M. Saito[1], Y. Kikuchi[1], A. Kawarai Lefor[2], M. Hoshina[1]

High-dose nebulized budesonide is effective for mild asthma exacerbations in children under 3 years of age

[1]Department of Pediatrics, Haga Red Cross Hospital, 2461 Daimachi Mouka, Tochigi, 321-4306, Japan
[2]Department of Surgery, Jichi Medical University, 3331-1 Yakushiji, Simotsuke, Tochigi, 320-0498, Japan
This study was conducted at Haga Red Cross Hospital, 2461 Daimachi Mouka, Tochigi, 321-4306, Japan

Key words
Asthma; budesonide; exacerbation; infants; steroid

Corresponding author
Mari Saito
Department of Pediatrics, Haga Red Cross Hospital
2461 Daimachi Mouka, Tochigi, 321-4306, Japan
Phone: +81 285 84 3332
Fax: +81 285 82 2195
E-mail: mari.saito@haga.jrc.or.jp

Summary
Background. *High-dose inhaled steroid therapy has been shown to be effective in children and adults with asthma exacerbations. However, few reports are available regarding its efficacy for asthma exacerbations in younger children.* ***Objective.*** *In this study, we administered high-dose nebulized budesonide therapy for mild asthma exacerbations in children < 3 years of age and compared its efficacy and safety with systemic steroid therapy.* ***Methods.*** *This study included children < 3 years old with mild asthma exacerbations. Patients were randomly assigned to two groups: the BIS group was given 1 mg of nebulized budesonide twice daily, and the PSL group received prednisolone 0.5 mg/kg iv three times daily. Days to disappearance of wheezing, days of steroid use, days of oxygen use, serum cortisol level, and incidence of adverse events during treatment were compared between the groups.* ***Result.*** *Wheezing disappeared after an average of five days, and steroids were administered for an average of five days in both groups, with no significant difference in days of oxygen use. Serum cortisol levels at initiation and during the course of treatment remained unchanged in the BIS group, and were decreased in the PSL group; however, the decrease in the latter group was not pathologic.* ***Conclusion.*** *For children < 3 years old with mild asthma exacerbations, high-dose nebulized budesonide therapy is equally as effective as systemic steroid therapy.*

Introduction

Since 1990, when nebulized budesonide was first approved, inhaled steroid therapy for asthma in infants has been widely used. Inhaled steroid therapy is considered the best treatment for long-term management of asthma, and has been reported to stabilize clinical symptoms, improve airway obstruction and quality of life, and reduce the frequency and progression of asthma exacerbations (1). Even for asthma exacerbations, high-dose inhaled steroid therapy has been reported to be as effective as systemic steroid therapy, mainly in school-age and older patients (2).

The main reason why high-dose inhaled steroid therapy is not commonly used for the treatment of acute asthma exacerbations in children below school age, is that repeated episodes of wheezing in younger children are often due to viral infections and that there are no clear differences of clinical symptoms between asthma exacerbation and acute bronchiolitis. However, the majority of children with asthma experience their first episode of wheezing as an infant, and these initial illnesses are almost always caused by viral infections (3). Early diagnosis and early intervention for asthma in infants are mandatory to maintain their airway function.

In this study, we carefully recruited infants with asthma according to the criteria of the Japanese Society of Allergology, which predicts persistent asthma in children less than 3 years of age and administered high-dose nebulized steroid therapy to children less than 3 years of age with exacerbations of asthma. The

efficacy and safety of inhaled steroid therapy is compared with conventional systemic steroid therapy.

