REVIEW

Does Treatment With Proton Pump Inhibitors for Gastroesophageal Reflux Disease (GERD) Improve Asthma Symptoms in Children With Asthma and GERD? A Systematic Review

S Miceli Sopo,[1] D Radzik,[2] M Calvani[3]

[1] Department of Pediatrics, Catholic University of Rome, Rome, Italy
[2] Department of Pediatrics, San Giacomo Hospital, Castelfranco Veneto (Treviso), Italy
[3] Department of Pediatrics, San Camillo de Lellis Hospital, Rome, Italy

Abstract

Objective: To evaluate pediatric studies of the effect on asthma symptoms of treatment with proton pump inhibitors (PPI) used to treat gastroesophageal reflux disease (GERD).
Methods: We entered the MeSH terms "gastroesophageal reflux AND asthma AND children" in the PubMed tool Clinical Queries, selecting "therapy" and "broad, sensitive search." The search ended on April 14, 2008. We included only clinical trials performed in pediatric patients.
Results: Four studies were considered to be relevant, although only 1 was a randomized, double-blind, placebo-controlled trial. The 3 nonrandomized trials showed that PPIs benefited patients with asthma. The randomized, double-blind, placebo-controlled trial found that omeprazole did not improve asthma symptoms. An improved (although not statistically significant) score was observed in the quality of life questionnaire in children with a reflux index greater than 10% and in those with more severe asthma treated with omeprazole compared with the placebo group.
Conclusions: Scant data in these studies mean that we cannot make solid recommendations. However, in specific cases, we think that treatment of asthma symptoms with a PPI is valid as long as at least 2 conditions are satisfied: asthma must not respond to standard treatment, and 1 instrumental parameter of GERD severity must be satisfied, that is, a reflux index greater than or equal to 10 must be present.

Key words: Asthma. Child. Gastroesophageal reflux disease. Proton pump inhibitors. Therapy.

Resumen

Objetivo: Evaluar en estudios pediátricos los efectos en los síntomas asmáticos del tratamiento con inhibidores de la bomba de protones (IBP) aplicados para el tratamiento del reflujo gastroesofágico (RGE).
Métodos: Introdujimos los términos MeSH (tesaurus) "gastroesophageal reflux AND asthma AND children" en la herramienta de consultas clínicas PubMed, seleccionando "therapy" y "broad, sensitive search."
La búsqueda finalizó el 14 de abril de 2008. Incluimos sólo los ensayos clínicos realizados en pacientes pediátricos.
Resultados: Se consideraron relevantes 4 estudios, aunque sólo uno de ellos era un ensayo aleatorizado, doble ciego y controlado con placebo. Los 3 ensayos no aleatorizados mostraron que los IBP beneficiaban a los pacientes con asma. El ensayo aleatorizado, doble ciego controlado con placebo mostró que el omeprazol no mejoraba los síntomas asmáticos.
Se observó una mejoría (aunque no estadísticamente significativa) en el resultado del cuestionario de calidad de vida en niños con un índice de reflujo mayor del 10% y en aquellos con un asma más grave tratado con omeprazol comparado con el grupo placebo.

Conclusiones: Los escasos datos obtenidos en estos estudios significa que no podemos dar recomendaciones sólidas. Sin embargo, en casos específicos, pensamos que el tratamiento de los síntomas asmáticos con un IBP es válido siempre y cuando se satisfagan 2 condiciones: asma que no responde al tratamiento convencional, y un parámetro instrumental de la gravedad del RGE tiene que ser justificado, esto es, tiene que estar presente un índice de reflujo mayor o igual que 10.

Palabras clave: Asma. Niño. Reflujo gastroesofágico. Inhibidores de la bomba de protones. Terapia.

Introduction

The association between asthma and gastroesophageal reflux disease (GERD) has been debated for decades, and the causal relationship between the 2 conditions remains unclear. In children, it is common practice to restrict diagnosis and treatment of any GERD to those whose asthma is not sufficiently controlled by suitable pharmacological therapy. Before diagnosing GERD, however, we must be reasonably certain that its treatment has a good chance of resolving the asthma. The first approach should be to consult summaries of the available evidence, such as guidelines and systematic reviews.

The guidelines drawn up by the British Thoracic Society (BTS) and the Scottish Intercollegiate Guidelines Network (SIGN) for asthma management [1] examine this topic. They report that the systematic review by Coughlan et al [2] selected 12 double-blind, randomized clinical trials with adults, and reported that GERD treatment did not improve asthma symptoms or lung function in concomitant asthma and GERD. A reduction in dry cough was reported, although this was probably not caused by asthma. The BTS-SIGN guidelines [1] conclude that any GERD must be treated, even if this generally has no impact on asthma.

