

A Clinical Comparison of Aerosol and Powder Administration of Beclomethasone Dipropionate in Childhood Asthma

H. BISGAARD,¹ J. B. ANDERSEN,³ N. BACH-MORTENSEN,¹ A. BERTENSEN,³ B. FRIIS,¹ C. KOCH,³ P. PRAHL,⁴ R. WICHMANN⁵ and O. ØSTERBALLE¹

¹Childrens Allergy Clinic and ²Dept. for Cystic Fibrosis, Rigshospital, Copenhagen, ³Childrens Allergy Clinic, Frederiksberg County Hospital, ⁴Childrens Allergy Clinic, Gentofte County Hospital, and ⁵Childrens Allergy Clinic, Fuglebakken Hospital, Copenhagen, Denmark

Forty children with childhood asthma were conducted through a double-blind cross-over study to compare the effect of 400 µg beclomethasone dipropionate administered as aerosol and powder (Rotacaps). Children with severe asthma derived more benefit from the steroid administered as aerosol judged from their peak flow performance in the morning, although neither evening peak flow nor symptom scores revealed any difference. It is concluded that the Rotacaps are an advantageous supplement to available medication for the treatment of asthmatic children, although it should be observed that, using equal amounts of BDP, powder administration seems less effective than aerosol.

Key words: Aerosol; beclomethasone dipropionate; patient compliance; Rotacaps.

Accepted for publication 27 December, 1983

A certain proportion of asthmatic children cannot be adequately controlled on conventional anti-allergic therapy. For the treatment of these children steroids are essential. The occurrence of highly topically active steroids with low systemic effects has changed the indications for the use of steroids from a last refuge to a medication of high therapeutic index for relieving our most "heavy" asthmatics. As these steroids have so far been administered as aerosol, the inhalation technique is of the utmost importance. Up to 50% of adults use their inhalers inefficiently (2, 7). The coordination between the "firing" of the aerosol and the deep inspiration is an even greater problem for children. Only rarely is it possible to prescribe pressurised aerosol to children below 6 years of age.

Beclomethasone dipropionate (BDP) formulated as powder (Rotacaps®), and a simple device for its inhalation (Rotahaler®), might

enable a larger group of asthmatics, especially young children, to benefit from this medicine, as indicated in earlier studies (1, 3, 6, 8). Powder, however, might be expected to have a different distribution in the airways, and thus influence efficacy, potency, and adverse effects. For this reason we have conducted a double-blind cross-over study to compare the effect of BDP Rotacaps with BDP aerosols in a group of asthmatic children between 6 and 14 years of age.

Study design

The study was undertaken at five allergy clinics for children in Copenhagen. 45 children entered the study. Each child was given BDP aerosol (Aer) for 3 weeks, BDP Rotacaps (Rot) for 3 weeks, and Placebo (Plac) for another 3 weeks. The periods were ordered in three separate sequences: Aer → Plac → Rot, Rot → Aer →

Plac, and Plac $\rightarrow$ Rot $\rightarrow$ Aer. No washout periods were interposed. The children were randomly allocated to the three treatment sequences. Using a double dummy technique the trial was double-blind. Salbutamol aerosol was used as rescue medication. If a patient's asthma exacerbated to an extent which could not be controlled by increased use of salbutamol aerosol the code for that patient was broken. If the exacerbation occurred during a period of double placebo administration the patient was transferred to the next trial period. If the exacerbation took place during active BDP therapy the patient was withdrawn from the trial.

BDP was administered in daily doses of 400 μ g, either as 4 puffs of 50 μ g BDP b.i.d. or as one Rotacap of 200 μ g BDP b.i.d. The children were instructed to take their medication before breakfast and dinner.

Salbutamol aerosol was administered 5 min before the BDP and was the only concomitant medication allowed during the trial. However, in a few cases, the severity of the asthma demanded extra medicine, such as methylxanthines, or the patients were unwilling to give up a habitual medication. This medication was kept constant during the whole trial, in the 6 children concerned.

During a run-in period of 2 weeks the patients were treated with 200 μ g BDP aerosol b.i.d. At the same time they were trained in using the Rotahaler, peak flow meter, and in symptom scoring.

For each treatment period the children were given a diary card for daily evaluation of wheezing, cough, and dyspnoea. The symptoms were scored from 0–3. Peak flow (PF) was measured daily by a Mini-Wright calibrated flow meter (Airmed) in the morning before, in the evening before, and in the evening after salbutamol administration. Supplementary medicine was recorded daily. After each treatment period the patients were seen by one of the authors. At each visit the administration technique, peak flow monitoring technique, and the record-keeping were checked. The children were asked about any adverse effects related to the trial medication, and they were all checked for thrush. Cases of clinical candida had to be

confirmed by culturing. Finally, the lungs were examined stethoscopically. At the end of the trial preferences regarding the way of administration were sought.

