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A randomized controlled trial showing efficacy of once daily intranasal budesonide in nasal polyposis*

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SUMMARY

A randomized, double-blind, placebo-controlled trial was performed to assess the efficacy of once daily budesonide in patients with nasal polyps. After a 2-week run-in period, 157 patients with symptomatic bilateral nasal polyposis were randomized to receive budesonide, 140 μg once or twice daily or 280 μg once daily (delivered doses) via Turbuhaler®, or placebo for 8 weeks. Polyp size was assessed endoscopically and, in two centres, by magnetic resonance imaging (MRI). Nasal symptoms (blocked nose, runny nose, sneezing) were recorded daily, and patients provided an overall assessment of efficacy at the end of the study. Budesonide, 280 μg/day (280 μg o.d. and 140 μg twice daily), significantly reduced polyp size, compared with placebo, whereas budesonide, 140 μg once daily, had no significant effect. Nasal polyp mass score, measured by MRI, was also significantly reduced in patients receiving 280 μg/day. All three doses of budesonide significantly reduced symptom scores, and there were no significant differences between the groups. Overall, approximately 70% of patients receiving budesonide, 280 μg/day, reported substantial or total control of symptoms, compared with 45% of placebo-treated patients. It is concluded that budesonide, 280 μg once daily, reduces polyp size and relieves symptoms in patients with nasal polyposis.

Key words: budesonide, glucocorticosteroids, magnetic resonance imaging, nasal polyposis, Turbuhaler®

INTRODUCTION

Although the aetiology of nasal polyps is not fully understood, it is widely accepted that chronic inflammation plays an important role. Histological examination of nasal polyps shows extensive infiltration by inflammatory cells, particularly eosinophils (Mygind, 1979; Baumgarten et al., 1980), and this is often associated with inflammatory mediator release and mast cell degranulation (Drake-Lee and McLaughlin, 1988; Venge et al., 1990). Inflammation can lead to progressive growth of polyps, resulting in nasal obstruction, and nasal polyposis is a frequent complication of asthma, cystic fibrosis and chronic rhinosinusitis. The hypothesis that nasal polyposis is an inflammatory disorder has focused attention on the role of anti-inflammatory treatment with glucocorticosteroids in the management of the condition. As a result, topical steroid therapy is now recommended as first line treatment for most patients with nasal polyps (Position statement on nasal polyps, 1994).

Budesonide (Rhinocort®, Astra Zeneca R&D, Lund, Sweden) is a glucocorticosteroid that has been shown to be effective in patients with nasal polyposis. Clinical trials have shown that intranasal budesonide reduces polyp size, relieves symptoms of nasal obstruction, and improves sense of smell when used as first line therapy (Ruhno et al., 1990; Lildholdt et al., 1995; Lildholdt et al., 1997; Tos et al., 1998; Jankowski et al., 1999), and can also reduce the frequency of recurrence after surgical treatment (Hartwig et al., 1988).

In studies in nasal polyposis in which budesonide was given via Turbuhaler® dry powder inhaler, it was found to be effective in a twice daily regimen at daily nominal (labelled) doses of 400 μg (Lildholdt et al., 1995; Lildholdt et al.,1997; Tos et al., 1998). Since approximately 30% of the dose is retained within Turbuhaler, this corresponds to a delivered dose of 280 μg. Studies in patients with allergic rhinitis have shown that budesonide is effective when given intranasally once daily at delivered doses

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from 64 μg to 280 μg (Andersson et al., 1993, 1995; Creticos et al.,1998; Meltzer, 1998). Hence, the present study was performed to compare the efficacy of budesonide administered via Turbuhaler at delivered doses of 280 μg and 140 μg once daily, and 140 μg twice daily in patients with nasal polyps.

MATERIALS AND METHODS

Study design

The trial was a randomized, double-blind, placebo-controlled, parallel-group study conducted at nine centres in Italy and one in Spain. It was conducted according to the principles of the Declaration of Helsinki, and was approved by local Ethics Committees at all centres.