In the Cochrane Library (CL) database, we found a second systematic review by the same authors [3]. This review also included pediatric studies, and the authors concluded that no overall improvement in asthma symptoms was observed in asthma patients with GERD following treatment of GERD. They did maintain, however, that some patient subgroups could benefit from treatment, but that it was difficult to identify factors that predicted a good response. The systematic review by Gibson et al [3] is updated to September 12, 2002. Therefore, we believe that the time is right for a new review of this area of asthma in the pediatric population.

Research Strategies and Results

We limited our search to clinical trials that have evaluated the efficacy of proton pump inhibitors (PPI, the gold standard pharmacological therapy for GERD) in children with asthma and GERD. We explored the MEDLINE database by entering the MeSH terms "gastroesophageal reflux AND asthma AND children" in the PubMed tool Clinical Queries, and selected "therapy" and "broad, sensitive search." The bibliography of the relevant resulting articles was then checked. The search ended on April 14, 2008, and revealed 96 articles, of which 4 [4-7] were considered to be relevant from the title, abstract, and, where necessary, the full text. A summary of these studies is given below.

Khoshoo et al, Chest 2003

The authors assert that theirs is the first published study to examine the efficacy of a GERD treatment in improving the management of asthma in children. The authors enrolled 46 nonatopic children aged 5 to 10.5 years with persistent moderate, poorly-controlled asthma in a nonrandomized, open-label study. After 24-hour pH monitoring, 27 patients were diagnosed with GERD due to a reflux index (RI, percentage of total time with pH <4) greater than 5% during the monitoring period. Of these, 18 children underwent medical treatment for 6 months and 9 underwent surgery (Nissen fundoplication). Medical treatment of GERD consisted of a prokinetic (cisapride 1 mg/kg in 2 daily doses or metoclopramide 0.15 mg/kg/d in 3 doses per day) in combination with a PPI (lansoprazole 30

Table 1. Mean (SD) Number of Days of Drug Use Before and After Therapy (Khoshoo et al, Chest 2003)

Children With Asthma	Short-Acting Bronchodilators		Inhaled Corticosteroids	
	Before	After	Before	After
GERD, medical treatment	66.4 (25.6)[a]	6.8 (11)[a]	180[a]	2.5 (7.4)[a]
GERD, surgical treatment	72.8 (20.4)[a]	4 (8.2)[a]	180[a]	0.9 (2.7)[a]
No GERD, medical treatment	64.4 (28.6)	45.1 (25.7)	180	113.8 (49.7)
No GERD, no treatment	68.3 (25.8)	61.6 (21	180	143.1 (29.9)

Abbreviation: GERD, gastroesophageal reflux disease.
[a] $P < .05$

Table 2. Number of Patients Using Asthma Drugs in the 6 Months Before and After Diagnosis (Khoshoo et al, Chest 2003, modified)

Children With Asthma	Short-Acting Bronchodilators		Inhaled Corticosteroids		Long-Acting Bronchodilators		Antileukotrienes	
	Before	After	Before	After	Before	After	Before	After
GERD medical treatment	18[a]	6[a]	18[a]	2[a]	18[a]	0[a]	18[a]	0[a]
GERD surgical treatment	9[a]	2[a]	9[a]	1[a]	9[a]	0[a]	9[a]	0[a]
No GERD, medical treatment	8	8	8	8	8	4	8	4
No GERD, no treatment	11	11	11	11	11	11	11	9

Abbreviations: GERD, gastroesophageal reflux disease.
[a] $P < .05$

mg/d once daily in the morning). Eight of the children without GERD also underwent medical treatment.

Khoshoo et al [4] report excellent results (Tables 1 and 2). Treatment (whether medical or surgical) of GERD was effective in terms of both mean number of days taking asthma treatment and number of patients using it. The number needed to treat was very good, varying between 1 and 2. However, this study is methodologically weak. It could be defined as a cohort study where exposure is represented by the presence or absence of GERD, although it could also be described as a case series (or a before-after study) and reveal some inconsistencies.

Khoshoo et al, J Ped Gastr 2007

Two of the authors from the above study published a second paper on the same topic [5]. They enrolled 44 children (aged 8-15 years) with nonatopic persistent asthma whose condition had improved after 1 year of treatment with a PPI plus metoclopramide. The children and their parents were asked if they wished to continue the same treatment or switch to ranitidine, given the lack of data on the possible long-term side effects of PPI therapy. Thirty patients chose to continue and 14 opted to switch to ranitidine. The control group consisted of 9 patients who had undergone Nissen fundoplication. Significantly more ranitidine patients (11/14, 79%) experienced exacerbation of their asthma symptoms than PPI patients (6/24, 20%) and than patients who had undergone fundoplication (3/9, 33%) ($P < .05$). Unlike the PPI patients and fundoplication patients, none of whom required hospitalization, 3 ranitidine patients required hospitalization for intensive care of their asthma exacerbation.