It was chosen to evaluate symptoms and PF based on the records for 5 consecutive days at the end of each treatment period. This was to ensure that the trial medication had been taken for at least 10 days prior to the period of monitoring. The 5-day period is considered to be stable with regard to the steroid effect on the lungs.

To avoid any fluctuations in asthma due to pollen and mold exposure the trial was conducted in the months from November to February. All children and their parents were fully informed of the implications of the trial in accordance with the Helsinki II Declaration, and gave their informed consent.

Patients

Forty-five patients, who were all suffering from perennial asthma, entered the study. Approximately half were on BDP therapy before the trial. The remaining patients were clinically judged to be in need of steroid aerosol therapy. No subject had taken oral steroids within the last year. Except for two cases the asthma was considered to be allergic, as judged by a positive case history and skin tests.

Two patients were excluded during the run-in period due to inadequate control of their asthma on the trial medication. Three children were excluded during the trial because of serious asthma exacerbation: one child during the double placebo period and one during the period of active Rotacaps. The third child experienced serious exacerbation during the period of active aerosol after she had forgotten her medicine for 4 days. 11 children were transferred from the placebo period to the following period because of serious exacerbation of symptoms. 40 children completed the whole trial (21 girls and 19 boys). Age range from 6–14 years, 25% were 6–8 years of age. Median age at the time of asthma debut was 4 years.

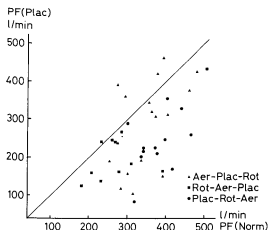


Fig. 1. PF during the placebo period compared with normal PF estimated from the height.

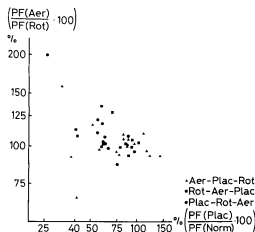


Fig. 2. The average morning peak flow during the period of active BDP aerosol (PF (Aer)) in per cent of the average morning peak flow in the period of active BDP Rotacaps (PF (Rot)), compared with the average-morning peak flow during the placebo period (PF (Plac)) in per cent of the mean normal peak flow (PF (Norm)).

RESULTS

In the majority of children the PF during the period of double placebo was well below normal, as estimated from their height (4) (Fig. 1). In Fig. 2 the values of PF (Aer) in per cent of PF (Rot) are compared with the corresponding values of the average morning PF in the placebo

period (PF (Plac)) in per cent of the mean normal PF (PF (Norm)) estimated from the height. The PF (Plac) in per cent of PF (Norm) may be interpreted as an estimate of the severity of the asthma. The figure shows a negative correlation between the two ratios. For the whole group of 40 children the regression coefficient is -0.21 ($P < 0.01$), i.e. in children with PF (Plac) corresponding to their normal PF no difference is observed between PF with aerosol and Rotacaps. For children with more severe asthma PF is improved on BDP aerosol compared with BDP Rotacaps.

It will appear from Fig. 2 that the three different sequences of BDP aerosol, BDP Rotacaps, and placebo administration intermingle uniformly around the estimated line of regression. The regression coefficients for the three sequences calculated separately coincide ($P \gg 0.05$). This indicates that no interaction between treatment and period has influenced the results.

No correlation was found between the PF (Aer) in per cent of PF (Rot) and PF (norm) in per cent of PF (Plac) on the basis of the PFs in the evening, and on the basis of the reversibility, i.e. PF after medication minus PF before medication.

No difference was observed between the Aer and Rot concerning the number of days with asthma symptoms (Table 1). Weighing of the symptom scores did not modify this result.

Candida confirmed by culturing was found only in one patient. The patient had at that time finished the double placebo period, and his symptoms vanished without therapy within 1

Table 1

Comparison between the frequency of dyspnoea, cough, and wheezing in the periods of placebo, BDP Rotahaler, and BDP aerosol

	Frequency (%) of days with symptoms		
	Dyspnoea	Cough	Wheezing
Plac	49.0	38.0	46.5
Aer	29.0	21.5	26.0
Rot	26.5	24.0	27.5
Aer	52 %	47 %	49 %
Aer + Rot			

week of the following period of active medication. Hoarseness was reported in one patient following the active BDP Rotacaps therapy, seven patients complained of cough: in four cases following active BDP Rotacaps therapy, one after active aerosol therapy, and two following placebo aerosol. 10 patients complained of irritation in the mouth following either active or placebo aerosol administration. Only one subject experienced irritation in the oropharynx after Rotacaps. Five subjects were, on one or more occasions, judged to have a poor inhalation technique. In four cases it was the aerosol technique that was poor. Three out of five cases of defaulting inhalation technique was found following the placebo period. Accordingly, defaulting inhalation technique could not have influenced the results significantly.

