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Frequency of voice problems and cough in patients using pressurized aerosol inhaled steroid preparations

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ABSTRACT: The aim of the study was to assess the prevalence of throat and voice symptoms in asthma patients using pressurized aerosol, metered-dose, inhaled corticosteroid preparations.

A questionnaire was administered to hospital out-patients in an asthma clinic and to a control group attending a diabetic clinic. Two hundred and fifty five consecutive out-patients using pressurized aerosol inhaled corticosteroids and 100 controls were surveyed.

One hundred and forty seven (58%) patients taking inhaled steroids reported voice dysphonia or throat symptoms compared with 13% of control patients. Women admitted to symptoms more frequently than men. Throat symptoms were more prevalent in patients using higher doses of inhaled steroid. Aerosol inhaler-induced cough was reported by 87 (34%) patients. Local side-effects were equally prevalent both with beclomethasone dipropionate and budesonide aerosol inhalers. The use of a large volume spacing device with either steroid aerosol did not appear to protect against these symptoms.

Local side-effects are common in asthmatics taking pressurized aerosol, metered-dose, inhaled steroids.

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Inhaled corticosteroids provide maintenance treatment for chronic asthma [1]. In view of the perceived safety of conventional doses (<800 μg·day^{-1}), they are now being used in higher doses (≥1,000 μg·day^{-1}) to control symptoms of severe chronic asthma [2, 3]. Local adverse effects, such as dysphonia and oral candidiasis, are well-known [4], but estimates of their frequency vary widely. Dysphonia has been reported to affect 0–50% of patients using steroid aerosols [2, 5–8], the variation probably reflecting differences in study design. Most studies with large patient numbers have been retrospective and, hence, likely to underestimate the true incidence, whilst small groups have been used in prospective studies. Likewise, the incidence of oral candidiasis varies in the range 0–77% [6, 9–11], often reflecting the different diagnostic criteria used. Difficulties have also arisen in distinguishing between sore throat, dysphonia and oral candidiasis, and any relationships between them.

There is a consensus that local adverse effects occur with all inhaled steroids [7, 12, 13], and are probably dose-related [13, 14], although there are no published reports comparing local side-effects associated with different steroid preparations. There are few reports of the prevalence of these symptoms in the general population. The present survey was designed to document the prevalence of voice and throat symptoms in patients using inhaled steroids and in a control group attending a diabetic clinic.

Patients and methods

All patients using steroid inhalers attending the chest clinic, Northern General Hospital, Edinburgh during a 6 week period completed an interview based questionnaire, which had been designed specifically for the purposes of this study. Information regarding inhalers used, dose frequency and treatment duration was recorded. Further questions related to the presence of any possible local oropharyngeal adverse effects experienced by the subject in the preceding month. These included symptoms of dysphonia, such as hoarseness and reduced voice power, throat symptoms, such as throat clearing and irritation, and the presence of steroid inhaler-induced cough. If symptoms were reported, their frequency was graded as occurring occasionally, most days or every day. Previous diagnosis or treatment for oral candidiasis was also noted. The same questionnaire was completed by a control group of 100 patients randomly selected from a diabetic out-patient clinic.

Statistical analyses

Continuous variables were compared using Student's t-test and categorical variables using Chi-squared tests, with odds ratios and their 95% confidence intervals stated where appropriate. A p-value less than 0.05 was regarded as significant.

Results

Two hundred and sixty nine patients using a steroid inhaler attended the chest clinic during the survey. Only 14 patients were using dry powder inhalation devices and were excluded from statistical analysis. One hundred and eighty nine (74%) patients were using beclomethasone dipropionate (BDP), whilst the remainder used budesonide (BUD). The duration of treatment ranged from 1 month to 18 yrs. Thirty nine (15%) patients were also taking systemic steroids.

The frequencies of symptoms reported by patients using corticosteroid aerosol inhalers are shown in table 1. One hundred and seventy two (67%) patients using a steroid MDI admitted to throat or voice symptoms or inhaler-induced cough, but 11 (6%) said their symptoms predated treatment. The commonest symptoms were those of throat clearing and huskiness, which were reported by approximately a third of patients. Symptoms were more commonly reported by women (80% female *versus* 64% male patients symptomatic; χ^2=9.6; df=1; p=0.004). There was no correlation of symptoms with age, smoking status, type of steroid aerosol used, dose frequency, duration of treatment, or use of other inhaled medication. Table 2 compares the symptom prevalence between patients using steroid aerosols and the control group. The latter was matched for age, but contained significantly fewer women. One hundred and forty seven (58%) patients admitted to voice or throat symptoms compared with only thirteen (13%) control subjects. All symptoms were more prevalent in patients using steroid aerosols (p=0.001), with odds ratios ranging from 5.1 for voice symptoms to 26 for throat symptoms.

