The influence of inhaled corticosteroids on normal voice production in adults: An acoustic study

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Abstract

Corticosteroids are the most potent and reliable of the available agents among the anti-inflammatory drugs, and have assumed a major role in the management of asthma. This has subsequently resulted in the global widespread use of inhaled corticosteroids (ICS). A variety of studies have been undertaken to examine the effects of ICS on voice production among people with asthma. Most research suggests that the long-term use of ICS has a negative effect on voice production. However, the results of these studies are limited because of the reliance upon examining an asthmatic population and not consistently recording the dose prescribed. As a result, one cannot exclude that some of the voice problems may have been previously caused by asthma and thus, the contributing effects of ICS are obscured. Therefore, an ideal approach to examine the influence of ICS on voice is to test its short-term effects on healthy individuals, using a specific ICS (Fluticasone Propionate) at a fixed dose (1000 µg/Day). Thirty healthy adults (15 females & 15 males) aged between 18 to 30 years participated in this study. All participants were non-smokers with no history of speech, language or voice disorder. No participants had a history of asthma, respiratory illness hospital admission or inhaler use within the past 3 months. All participants followed the treatment regime often prescribed by physicians (in Canterbury region) for treating asthma (500 µg in morning & 500 µg in evening). Each participant self administered (inhaled) two puffs of ICS in the morning and again in the evening over a six day period. Voice samples were audio-recorded prior to undergoing the ICS regime, at various points during the ICS regime, and at the conclusion of ICS regime. Each participant’s audio-recorded samples were submitted for acoustic analysis using a commercially available speech analysis system (CSL 4300B, Kay Elemetrics, 1994). Three measures were performed, (1) vocal fundamental frequency (F0), (2) long-time spectral analysis (LTAS) and (3) formant frequency and formant frequency bandwidth.
The result of this study indicates that ICS does have an effect on acoustic properties of voice. These effects were more evident in connected speech compared to isolated vowel productions. In particular, the spectral tilt and first spectral peak of continuous speech samples were found to change from baseline. The current results are discussed in regard to the phonatory deterioration associated with ICS use. The present study provides a framework for developing ICS treatment for respiratory disease in the phase of minimizing adverse effects on voice.
Introduction

Steroids can be divided into two categories, (1) anabolic steroids and (2) corticosteroids. Anabolic steroids are a class of steroid hormones related to the hormone testosterone. The steroid serves to increase protein synthesis within cells, which results in the build-up of cellular tissue in muscle called anabolism (de Bolster, 1997). Anabolic steroids also have androgenic properties, such as the development of masculine characteristics (e.g., body hair). The word anabolic derived from the Greek word *anabolein*, "to build up", and the word androgenic from the Greek *andros*, "man" + *genein*, "to produce". A corticosteroid is a steroid hormone that is produced naturally in the adrenal cortex. Corticosteroids are used by physicians to treat inflammatory conditions, such as asthma, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, chronic low back pain, shoulder injuries, polymyalgia, and preventing rejections in transplants (Barnes, 2001; Gaffo, Saag, & Curtis, 2006).

History of corticosteroids

Cortisol and adrenocorticotropic hormones (ACTH) were isolated and synthesised independently by Reichestein (1935). Philip Hench, a rheumatologist working at Mayo Clinic was the first to demonstrate the clinical efficacy of cortisone in 1948. He did this by giving intravenous injections of ACTH to patients with rheumatic arthritis (Glyn, 1998). Boardley, Carey and Harvey (1949) at John Hopkins University were the first to use cortisone in patients with asthma. They described five patients with asthma, all of whom had eosinophilic sputum, who improved rapidly with intramuscular injections of ACTH over a three week period. They later replicated the study and confirmed these observations in a larger group of patients. Subsequently, oral cortisone was shown to be an effective replacement for injections in patients with difficulty to control asthma. Oral steroids are now frequently used for patients with severe asthma but it is clear that side effects are a major problem, resulting in

To reduce systemic side effects, the need to give corticosteroids by inhalation was suggested by the Medical Research Council (U.K) in 1956. This has led to the development of two synthetic steroids, beclomethasone dipropionate (BDP) and betamethasone-17-valerate to be used for inhalation. Brown, Storey and George (1972) established that inhaled BDP was effective in reducing the need for oral corticosteroids and in many patients achieved better control of asthma. Fluticasone Propionate (FP) has become the most commonly prescribed inhaled corticosteroid (ICS) for patients with asthma and reactive airway disease because of its potency and safety margin (DelGaudio, 2002), and the activity of FP being two times greater than BDP (Ayres, Bateman, Lundback & Harris, 1995; Clark & Lipworth, 1997; Fabbri, Burge & Croonenborgh, 1993). FP is a highly lipophilic molecule (topical potency) with good uptake, binding and retention characteristics in human lung tissue. FP has rapid binding property with the receptors present on the cell membrane and acting rapidly on inflammatory cells (Fuller, Johnson & Bye, 1995). Orally administered FP is rapidly metabolized on the first pass through the liver, resulting in less than 1% oral bioavailability and has a longer elimination half-life than BDP (Harding, 1990).

**Steroids and Asthma**

Corticosteroids are the most potent and reliable of the available agents among the anti-inflammatory drugs, and have assumed a major role in the management of asthma (Szelfler, 1991). This has subsequently resulted in the widespread use of ICS. The vasoconstrictor activity of ICS aids to reduce bronchial mucosal oedema and thickening. ICS can be used as a monotherapy (i.e., using a single drug for treatment) or as a combination production (i.e., use of two or more drugs). The co-administration of an ICS with a long-lasting beta-2 (β2) agonist in a single inhaler has greatly simplified asthma therapy. The
action on β2 agonists contributes to relaxation of smooth muscles, resulting in dilation of the bronchial passages (Kips & Pauwels, 2001).

The two combination inhalers currently available are Symbicort and Seretide (Lotvall, 2004). Symbicort combines budesonide (a form of BDP) and formoterol in a single inhaler. Seretide combines salmeterol and FP (double dose of BDP) in a single inhaler. These inhalers comply with Step 3 (total 5 steps) of the international guidelines established by Global Initiative for Asthma (GINA) for asthma control (Humbert, Anderson & Buhl, 2008). The guidelines recommend the addition of a long-acting β2-agonist to ICS in patients who are inadequately controlled on ICS alone.

There are currently two approaches for treating asthma using combination therapy (1) fixed and (2) adjustable dosing. Fixed dosing with either Symbicort or Seretide provides effective asthma control in line with guideline goals recommended by GINA (Humbert, et al., 2008). However, given the inherent variability of asthma, there is increasing evidence that adjusting the dose of ICS according to fluctuations in symptoms is beneficial (Lotvall, 2004). Findings from a series of studies comparing fixed and adjustable symptom-guided dosing regimens demonstrate that adjustable dosing may improve asthma control at an overall lower steroid dose (Lotvall, 2004). However, in cases of persistent acute asthmatic symptoms the patients are using very high doses of ICS for longer periods (Hanania, Chapman, & Kesten, 1995). The long-term use of ICS may also reduce the number of mast cells in airway mucosa and decrease the immediate response to allergen and exercise (Barnes, 1993).

As with many types of medication that are taken for an extended period, corticosteroids should always be withdrawn slowly and with medical advice. While taking the medication, the adrenal gland’s natural production of the steroid diminishes significantly. A process of gradual withdrawal from the medication is required to allow the adrenal gland...
an opportunity to restart the natural synthesis of steroids again (Nahaczewski, Fowler, & Hariharan, 2004).

Complications of ICS

Systemic complications occur when using ICS because up to 80% of the dose delivered by a conventional metered-dose inhaler (MDI) is swallowed. Systemic side effects are dose-dependent, and obvious differences exist between ICSs in their ability to cause systemic glucocorticoid activity (Jones, Toogood, & Crilly, 1988). Some researchers have speculated that a “residue” from the inhaled substance irritates the pharyngolaryngeal mucosa. Both the propellant and lubricant components of MDI preparations have a pro-inflammatory local effect (Roland, Bhalla, & Earis, 2004). Long-term adverse effects associated with chronic corticosteroid use include osteoporosis, cushingoid appearance, accelerated atherosclerosis, early cataracts, skin thinning and purpura (Cope & Bova, 2008). Some of the probable causes of the complications include:

- The steroid (e.g., preparation, carrier substance, dose of steroid, and regime).
- The manner in which it is propelled into the airways (i.e. the inhaler device).
- Intrinsic inflammation of the upper airway in asthmatic patients.
- Mechanical irritation because of cough.
- Inflammatory disease (e.g., rhinitis and postnasal catarrh) and inflammatory stimuli (e.g., smoking and noxious agents in the workplace).

Inhaled Corticosteroid (ICS) and Voice Production

The impact of ICS on voice production has received considerable research attention (Gallivan, Gallivan & Gallivan, 2007). A majority of this research has focused on individuals with asthma. The bulk of these studies suggest that ICS has a negative impact on voice production (Bhalla, Watson, Taylor, Jones & Roland, 2009). However, there are studies
showing no adverse affects of ICS on voice production (Shaw & Edmunds, 1986) as well as an improvement in voice following ICS (Meyer, Scott & Chapman, 2001). A chronological review of the salient literature follows.

Williams et al. (1983) studied 14 patients for 18 months who presented with a complaint of severe and persistent dysphonia, while receiving ICS for chronic asthma. The average dose given was 400 µg/day of BDP. They observed that in 9 (64%) patients a characteristic bilateral adductor vocal fold abnormality (i.e., a bowing of the vocal cords during phonation) was present during laryngoscopic evaluation. They concluded that the etiology of dysphonia is a steroid myopathy affecting the thyroarytenoid (i.e., vocal fold) muscles. With cessation of ICS, the dysphonia and vocal cord deformity resolved completely within 12 weeks.