Protocol

Patients: Patients were eligible for inclusion if they were aged 18 years or over, and had symptomatic bilateral nasal polyposis. In addition, female patients were required to be postmenopausal or to have undergone surgical sterilization, or to be using adequate contraceptive measures. Patients were excluded from the trial if they had unstable asthma, cystic fibrosis, acute or purulent rhinosinusitis, or structural nasal abnormalities sufficient to cause obstruction, or significant medical conditions that could have influenced their ability to participate in the study. Other exclusion criteria included the use of nasal or systemic corticosteroids within 4 weeks prior to enrolment, or depot steroid therapy within 6 weeks prior to enrolment, previous surgery affecting the anatomy of the lateral wall of the nose, or the use of medications that might have masked the symptoms of nasal polyps. Written informed consent was obtained from all patients before inclusion in the study.

Treatment and assessments: Patients initially underwent a 2-week baseline monitoring period, during which they made daily records of nasal symptoms during the preceding 24 hours on diary cards. At the end of the baseline period, eligible patients were randomized to receive placebo or budesonide in delivered doses of 140 μg (70 μg per nostril) once or twice daily or 280 μg (140 μg per nostril) once daily, for 8 weeks. All treatments were given via Turbuhaler®. Topical or oral decongestants, vascoconstrictors, antihistamines, topical ipratropium and topical sodium chromoglycate or nedocromil sodium, were not permitted during the study; other medications considered necessary for the patient's welfare could be given at the investigator's discretion.

Nasal endoscopic examination was performed at the beginning and end of the run-in period, and after 4 and 8 weeks of treatment. Polyp size score was assessed on a four-point scale (*0:* no polyps; *1:* mild polyps small polyps not reaching the lower edge of the middle turbinate; *2:* moderate polyps medium-sized polyps extending between the upper and lower edges of the inferior turbinate; *3:* severe polyps large polyps extending below the lower edge of the inferior turbinate), as described by Johansen et al., (1993). In two centres, polyp size was also estimated by magnetic resonance imaging (MRI) at the end of the run-in and treatment periods. In these patients, polyp mass was assessed blindly as the degree of occupation of the nasal and paranasal (maxillary, sphenoid, frontal and ethmoid) sinuses by polyp tissue, and expressed on a five-point scale (*0:* no abnormality; *1:* occupying 0-25% of the nasal cavities/sinuses; *2:* occupying 26-50%; *3:* occupying 51-75%; *4:* occupying 76-100%). From these scores the nasal polyp mass score was calculated as the sum of the scores from the left and right nasal cavities (range 0-8), the sinus polyp mass score was calculated as the sum of the left and right paranasal sinuses (range 0-32), and the total polyp mass score as the sum of the nasal and sinus polyp mass scores (range 0-40).

Patients recorded their nasal symptoms (blocked nose, runny nose, sneezing) over the preceding 24 hours each evening on diary cards. Symptoms were rated on a four-point scale (*0:* no symptoms; *1:* mild symptoms that were not troublesome; *2:* moderate symptoms that were frequently troublesome but not sufficiently so to interfere with normal daily activities or sleep; *3:* severe symptoms that interfered with normal activities or sleep). Compliance with treatment was also recorded on the diary cards. At the end of the study, patients provided an overall assessment of treatment efficacy on a five-point scale (*0:* symptoms aggravated; *1:* no control of symptoms; *2:* minor control of symptoms; *3:* substantial control of symptoms; *4:* total control of symptoms).

Information about adverse events was obtained from patients' spontaneous reports and from the response to a standard question "Have you had any health problems since your last visit?" at the beginning and end of the run-in period and after 4 and 8 weeks of treatment. In addition, a general medical examination was performed at the same times.

Outcome measures: The primary efficacy variable was the mean change in polyp size score (sum of scores for both nostrils) from baseline over the 8-week treatment period. It was estimated that a sample size of 40 evaluable patients per group would provide 80% power to detect a treatment difference in polyp size score of 1.0, using a two-tailed test with an α value of 0.05 and assuming a standard deviation of approximately 1.6. Secondary efficacy measures were combined and individual symptom scores and the patients' overall evaluation of treatment efficacy.

