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OROPHARYNGEAL CANDIDIASIS IN PATIENTS TREATED WITH BECLOMETHASONE DIPROPIONATE DELIVERED BY METERED-DOSE INHALER ALONE AND WITH AEROCHAMBER

GARY A. SALZMAN, M.D.,
and
DENNIS R. PYSZCZYNSKI, M.D., FCCP
Kansas City, Mo.

From the Pulmonary Disease Section, Department of Medicine, University of Missouri-Kansas City School of Medicine, Truman Medical Center, Kansas City, Mo.

Reprinted from
THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY,
St. Louis

Vol. 81, No. 2, pp. 424-428, Feb., 1988

Oropharyngeal candidiasis in patients treated with beclomethasone dipropionate delivered by metered-dose inhaler alone and with Aerochamber

Gary A. Salzman, MD, and Dennis R. Pyszczynski, MD, FCCP
Kansas City, Mo.

We compared the incidence of Candida *infection,* Candida *colonization, and reduction in oral prednisone dose in patients with asthma treated with beclomethasone dipropionate delivered by metered-dose inhaler (MDI) alone and MDI plus Aerochamber. Group M contained 18 patients treated with beclomethasone, four actuations four times a day (672 μg/day), delivered by MDI alone. Group A contained 18 patients treated with the same dose of beclomethasone delivered by MDI plus Aerochamber. In group M, four of 18 patients had* Candida *infection, 12 of 18 patients had* Candida *colonization, and six of 18 patients were completely removed from oral prednisone. In group A, 0 of 18 patients had* Candida *infection* ($p = 0.05$), *six of 18 patients had* Candida *colonization* ($p < 0.05$), *and 12 of 18 patients were completely removed from oral prednisone* ($p < 0.05$). *We conclude that beclomethasone delivered by MDI plus Aerochamber is more efficacious in reducing oral prednisone dependency and produces less* Candida *infection and colonization than beclomethasone delivered by MDI alone. (J ALLERGY CLIN IMMUNOL 1988;81:424-8.)*

Inhaled corticosteroids are effective in controlling symptoms and reducing oral corticosteroid dependency in chronic asthma.[1-7] Many patients with asthma require large doses to achieve optimal control of their disease.[3, 8] With increasing doses of beclomethasone dipropionate, the reported incidence of oropharyngeal complications also rises.[4, 9] The overall incidence of oropharyngeal candidiasis in patients receiving inhaled corticosteroids ranges from 0% to 77%, caused in part to differing diagnostic criteria.[10-12] The increased incidence of oropharyngeal complications with large doses of inhaled corticosteroids may be due to the fact that 80% of the aerosol delivered by the MDI is deposited in the oropharynx.[13] The tube, cone, and pear spacer, along with the Aerochamber (Monaghan Medical Corp., Plattsburgh, N.Y.), have been demonstrated to significantly decrease the oropharyngeal deposition of inhaled isotope-labeled aerosols.[14-16] The Aerochamber used in our study is a 145-ml, one-way valved, rigid holding chamber designed to overcome the difficulties of hand-lung incoordination.[14]

Abbreviation used
MDI: Metered-dose inhaler

Between 14% to 74% of patients are unable to correctly use the MDI, which may lead to suboptimal results.[17-21] The addition of a spacer device to the MDI has been demonstrated to increase the effectiveness of inhaled terbutaline in adult patients with poor hand-lung coordination.[22, 23] Poor inhaler technique leading to inefficient intrapulmonary delivery and oropharyngeal complications related to a high percentage of aerosol deposited in the mouth may limit the effectiveness of inhaled corticosteroids delivered by MDI. Toogood et al.[24] have demonstrated that the addition of spacer devices to the MDI reduced the incidence of oropharyngeal candidiasis and doubled the antiasthmatic potency of the inhaled corticosteroid, budesonide.