Shaw and Edmunds (1986) examined 129 children between the ages of 6 to 15 years during a 6-month period of regular ICS use. They divided the children into two groups depending on the dose of ICS used per day. A total of 91 children were receiving less than 500 µg per day (range from 100-400 µg per day) and 38 were receiving more than 500 µg per day (range from 500-1500 µg per day) from the beginning of the study. At the conclusion of the 6-month period, the children were asked if they had a sore throat or hoarse voice. A total of 13 children reported having a sore throat. They found that dysphonia was not a problem in any of the two groups, although no objective (e.g., acoustic) measures of dysphonia were performed.

Shim and Williams (1987) studied 12 individuals with asthma who complained of severe cough and wheezing after using ICS (containing BDP). Each participant was required to take three puffs of BDP (120 µg), as well as three puffs of a placebo (in random order) using a metered dose inhaler (MDI). Following each puff, the total number of coughs elicited
by using the inhaler was tabulated. Across the three puffs, the group was found to produce a mean of 31 coughs following BDP and 19 coughs following the placebo. The results suggest that use of an inhaler device can lead to coughing, wheezing, and use of BDP is particularly prone to eliciting these negative side effects.

Williamson, Matusiewicz, Brown, Greening and Crompton (1995) assessed the prevalence of throat and voice symptoms in asthmatic patients compared to a non-asthmatic (control) group. A total of 255 out-patients using ICS (the average dose used was 800 µg-1000 µg) and 100 controls were surveyed. A total of 147 (58%) patients reported dysphonia or throat symptoms compared to 13% of the control group. Significantly more women (80%) reported having throat or voice symptoms in comparison to men (64%). Throat symptoms were more prevalent in patients using higher doses of ICS. However, the authors could not exclude that some of the voice problems may have been caused by asthma and may have actually improved on ICS therapy.

Hone et al. (1996) investigated 20 asthmatics, using a perceptual rating score of hoarseness, videolaryngoscopy (VLS) and videostroboscopy, prior to and after three months of high dose ICS therapy (1000 µg/day). A group of 22 healthy volunteers acted as controls. Erythema and oedema was noted in 10 (45%) asthmatics and vocal fold nodules in two (9%) asthmatics. Four (18%) of the control group had erythema and oedema. After 3 months of ICS therapy, improvement in voice was noted in 2 (33%) of the 6 patients complaining of hoarseness. This was associated with resolution of a vocal fold nodule in one participant and resolution of erythema in another. One asthmatic developed a mild glottic chink, which was attributed to steroid induced myopathy of the vocal folds. The researchers concluded that asthmatics have significantly more vocal fold pathology than healthy controls.
Lavy, Wood, Rubin and Harries (2000) performed a study on 22 patients receiving ICS for asthma, who had developed persistent troublesome hoarseness subsequent to the commencement of aerosol steroid treatment. Each patient was formally assessed in a voice clinic with VSL and stroboscopy. After this, a sample of speech and other vocal parameters were recorded using the “aerophone” and analysed using a visi-speech vocal analysis program. Using laryngoscopy, the vocal fold position, supraglottic hyperfunction, and mucosal changes were evaluated. For objective acoustic measures, mean fundamental frequency (F0), maximum phonation time and jitter (i.e., cycle-to-cycle variation in F0) were performed. The researchers found that 17 (77%) patients complained of hoarseness on a daily bases. Eight (36%) patients complained of other side effects, in most cases this was dryness and soreness of the throat. In nine (41%) patients there was some evidence of poor vocal fold positioning detected by laryngologists. Marked supraglottic hyperfunction and arytenoid over-ride was found in five (23%) patients. In 58% of the patients, opposition abnormalities were noted, supraglottic hyper function was noted in 40% patients. The acoustic analyses were revealing of cycle-to-cycle irregularity in 39% patients. Maximum phonation time was also reduced in 73% of the patients. A primary cause of these findings was attributed to use of ICS.

Meyer et al. (2001) recruited 77 patients who took 1000 µg/day of inhaled ICS (BDP) and 10 patients who received occasional ICS treatment. At 2, 4, 8, 12 and 16 weeks, each patient’s voice was audio recorded for later acoustic analysis. The results of the acoustic analysis indicated that mean jitter values did not differ significantly between the two groups. However, mean shimmer (i.e., cycle-to-cycle variation in vocal loudness) scores fell significantly (p<0.05) in the active treatment group. The researchers concluded that individuals with asthma who take 1000 µg/day of inhaled BDP could actually show an
improvement in their voice, suggesting that the dosage regime used in ICS is an important factor in regard to vocal function.

DelGaudio (2002) described a condition that is referred to as steroid inhaler laryngitis, a clinical entity that is caused by FP inhalation and manifested by dysphonia, throat clearing and fullness. The study population consisted of 20 patients with reactive airway disease and dysphonia, who were receiving inhaled FP therapy. The dose of FP used by the patients varied from 220 µg to 880 µg per day. The researcher reported laryngeal findings ranging from mucosal oedema, bilateral severe vocal cord and arytenoid hyperemia, thickening, leukoplakia, granulation, and candidiasis. In two cases, the vocal fold changes were severe enough to prompt direct laryngoscopy and biopsy to rule out malignancy. The researcher concluded that steroid inhaler laryngitis is a form of chemical laryngopharyngitis induced by topical steroid administration. Moreover, the severity of vocal fold mucosal changes was attributed to greater potency of FP as compared to other ICS.

Mirza, Schwartz and Ozerkis (2004) conducted a retrospective study to describe voice and laryngeal changes in patients who were administered a combination therapy of a corticosteroid (FP) and a long-term acting β2 agonist (LABA) (salmeterol xinafoilate) for treatment of asthma. All patients complained of dysphonia after starting the combination therapy over the last 1 to 6 months. Videostroboscopic and stroboscopy examinations were performed later to evaluate the laryngeal and voice changes. Videostroboscopy revealed vascular lesions like dilated blood vessels, and small areas of haemorrhages. Stroboscopy revealed that hemorrhagic areas displayed reduced amplitude of vibration and decreased propagation of the mucosal wave. Adding to this area of thickening, irregularity and leukoplakia involving the vibratory margins of the vocal folds was found. These findings were suggestive of vocal fold trauma and irritation. In summary this study highlighted the negative effects of ICS on the larynx and voice production.
Krecicki et al. (2006) assessed the influence of ICS on vocal fold functioning in patients treated for bronchial asthma. Participants consisted of 50 patients who received ICS (BDP & FP) for treatment of asthma and a control group of 41 healthy volunteers. All patients were non-smokers and had been receiving ICS for at least 18 months. The patients and the control group underwent a detailed laryngoscopic examination to evaluate the effects of ICS on larynx. The results showed vocal fold atrophy in 10 (20%) patients, atrophy of laryngeal mucosa in 22 (44%) patients and vocal fold bowing in 10 (20%) patients. All the above changes pertaining to the vocal folds were found in the patients, but no such changes were observed in the control group. The researchers concluded that the vocal fold pathologies were caused by inhaling corticosteroids. Moreover, vocal fold atrophy was significantly higher among those patients with the longest history of asthma treatment (minimum of 5 years of therapy). There was no correlation between laryngeal changes and doses of ICS.

Kosztyla-Honja, Rogowski, Rutkowski, Pepinski and Rycko (2006) examined the influence of ICS on the phonatory function of the larynx in patients suffering from asthma. The effect of ICS was measured in 15 patients after 30 minutes of ICS administration. Evaluation of voice function was done subjectively and objectively by using videostroboscopy. The researchers found that administration of ICS resulted in incidents of cough, mouth and throat dryness, sensation of polydipsia and skin inflammation around the mouth. On long-term administration, dysphonia, hoarseness and voice fatigue were noted due to dysfunction of the innermost laryngeal muscles, particularly the vocal fold adductors. They concluded that long-term treatment with ICS resulted in myopathy of proper muscles of the larynx.

Dogan, Eryuksel, Kocak and Sehitoglu (2007) performed a comparative, controlled, cross sectional study to evaluate the voice quality in patients with mild to moderate asthma using subjective and objective methods. Patients with mild to moderate asthma (n=40) were
age and sex-matched with a group of healthy controls (n=40). Acoustic analysis of jitter and shimmer was performed and the movements of the vocal cords were examined by videostrobscopy. In addition, the duration of asthma, maximum phonation time and vital (respiratory) capacity were evaluated. The Voice Handicap Index (VHI) scale was used for subjective evaluation of voice quality. The researchers found that maximum phonation time values were significantly shorter both in male and female patients with asthma compared to controls. Also the average shimmer values were higher for both sexes in the asthma group compared to the controls. Female patients with asthma had higher average jitter values compared to their healthy counterparts. The VHI score was outside the normative limits for patients with asthma (40%), and vital capacity findings were abnormal in 39 (97.5%) asthmatics. The researchers concluded that asthmatic patients demonstrated a generalized voice disorder compared to non-asthmatics. The outcome of the disorder was attributed to a laryngeal movement disorder and use of ICS. However, the authors could not exclude that some of the voice problems may have been caused by asthma.

