REVIEW ARTICLE

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Budesonide Inhalation Suspension for the Treatment of Asthma in Infants and Children

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Abstract

On the basis of the well recognised role of inflammation in the pathogenesis of asthma, anti-inflammatory therapy, in the form of inhaled corticosteroids, has become the mainstay of treatment in patients with persistent asthma. Budesonide inhalation suspension (BIS) is a nonhalogenated corticosteroid with a high ratio of local anti-inflammatory activity to systemic activity. Furthermore, BIS is approved in >70 countries for the maintenance treatment of bronchial asthma in both paediatric and adult patients (approval is limited to paediatric patients in the US and France).

Randomised, double-blind, placebo-controlled trials conducted in >1000 children have demonstrated the efficacy of BIS in children with persistent asthma of varying degrees of severity. In children frequently hospitalised with uncontrolled asthma, initiation of BIS therapy can reduce the need for emergency intervention. Moreover, limited data suggest that BIS is effective for the treatment of acute exacerbations of asthma in children and may reduce the need for short courses of oral corticosteroids.

BIS is well tolerated in children, with an adverse event profile similar to that of placebo, and no clinically relevant changes in adrenal function have been demonstrated during the course of short- and long-term (1-year) studies. Small but statistically significant reductions in growth velocity have been demonstrated with BIS over 1 year of treatment. However, available evidence suggests that growth effects are transient in children receiving budesonide and that these children eventually achieve full adult height.

According to the Global Initiative for Asthma, the prevalence of paediatric asthma worldwide is as high as 30%, depending on the population. Countries with the highest prevalence rates are Australia, New Zealand and England.[1] In the US, asthma is the most common paediatric chronic disease,[2] affecting approximately 6 million children, of whom one-fifth are younger than 4 years of age.[3]

Inflammation is a universal feature of asthma, occurring at all levels of disease severity.[4] Indeed, the role of inflammation in the pathogenesis of asthma is now clearly established, and it appears that persistent inflammation may lead to irreversible airway remodeling and chronic manifestations of asthma.[4,5] Thus, anti-inflammatory therapy has been regarded as a mainstay of treatment for persistent asthma in children.[4]

Until recently, nebulised sodium cromoglicate (cromolyn sodium) was the only anti-inflammatory agent approved for use in children younger than 4 years of age with asthma. However, after an evidence-based review of the literature, the National Asthma Education and Prevention Program (NAEPP) expert panel concluded that there is insufficient evidence that sodium cromoglicate has a beneficial effect as maintenance therapy in children with asthma, and that it should no longer be considered a preferred therapy.[4] Results of a meta-analysis of randomised placebo-controlled trials conducted between January 1966 and January 1999, in which sodium cromoglicate was used in the prophylactic treatment of asthma in children, similarly demonstrated that there was insufficient evidence to support the use of sodium cromoglicate as a first-line treatment in childhood asthma.[6] According to the NAEPP's 2002 recommendations, inhaled corticosteroids are now the preferred anti-inflammatory agents for the treatment of persistent asthma in infants and children.[4]

Inhaled corticosteroids have well established efficacy in the treatment of persistent asthma, as demonstrated by their ability to improve pulmonary function, decrease the need for bronchodilator rescue medication, improve quality of life and reduce asthma-related hospitalisation rates.[7] Budesonide inhalation suspension (BIS) is one of three inhaled corticosteroids available in >70 countries worldwide for nebulisation. BIS is approved for use in children and adults, except in the US and France where approval is limited to use in children. BIS is the only inhaled corticosteroid approved in the US for use in children younger than 4 years (approval is for age 12 months to 8 years).

This article reviews the pharmacological properties of BIS, along with clinical studies of its efficacy and safety in paediatric asthma, and further discusses the role of BIS in clinical practice. A MEDLINE search (using the search terms *budesonide*, *budesonide inhalation suspension*, *infant*, *children* and *asthma*) was conducted to identify relevant literature published between 1985 and 2005. For clinical efficacy, priority was placed on large, randomised clinical trials.

