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Nebulized budesonide after hospitalization for recurrent bronchial obstruction in children younger than 18 months

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A multi-center, double-blind, randomized dose–response study was performed to assess the effect of 3 months of treatment with two different doses of inhaled nebulized budesonide in children with acute recurrent bronchial obstruction (BO) causing hospitalization. Steroid-naive children younger than 18 months were included when admitted to hospital because of BO for at least the second time, and were followed-up monthly for 15 months. Forty-five of 49 subjects (43 boys, 2 girls) (mean age 9.3 months upon inclusion) completed the study. Twenty-four patients (20 boys, 4 girls) received nebulized budesonide 0.5 mg twice daily for 1 month followed by 0.25 mg daily for the next 2 months, whereas 25 children received 0.1 mg twice daily throughout the 3-month treatment period. Outcome (number of BO episodes, time to first BO after start of treatment, and use of rescue medication), as well as height/length and weight, were assessed at the start of treatment and monthly for the following 3 months, as well as for 12 months after cessation of treatment (15 months in total). There was an overall tendency towards better symptom control (fewer episodes of acute BO during treatment and follow-up, fewer hospital visits because of acute BO, lower clinical score during follow-up, and less use of rescue medication during follow-up) in the high-dose treatment group vs. the low-dose treatment group. However, the differences did not reach statistical significance for any of the outcomes. The only significant difference in effect between the groups was fewer children in the high-dose group treated openly with nebulized budesonide during follow-up. Length/height and weight gain did not differ significantly between the two treatment groups throughout the study. There was no significant dose-dependent beneficial effect of 3 months of treatment with nebulized budesonide in infants and toddlers with at least two hospitalizations for acute bronchial obstruction.

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Key words: inhaled nebulized budesonide; recurrent bronchial obstruction; wheeze; young children; hospital admission

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Acute bronchial obstruction (BO) (or wheeze) may affect as many as 25–30% of children younger than 3 years of age (1). In infants and children younger than 2 years of age, bronchiolitis occurs frequently, commonly as a result of infection with respiratory syncytical virus (RSV), and predominantly in typical winter epidemics: in Oslo this usually starts during November or December and reaches a peak in January (2). Clinical signs of bronchiolitis resemble those found in older children experiencing an acute asthma attack. Therefore, it can be difficult to distinguish between the two different etiologies. Furthermore, although still unclear (3–5), an association between early bronchiolitis and development of asthma has been demonstrated, with one study showing 30% of children with bronchiolitis developing asthma by 10 year of age (6).

As stated by Aas in 1981 (7), the common symptom entity of BO probably represents different etiologies. Whereas acute bronchiolitis,

as well as other lower respiratory tract infections, are the most common causes of wheeze among children younger than 2 years of age, atopic asthma is the major cause of wheeze in children of school age. Wheeze also occurs more often in children younger than 3 years of age than in school-age children (8,9). However, during the first few years of life, it is difficult to distinguish children with recurrent wheeze who will stop wheezing before school age from children with an underlying asthma. Both groups of children have attacks elicited by viral respiratory tract infections (10,11), as well as prolonged respiratory symptoms after a respiratory tract infection. However, treatment has, in general, followed guidelines based upon disease activity, and symptom frequency and severity, in the absence of criteria to discriminate between different underlying causes (12).

Some studies have demonstrated beneficial effects of inhaled glucocorticosteroids upon symptoms and disease activity in infants and young children with recurrent wheeze (13–15), whereas others have not (16). Furthermore, little is known about the lowest effective dose of inhaled steroids that might be appropriate in these young infants and children.

The aim of the present study was therefore to assess possible dose-dependent effects of inhaled glucocorticosteroids upon obstructive airways disease in young children.

Subjects and methods

Study design

A randomized, double-blind, parallel-group multi-centre study, with an active treatment period of 3 months and a follow-up period of 12 months, was performed in four centres in Norway between January 1990 and September 1993. Randomization, to ensure equal distribution in the severity of disease, was by block design at the size of two after stratification into three groups, depending upon the number of episodes of BO (two, three to four, or more than four) prior to inclusion.