Yüksel et al, Resp Med 2006

Yüksel et al [6] enrolled 25 nonatopic asthmatic children (aged 1-16 years) and 25 children in the same age group without asthma but with recurrent vomiting. All subjects underwent 24-hour pH montoring and those with reflux were offered lansoprazole (1 mg/kg/d for 3 months). pH parameters were significantly modified in asthmatic children with respect to the control patients, except for the number of reflux episodes lasting more than 5 minutes. The mean (SD) RI was 13.3% (13.1%) in asthmatic children compared with 3.9% (2.9%) in the controls. Treatment with lansoprazole resulted in a clear improvement in asthma symptoms. The differences (before and after treatment) in the mean symptoms score, use of bronchodilators and systemic corticosteroids, number of asthma attacks per patient, and days of hospitalization were all statistically significant ($P = .00$). This study was also nonrandomized and open-label, and there was no control population with asthma and GERD not treated with lansoprazole. This can again be classified as a case series or a before-after study, and, like the studies by Khoshoo et al [4,5], it is methodologically weak.

Størdal et al, Arch Dis Child 2005

These Norwegian authors performed the first—and so far only—methodologically sound, randomized, double-blind, placebo-controlled clinical trial analyzing the efficacy of a PPI (omeprazole) in pediatric patients with asthma and GERD. They enrolled 38 children (mean age 10.8 years, range 7.2-16.8) with bronchial asthma. The patients were given a questionnaire to identify any symptoms of GERD, and those presenting at least 1 symptom underwent 24-hour pH monitoring. All patients with an RI greater than or equal to 5% were considered eligible. Patients already taking treatment for GERD were excluded. Of the initial 165 children with asthma and GERD symptoms who consented to pH monitoring, 45 (28%) had an RI greater than or equal to 5%. Most patients suffered from mild or moderate persistent asthma, which was only partly controlled in all cases, and none had severe persistent asthma. Children with total serum IgE levels above the age-specific cut-off or with serum-specific IgE or a positive skin prick test result for the more common allergens were classified as atopic. Patients were randomized to omeprazole at 20 mg/d or placebo for 12 weeks. pH monitoring was conducted again in some consenting patients at the end of the study to confirm the efficacy of acid suppression. In the active group, 7 of 8 patients who repeated the test had an RI less than 5%, with a mean reduction of 4.9% (95% CI, 2.7-7.1; $P = .001$), while in the placebo group, the second test was abnormal in 5 of 7 patients.

As reported in Table 3, no significant differences were observed between the 2 groups with respect to the efficacy of omeprazole against asthma symptoms, instrumental

Table 3. Clinical Efficacy of Treatment With Omeprazole Against Placebo in Asthmatic Children With GERD, Expressed as Changes From Baseline (Størdal et al, 2005, modified)

Endpoints Considered	Omeprazole (n = 18)	Placebo (n = 18)	*P*
Asthma score (95% CI)	−1.28 (−2.65 to 0.1)	−1.28 (−3.27) to 0.72)	1.00
PAQLQ (95% CI)	−0.62 (−0.3 to −0.95)	−0.50 (−0.3 to −0.7)	.51
FEV_1,% (mean, median)	−1.38 (0.33)	−2.01 (−0.50)	.77
FEF_{25-75},% (mean, median)	−0.07 (−0.05)	0.04 (0.05)	.12
$ß_2$-agonists as needed (mean, median)	−1.9 (0.0)	−1.9 (0.5)	.89

Abbreviations: CI, confidence interval; ECP, eosinophilic cationic protein; FEF25%-75%, forced expiratory flow, midexpiratory phase; FEV_1, forced expiratory volume in 1 second; PAQLQ, Pediatric Asthma Quality of Life Questionnaire.

parameters, or the use of $ß_2$-agonists. Størdal et al [7] also performed a subgroup analysis and reported an improved score for the Pediatric Quality of Life Questionnaire in children with an RI less than 10% and in those with more severe asthma treated with omeprazole compared with the placebo group. However, the difference was not statistically significant, possibly due to the small sample size of the subgroups. No influence due to atopy was found.

The authors highlighted some limitations of their study:

1. Less than half of the patients agreed to undergo the second pH monitoring and some patients may have been inadequately treated. However, the omeprazole dose used was that which is considered sufficient for most children with GERD.
2. Longer treatment may be necessary to observe the effects on asthma.
3. Analysis of the subgroup of cases with the most severe reflux or asthma, while demonstrating a trend toward greater efficacy, is affected by bias from the lack of a priori randomization and the low sample size. This interesting theory should be verified with ad hoc studies.
4. The difference between acid and nonacid reflux may be important for respiratory symptoms. Therefore, the negative data on acid suppression in this study cannot be generalized to other types of treatment (such as surgery).
5. Endoscopy was not performed, with the result that there is no macroscopic or histological data on the condition of the esophageal mucosa. It has been postulated that asthma presents only in patients with GERD that triggers esophagitis through exposure of vagal afferent fiber to acid.