Statistical analysis: The principal aims of this study were to assess the efficacy of budesonide, 140 μg and 280 μg, in nasal polyposis, and to compare the efficacy of 140 μg or 280 μg once daily and 140 μg twice daily. Changes in polyp size scores (total scores for both nostrils), and combined and individual symptom scores, during the treatment period were analysed by analysis of covariance (ANCOVA), with treatment and centre as main factors and baseline scores as a covariate, followed by pairwise comparisons. Changes in nasal polyp mass scores, sinus polyp mass scores and total polyp mass scores, measured by MRI, were analysed in the same way. The patients' overall evaluation of efficacy was analysed by analysis of variance (ANOVA) with factors for treatment and centre. No imputation of data was

performed for withdrawn patients. All statistical tests were two-sided, and P values below 0.05 were considered statistically significant.

Assignment

On enrolment, patients were allocated a sequential enrolment number. At the end of the run-in period, randomization was performed in balanced blocks of four by allocating these numbers to the four treatment groups in consecutive order.

Masking

Inhalers used for placebo and budesonide treatment were identical in appearance, and labelled with the patient's enrolment number. Details of the treatment received by each patient were held in secure but accessible locations in each centre; the treatment code could only be broken in an emergency, if necessary for the appropriate management of the patient.

RESULTS

Participant flow and follow-up

A total of 165 patients were enrolled, of whom 158 were randomized and 157 started treatment (Figure 1). Overall, 13 patients discontinued treatment during the study. Of these, six were lost to follow-up, two discontinued because of adverse events, one discontinued because of lack of improvement, and four discontinued for other reasons. The demographic characteristics and disease history of the patients were comparable in the four groups (Table 1).

Table 1. Baseline demographic characteristics and disease history. Results are presented as means and ranges.

	Budesonide, 140 μg b.d.	Budesonide, 280 μg o.d.	Budesonide, 140 μg o.d.	Placebo
Number of patients	39	40	41	37
Males/females	28/11	26/14	29/12	30/7
Age (years)	47.0 (18-75)	48.5 (22-73)	47.5 (25-76)	48.7 (20-70)
Duration of disease (years)	6.8 (0-28)	4.4 (0-23)	6.4 (0-30)	9.1 (0-33)
Number of patients with previous polypectomies	17	14	18	15
Number of previous polypectomies	0.8 (0-5)	0.6 (0-4)	1.0 (0-7)	0.8 (0-4)
Time since last polypectomy (months)	49 (1-144)	52 (7-288)	48 (3-240)	65 (5-264)

Efficacy

Mean polyp size score decreased significantly in patients receiving budesonide, 140 μg twice daily or 280 μg once daily, compared with the placebo group (Table 2, Figure 2). After 4 weeks, the mean reductions were 0.79 and 1.0, respectively; polyp size

