

Nasal powder administration of budesonide for seasonal rhinitis in children and adolescents

Agertoft L, Wolthers OD, Fuglsang G, Pedersen S. Nasal powder administration of budesonide for seasonal rhinitis in children. *Pediatr Allergy Immunol* 1993; 4: 152–156. © Munksgaard 1993.

The effect of intranasal budesonide delivered from a new dry powder inhaler (Rhinocort Turbuhaler) was evaluated in a randomized, double blind, group parallel study of 83 children aged 4–16 years with seasonal allergic rhinitis. The doses 100 and 200 µg taken once daily in each nostril were compared with placebo. A one week run-in period was followed by a 4 weeks treatment period. Diary recordings of nasal symptoms, p.r.n. use of terfenadine tablets were made at home and rhinoscopy performed at hospital before and at the end of each treatment period. Total or substantial control of symptoms was achieved in 41% of the children in the 400 µg group ($p < 0.05$ compared with placebo), in 33% in the 200 µg group ($p = 0.07$ compared with placebo) and in 14% in the placebo group. The 400 µg but not the 200 µg group was statistically significantly better than placebo for most of the clinical effect parameters studied. The treatment was well tolerated and a battery of laboratory tests including cortisol excretion in the urine was not influenced by the various treatments. These results indicate that 400 µg budesonide given once daily from a Rhinocort Turbuhaler is clinically effective and safe in children with rhinitis. Further studies are needed to evaluate if this inhaler is preferable to other inhalers currently used for the treatment of rhinitis.

**L. Agertoft, O. D. Wolthers,
G. Fuglsang, S. Pedersen**

Department of Paediatrics, Kolding Hospital,
Denmark

Lone Agertoft, Department of Pediatrics, Kolding
Hospital, DK-6000 Kolding, Denmark

Key words: seasonal rhinitis; nasal powder;
budesonide; children

Received November 18, 1992
Accepted March 15, 1993

In recent years topical glucocorticosteroids have become accepted as an effective treatment for allergic rhinitis in both adults and children. So far freon-driven, metered-dose inhalers (MDI) have been the most widely used delivery system for the administration of these drugs. However, concern about the negative effects of the chlorofluorocarbons (CFCs) on the environment have increased research into such alternative freon-free delivery systems as aqueous suspensions delivered from a "pump spray". However, recent studies indicate that use of such devices is associated with a higher systemic effect of the nasal inhaled corticosteroids (1). Therefore, other alternatives are needed.

In asthma therapy, dry-powder inhalers have become established as the best alternatives to freon driven aerosols. Therefore, it is obvious that these devices should also be evaluated in the treatment of rhinitis. The present study of children with

seasonal rhinitis was to assess the effect and safety of budesonide delivered from a dry-powder inhaler: a Turbuhaler modified for nasal inhalation.

Patients and methods

In all 53 boys and 30 girls 4–16 years of age (mean 11.5 years) entered the study (Table 1). All had a clinical diagnosis of grass pollen induced allergic rhinitis or rhinoconjunctivitis and verified grass pollen allergy (skin prick-test or RAST).

The mean duration of allergic rhinitis was 4.7 years (range 1–12 years) (Table 1). None had used systemic or nasal steroids for 2 months prior to the study; 56 patients also suffered from asthma. Inhaled glucocorticosteroids and other anti-asthma treatment were allowed to continue unchanged throughout the study. Patients with septal deviation, nasal polyps, atrophic or infectious rhinitis

Table 1. Demographic characteristics of the three study groups.

	200 µg budesonide	400 µg budesonide	Placebo
No. of patients	27	27	29
No. with asthma	16	17	23
No. on inhaled budesonide	6*	11	13
Age (years)	11.5 (6–15)	11.4 (4–16)	11.7 (7–15)
Weight (kg)	41.6 (24–72)	43.4 (20–78)	41.4 (23–60)
Height (cm)	151 (129–189)	148 (109–177)	153 (121–178)
Duration of rhinitis (years)	4.2 (1–10)	5.2 (1–12)	4.7 (1–10)

Values are given as mean and range.

* $p < 0.05$ compared with the other groups

and acute or chronic infectious sinusitis were excluded. The use of antihistamines, intranasal cromoglycate, topical or oral decongestants or other medication which could mask the symptoms of rhinitis were not allowed from 3 days prior to enrollment. Astemizole was not allowed for 8 weeks prior to study start. The study was approved by the local ethics committee and informed consent was obtained from all children and their parents.