1. Clinical Pharmacology

1.1 Pharmacodynamics

Budesonide, like the endogenous corticosteroid cortisol, mediates its effects through its high-affinity binding to the intracellular glucocorticoid receptor (GCR). Budesonide is a nonhalogenated corticosteroid with a high ratio of local to systemic anti-inflammatory activity relative to oral corticoste-

roids.[8] This allows budesonide to be inhaled at therapeutically effective dosages with a low risk of systemic activity.[8] With a near 200-fold higher relative binding affinity for the GCR than that of cortisol and an anti-inflammatory activity that is 1000-fold higher,[9] budesonide possesses the ability to deliver a potent local anti-inflammatory effect upon inhalation with minimal systemic manifestations.

As with other corticosteroids, BIS has numerous anti-inflammatory properties that have been extensively reviewed elsewhere.[8-10] Briefly, corticosteroids such as budesonide inhibit the actions of lymphocytes, eosinophils, mast cells, neutrophils and macrophages. Budesonide also modulates allergic- and nonallergic-mediated inflammatory processes through the effects of the GCR on DNA transcription and/or the elaboration of immunologically active molecules (e.g. cytokines, histamine, eicosanoids, leukotrienes).[10] Budesonide has been shown to inhibit bronchial hyperresponsiveness to a variety of substances (e.g. histamine, methacholine, sodium metabisulfite, adenosine monophosphate) in patients with hyperreactive airways.[9,10] In addition, budesonide attenuates both the early- and late-phase responses to inhaled allergens.[9,10]

1.2 Pharmacokinetics

The pharmacokinetic parameters of BIS in children are summarised in table I. Agertoft et al.[11] assessed the systemic bioavailability and pharmacokinetics of BIS in ten children aged 3–6 years who had persistent asthma. In this *in vivo* trial, systemic bioavailability was measured from plasma concentrations of budesonide after nebulisation and intravenous administration. The children received intravenous budesonide 125µg followed by BIS 1.0mg administered via a Pari LC Jet Plus® [1] nebuliser.[11] Peak plasma concentration (2.6 nmol/L) was observed 10–30 minutes after the start of nebulisation.[10,12] The systemic exposure per milligram of nominal dose in these children, measured as the area under the plasma concentration versus time curve per milligram of nominal dose, was similar to that observed in adults (4.6 vs 3.9 nmol/L × hour/mg, respectively).[11]

Table I. Pharmacokinetic parameters of budesonide inhalation suspension in children aged 3–6 years[10,11]

Parameter	Value	95% CI
F (%)	6.1	4.6, 8.1
t_{max} (min)	10–30	NR
C_{max} (nmol/L)	2.6	NR
AUC/mg (nmol/L × h/mg)	4.6	NR
V_{ss} (L)	55	45, 68
$t_{1/2}$ (h)	2.3	2.0, 2.6
CL_s (mL/min)	536	461, 623

AUC = area under the curve (plasma concentration vs time); **CL_s** = total systemic clearance; **C_{max}** = peak plasma concentration; **F** = total systemic availability; **NR** = not reported; **$t_{1/2}$** = terminal elimination half-life; **t_{max}** = time to peak plasma concentration; **V_{ss}** = volume of distribution at steady state.

Lung deposition was calculated on the basis of the pharmacokinetic model and estimated from the amount of drug recovered from inspiratory and expiratory filters connected to a nebulised unit. Lung deposition of budesonide was estimated to be 18% of the dose received by the patient compared with an oropharyngeal deposition of 82%.[11] Although oropharyngeal deposition has the potential to be swallowed and subsequently absorbed, these investigators found that the total absolute bioavailability of BIS in children after administration via a jet nebuliser was low, representing approximately 6% of the administered dose.[11,13] The poor correlation between the inhaled dose and the systemic bioavailability suggests that factors other than inhaled dose affect lung deposition, and emphasises the need for lung deposition studies to be conducted in children, and not extrapolated from adult deposition studies.