Methods

Patients

This study enrolled children less than 3 years of age, diagnosed with bronchial asthma as defined by the Japanese Society of Allergology as follows: children with at least three repeated episodes of obvious expiratory wheezing and children satisfying any of the following six criteria with recurrent wheezing more than 2 episodes: 1. At least one parent of the child was diagnosed with bronchial asthma by a physician, or tested positive for IgE antibodies specific to an inhaled antigen; 2. The child was diagnosed with atopic dermatitis by a physician, or tested positive for IgE antibodies specific to an inhaled antigen; 3. The child or any member of his/her family has high serum level of IgE; 4. Eosinophils or creola bodies are found in the sputum; 5. The child has had an episode of wheezing in the absence of an apparent airway infection or 6. An improvement in wheezing or labored respiration, or an improvement in oxygen saturation was observed after inhaled beta 2-agonist. These children first received intravenous hydrocortisone and a single inhalation of procaterol for an asthma exacerbation. If they showed inadequate improvement in clinical symptoms, they were admitted with the diagnosis of a mild asthma exacerbation.

Study protocol

Children were randomly divided by a computer into a high-dose inhaled steroid therapy group (BIS group; nebulized budesonide 1 mg/dose, twice daily inhalations) and a systemic steroid therapy group (PSL group; intravenous prednisolone 0.5 mg/kg, three times daily) at the time of admission, and treated accordingly. Inhalation was conducted using PARI turbo BOY N (PARI international, Starnberg, Germany) with a face mask, and concluded when the aerosol was no longer visible. The amount of inhaled or injected steroid was gradually reduced from the day after disappearance of wheezing, and then discontinued. Children confirmed to have no recurrence of expiratory wheezing were discharged. During hospitalization, children continued to receive long-term asthma medication other than steroids and procaterol inhalation four times daily. Long-term asthma medication was administrated according to the guideline proposed by the Japanese Society of Allergology as follows: Children who have wheezing episodes less than once a month receive intermitted LTRA; Children who have wheezing episodes at least once a month but less than once a week receive daily LTRA; Children who have wheezing episode at least once a month with above treatment are added inhaled steroid. As post-discharge treatment, children who had asthma exacerbation within a month before their hospitalization received additional inhaled steroid or increased dosage of inhaled steroid along with LTRA. When percutaneous oxygen saturation was less than 94%, oxygen inhalation was added according to guideline by the Japanese Society of Allergology. Antibiotics were used when a bacterial infection of the respiratory tract was suspected. Children requiring mechanical ventilatory management, children with chronic systemic diseases or primary lung diseases, and children whose guardian did not consent to study participation were excluded. Clinical symptoms, the presence or absence of wheezing, percutaneous oxygen saturation, treatment details, and routine clinical data were recorded daily, and serum cortisol levels were measured at the time of admission, and between 8 am and 10 am at four days after admission.

Data collection

The primary outcome of this study was the number of days to disappearance of wheezing, and secondary outcomes included the number of days of steroid use, the number of days of oxygen use, presence of suppressed serum cortisol levels during the hospital course, and the incidence of adverse events.

Statistical analysis

Statistical analysis was carried out with JMP 9.0.0 software (SAS Institute, Cary, NC, USA). Student's t-test was used to compare values between the two groups, and Fisher's exact test was used to compare proportions between the two groups. A difference was considered significant with $p < 0.05$. Welch's test was used for total serum IgE and the peripheral blood eosinophil ratio.
This study was conducted with approval from the ethical review committee of this institution, and written consent was obtained from a guardian of each child after being provided with an explanation about the study by the physician who determined that the patient required inpatient treatment.

Results

Clinical characteristics

Fifty-one children with a mild asthma exacerbation admitted to the Department of Pediatrics at the Haga Red Cross Hospital (Tochigi, Japan), between April 2013 and November 2014 met the inclusion criteria, but one refused to participate. Thirty patients in the BIS group and 20 in the PSL group completed all follow-up including post-discharge follow-up. The mean ages were 20 and 21 months in the two groups, and the number of

Table 1 *- Patient background.*

	BIS (n = 30)	**PLS (n = 20)**	
Age (months)	20 ± 2	21 ± 2	
Males:Females	21:9	15:5	
Weight (kg)	11 ± 0	12 ± 0	
Height (cm)	81 ± 1	83 ± 2	
BA controller			
LTRA	18	15	
LTRA+ICS	11	4	
ICS	1	0	
Intermitted LTRA	11	9	
Total serum IgE (IU/mL)	160 ± 90	330 ± 100	
Respiratory rate at admission (/ min)	34 ± 1	34 ± 1	
SpO_2 on admission (%)	97 ± 0	96 ± 1	
Febrile patients	15	7	
Antibiotics therapy	4	2	
Laboratory findings			
WBC (/μL)	12100 ± 720	10700 ± 890	
Eosinophil (%)	2.9 ± 0	1.7 ± 0*	*$p = 0.0183$
Platelets (x10^4 /μL)	31 ± 2	27 ± 2	