Gallivan et al. (2007) examined a total of 38 patients with voice complaints associated with the use of ICS. Hoarseness and dysphonia were the primary reasons reported in these patients. The ICS initially used most frequently was FP/salmeterol-inhalation powder (22 patients), followed by FP inhalation aerosol pressurized MDI (11 patients) and five patients inhaled pulmicort (budesonide MDI). Duration of ICS usage varied from 2 weeks to 4-5 years. Each patient’s vocal fold vibratory behaviour was examined using video-stroboscopy. They concluded that abnormalities in voice production previously unrecognized by indirect mirror or fibre optic laryngoscopy could be identified using a video strobe. These abnormalities included abnormal mucosal wave symmetry/periodicity (76-63%), phase closure (74-63%), glottic closure (63-59%), mucosal wave amplitude/magnitude (50-35%), supraglottic hyperactivity (39-25%) and glottic plane (10-5%).
Ishizuka et al. (2007) performed a simple observational study to evaluate hoarseness/dysphonia in patients with bronchial asthma who were using or had used the FP dry powder inhaler (DPI). A total of 313 patients with persistent bronchial asthma were evaluated. The patients were divided into three groups according to the daily dose of FP. A total of 109 patients had used a low dose of FP (100 or 200 µg/day), 145 patients were on a medium dose (300-400 µg/day) and 49 patients were on high dose of FP (600-800 µg/day). The researchers found that 25.9% of patients complained about local adverse effects, including throat discomfort, throat irritation, cough and hoarseness. A total of 20.4% of all patients complained of hoarseness/dysphonia. Moreover, most patients complained of local adverse effects within 6 months after starting FP-DPI therapy. Hoarseness/dysphonia was found more in the high-dose group (28.6%) as compared to the medium dose (17.9%) and low dose groups (20.2%). Female patients (30.3%) complained of hoarseness/dysphonia more frequently than their male counterparts (19.5%).

The impact of ICS on the larynx and pharynx was assessed by Bhalla et al. (2009) using a prospective, cross-sectional and investigator blinded study. They recruited 46 volunteers. The participations were divided into three groups 1) non-asthmatics 2) occasional ICS users or seasonal asthmatics and 3) regular ICS users. Laryngeal effects were measured by correlating the results of a vocal performance questionnaire, a respiratory symptoms questionnaire, and acoustic measurement of voice. The researchers concluded that regular ICS users demonstrated significantly more pharyngeal inflammation and throat discomfort than the other two groups. Laryngeal function and vocal performances were also worse in this group than the other two groups and were more likely to have hoarseness, weakness of voice, aphonia and cough. Results of acoustic analysis showed that the cycle-to-cycle variation in vocal F0 (i.e., jitter) was a good objective measure of hoarseness. Regular ICS users were also more likely to have abnormal amplitude variations in their F0 (i.e., shimmer).
Statement of the Problem

The frequent use of ICS, especially at higher doses, has been accompanied by concern about side effects. Systemic side effects include lowering the number of mast cells in airway mucosa and a decrease in immediate response to allergen and exercise, muscle wasting, decrease in bone density (osteoporosis), glaucoma and cataracts, skin thinning, and bruising (Dahl, 2006). The use of ICS is also known to contribute to oral and oropharangeal candidiasis, cough during inhalation, tongue hypertrophy, and sensation of thirst (Hone et al., 1996; Roland, Bhalla & Earis, 2004). A variety of studies have been undertaken to examine the effects of ICS on voice production among people with asthma. Most research suggests that the long-term use of ICS has a negative effect on voice production (Williams et al., 1983; Bhalla et al., 2009). These findings would suggest a trade-off between controlling the symptoms of asthma and maintaining normal vocal functioning. However, individuals with asthma present with a wide range of co-morbidity factors such as smoking, chronic cough and co-existing allergic rhinitis, which may confound the effects of ICS on voice production.

One cannot exclude that some of the voice problems demonstrated by individuals with asthma is a result of their health condition rather than a consequence of using ICS. Furthermore, the type and dose of ICS has not been systematically controlled, thereby obscuring the direct effect of ICS on voice production. Interestingly, there is research to suggest that ICS may actually serve to improve voice production, if necessary precautions are taken in regard to control of dosage (Meyer et al., 2001). Normal voice production involves a combination of respiratory effort and vocal fold vibration. Because ICS is designed to improve respiratory functioning, it is possible that ICS could actually facilitate respiratory effort and concomitant vocal behaviour. Thus, it is not surprising to find reports (albeit limited) indicating that ICS may have a positive impact on voice production.
The recommended dosage of FP can range between 250 µg to 1000 µg per day (see Table 1). The most frequently prescribed daily dose of ICS in the Canterbury region of New Zealand is 1000 µg FP per day (Calverey et al., 2007). It seems that an ideal approach to examining the direct effects of ICS (FP) on voice production would be to exclude as many confounding factors as possible by recruiting healthy young adults without a history of smoking or respiratory illness including asthma, acute infection or allergic rhinitis.

The aim of the present study was to examine the isolated effects of ICS (fixed dose and type) on voice production in healthy adults. Based on audio-recorded voice samples collected before, during and after a short-term period of ICS use, the following research question was posed:

Does an ICS (FP) have an effect on the acoustic features of voice production in healthy adults within a period of one week?
Table 1. Recommended daily dose of inhaled corticosteroid (FP) for adults with asthma, according to guidelines established by GINA (2008).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose (µg)</th>
<th>Medium Daily Dose (µg)</th>
<th>High Daily Dose (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP</td>
<td>100-250</td>
<td>250-500</td>
<td>500-1000</td>
</tr>
</tbody>
</table>
Method

Participants

Thirty healthy young adults (15 females & 15 males) were recruited for the study. All participants were non-smokers with no history of speech, language or voice disorder. None of the participants had a history of asthma, respiratory illness, hospital admission or inhaler use within the past 3 months. The participants were recruited from the University of Canterbury student population. This study received ethical approval from the New Zealand Ministry of Health (Upper Southern B Health Ethics Committee), as well as the University of Canterbury Human Ethics Committee. The various consent forms and approvals granted for this study are listed in Appendix 2.

Data Collection

The data collection for each participant occurred over a consecutive 6-day period. All data collection took place within a sound treated laboratory at the Department of Communication Disorders. The specific phases of data collection were as follows:

Day 1 (Morning)

Audio Recording: On the morning of the first day of data collection, each participant’s voice was audio recorded. The first sample was collected prior to inhalation of ICS and termed the Pre-ICS sample. This voice sample served as a baseline of normal vocal fold vibratory behavior which was to be compared to later recordings. Each participant was seated in front of a tabletop microphone that was placed at a distance of 20 cm from the mouth of the participant. The participant was asked to sustain the vowels /i/ (as in “he”), /a/ (as in “hah”) and /u/ (as in “who”) for five seconds each. Three samples of each vowel were collected. Upon completion of the vowel prolongation task, each participant was asked to read the Rainbow Passage (Fairbanks, 1960), which is a 100-word passage that is commonly
used in speech-language therapy to sample vocal behavior (listed in Appendix 2). All voice samples were audio recorded using a condenser microphone (DSE-PC) connected directly to a laptop computer. Each of audio recording session lasted approximately 10 minutes.

ICS Administration: Upon completion of the vocal tasks, the participant was asked to inhale a small amount of corticosteroid (FP). The participant was provided with a spacer attached to a MDI. The dose chosen was 500 µg of FP, which is the most prescribed FP dose in the Canterbury region of New Zealand. Prior to inhalation of FP, the participant was asked to exhale fully and place the mouthpiece of the spacer in their mouth. The participant released 250 µg of FP into the spacing chamber by pressing the MDI once. When the chamber was filled with FP the participant was asked to take five tidal breaths so as to ensure inhalation of the steroid. This process was repeated so that the total dose administered was 500 µg of FP. The participant was provided with cold water for rinsing his/her mouth upon completion of the ICS administration. All morning doses of FP were taken under supervision during the period of 9-10 a.m.

Audio Recording: One hour after the morning ICS administration, each participant returned to the laboratory for a second audio recording of their voice. The one-hour lapse between ICS and audio recording was deemed necessary so as to allow for the maximum effect of the steroid on the vocal apparatus. This recording was termed ICS-1.

Day 1 (Evening)

Audio recording and ICS administration was carried out in the evening between the approximate hours of 4-6 pm. The first task involved ICS administration with the second task being the audio recording.

ICS Administration: The identical procedures used in the morning were used in the evening session. In total, the participant was asked to inhale a 500 µg dose of FP.
Audio Recording: One hour after the evening ICS administration, each participant returned to the laboratory for a second audio recording of their voice. The one-hour lapse between ICS and audio recording was deemed necessary so as to allow for the maximum effect of the steroid on the vocal apparatus. The same procedures used for the morning audio recording were used for the evening recording (i.e., vowel prolongations and oral reading of the Rainbow Passage). This recording was termed ICS-2.

Days 2-4

On the second, third, and fourth days of the study, each participant received the same doses of FP during the morning and evening sessions. There were no audio recordings collected on these days.

Day 5 (Morning & Evening)

On the morning of the fifth day of data collection, each participant received the same amount of FP similar to the previous four days. On the evening of the fifth day, audio recordings and ICS administration were carried out. The first task involved ICS administration with the second task being the audio recording.

ICS Administration: The identical procedures used in the morning were used in the evening session. In total, the participant was asked to inhale a 500 µg dose of FP.

Audio Recording: One hour after the evening session of ICS administration, each participant returned to the laboratory for another audio recording of their voice. The same procedures used for the audio recordings collected on Day 1 were used for the evening recording on Day 5 (i.e., vowel prolongations and Rainbow Passage). This recording was termed ICS-3.
Day 6 (Morning)

On the morning of the sixth day, only an audio recording of each participant’s voice was collected. This sample was termed Post-ICS and was used as a comparison to all previous samples to assess the cumulative effects of ICS administration over the 5-day period.

Acoustic Analysis

Each participant’s audio-recorded samples were submitted to acoustic analysis using a commercially available speech analysis system (CSL 4300B, Kay Elemetrics, 1994). Three measures were performed:

1) Vocal Fundamental Frequency (F0). Each vowel was displayed on a computer monitor as an amplitude-by-time waveform. The F0 of each vowel was determined by positioning a 50 ms window at the mid-point of each vowel. This section was then transformed into a power spectrum providing a cascading display of harmonics. A cursor was placed at the first harmonic peak of the display to determine F0. For each recording session, the second rendition of each repeated vowel production was measured. In total, one production of each of the three vowel (/i, u, a/) was measured for each recording session (Pre-ICS, ICS-1, ICS-2, ICS-3 & Post-ICS).

