



Evaluation of the Additive Effect of Domperidone on Patients with Refractory Gastroesophageal Reflux Disease Symptoms; A Randomized Double Blind Clinical Trial

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ABSTRACT

BACKGROUND

Gastroesophageal reflux disease (GERD) is a common problem with annoying symptoms. It is associated with negative impact on quality of life. Prokinetic agents may be used in combination with acid suppression agents as an adjunctive in patients with GERD refractory to proton pump inhibitors (PPI) therapy, rather than as sole treatment. This study aimed to evaluate the efficacy of combination of PPI with domperidone (a prokinetic agent) compared with PPI alone in the treatment of patients with refractory GERD.

METHODS

This study was a double blind clinical trial on 29 patients with GERD refractory to PPI during the period of one month. By randomization, the patients were divided into two groups. Group A was treated by pantoprazole 40 mg twice daily and domperidone 10 mg three times a day for a month, while group B was treated by pantoprazole 40 mg twice daily and placebo three times a day. In this study endoscopy was performed to evaluate the prevalence of erosive esophagitis, non-erosive reflux, and hiatal hernia. Manometry was conducted to study the prevalence of dysmotility. GERD symptom questionnaires including the Gastrointestinal Symptom Rating Scale (GSRSS), Carlson Dennett, and the Medical Outcomes Study Short Form-36 health survey (SF36) were used before and after treatment for screening GERD and assessing treatment response.

RESULTS

There were 17 (58.62%) women and 12 (41.37%) men. The prevalence of erosive esophagitis and non-erosive reflux, was 10.34% and 89.66%, respectively. There was a significant difference comparing reflux symptoms before and after treatment between the two groups according to reflux and Carlson Dennett questionnaires. At the end of the study, symptoms of reflux significantly improved by treatment. Although, the quality of life questionnaire scores improved by treatment, there was no statistically significant difference in response to treatment between the two groups.

CONCLUSION

In this research, we showed that adding domperidone to PPI could not make any improvement in patients with refractory reflux regarding the quality of life and improving the symptoms.

KEYWORDS:

Refractory GERD, PPI, Domperidone, Treatment

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INTRODUCTION

Gastroesophageal reflux disease (GERD) refers to reflux of gastric contents into the esophagus, which can cause esophagitis and symptoms affecting the



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quality of life. In this regard a study revealed that quality of life in patients with GERD is impaired in Iranian population.¹ The primary pathophysiology of reflux is transient relaxation of the lower esophageal sphincter. Some of the predisposal factors include obesity, smoking, and genetic factors. There are different methods for diagnosis including esophageal pH monitoring.² Incidence per 1000 person-year was approximately 5 in the overall UK and US populations, and 0.84 in childhood aged 1-17 years in the UK.³ A study showed that the prevalence of GERD in north of Iran (Sari city) is 13.09%⁴ and another investigation in Tehran estimated this prevalence up to 39.7%.⁵

Evidence suggests an increase in GERD prevalence since 1995 ($p < 0.0001$), particularly in North America and East Asia.³

The first step in the treatment is life style changes, but most of patients do not response to these methods and need empirical acid suppression with a proton pump inhibitor (PPI) or H₂ receptor antagonist.² There are other treatment modalities like domperidone that their effects are still under investigations. Domperidone is a dopamine-2 receptor antagonist. It acts as a prokinetic substance through its impacts on the chemoreceptor trigger zone and motor function of the gastric and small intestine. In contrast to metoclopramide, it does not lead to any adverse neurological effects. It has an excellent safety profile for long-term oral administration. Domperidone is widely used in the treatment of gastroparesis and any situations causing chronic nausea and vomiting. Some current studies used it for treatment of GERD in addition to PPI.⁶ Concerning the discrepancy in the results between studies on the role of domperidone in the treatment of GERD we decided to evaluate this option.

MATERIALS AND METHODS

This study was a randomized double blind clinical trial. The study population included consecutive patients with refractory reflux symptoms more than a month. Iranian Registry of Clinical Trials number is IRCT2017052134070N1.

Inclusion criteria

Patients who did not show any response or responded partially to treatment with pantoprazole (or its equivalent PPI) 40 mg twice a day for one month were enrolled in

this study. As compliance and proper use of drugs can be a cause of poor response, all collaborative colleagues asked these issues before sending the patients for the study enrolment.