BIS: high-dose inhaled budesonide therapy group; PSL: systemic steroid therapy group; BA: bronchial asthma; LTRA: leukotriene receptor antagonist; ICS: inhaled steroid; SpO_2: percutaneous oxygen saturation; WBC: white blood cell count.

male patients was greater than the number of females in both groups (**table 1**). The peripheral blood eosinophil ratio was significantly higher in the BIS group (BIS group 3.0%, PSL group 1.7%; p = 0.0183). No significant differences were noted in other clinical data, including total serum IgE, respiratory rate on admission, and percutaneous oxygen saturation.

Clinical course

Having undergone inpatient treatment as described above, wheezing was eliminated in five days on average in both the BIS and PSL groups with five days of steroid use on average (**table 2**). Hypoxemia occurred in eight patients in the BIS group and in six patients in the PSL group. The number of days of oxygen use tended to be fewer in the BIS group, although the difference was not statistically significant (BIS group n = 4.2 days, PSL group n = 6.3 days, p > .05).

Table 2 *- Course after hospitalization.*

	BIS (n = 30)	**PSL (n = 20)**	
Days of wheezing detected	5 ± 0	5 ± 1	
Days of steroid therapy	5 ± 0	5 ± 0	
Patients with desaturation	8	6	
Days of oxygen required	2 ± 1	3 ± 1	
Serum cortisol at admission (μg/dL)	15.0 ± 2.2	17.2 ± 2.1	
Serum cortisol at re-examination	17.0 ± 1.2	10.9 ± 1.5*	*$p = 0.0036$
Days after admission for re-examination	4 ± 0	4 ± 0	

In both groups, wheezing disappeared in 5 days on average with 5 days of steroid use on average. In the initial 4 days (mean) of hospitalization, the serum cortisol level remained unchanged in the BIS group, while it decreased significantly in the PSL group.

Laboratory data

Serum cortisol levels in the BIS and PSL groups at the time of admission were 15.0 μg/dL and 17.2 μg/dL (p > .05), respectively. However, serum levels on the fourth day of hospitalization were 17.0 μg/dL and 10.9 μg/dL, with significant suppression in the PSL group. Adverse events did not occur in either group.

Discussion

Treatment of children less than 3 years of age with mild exacerbations of asthma using high-dose nebulized budesonide therapy is as effective as systemic steroid therapy. Furthermore, serum cortisol suppression, which was observed in patients treated with systemic steroids, did not occur in patients treated with high-dose nebulized budesonide therapy. This suggests that high-dose nebulized budesonide therapy results in the same therapeutic outcome as systemic steroid therapy, without some of the systemic effects of steroid administration.

Making diagnosis of asthma in children less than 3 years of age is difficult since recurrent wheezing is often detected with vi-

ral infections and lower respiratory infections in this age. Our study included children with recurrent wheezing more than 3 episodes regardless of the existence of respiratory infections. Six of all received antibiotics therapy due to acute lower respiratory infections with increased white blood cell count and elevated C-reactive protein which indicated a bacterial infection. A presence of lower respiratory infection does not exclude a diagnosis of asthma exacerbation with recurrent wheezing children. In fact, the characteristic pathologic features of asthma such as thickening of the bronchial epithelial reticular basement membrane and eosinophilic airway inflammation were reported to be seen even in a part of children with recurrent wheezing at 3 years of age (4). Since steroid therapy is not effective to acute bronchiolitis (5), we carefully recruited asthma children less than 3 years of age. To identify which children will have persistent asthma, various predictions of persistent asthma in younger children have been proposed. According to the Japanese asthma diagnostic criteria, the recurrent wheezing more than 3 episodes is major criteria to identify persistent asthma in children less than 3 years of age. This highlights the importance of early intervention in younger children with asthma for maintaining their lung function. However, there is a limitation to include children with repeated acute bronchiolitis. The Asthma Predictive index (API) is another prediction to identify persistent asthma (6). A positive API at age 3 has a sensitivity of 17-19% and specificity of 99-100% for asthma between ages 6-8 years (7,8). Our study included 44 of 51 positive API children (80%). Remaining seven children with negative API had repeated wheezing episodes apart from colds, but had no family history of parental asthma, no medical history of eczema or allergic rhinitis in previous examinations. These children had possibility to be underestimated with eczema because of less chance to visit medical institutions and to be later diagnosed with eczema or allergic rhinitis until their 3-years-old birthday.