The volume of distribution of budesonide at steady state is 3 L/kg in children aged 4–6 years.[13] At plasma concentrations of 1–100 nmol/L, budesonide is approximately 85–90% bound to plasma proteins.[13] The drug exhibits little or no binding to corticosteroid-binding globulin.[13] Data from *in vitro* studies indicate that budesonide is rapidly and extensively metabolised, primarily via the cyto-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

chrome P450 isoenzyme 3A4.[13] The two primary metabolites (16α-hydroxyprednisolone and 6β-hydroxybudesonide) have <1% of the corticosteroid activity of the parent compound.[13] Budesonide is rapidly cleared from the plasma, a property that minimises systemic exposure. The clearance of budesonide after administration of nebulised BIS in children aged 3–6 years was approximately 30 mL/min/kg,[11] with a terminal half-life of 2.3 hours.[11] Data from adults indicate that budesonide is excreted primarily in the urine and faeces as metabolites, with no unchanged budesonide found in the urine.[13]

2. Clinical Efficacy

2.1 Persistent Asthma

2.1.1 Placebo-Controlled Trials

The efficacy of BIS was first evaluated in small placebo-controlled studies in infants and children with severe persistent asthma that were conducted outside the US.[14,15] In one study, 40 children younger than 30 months of age who had severe asthma (defined as one exacerbation per month requiring oral corticosteroid therapy in the 3 months before the study, or daily symptoms for ≥15 days before the study) were randomised to BIS 1.0mg or placebo twice daily for 12 weeks.[14] Significantly fewer children treated with BIS had one or more exacerbation requiring oral corticosteroid therapy compared with those receiving placebo (40% vs 83%; $p < 0.01$).[14] Moreover, the duration of oral corticosteroid use was shorter among children in the BIS group (0% vs 14.5% of total treatment time; $p < 0.05$). The incidence of daytime wheezing (2.2% with BIS vs 11.6% with placebo) and night-time wheezing (0.6% with BIS vs 6.5% with placebo) also was significantly lower in children receiving BIS ($p < 0.05$ and $p < 0.01$, respectively).[14]

In another study, 36 children younger than 5 years of age with severe asthma requiring a minimum therapy of prednisolone 0.75 mg/kg on alternate days for ≥4 weeks before the study were randomised to double-blind treatment with BIS 1.0mg or placebo twice daily for 8 weeks.[15] After the initial 8 weeks, all children received open-label treatment with BIS for an additional 8 weeks. Children in the BIS group had significant improvements in daytime symptoms and health status compared with children in the placebo group during the double-blind treatment period.[15] Moreover, at the end of the double-blind treatment period, children treated with BIS had an approximately 2-fold greater reduction in the use of oral corticosteroids compared with placebo recipients (80% vs 41%, respectively; $p < 0.05$).[15] Similarly to the BIS group, children in the placebo group had significantly improved health status ($p < 0.001$) and decreased oral corticosteroid use ($p < 0.00001$) when switched to open-label treatment with BIS.[15]

A larger randomised, double-blind, parallel-group study by Wennergren et al.[16] evaluated the efficacy of BIS maintenance therapy over 18 weeks in 102 children aged 5–47 months. Children had persistent asthma that was not controlled by the use of nonsteroidal medications. Children were randomised to receive nebulised budesonide 0.25 or 1.0mg twice daily. Children were assessed every third week at clinic visits to determine if they met the symptom criteria for dose reduction. Children in the 1.0mg treatment group had their dose halved if they met these criteria, whereas children in the 0.25mg group remained at the same dosage level.[16] The goal of this study was to identify the minimal effective dose of budesonide that would provide symptom control.[16] Patient flow through the study was similar for both treatment groups. Overall, a minimal effective dose of 0.25mg twice daily was achieved in 48 children: 12 in the high-dose group and 36 in the low-dose group. The median time to achieve 7 consecutive days without symptoms was not significantly different between children starting with the high- versus the low-dose treatment regimen (30 and 24 days, respectively).[16]