The frequencies of symptoms reported by patients taking increasing doses of inhaled steroid are given in table 3. Throat symptoms were more prevalent in patients taking higher doses of inhaled steroid (p<0.01). Although the other symptoms were also more common in patients taking daily doses greater than 1,500 µg, none attained statistical significance. Thirty six (92%) patients taking oral corticosteroids reported voice or throat symptoms. This was significantly greater than those using inhaled steroids alone (χ^2=7.11; df=1; p=0.008). However, these patients were also taking significantly higher doses of inhaled steroid (mean daily dose 1,470 *vs* 1,050 µg; p<0.001). Eighty seven (34%) patients reported cough after using their steroid MDI. This was equally prevalent with both BDP and BUD aerosol inhalers. Sixty six (26%) patients using a steroid MDI reported previous problems with oral candidiasis compared to only 6% controls.

Table 1. – Frequency of symptoms in the 255 subjects using a steroid aerosol inhaler

	Daily	Most days	Occasional	Totals
Throat symptoms				
Throat clearing	40 (16)	31 (12)	19 (7)	90 (35)
Throat irritation	9 (4)	10 (4)	18 (7)	37 (15)
Voice symptoms				
Huskiness	31 (12)	20 (8)	35 (14)	86 (34)
Reduced power	10 (4)	10 (4)	20 (8)	40 (16)
Steroid inhaler-induced cough	26 (10)	28 (11)	33 (13)	87 (34)

Data in parenthesis are percentages.

Table 2. – Frequency of local adverse effects in patients using corticosteroid aerosol inhalers compared to control group

	Steroid MDI	Controls	χ^2	df	p-value	OR	95% CI
Patients n	255	100					
Sex M/F	101/154	58/42	9.8	1	0.003		
Age yrs*	54±1 (11–90)	51±2 (15–83)					
Voice symptoms+	99 (39)	11 (11)	26	1	0.001	5.1	2.7–9.5
Throat symptoms+	103 (40)	4 (4)	45	1	0.001	26	10–66
Voice or throat symptoms+	147 (58)	13 (13)	58	1	0.001	9.1	5.1–16
Previous oral candidiasis+	66 (26)	6 (6)	17	1	0.001	5.5	2.4–1.2

M: male; F: female; MDI: metered-dose inhaler; df: degree of freedom; OR: odds ratio; 95% CI: 95% confidence interval. *: mean±SEM, and range in parenthesis; +: values in parenthesis are percentage.

Table 3. – Symptom frequency with increasing doses of inhaled steroid

	Steroid dose µg·day^{-1}				χ^2		
	<400	401–800	801–1500	>1500	trend	df	p-value
Number	60 (23)	58 (23)	64 (25)	73 (29)			
Spacer used	15 (25)	24 (41)	43 (67)	63 (86)	57.6	1	<0.001
Voice symptoms	22 (37)	20 (34)	22 (34)	35 (48)	1.62	1	NS
Throat symptoms	16 (27)	24 (41)	25 (39)	38 (52)	7.22	1	<0.01
Voice or throat symptoms	29 (48)	33 (57)	37 (58)	48 (68)	3.61	1	NS
Inhaler induced cough	15 (25)	22 (38)	18 (28)	32 (44)	3.17	1	NS

Values in parenthesis are percentages. df: degree of freedom; p-values denote a significant trend for a higher prevalence of symptoms or large volume spacer use in patients taking higher doses of inhaled steroid. NS: nonsignificant.

Discussion

The value of inhaled steroids in the management of asthma is unquestioned, but it has long been recognzed that their use is associated with oropharyngeal and laryngeal adverse effects. This study confirms a high prevalence of such effects, with approximately two thirds of patients experiencing at least one symptom. All symptoms were more common with high daily doses, but only the prevalence of throat symptoms was significantly greater in these patients. Various mechanisms have been proposed for the occurrence of dysphonia with steroid aerosols, but the consensus is that the symptoms are due to the steroid rather than to the propellant [13, 14]. It has also been suggested that vocal cord abuse or laryngeal stress might be an important contributory factor [12]. This may certainly account for some of the 13% symptomatic patients in our control group, but we were unable to ascertain whether patients who use a steroid aerosol and have laryngeal stress are more likely to develop throat or voice symptoms.

Local adverse effects have been reported with all inhaled steroid preparations, including BDP, BUD and triamcinolone acetonide, but no study has compared the prevalence of local adverse effects between different steroid preparations. We found the local side-effect profiles of BDP and BUD to be similar, and, therefore, a change to a different steroid aerosol, at an equivalent dose, is unlikely to influence the problem.

