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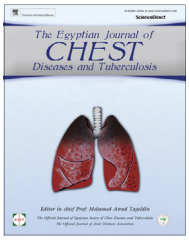

ORIGINAL ARTICLE

Combination therapy versus monotherapy for gastroesophageal reflux in children with difficult-to-treat bronchial asthma

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Abstract Gastroesophageal reflux (GER) is a common disorder in children with bronchial asthma. It has been identified as a potential trigger, complication and even differential diagnosis for asthma. Our aim was to find out the efficacy of the combined use of both the proton pump inhibitor esomeprazole and the antidopaminergic prokinetic domperidone versus the sole use of esomeprazole in improving asthma severity in children with difficult to treat asthma.

Patients and methods: Among 178 children with difficult-to-treat asthma, GER was assessed using upper GIT endoscopy. Those who had GER were randomly divided into 2 equal subgroups the first was treated with esomeprazole for 12 weeks while the other was treated with esomeprazole and domperidone for the same period (beside the usual treatment for asthma in both groups). Childhood-asthma control test (C-ACT), forced expiratory volume in 1st second (FEV_1) [% of predicted], peak expiratory flow (PEF) variability, induced sputum substance P (SP) and endoscopic reflux score (ERS) were recorded before and after the treatment.

Results: Gastro-esophageal reflux (GER) was observed in about 45% of children with difficult-to-treat asthma. The C-ACT, induced sputum SP, ERS and FEV_1 showed significant improvement while PEF variability showed no significant changes when comparing combination therapy subgroup (esomeprazole and domperidone) with esomeprazole only subgroup.

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Conclusions: Combination of domperidone and esomeprazole was more effective in improving the endoscopic reflux score, childhood-asthma control test (C-ACT) and FEV_1 (% of predicted) and significantly reduced the sputum SP than the use of esomeprazole only in children with difficult-to-treat asthma.

Introduction

Gastroesophageal reflux (GER) is a common finding in asthmatic children and has been identified as a potential trigger for asthma. GER is thought to affect asthma through the activation of vagal reflexes and/or microaspiration [1].

Previously, we found that the use of esomeprazole was effective in improving asthma symptoms as indicated by childhood-asthma control test (C-ACT), however it had insignificant effects on lung function as indicated by FEV_1 and peak expiratory flow variability [2]. Another previous study showed the efficacy of the combined use of omeprazole and domperidone in improving asthma in adult patients with asthma and gastroesophageal reflux [3].

This stimulated us to investigate the efficacy of the combined use of both esomeprazole and antidopaminergic prokinetic domperidone versus the sole use of esomeprazole in improving asthma severity as indicated by C-ACT, FEV_1, PEF variability and induced sputum levels of SP in children having difficult to treat asthma with GER.

Patients and methods

The study included 178 children between 6 and 10 years of age (diagnosed with difficult-to-treat bronchial asthma) and attending the Asthma Clinic of Pediatric and Pulmonology Departments at International Hospital of Bahrain, a tertiary care hospital, Kingdom of Bahrain. Patients were identified from the clinic database according to the guidelines of the National Asthma Education and Prevention Program [4].

The inclusion criteria of the study at screening included the following:

1- Asthma was diagnosed based on the symptoms, family history, and documented with the presence of reversible airflow obstruction (increase FEV_1 by more than 12% after inhaled short acting ß2-agonist) and PEF variability $\geqslant 20\%$.
2- Difficult-to-treat asthma was identified if the child has persistent refractory symptoms, was receiving maintenance therapy of inhaled steroids ($\geqslant 400$ µg beclomethasone dipropionate or equivalent per day) and long acting ß2-agonist and had received at least one course of systemic steroids in the preceding 12 months [5,6].

Exclusion criteria included the following:

1. Other chronic lung disease or systemic medical condition other than asthma, GER, allergic rhinitis or atopic dermatitis.
2. Using anti-reflux medications in the preceding 6 months before enrollment into the study.
3. Concurrent use of other medications that can affect the gastrointestinal motility.
4. Known hypersensitivity to esomeprazole or domperidone.
5. Children with long QT syndrome by pre-enrollment ECG study [7].
6. Enrollment in our previous study [2].