The protocol was a randomized, double-blind parallel group design. After a 1-week run-in period the children were allocated to 4 weeks' treatment with either 200 µg or 400 µg budesonide per day or placebo. Budesonide and placebo Turbuhalers modified for nasal insufflation were used. Each inhaler contained 200 doses and each sniff-actuation delivered either 100 or 200 µg budesonide or 100 µg lactose (placebo). The dose was one insufflation in each nostril every morning. The number of doses taken from each Turbuhaler was calculated after the study by counting the number of doses left in the Turbuhaler.

All children entered the study during 2 weeks at the early part of the grass pollen period. Visits to the outpatient clinic took place on entry (Day 1), at the end of the run-in period (Day 7) and at the end of the treatment period (Day 35).

If hay fever symptoms became intolerable rescue terfenadine tablets (60 mg) were allowed. The use of terfenadine was evaluated by counting the number of tablets given to the patient at entry at each subsequent visit.

Throughout the study the following symptoms were recorded in diaries: blocked nose; runny nose; sneezing.

Scoring was made according to the following scale: 0 = no symptoms; 1 = mild symptoms (present but not troublesome); 2 = moderate symptoms (weakly troublesome but not sufficient to interfere with normal activity or sleep); 3 = severe

symptoms (sufficiently troublesome to interfere with normal activity or sleep).

At the last visit the patient and the parents were asked to evaluate the overall effect of the study drug according to the following definitions: 0 = symptoms aggravated; 1 = no control of symptoms; 2 = minor control of symptoms; 3 = substantial control of symptoms; 4 = total control of symptoms.

In addition the use of terfenadine tablets and occurrence of side effects were recorded.

Rhinoscopy was performed at each visit. Hypertrophy of the conchae, oedema, secretion (0 = none, 1 = mild, 2 = moderate, 3 = severe), lividity (1 = normal, 2 = mild, 3 = pronounced), patency (1 = normal, 2 = mild obstruction, 3 = moderate obstruction and 4 = severe obstruction) were assessed.

Systemic effects of the treatments were evaluated by the following laboratory assessments: haemoglobin, haematocrit, thrombocytes, total and differential white blood counts (WBC), glucose, albumin, potassium, sodium, aspartic acid aminotransferase, gamma-glutamyltransferase, bilirubine, calcium, plasma cortisol and overnight cortisol excretion in the urine. The laboratory assessments were performed at visits 2 and 3. Daily pollen counts were obtained throughout the study.

Statistics

Prior to the study it was calculated that with a standard deviation of 0.7, 25 patients in each treatment group would provide an 80% power ($\alpha = 0.05$ 2-tailed) to detect a treatment difference of 0.6 in individual symptoms score.

The various assessments and comparisons of treatment effects were analyzed using ANOVA based on ranked scores followed by pair-wise com-

Table 2. Symptoms and terfenadine use during the various treatments

		Budesonide 200 µg	Budesonide 400 µg	Placebo
Blocked nose	Baseline	1.23±0.89	1.43±0.65	1.12±0.84
	Treatment	0.92±0.75	1.03±0.61*	1.20±0.80
Sneezing	Baseline	1.02±0.55	0.99±0.64	0.95±0.76
	Treatment	0.92±0.69	0.65±0.50*	0.84±0.72
Runny nose	Baseline	1.21±0.73	0.94±0.88	1.16±0.74
	Treatment	0.99±0.61	0.88±0.64	1.09±0.71
Combined nasal symptoms	Baseline	3.46±1.44	3.35±1.33	3.24±1.67
	Treatment	2.84±1.38	2.56±1.42*	3.14±1.69
Terfenadine use	Baseline	1.82±2.36	1.84±3.52	1.88±2.81
	Treatment	1.52±2.42	1.22±2.47	1.84±3.07

Values are given as mean ± SD

* $p < 0.01$ compared with baseline

Table 3. Overall patient assessment of treatment efficacy scored at the end of study

Assessment	Budesonide 200 µg Per cent	Budesonide 400 µg Per cent	Placebo Per cent
Aggravated	3.7	3.7	13.8
No control	29.6	29.6	34.5
Minor control	33.3	25.9	37.9
Substantial control	25.9	37.0	13.8
Total control	7.4	3.7	0.0

parison. Two-tailed alternatives were considered. The baseline mean score could be included in the model as a covariate. $P < 0.05$ was considered statistically significant.