The use of large volume spacer devices (Volumatic and Nebuhaler) for use with steroid MDIs is increasing, especially for patients taking higher doses. It has been shown that use of such a device may reduce the incidence of oral candidiasis [15] by reducing the amount of steroid deposited in the mouth, but their effect on voice and throat symptoms was unclear. This survey found that 86% of patients on daily inhaled steroid doses of greater than 1,500 µg were using a large volume spacer. The higher prevalence of local side-effects in this group indicates such spacers do not protect against throat or voice symptoms, but no account of the reasons why patients were recommended to use spacers was assessed. However, it is possible that holding chambers might increase vocal cord drug deposition and, thereby, exacerbate symptoms of dysphonia. Regular mouth rinsing after inhaler use was not routinely recommended, and was performed in only 13% of patients. As in previous studies [12, 13], this was found to have little effect on the prevalence of throat or voice symptoms, although may be of some benefit in reducing the risk of oral candidiasis.

The prevalence of steroid inhaler-induced cough has not been reported previously. SHIM and WILLIAMS [16] identified 24 patients who regularly coughed and wheezed after inhaling BDP; use of a spacing device was of no benefit, but symptoms improved on changing the steroid inhaler. However, it was likely that the lubricant used in the triamcinolone inhaler and not the drug was responsible for the improvement in cough. Our survey found that 34% of patients admitted to steroid inhaler-induced cough, which was equally prevalent with BDP and BUD. It was more common in patients taking higher daily doses, although this failed to reach statistical significance (p=0.07). Use of a large volume spacer also failed to protect against inhaler-induced cough.

In summary, we confirm a high prevalence of local adverse effects in patients using pressurized metered dose steroid aerosols.

References

1. British Thoracic Society. Guidelines for management of asthma in adults. *Thorax* 1993; 48 (Suppl.): S1–S24.
2. Smith MJ, Hodson ME. High dose beclomethasone inhaler in the treatment of asthma. *Lancet* 1983; i: 265–269.
3. Tarlo SM, Davies GM, Mintz S. Six month double-blind, controlled trial of high dose concentrated beclomethasone dipropionate in the treatment of severe chronic asthma. *Chest* 1988; 93: 998–1002.
4. Stead RJ, Cooke NJ. Adverse effects of inhaled corticosteroids. *Br Med J* 1989; 298: 403–404.
5. Cooper JE, Grant IWB. Beclomethasone dipropionate aerosol in treatment of chronic asthma. *Q J Med* 1977; 183: 295–308.
6. British Thoracic and Tuberculosis Association. A controlled trial of inhaled steroids in patients receiving prednisolone tablets for asthma. *Br J Dis Chest* 1976; 70: 91–103.
7. Pingleton WW, Bone RC, Kerby GR, Ruth WE. Oropharyngeal candidiasis in patients treated with triamcinolone acetonide aerosol. *J Allergy Clin Immunol* 1977; 60: 2543–2548.
8. Williams MH, Kane C, Shim CS. Treatment of asthma with triamcinolone acetonide delivered by aerosol. *Am Rev Respir Dis* 1974; 109: 538–543.
9. Kass I, Nair SV, Patil KD. Beclomethasone dipropionate aerosol in the treatment of steroid-dependent asthmatic patients. *Chest* 1977; 71: 703.
10. Willey RF, Milne LJR, Crompton GK, Grant IWB. Beclomethasone dipropionate aerosol and oropharyngeal candidiasis. *Br J Dis Chest* 1976; 70: 32–38.
11. Brompton/MRC Report. Double-blind trial comparing two dosage schedules of beclomethasone aerosol in the treatment of chronic bronchial asthma. *Lancet* 1974; ii: 303–307.
12. Toogood JH, Jennings B, Baskerville J, Anderson J, Johansson SA. Dosing regimen of budesonide and occurrence of oropharyngeal complications. *Eur J Respir Dis* 1984; 65: 35–44.
13. Toogood JH, Jennings B, Greenway RW, Chaung L. Candidiasis and dysphonia complicating beclomethasone treatment of asthma. *J Allergy Clin Immunol* 1980; 65: 145–153.
14. Williams AJ, Baghat MS, Stableforth DE, Clayton RM, Shenoi PM, Skinner C. Dysphonia caused by inhaled steroids: recognition of a characteristic laryngeal abnormality. *Thorax* 1983; 38: 813–821.
15. Salzman GA, Pyszczynski DR. Oropharyngeal candidiasis in patients treated with beclomethasone dipropionate delivered by metered-dose inhaler alone and with aerochamber. *J Allergy Clin Immunol* 1988; 81: 424–428.
16. Shim SC, Williams MH. Cough and wheezing from beclomethasone dipropionate aerosol are absent after triamcinolone acetonide. *Ann Intern Med* 1987; 106: 700–703.