While long-term systemic steroid administration has been known to cause some adverse reactions, such as growth suppression, bone metabolism disorders, and adrenal gland dysfunction, few side effects have been identified in short-term systemic steroid therapy. Recent reports have shown that symptoms of anxiety, depression and deterioration of memory emerge after short-term systemic steroid therapy (9,10), and bone metabolism disorders occur when short-term systemic steroid therapy is given repeatedly (11). Caution must be taken regarding systemic side effects even when short-term systemic steroid therapy is given.

Inhaled steroid therapy has been considered to have fewer systemic effects and to be safer than systemic steroid therapy. However, some reports have shown that bone metabolism disorders and growth suppression occur in long-term moderate- to high-dose inhaled steroid therapy (12,13), and that the growth tends to be suppressed when short-term (up to 10 days) high-dose inhaled steroid therapy is repeated (7 times on average in one year) (14). Therefore, the safety of inhaled steroids for long-term and repeated treatment has not been determined.

In the present study, the number of days of high-dose nebulized budesonide therapy was as long as nine days, and was five days on average. Only 10 children in both groups (20%) underwent repeated systemic steroid therapy or high-dose nebulized budesonide therapy after participation in the study with a mean of two treatments per child, indicating that a very low dose of steroid was required per child compared to previous studies. Possible reasons for this difference include that, in the report from Ducharme et al., high-dose nebulized budesonide therapy may have been given to some children who were not in need, because the treatment was chosen at guardians' discretion (10). If high-dose nebulized budesonide administration was used at the physicians' discretion based on the asthma exacerbation, as done in the present study, the number of treatments and days of treatment may be minimized, and thus the risk of growth suppression is likely to be further reduced.

Serum cortisol suppression, which was observed in patients treated with systemic steroid therapy, did not occur in patients treated with high-dose nebulized budesonide therapy, suggesting that high-dose nebulized budesonide therapy for approximately five days is unlikely to have systemic effects. Furthermore, no adverse event was noted during this study, suggesting that administration of high-dose nebulized budesonide therapy is safe. Nevertheless, peri-oral pruritus, pharyngeal pain, and hoarseness are possible in patients receiving high-dose inhaled steroid therapy as reported previously. In general, inhalation of fluticasone is considered to induce a stronger reaction and reports with budesonide are limited (15), suggesting possible differences in biological activity among different steroids.

In addition to anti-inflammatory effects via gene expression, inhaled steroids have recently been reported to exert an early anti-inflammatory effect that is not mediated by gene expression. Improved clinical symptoms have been noted as early as four hours after inhalation in reports on high-dose inhaled steroid therapy for asthma exacerbation in infants and toddlers (16), and high-dose inhaled steroid therapy improves respiratory function and clinical symptoms more rapidly than systemic steroid therapy (17,18) (**table 3**).