Study design

Children having difficult-to-treat-asthma were subjected to upper GIT endoscopy and were subsequently divided into two groups according to the presence or absence of GER. The group with GER was further double blindly randomly divided into two equal subgroups. The first subgroup received anti-reflux therapy in the form of proton pumps inhibitors [PPI] (Esomeprazole capsule 2 mg/kg/day) for 12 weeks beside the usual anti-asthma medications as mentioned before. The second subgroup received combined anti-reflux therapy in the form of proton pumps inhibitors (PPI) (Esomeprazole capsule 2 mg/kg/day) plus antidopaminergic gastroprokinetic drug (Domperidone 0.5 mg/kg of body weight) for 12 weeks beside the usual anti-asthma medications as mentioned before. The group of children who had difficult-to-treat asthma without reflux received placebo identical appearing capsules containing lactose (placebo capsule/day) for 12 weeks beside the usual anti-asthma medications as mentioned before. This placebo treatment was given to asthmatic patients without GER to rule out the placebo effect on improvement in the other group and to exclude the effect of better patient adherence to prescribed medications and better follow up by regular attendance to the clinic.

All asthmatic children had a pre-study phase of 6 month duration during which they were selected for eligibility for the study and to reach maximum asthma control according to the guidelines of the National Asthma Education and Prevention Program [4]. During this pre-study phase; all children were screened for *Helicobacter pylori* infection and the positive cases received metronidazole and clatrithromycin beside the esomeprazole (triple therapy). All children had chest X-ray postero-anterior and lateral views to exclude other lung diseases and abdominal ultrasonography was done when needed to exclude organomegaly. Pre-study ECG was done for all children to exclude the presence of long QT syndrome.

All children included in the study had detailed history taking and thorough clinical examination with special stress on: GIT symptoms suggestive of reflux including heart burn, acid regurgitation and food regurgitation. Childhood-asthma control test (C-ACT), pulmonary function test, and induced sputum substance P were done before and after the treatment phase for all the children. All the children had upper gastroin-

testinal endoscopic study at the beginning of the study to evaluate the presence or absence of GER, to classify the groups and to assess the severity of GER. Only the children who proved to have GER had another upper gastrointestinal endoscopic study at the end of the treatment phase, to evaluate the response for both types of anti-GER treatment.

Childhood-asthma control test (C-ACT) is a seven-item child- and caregiver-completed tool with a scoring range of 0–27; higher scores indicate better control. A score of 19 or less indicates that the asthma may not be well controlled. The C-ACT is intended for use in children up to the age of 12 years [8,9].

Pulmonary functions and spirometry were done for all cases using calibrated computerized machine (Jaeger Master-Screen-Body/Diffusion, Jaeger, Germany) with special stress on FEV_1 (% of predicted), and peak expiratory flow (PEF) variability. The PEF variability was calculated as the percentile ratio of the difference between maximum and minimum PEF to the mean daily PEF over a period of one week i.e. (maximum PEF − minimum PEF)/(mean of all PEFs over 1 week) × 100 [10].

Induced-sputum was produced and collected either spontaneously or induced with hypertonic saline nebulization from all subjects. Prior to sputum induction, children inhaled 200 μg of salbutamol to minimize broncho-constriction during the induction procedure. Sputum was induced by inhalation of 3% hypertonic saline solution for 5 min using an ultrasonic nebulizer, and the subjects were encouraged to cough and expectorate sputum into sterile containers. FEV_1 was measured after nebulization. Nebulization was stopped if a fall in FEV_1 of >20% compared to baseline values occurred or if troublesome symptoms appeared [9].

Sputum substance P (SP) measurement: SP was measured using a commercially available enzyme linked immunosorbent assay (ELISA) (R&D Systems, Oxon, UK). It has no significant cross-reactivity with neurokinin A, neurokinin B or neuropeptide K. The limit of detection of this assay is 0.06 ng/ml.

Upper gastrointestinal endoscopy was done in all cases with difficult-to-treat asthma to document or exclude the presence of GER using Olympus GIF-P140 Pediatric Video Gastroscope with 8.5 mm diameter, and 2.2 mm channel. The endoscopic diagnostic criteria of esophagitis followed Los Angeles classification grading: grade A (score 1): 1 or more mucosal breaks each ⩽5 mm in length. Grade B (score 2): At least one mucosal break >5 mm long, but not continuous between the tops of adjacent mucosal folds. Grade C (score 3): At least one mucosal break that is continuous between the tops of adjacent mucosal folds. Grade D (score 4): Mucosal break that involves at least three-fourth of the luminal circumferences. Patient took score 0 if there were no features of reflux [11].