We compared the incidence of oropharyngeal candidiasis and the effectiveness of beclomethasone dipropionate delivered by MDI alone and with Aero-

From the Pulmonary Disease Section, Department of Medicine, University of Missouri-Kansas City School of Medicine, Truman Medical Center, Kansas City, Mo.
Received for publication Jan. 12, 1987.
Accepted for publication July 30, 1987.
Reprint requests: Gary A. Salzman, MD, University of Missouri-Kansas City School of Medicine, 2411 Holmes, Kansas City, MO 64108.

TABLE I. Patient characteristics

	Group M		Group A	
	Mean	Range	Mean	Range
Age	35.7 yr	25-51 yr	32.9 yr	18-48 yr
FEV_1	2.0 L	0.8-2.8 L	2.0 L	1.4-2.9 L
Daily prednisone	(8 pt) 11.9 mg	5-20 mg	(9 pt) 10 mg	5-20 mg
Alternate-day prednisone	(10 pt) 23.5 mg	15-40 mg	(9 pt) 23.3 mg	10-40 mg
Sex	11 M, 7 F		8 M, 10 F	

Pt = patients.

chamber in oral steroid-dependent subjects with asthma.

MATERIAL AND METHODS

Forty-eight adult, oral prednisone-dependent patients with chronic asthma were selected for the study. These patients had not received corticosteroid aerosols for the preceding 6 months. All patients had been receiving oral prednisone for at least 1 year before the study. None of the patients were immunosuppressed, diabetic, or receiving antibiotic prophylaxis for infection. No patient had signs or symptoms of *Candida* infection. Oropharyngeal fungal cultures on Sabouraud's agar were performed at baseline and after 20 weeks of therapy. Cultures were obtained by swabs, and simple growth on agar slant was considered a positive culture. Twelve patients (25%) had positive cultures for *C. albicans* at baseline and were excluded from the rest of the study. The remaining 36 patients were randomly divided into two groups. The characteristics of these patients are summarized in Table I. Group M contained 18 patients treated with beclomethasone dipropionate (Glaxo Inc. Research Triangle Park, N.C.), four actuations (42 μg per actuation) four times a day (672 μg/day) delivered by MDI alone. Group A contained 18 patients treated with the same dose of beclomethasone delivered by MDI plus Aerochamber. The duration of the study was 20 weeks, and all 36 patients completed the study.

The patients in group M were administered two actuations of metaproterenol sulfate (Boehringer Ingelheim, Ridgefield, Conn.) from an MDI before the use of beclomethasone. After shaking the beclomethasone MDI, one actuation of the aerosol was inhaled into the opened mouth, between the lips, from functional residual capacity to inspiratory capacity, followed by holding the breath for 10 seconds before exhalation. There was a pause of 60 seconds between each beclomethasone actuation with a total of four actuations every 6 hours. The patients in group A inhaled two actuations of metaproterenol from an MDI attached to the Aerochamber before use of beclomethasone. The same dose was administered, and the same inhaler technique was performed as described in group M, but the Aerochamber was attached to the beclomethasone MDI, the aerosol was sprayed into the device, and inspiration was initiated within 1 second of actuation in group A. All patients used the MDI adeptly at baseline, and their technique was reevaluated throughout the study during clinic visits. The patients in both groups were not instructed to rinse their mouth after inhalation. All patients were receiving theophylline and inhaled metaproterenol. The doses of these drugs were not changed throughout the study period.

TABLE II. Incidence of oropharyngeal complications

	No. of patients		
	Total	*Candida* infection	*Candida* colonization
Group M	18	4 (22%)	12 (67%)
Group A	18	0	6 (33%)

At baseline, and at 2-week intervals throughout the study period, clinical evaluation, oropharyngeal examination, and spirometry that was performed on an automated electronic spirometer (Medical Equipment Designs, Inc., Broadview, Ill.) were performed in our pulmonary clinic. Each patient was supplied with a prednisone calendar, and the dose was gradually reduced from daily to alternate day, and then the patient was weaned from prednisone if symptoms were controlled and FEV_1 was stable. All patients were weaned by a standard schedule, with weaning stopped if FEV_1 deteriorated.

Candida infection was defined as a positive oropharyngeal culture for *C. albicans* along with physical findings and/or symptoms of infection. *Candida* colonization was defined as a positive culture for *C. albicans* without clinical findings.

