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Prevalance of Esophageal Candidiasis in Patients Treated With Inhaled and Short Course Systemic Steroids

İnhale Steroid Kullanmakta Olan ve Tedavilerine Kısa Süreli Sistemik Steroid Eklenen Hastalarda Özefagial Kandidiyazis Prevalansı

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ABSTRACT: ***Objective:*** We aimed to investigate the frequency of esophageal candidiasis by performing upper gastrointestinal system (GIS) endoscopy in patients with asthma and chronic obstructive pulmonary disease (COPD) who were already using inhaled steroids and hospitalized for acute attack and initiated systemic steroids.
Methods: Ten patients with COPD and 11 patients with asthma, hospitalized for acute attack, were accepted to the study (steroid group). These patients were using inhaled steroids for at least one year. They were initiated daily 40 mg methyl-prednisolone for acute attack in the hospital. Systemic steroid treatment was ceased at the 7-10th day when the patients were clinically stable. Upper GIS endoscopy was performed. Biopsy was obtained to confirm candidiasis when white plate was seen. Five hundred and fifty five consecutive patients who admitted to gastroenterology polyclinic with upper GIS complaints and do not have malignancy or immunosupression were accepted to the study as a control group.
Results: Frequency of esophageal candidiasis was 42.9% in the steroid group and 0.2% in the control group.
Conclusion: Frequency of esophageal candidiasis has been increased in patients using inhaled steroids for a long time. Addition of short course systemic steroids further increases this frequency.
Key Words: Esophageal candidiasis, inhaled steroids, systemic steroids

ÖZET: ***Amaç:*** İnhale steroid kullanmakta olan ve akut atak nedeniyle hastaneye yatırılarak sistemik steroid başlanan astım ve kronik obstrüktif akciğer hastalığı (KOAH) olan hastalarda üst gastrointestinal sistem (GİS) endoskopisi ile özefagial kandidiyazis sıklığını araştırmayı amaçladık.
Yöntem: Akut atak nedeniyle hastaneye yatırılmış olan 10 KOAH hastası ve 11 astım hastası çalışmaya alındı (steroid grubu). Bu hastalar en az 1 yıldır inhale steroid kullanmakta idiler. Bu hastalara akut atak tedavisi için günlük 40 mg metil-prednizolon başlandı. Tedavinin 7-10. gününde hastalar stabil hale gelince sistemik steroid kesildi ve üst GİS endoskopisi yapıldı. Beyaz plak görülen hastalardan biyopsi alındı. Gastroenteroloji polikliniğine üst GİS semptomlarıyla başvuran ve malignitesi ya da immünsüpresyonu olmayan grubu olarak çalışmaya alındı.
Bulgular: Özefagial kandidiyazis sıklığı steroid grubunda %42.9 ve kontrol grubunda %0.2 olarak bulundu.
Sonuç: Uzun süredir inhale steroid kullanan hastalarda özefagial kandidiyazis sıklığı artmaktadır. Bu tedaviye sistemik steroidlerin kısa süreli eklenmesi bu sıklığı artırmaktadır.
Anahtar Kelimeler: Özefagial kandidiyazis, inhale steroidler, sistemik steroidler

INTRODUCTION

Inhaled steroids are the basis of antiinflammatory treatment not only in asthma but also in chronic obstructive pulmonary disease (COPD) (1-3).

Oropharyngeal candidiasis is a known side-effect of inhaled steroids and the prevalance is notified as 10-30% (4,5). This side-effect disturbs the patients and decreases the compliance to the medication. Development of oropharyngeal candidiasis is positively correlated with the daily dose of inhaled steroids and also with the frequency and number of inhalations (6-8).

There are only few studies about esophageal candidiasis in patients using inhaled steroids (9-11). Kanda et al. (10) reported a 37% prevalance of

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esophageal candidiasis in patients using inhaled fluticasone propionate.

In our study, we investigated the frequency of esophageal candidiasis by performing upper gastrointestinal system (GIS) endoscopy in patients with asthma and COPD who were already using inhaled steroids and hospitalized for acute attack and initiated systemic steroids. To our knowledge there are no studies with this setting in the literature.

METHODS

Ten patients with COPD and 11 patients with asthma who were hospitalized for acute attack during the year 2004 and agreed to join the study were enrolled (steroid group). An informed consent was obtained. These patients were using inhaled steroids for at least 1 year. Thirteen (61.9%) patients were using high dose (800 mcg) and 8 (38.1%) patients were using low dose (400 mcg) budesonide. They were initiated daily 40 mg methyl prednisolone for acute attack in the hospital. Patients using high dose budesonid and sistemic steroids were defined as group 1, those using low dose budesonid and sistemic steroids were defined as group 2. Patients were said to wash their mouths out after using inhaled steroids in order to avoid oropharyngeal candidiasis. Systemic steroid treatment was ceased at the 7-10th day when the patients were clinically stable. Upper GIS endoscopy was performed. Biopsy was obtained from the patients in whom esophagial white plate was seen. The specimen was send to microbiology laboratory to prove the diagnosis of candidiasis by cultures. Five hundred and fifty five consecutive patients who admitted to gastroenterology polyclinic with upper GIS complaints and do not have malignancy or immunosupression were accepted to the study as control group.

Data were evaluated with SPSS (Statistical Programme for Social Sciences) 10.0 software. In the comparison of the data Fisher's Exact χ^2 test was used. Data were presented as mean ± standard deviation. The results with a "p" value smaller than 0.05 were accepted as statistically significant.

