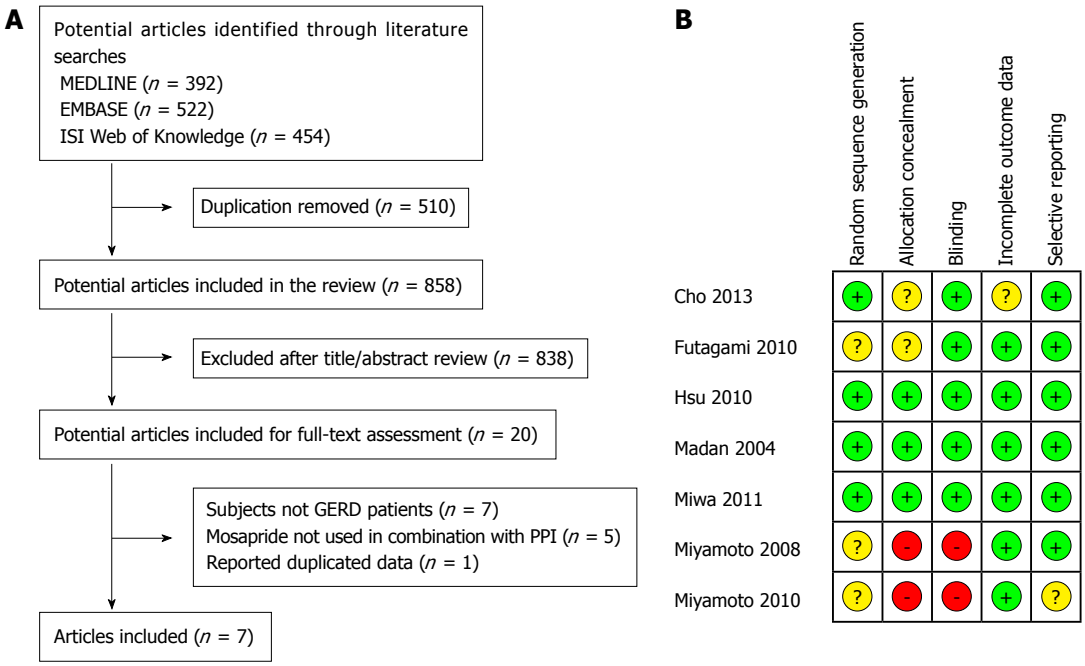

Figure 1 Flow chart of study selection and risk of bias summary. A: Flow chart of study selection; B: Risk of bias summary.

size of a standardized mean. The PRR was calculated using the Mantel-Haenszel method[18], and continuous variables were transformed from the means and standard deviation to determine a standardized effect size. We used the Hedges'g effect size, which is a variation of Cohen's *d*, to correct for bias associated with small sample sizes[19]. Statistical heterogeneity across the various studies was then tested with the use of Q-statistic[20]. A P_Q-value < 0.10 indicated a significant statistical heterogeneity across studies, allowing for the use of a random effects model. Additionally, we calculated I^2 statistics, which quantifies the percentage of variation across studies caused by heterogeneity, rather than chance, and, therefore are less biased by the number of studies included in a meta-analysis[21]. Finally, publication bias was quantified using Egger's test[22]. A two-tailed $P < 0.05$ was considered to be statistically significant. The above analyses were performed using Stata 11.0 (Stata Corp, College Station, TX, United States). Risk of bias was assessed using Cochrane Review guidelines[23].

RESULTS

Search results and study characteristics

The search strategy generated 858 references, 20 of which were selected for further assessment by full-text reading (Figure 1A). In this step, 7 articles were excluded because the subjects in the study were not GERD patients[24-30], 5 articles were excluded because mosapride was not used in combination with PPI[13,14,31-33], and one trial reported duplicated data[34]. Ultimately, 7 studies were included in this systematic review which contained information on a total of 587 patients, with the characteristics shown in Table 1. The diagnostic criteria of GERD in the 7 articles we included were basically based on typical reflux-associated symptoms (heartburn and/or regurgitation) which occurred at least twice a week, although the duration was obscure in three studies[16,37,39]. The subjects in 3 articles were non-erosive reflux disease (NERD) patients[16,38,39], but one study focused on reflux esophagitis (RE) patients[35]. With respect to the dose of mosapride, only one trial used this agent at a dose of 10 mg thrice daily[36]. All others employed 5 mg three times per day. Various PPIs were used in these studies including rabeprazole, omeprazole, pantoprazole, lansoprazole and esomeprazole.