Symptoms-based diagnosis is widely used with acceptable sensitivity and specificity.⁷ Some structural questionnaires were developed to standardize the symptoms-based diagnosis of GERD.⁸⁻¹⁵ The studies evaluating the validity of these types of questionnaire have conflicting results with reported sensitivity of 60-92%.⁶⁻¹⁵

Carlson-Dent Reflux Questionnaire,¹⁶ (questionnaire based assessment scales for GERD) has been utilized for assessment of the patients' disease severity and for response to treatment.¹⁷ SF-36 questionnaire (the Short-Form Health Survey)¹⁸ was used to assess the quality of life. Questioners were asked before and after the study by trained researchers.

Exclusion criteria

Patients aged less than 18 years, as well as patients with pregnancy, history of gastric or esophageal surgery, history of gastric or esophageal malignancy, congestive heart failure (grade 3 and 4), liver disease including cirrhosis and chronic liver disease, history of sensitivity to the drugs, and patients refusing to participate in the study were excluded from the study.

All patients were randomized and divided to two groups A and B. Group A received domperidone 10 mg three times a day 30 min before each meal with PPI (pantoprazole 40 mg) twice per day 30 min before meals for one month. Group B received placebo three times a day 30 min before each meal with PPI (pantoprazole 40 mg) twice per day 30 min before meals for one month.

Ethical Approval

All patients provided informed consent to inclusion in the study. This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran.

Statistical Analysis

Results were shown as median, mean, and standard deviation. The Chi square, Student t, and Fischer exact tests were used for analysis of data. The procedures included were transcription, preliminary data inspection,

Table 1: Results of endoscopic evaluation of the patients

Endoscopic findings		Presence	Absence	P value
Erosive esophagitis	Group A	3 (23.07%)	10 (76.92%)	0.078
	Group B	0 (0)	16 (100%)	
	Total	3 (10.34%)	26 (89.66%)	
Gastric or duodenal erosion	Group A	2 (15.38%)	11 (84.6%)	0.5
	Group B	1 (6.25%)	15 (93.7%)	
	Total	3 (10.43%)	26 (89.6%)	
Bile stained secretions in stomach	Group A	1 (7.69%)	12 (92.30%)	1.000
	Group B	1 (6.25%)	15 (93.75%)	
	Total	2 (6.89%)	27 (93.10%)	
Gastric ulcer	Group A	0 (0)	13 (100%)	0
	Group B	0 (0)	16 (100%)	
	Total	0 (0)	29 (100%)	
Duodenal ulcer	Group A	1 (7.69%)	12 (92.30%)	0.448
	Group B	0 (0)	16 (100%)	
	Total	1 (3.44%)	28 (96.55%)	
Hiatal hernia	Group A	8 (61.5%)	5 (38.5%)	0.74
	Group B	11 (68.8%)	5 (31.3%)	
	Total	19 (65.5%)	10 (34.5)	

Table 2: Manometry findings in the two groups

Study group	Normal	Weak	Others	P value
Group A	9 (69.2%)	3 (23.1%)	1 (7.7%)	1.000
Group B	11 (68.8%)	4 (25.0%)	1 (6.3%)	
Total	20 (69%)	7 (24.1%)	2 (6.9%)	

content analysis, and finally interpretation. Statistical analysis was performed with SPSS software (version 20, Chicago, IL, USA). *P* values less than 0.05 were considered as statistically significant.

RESULTS

Initially 30 patients were registered for this study and one patient was excluded with the diagnosis of achalasia. Group A included 16 patients and group B consisted of 13 patients.

Demographic data

There was six women (46.2%) and seven men (53.8%) in group A while group B consisted of 11 women (68.8 %) and five men (31.3%). There was no significant differences between sexes in these two groups ($p = 0.219$). Mean age of the patients in group A was 35.92 ± 9.97 years and in group B was 37.31 ± 9.29 years. There was no significant differences between the mean ages ($p = 0.7$).

None of the patients had history of smoking, or NSAID and ASA use.

Endoscopic findings

Findings of endoscopic assessment are summarized in table 1. None of the cases had history of gastrointestinal (GI) bleeding. Sliding hiatal hernia was more common in group B but not significantly. The prevalence of sliding hiatal herein was 34.5 % (table 1).

Manometry

Esophageal manometry is a test for assessing esophageal dysmotility. Esophageal manometry measures the rhythmic muscle contractions that occur in esophagus and also measures the coordination and force exerted by the muscles of esophagus. Fisher exact test showed no differences in manometry findings between the two groups. 69% had normal esophageal motility, 24.1% had weak esophageal motility, and 6.9% had other disorders (table 2).

