Inhaled Beclomethasone Dipropionate Improves Acoustic Measures of Voice in Patients With Asthma*

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Background: Inhaled corticosteroids have the potential to produce upper-airway side effects such as hoarseness. As new compounds and delivery devices are developed and compared, it is difficult to quantify their adverse upper-airway effects.

Objective: We undertook the following study to test the ability of an acoustic analysis technique to quantify changes in vocal function in steroid-naive patients with asthma who receive inhaled beclomethasone dipropionate (BDP), 1,000 μg/d for 4 months.

Methods: Patients self-administered one of four regimens of inhaled BDP. Group 1 patients received one 250-μg puff qid via metered-dose inhaler (MDI); group 2 patients received one 250-μg puff qid via MDI with a holding chamber; group 3 patients received two 250-μg puffs bid via MDI; and group 4 patients received two 250-μg puffs bid via MDI with a holding chamber. A smaller cohort of nonsmoking asthmatic patients was managed without steroid intervention for 4 months. At baseline and again at 8 weeks and 16 weeks after the initiation of BDP treatment, patients underwent spirometry and methacholine challenge. At baseline and again at 2, 4, 8, 12, and 16 weeks, patients underwent voice recording for analysis of voice parameters. The recorded vowels were low-pass filtered (10 KHz), digitized (22 KHz), and analyzed by software to obtain two acoustic measures: (1) jitter, the cycle-to-cycle variation in the time period of the voice signal; and (2) shimmer, the cycle-to-cycle variation in voice signal amplitude.

Results: We recruited 77 patients for randomization to inhaled steroid therapy and 10 patients who continued to receive only occasional inhaled bronchodilator therapy. In all active treatment groups, FEV1, FVC, and provocative concentration of methacholine causing a 20% fall in FEV1 improved significantly after BDP treatment. Mean jitter scores, a measurement of variation in voice pitch, were not significantly influenced by BDP treatment. However, mean shimmer scores, a reflection of perturbation in vocal amplitude, fell significantly (p < 0.05) in the active treatment groups. These reductions in shimmer scores were not significantly different in the active treatment groups. Shimmer scores in the bronchodilator-treated group were unchanged during the 16 weeks of follow-up.

Conclusions: Our data show that a simple and noninvasive acoustic analysis of voice is sensitive to subclinical changes associated with inhaled corticosteroid therapy. We have shown that 1,000 μg/d of inhaled BDP actually improves specific acoustic measures of voice in patients with inadequately controlled asthma. These improvements were uninfluenced by dosing schedule and whether a spacing chamber was used.

Key words: asthma; inhaled steroids; voice

Abbreviations: BDP = beclomethasone dipropionate; dB% = percentage of the average vocal pulse amplitude in decibels; MDI = metered-dose inhaler; PC20 = provocative concentration of methacholine causing a 20% fall in FEV1

The growing awareness by physicians of the inflammatory nature of asthma has led to increasing use of inhaled corticosteroids for disease control. Because these agents are espoused by a growing number of national and international guidelines, they are being used earlier and for milder disease than before.1–3 There is increasing reliance on high-dosage formulations of inhaled corticosteroids, and there is a bewildering choice of delivery devices designed to improve deposition of drug in the lung while minimizing oropharyngeal deposition. In the clinical setting, such a treatment strategy is generally

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regarded as safe, effective, and well tolerated. In a minority of patients, however, attempts to treat with adequate doses of inhaled corticosteroid are complicated by annoying upper-airway side effects. For some patients, suboptimal dosing or alternative therapy is necessary because of troublesome hoarseness. This problem is neither rare nor trivial; Toogood and colleagues have reported that up to 50% of patients report dysphonia at some time during inhaled steroid therapy, with 12 to 28% of patients discontinuing inhaled corticosteroid therapy after the appearance of the problem.