It has also been reported that, in patients with asthma undergoing high-dose inhaled steroid therapy, airway blood flow is reduced to about half at 30 minutes after inhalation and returns to the original level about 90 minutes after inhalation (19), suggesting that such changes may contribute to the improvement in airway narrowing and decrease in airway secretions. In children who developed hypoxemia in the present study, those in the BIS group had more rapid improvement of hypoxemia than those in the PSL group, although the difference was not signif-

Table 3 *- Reports on high-dose inhaled budesonide and systemic steroid therapy for acute exacerbation of moderate to severe infantile asthma.*

	No of patients (ages)		Protocol	Results
Volovitz et al. (1998)	22 (6-16 yr)	Moderately severe BA	Initial: pMDI BUD 1.6 mg vs. PDN 2 mg/kg After 1st day: reducing dose for 1 wk	BUD group: Clinical symptoms up to 4 hours after the start of treatment were improved earlier. PDN group: The serum cortisol level decreased in the first and third weeks after the start of treatment. No difference in the degree of respiratory disorders and the peak flow value
Matthews et al. (1999)	46 (5-16 yr)	Severe BA	Initial: neb BUD 2 mg x 3 times daily vs. PDN 2 mg / kg at immediately and 24 h After 1st day: pMDI BUD 0.8 mg for 24 d	BUD group: Greater improvement in 1-second volume 24 hours after the start of treatment
Sano et al. (2000)	71 (3-24 mo)	Acute wheeze with dyspnea	Initial: neb BUD 0.25 mg x 4 / d + HDC 40 mg/kg iv vs. HDC 40 mg/kg Continued till discharge	BUD group: Greater improvements in clinical symptoms after 12 hours after starting the treatment and the respiratory rate 24 hours after starting the treatment Treatment period was shorter (BUD 66.4h vs. HDC 93hr)

BA: bronchial asthma; pMDI: pressurized metered-dose inhaler; BUD: budesonide; PDN: prednisolone; HDC: hydrocortisone

icant, suggesting that high-dose nebulized budesonide therapy improves airway contraction/airway inflammation more rapidly. Unfortunately, airway inflammation could not be evaluated by objective means such as spirometry or exhaled nitric oxide measurement, because of the patients' age.

In children less than 3 years of age, tests to assess chronic airway inflammation and airway hyper-responsivity required to establish the diagnosis of asthma can be performed in only a few institutions. Therefore, asthma tends to be underdiagnosed in typical medical facilities. As a consequence, appropriate steroid therapy may not be given during asthma exacerbations in young children. It has been reported that infants with repeated past episodes of untreated wheezing have pulmonary impairment that persists until young childhood or even until adulthood (20-22). Although the side effects of inhaled steroids remain an issue, long-term preservation of pulmonary function can be expected from high-dose nebulized budesonide therapy given to improve airway inflammation and constriction during asthma exacerbations in infants, as in the present study. Therefore, clinicians should not hesitate to use this therapeutic option.

There are a number of acknowledged limitations to this study. A double blind study design was not used, thus the type of treatment was identifiable from the appearance of the drug. Biases among medical staff and parents cannot be ruled out. Second, making a confident diagnosis of asthma in children less than 3 years of age is difficult because wheezing is often detected with viral infections and lower respiratory infections in younger children. For this reason, we recruited children at high risk of developing asthma with repeated wheezing according to the guideline proposed by the Japanese Association of Allergology, but the possibility still remains to have included children without asthma. Third, while suppressed serum cortisol levels were observed in the PSL group, the suppression was not pathologic, and we could not determine if adrenal function was actually suppressed, because an adrenal function loading test was not conducted. Symptoms of adrenal insufficiency such as low activity, gastrointestinal symptoms, unexplained fever, or hypoglycemic symptom, were not observed in either group. Therefore, both high-dose nebulized steroid therapy and systemic steroid therapy for five days were considered unlikely to lead to immediate adrenal insufficiency.

Conclusion

High-dose inhaled steroid therapy was at least not inferior to systemic steroid therapy in therapeutic efficacy for children less than 3 years of age with mild exacerbations of asthma. More-

over, unlike in patients who received systemic steroid therapy, suppression of serum cortisol levels was not observed in patients receiving high-dose nebulized steroid therapy, suggesting that it has reduced systemic effects.

