Clinical use of nebulized budesonide inhalation suspension in a child with asthma

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Childhood asthma contributes to significant morbidity among patients and significantly impacts the quality of life and daily routines of their caregivers. The parents or caregivers assume responsibility for tasks that children are too young to perform; this often includes daily administration of controller medications and nightly administration of reliever medications. Most young children do not have the coordination or understanding to effectively use pressurized metered-dose inhalers or inhalation-driven devices; thus nebulizer therapy often is preferred for children younger than 4 years of age. Budesonide inhalation suspension will be the first inhaled corticosteroid available for children younger than 4 years of age and the first inhaled corticosteroid for delivery by nebulization in the United States. This is a case report of a 3-year-old boy who received budesonide inhalation suspension as part of several double-blind and open-label studies evaluating the drug. Before study entry, the boy was experiencing more breakthrough wheezing episodes at night than the parents were used to, resulting in an increase in nighttime awakenings that required nebulizer therapy. These nighttime awakenings had a substantial impact on the quality of life of the entire family and interfered with the parents' ability to function at work. Even though they wanted to have more children, this situation discouraged them from doing so. Budesonide inhalation suspension improved overall asthma control and was well tolerated. The boy had a decrease in nighttime symptoms and an increase in both height and weight percentiles for his age. Importantly, use of budesonide inhalation suspension in this boy eased the management of severe asthma and improved the quality of life of the entire family. The parents subsequently decided to have a second child. Budesonide inhalation suspension represents a major breakthrough for infants and young children by providing a formulation that, on approval, can be delivered reliably by nebulizer for effective maintenance treatment of persistent asthma. (J Allergy Clin Immunol 1999;104:S210-4)

Key words: *Budesonide, budesonide inhalation suspension, asthma, inhaled corticosteroid, pediatric, case report*

Asthma is the leading chronic disease of childhood.[1] National statistics continue to show that asthma prevalence, morbidity, and deaths are increasing, and children appear to be at highest risk.[2-4] Hospitalization rates for asthma from 1980 to 1993 were highest among persons 4 years of age and younger, and asthma accounts for one third of pediatric emergency department visits.[4,5]

Abbreviation used
pMDI: Pressurized metered-dose inhaler

The day-to-day management of asthma is the responsibility of the patient and, in the case of young children, the patient's family.[6,7] Quality-of-life studies indicate that parents and primary caregivers of children with asthma are limited in normal daily activities and experience anxieties and fears as a result of the child's illness.[8,9] Poor sleep quality and lower productivity levels are likely consequences of nocturnal awakenings. Key responsibilities of the parents and caregivers include instituting environmental controls that may be a hardship both monetarily and emotionally and administering multiple medications on a regular, but time-consuming, basis.[10] Pharmacologic therapy is used to prevent and control asthma symptoms, reduce the frequency and severity of asthma exacerbations, and reverse airflow obstruction.[6] To ensure the efficacy of drug therapy, the delivery system of drugs used in the treatment of asthma requires careful selection.[11] The age of the child is important in deciding which delivery device to use. Many pediatric patients, particularly those younger than 4 years of age, are unable to use pressurized metered-dose inhalers (pMDI) or inhalation-driven devices because of a lack of coordination and understanding.[12-14] Nebulizers are often the preferred delivery method for young children because they do not require the coordination and technique necessary to effectively use inhalers, they improve compliance, and they allow direct delivery of drug to the lungs, minimizing the risk of systemic side effects.[14]

Inhaled corticosteroid therapy is recommended for the management of patients with persistent asthma, including children younger than 2 years of age.[6] However, no inhaled corticosteroid is approved for use in children younger than 4 years of age and no inhaled corticosteroid preparation is indicated for nebulization in the United States. Consequently, many young children required regular treatment with systemic corticosteroids. An inhaled corticosteroid delivered by nebulizer has been needed to provide a safe and effective treatment option and to improve the quality of life of infants and young children with persistent asthma and their families.

Budesonide inhalation suspension (Pulmicort Respules™; AstraZeneca, Wayne, Pa) will be the first inhaled cortico-

