Not the Perfect Study, but Helpful Wisdom for Treating Asthma Patients With Gastroesophageal Reflux Disease

Several years ago for this same journal, I wrote an editorial entitled “Asthma and Gastroesophageal Reflux Disease: The Truth Is Difficult To Define.” In that editorial and another review article, I outlined the major limitations in current studies on this subject and lamented our progress over the last 20 years in resolving this complex interaction. Over the last 3 years in the adult literature, it is disappointing that only one study has addressed this subject using a placebo-controlled crossover design and omeprazole, 40 mg for 4 weeks. The sample size was only five patients, and they found no improvement in pulmonary function tests results. On the other hand, this issue of CHEST (see page 1008) has an excellent study by Khoshoo and colleagues, which overcomes many of the methodological limitations of other studies and defines better the role of gastroesophageal reflux disease (GERD) treatment with proton pump inhibitors (PPIs) in children with difficult-to-control asthma. Impressively, this study was not performed in an academic medical center but rather by dedicated physicians in private practice who are interested in asthma and GERD, and who worked together to define an effective clinical algorithm for approaching all of their difficult-to-manage asthma patients. Let us look at the relevance of this important study to the methodological limitations of many previous studies relating asthma and GERD.

Lack of Attempt To Optimize Conventional Asthma Therapy

These authors do a commendable job in defining their asthma population and the failure of those patients to respond to optimal asthma therapy. Children with the following criteria were included in the study: (1) no family history of asthma; (2) no personal or family history of atopic disease; (3) parents who did not smoke; and (4) no history of respiratory syncytial virus bronchitis. All children had been treated for their asthma for >2 years, and their conditions were difficult to manage, with at least three emergency department visits or hospital admissions in the last year, despite aggressive management of their asthma with a combination of short-acting and long-acting bronchodilators, leukotriene antagonists, and inhaled/oral corticosteroids. Despite this difficult group of patients, all of those individuals with abnormal 24-h pH studies (27 subjects) had at least a 50% reduction in their need for medications after 1 year of follow-up, while receiving lansoprazole, 30 mg, in the morning and a prokinetic drug. In the vast majority of patients, therapy with long-acting bronchodilators, leukotriene antagonists, and inhaled/oral steroids could be discontinued because the patient’s asthma could be easily controlled with as-needed puffs of short-acting bronchodilators.

Small Number of Patients

Over a 2.5-year period, 482 patients with asthma of >2 years duration were screened. A total of 46 consecutive patients (10%) with difficult-to-control asthma were referred to a pediatric gastroenterologist to rule out GERD and fulfilled all the entrance criteria for study enrollment. None of the patients were lost to follow-up, and all were treated by a team of experienced pediatric gastroenterologists and asthma specialists. Symptoms were assessed by personal diaries and the use of asthma drugs, the doses of which were adjusted based on National Institutes of Health guidelines and symptom responses that were observed for >1 year. The number of patients studied was very respectable, exceeding the number in all but two previous studies reported in the medical/surgical literature on this subject. Furthermore, these authors give us a realistic idea of the percentage of children who clinically require this approach, which is much more relevant than the reported GERD prevalence rates of 33 to 90% of asthmatic patients from various study populations.
OUTCOME PARAMETERS FOR ASTHMA CONTROL ARE NOT CONSISTENT

I believe this is one of the strongest features of the study by Khoshoo et al. Rather than using subjective symptom complaints, the authors required as their criteria of success a 50% reduction in the use of various classes of asthmatic drugs compared to the patient’s pretreatment baseline needs. This replicates the situation in clinical practice, in which dose adjustment is a gestalt consisting of patient symptom improvement and the improvement of various pulmonary function test results, such as peak expiratory flow rates. Using these clinically relevant criteria, 100% of the asthma patients with abnormal pH study findings who had been treated either medically (18 subjects) or surgically with fundoplication (9 subjects) had a significant reduction in their asthma medications over the 1-year study period, compared to a 20% reduction in medications among those patients with no documented GERD on pH testing who opted for a therapeutic trial of medical antireflux treatment (8 subjects) or who did not receive any antireflux treatment (11 subjects).

DURATION OF ACID SUPPRESSION MAY BE TOO SHORT TO SHOW A PREDICTABLE IMPROVEMENT IN ASTHMA

This is a second very strong feature of this PPI study in children with asthma. The authors wisely chose a 1-year window in which to assess the success of their treatment regimen compared to the 6-month period prior to referral for reflux evaluation. In fact, the initial 6-month phase of therapy was considered a washout period and only the last 6 months, after either medical or surgical treatment, were used for analysis. This was similar to the techniques that Harding et al. used in a study assessing the efficacy of omeprazole therapy with documented pH control by serial testing, although the study duration was only 3 months of reflux controlled with omeprazole therapy in doses ranging from 20 to 60 mg. Longer treatment periods are mandatory for the appropriate assessment of clinically relevant parameters of success (i.e., reduction in drug usage) and take into consideration seasonal variations of asthma.