Conclusions

Evidence on the correlation between asthma and GERD continues to be conflicting. On the one hand, we have the results of a recent systematic review [8] concluding that there is a significant association between GERD and asthma, but that there is little data on the direction of the causal relationship between the two. In fact, severe, poorly controlled asthma may trigger GERD, not the other way round. Nevertheless, at least 3 double-blind randomized controlled trials in adult patients [9-11] report improved asthma symptoms following PPI in patients with asthma and GERD. In contrast, in the only double-blind randomized controlled trial to date evaluating the efficacy of PPI in children with GERD whose asthma is poorly controlled by standard pharmacological treatment, Størdal et al [7] concluded that acid suppression in children with GERD and asthma does not improve asthma symptoms. Although 3 studies report very good results in children [4-6], their methodology is far weaker than that of Størdal et al [7]. The results of the latter must thus be given greater weight when making clinical decisions.

In conclusion, there are very few methodologically sound studies in this field with pediatric cases, and more double-blind randomized controlled trials are necessary to decide whether we should use PPI in children with concomitant asthma and GERD. This review does not provide sufficient data to answer this question. Moreover, Størdal et al [7] also stated that acid suppression could relieve the asthma symptoms of patients with the more severe forms of asthma and GERD. Therefore, bearing in mind that this is still a gray area, we conclude that, on the basis of the best scientific evidence currently available, at least 2 conditions must be satisfied before treating asthma symptoms with a PPI: first, the asthma must not respond to correctly applied traditional treatment, and this nonresponse must cause asthma symptoms which can disturb the child's quality of life; and second, that at least 1 instrumental parameter of GERD severity is satisfied, namely, an RI greater than or equal to 10% (with all the limitations of this determination).

Finally, the benefits of the treatment with a PPI will have to be carefully assessed.

References

1. British Guideline on the management of asthma. British Thoracic Society and Scottish Intercollegiate Guidelines Network. Revised edition November 2005. http://www.sign.ac.uk/guidelines/published/index.html
2. Coughlan JL, Gibson PG, Henry RL. Medical treatment for reflux oesophagitis does not consistently improve asthma control: a systematic review. Thorax. 2001;56:198:204.

3. Gibson PG, Henry RL, Coughlan JL. Gastroesophageal reflux treatment for asthma in adults and children. Cochrane Database of Systematic Reviews 2003. Date of most recent substantive amendment: 12 September 2002.
4. Khoshoo V, Le T, Haydel RM Jr, Landry L, Nelson C. Role of gastroesophageal reflux in older children with persistent asthma. Chest. 2003;123:1008-13.
5. Khoshoo V, Haydel R Jr. Effect of antireflux treatment on asthma exacerbations in nonatopic children. J Pediatr Gastroenterol Nutr. 2007;44:331-5.
6. Yüksel H, Yilmaz O, Kirmaz C, Aydoğdu S, Kasirga E. Frequency of gastroesophageal reflux disease in nonatopic children with asthma-like airway disease. Respir Med. 2006;100:393-8.
7. Stordal K, Johannesdottir GB, Bentsen BS, Knudsen PK, Carlsen KC, Closs O, Handeland M, Holm HK, Sandvik L. Acid suppression does not change respiratory symptoms in children with asthma and gastro-oesophageal reflux disease. Arch Dis Child. 2005;90:956-60.
8. Havemann BD, Henderson CA, El-Serag HB. The association between gastro-oesophageal reflux disease and asthma: a systematic review. Gut. 2007;56:1654-64.
9. Kiljander TO, Harding SM, Field SK, Stein MR, Nelson HS, Ekelund J, Illueca M, Beckman O, Sostek MB. Effects of esomeprazole 40 mg twice daily on asthma: a randomized placebo-controlled trial. Am J Respir Crit Care Med. 2006;173:1091-7.
10. Sharma B, Sharma M, Daga MK, Sachdev GK, Bondi E. Effect of omeprazole and domperidone on adult asthmatics with gastroesophageal reflux. World J Gastroenterol. 2007;13:1706-10.
11. dos Santos LH, Ribeiro IO, Sánchez PG, Hetzel JL, Felicetti JC, Cardoso PF. Evaluation of pantoprazol treatment response of patients with asthma and gastroesophageal reflux: a randomized prospective double-blind placebo-controlled study. J Bras Pneumol. 2007;33:119-27.

Manuscript received April 18, 2008; accepted for publication July 10, 2008.

Stefano Miceli Sopo

Department of Pediatrics
Catholic University of Rome
Rome, Italy
E-mail: smicelisopo@rm.unicatt.it