Quality and methodology of trials

Risk of bias was assessed using criteria specified by the Cochrane group. Overall, the risk of bias was high in some studies[37,39] and low in others[15,16,36,38] (Figure 2). A summary of individual quality assessment can be found in Figure 1B.

There was significant heterogeneity between trials with regard to methodology. In 3 studies[35,38,39], symptom evaluation was based on a frequency scale for the symptoms of GERD (FSSG), a GERD-specific questionnaire developed in Japan has been used for screening GERD patients[40]. The gastrointestinal symptom rating scale (GSRS) questionnaire[41] was adopted from another trial[37]. Two articles presented an explicit symptom assessment approach[15,36], and one used a visual analogue scale to evaluate the symptom[16].

Trials comparing mosapride plus PPI combination therapy with PPI monotherapy

Four trials compared the efficacy of combination therapy of mosapride plus a PPI with that of PPI monothera-

Table 1 Characteristics of the included studies

Ref.	Year	*n*	Male (%)	Mean age	BMI	Study design	Treatment agent (daily), dose	Treatment duration	Outcome measures
Trials comparing mosapride plus PPI combined therapy with PPI monotherapy									
Madan *et al*[15]/ India	2004	Cases 33	57.6	34.7	Unclear	Double-blind Randomized controlled trial	Pantoprazole 80 mg + mosapride 15 mg Pantoprazole 80 mg + placebo	8 wk	Symptom Questionnaire
		Controls 28	75.0	36.5	Unclear				
Hsu *et al*[35]/Taiwan	2010	Cases 50	46.0	47.0	23.7 ± 3.6	Double-blind Randomized Crossover trial	Lansoprazole 30 mg + mosapride 15 mg Lansoprazole 30 mg + placebo	4 wk	FSSG Questionnaire
		Controls 46	54.3	47.0	23.9 ± 4.6				
Miwa *et al*[16]/Japan	2011	Cases 97	38.1	52.1	22.3 ± 3.3	Double-blind Randomized Controlled trial	Omeprazole 10 mg + mosapride 15 mg Omeprazole 10 mg + placebo	4 wk	VAS
		Controls 95	36.8	52.2	22.0 ± 3.6				
Cho *et al*[36]/ South Korea	2012	Cases 24	62.5	49.0	21.3 ± 2.3	Double-blind Randomized Controlled trial	Esomeprazole 40 mg + mosapride 30 mg Esomeprazole 40 mg + placebo	4 wk	Reflux-symptoms Questionnaire
		Controls 19	47.4	43.0	21.5 ± 2.3				
Trials on addition of mosapride to PPIs for the treatment of PPI-resistant GERD patients									
Miyamoto *et al*[37]/ Japan	2008	34	Unclear	53.1[1]	23.0 ± 0.3[1]	Open trial	Rabeprazole 10 mg + mosapride 15 mg	12 wk	FSSG Questionnaire
Futagami *et al*[38]/ Japan	2010	44	50%	42.8	23.0 ± 1.9	Open trial	Omeprazole 20 mg + mosapride 15 mg	12 wk	GSRS Questionnaire
Miyamoto *et al*[39]/ Japan	2010	117	Unclear	47.4[1]	23.0 ± 3.6[1]	Open trial	PPI therapy[2] + mosapride 15 mg	4 wk	FSSG Questionnaire

[1]Data calculated based on the included participants at the beginning of study; [2]Patients were randomly administered rabeprazole 10 mg or lansoprazole 30 mg or omeprazole 20 mg or lansoprazole 15 mg or omeprazole 10 mg. PPI: Proton pump inhibitor; GERD: Gastrooesophageal reflux disease; FSSG: Frequency scale for the symptoms of GERD; GSRS: Gastrointestinal symptom rating scale; VAS: Visual analogue scale; BMI: Body mass index.

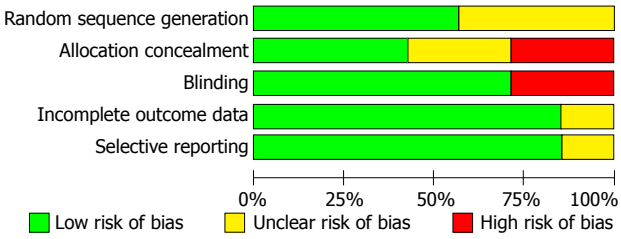

Figure 2 Risk of bias in trials.

py[15,16,35,36], all of which were designed as double-blind, randomized, placebo-controlled trials.

