

EFFECT OF INHALED BECLOMETHASONE DIPROPIONATE IN THE TREATMENT OF RECURRENT WHEEZING IN INFANCY AND EARLY CHILDHOOD

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Forty-one children, aged six to 36 months (mean, 23.3 months), with a past history of acute bronchiolitis with or without recurrent wheezing episodes were treated with either a beclomethasone dipropionate metered dose inhaler 150 µg twice daily, or a placebo for 12 weeks. Aerosols were inhaled through an AeroChamber (Trudell, Canada) using a mask. The patients were followed up biweekly. The two groups were well matched in anthropometric data and frequency of wheezing prior to the study being undertaken. At the end of four to six weeks, the beclomethasone dipropionate treatment group showed a significant improvement in both wheezing and sleep patterns, and systemic steroid therapy was able to be tapered. No significant side effect could be ascribed to this treatment.

(J Formos Med Assoc
1992;91:1066-9)

Key words:
beclomethasone dipropionate
bronchiolitis
AeroChamber
wheezing infants

Acute bronchiolitis in infancy is most often associated with respiratory syncytial viral infection. Three-quarters of these infants have recurrent coughing and wheezing episodes [1]. Recurrent wheezing and dyspnea may be difficult to treat in children under three years of age, and is a major cause of illness and admission to children's hospitals. Bronchodilators such as beta agonist, theophylline and ipratropium bromide are seldom helpful in children younger than 18 months [2, 3]. Inhaled glucocorticoid has been proven effective and safe in treating childhood and adult asthma [4, 5]. However, adequate delivery of aerosolized topical beclomethasone dipropionate to infants or young children may be difficult.

We have investigated whether inhaled topical beclomethasone dipropionate (BDP) from a metered dose inhaler (MDI) through a spacer with an attached mask could be used effectively in infants and young children with recurrent wheezing attacks after acute bronchiolitis.

Materials and Methods

Forty-one children with recurrent wheezing episodes, aged between six and 36 months, were randomly allocated to receive either placebo (21 patients) or beclomethasone dipropionate (20 patients) in a double-blind study. Included patients fulfilled the following criteria: 1) a past history of hospital admission with acute bronchiolitis; and 2) a history of at least two or more wheezing episodes after the initial bronchiolitis. No attempt was made to identify the underlying causes of wheezing, such as respiratory syncytial viral infection. Children were not included in this study if they had received oral or inhaled glucocorticosteroids or cromolyn during the month before the study.

Patients were randomized to receive 12 weeks' treatment with either BDP 150 µg twice daily (three 50 µg puffs) or a placebo from an MDI.

Aerosol was administered through a facemask at

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Received: June 3, 1993. Revised: July 2, 1993. Accepted: September 7, 1993.

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tached to a spacer (AeroChamber with mask, Trudell Medical, Canada) from an MDI (Figure). Children were allowed to breathe through the spacer for 30 seconds after each puff from the MDI. The spacer volume was 145 mL.

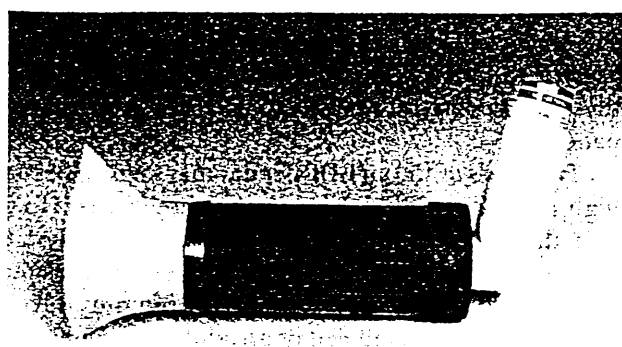


Figure. AeroChamber with mask and MDI.

Daily symptoms were assessed and recorded by each child's parents, who were instructed to assess wheezing, sleep disturbance caused by wheezing or severe coughing, and daytime and nocturnal coughing. These children were followed up biweekly to evaluate their inhaling technique. They were permitted to take oral or inhaled beta agonist, theophylline, and inhaled ipratropium bromide. Short courses of oral

prednisolone (1 mg/kg/day for three to five days) were prescribed if severe bronchopulmonary obstruction occurred during the study.

Data were analyzed using Student's *t* test. It was considered statistically significant when the corresponding *p* values were less than 0.05.

Results

Twenty children were randomized to receive BDP and 21 to receive placebo. In these two groups, no significant difference existed in anthropometric data, eczema, positive family history of atopy, smoking, and the level of immunoglobulin E (Table 1). The severity of previous bronchopulmonary obstruction was similar, and there was no significant difference in the frequency of hospitalization and the amounts of prescribed prednisolone.

No patient was withdrawn from this study. The symptoms improved significantly following BDP treatment. At the end of the fourth week, the episodes of wheezing in the treatment group was only one half that of the placebo ($p = 0.02$; Table 2). Sleep disturbance from severe coughing or wheezing had also decreased. Significant differences between the treatment and placebo groups were noted after six weeks of active treatment (Table 3).