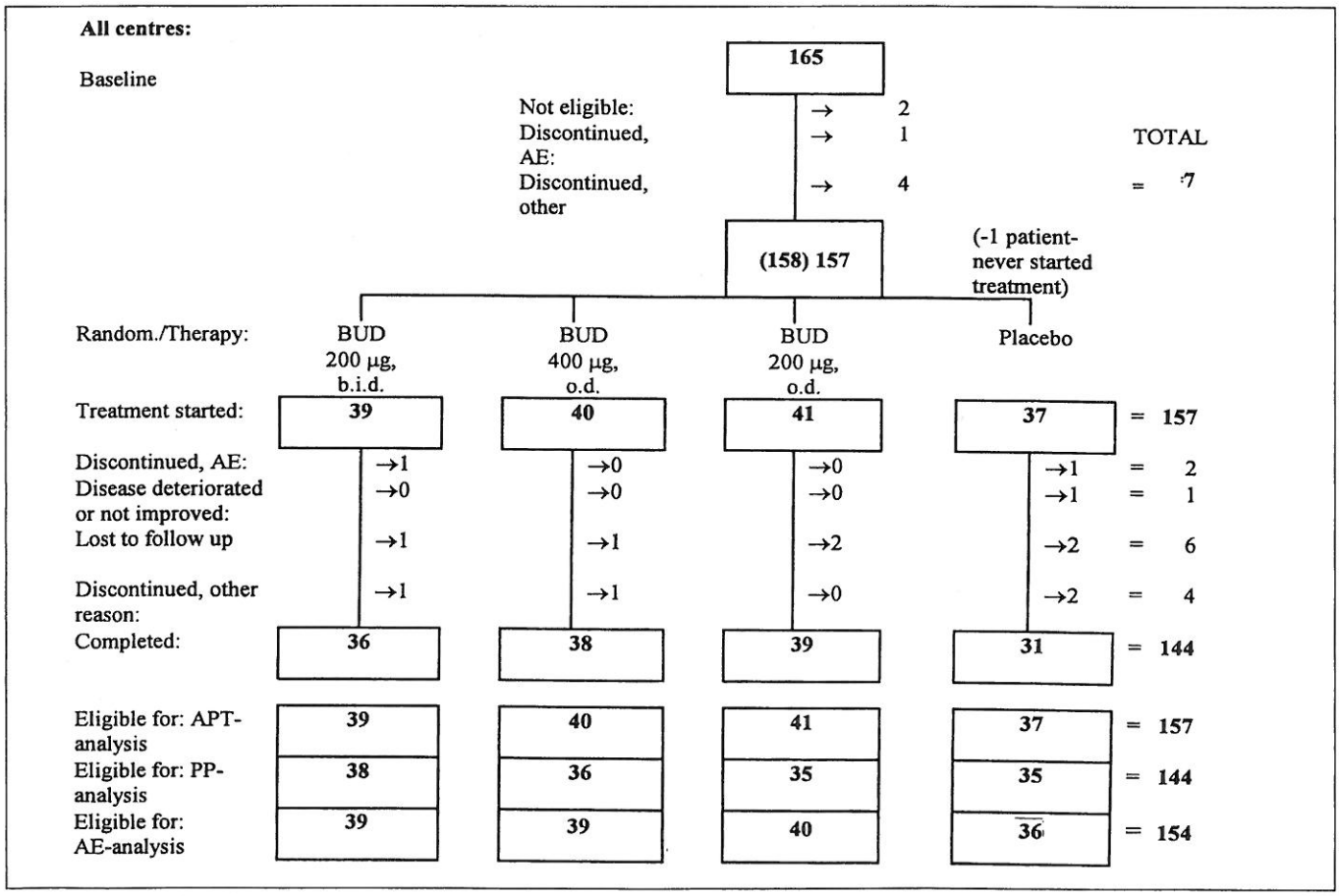

Figure 1. Patient disposition.

also decreased, by a mean of 0.52, in patients receiving budesonide, 140 μg once daily, but the effect did not reach statistical significance. Further improvements were seen after 8 weeks of treatment. The mean reductions in polyp size score in patients receiving budesonide, 140 μg twice daily and 280 μg once daily, were 1.17 (P=0.014) and 1.21 (P=0.009), respectively, compared with 0.52 in the placebo group; the mean reduction in patients receiving budesonide, 140 μg once daily, was 0.72, which was not significantly different from that in the placebo group. The difference between the effects of budesonide, 140 μg once daily and 280 μg once daily, was of borderline statistical significance (P=0.057) (Table 2).

All three doses of budesonide produced significant (P<0.001) reductions in combined nasal symptom scores (Table 2, Figure 3). The mean changes (with 95% confidence limits) in patients receiving budesonide, 140 μg twice daily, 280 μg once daily, and

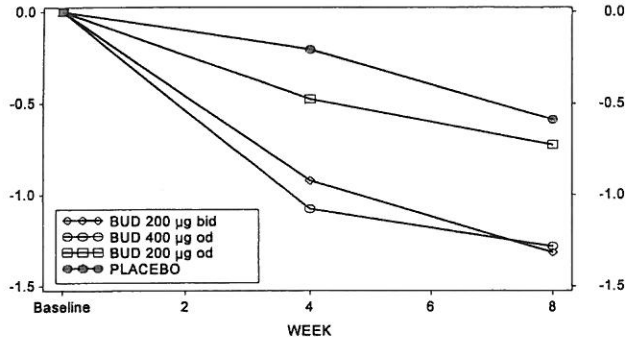

Figure 2. Mean change in polyp size score from baseline.

Table 2. Nasal polyp size and symptom scores: mean change from baseline and results of between-group comparisons.

