

Evaluation of Proper Usage of Glucocorticosteroid Inhalers and Their Adverse Effects in Asthmatic Patients

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Background: The frequent use of corticosteroid inhalers (CSIs), especially at higher doses, has been accompanied by concern about both systemic and local adverse reactions. The local adverse reactions of inhaled corticosteroids (ICSs) are considered to constitute infrequent and minor problems. However, while not usually serious, these local adverse reactions are of clinical importance. This study assessed the prevalence of local adverse reactions, their clinical features, role of inhaler devices and current measures that have been suggested to prevent the problem.

Materials and Methods: This study was performed in YAS clinic in Tabriz on 500 asthmatic patients. A questionnaire about the patients' demographic information, methods of using CSIs, local care after using CSIs, using spacer devices, doses of ICSs, and adverse reactions were filled then the patients were clinically examined for local adverse reactions.

Results: Only 56% patients were using CSIs properly. In general, the incidence of complications was: oropharyngeal candidiasis 25.6%, laryngeal weakness 8.8%, choking 17.6%, tooth decay 15.2%, speechlessness 36.2%, taste decrease 20.8%, tongue burning 29.8% and tongue abrasion 27.8%.

Conclusion: Persistent asthma can be effectively controlled with currently available CSIs. Although not life-threatening, local adverse reactions of ICSs are clinically significant and warrant attention. Use of spacer devices and changes in CSI usage, dosage amount and frequency and rinsing and gargling are the methods that have been used to reduce the incidence of local adverse reactions.

Key words: Asthma, Corticosteroids, Adverse reactions

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways characterized by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing (1). Bronchial hyperresponsiveness and variable air-flow obstruction in asthma are consequences of the activity of numerous mediators and inflammatory cells that can cause persistent airway inflammation and remodeling of the airways through fibrosis and smooth muscle cell proliferation (2, 3).

Asthma usually begins in childhood or adolescence but can develop at any time in life (4). The frequent use of CSIs for the treatment of persistent asthma, although highly effective, accompanies concern of both systemic and local adverse reactions (5). Systemic adverse reactions of ICSs have been extensively studied. Comparatively, few studies have been performed to specifically evaluate local adverse reactions of ICSs. These local adverse reactions – including

oropharyngeal candidiasis, dysphonia, pharyngitis, tongue abrasion, choking, tongue burning and cough – are generally considered to constitute infrequent and minor problems (4, 6-8). However, they can be clinically significant, affect patients' quality of life, may hamper compliance with therapy, and mask symptoms of more serious disease. Local adverse reactions result from deposition of actively ICSs in the oropharynx during administration of the drug (9). Numerous factors can influence the proportion of an inhaled dose that is deposited in the oropharyngeal cavity, including the ICS formulation, type of delivery system, and patient's compliance with administration instructions. Therefore, the incidence of local adverse reactions can vary widely (4, 7). The pharmacological effects of ICSs are mediated through glucocorticoid receptors in the cytoplasm of target cells (10). Many ICSs such as fluticasone propionate and budesonide are inhaled in their pharmacologically active form. Other ICSs including ciclesonide and beclomethasone dipropionate (BDP) are inhaled as inactive compounds and are then converted to active metabolites. They are activated by esterases that are present in the lungs, and very little activation occurs within the oropharynx (10). This on-site activation has important implications for reducing the potential local adverse reactions by limiting the availability of active drug outside the target tissue. The local adverse reactions associated with the use of currently available ICSs generally result from the deposition of an actively ICSs in the oropharynx during administration of the drug. The type of delivery system, the formulation of the ICS and patient's compliance with instructions for administration are some of the factors that can influence the proportion of an inhaled dose that is deposited in the oropharyngeal cavity. It is speculated that inflammation is a result of irritation of oropharyngeal mucosa caused by residue from the inhaled substance (7, 11). Lactose, a component in some dry powder inhalers (DPIs), may irritate the oropharyngeal mucosa. Some factors such as drug formulation, dose, and regimen, characteristics of the inhaler device, intrinsic

inflammation of the upper airway in asthmatic patients, mechanical irritation caused by cough and concomitant inflammatory environmental factors (e.g. air pollution) can explain the cause of local inflammation (7).

Patient factors in association with the inhaler device can also affect drug delivery. Physical disability, age or difficulties in cognition can lead to incorrect use of certain devices (12). Careful attention to proper technique for using a metered dose inhaler (MDI) and usage of spacer devices are advised for cognitively or physically impaired adults (13) and for most children (14).

