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Beclomethasone Dipropionate and Oropharyngeal Candidiasis

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Summary

A survey of 936 patients attending a respiratory diseases unit outpatient department was performed to assess the incidence of oropharyngeal candidiasis in patients inhaling beclomethasone dipropionate in daily doses of 400 μg or less. Throat swabs from 209 (41%) patients treated with beclomethasone were positive on culture for yeasts compared with positive swabs from 77 (27·2%) patients not receiving corticosteroid therapy either orally or by inhalation. Clinical oropharyngeal thrush, confirmed by culture, was detected in 28 (5·5%) patients inhaling beclomethasone, one (0·7%) patient receiving treatment with oral prednisolone, and two (0·7%) patients not being treated with corticosteroids.

Introduction

Inhalation of beclomethasone dipropionate is now an established and effective treatment of chronic asthma.[1 2] Beclomethasone therapy is free from systemic side effects unless high doses are given.[3] Local complications of treatment are not unexpected, however, since high concentrations of the drug are inevitable in certain sites. One such complication of beclomethasone aerosol therapy is fungus infection of the mouth and throat.[1 4 5] The incidence of this side effect is not known, though McAllen *et al.*[6] reported candidal infection of the pharynx or larynx in 13% of 120 patients treated with beclomethasone dipropionate or betamethasone valerate in varying doses. This investigation was planned to assess the incidence of fungal throat infection in patients with chronic asthma while being treated with beclomethasone in daily doses of 400 μg or less. Patients with chronic asthma receiving treatment with oral prednisolone alone and a group of patients with a variety of chest disorders but not being treated with corticosteroids of any type were used as control groups.

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Patients and Methods

All patients attending the outpatient department of the respiratory diseases unit, Northern General Hospital between July 1973 and December 1973 were questioned about sore throat and hoarseness of the voice and a throat swab was taken from each patient. One dry swab was used to sample both tonsillar areas. A record of beclomethasone, prednisolone, and antifungal therapy was kept (patients being treated with corticotrophin or tetracosactrin were included with those taking prednisolone and were not analysed separately). If lesions in the mouth or pharynx typical of thrush were seen when the swab was taken this was recorded. All patients treated with beclomethasone were inhaling a maximum dose of 400 μg daily (100 μg four times a day). A few patients whose chronic asthmatic symptoms had been well controlled had had their dose reduced to less than 400 μg a day.

MYCOLOGICAL METHODS

All throat swabs were inoculated on to malt peptone agar in Petri dishes within three hours of sampling. The growth of yeasts was recorded after incubation at 37°C for 48 hours. Identification of the yeasts was made primarily on the production of germ tubes (*Candida albicans*) and subsequently by conventional methods.

Results

During the survey 936 patients were investigated. Of these, 283 patients were not receiving treatment with corticosteroids (control group) and 143 patients were being treated with oral prednisolone, 333 with a combination of oral prednisolone and beclomethasone, and 177 with beclomethasone alone.

The isolation of yeasts from each treatment group is shown in table I. Seventy-seven swabs from patients in the control group and 47 from patients taking oral prednisolone yielded yeasts on culture. This difference was not statistically significant. Yeasts were isolated from 73 patients inhaling

TABLE I—*Isolation of Yeasts from 936 Patients*

Corticosteroid Treatment	No. of Patients	No. (%) in whom Yeast was Isolated
None	283	77 (27·2)
Prednisolone	143	47 (32·8)
Beclomethasone	177	73 (41·2)
Beclomethasone and prednisolone	333	136 (40·8)

beclomethasone alone and this represented a definite increase over the controls ($P < 0.01$) but it was not significantly greater than the frequency of isolation in the prednisolone group. The combination of oral prednisolone with beclomethasone produced a similar incidence of yeast colonization to that of the beclomethasone group. When the positive cultures from both control groups (those taking no corticosteroids and those taking prednisolone alone) were compared with those from both groups receiving treatment with beclomethasone the difference was highly significant ($P < 0.005$). The frequency of yeast species isolated was: *Candida albicans* 80·5%, *Torulopsis glabrata* 7·2%, *C. parapsilosis* 4·2%, *C. intermedia* 2·7%, *C. tropicalis* 1·8%, *C. krusei* 1·8%, and others (6) 1·8%.