		BUD 140 μg bid vs. 280 μg od	BUD 140 μg bid vs. 140 μg od	BUD 280 μg o.d vs. 140 μg od	BUD 140 μg bid vs. plac	BUD 280 μg o.d vs. plac	BUD 140 μg o.d vs. plac
Polyp size	Adjusted mean change	0.04	-0.45	-0.49	-0.65	-0.69	-0.20
	Confidence interval	-0.45, 0.54	-0.95, 05	-1.00, 0.02	-1.17, -0.14	-1.21, 0.18	-0.71, 0.31
	p-value	0.867	0.079	0.057	0.014	0.009	0.436
Combined symptom scores	Adjusted mean change	0.00	0.27	0.27	-1.00	-0.99	-1.26
	Confidence interval	-0.54, 0.53	-0.27, 0.81	-0.27, 0.81	-0.55, -0.44	--1.54, -0.44	-1.81, -0.71
	p-value	0.986	0.331	0.319	0.001	0.001	<0.001
Blocked nose	Adjusted mean change	0.10	0.18	0.07	-0.35	-0.45	-0.53
	Confidence interval	-0.18, 0.38	-0.11, 0.46	-0.21, 0.35	-0.64, -0.06	-0.74, -0.17	-0.81, -0.24
	p-value	-0.46	-0.56				
Runny nose	Adjusted mean change	-0.08	0.05	0.13	-0.36	-0.28	-0.41
	Confidence interval	-0.30, 0.14	-0.17, 0.27	-0.09, 0.35	-0.59, -0.14	-0.51, -0.05	-0.64, -0.19
	p-value	0.456	0.663	0.237	0.002	0.016	<0.001
Itchy nose	Adjusted mean change	0.00	0.06	0.06	-0.29	-0.28	-0.34
	Confidence interval	-0.18, 0.18	-0.12, 0.23	-0.12, 0.23	-0.47, -0.10	-0.47, -0.10	-0.52, -0.16
	p-value	0.992	0.532	0.523	0.003	0.002	<0.001

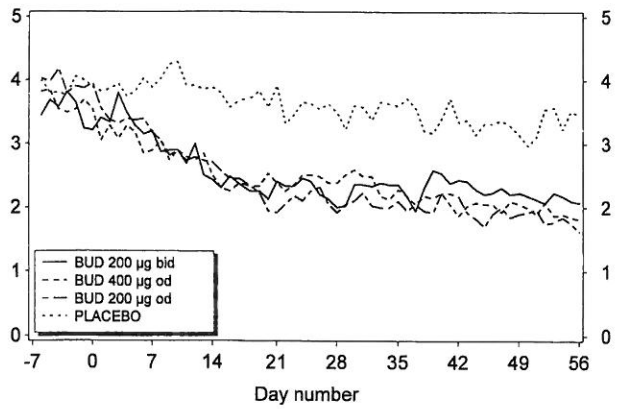

Figure 3. Combined nasal symptom scores.

Table 3. Combined and individual symptom scores: mean change from baseline.

		BUD 140 μg bid	BUD 280 μg od	BUD 140 μg od	Placebo
Combined symptoms	Baseline mean	3.50	3.50	3.83	3.84
	Adjusted Mean Change	-1.15	-1.15	-1.41	-0.15
Blocked nose	Baseline mean	1.70	1.65	1.75	1.62
	Adjusted Mean Change	-0.46	-0.56	-0.64	-0.11
Runny nose	Baseline mean	1.18	1.19	1.39	1.29
	Adjusted Mean Change	-0.44	-0.36	-0.49	-0.08
Itchy nose	Baseline mean	0.63	0.68	0.69	
	Adjusted Mean Change	-0.23	-0.23	-0.28	0.06

140 μg once daily, were -1.15 (-1.54, -0.75), -1.14 (-1.53, -0.75), and -1.41 (-1.80, -1.03), respectively, compared with -0.15 (-0.56, 0.26) in placebo-treated patients. All three budesonide doses also produced significant reductions in individual symptom scores (Tables 2 and 3), whereas placebo had very little effect; there were no significant differences between the three budesonide-treated groups.

At the end of the study, substantial or total control of nasal symptoms was reported by 27 of 37 patients (72.9%) receiving budesonide, 140 μg twice daily, 26 of 38 (68.4%) receiving 280 μg once daily, and 25 of 39 (64.1%) receiving 140 μg once daily, compared with 14 of 31 (45.1%) patients in the placebo group. The overall assessment in the groups receiving budesonide, 140 g twice daily and 280 g once daily, was significantly superior to that in the placebo group.