The incidences of oropharyngeal adverse reactions reported in the literature are highly variable. This variability is related to the type and dose of ICS used, as well as the delivery device (MDI versus DPI). However, this variability in reported incidences is also a function of methodologic issues, such as type of study, length of observations, and method of data collection (for example patient questionnaire or physician examination) (7). This study considers the prevalence of local adverse reactions, their clinical features, role of inhaler devices, and current measures that have been suggested to prevent the problem.

MATERIALS AND METHODS

This study was performed at the YAS clinic in Tabriz on 500 asthmatic patients from July 2011 to July 2012. They were consecutively enrolled at the time of a scheduled visit. Patients with asthma as defined by Global Initiative of Asthma (GINA) without any of the important immune suppressive illnesses, those receiving any of the immunosuppressive drugs, or smokers were excluded from the study. Demographic characteristics of patients including age, sex, education, and etc., characteristics of ICS therapy such as type of drugs and their daily doses, use of a spacer device, drug delivery system (drug powder inhaler or pressurized metered dose inhaler, practice of mouth rinsing or using of mouth wash), and local adverse reactions (subjective adverse reactions: tongue abrasion, tongue burning, taste decrease, speechlessness, choking, palpitation, tremor and objective adverse reactions:

laryngeal weakness, oropharyngeal candidiasis, tooth decay) were assessed both by questionnaire and clinical examination. Oral candidiasis was clinically observed or the patients complained about it during treatment. The inhaled doses of corticosteroids were also considered, low doses were defined as less than or equal to 500 µg/day and high doses were defined as more than 500 µg/day ICSs.

Data were analyzed by the Pearson's Chi-Square test using SPSS (Ver.21) software package. A P value lower than 0.05 was considered statistically significant.

RESULTS

Five hundred asthmatic patients were assessed. There were 42.6% males (n=213) and 57.4% females (n=287) between 3 and 88 years (median: 50). Minimum and maximum range of age in patients were 3% under 10 years old (n=15) and 31.4% older than 61 years (n=157) respectively; 57.6% (n=288) of patients lived in Tabriz and the rest (42.4%, n=212) in suburbs. Patients' education ranged from high school (1.6%, n=8) to illiterate (27.2%, n=136). Demographic characteristics of the patients are shown in Table 1.

Table 1. Demographic characteristics of asthmatic patients in Tabriz

Sex:	Males	213 (42.6%)
	Females	287 (57.4%)
Age Range (year):	<10	15 (3.0%)
	11-20	38 (7.6%)
	21-30	42 (8.4%)
	31-40	59 (11.8%)
	41-50	105 (21.0%)
	51-60	84 (16.8%)
	>60	157 (31.4%)
Education:	Illiterate	136 (27.2%)
	Elementary School	131 (26.2%)
	Middle School	49 (9.8%)
	High School	8 (1.6%)
	Diploma	114 (22.8%)
	University education	62 (12.4%)
Residence:	Tabriz	288 (57.6%)
	Suburbs	212 (42.4%)

Frequency of the usage of CSIs compared to oral prednisolone is described in Figure 1. Maximum and

minimum frequency of using ICSs was 61.6% (n=308) for seretide and 2.6% (n=13) for Beclomethasone, respectively. In general, occurrences of the complications were as described in Figure 2. The prevalence of these complications was different from 8.8% (n=44) laryngeal weakness to 36.2% (n=181) speechlessness.

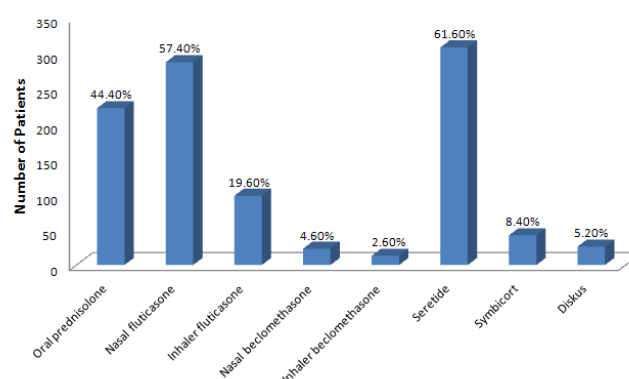


Figure 1. Frequency of treatment with ICSs and oral prednisolone among the study patients

