

Local side-effects during 4-year treatment with inhaled corticosteroids – a comparison between pressurized metered-dose inhalers and Turbuhaler®

Selroos O, Backman R, Forsén K-O, Löfroos A-B, Niemistö M, Pietinalho A, Äikäs C, Riska H. Local side-effects during 4-year treatment with inhaled corticosteroids – a comparison between pressurized metered-dose inhalers and Turbuhaler®.

Allergy 1994; 49: 888–890. © Munksgaard 1994.

O. Selroos, R. Backman, K.-O. Forsén,
A.-B. Löfroos, M. Niemistö,
A. Pietinalho, C. Äikäs, H. Riska

Mjölbolsta Hospital, Karis, Finland

Local side-effects, such as hoarseness and oropharyngeal candidiasis, are often seen during treatment of patients with inhaled corticosteroids (ICS). We investigated whether changing from pressurized metered-dose inhalers (pMDI) to Turbuhaler® influenced the type and frequency of local side-effects. Local side-effects were recorded for a 2-year period in which 154 patients used ICS pMDI with a spacer device. They were followed for an equally long period of time (26.2 ± 5.7 months) while using Turbuhaler, as were 90 patients who received Turbuhaler as their first ICS preparation. After inhalation, all patients rinsed out their mouths with water. In experienced pMDI-users, the frequency of local side-effects decreased from 21% to 6%. The reduction was due to a lower incidence of hoarseness. Candidiasis or hoarseness was not seen in patients given Turbuhaler as their first ICS device. Our fear of an increased incidence of local side-effects when giving ICS in Turbuhaler was unwarranted.

Key words: candidiasis; glucocorticosteroids; hoarseness; inhalation therapy; powder inhaler; pressurized aerosol; side-effects.

Dr Olof Selroos
Sångarevägen 14 F
S-224 71 Lund
Sweden

Accepted for publication 7 April 1994

Inhaled corticosteroids (ICS) are widely used for the treatment of inflammatory airway diseases. Although systemic side-effects may occur with high doses of ICS, the limiting factors in ordinary clinical use are the local side-effects, such as oropharyngeal candidiasis and hoarseness. The overall frequency of local side-effects diminishes when large-volume spacer devices are used in conjunction with pressurized metered-dose inhalers (pMDI) (8). Mouth rinsing after inhalation is recommended by all manufacturers of ICSs, but it is not known how well this advice is followed.

Positive throat culture for *Candida* is a common finding in children (5), as well as in adult patients with asthma (7). The occurrence of clinically significant oropharyngeal candidiasis is about 10% in adults (6, 7) and 1% in children (5). The frequency is related to the total daily dose of ICS, but not to the duration of treatment (9), and can be reduced by lowering the frequency of administrations and the daily dose, i.e., the number of inhalations per day

(7, 8). The use of large-volume spacer devices for pMDIs (8) and careful mouth rinsing after using inspiratory-flow-driven powder inhalers (4) also reduce the risk of *Candida* infections.

Temporary hoarseness is a more frequent side-effect than candidiasis; it can be seen in up to 30% of patients (7, 8). This side-effect is unrelated to candidiasis and is most frequently seen in patients with voice stress, such as sports coaches, switchboard operators, teachers, singers, etc. A bilateral adductor vocal cord deformity with bowing of the cords on phonation has been described, but this seems to be a rare explanation of the common side-effect (10). Hoarseness has been shown to improve with the same measures as candidiasis; i.e., reduction of dose and dosing frequency, and the use of spacer devices (8, 9).

Because Turbuhaler® is used without a spacer, we wanted to investigate whether changing ICS treatment from pMDI to Turbuhaler influences the frequency and type of local side-effects.

Material and methods

Patients

From 1 February 1990, when budesonide (Pulmicort®) became available as Turbuhaler, we registered local side-effects in 244 patients who started to use this inhaler before September 1990. There were 133 women and 111 men with a mean age of 52.7 ± 15.6 years (mean $\pm$ SD); range 17–87 years.

Bronchial asthma was the diagnosis in 206 cases, chronic obstructive pulmonary disease (COPD) in 22, a combination of asthma and COPD in seven, and pulmonary parenchymal sarcoidosis in nine.