A comparison of patients in the two groups with respect to *Candida* infection was analyzed by Fisher's exact test. *Candida* colonization and reduction in prednisone dose with the two methods of drug delivery were analyzed by chi-square. Changes in FEV_1 were analyzed by the analysis of variance for repeated measures. The results were analyzed with the Statistical Analysis System computing package.[25]

RESULTS

The incidences of *Candida* infection and *Candida* colonization are summarized in Table II. A one-sided significance level was used. There were significantly

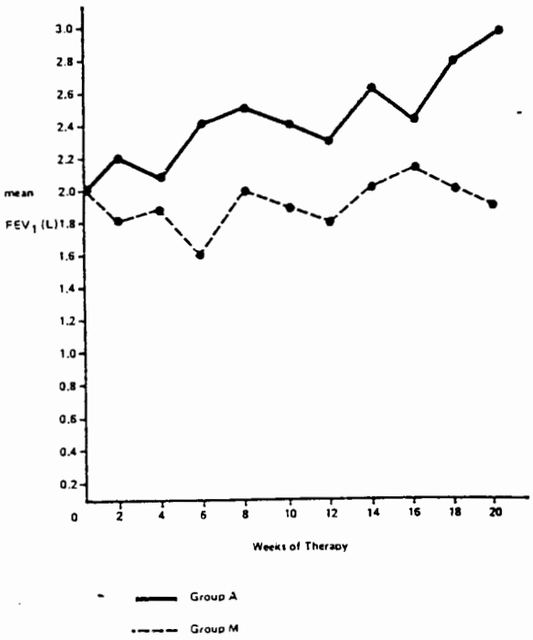

FIG. 1. Mean FEV_1 for group M, beclomethasone delivered by MDI alone, and for group A, MDI plus Aerochamber.

lower incidences of *Candida* infection ($p = 0.05$) and *Candida* colonization ($p < 0.05$) in group A (Aerochamber plus MDI), as compared to group M (MDI alone). Four patients in group M developed oropharyngeal *Candida* infections. One patient had white oral lesions with no symptoms, two patients had white and erythematous lesions with sore mouth and throat, and one patient had white and erythematous lesions with sore throat. All four cases of *Candida* infection were diagnosed during the last 4 weeks of the study and were treated successfully with nystatin after the conclusion of the study.

The reductions in oral prednisone dose in the two groups from baseline to the last day of the 20-week study are summarized in Table III. The posttrial mean prednisone dose included only those patients still receiving prednisone on the last day of the study. Significantly more patients were completely removed from oral prednisone in group A, 12 of 18, as compared to group M, six of 18 ($p < 0.05$).

All nine patients in group A, starting with alternate-day prednisone, were completely weaned from the drug. Only six of 10 patients in group M, starting with alternate-day dosing, were completely weaned from prednisone. The patients in group A, starting with daily prednisone, were either completely weaned from the drug (three of nine patients) or reduced to alternate-day therapy (six of nine patients). No patients in group A were receiving daily prednisone therapy by the end of the study. Four of eight patients were still receiving daily prednisone dosing i group M at the end of the study. No patient in grou M was completely weaned from daily prednisone, and only four of eight patients were weaned to alternate-day dosing.

The mean FEV_1 from the two groups recorded at 2-week intervals is illustrated in Fig. 1. The overall mean increase from baseline in FEV_1 was significantly higher in group A ($p < 0.05$) than in group M in which the mean FEV_1 actually fell 100 ml.