Table 3: The prevalence of dysmotility between the two groups

Study group	Dysmotility (absence)	Dysmotility (presence)	P value fisher exact test
Group A	9 (69.2%)	3 (30.8%)	1.00
Group B	11(68.8%)	5 (31.3%)	1.00
Total	20 (69%)	9 (31%)	

Table 4: The results of Kolmogorov-Smirnov test before and after treatment

Study group	P value Kolmogorov-Smirnov before treatment	P value Kolmogorov-Smirnov after treatment
GERD questionnaire	A	0.2
	B	0.195
Carlson Dennett questionnaire	A	0.2
	B	0.2
SF-36 questionnaire	A	0.2
	B	0.2

Table 5: Comparison of GERD, Carlson Dennett, and SF-36 questionnaires before and after treatment

Questionnaire	A	B	P value paired t test
GERD questionnaire	Before treatment	6.94 ± 2.67	8.06 ± 2.67
	After treatment	3.38 ± 3.30	4.31 ± 3.45
Carlson Dennett questionnaire	Before treatment	9.62 ± 4.23	6.94 ± 4.49
	After treatment	6.46 ± 1.89	3.88 ± 1.00
SF-36 questionnaire	Before treatment	70.86 ± 9.88	58.63 ± 15.79
	After treatment	76.14 ± 8.21	63.21 ± 18.53

Table 6: Comparison of GERD, Carlson Dennett, and SF-36 questionnaires before and after treatment

Questionnaire	A	B	P value paired t test
GERD questionnaire	A	6.94 ± 2.67	3.38 ± 3.30
	B	8.06 ± 2.67	4.31 ± 3.45
Carlson Dennett questionnaire	A	9.62 ± 4.23	6.46 ± 1.89
	B	6.94 ± 4.49	3.88 ± 1.00
SF-36 score	A	70.86 ± 9.88	76.14 ± 8.21
	B	58.63 ± 15.79	63.21 ± 18.53

There was no significant difference in the prevalence of dysmotility between the two groups (table 3).

Kolmogorov-Smirnov test showed normal distribution for questionnaires before and after the treatment, which is summarized in table 4.

Comparison of GERD, Carlson Dennett, and SF36 questionnaires

Carlson Dennett and GERD questionnaire results revealed no significant differences between the study

arms. This means that application of domperidone was not effective in reducing reflux. SF-36 questionnaire examined the quality of life of the study population. The outcomes indicated that the quality of life of the patients who received domperidone was significantly higher. But at the baseline the quality of life of group B was higher and on the other hand at the end of the study both groups could not show any valuable increase in SF-36 questionnaire results. We can conclude that the final significant changes might be related to primary alterations (table 5, and 6).

Table 7: Mean psychological scores for SF-36 questionnaire

	Group	Before treatment	After treatment	P value paired t test
Total psychological score SF-36	A	70.09 ± 11.44	75.12 ± 11.08	0.055
	B	53.42 ± 17.40	58.69 ± 18.12	0.132
P value independent t test		0.043	0.069	
Total physical score SF-36	A	69.18 ± 10.95	73.99 ± 10.29	0.232
	B	58.19 ± 15.85	62.96 ± 18.78	0.123
P value independent t test		0.043	0.069	

One of the objectives of this study was to evaluate the quality of life with the use of SF-36 questionnaire in patients with GERD. Mean Physical scores of SF-36 questionnaire were summarized in table 7. There was no significant difference in the results.

Mean psychological scores of SF-36 questionnaire were reported in table 7. When assessing the quality of life, according to the domains of the SF-36, we found no statistically significant difference in the outcomes.

DISCUSSION

GERD can be divided to erosive esophagitis (EE) and non-erosive reflux disease (NERD). In this study 10.34% of the patients had EE. 89.66% were in NERD group. This prevalence was approved by other studies. In this regards, Masaki Miyamoto and colleagues¹⁹ reported that the prevalence of EE in their population was 25.3% and prevalence of NERD was 74.7%. The importance of this issue is that patients with NERD are more resistant to treatments, which were approved by Masaki Miyamoto,¹⁹ Bonnie B. Dean,²⁰ and Ronnie Fass and their colleagues.²¹ Bonnie B. Dean and co-workers²⁰ revealed that the response rate to medical therapy for patients with NERD was 37% but in EE group was 56%.