The inclusion criterion was at least two episodes of acute BO leading to hospitalization in children younger than 18 months. BO was defined as the presence of at least three of the following signs: wheezing; expiratory dyspnoea; inspiratory chest recessions; rapid respiratory rate (>40/min); audible rales; or sibilating rhonchi.

Exclusion criteria were: any major disabling disease (malignant disease, immunodeficiency, cerebral palsy, severe congenital cardiac malformation or other malformation); children whose parents were unlikely to attend the clinic visits (consultations or admissions); administration of systemic glucocorticosteroids during the previous 2 months; or a prolonged course (at least 0.75 mg/kg every other day for 6 days) of systemic glucocorticosteroids at any time.

The 24 infants randomized to the high-dose group received a daily dose of 1 mg (0.25 mg/ml, 2 ml twice daily) of nebulized budesonide for 1 month and then 0.5 mg (0.125 mg/ml, 2 ml twice daily) of nebulized budesonide per day during the subsequent 2 months. The 25 infants in the low-dose group received a daily dose of 0.2 mg (0.05 mg/ml, 2 ml twice daily) of nebulized budesonide during the 3-month treatment period.

The patients were assessed clinically according to a score system (Table 1) at monthly visits (throughout the study) as well as whenever they had symptoms of respiratory infection or BO. (Chest X-ray was not performed routinely in our department, being carried out only when suspicion of complications, such as pneumonia, atelectasis, etc., arose.) Rescue medication (mostly nebulized β2-agonist) was taken on an as-required basis, administered by the parents. The use of rescue medication – nebulized β2-agonist (0.1 ml of a 5-mg/ml salbutamol solution/10 kg of body weight, prepared in 2 ml saline, maximum every 3 h), occasionally nebulized racemic epinephrine (0.1 ml of a 20-mg/ml solution in 2 ml saline), and infrequently theophyllin (a rectal solution of 50 mg, one to three times per day if severe BO occured) – was recorded as the mean number of doses per day, at every clinic visit throughout the duration of the study.

On inclusion and at the end of the follow-up period, a skin-prick test and evaluation of total serum immunoglobulin E (IgE) were performed in all patients. Blood samples for analyses of safety parameters (hematology, liver function tests) were collected on inclusion, at the end of treatment, and at completion of the study.

Ethical consideration

The Regional Ethical Committee did not allow the use of placebo when the study was started (1990) because of published encouraging results for inhaled steroid treatment of very young children with asthma (13, 17–18). The present study (as described above) was, however, approved by the ethical committee, and all subjects were included after written, informed consent of the parents was obtained. The study was performed in accordance with the guidelines of the declaration of Helsinki.

Table 1. Clinical score used during each clinical visit during the study

	0	1	2
Respiratory rate	0<40	40–59	≥60
Bronchial obstruction	None	Moderate (prolonged expiration, moderately wheezing, audible rales)	Marked (rib recessions, use of accessory respiratory muscles, marked wheezing)
General condition	Not affected (normal activity)	Moderately affected (pallid)	Severely affected (cyanotic or lying quite still)
Chest X-ray	Normal or not performed	Over-inflation or increased translucency of the lungs	Signs of consolidations or atelectasis

Methods

Eligible patients were recruited successively during admission to hospital for BO, and were invited to attend the inclusion visit. Budesonide suspension (AstraZeneca, Lund, Sweden) was supplied in 100-ml bottles in three concentrations: 0.25 mg/ml, 0.125 mg/ml, and 0.05 mg/ml. Parents were carefully instructed to rotate the bottles to ensure even distribution, and returned the bottles after each of the treatment months for assessment of compliance, which was determined by weighing the bottles. With a high-precision pipette, the parents placed 2 ml of budesonide suspension from the bottle into a system 22 Acorn nebuliser system (CR60 compressor, Mizer inhalation spacer, Vital Signs air-inflated soft plastic face mask; all Medic-Aid, Ltd, Bognor Regis, UK), as previously described (19). The facemask was kept firmly on the face, covering the nose and mouth, whilst the budesonide suspension was nebulized until dryness (≈ 5 min). The faces of the patients were wiped clean with water, and the nebulisers were washed with a soap detergent after each nebulization.