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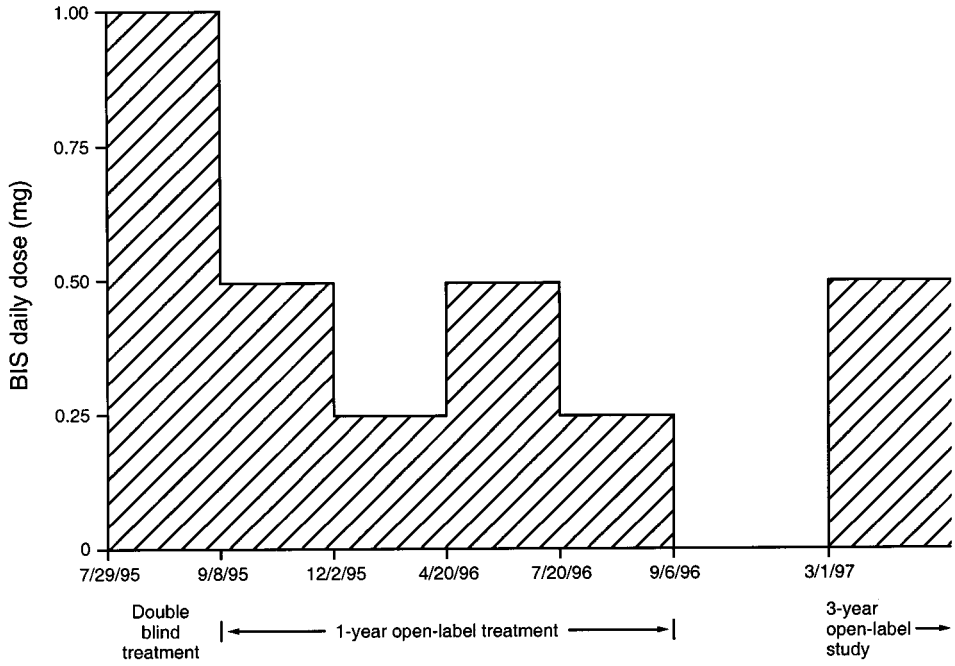

FIG 1. Timeline of patient's participation in double-blind and open-label studies of budesonide inhalation suspension (*BIS*).

steroid formulation approved for delivery by nebulization in the United States and will be the first inhaled corticosteroid available for infants and children younger than 4 years of age. Budesonide inhalation suspension was first introduced in Finland in 1990 and is now available in more than 30 countries. The following case study describes the clinical use of budesonide inhalation suspension administered by nebulization in a young child with severe asthma and the effects of the treatment on the family.

CASE REPORT

In June 1995, a 3-year-old boy with a history of asthma was referred to the Children's Hospital of Pittsburgh Asthma & Allergic Disease Center for enrollment into a randomized, double-blind, placebo-controlled, 12-week trial of budesonide inhalation suspension.[15] This patient was referred primarily as a result of an increase in nighttime awakenings because of breakthrough wheezing. Both parents worked outside of the home, and frequent nighttime awakenings that required nebulizer therapy substantially interfered with the parents' ability to function normally at work.

Asthma symptoms began soon after the patient entered day-care at the age of 2 years. His asthma symptoms were especially problematic during the April and May pollen seasons and less problematic during July. At the time of referral, maintenance medications consisted of cromolyn sodium pMDI (2 inhalations 3 times daily) with AeroChamber (Trudell Medical International, London, Ontario, Canada) and mask, and albuterol (2 inhalations every 4 hours as needed) by pMDI with AeroChamber and mask during the daytime hours for breakthrough symptoms. The child also had a nebulizer at home that was used to deliver albuterol at night as needed. Brompheniramine (Dimetapp) was administered before outdoor play. Other symptoms at the time of referral included rhinorrhea, nasal stuffiness, and sneezing possibly related to an upper respiratory infection.

Medical history included allergic rhinitis and several episodes of sinusitis that were treated with multiple courses of antibiotics, including amoxicillin and clarithromycin. The patient had never been hospitalized. He had received 2 courses of oral prednisolone (Prelone Syrup) and beclomethasone by pMDI with AeroChamber and mask before study entry. He had no known allergy to medications or foods although skin testing revealed sensitivity to cat allergens. Cats were present in the family home at the time of testing, and environmental control measures were recommended to minimize patient exposure to cat, dog, and mite allergens. Family history was significant for late-onset asthma in the paternal grandmother and atopic dermatitis in the mother and a maternal aunt. The child lived in a tobacco-free environment and slept on a cotton-stuffed mattress with a nonallergy mattress cover in a room with wall-to-wall carpeting. The home had gas forced-air heating, an electronic air cleaner, a humidifier, and central air conditioning.

At the initial study screening visit in July 1995, the child's weight was 13.2 kg (20th percentile for age), and his height, as measured by stadiometry, was 91.6 cm (5th percentile for age). Overall physical examination findings were unremarkable, except for the presence of mild eczema