The efficacy of BIS for the treatment of infants and children was further established in three large randomised, placebo-controlled US trials that included 1018 infants and young children aged 6 months to 8 years with mild-to-severe persistent

asthma.[17-20] In all three studies, children old enough to perform pulmonary function tests were required to have a forced expiratory volume in 1 second (FEV_1) of ≥50% of predicted normal and reversibility of ≥15% after a standard dose of salbutamol.[17-19] In the study by Kemp et al.,[18] children were included who had exacerbations of cough or wheeze in the 6 months before the study, daily use of one or more asthma controller medication (excluding inhaled corticosteroids) and periodic use of a rescue bronchodilator for ≥3 months before the study. In the study by Baker et al.,[17] children must have had exacerbations of cough/wheeze on a recurrent basis, with infrequent severe exacerbations during the 6 months before the study. These patients could be receiving an inhaled corticosteroid as controller medication before the study.[17] Shapiro et al.[19] assessed the efficacy and tolerability of BIS in children with severe inhaled corticosteroid-dependent asthma who required rescue medication on ≥5 of 7 days during the baseline period.

Each study included a 2-week run-in phase, after which patients were randomised to receive BIS at varying doses once or twice daily, or placebo for 12 weeks (table II).[17-20] At the end of the 12-week treatment period, eligible patients were randomised to an additional 52 weeks of open-label treatment with BIS or conventional asthma therapy.[21] Conventional asthma therapy included β_2-adrenoceptor agonists, methylxanthines and sodium cromoglicate. In the open-label extensions of the studies by Baker et al.[17] and Shapiro et al.,[19] conventional asthma therapy could also include inhaled corticosteroids. The primary objective of these 52-week studies was to assess the long-term safety of BIS maintenance therapy. Safety results of these studies are discussed in section 3.

In the 12-week studies of BIS, efficacy was assessed on the basis of asthma symptoms, rescue medication use and pulmonary function (morning and evening peak expiratory flow [PEF], and FEV_1) in those patients able to consistently perform pulmonary function tests. Asthma symptoms were rated on a 4-point scale, where 0 = no symptoms, 1 = mild symptoms (awareness of asthma symptoms and/or signs that were easily tolerated), 2 = moderate symptoms (asthma symptoms and/or signs with some discomfort, causing interference with daily activities or sleep) and 3 = severe symptoms (incapacitating symptoms and/or signs, with inability to perform daily activities or to sleep).[17-19] Efficacy results of the three pivotal BIS studies are shown in table II. In the BIS treatment group, improvements in asthma symptoms were evident within 2 weeks of initiating treatment in all three studies and were maintained throughout the 12-week study periods.[17-19] Among patients with mild persistent asthma in the study by Kemp et al.,[18] once-daily BIS (0.25, 0.5 and 1.0 mg/day) provided statistically significant improvements in daytime and night-time symptom scores ($p \leq 0.05$ for all) versus placebo. Improvements were similar across all once-daily BIS treatment groups. With the exception of once-daily treatment with BIS 0.25mg in children with moderate persistent asthma,[17] improvements in daytime and night-time asthma symptom scores in patients with moderate-to-severe disease were significant for all BIS dosages.[17,19]

Pulmonary function generally improved with BIS treatment (table II). In children with moderate asthma, BIS dosages of 0.25–1.0 mg/day produced statistically significant improvements versus placebo in PEF. Changes from baseline morning PEF ranged from 10.9 to 24.8 L/min, and changes from baseline evening PEF ranged from 14.1 to 21.0 L/min.[17] In children with inhaled corticosteroid-dependent asthma, all BIS dosages (0.25, 0.50 and 1.0mg twice daily) produced statistically significant improvements compared with placebo in morning PEF; significant improvement in evening PEF was demonstrated only with the 0.25mg twice-daily regimen.[19] Improvements in morning PEF values were also observed in children with mild asthma; however, improvements did not reach statistical significance.[18] With the exception of the BIS 0.25mg once-daily dose in children with mild persistent asthma reported by Kemp et al.,[18] FEV_1 increased from baseline in all three studies. Improvements from baseline were statistically significant versus placebo in children with mild persistent asthma