In the development of novel corticosteroids and their delivery devices, the demonstration of clinical efficacy is relatively straightforward. Depending on the severity of asthma under study, a variety of pulmonary function and clinical end points can be used to quantify the improvement in asthma control. By contrast, the evaluation of side effects is more difficult. Hoarseness, in particular, is a highly subjective symptom. Patients who rely on their voices professionally might be sensitive to and intolerant of a trivial change in voice quality that would go unnoticed by patients who do not use their voices in such a fashion. Although self-reporting by patients may lack the necessary detail and sensitivity, it is the usual means of monitoring for upper-airway side effects in clinical trials of inhaled corticosteroids. Visual inspection of the upper airway for Candida growth or quantitative cultures for Candida species are also occasional components of inhaled corticosteroid clinical trials; however, these strategies measure a phenomenon usually unrelated to changes in voice quality itself. Williams and colleagues attributed the dysphonia of inhaled corticosteroid use to steroid myopathy of the vocal cords. Using laryngoscopy, they studied a small group of patients prospectively and found subtle myopathic changes appearing in the vocal cords of patients even before changes in voice quality were clinically apparent. Laryngoscopy is an invasive procedure that is ill suited for routine clinical monitoring of voice abnormalities. During the past 20 years, several acoustic measures have been developed for the objective and noninvasive measurement of vocal function. In addition, advances in computer hardware and software have led to the development of many inexpensive and commercially available systems for obtaining these objective acoustic measures of voice. Two of the most commonly used acoustic measures of voice quality are vocal jitter and vocal shimmer. These measures have been reported in at least 30 published articles during the past 20 years.

In the present study, we obtained vocal jitter and shimmer measures in an attempt to quantify changes in vocal function in patients who were receiving inhaled corticosteroids. In particular, we sought to determine the effect of inhaled beclometasone dipropionate (BDP), 1,000 μg/d for 4 months, on acoustic measures of voice in steroid-naïve patients with asthma. In addition to testing the pretreatment and posttreatment voice measures of asthmatics receiving BDP, we compared voice measures in the steroid-treated group to voice measures in a population of patients with asthma who had not received inhaled steroids. Finally, we assessed the impact of a holding chamber and the impact of twice-daily vs four-times-daily dosing schedules on voice changes resulting from inhaled steroid use.

**Materials and Methods**

**Patients**

Patients were considered eligible for the study if they were between 16 years and 60 years of age and had a history and clinical findings compatible with asthma. In addition, all patients demonstrated either a 15% improvement in FEV₁ after two puffs of inhaled salbutamol, 100 μg per puff (Ventolin; GlaxoSmithKline; Middlesex, UK), or a provocative concentration of methacholine causing a 20% fall in FEV₁ (PC20) of ≤ 2.0 mg/mL. Potential subjects were excluded if they (1) had smoked tobacco in the year before enrollment; (2) had received treatment with systemic or inhaled steroids in the 2 months before enrollment; (3) had been hospitalized for asthma management in the 2 months before enrollment; (4) had suffered an upper respiratory tract infection in the month before enrollment; or (5) had a history of laryngeal disease. Each patient signed an informed consent form. The study was approved by the Human Subjects Review Committee of the University of Toronto.

**Study Design**

In two university hospital asthma centers, we recruited nonsmoking patients with asthma who were not receiving inhaled corticosteroids, and we randomized them to one of four treatment groups. For 4 months, patients self-administered one of four regimens of inhaled BDP. Group 1 patients received one 250-μg puff qid via metered-dose inhaler (MDI); group 2 patients received one 250-μg puff via MDI with a holding chamber (Aerobid; Trudell Medical; London, Ontario); group 3 patients received two 250-μg puffs bid via MDI; and group 4 patients received two 250-μg puffs bid via MDI with a holding chamber. All patients were taught the proper use of their delivery devices and were advised to rinse their mouths with water, and gargle and spit after receiving inhaled corticosteroids. We also recruited a smaller cohort of nonsmoking patients with asthma who were not in need of inhaled steroid therapy or did not wish to use them, and who were monitored without steroid intervention for 4 months. At baseline and again at 2, 4, 8, 12, and 16 weeks after the initiation of inhaled BDP therapy, patients underwent voice recording for later blinded analysis of voice parameters. At baseline and again at 8 weeks and 16 weeks after the initiation of inhaled BDP treatment, patients in the active treatment groups underwent spirometry and methacholine challenge. Patients in the control group were assessed by spirometry but not by methacholine challenge.
Procedures

Spirometry was performed using a dry rolling seal spirometer, following the recommendations of the American Thoracic Society. Methacholine challenges were performed by a modification of the method of Cockcroft et al.10

All voice recordings were made using a head-mounted condenser microphone (model HY3; TOA; Edmonton, Alberta), with a constant mouth-to-microphone distance of 7 cm, and an audiocassette recorder (model 112R; TASCAM; Mississauga, Ontario). After a demonstration, patients were asked to take a deep breath and to sustain the vowel sound “ah” steadily at a comfortable intensity and pitch for as long as possible. During the study, patients were asked to take a second production of the vowel sound was used in all subsequent analyses.