One of the goals of this study was to evaluate esophageal dysmotility by manometry. We found that 69% had normal motility, 24.1% had weak, and 6.9% had other types of esophageal motility dysfunctions. The prevalence of dysmotility in patients with resistant GERD was 31% (nine cases). All of these nine patients were in NERD group.

This study was in contrast with the studies by Kim²² and Wu and their colleagues.²³ They revealed that NERD group had more esophageal dysmotility. Like these investigations, our current research showed that the prevalences of hiatal hernia and dysmotility were

more in patients with NERD patients with EE.

A study by Ndraha and others examined the effect of domperidone on efficacy of treatment. They used frequency scale for the symptoms of GERD for evaluation of 60 patients. Group A received omeprazole plus domperidone and the other group received only omeprazole.²⁴ This study showed a better response in group A in comparison with group B.

In another study, Hu Yi min and colleagues²⁵ evaluated 66 patients with GERD. Also they proved that domperidone plus PPI was more effective than famotidine plus domperidone. In contrast with these studies the current study did not show the same results. Although both groups have improved but there was no significant difference between the groups.

In this regards, in a study by Biltagi and co-workers,²⁶ that examined those who had GERD, the patients were randomly and blindly divided into two equal groups. The first group was treated with esomeprazole and domperidone for 12 weeks while the other subgroup was treated with esomeprazole. They concluded that combination of domperidone and esomeprazole was more effective in improving the endoscopic reflux score. One of the limitations of their study was that they did not use various questionnaires to evaluate the patients but in the current study the patients were evaluated by using three different questionnaires.

In another study, Masci E and colleagues²⁷ evaluated 45 outpatients with reflux esophagitis who were randomly treated with either ranitidine (150 mg twice a day) or domperidone maleate (20 mg three times a day) or both drugs for six weeks. Before and after therapy the severity of dyspeptic symptoms and the grade of endoscopic and histological alterations were noted. Like the current investigation the three therapeutic regimens were significantly

and equally effective in inducing symptomatic relief and promoting endoscopic and histological disappearance or improvement of esophagitis. The combined use of ranitidine and domperidone maleate failed to indicate any additional benefit compared with treatment with either drugs alone.

Foocharoen and co-workers²⁸ studied 148 patients with systemic scleroses-GERD. 80 cases were randomized for either domperidone (n = 38) or algycon (n = 37) therapy. At the end of the study, no significant difference in symptom grading was found between the groups. After treatment and compared with the baseline, the severity of symptoms, frequency scale for symptoms of GERD, and quality of life significantly improved in both groups. Five (13.2%) and 8 (21.6%) respective cases in the domperidone and algycon groups did not respond.

Rodríguez-Sánchez and others²⁹ evaluated 100 cases with GERD diagnosed by Carlsson scale. They were randomized to receive magaldrate/domperidone combination or domperidone alone during a month. They reported that magaldrate/domperidone combination had better outcomes than domperidone alone. Moreover they found that, magaldrate/domperidone combination could statistically improve the quality of life. Both treatments were well tolerated. Their study showed that combination of anti-acid and domperidone had better outcomes.

Interestingly our study revealed the same results that adding domperidone to a PPI improved the quality of life of the patients. But Rodríguez-Sánchez and others did not use different questionnaires to examine the cases and therefore all results cannot be compared.

We think that the outcomes of this study should be viewed in the light of its limitations. One limitation of this study was the few number of enrolled cases; however we conducted the study as a preliminary study to suggest further studies if any reasonable result is achieved.

The concept of using domperidone in GERD is an active concept, although it is not supported in references. In a recent study that was published in 2017, Marakhouski and colleagues showed that Omeprazole-domperidone combination would be more effective than omeprazole alone in reducing GERD symptoms and healing of esophagitis in patients with GERD.³⁰

CONCLUSION

In summary, the group receiving domperidone therapy showed significant increases in the SF-36 score after treatment, which means the improvement of the quality of life in this group. But Carlson Dennett and GERD questionnaires outcomes showed no difference between domperidone and placebo; however as the included patients were a small group, we do recommend further studies in this field with larger patient populations.

Recommendations

One of the main ways of detecting GERD is pH-metry, which can measure esophageal pH. The procedure includes establishing the pH in the esophageal tract.³¹ The results would be considered as significant at the pH < 4.³² The authors of this paper recommend that adding pH monitoring and manometry to current diagnostic procedures on more cases would result in better outcomes.

ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

REFERENCES

1. Maleki I, Masoudzadeh A, Khalilian A, Daheshpour E. Quality of life in patients with gastroesophageal reflux disease in an Iranian population. *Gastroenterol Hepatol Bed Bench* 2013;**6**:96-100.
2. Moayyedi P, Talley NJ. Gastro-oesophageal reflux disease. *Lancet* 2006;**367**:2086-100. doi:10.1016/S0140-6736(06)68932-0.
3. El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2014;**63**:871-80. doi:10.1136/gutjnl-2012-304269.
4. Ehsani MJ, Maleki I, Mohammadzadeh F, Mashayekh A. Epidemiology of gastroesophageal reflux disease in Tehran, Iran. *J Gastroenterol Hepatol* 2007;**22**:1419-22. doi: 10.1111/j.1440-1746.2006.04616.x.
5. Shahravan S, Maleki I. Prevalence and clinical conditions of gastroesophageal reflux: A population based study in Sari city, Iran. *Govaresh* 2013;**18**:112-3.
6. Reddyasu SC, Soykan I, McCallum RW. Domperidone: review of pharmacology and clinical applications in gas-

- troenterology. *Am J Gastroenterol* 2007;**102**:2036-45. doi:10.1111/j.1572-0241.2007.01255.x.
7. Shaw M. Diagnostic utility of reflux disease symptoms. *Gut* 2004;**53**(suppl 4):iv25-7.
 8. Jones R, Junghard O, Dent J, Vakil N, Halling K, Wernersson B, et al. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. *Aliment Pharmacol Ther* 2009;**30**:1030-8. doi:10.1111/j.1365-2036.2009.04142.x.
 9. Stanghellini V, Armstrong D, Mönnikes H, Bardhan K. Systematic review: do we need a new gastro-oesophageal reflux disease questionnaire? *Digestion* 2007;**75**(Suppl. 1):3-16. doi:10.1159/000101077.
 10. Wang J-H, Luo J-Y, Dong L, Gong J, Zuo A-L. Composite score of reflux symptoms in diagnosis of gastroesophageal reflux disease. *World J Gastroenterol* 2004;**10**:3332-5. doi:10.3748/wjg.v10.i22.3332.
 11. Ho KY, Gwee KA, Khor JL, Selamat DS, Yeoh KG. Validation of a graded response questionnaire for the diagnosis of gastroesophageal reflux disease in an Asian primary care population. *J Clin Gastroenterol* 2008;**42**:680-6. doi:10.1097/MCG.0b013e3180653613.
 12. Wong W, Lam K, Lai K, Hui W, Hu W, Lam C, et al. A validated symptoms questionnaire (Chinese GERDQ) for the diagnosis of gastro-oesophageal reflux disease in the Chinese population. *Aliment Pharmacol Ther* 2003;**17**:1407-13. doi:10.1046/j.1365-2036.2003.01576.x.
 13. Shimoyama Y, Kusano M, Sugimoto S, Kawamura O, Maeda M, Minashi K, et al. Diagnosis of gastroesophageal reflux disease using a new questionnaire. *J Gastroenterol Hepatol* 2005;**20**:643-7. doi:10.1111/j.1440-1746.2005.03776.x.
 14. Carlsson R, Dent J, Bolling-Sternevald E, Johnsson F, Junghard O, Lauritsen K, et al. The usefulness of a structured questionnaire in the assessment of symptomatic gastroesophageal reflux disease. *Scand J Gastroenterol* 1998;**33**:1023-9. doi:10.1080/003655298750026697.
 15. Kusano M, Shimoyama Y, Sugimoto S, Kawamura O, Maeda M, Minashi K, et al. Development and evaluation of FSSG: frequency scale for the symptoms of GERD. *J Gastroenterol* 2004;**39**:888-91. doi:10.1007/s00535-004-1417-7.
 16. Netinatsunton N, Attasaranya S, Ovartharnporn B, Sangnil S, Boonviriyaya S, Piratvisuth T. The value of Carlsson-Dent questionnaire in diagnosis of gastroesophageal reflux disease in area with low prevalence of gastroesophageal reflux disease. *J Neurogastroenterol Motil* 2011;**17**:164-8. doi:10.5056/jnm.2011.17.2.164.
 17. Mouli VP, Ahuja V. Questionnaire based gastroesophageal reflux disease (GERD) assessment scales. *Indian J Gastroenterol* 2011;**30**:108-17. doi:10.1007/s12664-011-0105-9.