Madan *et al*[15] demonstrated that the combination therapy with pantoprazole and mosapride was more effective than pantoprazole alone in providing symptomatic relief to patients with erosive GERD. However, the number of patients who responded to therapy was not statistically different between combination therapy and monotherapy with pantoprazole (89.2% *vs* 69.7%). However, at the end of the treatment duration, the mean symptom score was significantly lower in patients receiving combination therapy (1.67 *vs* 3.78, $P = 0.009$).

Hsu *et al*[35] conducted a double-blind randomized trial studying the effects of adding mosapride to lansoprazole for the management of reflux esophagitis. The reduction in symptom score after 4 wk of treatment with lansoprazole and mosapride was not significantly higher compared with lansoprazole plus placebo (13.42 *vs* 10.85, $P = 0.103$), indicating little benefit from the addition of mosapride to a PPI in RE patients. However, in the subgroup of severely symptomatic patients, the difference was marginally significant ($P = 0.039$), indicating that mosapride as an adjunct to PPI may be beneficial in patients with severe symptoms.

Miwa *et al*[16] targeted on patients with NERD in a double-blind placebo-controlled study and found that there was no significant difference between the rates of responders from omeprazole plus mosapride, and omeprazole plus placebo groups in ITT (46% *vs* 44%) and PP (50% *vs* 43%) analyses. The change in symptom score in the treatment group was not significantly different from the placebo group in ITT analysis (-3.8 *vs* -3.4, $P = 0.128$). Therefore, the addition of mosapride to omeprazole was not found to be more effective than omeprazole alone in NERD patients.

Theoretically, prokinetic drugs can improve GERD by increasing lower esophageal sphincter basal pressure, improving esophageal peristalsis, accelerating esophageal acid clearance and facilitating gastric emptying. Cho *et al*[36] focused on the change of high-resolution manometry parameters to evaluate the efficacy of mosapride on esophageal motility and reflux symptoms in patients with GERD when used in combination with a PPI. The authors found that a combination of mosapride with esomeprazole affected esophageal peristalsis by improving esophageal contractibility and lowering intrabolus pressure that could lead to facilitation of esophageal bolus transit in patients with GERD. However, with regard to symptom assessment, treatment responsiveness in the combined therapy group was not different from that of the monotherapy group (79% *vs* 68%).

Of note, for the statistical analysis, one study was

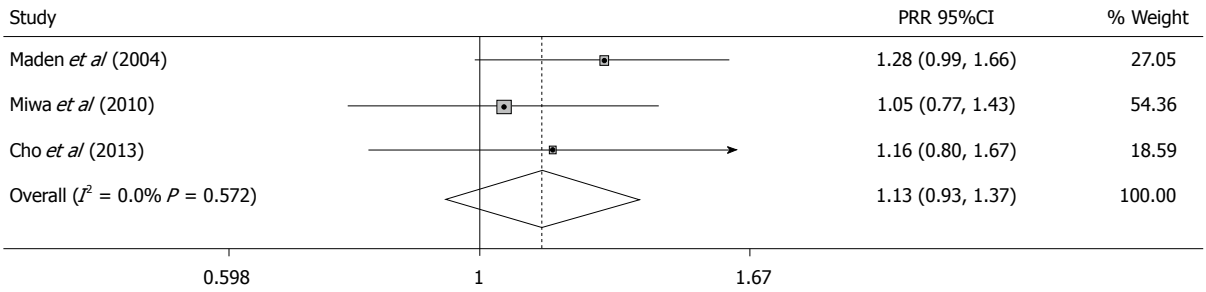

Figure 3 Meta-analysis of three trials that used mosapride as combined therapy with proton pump inhibitor compared with placebo in gastroesophageal reflux disease, a fixed-effects model was used and pooled relative rate was the measure of effect size. I^2, total variation across studies that is attributable to heterogeneity rather than to chance; PRR: Pooled relative rate.