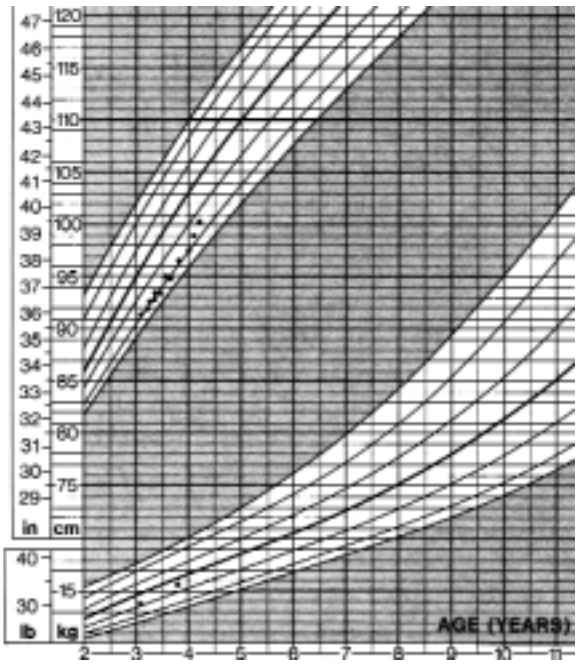

FIG 2. Patient growth for both height and weight according to the National Center for Health Statistics percentiles during budesonide inhalation suspension study participation. (Adapted from Hamill PVV, Drizd TA, Johnson CL, Reed RB, Roche AF, Moore WM. Physical growth: National Center for Health Statistics percentiles. Am J Clin Nutr 1979;32:607-29. ©Am J Clin Nutr. American Society for Clinical Nutrition.)

and slightly enlarged, pale nasal turbinates, consistent with his atopic constitution. Pulse and blood pressure were normal (116 bpm and 102/50 mm Hg, respectively).

Before study randomization, nighttime asthma symptom scores were recorded over 6 nights in a parent-completed diary. The nighttime asthma symptom score ranged from 0 to 3 points (0 = no symptoms and 3 = severe, incapacitating symptoms) and captured the frequency of symptoms during the week before randomization. To be eligible for study entry, a minimum score of 5 of a possible 18 points was required. This patient scored 7 of 18 points; recorded scores were 0 for 1 night, 1 for 3 of the nights, and 2 for 2 of the nights.

The patient was enrolled in the study and began receiving study medication with a mouthpiece in July 1995. When the study was unblinded, it was revealed that he had been receiving budesonide inhalation suspension 1 mg once daily. His participation in the double-blind study extended through September 1995, at which time he had an exacerbation and required treatment with oral prednisolone. After resolution of the exacerbation, he began an open-label, 52-week extension study. In the open-label phase, the patient was randomized to treatment with budesonide inhalation suspension at an initial dose of 0.5 mg once daily. The open-label study protocol was designed with the intent of tapering the dose to 0.25 mg once daily and, if tolerated, to 0.25 mg every other day and eventually discontinuing the drug. The treatment timeline shown in Fig 1 shows that this patient was unable to tolerate the taper of the budesonide dose to an alternate-day schedule, attesting to the high degree of asthma severity. However, despite the respiratory tract infection season, the budesonide dose was tapered to 0.25 mg once daily in December 1995 because the patient was doing well. In April 1996, his symptoms increased as the result of several upper respiratory tract infections, and the budesonide dose was increased to 0.5 mg once daily. As his disease stabilized, the dose was reduced to 0.25 mg once daily in July 1996 until the study ended in September 1996.

At the end of the 52-week trial, the patient's asthma was well-controlled with budesonide. Nighttime symptom severity decreased during both the double-blind and open-label studies. The patient recorded nighttime symptom scores of 0 for each night of the 2 weeks before his final visit of the open-label study. Physical examination findings indicated no candidiasis during treatment, and laboratory parameters were within normal limits. No subsequent episodes of sinusitis were observed. Notably, the patient grew approximately 8 cm to a height of 100.2 cm, an increase from the 5th percentile to approximately the 25th percentile for his age (Fig 2). It is important to note that the patient's height was measured by a stadiometer and was plotted on a standard growth chart.[16] His weight also increased from 13.2 kg to 15.5 kg. Nasal turbinates remained enlarged and pale, and pulse and blood pressure were largely unchanged (96 bpm and 102/52 mm Hg, respectively).

At the end of the 52-week open-label trial in September 1996, the patient lost access to budesonide inhalation suspension and was given beclomethasone (Vanceril double-strength [84 μg]) pMDI 2 puffs twice daily with InspirEase (Key Pharmaceuticals, Inc., Kenilworth, NJ) and albuterol 4 times daily as needed. The patient's technique for using the pMDIs was fair. His symptoms recurred with increased sneezing, rhinorrhea, and congestion and an increase in nighttime asthma symptoms. Because of the worsening of his symptoms, the patient was enrolled into a 3-year open-label study of budesonide inhalation suspension in March 1997. The patient began receiving budesonide 0.5 mg daily, and, presently, his asthma is well-controlled. Importantly, the improvements in asthma symptoms observed in this child who received budesonide inhalation suspension contributed to overall improvements in the quality of life of the parents. Before their son's treatment with budesonide inhalation suspension, the parents had decided not to have more children because of the difficulties of managing asthma and, based on family history, the likelihood of a second child having asthma. However, after observing the improvements in their son's asthma and the convenience of asthma management with a once-daily nebulized corticosteroid, the parents had a second child.