2) Formant Frequency and Formant Bandwidth.

The first (F1) and second (F2) formant frequencies, as well as the first (BW1) and second (BW2) formant frequency bandwidth values were obtained for each sustained vowel. The F1 and F2 values provided information regarding the vocal resonance qualities of the vocal tract. The corresponding BW1 and BW2 measures provided information regarding the sound absorption qualities of the vocal tract (Rabiner & Schafer, 1978; Rothenberg, 1981). Measurement of these formant features was performed by examining the amplitude-by-time waveform and positioning a 50 ms time window at the approximate midpoint of each vowel.
This was the same location that was used for determination of vocal F0 for each vowel. The F<sub>1</sub> and F<sub>2</sub> values were obtained using linear predictive coding (LPC) autocorrelation analysis (36 coefficients). Bandwidths were computed automatically on the LPC spectrum by the CSL software and numeric results were provided in Hertz (Hz).

(3) Long-Time Spectral Analysis (LTAS). The LTAS analysis involved examining the spectral characteristics of one phrase of the Rainbow Passage, “The rainbow is a division of bright lights into many beautify colours.” Human voice production is assumed to reflect an interaction between a source (i.e., the vocal folds) and a filter. An LTAS analysis, limited to voiced sounds, can serve to average-out the effects of the filter, leaving a representation of the vibratory pattern of the vocal folds (Lofqvist & Mandersson, 1987). The amplitude-by-time waveform of the entire Rainbow Passage was displayed on the computer monitor. A pair of vertical cursors was superimposed over the waveform to identify the above phrase. Based on this demarcation, an LTAS display was calculated through an averaging of individual Fast Fourier Transform (FFT) computations performed every 25 m/sec across the entire phrase. Once calculated, the LTAS data were stored as a file containing discrete frequency (Hz) values and the corresponding amplitude (dB) values. An example of a typical LTAS is shown in Figure 1. The following two measurements were performed using the LTAS file:

First spectral peak (FSP). This is defined as the frequency value associated with the first amplitude occurring between a rising and subsequent falling amplitude value. The FSP is a representation of the average F0 across the sample (Lofqvist & Mandersson, 1987).

Spectral tilt (ST). This is defined as the ratio of energy (sum of amplitudes) between 0-1000 Hz, and 1000-5000 Hz. The ST is a representation of how quickly the amplitudes of the harmonics decline (Lofqvist & Mandersson, 1987).
Figure 1. Display of a typical long time average spectrum (LTAS) taken from Goberman and Robb (1999). In this example, the location of the first spectral peak (FSP) is shown at approximately at 500 Hz. The general location of spectral tilt (ST) is also demarcated.

Measurement Reliability

Fifteen percent of the entire data base of vocal samples was randomly selected across 10% of the participants for the assessment of intra-judge measurement reliability for the acoustic measurements (vocal F0, LTAS, formants/bandwidths, FSP & ST). A total of 6 participants’ data was re-measured for F0, LTAS and formants/bandwidths. The original measurements were compared to the re-measurements. The average re-measurement difference for F0 was 34 and 12 Hz for females and males, respectively. The average re-measurement difference for F1 was 24 and 14 Hz for females and males, respectively. The
average re-measurement difference for \( F_2 \) was 76 and 58 Hz for females and males, respectively. The average re-measurement difference for \( BW_1 \) was 16 and 11 Hz for females and males, respectively. The average re-measurement difference for \( BW_2 \) was 35 and 29 Hz for females and males, respectively. The average re-measurement difference for FSP was 22 and 12 Hz for females and males, respectively. The average re-measurement difference for ST was 1.1 and 0.8 Hz for females and males, respectively. Collectively these re-measurements are within normal limits for acoustic measurement of voice in women and men (Kent, 1995).

*Statistical Analysis*

A two-way repeated measures analysis of variance (ANOVA) served as the primary statistical procedure to evaluate possible changes in vocal behaviour across the five sampling sessions. The between-groups factor was sex and the within-groups factor was sampling session. Separate ANOVAs were performed for each acoustic measure.
Results

F0

The results of the F0 analysis for male and female participants for each vowel type are listed in Table 2. As expected across all sampling periods the F0 of female voices was higher compared to male voices. Results of two-way repeated measures ANOVA for each vowel indicated a significant gender effect. [ /i/ $F(1,28) = 49.46, p<.001$; /u/ $F(1,28) = 52.14, p<.001$; /a/ $F(1,28) = 59.75, p<.001$]. Across the three vowels there was no significant time and no significant time-by-gender interaction.

F1 Frequency

The results of the F1 analysis for male and female participants for production of each vowel type are listed in Tables 3, 4 and 5, respectively across all sampling periods the F1 of female voices was higher compared to male voices. Results of a two-way ANOVA identified a significant gender effect for the vowels /i/ [$F(1, 28) = 35.25, p<.001$] and /a/ [$F(1, 28) = 35.84, p<.001$]. There was no time-by-gender interaction for any of the vowel productions. However, there was a significant time effect for /i/ [$F(1, 4) = 2.85, p<.04$]. Follow up t-tests identified a difference in F1 between Pre-ICS and ICS-1 ($p = .033$), as well as between ICS-1 and ICS-2 ($p = .046$). The results for F1 /i/ are displayed in Figure 2.
Table 2. Mean (M) and standard deviation (S.D.) of the fundamental frequency (F0) in Hz for the vowels /i/, /u/ and /a/.

<table>
<thead>
<tr>
<th></th>
<th>F0 /i/</th>
<th></th>
<th>F0 /u/</th>
<th></th>
<th>F0 /a/</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group M</td>
<td>241.6</td>
<td>239.4</td>
<td>237</td>
<td>241.7</td>
<td>240.2</td>
</tr>
<tr>
<td></td>
<td>41.7</td>
<td>40.2</td>
<td>49.2</td>
<td>48.7</td>
<td>51.8</td>
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<td>152</td>
<td>157.4</td>
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<td>25.5</td>
<td>24.5</td>
<td>24.5</td>
<td>26.7</td>
<td>31.2</td>
</tr>
</tbody>
</table>

<p>| | | | | | |</p>
<table>
<thead>
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<tbody>
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<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group M</td>
<td>241.6</td>
<td>237.8</td>
<td>235.4</td>
<td>243.2</td>
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<tr>
<td></td>
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<td>50.3</td>
<td>49</td>
<td>48.4</td>
</tr>
<tr>
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<td>151.9</td>
<td>142.6</td>
<td>148.8</td>
<td>147.3</td>
</tr>
<tr>
<td></td>
<td>25.5</td>
<td>29</td>
<td>18.4</td>
<td>23.5</td>
<td>28.5</td>
</tr>
</tbody>
</table>

Data are presented for both females and males across the five inhaled corticosteroids (ICS) sampling points.
**Table 3.** Mean (M) and standard deviation (S.D.) of the first (F1) and second (F2) formant frequency in Hz for the vowel /i/.

<table>
<thead>
<tr>
<th>F1 /i/</th>
<th>F2 /i/</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td><strong>Male</strong></td>
</tr>
<tr>
<td>Group</td>
<td>M</td>
</tr>
<tr>
<td>PreICS</td>
<td>323.7</td>
</tr>
<tr>
<td>ICS.1</td>
<td>326.7</td>
</tr>
<tr>
<td>ICS.2</td>
<td>333.7</td>
</tr>
<tr>
<td>ICS.3</td>
<td>2542.0</td>
</tr>
<tr>
<td>PostICS</td>
<td>2552.9</td>
</tr>
</tbody>
</table>

Data are presented for both females and males across the five inhaled corticosteroid (ICS) sampling points.
Table 4. Mean (M) and standard deviation (S.D.) of the first (F1) and second (F2) formant frequency in Hz for the vowel /u/.

<table>
<thead>
<tr>
<th></th>
<th>F1 /u/</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PreICS</td>
<td>ICS.1</td>
<td>ICS.2</td>
<td>ICS.3</td>
<td>Post ICS</td>
<td>PreICS</td>
<td>ICS.1</td>
<td>ICS.2</td>
<td>ICS.3</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>344.7</td>
<td>329.3</td>
<td>345.2</td>
<td>344.4</td>
<td>335.9</td>
<td>1121.8</td>
<td>1091.9</td>
<td>1087.7</td>
<td>1162.6</td>
</tr>
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<td>S.D.</td>
<td></td>
<td>55.8</td>
<td>47.2</td>
<td>48.9</td>
<td>45.4</td>
<td>95.6</td>
<td>218.1</td>
<td>209.9</td>
<td>199.7</td>
<td>253.5</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Group</td>
<td></td>
<td>M</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
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<td>346.7</td>
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<td>1092.2</td>
<td>1067.2</td>
<td>988.8</td>
<td>1049.3</td>
</tr>
<tr>
<td>S.D.</td>
<td></td>
<td>180.7</td>
<td>63.8</td>
<td>123.9</td>
<td>181.1</td>
<td>41.4</td>
<td>545.8</td>
<td>582.8</td>
<td>382.7</td>
<td>590.4</td>
</tr>
</tbody>
</table>

Data are presented for both females and males across the five inhaled corticosteroid (ICS) sampling points.
Table 5. Mean (M) and standard deviation (S.D.) of the first (F1) and second (F2) formant frequency in Hz for the vowel /a/.