Table 1. Clinical data of children treated with inhaled beclomethasone dipropionate and placebo

	Placebo mean $\pm$ SD	Beclomethasone mean $\pm$ SD
Age (months)	23.7 $\pm$ 7.8	22.7 $\pm$ 8.3
Body weight (kgs)	11.8 $\pm$ 2.3	12.3 $\pm$ 2.1
Birth weight (kgs)	3.2 $\pm$ 0.5	3.3 $\pm$ 0.7
Sex (male/female)	13/8	14/6
Past history		
hospital admission (times)	1.5 $\pm$ 0.8	1.3 $\pm$ 0.7
prednisolone (mgs)	12.5 $\pm$ 3.4	11.4 $\pm$ 4.0
days of prednisolone	8.1 $\pm$ 2.4	7.8 $\pm$ 2.2
eczema	3	3
Family history		
atopy in first-degree relatives		
nasal allergy	3	3
asthma	3	4
eczema	4	2
smoking parents	6	5
IgE (IU/mL)	386 $\pm$ 585	406 $\pm$ 617

Table 2. Accumulated episodes of wheezing attacks during treatment for 12 weeks

Week	Placebo mean $\pm$ SD	Beclomethasone mean $\pm$ SD	<i>p</i> value
2	0.4 $\pm$ 0.5	0.4 $\pm$ 0.5	0.45
4	1.2 $\pm$ 0.6	0.7 $\pm$ 0.7	0.02
6	1.5 $\pm$ 0.7	0.8 $\pm$ 0.7	0.005
8	2.0 $\pm$ 0.6	0.9 $\pm$ 0.6	< 0.005
10	2.3 $\pm$ 0.7	0.9 $\pm$ 0.6	< 0.005
12	2.7 $\pm$ 0.8	1.0 $\pm$ 0.7	< 0.005

Table 3. Accumulated nights with sleep disturbance during treatment for 12 weeks

Week	Placebo mean $\pm$ SD	Beclomethasone mean $\pm$ SD	<i>p</i> value
2	1.8 $\pm$ 0.9	2.0 $\pm$ 0.9	0.42
4	3.6 $\pm$ 1.2	2.9 $\pm$ 1.2	0.06
6	4.8 $\pm$ 1.1	3.5 $\pm$ 1.4	< 0.005
8	6.3 $\pm$ 1.4	3.8 $\pm$ 1.7	< 0.005
10	7.6 $\pm$ 1.4	4.3 $\pm$ 1.8	< 0.005
12	8.9 $\pm$ 1.5	4.7 $\pm$ 1.8	< 0.005

Table 4. Accumulated doses of prednisolone administered during treatment for 12 weeks

Week	Placebo mean $\pm$ SD (mg)	Beclomethasone mean $\pm$ SD (mg)	p value
2	2.8 $\pm$ 3.4	3.0 $\pm$ 3.4	0.41
4	7.0 $\pm$ 3.4	5.8 $\pm$ 3.4	0.13
6	12.5 $\pm$ 3.5	7.6 $\pm$ 3.1	0.005
8	16.0 $\pm$ 3.5	10.0 $\pm$ 4.6	< 0.005
10	19.3 $\pm$ 4.7	10.8 $\pm$ 4.4	< 0.005
12	22.8 $\pm$ 4.9	13.0 $\pm$ 4.4	< 0.005

The control group had significantly more bronchopulmonary obstructions, as evidenced by the amount of prednisolone administered, after six weeks of active treatment (Table 4).

The full effect of BDP treatment could be seen after four to six weeks of treatment. No patient suffered from side effects such as hoarseness or oral or nasal candidiasis.

Discussion

The inhalation of steroids has been used in the treatment of bronchial hyperreactivity. However, the mechanisms of its action are complex and not fully understood [6]. Carlsen et al [7] reported 22 children who had acute bronchiolitis treated with nebulized BDP. The patients experienced fewer episodes of wheezing and received less bronchodilator treatment after receiving inhaled BDP for eight weeks. The effect of BDP persisted for several weeks beyond the treatment period. In infants with persistent wheezing, significant improvement in tachypnea, chest retraction, wheezing and airway conductance was found after treatment with nebulized BDP for only two weeks [8], but this effect disappeared rapidly after BDP treatment ceased. In this study, there was significant therapeutic improvement after four to six weeks of BDP treatment, evaluated by the frequency of wheezing, disturbance of sleep and amount of oral prednisolone required to control symptoms. As the trial continued, the difference in the severity of symptoms between the two study groups reached statistical significance. This result was similar to that reported by Bisgaard et al [9].

Although BDP can be effectively inhaled by older children, adequate delivery to infants and young children is difficult. Infants and young children generally have low tidal volumes and an unreliable compliance. A simple and low-cost spacing device, the polystyrene coffee cup, has been in use for several years to deliver bronchodilators to young children [10]. Unfortunately,

this system involves firing the MDI directly onto the patient's face; frequently, an infant will not tolerate this form of therapy. Use of an AeroChamber with an attached mask, which is a simple, inexpensive and easily portable device, can solve this problem. The aerosol from an AeroChamber, which is equipped with a valve, is not fired directly into the infant's face. The attached soft mask ensures that there is no discomfort when it is applied to the face. Because of the above advantages, these devices are more likely to be accepted by young patients.

Two doses of 150 μ g BDP per day may seem to be too high for children under the age of three years. However, this level of dosage was chosen because the device usually reduces the drug delivery. Previous isotopic studies have shown that 37% of the dose introduced into a Nebuhaler is inhaled by an adult [11], while it is around 14% though an AeroChamber [12]. With a facemask attached, the drug actually delivered by an AeroChamber may be less than 5.3% [13]. Our study demonstrated that inhaled BDP had a good prophylactic effect in obstructive airway disease in infants and small children. Use of an AeroChamber with an attached mask potentially offers a major advance in the treatment of respiratory disease in these patients.

A short course of inhaled BDP reduces the frequency of viral upper respiratory tract infection [7, 14] and the severity of viral induced asthma [14]. It is still unknown whether prolonged use will alter the airway defense mechanism resulting in increased airway infections.

Although few side effects were observed by Bisgaard et al [9], the systemic effect from BDP cannot be excluded. The optimal dose of inhaled BDP through an AeroChamber with a mask in children under the age of three years must be further studied. The influence of prolonged use of BDP on adrenal and immunologic function should also be clarified.

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