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RAPID COMMUNICATION

Randomized, double-blind, comparative study of dexrabeprazole 10 mg *versus* rabeprazole 20 mg in the treatment of gastroesophageal reflux disease

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Abstract

AIM: To compare the efficacy and safety of dexrabeprazole 10 mg *versus* rabeprazole 20 mg in the treatment of gastroesophageal reflux disease (GERD).

METHODS: This was a randomized, double-blind clinical study. Fifty patients with GERD were randomly assigned to receive dexrabeprazole 10 mg or rabeprazole 20 mg once daily. Efficacy was assessed by evaluating improvement in visual analog scale (VAS) scores of heart-burn and regurgitation and safety was assessed by recording incidence of any adverse drug reactions. Laboratory investigations and upper gastro-intestinal endoscopy was conducted at baseline and after 28 d of therapy.

RESULTS: A total of 50 patients (n = 25 in dexrabeprazole group and rabeprazole group each) completed the study. There were no significant differences in the baseline characteristics between the two groups. The VAS score (mean ± SD) of heartburn and regurgitation in dexrabeprazole (64.8 ± 5.1 and 64 ± 8.1, respectively) and rabeprazole (64.4 ± 8.7 and 57.6 ± 9.7, respectively) groups significantly reduced (P < 0.0001) to 30 ± 11.5, 24 ± 10 and 32 ± 9.5, 29.2 ± 11.9, respectively on d 28. A significantly higher (P = 0.002) proportion of patients showed ⩾ 50% improvement in regurgitation with dexrabeprazole 10 mg (96%) compared to rabeprazole 20 mg (60%). Onset of symptom improvement was significantly earlier with dexrabeprazole than with rabeprazole (1.8 ± 0.8 d *vs* 2.6 ± 1.4 d; P <0.05). The incidences of esophagitis in the dexrabeprazole group and rabeprazole group before therapy were 84% and 92%, respectively (P = 0.38). The incidence of improvement/healing of esophagitis after therapy was more (P = 0.036) in the dexrabeprazole group (95.2%) compared to the rabeprazole group (65.2%). No adverse drug reaction was seen in either group.

CONCLUSION: In the treatment of GERD, efficacy of dexrabeprazole 10 mg is better than rabeprazole 20 mg, with regards to improvement/healing of endoscopic lesions and relief from symptoms of regurgitation.

Key words: Dexrabeprazole/R(+) rabeprazole; Gastroesophageal reflux disease; Efficacy; Safety

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INTRODUCTION

Rabeprazole is a mixture of two isomers: R(+) and S(-)[1]. Efficacy of dexrabeprazole [R(+) rabeprazole] has been confirmed in animal studies at half the dose of the racemate with the R-isomer being more effective than S-isomer in aspirin-induced ulcers[1]. Pharmacokinetics in human volunteers have shown that, irrespective of the metabolizer status, the ratio of R:S isomer of rabeprazole in terms of C-max was between 1.7 to 1.9, with the ratio for area under the curve (AUC) being between 1.8-2.4. This may explain why dexrabeprazole at lower dose than racemate can be as effective as racemate[2].

MATERIALS AND METHODS

This was a randomized, double-blind, comparative, clinical study permitted by Drugs Controller General of India (DCGI) on November 29, 2006 and was conducted in compliance with the 'Guidelines for Clinical Trials on Pharmaceutical Products in India-GCP Guidelines' issued by the Central Drugs Standard Control Organization, Ministry of Health, Government of India (http://www.cdsco.nic.in/html/GCP1.html). The Ethical Committee Approval was taken from Independent Ethics Committee, Center for Behavioral Medicine, Pune, India. The study was initiated on December 5, 2006 and completed on April 5, 2007.