<table>
<thead>
<tr>
<th></th>
<th>F1 /a/</th>
<th></th>
<th>F2 /a/</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PreICS</td>
<td>ICS.1</td>
<td>ICS.2</td>
<td>ICS.3</td>
<td>Post</td>
<td>PreICS</td>
<td>ICS.1</td>
<td>ICS.2</td>
<td>ICS.3</td>
</tr>
<tr>
<td>Female</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>M</td>
<td>809.6</td>
<td>804.6</td>
<td>858.5</td>
<td>836.5</td>
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<td></td>
<td>114.9</td>
<td>165.6</td>
<td>122.3</td>
<td>128.6</td>
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<td>111.7</td>
<td>136.5</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>M</td>
<td>577.7</td>
<td>582.2</td>
<td>528.9</td>
<td>614.8</td>
<td>587.1</td>
<td>1175.8</td>
<td>1152.4</td>
<td>1185.5</td>
<td>1195.8</td>
</tr>
<tr>
<td></td>
<td>143.6</td>
<td>109.9</td>
<td>149.2</td>
<td>155.7</td>
<td>147.4</td>
<td>95.4</td>
<td>120</td>
<td>80.4</td>
<td>95</td>
</tr>
</tbody>
</table>

Data are presented for both females and males across the five inhaled corticosteroid (ICS) sampling points.
Table 6. Mean (M) and standard deviation (S.D.) of the first (BW1) and second (BW2) bandwidth for the vowel /i/.

<table>
<thead>
<tr>
<th></th>
<th>BW1 /i/</th>
<th></th>
<th>BW2 /i/</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PreICS</td>
<td>ICS.1</td>
<td>ICS.2</td>
<td>ICS.3</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>73.9</td>
<td>75.0</td>
<td>87.8</td>
<td>83.4</td>
</tr>
<tr>
<td>S.D.</td>
<td>36.4</td>
<td>43.4</td>
<td>37.3</td>
<td>44.4</td>
</tr>
<tr>
<td><strong>Male</strong></td>
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<td>67.0</td>
<td>79.6</td>
<td>78.2</td>
</tr>
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<td>S.D.</td>
<td>39.9</td>
<td>56.2</td>
<td>137.5</td>
<td>40.5</td>
</tr>
</tbody>
</table>

Data are presented for both females and males across the five inhaled corticosteroid (ICS) sampling points.
Figure 2. Display of first formant frequency of the vowel /i/ across the five inhaled corticosteroid (ICS) sampling periods.

**F2 Frequency**

The results of the F2 analysis for male and female participants for each vowel type are listed in Tables 3, 4 and 5, respectively. Across all sampling periods, the F2 of female voices was higher compared to male voices. Results of a two-way ANOVA identified a significant gender effect for the vowel /i/ \(F(1, 28) = 5.45, p = .027\) and /a/ \(F(1, 28) = 71.9, p < .001\]. There was no significant time effect or time-by-gender interaction for any of the vowel productions.

**BW1**

The results of the BW1 analysis for male and female participants for each vowel type are listed in Tables 6, 7, and 8, respectively. Across all sampling periods, the BW1 of female voices was higher compared to male voices for the vowel /i/ and /a/. However, the BW1 value for the vowel /u/ was higher for male voices in comparison to female voices across all sampling periods. Results of a two-way ANOVA identified a significant gender effect for /u/
\[ F (1, 28) = 5.38, \ p = .028 \]. There was no significant time effect or time-by-gender interaction for any of the vowel productions. The results for BW1 /u/ are shown in Figure 3.

Figure 3. Display of first formant frequency bandwidth for the vowel /u/ across the five inhaled corticosteroid (ICS) sampling periods.
Table 7. Mean (M) and standard deviation (S.D.) of the first (BW1) and second (BW2) bandwidth for the vowel /u/.

<table>
<thead>
<tr>
<th>Group</th>
<th>BW1 /u/</th>
<th></th>
<th></th>
<th></th>
<th>BW2 /u/</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PreICS</td>
<td>ICS.1</td>
<td>ICS.2</td>
<td>ICS.3</td>
<td>Post</td>
<td>ICS</td>
<td>PreICS</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>118.2</td>
<td>98.0</td>
<td>86.2</td>
<td>137.5</td>
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<td>297.3</td>
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<td>250.5</td>
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<td></td>
</tr>
<tr>
<td>M</td>
<td>192.4</td>
<td>198.7</td>
<td>160.3</td>
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<td>636.2</td>
<td>450.2</td>
<td>548.2</td>
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<tr>
<td>S.D.</td>
<td>135.1</td>
<td>155.0</td>
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<td>161.4</td>
<td>93.4</td>
<td>651.1</td>
<td>295.3</td>
<td>409.3</td>
</tr>
</tbody>
</table>

Data are presented for both females and males across the five inhaled corticosteroid (ICS) sampling points.
Table 8. Mean (M) and standard deviation (S.D.) of the first (BW1) and second (BW2) bandwidth for the vowel /a/.

<table>
<thead>
<tr>
<th></th>
<th>BW1 /a/</th>
<th></th>
<th>BW2 /a/</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PreICS</td>
<td>ICS.1</td>
<td>ICS.2</td>
<td>ICS.3</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group M</td>
<td>231.4</td>
<td>314.4</td>
<td>231.3</td>
<td>242.2</td>
</tr>
<tr>
<td>S.D.</td>
<td>192.2</td>
<td>206.9</td>
<td>130.0</td>
<td>102.5</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group M</td>
<td>353.9</td>
<td>328.6</td>
<td>343.2</td>
<td>314.0</td>
</tr>
<tr>
<td>S.D.</td>
<td>188.9</td>
<td>144.3</td>
<td>222.9</td>
<td>212.0</td>
</tr>
</tbody>
</table>

Data are presented for both females and males across the five inhaled corticosteroid (ICS) sampling points.
The results of the BW2 analysis for male and female participants for each vowel type are listed in Tables 6, 7, and 8, respectively. Across all sampling periods, the BW2 of female voices was higher compared to male voices for the vowel /i/ and /a/. However, the BW2 value for the vowel /u/ was higher for male voices in comparison to female voices across all sampling periods. Results of a two-way ANOVA identified a significant gender effect for /u/ \[ F (1, 28) = 5.17, p = .031 \]. There was no significant time effect or time-by-gender interaction for any of the vowel productions. The results for BW2 /u/ are shown in Figure 4.

Figure 4. Display of second formant frequency bandwidth for the vowel /u/ across the five inhaled corticosteroid (ICS) sampling periods.
FSP

The results of the FSP analysis for male and female participants for each rendition of the Rainbow Passage are listed in Table 9. The FSP of female voices was higher compared to male voices across all sampling periods. Results of a two-way ANOVA identified a significant gender effect for FSP \[ F(1, 28) = 26.29, p < .001 \]. The effects of time on FSP approached significance \[ F(1, 4) = 2.61, p = .06 \]. Follow up t-tests identified a significant difference in FSP between ICS 2 and ICS 3, \( p = .024 \). There was no significant time-by-gender interaction. The results for FSP analysis are displayed in Figure 5.

Figure 5. Display of combined mean first spectral peak (FSP) of males and females across the inhaled corticosteroid (ICS) sampling periods.
The results of the ST analysis for male and female participants for each speech sample are listed in Table 10. Results of a two-way ANOVA identified a significant time effect for ST \( F(1, 4) = 3.5, p = .02 \). Follow up \( t \)-tests identified a significant difference in ST between Pre-ICS and ICS-1, \( p = .034 \), as well as between ICS-2 and ICS-3, \( p = .033 \). There was no any significant gender effect or time-by-gender interaction. The results for ST are displayed in Figure 6.

Figure 6. Display of combined mean spectral tilt (ST) of males and females across the five inhaled corticosteroid (ICS) sampling periods.
**Table 9.** Long-time average spectrum (LTAS) characteristics for groups of adult females and males.

<table>
<thead>
<tr>
<th></th>
<th>FSP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td></td>
</tr>
<tr>
<td>Group M</td>
<td>Pre ICS</td>
</tr>
<tr>
<td></td>
<td>205.1</td>
</tr>
<tr>
<td>S.D.</td>
<td>44.4</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
</tr>
<tr>
<td>Group M</td>
<td>134.3</td>
</tr>
<tr>
<td>S.D.</td>
<td>38.5</td>
</tr>
</tbody>
</table>

The table contains the average first spectral peak (FSP) and the mean (M) and standard deviation (S.D) derived across five inhaled corticosteroid (ICS) sampling points.
Table 10. Long-time average spectrum (LTAS) characteristics for groups of adult females and males.

<table>
<thead>
<tr>
<th></th>
<th>Pre ICS</th>
<th>ICS.1</th>
<th>ICS.2</th>
<th>ICS.3</th>
<th>Post ICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group M</td>
<td>4.0</td>
<td>3.2</td>
<td>3.9</td>
<td>2.4</td>
<td>3.1</td>
</tr>
<tr>
<td>S.D.</td>
<td>2.4</td>
<td>1.6</td>
<td>2.3</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group M</td>
<td>4.0</td>
<td>3.0</td>
<td>2.7</td>
<td>2.4</td>
<td>3.1</td>
</tr>
<tr>
<td>S.D.</td>
<td>3.1</td>
<td>2.2</td>
<td>1.8</td>
<td>2.0</td>
<td>2.5</td>
</tr>
</tbody>
</table>

The table contains the average spectral tilt (ST) and the mean (M) and standard deviation (S.D) derived across five inhaled corticosteroid (ICS) sampling points sampling points.

ST is expressed as the following: $\sum \text{dB}_0-1000\text{Hz} / \sum \text{dB}_{1-5000}\text{Hz}$.
Summary of Major Findings

1. The F0 values for females were higher in comparison to males across all sampling periods. In addition there was no significant change in F0 across the sampling intervals.

2. The F1 frequency values for females were higher in comparison to males across all sampling periods. There was a significant time effect for the vowel /i/ with the F1 frequency at ICS-1 being significantly lowered compared to the Pre-ICS and ICS-2 sampling points.

3. The F2 values for females were higher in comparison to males across all sampling periods. There was no significant change in F2 across sampling intervals.

4. Across all sampling periods, the BW1 and BW2 of female voices was higher compared to male voices for the vowels /i/ and /a/. However, the BW1 and BW2 values for the vowel /u/ were higher for males in comparison to females across all sampling periods. There were no significant changes in BW1 or BW2 across the sampling intervals.