Method

When budesonide Turbuhaler was prescribed for the first time to a patient, a notification card was filled in, and a clinical research team interviewed the patient, reviewed the patient's hospital records, and filled in a specific case record form indicating the local side-effects during the preceding 2-year period. When data were analyzed, retrospective registrations were used for an equally long period of time as the follow-up study with Turbuhaler, which was 26.2 ± 5.7 months (mean $\pm$ SD).

At each follow-up visit, patients were asked about local side-effects, the oropharyngeal cavity was inspected (clinical signs of oropharyngeal candidiasis; culture only in suspected cases), and a detailed follow-up case record form was completed.

Patients were instructed to inhale forcefully and deeply through Turbuhaler, to rinse their mouths with two gulps of water after inhalation, and to spit out the rinse water.

The treatment of patients using budesonide pMDI (200 µg per dose) with a spacer (Nebuhaler®) was, in principle, changed to the same dose of budesonide Turbuhaler. The treatment of patients using beclomethasone dipropionate (BDP) pMDI (250 µg per dose) with a spacer (Volumatic®) was changed to the nearest possible dose of budesonide Turbuhaler, delivering either 200 µg or 400 µg per dose.

The starting doses of budesonide Turbuhaler and the doses at the last follow-up visit are shown in Table 1. The reasons why 23 patients stopped treatment with budesonide Turbuhaler are given in Table 2.

Results

Prospective registration of local side-effects in patients changing from pMDI to Turbuhaler

From February 1990 to September 1992, we prospectively registered local side-effects in 107 patients changing from BDP pMDI to budesonide Turbu-

Table 1. Daily doses of budesonide Turbuhaler initially, when changing treatment from pMDIs to Turbuhaler, and after mean follow-up period of 26.2 ± 5.7 months

Daily dose (µg)	Initial dose (no. of patients)	Dose at follow-up (no. of patients)
0	0	23
200	0	12
400	5	77
600	1	1
800	174	73
1200	27	20
1600	30	34
2000	1	0
2400	5	2
3200	1	2

haler, and in 47 patients changing from budesonide pMDI to budesonide Turbuhaler. The side-effects are listed in Table 3. The mean age of these patients was 58.2 ± 10.6 years. The side-effects occurred after treatment with Turbuhaler for 4–29 months (mean $\pm$ SD 17.9 ± 9.3 months) when the actual daily doses of budesonide were 2400 µg (four patients), 1600 µg (one patient), and 800 µg (four patients).

The cases of sore throat and sore gums occurred in association with upper respiratory tract infections and were probably not caused by the steroid therapy. The seven patients with *Candida* infection or hoarseness had had the same local side-effects also when using pMDI with spacer.

Local side-effects during earlier treatment with pMDI

When the prospective follow-up time was known for each patient (mean 26.2 ± 5.7 months), a retrospective calculation of earlier registered local side-effects was done. The results are shown in Table 3. During earlier treatment with BDP pMDI with spacer, local side-effects had been registered in 25/107 patients (23%), and, during treatment with budesonide pMDI with spacer, in 8/47 patients (17%). In total, local side-effects had been seen in 33/154 patients (21%). The most frequent side-effect was hoarseness. Local side-effects were present in 10/33 patients when changing treatment from pMDI to Turbuhaler.

Table 2. Reasons for stopping treatment with budesonide Turbuhaler

Reason	No. of patients
Symptom-free, no steroid treatment	8
Preferred pMDI	5
Died of unrelated disease	4
Side-effects (<i>Candida</i> infection)	2
Prescribed nedocromil instead	2
Psychiatric illness; unable to use inhaler	2
Total	23

Table 3. Frequency of local side-effects in patients changing treatment from pMDI with spacer to Turbuhaler

Side-effect	1987-90 Beclomethasone (pMDI+spacer) (n = 107)	1987-90 Budesonide (pMDI+spacer) (n = 47)	1990-2 Budesonide Turbuhaler (n = 154)
Oropharyngeal candidiasis	4	1	4
Hoarseness	21	6	3
Sore throat/gums	0	1	2
Total	25	8	9
Percentage	23.4	17.0	5.8
Combined pMDI	33; 21.4%		

Change in frequency of local side-effects

A reduction in the frequency of local side-effects occurred when patients changed treatment from pMDI with spacer to Turbuhaler (21% during treatment with pMDI and 6% during treatment with Turbuhaler). This difference in frequency of local side-effects was statistically significant (chi-square test; $P < 0.001$).

Frequency of local side-effects in patients using Turbuhaler as their first ICS preparation

Three cases of throat irritation were reported from a group of 90 patients who used Turbuhaler as their first ICS device. No cases of oropharyngeal candidiasis or hoarseness were found.