Table II. Mean changes from baseline in efficacy variables during the three 12-week US pivotal randomised, placebo (PL)-controlled studies of budesonide inhalation suspension (BIS) in infants and children

Study[a]	Patient age	Treatment group (total no. of patients)	Asthma symptom score[b] (no. of patients)		Rescue medication use [days/2 weeks]	PEF [L/min][c] (no. of patients)		FEV_1[c] (L) (no. of patients)
			daytime	night-time	(no. of patients)	morning	evening	
Kemp et al.[18,20]	6mo–8y	BIS 0.25mg od (91)	−0.57** (91)	−0.49*** (91)	−6.26* (91)	14.4 (44)	NR	−0.01 (29)
		BIS 0.5mg od (83)	−0.46* (83)	−0.42** (83)	−6.31* (83)	6.5 (41)	NR	0.03* (28)
		BIS 1.0mg od (93)	−0.50* (93)	−0.42** (93)	−5.98* (93)	10.9 (55)	NR	0.03* (33)
		PL (92)	−0.26 (92)	−0.16 (92)	−4.19 (92)	7.1 (55)	NR	−0.07 (38)
Baker et al.[17,20]	6mo–8y	BIS 0.25mg od (94)	−0.28 (92)	−0.28 (93)	−4.4* (94)	10.9 (32)	16.8* (32)	0.07 (31)
		BIS 0.25mg bid (99)	−0.40* (97)	−0.49*** (97)	−5.2* (99)	23.0** (34)	19.2* (34)	0.08 (33)
		BIS 0.5mg bid (98)	−0.46** (96)	−0.42** (96)	−4.9* (98)	24.8** (29)	21.0** (29)	0.17* (29)
		BIS 1.0mg od (95)	−0.37* (93)	−0.40** (93)	−4.4* (95)	17.1* (34)	14.1 (34)	0.11 (34)
		PL (95)	−0.19 (92)	−0.13 (92)	−2.4 (95)	−0.20 (32)	1.9 (32)	0.04 (28)
Shapiro et al.[19,20]	4–8y	BIS 0.25mg bid (47)	−0.45* (47)	−0.36* (47)	Decrease*[d] (47)	15.3** (47)	14.9* (47)	0.05 (47)
		BIS 0.5mg bid (42)	−0.53** (42)	−0.37* (42)	Decrease**[d] (42)	11.8* (42)	11.6 (42)	0.08* (42)
		BIS 1.0mg bid (45)	−0.55** (45)	−0.36* (45)	Decrease*[d] (45)	10.4* (45)	13.2 (45)	0.07 (45)
		PL (44)	−0.11 (44)	−0.08 (44)	Decrease (44)	−1.3 (44)	3.0 (44)	−0.01 (44)

a Mellon, on behalf of the Budesonide Inhalation Suspension Study Group,[20] reviewed the efficacy results from all three privotal trials. This paper provided additional details not originally published.

b Based on a 4-point scale from 0 = no symptoms to 3 = severe symptoms.

c Assessed in children capable of consistently performing pulmonary function tests.

d Statistically significant; values not provided.

bid = twice daily; **FEV_1** = forced expiratory volume in 1 second; **NR** = not reported; **od** = once daily; **PEF** = peak expiratory flow; * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs PL.

treated with BIS 0.5 or 1.0mg once daily,[18] and in children with moderate or severe persistent asthma treated with BIS at the 0.5mg twice-daily dosage level.[17,20]

In all three studies, BIS therapy significantly reduced the need for rescue bronchodilator use compared with placebo (table II).[17-20] In children with mild or moderate persistent asthma, BIS decreased the number of days that bronchodilators were required by 4.4–6.3 days per 2-week period compared with reductions of 2.4–4.2 days per 2-week period for children receiving placebo.[17,18] Furthermore, children with inhaled corticosteroid-dependent asthma who were treated with BIS were less likely to receive a course of parenteral or oral corticosteroids during the course of the study (5–18%) than those treated with placebo (36%).[19]