5. The FSP of female voices was higher compared to male voices across all sampling periods. Results revealed that there was a significant time effect for FSP for the combined groups. The FSP values increased significantly on day five (ICS 3) after the inhalation of ICS in comparison to day one (ICS 2).

6. The ST values across all sampling periods revealed no significant gender effect. For the combined group of females and males, the ST values decreased after the inhalation of ICS in the morning of day one (ICS-1) in comparison to Pre-ICS. Also the ST values significantly decreased at ICS-3 in comparison to ICS-2.
Discussion

Corticosteroids are the most potent and reliable of the available agents among the anti-inflammatory drugs, and have assumed a major role in the management of asthma (Szelfer, 1991). This has subsequently resulted in the widespread use of ICS. The impact of ICS on voice production has received considerable research attention. Some of the research in this field implicates ICS in the development of dysphonia (Williams et al., 1983; Bhalla et al., 2009). However, many studies have the weaknesses of including an asthmatic population and not consistently recording the dose prescribed. As a result, one cannot exclude that some voice problems may have simply been caused by asthma rather than use of an ICS (Meyer et al., 2001). Keeping this in mind, the purpose of the present study was to examine the effects of ICS using a fixed dose and type on voice production in healthy adults. The research question posed for this study was:

*Does an ICS (FP) have an effect on the acoustic features of voice production in healthy adults within a period of one week?*

Vocal F0

Fundamental frequency (F0) is defined as the lowest frequency component of a complex periodic sound (Borden, Harris & Raphael, 1994). When describing the F0 of the human voice, the term refers to the rate of vocal fold vibration. The average F0 of an adult male voice is approximately 125 Hz, while women phonate with an F0 of approximately 200 Hz. Children have an F0 in excess of 300 Hz (Borden et al., 1994). The length, size, and stiffness of the thyroarytenoid muscle (i.e., vocal folds) are the primary contributing factors to F0. Typically, men have larger vocal folds than women, with children having the smallest vocal folds, thereby explaining the often cited
differences in F0 between these speaker groups (Baken & Orlikoff, 2000; Guimaraes & Abberton, 2005; Sussman & Sapienza, 1994).

Results of the present F0 analysis indicated there was a sex difference for the F0 of each vowel type across the five sampling points, with females showing a significantly higher F0 than men. There was no change in F0 across time, indicating that the use of ICS did not appear to affect the average rate of vocal fold vibration. Three possibilities for the lack of change in F0 across time are presented. First, it is possible that the lack of change in F0 is a result of the speech samples measured in the present study. The F0 analysis was confined to isolated vowel production. Use of a larger and more natural speech sample, such as conversational speech, may have provided a more revealing influence of ICS on vocal fold vibrations. A second possibility for the lack of change in F0 across the sampling periods is to consider the pharmacology of ICS. The inhalation of corticosteroids is designed to serve as an anti-inflammatory agent (Barnes, 2001). However, among the present group of participants there was no pre-existing inflammation of the vocal folds, so it is possible the corticosteroid had no direct affect on the vocal fold musculature (i.e., no change in F0). Finally, it is important to note that past studies which have found a change in F0 have attributed this change to the irritating affects of ICS (Roland et al., 2004). This irritation results from the use of propellant and lubricant components of MDI preparations. These “residue” components, when inhaled, irritate the pharyngolaryngeal mucosa. However, in the present study this irritation did not appear to affect average vocal fold vibration (i.e., F0), most likely due to short-term use of ICS.

**F₁ and F₂ Frequency**

The resonances of the vocal tract are referred as formants. A formant is an acoustic feature which is associated with a peak in the acoustic spectrum that is shaped by the configuration of the vocal tract (Borden et al., 1994). The F₁ frequency represents vocal
tract resonance occurring at the pharyngeal level (Kent, 1995). The $F_1$ frequency depends on the volume of the pharyngeal cavity, as well as how tightly the vocal tract is constricted (Ferrand, 2001). The $F_2$ frequency represents vocal tract resonance occurring at a more superior level, within the general region of the oro-pharynx. The $F_2$ frequency depends on the length of the oral tract. These volumes (and corresponding formant frequency values) can be changed by altering tongue positioning.

Results of the present $F_1$ analysis indicated there was a significant time effect for production of the vowel /i/. Specifically, $F_1$ frequency was found to lower between pre-ICS and ICS-1 sampling points; with a rise in $F_1$ between ICS-1 and ICS-2. The $F_1$ frequency at ICS-1 was the lowest frequency value observed across the five sampling points. Interestingly, the unusually low $F_1$ frequency at ICS-1 was the point at which each participant received their first dose of ICS. The low $F_1$ frequency would suggest that the volume of the pharyngeal cavity was enlarged compared to the sampling periods before and after ICS-1. This enlargement can occur in two-ways. First, the length of the vocal tract can be increased by either moving the tongue forward in the vocal tract and/or lowering of the larynx. A second possibility for the increased volume is that the diameter of the vocal tract area increased. Assuming, ICS serves as a bronchodilator, it is intriguing to consider that the dilating effects of this steroid could also influence the volume of the pharyngeal cavity, resulting in an increase of vocal tract area (i.e., lowering of $F_1$ frequency).

A sex difference was also found for the production of each vowel. The $F_1$ and $F_2$ frequency of each vowel was higher for females compared to males, with significant differences noted for the vowels /i/ and /a/. This sex difference is not surprising. Past research has consistently shown that the formant frequencies of the female voice are higher compared
to the male voice, as a result of smaller female vocal tract anatomy (Borden et al., 1994; Kent, 2001).

**Formant Frequency Bandwidth (BW₁ & BW₂)**

Bandwidth is defined as a measure of frequency band of a sound especially a resonance. Conventionally, bandwidth is determined at the half power (“3 dB down”) points of the frequency response curve. That is, both the lower and higher frequencies that define the bandwidths are 3 dB less intense than the peak energy in the band (Kent, 1995). The bandwidths of the lowest formant depend upon vocal tract wall loss and source-tract interaction (Rabiner & Schafer, 1978; Rothenberg, 1981). Bandwidths of the higher formants depend primarily upon the viscous friction, thermal loss, and radiation loss. These factors may differ between genders leading to gender differences in bandwidths and overall spectral shape (Flanagan, 1972).

In the present study, across all sampling periods, the BW₁ and BW₂ of female voices was larger compared to male voices for the vowels /i/ and /a/. However, the BW₁ and BW₂ values for the vowel /u/ were larger for males in comparison to females across all sampling periods. There were no significant changes in BW₁ and BW₂ across the sampling intervals. Past research has shown that females have larger formant frequency bandwidths compared to males (Bladon, 1983). The main reason for females having larger bandwidths can be primarily attributed to the vocal tract wall loss and source-tract interactions noted above (Rothenberg, 1981). The larger formant bandwidths noted for male production of /u/ was unexpected and suggests that there may be vowel-specific differences between men and women in regard to formant bandwidths.
Long Time Average Spectra (LTAS)

First Spectral Peak (FP) is defined as the frequency value (in Hz) associated with the first amplitude peak across the LTAS display. The first spectral peak is assumed to provide a representation of the average F0 across the phonatory sample (Fuller & Horii, 1988). Any upward or downward change in the frequency of the spectral peak would reflect corresponding increases or decreases in sub-glottal pressure and vocal fold stiffness.

FSP was used in present study as a way of estimating F0 in a connected speech sample (i.e., the Rainbow Passage). Across all sampling periods, women had a higher FSP than males, which corresponds to the F0 results obtained from isolated vowel productions. It is difficult to compare the present results to past studies examining ICS because they have not used LTAS. However, past ICS studies have examined F0. The present results obtained for FSP supports past F0 studies that have found a higher F0 values for females compared to males. The primary reason for the sex difference is attributed to laryngeal size differences (Childers & Wu, 1991; Sussman & Sapienza, 1994; Whalen & Levitt, 1995; Baken & Orlikoff, 2000; Torre & Barlow, 2009).

An interesting finding in the present study was that for the combined groups, FSP was found to significantly change across ICS sampling intervals. Specifically, FSP increased between the evening of day one (ICS-2) compared to the recording on the evening of day 5 (ICS-3). In the present study changes in FSP were evident in the running speech sample; however no such changes were detected in isolated vowels based on measurement of F0. The likely reason for these discrepant findings is due to the amount of speech being sampled to estimated average vocal fold vibration. Based on measuring a large sample of speech, a significant change in vocal fold vibratory behaviour was evident during the course of ICS use. The increase in FSP at ICS-2 is in agreement with past studies which attributed the increase in F0 to the irritating effects of corticosteroids (Watts, Clark & Early, 2001). Thus,
the present findings would appear to suggest that the effects of ICS use were more evident in connected speech samples compared to production of isolated vowels.

Spectral Tilt (ST) is defined as the ratio of energy (sum of amplitudes) between 0 and 1000 Hz, and 1000 and 5000 Hz. The ST is a representation of how quickly the amplitudes of the harmonics decline (Lofqvist & Mandersson, 1987). Past research among adults has shown that a high ST value corresponds to hypoadduction of the vocal folds, whereas a low ST value corresponds to a hyperadduction of the vocal folds (Mendoza, Munoz, & Naranjo, 1996).

In the present study, ST was measured using connected speech from the Rainbow Passage (Fairbanks, 1960). ST was found to be significantly lower following use of ICS in the morning of day one (ICS-1) in comparison to Pre-ICS. The ST was also significantly lower at ICS-3 in comparison to ICS-2. These significantly lower ST values are suggestive of hyperadduction of the vocal folds. Similar to the results obtained from FSP, the effects of ICS were evident in connected speech samples. Based on the combined results for FSP and ST it would appear that use of ICS contributed to an overall hyperfunctional voice at distinct points across the one-week period of the study.