Fifty patients had symptoms of sore throat or hoarseness or both and there was a significant association of symptoms with beclomethasone treatment (table II). Seven (1·2%) patients not being treated with beclomethasone had throat symptoms compared with 43 (8·6%) receiving treatment with this drug alone or in combination with prednisolone. This difference was highly significant ($P < 0.005$). The number of patients in each group with throat symptoms and a positive throat swab is shown in table II. Nineteen patients complained of throat symptoms but had negative cultures. Four were not being treated with corticosteriods and the remainder were inhaling beclomethasone. All yeasts isolated from patients with symptoms were *C. albicans*. The proportion of patients with symptoms and positive throat swabs was similar in the groups treated with beclomethasone and beclomethasone combined with prednisolone. Hence probably concurrent treatment with oral prednisolone does not increase fungal colonization of the throat of patients treated with beclomethasone.

TABLE II—*Incidence of Symptoms and Isolation of Candida albicans*

Corticosteroid Treatment	No. of Patients	No. (%) with Symptoms	No. (%) with Symptoms and Candida
None	283	6 (2·1)	2 (0·7)
Prednisolone	143	1 (0·7)	1 (0·7)
Beclomethasone	177	14 (7·9)	10 (5·6)
Beclomethasone and prednisolone	333	29 (8·7)	18 (5·4)

Discussion

This survey shows that patients with chronic asthma receiving treatment with beclomethasone have a significantly higher incidence of faucial colonization with yeast fungi than patients not being treated with corticosteroids. Prednisolone did not significantly increase colonization. Most patients, however, did not have symptoms. Of the 510 patients receiving treatment with beclomethasone alone or in combination with prednisolone, 209 (41%) were found to harbour yeasts in their throats but only 28 (5·5%) had clinical faucial candidiasis. In only three cases did inhalation of beclomethasone have to be discontinued because of oropharyngeal thrush.

No yeasts were isolated from 15 patients who complained of symptoms and were being treated with beclomethasone. None of them had typical thrush on clinical examination though one had redness of the throat and one was being treated with amphotericin B. No bacteriological investigations were performed.

The results of this investigation must be interpreted with caution since they may not accurately represent the incidence of faucial candidiasis as a complication of beclomethasone therapy. Each patient was examined on one occasion only and hence the results simply indicate the incidence of this complication at one point in time. This data may be misleading since duration of therapy was not taken into account, and possibly some of our patients may not have been on treatment long enough for candidal infection to develop or that susceptible patients may have been previously eliminated. Our clinical experience suggests that the latter is unlikely as few patients have had to stop beclomethasone because of intractable candidal infection not controlled by a local antifungal agent such as amphotericin B. At the time of the survey only four patients were being treated with antifungal preparations, but we do not know how many had received antifungal therapy before the investigation.

McAllen *et al.*[6] mycologically confirmed the clinical diagnosis of thrush in all their patients, but throat swabs taken from 25 randomly selected patients receiving treatment with corticosteroid aerosols were negative. That no fungal growth was found in these patients is surprising since 27·2% of our patients who were not receiving any form of corticosteroid therapy had yeasts cultured, and this finding is similar to those of other workers. Smits *et al.*[7] cultured yeast fungi from the throats of 28% of patients admitted to a general medical unit and Blyth[8] found 36% of patients admitted to a gastrointestinal unit to have throat swabs positive for yeasts.

The reasons for the greater incidence of yeasts in the throats of patients inhaling beclomethasone are not clear but preliminary tests in this laboratory with beclomethasone dipropionate pure substance have shown that there is no direct effect on the growth or production of pseudomycelium of *C. albicans* in vitro. Hence probably beclomethasone may induce a local impairment in the defence mechanisms of the host. In this study *C. albicans* was the sole species isolated from patients with symptoms but this may simply reflect its greater occurrence as a commensal organism in the throat. In routine investigations of other cases of oropharyngeal thrush induced by beclomethasone we have isolated yeast species other than *C. albicans*.

This investigation confirms that fungal colonization of the mouth and pharynx is a complication of treatment with beclomethasone by inhalation in daily doses of 400 μg or less. A prospective study designed to estimate the incidence of this complication more accurately is in progress, and we hope that this will show the effect of the duration of treatment with beclomethasone on the development of faucial colonization with fungi.

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