Results

All 83 children completed the study according to the protocol; 27 children received 200 µg budesonide per day, 27 received 400 µg per day and 29 received placebo. The 3 groups were comparable with respect to age, height, weight, duration of allergic rhinitis, occurrence of asthma and hay fever symptoms during run-in (Tables 1, 2). Compared with the other groups significantly fewer children in the 200 µg group received inhaled budesonide for their asthma.

Compliance defined as number of doses taken as a percentage of the prescribed number of doses was 92% (placebo), 106% (200 µg) and 114% (400 µg) in the 3 groups. The difference in compliance between 400 µg budesonide and placebo was statistically significant ($p < 0.01$).

Symptom scores

The mean daily nasal symptom scores during run-in are given in Table 2. Throughout the run-in period the pollen counts were low (Fig. 1) and symptoms were mild and almost identical in the 3 groups. Only treatment with 400 µg budesonide per day was associated with a significant improvement in symptoms. The mean severity in blocked nose was reduced with 0.4 ($p = 0.008$) and sneezing with 0.34 ($p = 0.002$) (Table 2). When the 3 nasal symptoms were combined the reduction from base line in total score was also statistically significant ($p = 0.002$) in the 400 µg group. However, the placebo group also improved to some extent so that the differences in changes in scores from baseline between 400 µg budesonide and placebo were only statistically significant for blocked nose ($p = 0.019$) and sneezing ($p = 0.046$).

Overall assessment

Table 3 shows the result of the overall assessment of treatment effect made by the children/parents at the end of the study period. Substantial or total control was achieved by 41% in the 400 µg group, by 33% in the 200 µg group and by 14% of the children receiving placebo. When the mean scores were compared there was a statistically significantly better score in the 400 µg group as compared with placebo ($p = 0.043$).

Terfenadine use

The mean weekly use of terfenadine during run-in was the same in the 3 groups: 1.84 (400 µg), 1.82 (200 µg) and 1.88 (placebo). During treatment the mean changes from baseline were -0.62 (400 µg) -0.36 (200 µg) and -0.03 (placebo) tablets per week. The differences between the various treatment groups were not statistically significant neither was there any significant changes when the individual groups were compared with baseline.

Rhinoscopy

Most of the objective signs aggravated during run-in and there were no differences between the 3 groups. During the treatment period statistically significant improvements were seen in all parameters except pus and hypertrophy of the chonchae for both budesonide groups ($p < 0.05$). However, significant improvements were also seen in hypertrophy, edema and secretion in the placebo group so that only the change in hypertrophy score was significantly better for the budesonide group than for placebo ($p < 0.05$).

Side effects

No serious side effects were reported and no drop-outs occurred due to an adverse event. Epistaxis was reported by 2 placebo patients and by 4 and 1 patients in the 200 µg and 400 µg budesonide groups.

There was no statistically significant difference in overnight cortisol excretion in the urine between the 3 treatment groups during run-in (400 µg = 18.5 mmol, 200 µg = 16.8 mmol and placebo = 13.6 mmol) or at the end of treatment (400 µg = 16.7 mmol, 200 µg = 15.7 mmol and placebo = 12.9 mmol). Furthermore, compared with run-in none of the treatments caused any changes in urine cortisol excretion. In agreement with this, no significant changes were observed in any of the other laboratory assessments.

Discussion

Because of the seasonal nature of the disease and the day-to-day variation in pollen counts which may occur, we used a placebo-controlled, parallel group design as recommended by others (2). Furthermore, since no dose response studies have been conducted in children, two different doses of budesonide were evaluated. Finally, pollen counts were recorded to assess the severity of exposure and to facilitate the interpretation of the results.

Under these conditions we found a dose-related effect on most parameters. However, only in children receiving 400 µg budesonide per day did the effect reach statistical significance. To our knowledge 200 µg budesonide once daily has not previously been evaluated in patients with rhinitis, whereas 400 µg per day has also been found effective in adults (3, 4). Though statistically significant the effect of 400 µg budesonide per day was not as impressive as the effect that was seen of the same dose of budesonide from a metered dose inhaler (5). The reason for this is not clear, it may be a coincidence but other factors may also be important.