Parents of all included children subjects signed a written informed consent before enrollment into the study. The local Institutional Research Ethics Committee approved the study protocol.

Statistical analysis

The power level of the number of cases in the study was more than 85%. Statistical analysis was performed with Statistical Package for Social Sciences (SPSS), version 16.0 (Chicago, IL, USA). Data are presented as mean (±SD) values. Comparison between the studied groups was performed with Student *t*-test, with $P < 0.05$ was considered statistically significant. Wilcoxon's signed rank test was used to assess the normality of distributions of the data. The Bonferroni correction/adjustment procedure was done to avoid "significance" due to chance only; in multiple comparison with many parameters. Correlation between variables was evaluated using Pearson's correlation coefficient. Chi-square was used to compare percentages (e.g. male to female ratio).

Results

The demographic data of patients groups and subgroups as well as their clinical data are shown in Tables 1 and 2.

Gastro-esophageal reflux (GER) was found in 80 out of 178 children with difficult to treat bronchial asthma (45%).

There was no significant difference in age and sex in children with difficult to treat asthma with and without GER. However, the body mass index (BMI) was significantly lower in the patient group with GER than asthmatic children without GER. Table 1 also showed that there were no significant differences in the blood eosinophils, C-ACT, FEV_1 (% of predicted), and PEF variability, but the sputum SP was significantly higher in children with difficult-to-treat asthma and GER than in children with difficult-to-treat asthma without GER.

Table 2 showed the demographic and clinical data of the two subgroups of children with difficult-to-treat asthma and GER who were treated for GER with either esomeprazole alone or with both esomeprazole and domperidone. There was no significant difference in age, sex, BMI, C-ACT, PEF variability, FEV_1 (% of predicted) and the sputum SP between the two subgroups.

Table 3 showed the effect of 12 weeks of anti-GER treatment on children with difficult-to-treat asthma and GER when compared to children with difficult-to-treat asthma without GER and received placebo treatment to overcome the placebo effects. It showed significant reduction of blood eosinophils (%), improvement of C-ACT and FEV_1 (% of predicted) with significant reduction of sputum SP after treatment than before treatment. However, PEF variability showed no significant changes.

Table 4 showed significant reduction of both blood eosinophils (%) and sputum SP and improvement of C-ACT in the subgroup treated with both esomeprazole and domperidone than asthmatic children treated with esomeprazole. Also the FEV_1 (% of predicted) showed a significant improvement in the subgroup treated with both esomeprazole and domperidone ($P = 0.047$). On the other hand, despite the improvement of endoscopic reflux scores in the subgroup with difficult-to-treat asthma and GER who was treated with both esomeprazole and domperidone than the subgroup with GER and treated with esomeprazole only, but it was of no statistical significance.

In children subgroup who were treated with esomeprazole, there were 14 children with grade A (35%), 8 children with grade B (20%), 8 children with grade C (40%), and 10 children with grade D (25%). After 12 weeks of esomeprazole therapy; there were 14 with no evidence of GER disease, 8 children with grade A (20%), 8 children with grade B (20%), 10 children with grade C (25%), and no children with grade D (0%).

Table 1 Demographic data, C-ACT, FEV_1; PEF variability and induced sputum SP in asthmatic children with and without GER.

	Asthmatic without GER (n = 98)	Asthmatic with GER (n = 80)	t	P
Age	8 ± 1.4	7.9 ± 1.3	0.2	0.8
BMI	19.5 ± 1.4	20.6 ± 2.4	6.1	0.003*
M/F	1.2:1	1:1	χ^2 = 1.7	0.5
Age at diagnosis	3.9 ± 1.4	3.1 ± 0.9	2.7	0.008*
Associated nasal allergy	52 (53%)	44 (58%)	χ^2 = 2.0	0.4
Atopic dermatitis	42 (43%)	38 (47%)	χ^2 = 2.7	0.3
Immediate family history of Asthma	60 (61%)	46(60%)	χ^2 = 1.8	0.45
Blood eosinophils (%)	6 ± 1.4	5.9 ± 2.0	0.48	0.63
C-ACT	12.4 ± 3.4	12.8 ± 3.9	0.36	0.72
FEV_1 (% of predicted)	59.6 ± 4.4	58.1 ± 7.3	1.1	0.27
PEF variability (%)	39.45 ± 3.5	40.3 ± 5.2	1.02	0.31
Sputum SP (pg/ml)	1069.75 ± 58.9	1385.6 ± 208	9.3	< 0.001*
Reference GER score	2.57 ± 1.17			

* significant.