Male or female patients between 18-65 years of age,

Table 1 Results of endoscopic findings

Parameters	Baseline (d 0)		After therapy (d 28)		Analysis of findings				
	Dexrabeprazole 10 mg (n = 25)	Rabeprazole 20 mg (n = 25)	Dexrabeprazole 10 mg (n = 25)	Rabeprazole 20 mg (n = 25)	CER	TER	ARR	RRR	NNT
Patients with esophagitis[4]	21	23	8	15	0.65	0.38	0.27	42%	4
Grade A	1	7	8	11					
Grade B	20	16	0	4					
Grade C	0	0	0	0					
Grade D	0	0	0	0					
Investigator-reported improvement in endoscopic findings and healing									
-Yes	NA	NA	20	15	0.652	0.952	0.30	46%	3
-No	NA	NA	1	8					

NA: Not applicable; CER: Control event rate; TER: Test event rate; ARR: Absolute risk reduction; RRR: Relative risk reduction; NNT: Number needed to treat.

clinically diagnosed with GERD were included after obtaining written informed consent. Patients with a known history of hypersensitivity to any proton pump inhibitors (PPIs) or history of infectious or inflammatory conditions of the intestine such as inflammatory bowel disease, malabsorption syndromes, intestinal obstruction, gastrointestinal malignancy, gastric or intestinal surgery (vagotomy), Barrett's esophagus, esophageal stricture, pyloric stenosis, and scleroderma were excluded from the study. Pregnant and lactating females, patients with abnormal laboratory tests at baseline (including liver enzymes greater than twice the upper limit of normal), patients refractory to a 2-mo course of H_2-blocker or PPI therapy for GERD treatment, patients who took PPI within 14 d of screening or a H_2-blocker or prokinetic agent within 7 d of screening, patients who required daily use of non-steroidal anti-inflammatory drugs (NSAIDs), oral steroids, aspirin or who were unable to discontinue the use of anticholinergics, cholinergics, spasmolytics, opiates or sucralfate and patients with poorly controlled associated disease (such as heart disease, coagulation disorders, thyroid disorders) were also excluded from the study.

Enrolled patients were randomized (as per the computer generated randomization chart, www.randomization.com) in blocks of ten to receive identical looking tablets of dexrabeprazole 10 mg once daily (OD) or rabeprazole 20 mg OD in coated opaque envelopes to conceal the identity of the treatment allocated.

Patients recorded severity/relief of their symptoms on a visual analog scale (VAS)[3] [at baseline (d 0) and on d 14 and 28 of therapy] and in a diary card (daily throughout the study duration). Laboratory investigations (SGPT, SGOT, serum creatinine, platelet count, total and differential WBC count) and upper gastro-intestinal endoscopy were conducted at baseline and after 28 d of therapy.

Statistical analysis

Student's t test was applied for VAS scores and Chi-square for proportions showing $\geqslant$ 50% improvement. CLINSTAT software was used for statistical analysis (Martin Bland, CLINSTAT). $P < 0.05$ was considered statistically significant.

RESULTS

A total of 50 patients (n = 25, M:F = 16:9, mean age: 39.32 ± 10.6 years, mean weight: 60.4 ± 11.27 kg in 10 mg dexrabeprazole group; n = 25, M:F = 20:5, mean age: 35.7 ± 6.4 years, mean weight: 64.3 ± 13.4 kg in 20 mg rabeprazole group) completed the study. There were no significant differences in the baseline characteristics of the two groups. The VAS score (mean ± SD) of heartburn and regurgitation in dexrabeprazole and rabeprazole groups reduced significantly ($P < 0.0001$) from 64.8 ± 5.1, 64 ± 8.1, and 64.4 ± 8.7, 57.6 ± 9.7 on d 0 to 42 ± 10.4, 34.8 ± 10.8 and 46.4 ± 11.5, 35.4 ± 10.8 on d 14 with further reduction to 30 ± 11.5, 24 ± 10 and 32 ± 9.5, 29.2 ± 11.9 on d 28 of the therapy, respectively. There was no significant intergroup difference in improvement of symptom scores. A significantly higher ($P = 0.002$) proportion of patients showed at least 50% improvement in symptoms of regurgitation with dexrabeprazole 10 mg (96%) than with rabeprazole 20 mg (60%). Onset of symptom improvement was earlier ($P < 0.05$) at 1.8 ± 0.8 d with dexrabeprazole than with rabeprazole at 2.6 ± 1.4 d. Endoscopy showed that the incidence of 'residual esophagitis' (any grade of esophagitis as per Los Angeles Classification[4]) after 28 d was higher in the 20 mg rabeprazole group compared to 10 mg dexrabeprazole group. Similarly, incidence of healing was significantly higher ($P = 0.036$) in the dexrabeprazole group compared to the rabeprazole group (Table 1). This represents an absolute improvement of 30% and relative improvement of 46% over racemate. No adverse drug reaction was seen in either group. Laboratory parameters did not show any significant differences as compared to baseline.