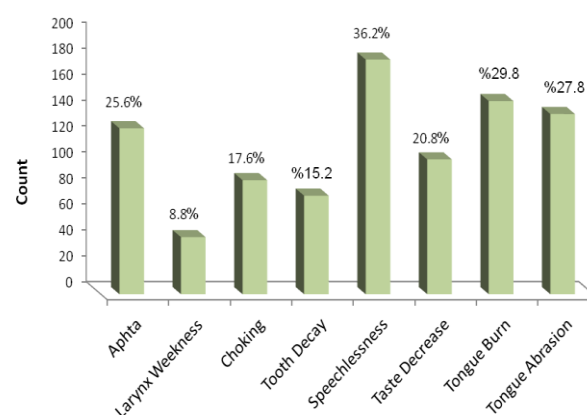


Figure 2. Frequency of local adverse reactions to ICSs among the study patients

Local adverse reactions caused by oropharyngeal deposition of the inhaled steroids may be reduced by the use of spacer devices and mouth washing. Systemic adverse reactions caused by gastrointestinal absorption of the fraction deposited in the oropharynx may also be reduced by these devices (15); 36.1% of our patients were using spacers with inhaled corticosteroids, and the results showed that not using spacers is one of the risk factors for precipitation of drug and its related local adverse effects.

The difference between effects of using and not using spacers on the numbers of local adverse reactions is shown in Figure 3. The patients who did not use spacers showed significantly more adverse reactions compared to those who did ($P<0.001$). The prevalence of different local adverse reactions in the patients who were using and not using spacers is shown in Figure 4. All local adverse reactions were significantly greater in patients who did not use spacers compared to those who did ($P<0.001$).

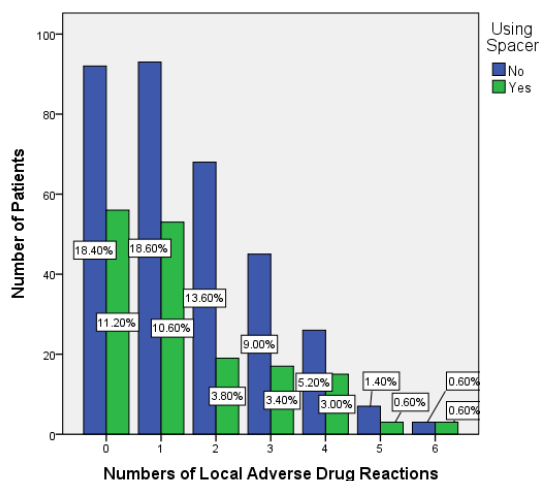


Figure 3. Frequency of local adverse reactions to ICSs among the study patients in relation to using spacers. Patients who used spacers showed fewer adverse reactions compared to those who did not ($P<0.05$).

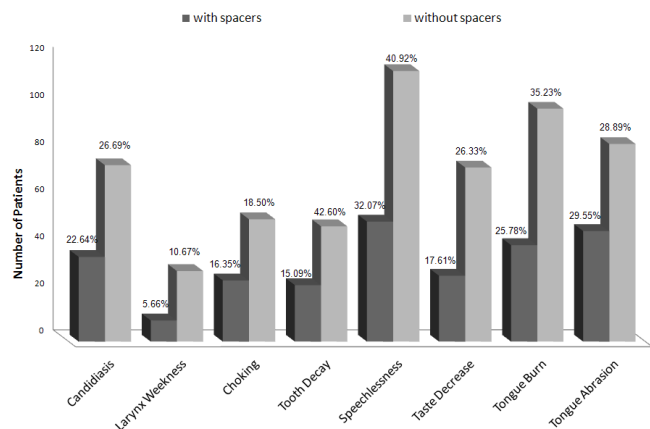


Figure 4. Comparison of the occurrence of different local adverse reactions between patients who used spacers and those who did not.

The effect of mouth wash on the removal of drug residues from both mouth and pharynx after the use of

CSIs was also reported (16, 17); 52.4% of our patients used mouth wash after ICSs, and the results showed that not using mouth wash affected local adverse reactions ($P<0.01$). The prevalence of different local adverse reactions in the patients who were using mouth washes and those not washing their mouths after using CSIs is shown in Figure 5. All local adverse reactions were significantly greater in those who washed their mouths after using CSIs compared to those who did not ($P<0.001$) (Figure 6).

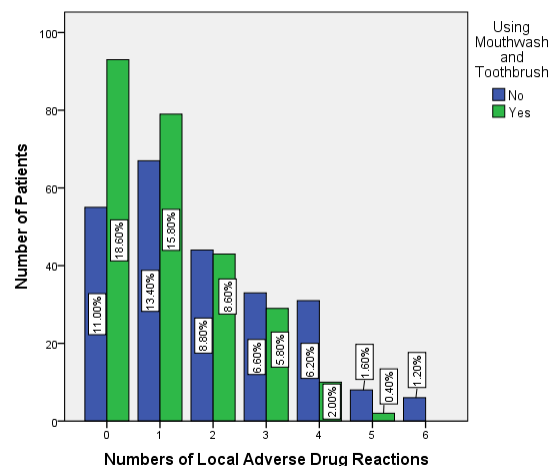


Figure 5. Numbers of local adverse reactions to ICSs among the study patients in relation to using mouthwash and toothbrush after receiving ICSs. Fewer adverse reactions were observed in patients who washed and brushed their teeth following inhalation of corticosteroids ($P<0.001$).