Table 2 Demographic data, C-ACT, FEV_1; PEF variability and induced sputum SP in the 2 subgroups of asthmatic children with GER before starting 2 types of anti-GER treatment.

	Esomeprazole subgroup (n = 40)	Esomeprazole and domperidone subgroup (n = 40)	t	P
Age	7.75 ± 1.25	8.1 ± 1.3	0.8	0.4
BMI	20.5 ± 2.7	20.7 ± 2.1	0.26	0.79
M/F	1.2:1	1:1	χ^2 = 1.6	0.6
Blood eosinophils (%)	5.95 ± 1.7	5.9 ± 2.3	0.07	0.94
C-ACT	12.9 ± 4.4	12.7 ± 3.6	0.17	0.8
FEV_1 (% of predicted)	58.5 ± 8.3	57.6 ± 6.2	0.4	0.6
PEF variability (%)	40.4 ± 5.8	40.2 ± 4.5	0.1	0.9
Sputum SP (pg/ml)	1424.5 ± 175.7	1325.3 ± 231	1.9	0.06

Table 3 The C-ACT, FEV_1; PEF variability and induced sputum SP in asthmatic children with and without GER after treatment phase.

	Asthmatic with GER (active treatment phase) (n = 80)	Asthmatic without GER (placebo treatment phase) (n = 98)	t	P
Blood eosinophils (%)	3.7 ± 1.5	4.5 ± 1.1	3.1	0.004*
C-ACT	18.1 ± 4.1	12.9 ± 3.1	5.9	< 0.001*
FEV1 (% of predicted)	67.9 ± 7.3	60.5 ± 4.5	5.1	< 0.001*
PEF variability (%)	38.3 ± 5.3	38.5 ± 3.5	0.19	0.84
Sputum SP (pg/ml)	1224 ± 209	969.7 ± 59	7.4	< 0.001*

* significant.

Table 4 The C-ACT, FEV_1; PEF variability and induced sputum SP in the 2 subgroups of asthmatic children with GER after starting 2 types of anti-GER treatment.

	Esomeprazole subgroup (n = 40)	Esomeprazole & Domperidone subgroup (n = 40)	t	P
Blood eosinophils (%)	4.4 ± 1.6	3.05 ± 0.9	3.4	0.003*
C-ACT	17.4 ± 3.5	19.758 ± 2.7	2.6	0.02*
FEV_1 (% of predicted)	66.05 ± 8.3	69.75 ± 6.2	2.1	0.047*
PEF variability (%)	39.55 ± 5.7	37.1 ± 4.6	1.6	0.12
Sputum SP (pg/ml)	1242.75 ± 185.4	1130.3 ± 174	2.1	0.02*
Reference GER score	1.35 ± 1.2	0.85 ± 0.81	1.3	0.18

* significant.

In children subgroup who was treated with esomeprazole and domperidone, and before starting the treatment there were 6 children with grade A (15%), 10 children with grade B (25%), 10 children with grade C (25%), and 14 children with grade D (35%). After 12 weeks of esomeprazole and domperidone therapy; there were 16 with no evidence of GER disease (40%), 14 children with grade A (35%), 10 children with grade B (25%), and no children with grades C or D (0%).

Discussion

GER is a common finding in asthmatic children. It may be just an associated disorder or may be caused or aggravated by asthma. There are different mechanisms that worsen GER in asthma. Asthma increases the pressure gradient between the thorax and the abdomen, decreases the lower esophageal sphincter pressure and lengthens the time needed to perform esophageal clearance and hence increases the GER severity [12]. The asthma medications also increase the GER severity. Beta agonists and theophyllin reduce lower esophageal sphincter tone and increase gastric acid secretion [13] while systemic steroids increase esophageal acid contact times [12]. On the other hand GER worsen asthma status through vagally mediated esophageal tracheobronchial cough reflex, a local axonal reflex, heightened bronchial reactivity, and micro- or macro-aspiration into tracheobronchial tree [14,15].