BIS is effective across all age groups. In the studies evaluating infants and children with mild or moderate persistent asthma, similar improvements in all age groups were observed when patients were stratified by age.[17,18] Similar results were obtained in retrospective analyses of pooled data from these two trials. When patients were stratified according to age (<4 vs ≥4 years), BIS was similarly effective in both age groups when administered once daily[22] or twice daily.[23]

2.1.2 Comparative Trials

Recent studies have compared the efficacy of BIS with that of other controller medications in children with persistent asthma. In a 52-week randomised trial conducted in young children with mild-to-moderate persistent asthma, BIS provided significantly greater asthma control compared with sodium cromoglicate nebuliser solution.[24] In this study, 335 children aged 2–6 years were randomised to receive treatment with BIS 0.5 mg/day (either once or in two divided doses, n = 168) or sodium cromoglicate 80 mg/day (n = 167) for an initial 8 weeks, after which study drug dosages were titrated at investigators' discretion.[24] At the completion of the study, the mean daily dose of BIS ranged from 0.54 to 0.61mg. The corresponding range for sodium cromoglicate was 76.3 to 65.0mg.[24] Children in the BIS group had a significantly lower mean exacerbation rate (1.23 vs 2.41 exacerbations per year; $p < 0.001$), a longer mean time to first exacerbation (217 vs 148 days; $p < 0.001$) and a longer mean time to first added long-term asthma medication (321 vs 235 days; $p < 0.001$) compared with children in the sodium cromoglicate group.[24] Children treated with BIS also had improvements in daytime and night-time symptom scores that were almost double those of children treated with sodium cromoglicate ($p < 0.001$).[24] In addition, BIS was associated with a significantly greater decrease in the need for rescue medication ($p < 0.001$) and reduced emergency department and urgent care visits (figure 1).[24] Decreased healthcare resource use in this study was consistent with the findings of a named-patient case series (n = 15), in which ≥1 year of treatment with BIS 0.25–1.5 mg/day reduced the need for emergency intervention in children aged 10–35 months who had frequent asthma-related hospitalisations (figure 2).[25]

Analysis of child health status and the quality of life of caregivers of children treated with BIS or sodium cromoglicate demonstrated a trend towards a greater improvement in overall health status with BIS than sodium cromoglicate.[26] Significantly greater improvements in quality of life overall, and in activities and emotional functioning, were also shown in caregivers of children treated with BIS.

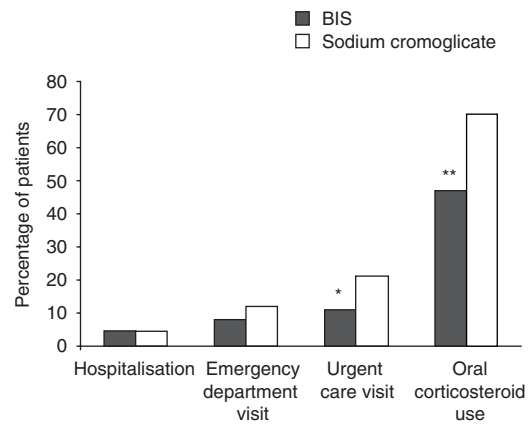

Fig. 1. Healthcare resource utilisation over 1 year in children treated with budesonide inhalation suspension (BIS) and sodium cromoglicate (cromolyn sodium) nebuliser solution.[24] * p = 0.02, ** p < 0.01 vs sodium cromoglicate.