Limitations

Results of the present study found changes in some, but not all of the acoustic measures of voice as a function of ICS sampling and/or sex. These changes were confined to LTAS measures of connected speech. When considering these results, it is important to recognize some possible limitations in the present study. Examples of these limitations are provided below.

1. In the present study, some of the participants’ first language was not English. As a result of accent/dialect differences in the articulation of speech it is possible that these
speaker differences could have contributed to variations in the acoustic measures. However, it is important to stress the present set of acoustic measures were designed primarily to assess vocal fold vibratory characteristics (e.g., F0, FSP, ST). Therefore, the influence of language differences on these measures is likely to be minimal.

2. The present study did not involve perceptual evaluation of voice across the duration of sampling periods. By having the participants self evaluate their voice, possible changes in voice resulting from ICS use may have been detected that were not detected using acoustic analysis.

3. The present study was exploratory by only examining the short term effects of ICS on voice production. The one-week sampling used in the present study may have been too short to determine the major influences of ICS on voice production. Still, it is noteworthy that in spite of the short timeframe of sampling, ICS effects of voice production were evident.

4. Each of the participants was asked to prolong vowels and read the Rainbow Passage (Fairbanks, 1960). The researcher provided a model to each participant in regard to the prolongation of vowels. For the oral reading of the Rainbow Passage, each participant was simply asked to read the passage at their normal speaking rate. By not controlling for the speaking rate of the Rainbow Passage, it is possible that the acoustic results measured in this passage (i.e., FSP, ST) could have been affected. Past research has shown that alterations in speaking rate (fast or slow) can have an influence on the subsequent acoustic features of speech production (Kent, 2001). While each participant was judged by the researcher to read the passage at a normal speaking rate, the precise rate of speaking was not measured. Thus, one cannot rule out the possibility that rate differences had an influence in the present results.
Clinical Implications

Past research examining the acoustic effects of voice resulting from ICS have focused primarily on patients with asthma. Most research indicates that the long-term use of ICS has a negative effect on voice production (Williams et al., 1983; Lavy et al., 2000 & Bhalla et al., 2009). These findings would suggest a trade-off between controlling the symptoms of asthma and maintaining normal vocal functioning. However, individuals with asthma present with a wide range of co-morbidity factors such as smoking, chronic cough and co-existing allergic rhinitis, which may confound the effects of ICS on voice production. In the present study, these co-morbidity factors were controlled by examining healthy non-asthmatic men and women. On the basis of using the recommended dosage of 1000 µg FP per day (Calverey et al., 2007), effects on voice production were evident within one-week of ICS usage. These results suggest that the short term use of ICS is associated with negative effects on voice production. However, the negative changes in voice reversed to normalcy within one day of discontinuation of ICS use (i.e., at Post-ICS). From these present results, it seems clear that caution is warranted when prescribing ICS for individuals with asthma. While short-term use is likely to have minimal long-lasting effects on voice production; long term effects may result in significant damage to the voice.

Directions for Future Research

In the present study it was observed that some acoustic features of voice production changed during the period of ICS use. However, these same acoustic features were found to return to their Pre-ICS values after discontinuing ICS. This pattern of change would seem to indicate that the irritating effects of short term ICS on vocal fold vibratory behavior are temporary. A logical next step in this line of research would be to determine whether the effects are temporary or long lasting by examining ICS use over a longer time period. A secondary area of research could be to determine the effects of various doses of ICS on voice
production. The present study used a well established dose of 1000 µg/day. However, it is not unusual to find doses ranging from 200 µg/day to 2000 µg/day (Humbert et al., 2008). Presumably, ICS use at a lower dose would have a less severe impact on voice production compared to higher doses of ICS. However, it is possible that low doses such as 200 µg/day may have the same effects as larger doses. Finally, a continuation of this study would be to examine the perceptual voice characteristics of the present group of participants. While acoustic changes were evident at various points in the ICS regime, no attempts were made to determine whether these acoustic changes were perceptible.

**Conclusion**

In summary the purpose of the present study was to examine the short term effects of ICS (FP) on acoustic features of voice production. The general question was to determine whether ICS has an effect on acoustic features of voice following short term exposure to ICS. The results of this study indicate that ICS does have an effect on acoustic properties of voice. These effects were more evident in connected speech compared to isolated vowel productions.
References


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Medical Research Council. (1956). Controlled trial of effects of cortisone acetate in status asthmaticus reort to the medical research council by the sub committee of clinical trials in asthma. *Lancet, 271,* 803-806.


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Appendix 1

Undesirable effects of FP and treatment as specified by the New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE)
**FP propionate Inhaler (CFC-Free) (50, 125 or 250 micrograms per actuation).**

**Overdose.** Acute inhalation of FP doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as adrenal function is recovered in a few days, as verified by plasma cortisol measurements.

**Undesirable Effects.** Candidiasis of the mouth and throat (thrush) of voice occurs in some patients, such patients may find it helpful to rinse out their mouth with water after using the inhaler. Symptomatic candidiasis can be treated with topical anti-fungal. In some patients, FP may cause hoarseness or throat irritation. It may be helpful to rinse out the mouth with water immediately after inhalation. The use of a large volume ‘spacer’ device may be considered. There may be contusion on skin in some patients. Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods.

**Preclinical Safety Data.** Preclinical safety studies indicate that FP shows negligible systemic toxicity when administered by the inhaled route. FP propionate is devoid of mutagenic activity *in-vitro* and *in-vivo* and showed no tumorigenic potential in rodents. It is both non-irritant and non-sensitising in animal models. The non-CFC propellant, HFA 134a, has been shown to have no toxic effect at very high vapour concentrations.

**Contra-indications.** FP Inhaler is contra-indicated in patients with a history of hypersensitivity to any of its components.

**Effects on Ability to Drive and Use Machines.** FP propionate is unlikely to produce an effect on driving or operating machines.
Appendix 2

Ethics Approval and Consent Forms
27 July 2009

Professor Michael Robb
Department of Communication Disorders
University of Canterbury
Private Bag 4800
Christchurch

Attention: Mr Ramesh Sahrawat

Dear Professor Robb

Ethics Reference Number: URB/09/07/027
Influence Of Inhaled Corticosteroids on Acoustic Features of Normal Voice Production in Adults
Investigators: Professor Michael Robb, Mr Ramesh Sahrawat, Dr Lutz Beckert, Dr. Ray Kirk
Locality: University of Canterbury

The above study has been given ethical approval by the Upper South B Regional Ethics Committee.

Approved Documents
Information sheet amended version dated 01/05/2009*
Consent form amended version dated 01/05/2009*
Advertisement amended version dated 01/05/2009*
Study protocol dated 01/05/2009
Questionnaire dated 01/05/2009

*Please send the committee copies of these documents with the footer updated to reflect that the amended versions are version 2.

Accreditation
The Committee involved in the approval of this study is accredited by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, April 2006.

Progress Reports
The study is approved until 1 September 2010. The Committee will review the approved application annually and notify the Principal Investigator if it withdraws approval. It is the Principal Investigator’s responsibility to forward a progress report covering all sites prior to ethical review of the project in August 2010. The report form is available at http://www.ethicscommittees.health.govt.nz. Please note that
failure to provide a progress report may result in the withdrawal of ethical approval. A final report is also required at the conclusion of the study.

Amendments
It is also a condition of approval that the Committee is advised of any adverse events, if the study does not commence, or the study is altered in any way, including all documentation eg advertisements, letters to prospective participants.

Please quote the above ethics committee reference number in all correspondence.

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. Where applicable, authority for this must be obtained separately from the appropriate manager within the organisation.

The committee would like to take this opportunity to wish you all the best with your study.

Yours sincerely

Diana S. Whipp

Mrs Diana Whipp
Upper South B Regional Ethics Committee Administrator

Email: diana_whipp@Moh.govt.nz
Ref: HEC 2009/102

12 August 2009

Ramesh Sahrawat
Health Sciences Centre
UNIVERSITY OF CANTERBURY

Dear Ramesh

The Human Ethics Committee advises that your research proposal “Influence of inhaled corticosteroids on acoustic features of normal voice production in adults” has been considered and approved.

Please note that this approval is subject to the incorporation of the amendments you have provided in your email of 11 August 2009.

Best wishes for your project.

Yours sincerely

Dr Michael Grimshaw
Chair, Human Ethics Committee
The Department of Communication Disorders is looking for participants for a study entitled:

**Studying the Effects of Inhaled Corticosteroids on Normal Voice Production in Adults**

We are looking for healthy adult females between the ages of 18-21 years

This study will take place at the Department of Communication Disorders Research Laboratory
University of Canterbury Campus
19 Creyke Road, Christchurch

Each session will take approximately 15 minutes of your time every morning (9-10am) and evening (4-5pm) for a 5-day period.

You may be provided with two Hoyts movie passes at the end of your participation.
If you are interested and would like more information, please contact

Prof. Michael Robb
Phone: 03 3642987 Extn :7077
Mobile: 021 0630311
michael.robb@canterbury.ac.nz

Ramesh Sahrawat
Phone: 03 3557980
Mobile: 021 1816115
rsa61@student.canterbury.ac.nz

This project has been reviewed and approved by Upper Southern Health Ethics Committee and the University of Canterbury Human Ethics Committee.
INFORMATION SHEET

Studying effects of inhaled corticosteroids on normal voice production in adults.