 18. Ciconelli RM, Ferraz MB, Santos W, Meinão I, Quaresma M. Brazilian-Portuguese version of the SF-36. A reliable and valid quality of life outcome measure. *Rev Bras Reumatol* 1999;**39**:143-50.
 19. Miyamoto M, Manabe N, Haruma K. Efficacy of the addition of prokinetics for proton pump inhibitor (PPI) resistant non-erosive reflux disease (NERD) patients: significance of frequency scale for the symptom of GERD (FSSG) on decision of treatment strategy. *Intern Med* 2010;**49**:1469-76. doi:10.2169/internalmedicine.49.3615.
 20. Dean BB, Gano AD, Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. *Clin Gastroenterol Hepatol* 2004;**2**:656-64. doi:10.1016/S1542-3565(04)00288-5.
 21. Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: proton-pump inhibitor failure in gastro oesophageal reflux disease—where next? *Aliment Pharmacol Ther* 2005;**22**:79-94. doi:10.1111/j.1365-2036.2005.02531.x.
 22. Kim N, Lee S, Cho S, Park C, Yang C, Kim H, et al. The prevalence of and risk factors for erosive oesophagitis and non-erosive reflux disease: a nationwide multicentre prospective study in Korea. *Aliment Pharmacol Ther* 2008;**27**:173-85. doi:10.1111/j.1365-2036.2007.03561.x.
 23. Wu JC, Cheung CM, Wong VW, Sung JJ. Distinct clinical characteristics between patients with nonerosive reflux disease and those with reflux esophagitis. *Clin Gastroenterol Hepatol* 2007;**5**:690-5. doi:10.1016/j.cgh.2007.02.023.
 24. Ndraha S. Combination of PPI with a prokinetic drug in gastroesophageal reflux disease. *Acta Med Indones* 2011;**43**:233-6.
 25. Hu Ym, Xu XI, Ding Y. Treatment of Gastroesophageal Reflux Disease with Pantoprazole and Domperidone. *Med J Nation Defend Force North China* 2007;**3**:005.
 26. Al-Biltagi M, Bediwy AS, Deraz S, Amer HG, Saeed NK. Esomeprazole, versus esomeprazole and domperidone in treatment of gastroesophageal reflux in children with difficult-to-treat asthma. *Eur Resp J* 2013;**1138**.
 27. Masci E, Testoni P, Passaretti S, Guslandi M, Tittobello A. Comparison of ranitidine, domperidone maleate and ranitidine + domperidone maleate in the short-term treatment of reflux oesophagitis. *Drugs Exp Clin Res* 1985;**11**:687-92.
 28. Foocharoen C, Chunlertrith K, Mairiang P, Mahakannukrauh A, Suwannaroj S, Namvijit S, et al. Effectiveness of add-on therapy with domperidone vs alginate acid in proton pump inhibitor partial response gastro-oesophageal reflux disease in systemic sclerosis: randomized placebo-controlled trial. *Rheumatology* 2017;**56**:214-22. doi:10.1093/rheumatology/kew216.
 29. Rodríguez-Sánchez SN, Rocha-González HI, del Valle-Laisequilla CF, Rodríguez-Silverio J, Flores-Murrieta FJ, Reyes-García JG. Fixed dose combination of magaldrate

- plus domperidone is more effective than domperidone alone in the treatment of patients with gastroesophageal reflux symptoms: a randomized double-blind study. *Pharmacology & Pharmacy* 2014;**5**:216-23. doi:10.4236/pp.2014.52028.
30. Marakhouski K, Karaseva G, Ulasivich D, Marakhouski YK. Omeprazole-Domperidone Fixed Dose Combination vs Omeprazole Monotherapy: A Phase 4, Open-Label, Comparative, Parallel Randomized Controlled Study in Mild to Moderate Gastroesophageal Reflux Disease. *Clin Med Insights Gastroenterol* 2017;**10**:1179552217709456. doi: 10.1177/1179552217709456.
 31. Streets CG, DeMeester TR. Ambulatory 24-hour esophageal pH monitoring: why, when, and what to do. *J Clin Gastroenterol* 2003;**37**:14-22.
 32. Chiou E, Rosen R, Jiang H, Nurko S. Diagnosis of supra-esophageal gastric reflux: correlation of oropharyngeal pH with esophageal impedance monitoring for gastro-esophageal reflux. *Neurogastroenterol Motil* 2011;**23**:717-e326. doi:10.1111/j.1365-2982.2011.01726.x.