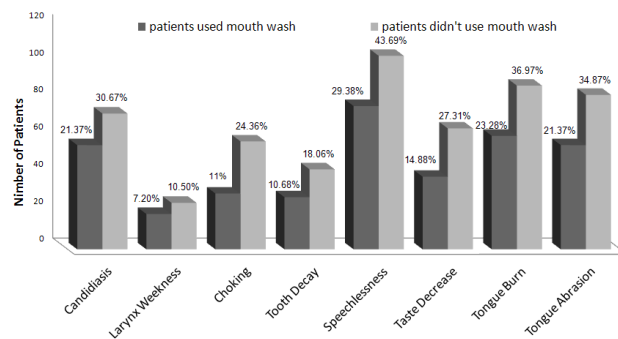


Figure 6. Comparison of the occurrence of different local adverse reactions between patients who washed and brushed their teeth following inhalation of corticosteroids and those who did not.

Frequency of drug reactions in relation to the doses of ICSs are shown in Figure 7. Patients who received ICSs more than 500 µg/day, showed more local adverse

reactions compared to those who received less than 500 µg/day ($P<0.05$). Patients, who also received oral corticosteroids (prednisolone) in addition to ICSs, were compared to those who received ICSs only regarding the frequency of local adverse reactions (Figure 8); significantly more local adverse reactions were observed in patients receiving prednisolone in addition to ICSs ($P<0.05$).

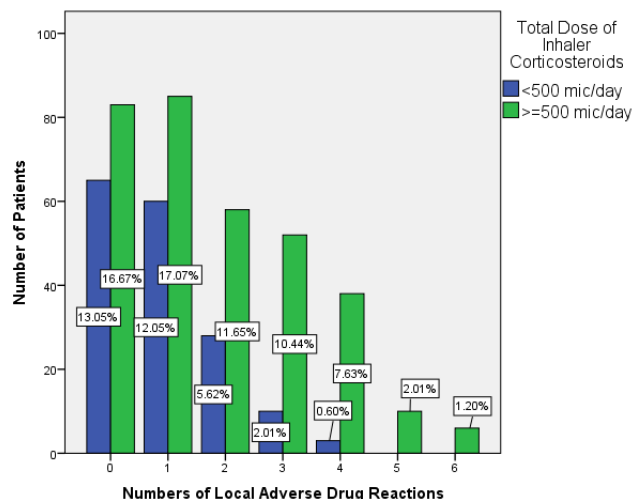


Figure 7. Numbers of local adverse reactions to ICSs among the study patients in relation to the total doses of ICSs ($P<0.05$).

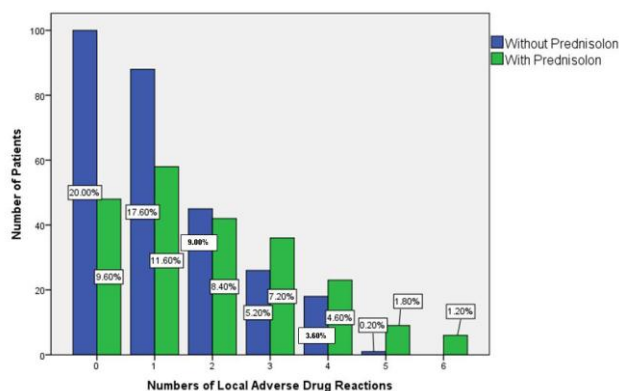


Figure 8. Frequency of local adverse reactions to ICSs in patients who took prednisolone in combination with ICSs compared to those who did not ($P<0.05$).

DISCUSSION

Persistent asthma can be effectively controlled with currently available CSIs. However, local adverse reactions such as oropharyngeal candidiasis, dysphonia, pharyngitis, and cough are common. Although not life-threatening,

these local adverse reactions are clinically significant and need attention. The available data are widely variable and related, in part, to study methodology. Use of spacer devices and changes in ICS formulation, dosage amount, and dosage frequency are among the strategies that have been used to reduce the incidence of local adverse reactions. Patients are advised to rinse their mouths and oropharynx by gargling with water immediately after using the inhaler. Provision of a spacer device is an attempt to minimize laryngeal and pharyngeal deposition of the inhaled material. In one study, this has been shown to be of some benefits (8). However, in contrast, another study found that cough was a spacer device-dependent side effect (6). Previous treatment with other ICSs and devices resulting in local adverse reactions may lead to carry-over effects.