ATTEMPT TO DEFINE PREDICTORS OF OUTCOME

In children, this study convincingly shows that the presence of abnormal amounts of distal and proximal reflux measured by 24-h pH testing was highly predictive of the successful response to lansoprazole and prokinetic drug therapy. In fact, only 20% of children with normal pH study findings got better over the 1-year follow-up period, either spontaneously or after receiving antireflux therapy. These results compliment similar findings in large adult studies by Harding et al. and Kiljander et al. Furthermore, it is this observer’s belief that all future studies assessing the relationship between asthma and GERD should require baseline pH testing and segregation of populations based on these results. In clinical practice, this may not be realistic, but certainly all difficult-to-manage asthmatic patients should undergo 24-h pH testing, as has been suggested by Irwin et al. Interestingly, this study also supports other predictors of success reported in the literature, including the presence of nonallergic asthma and difficult-to-control asthma.

No study is perfect, and neither was this one. For ethical reasons, a placebo control was not used. However, this seems a minor shortcoming considering that data from a variety of experimental trials of anti-inflammatory agents for treatment of chronic steroid-dependent asthma find only a 20 to 40% improvement from simply participating in a clinical trial. Furthermore, their group with a normal pH test finding really serves as an adequate control with a spontaneous rate of improvement of only 20%. The authors criticized themselves for not using a crossover design, but I believe this study technique is inappropriate in these trials when a placebo is used because order and carryover effects regularly bias the data, making them more difficult to logically analyze. Rather, placebo control studies for asthma and GERD should employ a parallel design with separate groups of treated and control patients. As with all medical studies except one, the control of GERD with lansoprazole was not assessed by serial pH testing. However, this is unrealistic in the clinical setting and is very difficult to accomplish in large patient trials. Furthermore, who is to argue with the adequacy of PPI therapy when 100% of treated patients responded well? It is only a factor in the treated patients who did not respond, but this was unlikely to be much of a factor as these patients had normal baseline pH tests. Finally, we do not know if these data only apply to patients with symptomatic GERD or is also useful for the many asthmatics with “silent” GERD. Symptom data about GERD were not given in the patient summaries and the criteria for referral to a gastroenterologist appears to only be the difficult-to-manage quality of their asthma. Addressing this issue in future studies is important as 40 to 60% of asthmatic patients have silent reflux, while a recent study found their 24-h pH profiles similar to those of asthmatic patients with symptomatic GERD.

Khoshoo and colleagues are to be congratulated for performing a practical clinical study that is the first of its kind in the pediatric population to assess the role of PPIs in treating patients with GERD associated with asthma. Although it is not the perfect study, many of its features helped to overcome...
Lung Volume Reduction Surgery Update

We were delighted to review the article by Yusen et al in this issue of CHEST (see page 1026), who evaluated 200 consecutive patients who underwent lung volume reduction surgery (LVRS). We previously reviewed the mostly short-term and scant long-term experience following LVRS for emphysema.1 We looked forward to the article by Yusen et al with the enthusiasm usually reserved for attending a smash Broadway show that is completely sold out for 1 year, or dining in a three- or four-star Paris restaurant that is impossible to get reservations. After all, this formidable group is led by Joel D. Cooper, MD, the capo di tutti capo of the LVRS cognoscenti. Also, this is the first peer-reviewed publication that describes their 5-year observational results following LVRS, whereas their 2-year results were published in 1998.2

Needless to say, we were not disappointed. The article describes in great detail the year-by-year impressive clinical and physiologic results in a large cohort of patients, prospectively followed up, undergoing bilateral LVRS for severe emphysema. They evaluated 200 patients 3.7 ± 1.6 years (mean ± SD) after LVRS. Rigid screening criteria emphasized heterogeneous anatomic distribution of emphysema with obvious target areas for resection, usually in upper lobes. Additionally, durable physical conditioning and pulmonary rehabilitation prior to surgery was stressed. Those patients selected for LVRS had clinical impairment and physiologic abnormalities similar to previous reports.1 All patients underwent sequential, bilateral LVRS using a median sternotomy incision; 177 patients had upper-lobe-worst emphysema, and 23 patients had lower-lobe-worst emphysema. Incidence of α1-antitrypsin deficiency was not reported. Patients were restudied at 0.6 months, 3 years, and 5 years after LVRS, and 90% of the evaluable patients completed testing. The 90-day post-LVRS mortality rate was 4.5%, similar to that of previous reports.3 Annual Kaplan-Meier survival rates 1 to 5 years after LVRS were 93%, 88%, 83%, 74%, and 63%. Dyspneic scores were improved 81%, 52%, and 40% at 6 months, 3 years, and 5 years after LVRS; and improvements in quality-of-life questionnaires were 93%, 78%, and 69% at similar time intervals. Compared to baseline values, FEV1 was also significantly improved at 6 months, 3 years, and 5 years after LVRS. Need for supplemental oxygen also improved. The authors noted that changes in residual volume showed poor correlation with change in dyspnea scale and the Medical Outcomes Study Short Form-36 physical function scale score. Results from upper-lobe vs lower-lobe predominant emphysema were not segregated.

We would be most cautious not to overinterpret the significance of the data in Tables 4 and 5 with respect to the percentage of patients improved, and

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## REFERENCES

1 Richter JE. Asthma and gastroesophageal reflux disease: the truth is difficult to define. Chest 1999; 116:1150–1152