MRI imaging was performed in a total of 23 patients in two centres. Changes in nasal polyp mass score, sinus polyp mass score, and total polyp mass score are summarized in Table 4. The effects on nasal polyp mass score of budesonide, 140 μg twice daily and 280 μg once daily, were significantly greater than those of placebo, and the effect of the 140 μg twice daily dose was significantly (P=0.012) greater than that of the same dose given once daily. The mean reduction in total polyp mass score was significantly greater in the group receiving budesonide, 140 μg

Table 4. Mean changes from baseline in nasal polyp mass score, sinus polyp mass score, and total polyp mass score.

	Budesonide, 140 μg o.d.	Budesonide, 140 μg b.d.	Budesonide, 280 μg o.d.	Placebo
Nasal polyp mass score	0.1*b	-1.8**a	-1.1*a	0.8
Sinus polyp mass score	-0.8	-2.5	-1.1	0.1
Total polyp mass score	-0.9	-4.4*a	-2.1*a	1.0

*,**$P<0.05$, 0.01 [a]versus placebo. [b]versus 140 μg b.d.

twice daily, than in the placebo group; there were no significant differences in change in sinus polyp mass scores between the groups.

Tolerability

Budesonide was well tolerated. A total of 45 adverse events were reported by 30 patients, and the proportions of patients reporting adverse events were similar in the four treatment groups. The most commonly reported adverse events are listed in Table 5; in addition to these, blood- tinged nasal secretion occurred in one patient receiving budesonide, 280 μg/day. Most adverse events (80%) were mild or moderate in intensity. Two patients withdrew from the study because of adverse events during the baseline period.

Table 5. Most frequently reported adverse events.

	Number of adverse events (% of patients reporting)				
	Baseline period	Budesonide, 140 μg b.d.	Budesonide, 280 μg o.d.	Budesonide, 140 μg o.d.	Placebo
Viral infection	0 (0%)	1 (3%)	2 (5%)	1 (3%)	1 (3%)
Abdominal pain	0 (0%)	0 (0%)	1 (3%)	1 (3%)	0 (0%)
Bronchitis	0 (0%)	0 (0%)	2 (5%)	0 (0%)	0 (0%)
Respiratory infection	1 (1%)	1 (3%)	0 (0%)	1 (3%)	1 (3%)

DISCUSSION

The results of this study show that budesonide, administered via Turbuhaler® in delivered doses of 280 μg once daily or 140 μg twice daily, reduces polyp size and provides effective symptom relief in patients with nasal polyposis. The mean polyp size at the start of the study was 3.9 (maximum possible score 6); this was regarded as moderate, and was associated with troublesome obstruction. Budesonide treatment produced a maximum reduction in polyp size score of 1.17, compared with 0.52 in placebo-treated patients. Since the improvement appeared to progress throughout the study, it seems possible that even greater reductions would have been achieved with a longer duration of treatment. In a 1-year study in patients with a comparable severity of polyposis, for example, mean polyp size score was reduced by 2-3 score steps in patients receiving -budesonide via Turbuhaler® at delivered daily doses of 280 μg in a twice daily regimen (Lildholdt et al., 1995).

Relatively few studies of the effects of intranasal steroids in nasal polyposis have included objective evidence of effects on obstruction. In this study, objective evidence for the effects of budesonide on polyp size was provided by MRI measurements in a subgroup of patients, in addition to the investigators' assessments. Although the number of patients in this subgroup was small, budesonide, 280 μg/day, produced a significant reduction in nasal polyp mass score when given in one or two daily doses; twice daily treatment also produced a significant reduction in total polyp mass score. The nasal polyp mass score is perhaps the most clinically relevant of the MRI parameters studied, since it relates to nasal obstruction and impairment of nasal breathing. Thus, the finding that budesonide, 280 μg once daily, significantly reduces this variable highlights the potential clinical benefits that can be achieved with such treatment in nasal polyposis. Objective evidence for the efficacy of intranasal budesonide in nasal polyposis has also been provided by measurements of nasal peak flow (Lildholdt et al., 1995; Jankowski et al., 1999) and anterior rhinomanometry (Paul Keith, personal communication, 1999).