DISCUSSION

This study demonstrated that this group of oral steroid-dependent subjects with asthma treated with beclomethasone dipropionate delivered by MDI plus Aerochamber had a lower incidence of *Candida* infection and colonization than patients treated with the same drug delivered by MDI alone. The significance of the decreased incidence of *Candida* colonization is unclear, since up to 57% of normal subjects have been found to have positive oral cultures for *C. albicans*.[26] *C. albicans* can overgrow under the influence of inhaled or systemic corticosteroids without producing a pathologic condition.[27]

The presence of classic white patches in the oropharyngeal region along with a positive culture for *C. albicans* are required to make the diagnosis *Candida* infection.[12] Symptoms of sore throat and dysphonia have been found in patients with and without *Candida* infection.[28] Relying on cultures alone or symptoms alone may greatly overestimate the incidence of candidiasis. The wide range of reported incidences of oropharyngeal candidiasis, 0% to 77%, may be due to varying diagnostic criteria.[12]

Candida infection is usually not severe, and symptoms are usually just bothersome for the patient, although some patients may stop or have poor compliance with inhaled steroids because of this complication. The lower incidence of oropharyngeal complications with the Aerochamber can be explained by the decreased oropharyngeal deposition of the aerosol.[14] An increase concentration of glucose in saliva resulting from the effect of deposited oropharyngeal corticosteroids may be responsible for the candidiasis.[29] We feel the decreased incidence of this complication with the Aerochamber will improve compliance with the drug and eliminate bothersome symptoms.

Inhaled corticosteroids were developed to control the symptoms of asthma, allowing the patients to reduce the dose or to eliminate oral corticosteroids completely.[1-7] This study demonstrated that the Aerochar

TABLE III. Reductions in oral prednisone dose

Group	Pretrial prednisone dose		Posttrial prednisone dose			
	Dosing interval	Mean dose (mg) (range)	No. of patients	Drug eliminated	Reduced to alternate day	Mean dose (mg) (range)
A	Daily	10 (5-20)	9	3 (33%)	6 (67%)	15.8 (10-20)*
A	Alternate day	23.3 (10-40)	9	9 (100%)	—	—
A	All patients		18	12 (67%)	—	—
M	Daily	11.9 (5-20)	8	0	4 (50%)	22.5 (15-40)* 8.8 (5-20)†
M	Alternate day	23.5 (15-40)	10	6 (60%)	—	13.8 (5-20)*
M	All patients		18	6 (33%)	—	—

*Alternate-day dose.
†Daily dose.

ber improved the efficacy of beclomethasone by reducing the oral prednisone dose to alternate day or completely eliminating prednisone in a significantly greater number of patients than with beclomethasone delivered by MDI alone. The improved efficacy is related to greater intrapulmonary delivery of the beclomethasone aerosol. For the patient who has poor hand-lung coordination and improperly uses the MDI, the Aerochamber will overcome these problems and improve delivery of the aerosol. The Aerochamber enhances vaporization of the propellant, achieving smaller particle size with potentially improved delivery.[14] Radiolabeled isotope aerosol studies demonstrate more diffuse intrapulmonary deposition with the addition of the Aerochamber to the MDI.[14] Toogood et al.[24] demonstrated a reduced incidence of oropharyngeal candidiasis and a doubling of the overall antiasthmatic potency of budesonide with the tube and cone spacer. There is less deposition of aerosol in the oropharynx with spacers and greater intrapulmonary delivery.[15-17, 24]

During the course of our study, while the prednisone dose was being tapered, there was a significant increase in FEV_1 in patients using the Aerochamber while there was a decrease in FEV_1 in those patients using the MDI alone to deliver beclomethasone. The improved lung function, along with the greater reduction in oral prednisone dependency, demonstrates the improved efficacy of MDI beclomethasone delivered by Aerochamber. This improved efficacy is probably due to increased intrapulmonary delivery with the Aerochamber.

Only one other published study has similarly demonstrated that spacer devices can significantly reduce oropharyngeal candidiasis and increase the intrapulmonary delivery of inhaled steroid drugs.[24] One study of children with asthma demonstrated no improvement in symptoms or flow rates with the addition of a pear spacer to the MDI budesonide.[30] This study did not observe oropharyngeal candidiasis. There is much controversy about the value of spacer devices in asthma treatment.[31] We believe this study provides strong support for the addition of the Aerochamber to the MDI of beclomethasone for those patients with asthma who use chronically inhaled steroids.

We thank Ms. Dorthea Shields and Paul Cuddy, PharmD, for assistance with the statistical analysis, and Ms. Harriett Silver for secretarial services.

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