DISCUSSION

GERD is characterized by recurrent return of gastric contents back into the esophagus. The goal of treatment is to improve patient's quality of life by providing rapid relief of symptoms and reducing the severity and number of recurrent episodes. Therefore, an important endpoint in clinical trials assessing the efficacy of treatment in GERD patients is time taken for complete relief of symptoms, especially the pivotal symptoms of heartburn and regurgitation. This can be measured as time to the first 24-h interval free from GERD symptoms of heartburn or acid regurgitation. Other endpoints include global symptom improvement, satisfactory, and complete relief of symptoms, *etc*.

In the present study, onset of action (time to the first 24-h interval free from GERD symptoms) was significantly earlier ($P < 0.05$) with dexrabeprazole than with rabeprazole. Although, the VAS score of heartburn and regurgitation in dexrabeprazole and rabeprazole groups reduced significantly ($P < 0.0001$), a higher ($P = 0.002$) proportion of patients showed at least 50% improvement in symptoms of regurgitation with 10 mg dexrabeprazole (96%) than with 20 mg rabeprazole (60%). Endoscopic findings also showed that the incidence of healing was significantly higher ($P = 0.036$) in the dexrabeprazole group as compared to the rabeprazole group (Table 1). This represents an absolute improvement of 30% and relative improvement of 46% over racemate, yielding an NNT (number of patients needed to treat to benefit at least one patient) of only 3 patients. No adverse drug reaction was seen in either group. Laboratory parameters did not show any significant differences as compared to baseline.

This study shows that in the symptomatic management of GERD, dexrabeprazole will provide better results than the racemate, even when used at half the normal dose. Our results are in conformity with previously published pre-clinical studies[1], confirming the efficacy of dexrabeprazole at half the dose of the racemate. Thus it would, therefore, be advantageous to use the R(+) isomer in favor of the racemate to reduce metabolic load on the body, to simplify pharmacokinetics and have better efficacy with equal safety.

The therapeutic value of chiral purification of PPI racemates is already confirmed with earlier introductions of esomeprazole and S-pantoprazole[5]. Findings of the present study strengthen this further.

In summary, for GERD treatment, efficacy of dexrabeprazole 10 mg is better than rabeprazole 20 mg, with regards to improvement and healing of endoscopic lesions and relief from symptoms of regurgitation.

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COMMENTS

Background

Gastroesophageal reflux disease (GERD) is very common, presenting as heartburn and regurgitation. GERD can be associated with inflammation of esophageal mucosa (esophagitis) and even abnormal cellular changes (Barett' s esophagus). Proton pump inhibitors (PPIs) form the mainstay of therapy for GERD.

Research frontiers

PPIs are mixtures of enantiomers. Chiral purification of PPI is a useful way to improve existing therapy. Early improvement in healing of esophagitis is very important.

Innovations and breakthroughs

Chiral purification has previously allowed introduction of better version of omeprazole and pantoprazole as esomeprazole and S-pantoprazole in terms of better efficacy.

Applications

The existing racemate rabeprazole when used as chirally pure dexrabeprazole lessens the drug dosage, metabolic load on body, and provides faster healing of esophagitis with more patients getting relief from symptoms of GERD.

Terminology

GERD = Gastroesophageal reflux disease, VAS = Visual analog Scale used to score symptoms, CER = Control event rate (i.e. incidence with the reference product), TER = Test event rate (i.e. incidence with the test product), ARR = Absolute risk reduction (in the event of interest), NNT = number (of patients) needed to treat to benefit at least one patient.

Peer review

This is a randomized, double-blind clinical study comparing efficacy and safety of dexrabeprazole 10 mg *versus* rabeprazole 20 mg in the treatment of gastroesophageal reflux disease (GERD). The paper is well written and the results show efficacy of dexrabeprazole 10 mg is better than rabeprazole 20 mg, with regards to improvement/healing of endoscopic lesions and relief from symptoms of regurgitation

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