DISCUSSION

The use of nebulized budesonide inhalation suspension in this individual patient exemplifies the efficacy

and safety of the drug that were demonstrated in 3 multicenter, randomized, double-blind, placebo-controlled clinical trials of children with asthma.[14,15,17] Notably, use of the drug also contributed to quality-of-life improvements for both the patient and his caregivers.

The diagnosis of asthma in infants and young children often is difficult, and underdiagnosis and undertreatment are key problems in this age group.[6] As observed in this patient, symptoms of asthma often develop in children before the age of 2 years, and such early wheezing episodes are often associated with future persistent asthma.[13,18] Furthermore, respiratory symptoms that begin at, or persist through, the ages of 3 to 4 years are associated with the development of persistent asthma.[19] A family history of asthma and atopic disease were also relevant to the diagnosis of asthma in this patient.[6] Despite the difficulty in obtaining spirometry measurements as an accurate indication of pulmonary function and asthma severity in young children, nighttime symptoms in this child supported the diagnosis of at least moderately severe persistent asthma at baseline and were the impetus for clinical study referral.

Inhaled corticosteroids are the most potent and effective anti-inflammatory agents available for treatment of patients with persistent asthma whose disease cannot be controlled with bronchodilators or noncorticosteroid anti-inflammatory agents alone.[6] Treatment with budesonide inhalation suspension by nebulization during the 12-week double-blind and open-label studies dramatically improved asthma symptoms in this patient who had breakthrough wheezing while undergoing cromolyn sodium and albuterol therapy. Treatment was well tolerated, and no candidiasis was observed. An important observation in this case was that the patient's height increased from July 1995 to September 1996 while he received budesonide inhalation suspension therapy. As shown in Fig 2, the initial height at enrollment was at the 5th percentile for the child's age and increased by approximately 8 cm, reaching the 25th percentile, during the 1-year open-label study. In addition, growth continued after the child entered the 3-year open-label budesonide inhalation suspension study in March 1997. Although inhaled corticosteroids have been associated with growth suppression and decreased bone density,[20,21] clinical studies[22-24] of budesonide inhalation suspension administered for greater than 6 months have not shown any definitive effects of the drug on growth ("Short-term and long-term safety of budesonide inhalation suspension in infants and young children with persistent asthma," in this issue). In addition, evidence exists that severe, poorly controlled asthma itself may adversely affect growth.[6] It is likely that the substantial clinical improvement in asthma control in this patient contributed to an increase in height during this period.

Perhaps the most important aspect of this case was the improvement in the quality of life of the patient and his family. At the time of referral, the child's parents were struggling with the challenges of managing his nighttime awakenings and maintaining demanding daily activities at work and home. Combined with these challenges and a family history of asthma, the family decided not to have any more children. After their son's successful participation in the budesonide inhalation suspension studies, they realized that his asthma could be effectively managed, and the quality of their lives improved. Budesonide inhalation suspension was easily delivered by nebulizer, and once-daily administration was convenient and enhanced compliance. The parents subsequently had a second child during their son's participation in the 3-year open-label trial.

In an effort to maximize efficacy with inhaled corticosteroids and minimize potential adverse effects, children with asthma should be managed according to the following NHLBI guidelines.[6] First, treatment should be initiated with anti-inflammatory controller medications, inhaled corticosteroids being the agent of choice, soon after diagnosis of persistent asthma; this is especially true in patients with moderate and severe persistent asthma. Second, it is recommended that inhaled corticosteroids be dosed individually according to disease severity. Patients with more severe asthma may require higher doses initially, although lower doses may be reserved for patients with milder disease. Third, once adequate control has been established, the dose and possibly dosing frequency should be stepped down with careful monitoring (every 1 to 6 months) to maintain maximum efficacy at the lowest effective dose. Fourth, physicians should take an active role in educating peers and parents/guardians on the benefits of anti-inflammatory medications such as inhaled corticosteroids for treating the inflammatory component of asthma as opposed to only the use of quick-relief bronchodilators for treating acute symptoms. Additional measures should be taken to minimize systemic absorption, including once-daily dosing, use of newer inhaler devices that increase lung uptake and decrease oropharyngeal deposition with subsequent systemic absorption, and providing instructions to patients and/or patients' parents/guardians to rinse the mouth after dosing.

As demonstrated by this case, budesonide inhalation suspension represents an important advance in the maintenance treatment of pediatric asthma. For children with persistent asthma who are younger than 4 years of age, when available, budesonide inhalation suspension offers a new therapeutic option that will allow children to receive the most effective anti-inflammatory therapy for asthma with the potential to reduce long-term bronchial damage.

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