Patients with difficult-to-treat asthma have increased incidence of GER with much greater prevalence of GER symptoms than the general population. In the current study, we found that 80 out of 178 (45%) children with difficult-to-treat asthma had GER. This confirmed our previous finding where we found an increased incidence of GER in children with difficult-to-treat asthma (49%) [2]. Other studies showed that the incidence of GER in such cases varies between 19.3% and 80% according to the method of reporting of GER and the individual characteristics [16].

Proper identification and treatment of asthma-associated GER is of vital importance for proper management of such cases. In the current study we found a significantly higher level of the induced-sputum substance P in asthmatic children with GER than in those without GER which confirms the data presented in our previous study [2]. These findings agreed with the work of Patterson et al. [17], who found that sputum SP was significantly higher in adult asthmatic patients with reflux than in adult asthmatic patients without reflux [17]. This substance plays an important role in the development of asthma-associated inflammation. It has a potent effect on the bronchomotor tone, airway secretion, bronchial circulation (vasodilatation and microvascular leakage) as well as on inflammatory and immune cells [18]. Presence of higher levels of sputum SP can guess the presence of associated GER.

The current study was mainly planned to find an answer to the question about the efficacy of GER treatment in improving childhood-asthma outcomes especially in a well recognized cohort of children with difficult-to-treat-asthma associated with GER. In our previous study, we found that 12 weeks of esomeprazole significantly improved C-ACT and reduces the induced sputum SP but it did not improve the FEV_1 (% of predicted) or PEF variability. So, in the current study we aimed to investigate the effect of adding domperidone to the esomeprazole anti-GER therapy on the pulmonary functions and the C-ACT.

There is growing evidence that GER is related mainly to motility disorders and not only due to acid hypersecretion. The main pathological factor in the development of GER is lower esophageal sphincter dysfunction. Delayed gastric emptying and decreased esophageal peristalsis are other important contributing factors [19].

Many studies investigated the effects of proton pump inhibitors (PPI) effects on improving the asthma symptoms and pulmonary functions [20–22]. However, fewer studies investigated the efficacy of combination of PPI and gastrointestinal prokinetic drugs in improving the asthma symptoms and pulmonary functions [23,24]. However, up to the best of our knowledge, the current study is the first study which investigated the efficacy of combination of both esomeprazole and domperidone in asthmatic children with GER.

In the current study, we found that adding domperidone to esomeprazole significantly improved C-ACT, and reduced the induced sputum SP in children with difficult-to-treat asthma associated with GER. The FEV_1 (% of predicted) showed a significant improvement in the subgroup with combined treatment with esomeprazole and domperidone than the subgroup treated with esomeprazole alone. We also observed more improvement of endoscopic reflux scores in children who received combination therapy than who received esomeprazole only.

Domperidone is a prokinetic peripheral dopamine D2-receptor antagonist that increases motility and gastric emptying which is used to treat slowed movement in the gastrointestinal tract associated with various gastrointestinal motility disorders. It decreases postprandial reflux time and is therefore used to treat regurgitation and vomiting [25].

The add on effect of domperidone to the effect of esomeprazole observed in the current study in improving the C-ACT and pulmonary function can be explained by combination synergistic effect of decreasing acid production as well as increasing lower esophageal tone and esophageal clearance thus producing a better therapeutic response [26]. Normalizing the underlying dysmotility or augmenting existing motility would decrease esophageal acid contact time, decreasing the risk of acid aspiration and hence decrease airway inflammation and improve the pulmonary functions [26–28]. Dupont et al. found that the use of domperidone provided a satisfactory control of nocturnal GOR and therefore emerges as a valuable agent for the treatment of chronic GOR-associated respiratory disorders in childhood [28].

Sharma et al. found that the combined therapy with omeprazole and domperidone for 16 weeks in asthmatics with GER may be beneficial by reducing asthma symptoms and rescue medication use, as well as improving pulmonary function. However, their study was conducted in the adult asthmatics of various subtypes and used the combination therapy for 16 weeks [24]. However, Yan-hong et al. [29], found the same beneficial effects of the combined therapy with omeprazole and domperidone but in asthmatic children with no significant side effects of such combination [29].