At the completion of the study, recordings were supplied in random sequence and in blinded fashion to a speech pathologist who was unaware of the patient’s treatment allocation and whether the recording represented a pretreatment or posttreatment condition. The recorded vowels were low-pass filtered (10 KHz), digitized (22 KHz), and analyzed using a computer, an IBM Audio Capture and Playback Adapter board (IBM; Toronto, Ontario), and CSpeech Software (Madison, WI). A 1,000-ms segment starting 500 ms from the onset of the vowel was used to obtain two acoustic measures: jitter, the cycle-to-cycle variation in the time period of the voice signal; and shimmer, the cycle-to-cycle variation in voice signal amplitude.

Jitter and shimmer are indirect acoustic measures of variations in vocal fold vibration. Several previous studies15–17 have found that jitter and shimmer can be significantly correlated with the perception of abnormal voice qualities, including hoarseness, breathiness, and harshness. During the production of voice, the vocal folds rapidly alternate between adduction (the folds come together) and abduction (the folds separate). For most adults, this adductory/abductory cycle generally occurs at rates between 100 cycles per second and 300 cycles per second. Thus, the period between vocal cord vibratory cycles is between approximately 4 ms and 10 ms. Each of these adductory/abductory voice cycles is associated with the production of a transient pulse of sound. Using acoustic analysis techniques, it is possible to precisely measure the peak amplitude and timing of these sound pulses. Vocal shimmer is determined by measuring the duration between vocal pulses produced during phonation. Jitter is often expressed in milliseconds (ms) and 10 ms. Each of these adductory/abductory voice cycles is associated with the production of a transient pulse of sound. Vocal shimmer is determined by measuring the amplitude of one vocal pulse and subtracting it from the amplitude of the next adjacent vocal pulse. This difference in amplitude is calculated for each set of adjacent pulses across several hundred pairs of pulses. The average of these amplitude difference values is calculated and referred to as shimmer. Thus, shimmer is an estimate of the peak amplitude in decibels (dB%). The average shimmer value obtained for normal adults is approximately 1.6 dB% (SD, 0.5 dB%).18,19

Vocal jitter is determined by measuring the duration between adjacent vocal pulses. The difference in time is calculated for each pair of adjacent pulses across several hundred pairs of voice pulses. The average of these durational difference values is calculated and referred to as jitter. Thus, jitter is an estimate of the cycle-to-cycle variation in the time period between adjacent vocal pulses produced during phonation. Jitter is often expressed in millisecond units. The average jitter value for normal adults is approximately 0.02 ms (SD, ± 0.01 ms).18,19 More detailed descriptions of jitter, shimmer, and related acoustic vocal perturbation measures can be found elsewhere.20,21

Data Analysis

All statistical procedures were performed using software (Minitab; State College, PA). Pretreatment and posttreatment spirometric variables were compared by Student paired t test. Differences among groups in spirometric variables were compared by one-way repeated analysis of variance with specific pairwise comparisons between groups when indicated by unpaired t tests. Wilcoxon signed-rank test was used to compare pretreatment and posttreatment voice parameter scores and PC20 within treatment groups. The Mann-Whitney U test was used to examine differences among groups. Differences were considered significant at the p < 0.05 level.