The same nurse at each center measured the length/height and weight of each child on each occasion using the same equipment. Length was measured supine on a board scale until the child was able to stand correctly, and thereafter height was measured by wall scale, positioning the child with his/her back against the wall with nude feet. Weight was measured on the digital scale available in the out-patient clinic, with the child wearing panties only.

The following parameters were assessed during every visit: clinical score (Table 1); length/height and weight; and, for the previous month, average daily doses of asthma medication as well as any other medication, any acute out-patient visits or hospital admissions, any disease (whatever cause) and possible side-effects.

Tests for atopy

The presence of atopy was assessed (on visits 1 and 16) by using a skin prick test (Phazet Pharmacia, Uppsala Sweden), and the patient was judged as atopic when a wheal was obtained that was at least 50% of the wheal size of the histamine control (Phazet Pharmacia), corresponding to 3–5 mg of histamindihydrochloride and/or specific IgE (radioabsorbent test Phadebas PRIST; Pharmacia) to common inhalant allergens (house dust mite – *Dermatophagoides* p1 [Der p1] – cat, dog, grass pollen, birch pollen, mugwort, and cladiosporum) as well as to hen egg-white, cow's milk, and hazel (nut).

Subjects

Forty-nine children (43 male, five female), mean age 9.2 months (range 1–17 months), were included in the study; 45 of these children completed the study. Mean age (range) at first reported lower respiratory tract infection was 4.5 months (1–11 months); number of reported episodes of BO was 4.5 (1–15); and the number of hospitalizations as a result of BO, prior to inclusion in the study, was 2.4 (1–5). At the time of inclusion, the mean number of days of the current BO was 17.9 (range 0–120). Upon inclusion there were no significant differences between the high-dose and the low-dose groups regarding gender, age, weight or length (Table 2), number of episodes of BO or hospitalizations as a result of BO, family history of atopic disease, or parental smoking habits.

Nasal aspirate for rapid immunofluorescence analysis of viral infections, analyzed locally upon inclusion at each site, was positive for RSV in eight of 36 children (three in the high-dose group) and for adenovirus (not serotyped further) in one child in the low-dose group.

One child in the high-dose group had persistent sensitization to hen egg, whereas in the low-dose group five children (three on both visits) were sensitized to hen egg at inclusion and one child to hazelnut at visit 16. Inhalant allergies (to Der p1 in one child and to dog in two others) were found in three children in the high-dose group at inclusion, but not at the end of the study, whereas three children in the low-dose group were sensitized (to cat or dog) at the end of the study only. The presence of atopic dermatitis was reported in two children of the high-dose group and in six children of the low-dose group.

Table 2. Demographic data upon inclusion of children in the high-dose vs. the low-dose treatment groups

	High dose* [mean (SD)]	Low dose† [mean (SD)]	p-value
Age (months)	9.30 (3.80)	9.20 (4.20)	0.93
Weight (kg)	9.37 (1.92)	8.85 (1.59)	0.44
Length (cm)	73.00 (6.30)	70.80 (5.10)	0.10

*n=24.
†n=25.

Four patients (two in each group) discontinued the active treatment period: one was excluded owing to non-compliance and the other three withdrew as a result of parental decision from causes unrelated to the drug. There were no treatment discontinuations owing to lack of efficacy or adverse effects.