Discussion

With pMDI without spacer, approximately 75% of the metered dose, and 80% of the delivered dose, is deposited in the oropharyngeal cavity (1). This oropharyngeal deposition may cause local side-effects. The introduction of large-volume spacer devices reduced the oropharyngeal deposition to 10–15% of the metered dose (2). This also resulted in a decrease in local side-effects (8, 9).

Inspiratory-flow-driven, multidose, dry-powder inhalers, such as Turbuhaler, have clinical advantages over pMDI (4). However, the oropharyngeal deposition is still around 45% of the metered dose and 60% of the delivered dose (3), which is significantly more than with a spacer. Therefore, we feared an increase in the frequency of local side-effects when changing treatment from ICS to Turbuhaler.

It is possible to remove 80% of the dose deposited in the oropharyngeal cavity by rinsing the mouth just once with 10 ml of water. This study shows that careful rinsing of the mouth can keep the frequency of *Candida* infections low also with Turbuhaler.

Hoarseness is generally believed to be an adverse effect of corticosteroids. The absence of hoarseness during use of bronchodilator pMDI agrees with this. Interestingly, in this study, the incidence of side-effects was reduced also when the drug (budesonide)

remained the same. In these patients, the daily doses of budesonide remained almost unchanged (4). It therefore seems that local irritation and hoarseness may be related also to the additives in the pMDI, and not only to the ICS. Because we did not have a placebo pMDI group in our study, we cannot, of course, prove this hypothesis. It is more likely that our careful instructions on rinsing the mouth after inhalation significantly contributed to the reduced frequency of local side-effects.

It could be argued that the lower frequency of local side-effects with Turbuhaler was due to the concomitant reduction in ICS doses, which was seen in the group of patients changing from BDP pMDI to budesonide Turbuhaler (4). However, this was probably not the case since the number of patients using a daily dose of 1200 µg or more did not change significantly. It is well known that local side-effects are mainly seen in patients using high doses of ICS. In this study, the daily dose of budesonide via Turbuhaler was 2400 µg in four of the nine patients with local side-effects.

This study shows that our initial fear of an increased incidence of local side-effects with Turbuhaler was unwarranted.

References

1. NEWMAN SP, PAVIA D, MORÉN F, SHEAHAN NF, CLARKE SW. Deposition of pressurized aerosols in the human respiratory tract. *Thorax* 1981; 36: 52–5.
2. NEWMAN SP, MILLAR AB, LENNARD-JONES TR, MORÉN F, CLARKE SW. Improvement of pressurised aerosol deposition with Nebuhaler spacer device. *Thorax* 1984; 39: 935–41.
3. NEWMAN SP, MORÉN F, TROFAST E, TALAEE N, CLARKE SW. Deposition and clinical efficacy of terbutaline sulphate from Turbuhaler, a new multi-dose powder inhaler. *Eur Respir J* 1989; 2: 247–52.
4. SELROOS O, BACKMAN R, FORSÉN K-O, et al. Clinical efficacy of budesonide Turbuhaler® compared with that of beclomethasone dipropionate pMDI with volumatic spacer. A 2-year randomized study in 102 asthma patients. *Allergy* 1994; 49: this issue.
5. SHAW NJ, EDMUNDS AT. Inhaled beclomethasone and oral candidiasis. *Arch Dis Child* 1986; 61: 788–90.
6. SMITH MJ, HODSON ME. High-dose beclomethasone inhaler in the treatment of asthma. *Lancet* 1983; i: 265–9.
7. TOOGOOD JH, JENNINGS B, GREENWAY RW, CHUANG L. Candidiasis and dysphonia complicating beclomethasone treatment of asthma. *J Allergy Clin Immunol* 1980; 65: 145–53.
8. TOOGOOD JH, BASKERVILLE J, JENNINGS B, LEFCOE NM, JOHANSSON S-A. Use of spacers to facilitate inhaled corticosteroid treatment of asthma. *Am Rev Respir Dis* 1984; 129: 723–9.
9. 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.
10. WILLIAMS AJ, BAGHAT MS, STABLEFORTH DE, CAYTON RM, SHENOI PM, SKINNER C. Dysphonia caused by inhaled steroids: recognition of a characteristic laryngeal abnormality. *Thorax* 1983; 38: 813–21.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.