CHEST

Original Research

SIGNS AND SYMPTOMS OF CHEST DISEASES

Response of Chronic Cough to Acid-Suppressive Therapy in Patients With Gastroesophageal Reflux Disease

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Background: **Epidemiologic and physiologic studies suggest an association between gastroesophageal reflux disease (GERD) and chronic cough. However, the benefit of antireflux therapy for chronic cough remains unclear, with most relevant trials reporting negative findings. This systematic review aimed to reevaluate the response of chronic cough to antireflux therapy in trials that allowed us to distinguish patients with or without objective evidence of GERD.**

Methods: **PubMed and Embase systematic searches identified clinical trials reporting cough response to antireflux therapy. Datasets were derived from trials that used pH-metry to characterize patients with chronic cough.**

Results: **Nine randomized controlled trials of varied design that treated patients with acid suppression were identified (eight used proton pump inhibitors [PPIs], one used ranitidine). Datasets from two crossover studies showed that PPIs significantly improved cough relative to placebo, albeit only in the arm receiving placebo first. Therapeutic gain in seven datasets was greater in patients with pathologic esophageal acid exposure (range, 12.5%-35.8%) than in those without (range, 0.0%-8.6%), with no overlap between groups.**

Conclusions: **A therapeutic benefit for acid-suppressive therapy in patients with chronic cough cannot be dismissed. However, evidence suggests that rigorous patient selection is necessary to identify patient populations likely to be responsive, using physiologically timed cough events during reflux testing, minimal patient exclusion because of presumptive alternative diagnoses, and appropriate power to detect a modest therapeutic gain. Only then can we hope to resolve this vexing clinical management problem.** ***CHEST 2013; 143(3):605–612***

Abbreviations: GERD = gastroesophageal reflux disease; LPR = laryngopharyngeal reflux; PPI = proton pump inhibitor

Chronic cough, defined as cough that persists for > 8 weeks, affects 11% to 20% of the adult population[1] and significantly impairs health-related quality of life,[2] leading to substantial socioeconomic burden. Epidemiologic studies suggest an association between gastroesophageal reflux and chronic cough,[3] and this relationship is supported by convincing physiologic data. First, in patients with chronic cough, acid infusion into the distal esophagus increases the frequency of coughing[4] and cough reflex sensitivity.[5] Second, approximately one-half of unselected patients with chronic cough show a positive symptom association between cough and reflux during reflux monitoring.[6] However, unlike heartburn, which is usually caused by acid reflux,[7] chronic cough has a diverse range of potential causes. Estimates of the proportion of patients with chronic cough in whom reflux is the underlying cause vary greatly among specialists, ranging from 0% to 41%.[8] Given the implicit variation in approaches used to identify patients with reflux-related cough, it is perhaps not surprising that a Cochrane review found insufficient evidence to conclude that proton pump inhibitor (PPI) treatment is beneficial in treating nonspecific chronic cough.[9]

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The relationship between gastroesophageal reflux and reflux symptoms is complex in general, but it is particularly complex in the case of chronic cough, in which other disease processes, issues of cause and

effect, and hypersensitivity all come into play. Hence, a more thoughtful exploration of the literature may be required to elucidate any treatment benefit for acid-suppressive therapy in this patient group and/or to identify factors that may have prevented studies from detecting benefit with acid-suppressive treatments. For example, with another potential gastroesophageal reflux disease (GERD) syndrome, unexplained chest pain, a recent analysis showed that PPI therapy was effective in patients with objective evidence of GERD (pathologic esophageal acid exposure and/or reflux esophagitis) but not in those without.[10] To our knowledge, the impact of this and other variations in study design on therapeutic outcomes for acid-suppressive therapy in patients with chronic cough has not been explored. Thus, the aim of this systematic review was to evaluate the response of chronic cough to acid-suppressive therapy in relation to variations in study design, with a particular focus on distinguishing between studies that included patients with and without objective measures of GERD.

Materials and Methods

Systematic Searches

A systematic search of PubMed and Embase (for all years until August 20, 2011) was conducted (Fig 1) as well as a search of recent review articles and abstracts from recent congresses (Digestive Diseases Week, 2008-2011; United European Gastroenterology Week, 2008-2011). Included studies were placebo-controlled clinical trials reporting data on the impact of antireflux therapy on cough in patients selected based on the presence of chronic cough or laryngopharyngeal reflux (LPR), of which cough was a component symptom, and diagnosed with GERD or LPR by objective measures and/or reflux symptoms.

Reviews, studies not conducted in adult humans, and studies not published in English were excluded using search engine filters. Studies were also excluded if they did not specify the type of acid-suppressive therapy used or if they used a crossover study design without presenting data separately for the first period. The latter exclusion criterion was based on likely period effects for cough (ie, that it tends to improve with time) and the bias associated with carryover effects when an adequate washout period is not used.[1] The remaining studies were screened based on titles and abstracts and on the full article when the relevancy of the study was not clear from the abstract.

Analysis of Therapeutic Gain

Where possible, the therapeutic gain associated with acid-suppressive treatment of chronic cough was calculated. This approach was used in recent systematic reviews to compare the therapeutic response of heartburn, regurgitation,[11] and unexplained chest pain[10] to PPIs across different studies. Therapeutic gain was calculated by subtracting the percentage change from baseline in cough (symptom score or proportion of responders) in the placebo group from that in the treatment group. Second-arm data from crossover studies were not included in the analysis, as discussed previously. Attempts were made to contact study authors for additional information needed for full analysis of their data.[12-16]

Results

Systematic Searches and Study Selection

The systematic searches are summarized in Figure 1. Seven studies were excluded for the following reasons: Four were epidemiologic studies,[17-20] one was not published in English,[21] and two did not select patients based on the presence of chronic cough or LPR reflux.[12,22] A citation list search of the remaining 24 studies identified four additional studies for potential inclusion (28 in total). A placebo control group was not included in 10 of these, and they were excluded.[23-32] Another study was excluded because it did not specify the definition of GERD used.[33]

Study Characteristics

Characteristics of the nine included studies are summarized in Table 1.[13-16,34-38] All assessed pharmacologic interventions for cough (no placebo-controlled studies assessing surgery were found); eight assessed PPIs (once daily or bid for 8-16 weeks)[13-16,34-37]; and one assessed the histamine type 2-receptor antagonist ranitidine, 150 mg daily for 8 weeks.[38] No unpublished data were used in this review because no additional information that aided the analysis was obtained from authors.

Methods for assessing cough varied substantially across studies. Five used patient diaries consisting of visual analog scales to assess cough severity and/or frequency (Table 1),[13,16,34,36,38] questionnaires were used in two studies (Table 1),[14,35] and two studies did not specify the method of data acquisition (Table 1).[15,37] Two studies assessed efficacy in terms of the proportion of patients who met prespecified criteria for response (Table 1)[16,36]; the remainder measured change in mean cough scores relative to baseline for treatment vs placebo. Sample sizes across the studies were 15 to 40, and the sample sizes for placebo and active

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