Statistical analyses

The sample size was based on the outcome of a similar study (a placebo-controlled study of beclomethasone diproprionate [see ref. 13], in which a sample size of 44 children was sufficient to obtain p-values of $\approx 1\%$), rather than on an explicit power calculation. All analyses were based upon all patients treated. The two treatment strategies were compared using the Wilcoxon rank sum test for counted variables and the unpaired *t*-test (assuming equal variances) for the remaining variables. Survival-type variables were analyzed using Gehan's test. No adjustment for center or strata was performed. Results are given as mean (SD) unless stated otherwise.

The effect of treatment strategy was investigated separately for the 3-month treatment period and the follow-up, with the exception of the survival variables. The end-point in the analysis was the total number of events during the period, the value at the end of the period, or the change during the period, whichever was most appropriate. A p-value of less than 5% was considered statistically significant, and all analyses were two-tailed. No interim analysis was carried out.

Results

There was an overall tendency towards better symptom control in the high-dose treatment group vs. the low-dose treatment group (Table 3). The low-dose group had a mean of 4.32 episodes of BO during active treatment and 12.68 during follow-up as compared to 3.92 and 10.48, respectively, in the high-dose group. The mean number of acute visits to hospital (for the whole study group) for BO were 0.96 and 1.72 during active treatment and follow-up, respectively, with corresponding values of 0.71 and 1.09 for the high-dose group. The mean number of days to the first episode of BO, was lower (31 days) in the high-dose vs. the low-dose group (41 days). However, this was largely because of one child in the low-dose group who had 271 days to the first BO. Children in the low-dose group used, on average, more rescue medication (β2-agonists) during the last months of follow-up compared to the high-dose group. However, none of the differences between treatment groups for any of these outcomes reached statistical significance.

Nine children in both treatment groups were treated with nebulized budesonide (not blinded) during follow-up. However, among these children, the average number of visits with budesonide treatment was significantly lower in the high-dose group (5.22) compared to the low-dose group (8.11) ($p = 0.02$).

The mean increase of height/length during treatment was 4.2 cm (1.9 cm) in the high-dose group compared to 4.8 cm (2.5 cm) in the low-dose group, and 15.68 cm (3.79 cm) vs. 16.45 cm (3.94 cm), respectively, during follow-up. The corresponding results for weight gain were 1.21 kg (0.80 kg) vs. 1.09 kg (0.57 kg) during active treatment and 4.06 kg (1.62 kg) vs. 3.66 kg (1.19 kg) during follow-up, respectively. None of these differences reached statistical significance (Table 3).

Serious adverse events were reported in 11 patients on 15 occasions; all were episodes of BO or respiratory infections. No clinically significant abnormal changes were found in any of the blood analyses.

No obvious non-compliers were detected by weighing the bottles.

Discussion

The present study was unable to demonstrate any significant dose-dependent effect of nebulized inhaled budesonide in children with recurrent hospitalizations caused by BO. However, there was a tendency in favor of high-dose nebulized budesonide (0.5 mg twice daily for 1 month and 0.25 mg twice daily in the subsequent 2 months)

Table 3. Outcome after 3 and 12 months of follow-up of high- vs. low-dose treatment with nebulized budesonide in children with recurrent hospital admissions for bronchiolitis