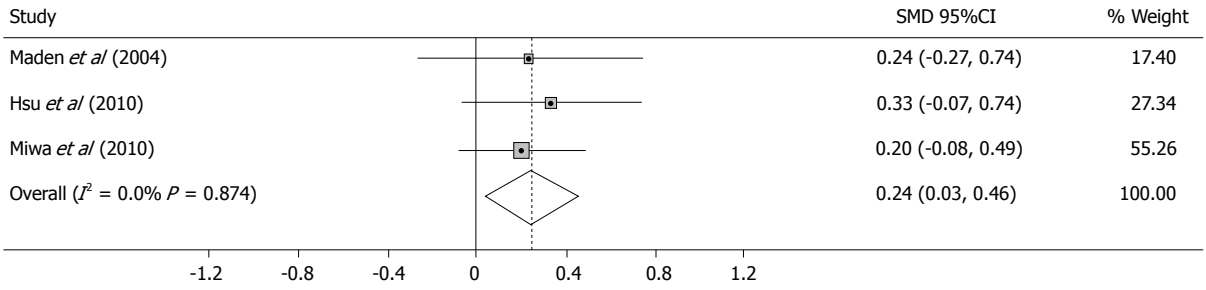

Figure 4 Meta-analysis of three trials that used mosapride as combined therapy with proton pump inhibitor compared with placebo in gastroesophageal reflux disease, a fixed-effects model was used and Hedges'g was the measure of effect size. I^2, total variation across studies that is attributable to heterogeneity rather than to chance; SMD: Standardized mean difference.

excluded from the above 4 trials for the calculation of responder rate[35] and change in symptom scores[36] respectively because of insufficient information. Concerning the comparison between mosapride combined therapy and PPI monotherapy, use of mosapride did not significantly elevate the rate of responders (PRR = 1.132; 95%CI: 0.934-1.372; P = 0.572; I^2 = 0.0%) (Figure 3). However, the treatment arm achieved a greater symptom relief than that in placebo arm (Hedges'g = 0.24; 95%CI: 0.03-0.46; P = 0.874; I^2 = 0.0%) (Figure 4). No heterogeneity was found among the studies, both Egger's tests (P = 0.587; P = 0.636) failed to show significance for these studies, indicating no statistically significant publication bias. Only one trial[16] reported a safety analysis, which showed a similar incidence of adverse effects in the two groups.

Trials on addition of mosapride to PPIs for the treatment of PPI-resistant GERD patients

Three open-labeled trials evaluated the additional efficacy of mosapride in PPI-resistant patients. Miyamoto *et al*[37] used an FSSG questionnaire which comprised 12 questions concerning not only acid-related symptoms, but also dysmotility symptoms. They treated 163 GERD patients with rabeprazole 10 mg daily for 3 mo. Thirty-four patients were dissatisfied with the PPI monotherapy and, therefore, were considered to be PPI-resistant. Three months of combined therapy with mosapride resulted in high efficacy. Futagami *et al*[38] explored the function of gastric emptying in PPI-resistant NERD patients, and found that PPI-resistant NERD patients showed significant disturbances of gastric emptying compared to healthy volunteers. Moreover, administration of mosapride in addition to omeprazole alleviated reflux symptoms and improved gastric emptying in PPI-resistant NERD patients. Another study by Miyamoto *et al*[39] analyzed FSSG-reflux score (RS) and -dyspeptic score (DS) of PPI-resistant NERD patients. Significant improvement in FSSG-total score and FSSG-DS was observed after the addition of mosapride in PPI non-response NERD patients. These results indicate that patients with significant dysmotility and functional dyspepsia were more likely to be PPI-resistant and suggest the need for the addition of a prokinetic agent to PPI therapy.

DISCUSSION

With respect to the comparison between mosapride combined treatment with PPI and PPI monotherapy, similar efficacy was found between these two groups in most[16,35,36] of the four randomized controlled trials, the meta-analysis showed similar treatment responsiveness but a significant difference in symptom score improvement between the treatment arm and the placebo arm. However, all the four trials used different symptom scores, the one point improvement should not mean the same symptom relief in different scoring systems. They cannot be standardized, compared or combined easily. Therefore, the rate of responders is more appropriate as the measure of effect size, since the criteria of improvement in each paper was decided to be feasible at least by

the author of each paper. The results indicated that the addition of mosapride to PPI therapy might be useful for patients with GERD, but could not achieve satisfactory effects. Of note, type Ⅱ error should also be considered as a reason for the failure to show a significant difference in the rate of responders. The number of patients may not have been enough. In addition, the analysis of open-label trials showed that mosapride plus PPIs might be of benefit to PPI-resistant GERD patients. However, since these trials did not set the control group, the results may be considerably biased.