Our study showed that more than 60% of the asthmatic patients treated with CSIs were affected by at least one local side effect in daily life. This high incidence of ICS-induced adverse reactions in patients was in contrast to the results of a recent questionnaire survey which estimated that only 3% of adults and adolescents developed frequent local oropharyngeal side-effects (18). This unexpected gap between both reports may be due to our clinical population with moderate to severe asthma requiring relatively high doses of ICSs. Oral candidiasis has been widely studied in ICS therapy and has an incidence of 0–77% due to differences in diagnostic criteria (19–23). This side effect may be due to a decreased local immunity or to an increase in salivary glucose, which stimulates *Candida albicans*’ growth (22, 23). In our study, where clinical criteria were used, oral candidiasis was observed in 25.6% of the patients. However, the frequency of candidiasis may be underestimated, as Shaw and Edmunds (21) isolated *C. albicans* in 29% of healthy children and 45% of children treated with BDP, whereas only one case of thrush was reported in the treated group. Moreover, we were unable to confirm the well-known risk factors (high doses of ICS

or multiple daily administrations) or protective factors (use of a spacer device with CSI or mouth rinsing after drug delivery) (19-22) in oral candidiasis.

Dysphonia is probably caused by cortisone myopathy and not by laryngeal candidiasis (22, 24). Indeed, Toogood et al. (19) showed that BDP, but not chlorofluorocarbon or excipients, induced dysphonia. In a similar manner, dysphonia was reported with the budesonide (BUD) turbuhaler, which contains no excipients or propellant (8, 25-27). Finally, dysphonia ceased when CSI use was stopped (8, 26). As in adults (8, 25-27), dysphonia was more frequently observed in children using a spacer device. The possible protective effect of dry powder inhalers, pressurized metered-dose inhalers (P-MDIs), and autohaler, in comparison with spacer devices, may be related to the position of the vocal cords, which are open during inhalation against resistance (28). Also, ICSs have been shown to induce a dose-dependent dysphonia in asthmatic adults (19, 23, 29, 30). Only 56% of patients used CSIs correctly.

Delivery systems for ICSs commonly incorporate spacer devices. Spacer devices are classified into one of two general categories: holding chambers or extension devices. Holding chambers provide a reservoir of drug from which it is easier for adults and children to consistently administer an appropriate dose. An extension device increases the distance that an aerosolized drug particle travels before it is inhaled, trapping larger (nonrespirable) particles within the spacer and allowing the propellant to evaporate (which reduces the size of aerosolized droplets), resulting in reduced oropharyngeal deposition of the drug (7, 31).

Using CSIs by spacers reduces many of the local adverse reactions but the majority of the patients (63.9%) did not use spacers. Administration of ICSs to patients with defective inhalation has been improved with the addition of spacers. In adults and older children with a correct technique of inhaling corticosteroids, the spacer devices do not seem to have any advantage over the simple metered-dose inhalers. Young children (two to five years)

benefit from inhaled bronchodilators or corticosteroids by use of spacer devices with one-way valves. Older children and especially adults who suffer from dysphonia or thrush from CSIs can also benefit from spacers. In patients whose condition is well controlled with the usual inhaled doses of corticosteroids with no local adverse reactions, spacer devices yield promising results but more studies are needed (32).

The use of a large volume spacing device with steroid aerosol did not appear to protect against voice dysphonia or throat symptoms (23). Mouth washing after inhalation of corticosteroids is effective for prevention of local adverse effects such as hoarseness and oropharyngeal candidiasis (17).

The effect of mouth wash on the removal of drug residues in both mouth and pharynx after the use of fluticasone propionate dry powder inhaler (FP-DPI) was reported in a study (16). It removed 90% of the totally recovered FP following mouth wash twice daily. This data suggest that mouth wash is an effective precaution for candidiasis induced by FP delivered by DPI.

Another study suggests that the amount of drugs removed by mouth washing is associated significantly with the time lag between inhalation and mouth washing. Immediate gargling and rinsing after inhalation are most useful for the removal of inhalants following inhalation of corticosteroids (17).

CONCLUSION

Persistent asthma can be effectively controlled with currently available CSIs. Although not life-threatening, local adverse reactions of ICSs are clinically significant and warrant attention. Use of spacer devices and changes in ICS, dosage and frequency, rinsing and gargling are the methods that have been used to reduce the incidence of local adverse reactions.

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