Preferences for the two administration forms were equally distributed, as 16 preferred Rotacaps and 18 aerosol. Six subjects were indifferent to the way of administration. Separating the study population into those of 6–8 years and those of 9–14 years revealed no preferences among youngsters for the Rotacaps (3 of 9 between the age of 6 and 8 versus 13 of 25 between the age of 9 and 14).

DISCUSSION

A double-blind cross-over design was chosen, although the problem of interaction is well known (5). In the present study this "carry-over" effect would have revealed itself by different regressions in the three treatment groups. We found, to the contrary, that the respective coefficients coincided, thus ruling out the possible interaction between treatment and period.

We found that a baseline for comparison of the child's improvement on BDP therapy was best made within the actual period of investigation rather than before, as childhood asthma runs a most labile course. Consequently, the placebo period was performed double-blind during the period of investigation. This design carries the obvious drawback that the selection

of children for the trial can be made only on clinical grounds, as the actual improvement on BDP therapy is first revealed after the trial.

Other studies have found BDP Rotacaps and aerosol to be equally effective when given in equal amounts (3, 8), but only one previous study (3) was double-blind and included only 14 children clinically judged to require treatment with BDP. Comparison of the symptom scores revealed a significant improvement during the period with active BDP aerosol. Other parameters revealed no difference between the administration forms. The authors concluded that the two devices for delivering BDP were equally good. As improvement on BDP therapy was not shown during a period of double placebo the design carries a high risk of type II fault.

We find in our study that the difference in effect between the two formulations is revealed only in children with a more severe asthma. The inclusion of a large number of patients who either do not respond to, or derive only little benefit from BDP, would tend to mask the difference in effect found among patients with a more severe asthma. This might be the reason why the previous studies did not find any difference between Aer and Rot.

Studies comparing BDP aerosol with a double amount of Rotacaps have also concluded that no difference is seen (1, 6). These studies, performed on adults, also lacked a placebo period, thereby carrying a similar risk of type II fault.

In the present study only the level of the morning PF before medication showed any difference between the two ways of administration. Neither the PFs in the evening nor the symptom scores revealed any difference between aerosol and Rotahaler administered BDP. Judged from these morning PF measurements the efficacy of BDP aerosol seemed better than that of the BDP Rotahaler, as it was seen in the children with a more severe asthma. The difference could be caused by a lack of potency or a lack of efficacy in the powder. A dose-response study would be needed to clarify this point. To the knowledge of the authors such a study has never been published. The manufacturers recommend that Rotacaps should be given at twice the dosage of the aerosol. Whether this could make up for the

reduced effect found for the BDP powder is not known.

An advantage with Rotacaps is the avoidance of fluocarbon propellants, which are suspected to sensitize the heart to catecholamines. More important is that many poor coordinators who are unable to use the aerosol reliably can use the Rotahaler satisfactorily.

In conclusion, we find the BDP Rotacaps to be an advantageous supplement to the available medication for the treatment of asthmatic children, although it should be observed that, using equal amounts of BDP, powder administration seems less effective than aerosol.

ACKNOWLEDGEMENTS

The authors are greatly indebted to Flemming Abildgaard, statistician, for his invaluable help. Glaxo Denmark is acknowledged for supplying the means for this trial.

REFERENCES

1. Chatterjee, S. S. & Butler, A. G.: Beclomethasone dipropionate in asthma: a comparison of two methods of administration. *Br. J. Dis. Chest* 74, 175-179, 1980.
2. Coady, T. J., Stewart, C. J. & Davies, H. J.: Synchronization of bronchodilator release. *Practitioner* 217, 273-275, 1976.
3. Edmunds, A. T., McKenzie, S., Tooley, M. & Godfrey, S.: A clinical comparison of beclomethasone dipropionate delivered by pressurized aerosol and as a powder from a Rotahaler. *Arch. Dis. Child.* 54, 233-235, 1979.
4. Godfrey, S., Kamburoff, P. L. & Nairn, J. R.: Spirometry, lung volumes and airway resistance in normal children aged 5-18 years. *Br. J. Dis. Chest* 64, 15-24, 1970.
5. Hills, H. & Armitage, P.: The two-period cross-over clinical trial. *Br. J. Clin. Pharmacol.* 8, 7-20, 1979.
6. Lal, L., Malhotra, S. M., Gribben, M. D. & Butler, A. G.: Beclomethasone dipropionate aerosol compared with dry powder in the treatment of asthma. *Clin. Allergy* 10, 259-262, 1980.
7. Paterson, J. C. & Crompton, G. M.: Use of pressurized aerosols by asthmatic patients. *Br. Med. J.* 1, 76-77, 1976.
8. Smith, J. M. & Gwynn, C. M.: A clinical comparison of aerosol and powder administration of beclomethasone dipropionate in asthma. *Clin. Allergy* 8, 479-481, 1978.

Address:

Hans Bisgaard

Childrens Allergy Clinic 5003

The University Hospital

Blegdamsvej 9

DK-2100 Copenhagen

Denmark

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.