Results

Baseline

The baseline characteristics of the patients are shown in Table 1. There were no significant differences among groups with respect to age, sex, spirometric measures, or PC20. It should be noted that a separate preliminary analysis of the subject’s average vocal pitch or fundamental frequency was performed and revealed no significant differences among the groups. This was a concern because higher fundamental frequency values (such as those found in female voices) can be associated with higher jitter values.22 Because there was no statistically significant difference in average fundamental frequency values across the groups and because there was gender balance across treatment groups, we did not analyze data from men and women separately. However, mean jitter and mean shimmer scores differed significantly among groups; these scores were lower in the bronchodilator-only group. For jitter, the aver-

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Age, yr</th>
<th>Male/Female</th>
<th>FEV1, L</th>
<th>FEV1, % predicted</th>
<th>FVC, L</th>
<th>FVC, % predicted</th>
<th>PC20, mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 19)</td>
<td>34.7 ± 10.0</td>
<td>3/16</td>
<td>2.56 ± 0.73</td>
<td>82.3 ± 17.5</td>
<td>3.74 ± 1.12</td>
<td>100.1 ± 19.4</td>
<td>1.85 ± 3.83</td>
</tr>
<tr>
<td>2 (n = 19)</td>
<td>33.4 ± 11.5</td>
<td>8/11</td>
<td>2.42 ± 0.61</td>
<td>70.9 ± 20.4</td>
<td>3.78 ± 0.67</td>
<td>90.3 ± 14.2</td>
<td>3.65 ± 6.23</td>
</tr>
<tr>
<td>3 (n = 21)</td>
<td>34.0 ± 9.6</td>
<td>10/11</td>
<td>2.71 ± 0.71</td>
<td>79.5 ± 17.9</td>
<td>3.98 ± 0.88</td>
<td>93.2 ± 15.7</td>
<td>3.11 ± 5.63</td>
</tr>
<tr>
<td>4 (n = 18)</td>
<td>33.9 ± 12.6</td>
<td>7/11</td>
<td>2.87 ± 0.91</td>
<td>82.1 ± 18.1</td>
<td>4.04 ± 1.15</td>
<td>95.9 ± 17.0</td>
<td>2.68 ± 4.50</td>
</tr>
<tr>
<td>Control (n = 10)</td>
<td>30.7 ± 6.1</td>
<td>3/7</td>
<td>3.10 ± 1.57</td>
<td>98.0 ± 12.12</td>
<td>3.52 ± 1.91</td>
<td>83.7 ± 24.0</td>
<td>–</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± 1 SD unless otherwise indicated.
age baseline value in all patients in the active treatment groups was 0.0298 ± 0.006 ms vs 0.017 ± 0.001 ms in the control group (p < 0.05). For shimmer, the average baseline value in all patients in the active treatment groups was 2.58 ± 0.79 dB% vs 1.50 ± 0.87 dB% in the control group (p < 0.05).

It should be noted that the jitter and shimmer values obtained for the bronchodilator-treated group were approximately the same as those values that have been previously reported for healthy nonasthmatic adults. However, the jitter and shimmer values obtained for the combined active treatment groups were at least 65% higher than the control and healthy group values. We could detect no relationship between baseline FEV₁, magnitude of bronchodilator response, or other pulmonary function variable and jitter or shimmer scores.

**Respiratory Responses to Inhaled BDP**

In all active treatment groups, FEV₁, FVC, and PC₂₀ improved significantly after inhaled BDP treatment. Mean FEV₁ rose from 2.60 ± 0.52 to 2.92 ± 0.69 L (p < 0.0001), mean FVC rose from 3.86 ± 0.94 to 4.06 ± 1.26 L (p < 0.005), and mean PC₂₀ fell from 4.60 ± 5.77 to 1.33 ± 2.52 mg/mL (p < 0.001).

**Response of Voice Parameters to Inhaled BDP**

Mean jitter scores were not significantly influenced by inhaled BDP treatment. However, mean shimmer scores fell significantly in the active treatment groups (p < 0.05). Changes were evident at week 2 and were essentially maximal by week 4 (Fig 1). Subsequently, shimmer scores did not change significantly during the remaining 12 weeks of active treatment. Overall, the combined active treatment groups showed average vocal shimmer values that fell from approximately 65% above normal to approximately 30% above normal after treatment. These reductions in shimmer score were not significantly different among the active treatment groups. Shimmer values in the bronchodilator-treated group remained unchanged and approximately equivalent to previously reported normal values during the 16 weeks of follow-up.