Limitations of the study

The first limitation in the current study is that we did not answer the question about the efficacy of adding H_2 receptor antagonist to the poly therapy in improving C-ACT and the pulmonary functions in asthmatic children. Still we need to determine the cut-off point for sputum SP that is more sensitive to detect the presence of GER in asthmatic children. Another limitation of the current study is using endoscopy for diagnosing GER not pH or impedance studies that may be more helpful as there will be some false negative cases with the use of endoscopy. Endoscopy was used because it was the available tool in our hospital.

Conclusion

Gastro-esophageal reflux (GER) is a frequent association with childhood difficult-to-treat asthma as it was observed in about 45% of them. Combination of domperidone and esomeprazole was more effective in improving the endoscopic reflux score, childhood-asthma control test (C-ACT) and FEV_1 (% of predicted) and significantly reduced the sputum SP than the single use of esomeprazole in children with difficult-to-treat asthma.

References

[1] S.M. Harding, Recent clinical investigations examining the association of asthma and gastroesophageal reflux, Am. J. Med. 115 (Suppl. 3A) (2003) 39S.

[2] A.S. Bediwy, M.G. Elkholy, M. Al-Biltagi, H.G. Amer, E. Farid, Induced sputum substance P in children with difficult-to-treat bronchial asthma and gastro esophageal reflux: effect of esomeprazole therapy, Int. J. Pediatrics (2011) 1–8, Article ID 967460, doi:10.1155/2011/967460.

[3] S.P. Jiang, R.Y. Liang, Z.Y. Zeng, Q.L. Liu, Y.K. Liang, J.G. Li, Effects of antireflux treatment on bronchial hyperresponsiveness and lung function in asthmatic patients with gastroesophageal reflux disease, World J. Gastroenterol. 9 (5) (2003 May) 1123–1125.

[4] U.S. Department of Health and Human Services, National Institute of Health, National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report 3: "Guidelines for the Diagnosis and Management of Asthma," website: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf>, Full Report 2007. (Last accessed 21.07.11).

[5] British Thoracic Society/Scottish Intercollegiate Guidelines Network, British guidelines on the management of asthma, Thorax 58 (Suppl. 1) (2003) i1–94.

[6] J.J. Leggett, B.T. Johnston, M. Mills, J. Gamble, L.G. Heaney, Prevalence of gastroesophageal reflux in difficult asthma: relationship to asthma outcome, Chest 127 (4) (2005) 1227–1231.

[7] M. Rossi, G. Giorgi, Domperidone and long QT syndrome, Curr. Drug Saf. 5 (3) (2010 Jul 2) 257–262.

[8] A.H. Liu, R. Zeiger, C. Sorkness, T. Mahr, N. Ostrom, S. Burgess, et al, Development and cross-sectional validation of the childhood-asthma control test, J. Allergy Clin. Immunol. 119 (2007) 817–825.

[9] M.A. Biltagi, A.A. Baset, M. Bassiouny, M.A. Kasrawi, M. Attia, Omega-3 fatty acids, vitamin C and Zn supplementation in asthmatic children: a randomized self-controlled study, Acta Paediatr. 98 (4) (2009) 737–742.

[10] K.W. Bundy, J.F. Gent, W. Beckett, M.B. Bracken, K. Belanger, E. Triche, B.P. Leaderer, Household airborne penicillium associated with peak expiratory flow variability in asthmatic children, Ann. Allergy Asthma Immunol. 103 (1) (2009) 26–30.

[11] Standards of Practice Committee, D.R. Lichtenstein, B.D. Cash et al., Role of endoscopy in the management of GER. Gastrointest Endosc. 66 (2007) 219–224. <http://www.asge.org/WorkArea/showcontent.aspx?id=4182> (last accessed 25.10.11).

[12] J.P. Lazenby, M.R. Guzzo, S.M. Harding, P.E. Patterson, L.F. Johnson, L.A. Bradley, Oral corticosteroids increase esophageal acid contact times in patients with stable asthma, Chest 121 (2) (2002 Feb) 625–634.

[13] O. Sacco, B. Fregonese, M. Silvestri, F. Sabatini, G. Mattioli, G.A. Rossi, Bronchoalveolar lavage and esophageal pH monitoring data in children with "difficult to treat" respiratory symptoms, Pediatric Pulmonol. 30 (4) (2000) 313–319.