	High dose [mean (SD)]	Low dose [mean (SD)]	p-value
Number of BO episodes during			
Active treatment (3 months)	3.92 (3.50)	4.32 (3.16)	0.53
Follow-up period (12 months)	10.48 (7.36)	12.68 (8.03)	0.28
Days to first BO	31.0 (37.7) 7–174 (range)	41.3 (59.4) 3–272 (range)	0.91
Clinical score at visit			
1 month of treatment	0.92 (1.32)	0.80 (0.1)	0.73
3 months of treatment	0.42 (0.65)	0.48 (0.82)	0.78
End of study	0.00 (0.00)	0.18 (0.50)	0.09
Daily dose of $ß_2$-agonist last month			
3 months of treatment	1.14 (1.25)	0.84 (0.91)	0.35
End of study	0.58 (0.91)	1.16 (1.43)	0.13
Number of acute visits during			
Treatment	0.71 (1.04)	0.96 (0.98)	0.25
Follow-up	1.09 (1.53)	1.72 (1.74)	0.12
Number of follow-up visits with current use of			
Disodium-chromoglycate	5.25* (4.19)	3.60† (2.19)	0.50
Budesonide‡	5.22 (2.49)	8.11 (2.93)	0.02
Number of hospitalizations (whole group) during			
Active treatment (3 months)	1.71 (2.07)	2.32 (2.50)	0.43
Follow-up period (12 months)	3 17 (3.68)	4.24 (3.81)	0.19
Weight (kg)			
1 month of treatment	9.00 (3.08)	9.38 (1.47)	0.84
3 months of treatment	10.69 (1.87)	9.94 (1.38)	0.11
1 month of follow-up	10.93 (1.88)	10.19 (1.27)	0.12
End of follow-up	13.54 (2.36)	11.66 (1.37)	0.29
Length/height (cm)			
1 month of treatment	73.6 (7.9)	73.2 (5.4)	0.51
3 months of treatment	77.7 (5.4)	75.8 (4.9)	0.13
1 month of follow-up	78.4 (5.4)	77.1 (4.6)	0.34
End of follow-up	88.9 (5.2)	88.2 (4.4)	0.78

*n=4; †n=5; ‡n=9 in both groups.

compared to 0.1 mg twice daily for 3 months, in relation to symptom control.

The lack of significant differences between the high-dose and the low-dose groups, in any of the main outcomes, may have several explanations. The first possibility is that both treatment dosages are equally effective, although our data indicate slightly better results in the high-dose group. Supporting our results, a similar lack of dose–response has recently been reported using dose-titration techniques of nebulized budesonide, and a minimal effective dose could not be defined by Wennergren et al. (20). Vikre-Jørgensen et al. reported a minimal effective dose in the range of 0.5–2.0 mg of nebulized budesonide (nominal dose), but without significant differences in dose effectiveness in this range (16). Also, in a 12-week standardized dose–response study, Baker et al. (21) could not demonstrate significant differences in clinical outcome between 0.25 mg of nebulized budesonide once daily and doubling doses to a maximum dose of 1 mg per day. Volovitz et al. (22), on the other hand, demonstrated a significantly better clinical effect after 1 week of treatment with an initial high dose (2 mg of nebulized budesonide daily tapering with 25% every second day) compared to 0.5 mg daily, but with no significant differences in effect during the 9-week follow-up. In a 12-week study, Shapiro et al. (23) found a significant effect of all three doses of nebulized budesonide (0.5, 1.0 and 2.0 mg daily) compared with placebo in an older group of children (4–8 years) with established asthma. Although the patients in the latter study differed from ours in having established asthma, there is support (16,20–23) for suggesting that both dosage regimens in the present study may be effective.

Lack of dose-related differences could be the result of both doses being ineffective. Optimally, this should have been investigated as a double-blind placebo-controlled study. Unfortunately, in the present study, a placebo group was regarded as unacceptable by the Regional Medical Ethical Committee. Other groups, on the other hand, have demonstrated clinical effect upon asthma symptoms of inhaled budesonide compared to placebo (13,14,18,24). Therefore, lack of clinical effect of both dosage regimens seems less likely to explain the results of the present study.

Without acceptance for a placebo group, the daily dose of 0.2 mg of nebulized budesonide for 3 months was considered at the start of the study (1990) to be such a low dose that it was unlikely to have any major impact on the respiratory tract. This view has subsequently been challenged. Baker et al. reported significant clinical efficacy for 0.25 mg of nebulized budesonide compared to placebo (21). Several other studies with placebo or control groups have reported beneficial effects upon symptoms in very young children with recurrent BO leading to hospitalization (13,14,18,24); however, this is not the case in all studies (25). Dosages in the studies reporting beneficial effects ranged from 0.25 mg (21) to 2.0 mg (14) of budesonide daily.