The reduction in polyp size achieved with budesonide, 280 μg/day in a once or twice daily regimen, was associated with clinically and statistically significant improvements in symptom scores. These beneficial effects were also reflected in the patients' overall evaluation of efficacy, where approximately 70% of patients receiving budesonide, 280 μg/day, reported substantial or total control of symptoms, compared with only 45% of placebo-treated patients.

The efficacy of budesonide, 140 μg once daily, seems to have been suboptimal in this study. Symptom scores and overall assessments were improved, but neither measure was significantly different from those in the placebo group. Furthermore, neither of the two measurements of polyp size showed a significant difference between the groups receiving this dose of budesonide and placebo. Thus, a dose of 140 μg, given once daily via Turbuhaler®, appears to be insufficient for the effective treatment of nasal polyposis over 8 weeks.

Nasal polyp size reduction has also been reported with beclometasone diproprionate, 200 μg twice daily, but only after 30 weeks treatment (Holmberg et al., 1997). Fluticasone propionate, 200 μg twice daily, reduced polyp size after 12 weeks in a selected patient population with severe polyps (Lund et al., 1998), but other studies have suggested that doses approximately double those recommended for allergic rhinitis (i.e., fluticasone propionate 800 μg daily), and complicated head down daily administration, may be necessary to reduce polyp size (Holmström et al., 1999). Thus, the daily doses of beclometasone diproprionate and fluticasone propionate needed to reduce polyp size could be at least 400 μg. By contrast, intranasal budesonide appears to be effective in reducing polyp size at lower doses and in a shorter time (Creticos et al., 1998; Meltzeret al., 1998; Jankowski et al., 1999); in the latter respect, doubling the dose did not seem to add further benefit in a previous study (Lildholt et al., 1997). Data from that study, together with the present results, indicate that with the dry powder formulation of budesonide a dose of 280 μg daily is optimal. The 140 μg

once daily dose does not reduce polyp size significantly in 8 weeks and a daily dose of 560 μg (Lildholdt et al., 1997) did not add further benefit.

It is possible that one reason for the apparently higher potency of budesonide, compared with other intranasal steroids, might be a longer duration of action due to prolonged retention within the target tissue. Budesonide is known to form intracellular esters with long-chain fatty acids after topical application to airway mucosa, resulting in prolonged retention within the tissue (Miller-Larsson et al., 1998); this prolonged retention is associated with an extended anti-inflammatory effect, compared with steroids that do not undergo esterification (Wieslander et al., 1998). Esterification of budesonide, and a prolonged retention of the esterified steroid, have been shown to occur in human nasal mucosa (Petersen et al., 2000). This prolonged duration of effect supports the use of once daily regimens with budesonide. Furthermore, a once daily regimen is preferable since it can add to patient convenience and may improve compliance (Eisen et al., 1990).

In conclusion, this study has shown that once daily treatment with budesonide, 280 μg/day, reduces polyp size and improves nasal symptoms in patients with nasal polyposis.