[14] S.M. Harding, M.R. Guzzo, J.E. Richter, The prevalence of gastroesophageal reflux in asthma patients without reflux symptoms, Am. J. Respir. Crit. Care Med. 162 (1) (2000) 34–39.

[15] S.M. Harding, Gastroesophageal reflux and asthma: insight into the association, J. Allergy Clin. Immunol. 104 (2 Pt. 1) (1999 Aug) 251–259.

[16] K. Thakkar, R.O. Boatright, M.A. Gilger, H.B. El-Serag, Gastroesophageal reflux and asthma in children: a systematic review, Pediatrics 125 (2010) e925–e930.

[17] R.N. Patterson, B.T. Johnston, J.E.S. Ardill, L.G. Heaney, L.P.A. McGarve, Increased tachykinin levels in induced sputum from asthmatic and cough patients with acid reflux, Thorax 62 (6) (2007) 491–495.

[18] G.F. Joos, P.R. Germonpré, R.A. Pauwels, Role of tachykinins in asthma, Allergy 55 (4) (2000) 321–337.

[19] M.C. Champion, Prokinetic therapy in gastroesophageal reflux disease, Can. J. Gastroenterol. 11 (Suppl. B) (1997 Sep) 55B–65B.

[20] Y.B. Lee, J.H. Lim, Y.J. Choi, J.Y. Kim, J.H. Son, S.M. Choi, H.J. Jo, C.M. Shin, S.H. Lee, Y.S. Park, J.H. Hwang, J.W. Kim, S.H. Jeong, N. Kim, D.H. Lee, H.C. Jung, I.S. Song, Effects of proton pump inhibitors in asthmatics with gastroesophageal reflux disease, Korean J. Gastroenterol. 58 (4) (2011 Oct 25) 178–183.

[21] W.W. Chan, E. Chiou, K.L. Obstein, A.S. Tignor, T.L. Whitlock, The efficacy of proton pump inhibitors for the treatment of asthma in adults: a meta-analysis, Arch. Intern. Med. 171 (7) (2011 Apr 11) 620–629.

[22] T.O. Kiljander, O. Junghard, O. Beckman, T. Lind, Effect of esomeprazole 40 mg once or twice daily on asthma: a randomized, placebo-controlled study, Am. J. Respir. Crit. Care Med. 181 (10) (2010 May 15) 1042–1048.

[23] S.M. Sopo, D. Radzik, M. Calvani, Does treatment with proton pump inhibitors for gastroesophageal reflux disease (GER) improve asthma symptoms in children with asthma and GER? A systematic review, J. Investig. Allergol Clin. Immunol. 19 (1) (2009) 1–5, Review.

[24] B. Sharma, M. Sharma, M.K. Daga, G.K. Sachdev, E. Bondi, Effect of omeprazole and domperidone on adult asthmatics with gastroesophageal reflux, World J Gastroenterol. 13 (11) (2007 Mar 21) 1706–1710.

[25] A.J. Reyntjens, Clinical pharmacology and therapeutics of domperidone, Clin. Res. Rev. 3 (1983) 91–100.

[26] S.D. Singhal. P. Dhawan, A. Bhatt, R. Pokharna, D. Sharma, G. Kumar, P. Kar P, Copyright 2007 Internet Scientific Publications LLC (Hide copyright information) Evaluation of safety and efficacy of pantoprazole and domperidone combination in patients with gastroesophageal reflux disease. (Clinical report) The Internet, J. Gastroenterol. August 22 (2006).

[27] R. Tutuian, D.O. Castell, Management of gastroesophageal reflux disease, Am. J. Med. Sci. 326 (5) (2003) 309–318.

[28] C. Dupont, P. Molkhou, N. Petrovic, B. Fraitag, Treatment using Motilium of gastro-esophageal reflux associated with respiratory manifestations in children, Ann. Pediatr. (Paris) 36 (2) (1989 Feb) 148–150.

[29] L. Yan-hong, Y. Jie-yu, X. Bin, Clinical observation of omeprazole and domperidone therapy for gastroesophageal reflux disease in asthma children. Pract. Prevent. Med. (2009) 01-085.