RESULTS

The mean age of 21 patients in the steroid group was 61.2±12.4 (33-80) and that of 555 patients in the control group was 51.0±15.8 (20-90).. None of the patients in the steroid group had diabetes mellitus. The mean period of disease in steroid group (asthma and COPD) was 12.8±5.6 (4-21) years (Table 1). White plate was seen in 9 (42.9%) of 21 patients in the steroid group and biopsy was obtained from this regions. *Candida albicans* reproduced in all the specimen. White plate was seen in only 3 (0.5%) of 555 patients in control group and biopsy was obtained. *Candida glabrata* reproduced in only 1 (0.2%) of them. There was a statistically significant difference between the two groups according to the frequency of esophageal candidiasis (p=0.000).

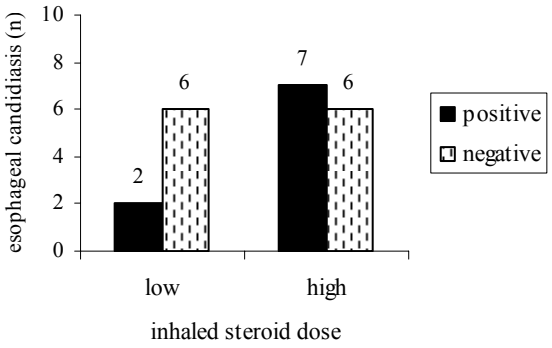
Frequency of esophageal candidiasis according to the disease, smoking status and alcohol consumption was shown in Table 2.

Esophageal candidiasis was observed in 53.8% of the patients in group 1 and in 25.0% of patients in group 2 (Graphic 1). There were no statistically significant differences between the groups for esophageal candidiasis (p=0.367).

TABLE I. Mean changes in body weight and blood glucose levels of control, glyburide - treated control, diabetic and glyburide -treated diabetic rats.

Group	Body Weight(g)	Blood glucose(mg\dl)
Control	270±35.3	75.2±13.0
Control+GLY	221±34.3	83.4±13.8
Diabetic	164±39.2*	343.5±64.9*
Diabetic+GLY	185±43.8**	230.5±50.4**

*p<0.01 significance relative to control; **p<0.01 significance relative to Diabetic.



Graphic 1: The association between dose of inhaled steroids and esophageal candidiasis frequency (p=0.367, Fisher's Exact χ^2 test).

TABLE II. *Muscle CAT activities obtained from control, glyburide-treated control, diabetic and glyburide-treated diabetic rats.*

Group	**CAT (mg\U\protein)**		
Muscle	**M. Gastrocinemius**	**M. Soleus**	**M.Quadriceps femoris**
Control	0.095±26.6	0.074±12.0	0.047±12.6
Control+GLY	0.053±18.8	0.045±11.1	0.027±8.6
Diabetic	0.019±7.8*	0.019±9.0*	0.016±6.0*
Diabetic+GLY	0.021±5.2**	0.033±13.2**	0.021±6.6**

M.Gastrocinemius *p<0.001
M.Soleus *p<0.001 significance relative to Control
M.Quadriceps femoris *p<0.001

DISCUSSION

Candida albicans colonize in the esophagus of 20% of the healthy adults (9). Esophagus infection occurs when *Candida albicans* penetrates the epithelium and esophageal candidiasis is not seen in healthy adults (12). In an autopsy study prevalance of GIS candida infection was reported as 1.6% in patients without malignancy (13). Oropharyngeal candidiasis is a frequent side-effect of inhaled steroids. Keneddy et al. (14) reported oral candidiasis in 7.3% of 25762 patients using inhaled steroids. There are few studies about esophageal candidiasis in patients using inhaled steroids (9-11). There are also case reports of candida esophagitis developed after inhaled steroid use (11,15,16). Kanda et al. (10) demonstrated esophageal candidiasis in 37% of 49 patients using inhaled fluticasone propionate (FP) and noted that the prevalance was significantly higher in patients using high dose inhaled steroids or those with diabetes mellitus. They observed esophageal candidiasis in only 0.3% of control group. There were no significant differences between patients with and without reflux esophagitis according to the prevalance of candida esophagitis. Shuto et al. (9) found esophageal candidiasis in 7 (35%) of 20 patients with asthma using FP for a long time. In our study, patients with asthma and COPD, who were using inhaled steroids for a long time, were evaluated for the frequency of esophageal candidiasis when they were hospitalized for acute attack and administered short course systemic steroids (7-10 days). To our knowledge there are no studies with this setting in the literature. Esophageal candidiasis was observed in 42.9% of these patients. This rate was higher than those reported for patients using only inhaled steroids. We think that short course systemic steroids added to the inhaled steroid treatment is responsible for this high rate. Keneddy et al. (14) reported that the risk for oral candidiasis was increased 2.29 times with concomitant oral steroid therapy in patients using inhaled steroids.

It is not fully understood with which mechanisms inhaled steroids increase esophageal candidiasis but the immunosuppressive and antiinflammatory effects of steroids are thought to play the major role in the pathogenesis (17). Shuto et al. (9) suggested that steroids might penetrate the esophagus during deep inhalation. To prove this they obtained esophageal wash fluids of 4 healthy adults just after they inhaled 200 mcg of FP and 30 minutes later. The FP concentration was 3.3 mcg just after the inhalation and 0.67 mcg 30 minutes after the inhalation. This observation shows that FP distributes quickly and there is still steroid in the esophagus 30 minutes after the inhalation.

As a conclusion, frequency of esophageal candidiasis increase in patients using inhaled steroids for a long time. Short course systemic steroids added to the treatment further increases this frequency. Furthermore, in our study, frequency of esophageal candidiasis in patients using high dose inhaled steroids was higher than those using low dose inhaled steroids, but the difference was not statistically significant. This was considered to be related with the small number of patients.

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