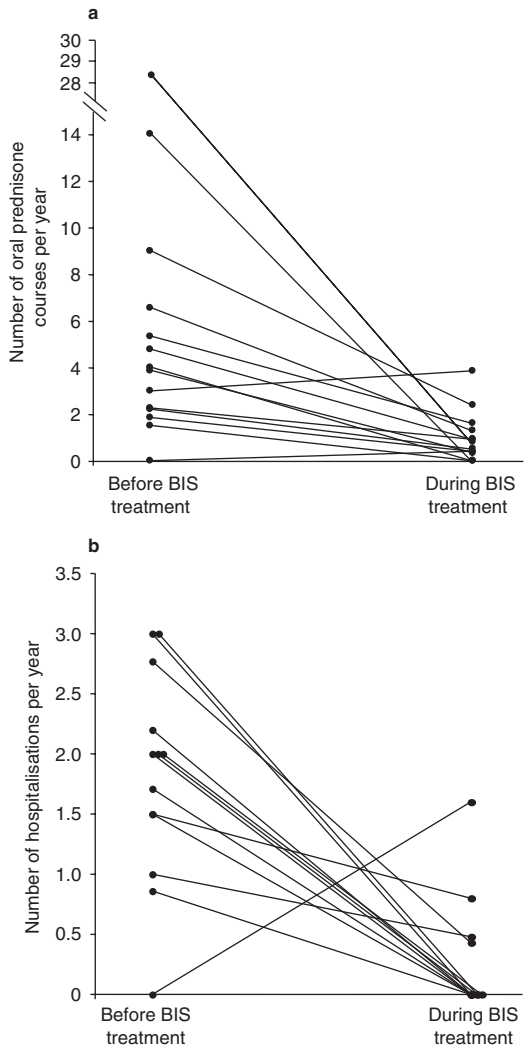

Fig. 2. Yearly number of (**a**) 1-week oral prednisone courses and (**b**) hospitalisations for asthma and upper respiratory tract infection in children before and during treatment with budesonide inhalation suspension (BIS) [copyright 2003 from Chipps et al.[25] Reproduced by permission of Taylor & Francis Group, LLC., http://www.taylorandfrancis.com].

Quality-of-life improvements with BIS were clinically meaningful (≥0.5 unit change) throughout the 1-year study.[26]

Two randomised trials have compared the efficacy of BIS with that of nebulised beclometasone in children with persistent asthma.[27,28] In one study, 127 children aged 6–14 years with mild-to-moderate asthma were randomised to receive nebulised beclometasone 0.8 mg/day or BIS 1.0 mg/day administered twice daily for 4 weeks.[28] Children in both treatment groups demonstrated significant improvements from baseline in pulmonary function, asthma symptoms and rescue medication use. Mean clinic PEF, the primary study variable, increased similarly for patients receiving BIS (from 180.4 to 260.9 L/min; $p < 0.001$) and beclometasone (from 177.5 to 246.6 L/min; $p < 0.001$).[28] Improvements in FEV_1, forced vital capacity, asthma symptom scores, use of rescue medication, nocturnal awakening and diurnal dyspnoea were similar between treatments.[28]

Similar results were obtained in a second study in which BIS (0.75 mg/day) and nebulised beclometasone (0.8 mg/day) were administered in a twice-daily regimen for 14 weeks to 130 infants and children aged 6 months to 6 years who had severe persistent asthma.[27] There was no significant difference observed between children treated with BIS and those treated with beclometasone with respect to the primary efficacy endpoint, the proportion of children who were exacerbation-free (51.7% vs 40.4%, respectively; $p = 0.22$).[27] Improvements in oral corticosteroid use, salbutamol use, and days or nights with wheezing or coughing were also similar between groups.[27]

2.2 Acute Asthma or Wheezing

The risks associated with repeated oral corticosteroid therapy are well established and include fracture,[29] cataract formation,[30] infection,[31] and cognitive or mood changes[32] among others. Thus, the value of inhaled corticosteroid therapy for the treatment of asthma cannot be understated. The efficacy of BIS in the treatment of acute exacerbations of asthma has been assessed as an adjunct to oral prednisone therapy[33] and compared with oral prednisolone,[34-37] nebulised ipratropium bromide,[38] nebulised terbutaline[35] and placebo.[35] Although limited, data demonstrate that BIS is clinically effective for the treatment of acute asthma in children.[33-38] In the randomised, double-blind, parallel-group study by Matthews et al.,[34] 46 children and