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REFERENCES

1. Andersson M, Lindqvist N, Svensson C, Ek L, Pipkorn U (1993) Dry powder inhalation of budesonide in allergic rhinitis. Clin Otolaryngol 18:30-33.
2. Andersson M, Berglund R, Greiff L, Hammarlund A, Hedbys L, Malcus I, Nilsson P, Olsson P, Sjolin IL, Synnerstad B (1995) A comparison of budesonide nasal dry powder with fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis. Rhinology 33:18-21.
3. Baumgarten C, Kunkel G, Rudolph R, Stand RD, Sperner I, Gelderblom H (1980) Histopathologic examinations of nasal polyps of different etiology. Arch Otolaryngol 226:187-197.
4. Creticos P, Fireman P, Settipane G, Bernstein D, Casale T, Schwartz H (1998) Intranasal budesonide aqueous pump spray (Rhinocort Aqua) for the treatment of seasonal allergic rhinitis. Rhinocort Aqua Study Group. Allergy Asthma Proc 19:285-294.
5. Drake-Lee AB, McLaughlan P (1988) The release of histamine from nasal polyp tissue and peripheral blood when challenged with anti-human IgE, house dust mite extract and mixed grass pollen extract and compared with positive skin tests. J Laryngol Otol 102:886-889.
6. Eisen SA, Miller DK, Woodward RS (1990) The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med 150:1881-1884.
7. Hartwig S, Linden M, Laurent C, Vargö AK, Lindquist N (1988) Budesonide nasal spray as prophylactic treatment after polypectomy-A double-blind clinical trial. J Laryngol Otol 102:148-151.
8. Holmström M (1999) Clinical Performance of fluticasone propionate nasal drops. Allergy 54 (Suppl 53).
9. Holmberg K, Juliusson S, Balder B, Smith DL, Richards DH, Karlsson G (1997) Fluticasone propionate aqueous nasal spray in the treatment of nasal polyposis. Ann Allergy Asthma Immunol 78:270-276
10. Jankowski R, Bonfils P, Castillo L, Gilain L, Prades JM, Strunski V (1999) Once-daily dose of budesonide aqueous nasal spray 128 g is efficacious primary treatment with rapid onset in nasal polyps. J Allergy Clin Immunol 103:166 (abstract).
11. Johansen LV, Illum P, Kristensen S, Winther L, Petersen SV, Synnerstad B (1993) The effect of budesonide (Rhinocort®) in the treatment of small and medium-sized nasal polyps. Clin Otolaryngol 18:524-527.
12. Lildholdt T, Rundcrantz H, Bende M, Larsen K (1997) Glucocorticoid treatment for nasal polyps. The use of topical budesonide powder, intramuscular betamethasone, and surgical treatment. Arch Otolaryngol Head Neck Surg 123:595-600.
13. Lildholdt T, Rundcrantz H, Lindqvist N (1995) Efficacy of topical corticosteroid powder for nasal polyps: a double-blind, placebo-controlled study of budesonide. Clin Otolaryngol 20:26-30.
14. Lund VJ, Flood J, Sykes AP, Richards DH (1998) Effect of fluticasone in severe polyposis. Arch Otolaryngol Head Neck Surg 124:513-518.
15. Meltzer EO (1998) Clinical and antiinflammatory effects of intranasal budesonide aqueous pump spray in the treatment of perennial allergic rhinitis. Ann Allergy Asthma Immunol 81:128-134.
16. Miller-Larsson A, Mattson H, Hjertberg E, Dahlbäck M, Tunek A, Brattsand R (1998) Reversible fatty acid conjugation of budesonide. Novel mechanism for prolonged retention of topically applied steroid in airway tissue. Drug Metab Dispos 26:623-630.
17. Mygind N (1979) Nasal polyps. In: Mygind N (Ed). Nasal allergy. Blackwell Scientific Publications, London, UK, pp. 233-238.
18. Petersen H, Kullberg A, Edsbäcker S, Greiff L (2000) Fatty acid ester formation appears to increase and prolong the retention of budesonide in human nasal mucosa in vivo as compared with fluticasone propionate. J Allergy Clin Immunol 105 (1 part 2): s202 (abstract).
19. Position statement on nasal polyps (1994) Rhinology 32:126.
20. Ruhno J, Andersson B, Denburg J, Anderson M, Hitch D, Lapp P, Vanzieleghem M, Dolovich J (1990) A double-blind comparison of intranasal budesonide with placebo for nasal polyposis. J Allergy Clin Immunol 86:946-953.
21. Tos M, Svendstrup F, Arndal H, Ørntoft S, Jakobsen J, Borum P, Schrewelius C, Larsen PL, Clement F, Barfoed C, Rømeling F, Tvermosegaard T (1998) Efficacy of an aqueous and a powder formulation of nasal budesonide compared in patients with nasal polyps. Am J Rhinol 12: 183-189.
22. Venge P, Håkansson L, Rak S, Dahl R, Fredens K (1990) Inflammatory cells in asthma and rhinitis. In: Mygind N, Pipkorn U, Dahl R (Eds). Rhinitis and asthma: similarities and differences. Munksgaard, Copenhagen, Denmark, pp.188-202.
23. Wieslander E, Delander E-L, Järkelid L, Hjertberg E, Tunek A, Brattsand R (1998) Pharmacologic importance of the reversible fatty acid conjugation of budesonide studied in a rat cell line in vitro. Am J Respir Cell Mol Biol 19:477-484.

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