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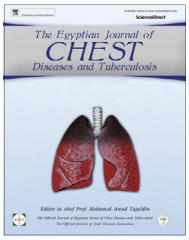

ORIGINAL ARTICLE

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

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KEYWORDS

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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-