There were marked differences in pollen counts during the treatment periods between the present study and the former MDI study. The pollen counts in the present study were lower than 100 pollen/m³ on 95% of the study days whereas they were between 100 and 250 pollen/m³ on 85% of the days in the MDI study. Obviously, a high pollen-exposure increases the chance of detecting significant and marked differences between treatments. When the symptom score is low during run-in and even tends to decrease a little during the placebo-treatment period it is difficult to improve the condition markedly. The majority of patients in the present study also participated in the MDI study, so we believe that the severity of disease was the same in the two patient populations.

Inhalation from a dry powder inhaler seems to result in a similar distribution of drug particles in the nostrils in adult patients as a MDI (6). In accordance with this studies in adults indicate that the Turbuhaler has the same effect as a metered-dose inhaler in the treatment of rhinitis (3, 4). In the present study some children found it difficult to inhale from the Turbuhaler because they suffered from some nasal obstruction in the morning when they inhaled the drug. To clarify the importance of this observation more studies are needed to assess the nasal inspiratory flow rates that various age groups of children with and without rhinitis can generate through the Turbuhaler.

We do not know how the dosing frequency has influenced the results. Dosing once daily is con-

venient and normally associated with a high compliance as in the present study. Some studies indicate that dosing once daily is as effective as dosing twice daily in the treatment of rhinitis (7). However, it is our clinical experience that some children with rhinitis require b.i.d. dosing to control their disease. This is probably a question of severity of the disease. The studies evaluating the efficacy of the Turbuhaler in adult patients with rhinitis have also used administration once daily with an apparently good effect (3, 4). In the dose-response study the maximal effect seemed to be achieved at a daily dose of 400 µg in patients with mild and moderate symptoms (3).

The occurrence of local side effects such as sneezing, dry nose and nose bleeding was low and did not differ from placebo treatment. The systemic side effect of an intranasal glucocorticosteroid seems to depend upon the administration form of the drug. Thus, the systemic availability of nasal administration of budesonide in aqueous suspension is around 100% (8) and from a MDI around 13% (pers. comm. ASTRA). The bioavailability of budesonide after nasal administration with a Turbuhaler is not known in children. Therefore, we also made careful evaluations of the systemic effect on various biochemical parameters and the HPA axis. These results indicated that even the highest budesonide dose was safe in children. The asthma treatment was kept constant throughout the study, so we do not believe that the difference between the three groups in the use of inhaled budesonide affected the interpretation of the urine cortisol data.

Conclusion

200 µg budesonide insufflated in each nostril from a Turbuhaler once daily is a safe and effective treatment against grass pollen induced rhinitis in children. Further studies are needed to evaluate whether this administration is preferable to the inhalers currently used for the treatment of rhinitis.

References

1. WİHL JA, ANDERSSON K-E, JOHANSSON SÅ. Påverkan av kortisol i urin av en engångsdos intranasal steroid. In: proceedings from XVII Nordiske kongres i Allergologi. Århus 17-19 May 1990: p. 146.
2. CLISSOLD SP, Rhinitis. In: BARNES PJ et al. Budesonide - clinical experience in asthma and rhinitis. Manchester: Adis Press 1988: 51-64.
3. PEDERSEN B, BUNDGÅRD LARSEN B, DAHL R, LINDQUIST N, MYGIND N. Powder administration of pure budesonide for the treatment of seasonal allergic rhinitis. *Allergy* 1991; 46: 582-7.

4. MALMBERG H, HOLOPAINEN E, SIMOLA M, BÖSS I, LINDQUIST N. A comparison between intranasal budesonide aerosol and budesonide dry powder in the treatment of hay fever symptoms. *Rhinology* 1991; 29: 137–41.
5. WOLTERS OD, JØRGENSEN BA, PEDERSEN S. A double-blind, placebo-controlled study of the effect of intranasal budesonide in the treatment of children with seasonal rhinitis. *Acta Pædiatr* 1992; 81: 902–6.
6. THORSSON L, NEWMAN SP, WEISZ A, TROFAST E, MORÉN F. Nasal distribution of budesonide inhaled via dry powder inhaler. *Rhinology* (in press).
7. RATNER PH, PAULL BR, FINDLAY SR et al. Fluticasone propionate given once daily for seasonal allergic rhinitis as beclometasone dipropionate given twice daily. *J Allergy Clin Immunol* 1992; 90: 285–91.
8. EDSBÄCKER S, ANDERSSON K-E, RYRFELDT Å. Nasal bioavailability and systemic effects of the glucocorticoid budesonide in man. *Eur J Clin Pharmacol* 1985; 29: 477–81.