References

1. Rachelefsky G. Inhaled corticosteroids and asthma control in children: assessing impairment and risk. Pediatrics. 2009;123:353-66.
2. Beckhaus AA, Riutort MC, Castro-Rodriguez JA. Inhaled versus systemic corticosteroids for acute asthma in children. A systematic review. Pediatr Pulmonol. 2014;49:326-34.
3. Yousef E, Hossain J, Mannan S, et al. Early intervention with high-dose inhaled corticosteroids for control of acute asthma exacerbations at home and improved outcomes: a randomized controlled trial. Allergy and asthma proceedings: the official journal of regional and state allergy societies. 2012;33:508-13.
4. Saglani S, Payne DN, Zhu J, et al. Early detection of airway wall remodeling and eosinophilic inflammation in preschool wheezers. Am J Respir Crit Care Med. 2007;176:858-64.
5. Panickar J, Lakhanpaul M, Lambert PC, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. N Engl J Med. 2009;360:329-38.
6. Castro-Rodriguez JA, Holberg CJ, Wright AL, et al: A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care Med. 2000;162:1403-6.
7. Castro-Rodriguez JA: The Asthma Predictive Index: a very useful tool for predicting asthma in young children. J Allergy Clin Immunol. 2010;126:212-6.
8. Rodriguez-Martinez CE, Sossa-Briceno MP, Castro-Rodriguez JA. Discriminative properties of two predictive indices for asthma diagnosis in a sample of preschoolers with recurrent wheezing. Pediatr Pulmonol. 2011;46:1175-81.
9. Bender BG, Lerner JA, Poland JE. Association between corticosteroids and psychologic change in hospitalized asthmatic children. Ann Allergy. 1991;66:414-9.
10. Newcomer JW, Craft S, Hershey T, et al: Glucocorticoid-induced impairment in declarative memory performance in adult humans. J Neurosci. 1994;14:2047-53.
11. Matsumoto H, Ishihara K, Hasegawa T, et al. Effects of inhaled corticosteroid and short courses of oral corticosteroids on bone mineral density in asthmatic patients: a 4-year longitudinal study. Chest. 2001;120:1468-73.
12. Allen HD, Thong IG, Clifton-Bligh P, et al. Effects of high-dose inhaled corticosteroids on bone metabolism in prepubertal children with asthma. Pediatr Pulmonol. 2000;29:188-93.
13. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. N Engl J Med. 2000;343:1064-9.
14. Ducharme FM, Lemire C, Noya FJ, et al: Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. N Engl J Med. 2009;360:339-53.
15. Adams N, Lasserson TJ, Cates CJ, et al. Fluticasone versus beclomethasone or budesonide for chronic asthma in adults and children. The Cochrane database of systematic reviews. 2007;Cd002310.
16. Volovitz B, Bentur L, Finkelstein Y, et al. Effectiveness and safety of inhaled corticosteroids in controlling acute asthma attacks in children who were treated in the emergency department: a controlled comparative study with oral prednisolone. J Allergy Clin Immunol. 1998;102:605-9.
17. Matthews EE, Curtis PD, McLain BI, et al. Nebulized budesonide versus oral steroid in severe exacerbations of childhood asthma. Acta paediatrica (Oslo, Norway: 1992). 1999;88:841-3.
18. Sano F, Cortez GK, Sole D, et al. Inhaled budesonide for the treatment of acute wheezing and dyspnea in children up to 24 months old receiving intravenous hydrocortisone. J Allergy Clin Immunol. 2000;105:699-703.
19. Kumar SD, Brieva JL, Danta I, et al. Transient effect of inhaled fluticasone on airway mucosal blood flow in subjects with and without asthma. Am J Respir Crit Care Med. 2000;161:918-21.
20. Horak E, Lanigan A, Roberts M, et al. Longitudinal study of childhood wheezy bronchitis and asthma: outcome at age 42. BMJ (Clinical research ed). 2003;326:422-3.
21. Phelan PD, Robertson CF, Olinsky A. The Melbourne Asthma Study: 1964-1999. J Allergy Clin Immunol. 2002;109:189-94.
22. Strachan D, Gerritsen J. Long-term outcome of early childhood wheezing: population data. The European respiratory journal. Supplement 1996;21:42-7s.