Another explanation for the lack of dose-dependent efficacy could be related to the route of administration. This issue was, however, addressed early in the study, whence the proportion of the nominal dose available at the opening of the respiratory tract was assessed (19). Depending on age, from nine to 19% of the nominal dose was available for inspiration from the nebuliser equipment. With this in mind, the low-dose group would at best receive ≈ 0.04 mg budesonide per day. On the other hand, similar routes of administration were used in several of the studies reporting an effect of inhaled glucocorticosteroids. Therefore, inefficient administration of budesonide is an unlikely explanation for the lack of differences in the two groups.

A further possibility is that inhaled glucocorticosteroids may be effective only in those children who are destined to later develop asthma, but with no beneficial effect in recurrent wheezers with other pathogenetic underlying causes. Six children in the low-dose group had atopic dermatitis compared to two children in the high-dose group, and only three children in the low-dose group were sensitized to inhalant allergens at the end of the study. This may indicate that risk factors for future asthma were present in a greater number of children in the low-dose group. However, the number of atopic subjects was so low that no sub-group analyses could be performed to evaluate whether or not atopy influenced the results. With the exception of risk factors, during infancy there are no definite methods for characterizing asthma from several other obstructive airways diseases. It is therefore not possible in the present study to distinguish between different etiologies. With the possible exception of atopy favoring asthma, it is probable that possible etiologies are represented similarly in the high- and low-dose groups. Thus, in order to demonstrate possible statistically significant differences, a much greater number of children may be required than calculated for the present study. This is in line with the findings of Vikre-Jørgensen et al. (16), who demonstrated large individual variation in the minimal effective dose of budesonide. The tendency for better outcome in the high-dose group in the present study supports this view.

Lack of dose-dependent differences in relieving symptoms of asthma could be caused by the inadequate number of subjects enrolled. However, Volovitz et al. found a dose-dependent clinical efficacy in a study of 42 children (22), and Noble et al. demonstrated the effect of budesonide (by a large volume spacer) in a study of only 15 subjects younger than 18 months of age (26). Therefore, an inadequate number ($n=49$) of subjects in the present study cannot be ruled out but is a less likely explanation for the lack of dose-dependent effects.

The present study did not show any significant difference in length/height or weight gain during the treatment or follow-up periods. However, the study was not designed to assess small differences in weight and length/height gain, and therefore our measurements of length/height and weight may not be sufficiently sensitive or precise (26) to discriminate small differences. However, measurements were performed similarly in each individual during every visit and are therefore potentially valuable as indicators of possible systemic effects of inhaled glucocorticosteroids.

No obvious non-compliers were detected by the weighing of the returned budesonide suspension bottles. Also, the parents were encouraged to call or visit the clinic on every occasion of BO or respiratory tract infection in addition to the monthly visits. Hence, there was relatively close contact between the investigators and parents to ensure the best possible compliance.

The present study did not demonstrate significant dose–response effects after 4–12 weeks of treatment. This is in agreement with several other studies (16,21–23). Volovitz et al. (22), on the other hand, studied the effect of nebulized inhaled budesonide during the first week of treatment commencement, during which time there was a significantly better clinical outcome in the high-dose group. However, this difference was not sustained during the next 9 weeks. This may indicate that in children with severe BO, where rapid symptom relief is important, an initial high dose may be preferable. Also, our study did not demonstrate significant systemic effects within the dose range of 0.2–1.0 mg of budesonide within this age group. However, as demonstrated in the present study, in other

circumstances, a low dose of inhaled nebulized budesonide may be justifiable.

In conclusion, the present study did not demonstrate statistically significant dose-dependent differences during 3 months of treatment with nebulized budesonide in young children hospitalized with recurrent BO. However, there was a tendency for fewer hospitalizations and less use of anti-asthmatic medication in children treated with the highest doses of nebulized budesonide.

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