**DISCUSSION**

Our data show that a simple and noninvasive acoustic analysis of voice is sensitive to subclinical changes associated with asthma and its therapy. In a large group of patients with inadequately controlled asthma, we have shown that 1,000 μg/d of inhaled BDP actually improves one voice acoustic measure (shimmer) in as little as 2 weeks, with the improvement sustained over a period of 4 months. This improvement was similar in magnitude whether a four-times-daily or twice-daily dosing schedule was used. Similarly, the use of a spacing chamber did not affect this improvement in voice acoustics. Although our data are limited, the lower baseline values for
shimmer score in the bronchodilator-treated control group with minimal disease and their lack of change over time suggest that undertreated or poorly controlled asthma is associated with measurable abnormalities of voice acoustics that are reduced by improved asthma control.

Our findings are important in several ways. First, the data are reassuring for patients with asthma who fear impaired voice performance if inhaled corticosteroids are prescribed. Second, our findings provide a potentially useful clinical and, more important, clinical trial tool for assessment and quantification of vocal function during long periods of time. All patients received corticosteroid therapy for frequent episodes of cough, wheeze, or both; at baseline, the average FEV₁ was 20% below the predicted normal value. Our data are most consistent with impairment in voice acoustics arising from troublesome cough in patients with untreated or undertreated asthma. We cannot rule out the possibility that coexisting upper-airway disease, particularly allergic rhinoconjunctivitis, contributed to the elevated baseline shimmer scores in the treated groups. However, our therapy was not directed toward the upper airway, and we doubt that significant changes in nasal symptoms or postnasal drip occurred as a consequence of the active treatment. It might be argued that the use of increased shimmer scores as an index of voice impairment could be the consequence of frequent β₂-agonist use. β₂-Agonists do produce skeletal muscle tremor, an effect most notable in the out-stretched extremities. We cannot rule out such an effect on vocal cord motion arising from β₂-agonist use. One could postulate that the inhaled corticosteroids reduced β₂-agonist use and thus resulted in less perturbation of normal vocal cord motion by the adrenergic drug. We think that this explanation of our findings is unlikely. We found no evidence of impaired voice acoustics in patients treated with β₂-agonists alone.

Some limitations to our findings should be noted. Our study was limited to 4 months. We cannot rule out the possibility that continued inhaled corticosteroid use would have resulted in subsequent deterioration in voice acoustics. One explanation for dysphonia after inhaled corticosteroid use is vocal cord muscle atrophy. Nevertheless, the present trend toward controlling asthma is to obtain control at a reasonable initial dose of inhaled corticosteroids and then to titrate the dosage downwards to the least amount needed to maintain control. Our findings would reassure that the voice will not likely be impaired by doses of BDP as high as 1,000 μg/d during at least a 4-month period, a period sufficient to obtain control in the majority of asthma sufferers. Our findings did not compare various doses of inhaled corticosteroid, and we do not know whether the changes in voice acoustics are dose related. We suspect that improvement in voice quality is the consequence of improved asthma control and as such is unlikely to have any simple dose-response relationship. Our study did not examine the influence of alternative delivery systems on vocal function. The development of alternatives to chlorofluorocarbon-containing MDIs will include alternative propellant pressurized inhalers, dry-powder inhalers, and other technologies. However, our study does provide information on how the impact of these technologies on voice acoustics could be evaluated. Our study did not incorporate a placebo-treated group. Therefore, we cannot rule out changes in voice occurring spontaneously or as “regression toward the mean” in a group of patients who presented with symptomatic asthma and associated voice abnormalities. However, we believed that the incorporation of a placebo-treated group would be unethical for the 4-month treatment of patients with poorly controlled disease. We also think that the time course of improvement in shimmer scores is more consistent with active treatment response than seasonal variability in asthma.

The results of this vocal acoustics study provide significant evidence of a change in vocal function in asthmatic patients after treatment with inhaled BDP. These results also suggest that this treatment may be associated with improvements in perceived voice quality. Additional studies using listener judgments and perceptual analysis procedures could be useful. Despite studies23–25 that have questioned the sensitivity and reliability of perceptual voice quality measures, we believe that both acoustic and perceptual measures can provide important information about vocal function in patients receiving treatment for asthma.

Our study removes one of the smaller barriers that may have discouraged early administration of inhaled corticosteroids to patients with poorly controlled asthma. The unexpected finding of improvement in voice acoustics is most readily explained by a reduction in cough with a consequent reduction in upper-airway stress. The measurement and analytic techniques described are simple enough for clinical use but are most likely to find their application in clinical research.

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