Principal Investigator:

Prof. Michael Robb
Department of Communication Disorders
University of Canterbury
Christchurch NZ
Phone: 03 3642987 Extn: 7077

Co-Investigators:

Ramesh Sahrawat
Department of Health Sciences.
University of Canterbury
Christchurch NZ
Phone: 03 3557980

Dr Lutz Beckert MD, MRCP
Department of Medicine.
University of Otago

Prof Ray Kirk, (Director).
Department of Health Sciences.
University of Canterbury
Christchurch NZ
Phone: 03 3640640

Introduction and aims of the project:

You are invited to participate in a research project investigating the influence of inhaled corticosteroid (Fluticasone) on normal voice production. This study will contribute to completion of Master’s of Health Science Degree. This study will gather information whether inhaled corticosteroids (ICS) have immediate or delayed side effects on voice production. As research, so far carried out is on people with asthma and other respiratory conditions. This is an exploratory research to find the effects of ICS on voice production in healthy adult females. This may become relevant in the management of individuals with asthma.
You have the right not to participate in the study, or subsequently withdraw from this study at any time. Any decision not to participate will not affect your current, continuing or future health care at this or any other health care facility, nor will it affect your academic progress through the university, if applicable. We would appreciate a decision regarding your participation within one week.

Participants:

You have been invited to attend a screening visit following your reply to our advertisements for research participants. You may be selected for this study if you are judged to have no health problems that may affect your participation. The study will include a total of 20 participants.

Procedure:

The research will take place at the University of Canterbury Communication Disorders Research Laboratory (Room 121) located at 19 Crekye Road. If you agree to participate in the study, the following will occur:

1. You will be given a specific appointment to arrive at the Communication Disorders Research Laboratory. Ample, free parking is located in front of the facility.

2. You will be asked to complete a brief medical questionnaire to confirm that you meet the inclusion criteria for study participation.

3. The exact procedures involved in this research project will be explained to you in detail. You will also have the opportunity to raise and discuss any questions with the investigator.

4. If you agree to participate in the study, you will be given a consent form to sign. You will be assigned a participant number for identification of all subsequent data. If you wish you can have your whanau / family to be present during the study.
5. At the commencement of the study you will be seated in a chair directly facing the investigator.

6. The investigator will provide you with a demonstration and directions about how to perform the two different vocal tasks: (1) sustaining three vowels /i/ (as in “he”), /a/ (as in “hah”) and /u/ (as in “who”) for 5 seconds each (repeated 3 times), and reading aloud a 100 words passage.

7. After this instructional period, you will remain seated at a table. A tabletop microphone attached to a laptop computer will be kept at a distance of 20cm from your mouth and you will be asked to sustain each vowel and read the passage. These vocal samples will be recorded directly into the computer.

8. Upon completion of the vocal tasks, you will be asked to inhale a small amount of corticosteroid known as FP. You will be provided with a spacer attached to a metered dose inhaler (Puffer). The dose chosen is FP 500mcg, which is the most prescribed FP dose in Canterbury.

9. Prior to inhalation of FP, you will first need to exhale all the air out of your lungs and put the mouthpiece of the spacer in your mouth. At this time, you will be asked to push the puffer once to release the FP 250 mcg into the spacing chamber. Once the chamber is filled with FP you will take several deep breaths (inhalations). This process will happen twice, so that the total dose administered will be FP 500 mcg.

10. The same process of FP inhalation will be carried out in the afternoon (between 4-5 pm).

11. Another vocal sample of vowel prolongations and oral reading will take place approximately one hour following the evening dose of FP.
12. You will be asked to perform the same procedures of inhalation of FP in the morning (between 9-10 am) and evening (between 4-5 pm) for the next 4 days (total of five days).

13. Each dose administration will take place at the Communication Disorders Research Laboratory and directly supervised by the investigators.

14. Following the last dose of FP on the fifth day (evening sample), the third and final voice recording will be obtained. The vocal recording will involve the same vowels and oral reading passage. This recording will occur approximately one hour after the last dose of FP.

The information gathered during the study will be stored for subsequent analysis. Confidentiality will be assured by assigning you a coded numerical identification. Data will be stored in the locked Communication Disorders Research Laboratory at the University of Canterbury.

**Risks or Benefits:**

There will be no direct benefit to you by participating in this research. Each participant will be provided with two movie passes to Hoyts Cinema. There may be some associated local side effects with short-term use of FP. These side effects include oral candidiasis (fungal infection in the mouth), oral thrush and feeling of thirst. Any local side effects associated with FP will resolve within two weeks of discontinuing the steroid.

You will be monitored carefully by the investigators for any negative outcomes arising from your participation in this study. In the event of any adverse reactions to FP, Dr Lutz Beckert, Respiratory Physician Christchurch Hospital, will make time to assess you. Dr Beckert is one of the co-investigator of this study and has considerable clinical experience in prescribing and use (treating patients) of FP. He will be constantly involved throughout this study. In addition, your G.P can be notified upon receiving permission from you to do so.
**Participation:**

Your participation is entirely voluntary. If you do agree to take part in this study, you are free to withdraw at any time, without having to give a reason. This will in no way affect any future care or treatment or your academic status if you are a University student. Your participation in the study will be stopped should any harmful effects appear as a result of inhaling FP.

**Confidentiality:**

The results of this study will be published in a peer reviewed journal and may also be presented at international conferences. However, no material which could personally identify you will be used in any reports on this study. With the exception of the consent form, all data will be identified using a number coding system. Thus, you will be identified only by a participant number and will not be referred to by name when identifying or discussing the data. Only those individuals directly associated with the project will have access to any data collected. All information associated with this project, including the consent form containing your name, will be kept in a locked filing cabinet within the Department of Communication Disorders, at the University of Canterbury. The data will be stored for a period of ten years, and then it will be destroyed. Written documents will be shredded.

**Results:**

Upon completion of this research, you will be offered both a copy of the final manuscript and a copy of the results in lay language. However, you should be aware that a significant delay may occur between completion of data collection and completion of the final report. Alternatively, or in addition, you can choose to have the results of the study discussed with your personally by the lead investigator.

**Questions**

You can contact one of the investigators or the research supervisor if you require any further information about the study.
The lead investigator, Prof. Michael Robb, can be contacted during work hours at (03) 364 2987 Extn: 7077, or 021 0630311 or via email: michael.robb@canterbury.ac.nz

The co-investigator, Ramesh Sahrawat, can be contacted during work hours (03) 3642987 Extn: 8691, or 021 1816115 or via email: rsa61@student.canterbury.ac.nz

The co-investigator, Dr Lutz Beckert, can be contacted during work hours (03) 3640640 or 027 4677583 or via email: lutz.beckert@cdhb.govt.nz

The co-investigator, Prof. Ray Kirk, can be contacted during work hours (03) 3643108 or 027 2143338 or via email: ray.kirk@canterbury.ac.nz

If you need an interpreter, this can and will be provided.

If you have any queries or concerns about your rights as a participant in this study, you may wish to contact a Health and Disability Advocate, telephone:

    South Island  0800 377 766  or (03) 377 7501 in Christchurch.
    Free Fax (NZ wide): 0800 2787 7678 (08002SUPPORT)
    Email (NZ wide):  advocacy@hdc.org.nz

This study has received ethical approval from the Upper South B Regional Ethics Committee.

Ethics Reference Number:  URB/09/07/027.

This project has been reviewed and approved by Upper Southern Health Ethics Committee and the University of Canterbury Human Ethics Committee.
CONSENT FORM
STUDYING INFLUENCE OF INHALED CORTICOSTEROID ON NORMAL VOICE PRODUCTION IN HEALTHY ADULTS

<table>
<thead>
<tr>
<th>Language</th>
<th>Translation</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>English</td>
<td>I wish to have an interpreter.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.</td>
<td>Ae</td>
<td>Kao</td>
</tr>
<tr>
<td>Samoan</td>
<td>Oute mana’o ia iai se fa’amatala upu.</td>
<td>Ioe</td>
<td>Leai</td>
</tr>
<tr>
<td>Tongan</td>
<td>Oku ou fiema’u ha fakatonulea.</td>
<td>Io</td>
<td>Ikai</td>
</tr>
<tr>
<td>Cook Island</td>
<td>Ka inangaro au i tetai tangata uri reo.</td>
<td>Ae</td>
<td>Kare</td>
</tr>
<tr>
<td>Niuean</td>
<td>Fia manako au ke fakaaoa e taha tagata fakahokohoko kupu.</td>
<td>E</td>
<td>Nakai</td>
</tr>
</tbody>
</table>

I have read and I understand the Information Sheet dated 01/05/2009 for volunteers taking part in the study designed to investigate the effects of inhaled corticosteroid (Fluticasone) on normal voice production. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I have had this project explained to me by______________________________.

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my current, continuing or future health care. I understand that if I choose to withdraw from the study, I may also withdraw all information that I have provided.
I understand that the information obtained from this research may be published. However, I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.

I understand that the investigation will be stopped if it should appear harmful to me and I know whom to contact if I have any side effects to the study or have any questions about the study.

I understand the potential risks of participation in the study as explained to me by the researcher.

I understand the compensation provisions for this study.

I have had time to consider whether to take part.

I wish to receive a copy of the results.
YES / NO

* Please note that a significant delay may occur between data collection and publication of the results

I would like the researcher to discuss the outcomes of the study with me
YES / NO

I wish that my whanau / family to be present during the study.
YES / NO

I, ____________________________ hereby consent to take part in this study.

I wish to consent that the data collected from this study may be used for further research
YES / NO
Signature_____________________________________Date____________________

Signature of researcher_____________________

Name of researcher________________________

Name of primary researcher and contact phone numbers:

Prof. Michael Robb
Work ph.  03 364 2987 ext 7077
Mobile: 0210630311

(Note: A copy of the consent form to be retained by participant)

This project has been reviewed and approved by Upper Southern Health Ethics Committee and the University of Canterbury Human Ethics Committee.
The Rainbow Passage

When the sunlight strikes raindrops in the air, they act as a prism and form a rainbow. The rainbow is a division of white light into many beautiful colours. These take the shape of a long round arch, with its path high above, and its two ends apparently beyond the horizon. There is, according to legend, a boiling pot of gold at one end. People look, but no one ever finds it. When a man looks for something beyond his reach, his friends say he is looking for the pot of gold at the end of the rainbow.