Mosapride is a selective 5-HT$_4$ receptor agonist with no affinity for 5-HT$_1$, 5-HT$_2$ or dopamine D$_2$ receptors[42]. It is devoid of anti-dopaminergic and direct cholinomimetic effects. It is well tolerated. Diarrhea, dry mouth, malaise and headache are the most frequent side effects and they were reported in < 5% of patients[43]. Currently, mosapride is commercially available in many Asian countries, but not in United States and Europe. An interesting feature of mosapride is that its action seems to differ along the gastrointestinal tract. Mosapride decreases acid reflux to the esophagus by modulating esophageal motor function in patients with GERD[14], or improving gastric emptying for both solids and liquids in healthy volunteers and diabetic patients[44,45]. It is known that gastric motility is impaired in some NERD patients, and mosapride improves the symptoms in such patients[32]. Mosapride has a distinctly lower affinity to receptors located in the colon[13]. These findings indicate that mosapride selectively stimulates upper gastrointestinal motility, and interacts heterogeously with 5-HT$_4$ receptors. Mosapride has also been shown to modulate visceral sensation *via* raising the threshold of visceral pain caused by balloon expansion in rat stomach[46]. Moreover, it has been reported that mosapride increased the pharmacokinetics of PPIs such as rabeprazole[47], indicating that it is able to facilitate the acid inhibitory effect of PPIs. However, the current results showed that mosapride as an add-on therapy was not more effective than PPI alone in the treatment of GERD. This may be partially due to the effect of the PPI, which might be beneficial to the relief of dyspeptic symptoms[48,49] and obscure the effect of prokinetic treatment.

The strengths of our systematic review could be summarized as follows. We sought to find as many publications as possible using various search approaches. The explicit, detailed eligibility criteria were set up to minimize the selection bias. And we used Cochrane Review Guidelines to assess the quality of the evidence. We also placed emphasis on calculating the possibility of publication bias by Egger's test and evaluating bias across studies, while no heterogeneity was found in our statistical analysis.

There are several limitations of this review. First, the number of patients in the individual studies was relatively small. Second, with respect to PPI-resistant subjects, all of the three studies were open trials, without a placebo control group who did not receive the additional prokinetic agents, therefore, the results could be considerably biased by placebo effect of mosapride administration in this setting. Further randomized, placebocontrolled trials should be performed. Moreover, in two[38,39] out of these three studies, the investigators focused mainly on dyspeptic rather than reflux symptoms. Third, the subtypes of GERD (RE and NERD) patients were not discussed in this review due to little available information. Moreover, there was significant heterogeneity between trials with regard to methodology. Standardized methodology for GERD symptom questionnaire are needed to facilitate the comparison of outcomes and minimize the operating bias.

In conclusion, this review shows that mosapride combined therapy is not more effective than PPI alone as the first-line therapy in GERD patients. Whether it is effective in the treatment of PPI-resistant reflux disease needs to be determined. However, the results of this review are still at the level of descriptive analysis. Further clinical studies with better design and larger number of participants are needed to verify the efficacy of this combined therapy.

COMMENTS

Background

Gastroesophageal reflux disease (GERD) is the most common gastrointestinal diagnosis recorded during visits to outpatient clinics, and the patients sometimes do not respond to proton pump inhibitor (PPI) therapy. Prokinetic agents have been widely used to relieve the GERD symptoms, and mosapride is a selective 5-HT$_4$ receptor agonist that can be safely used. However, the potential benefit of the addition of mosapride to PPIs in the treatment of GERD is unclear.

Research frontiers

Mosapride is a selective 5-HT$_4$ receptor agonist devoid of anti-dopaminergic and direct cholinomimetic effects. Many studies have shown that mosapride can reduce acid reflux episodes and esophageal clearance of refluxate, suggesting potential efficacy in the treatment of GERD.

Innovations and breakthroughs

Based on this systematic review and meta-analysis, mosapride combined therapy was not more effective than PPI alone as the first-line therapy. This has not been identified clearly in previous studies.

Applications

The addition of mosapride to PPI therapy might be useful for patients with GERD, but could not achieve satisfactory effects. Moreover, the fact that mosapride is not yet available in Europe and the United States makes this study more relevant giving physicians some basis for the use in these countries once it is licensed.

Peer review

This is a well-performed systematic review of currently available studies on the potential benefits of the addition of mosapride to PPIs in the treatment of GERD. The authors found that mosapride combined therapy was not more effective than PPI alone as first-line therapy. The conclusions are unbiased and give informative clues to the readers.

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