adolescents aged 5–16 years who were hospitalised with a severe asthma exacerbation were randomised to receive BIS 2.0mg every 8 hours or prednisolone 2.0 mg/kg (up to a maximum of 40mg) at randomisation and 24 hours. Improvements in the BIS and oral prednisolone groups at 24 hours were similar for most efficacy parameters (FEV_1, PEF, severity of cough and wheeze); improvement in shortness of breath was significantly greater in children treated with BIS.[34] A second randomised, double-blind study conducted in children aged 2–12 years with acute attacks of asthma demonstrated superiority of BIS 0.8mg plus nebulised salbutamol administered three times at half-hourly intervals (n = 41) over a single dose of oral prednisolone 2.0 mg/kg plus salbutamol administered at half-hourly intervals (n = 39). After the third dose of nebulised treatment, the oxygen saturation, respiratory rate, pulmonary index and respiratory distress score were significantly improved with BIS versus prednisolone ($p < 0.01$).[36] Two hours after the third treatment, significantly more patients in the BIS group were fit for discharge (54% vs 18%; $p < 0.001$).[36]

In infants and children aged ≤24 months who were hospitalised with acute wheeze and dyspnoea, the addition of BIS 0.25mg administered every 6 hours to a regimen of intravenous fluid, hydrocortisone and nebulised fenoterol improved clinical scores more rapidly and decreased hospital length of stay compared with the addition of a similar regimen of nebulised ipratropium bromide 0.1mg.[38] In an earlier study of 123 children aged ≤18 months with acute wheeze, BIS was associated with a shorter hospital length of stay compared with nebulised terbutaline.[35] Improvement in the symptom score compared with placebo was significant for children treated with BIS but not for those treated with terbutaline or prednisolone.[35]

Another study demonstrated that BIS also effectively decreases symptoms in infants and children aged 6 months to 3 years who have had recurrent episodes of wheeze.[39] Forty-two children who had three or more wheezing episodes and asthma symptoms on >40% of days in the 3 months before the study were assessed.[39] A high starting dose of BIS (1.0mg twice daily followed by a stepwise decrease) was more effective than a lower starting dose (0.25mg twice daily) in decreasing early symptoms, resulting in a significantly earlier mean time to clinical response (3.0 vs 5.7 days; $p = 0.02$) with the higher BIS dosage regimen.[39]

3. Safety

3.1 Adverse Events

In the three pivotal US BIS trials, the overall type, incidence and severity of adverse events did not differ significantly in children treated with BIS compared with those who received placebo.[17-19] Moreover, there were no apparent dose-related trends in the incidence of adverse events, with similar rates across dosage groups.[17-19,40] Overall, rates for the most frequent adverse events were similar for children treated with BIS and placebo: respiratory infections (34–38% vs 36%, respectively), fever (9–19% vs 23%), sinusitis (12–16% vs 17%), otitis media (7–12% vs 12%) and rhinitis (8–12% vs 10%).[40] In addition, the incidences of serious adverse events in children who received BIS or placebo were similar (2% and 3%, respectively) as was the proportion of children who discontinued treatment because of adverse events (2% and 1%).[40]

Although specific ophthalmological examinations were not performed in the three pivotal trials, there were no reports of subcapsular or lenticular cataracts.[41] In worldwide postmarketing surveillance of BIS that extended from January 1990 through to June 2002, three reports of cataract were identified in children (aged 9 months, 24 months and 14 years); however, two of these cases had confounding factors (e.g. prematurity, history of congenital cataracts).[41] There were also no clinically significant differences reported between children treated with BIS or placebo in vital signs, physical examination findings or laboratory test results (including nasal and fungal cultures) over the course of the studies.[17-19] Dysphonia was reported in <3% of patients in the three US double-blind and open-label studies of BIS and occurred in one patient from each treatment group in the 52-week open-label compara-

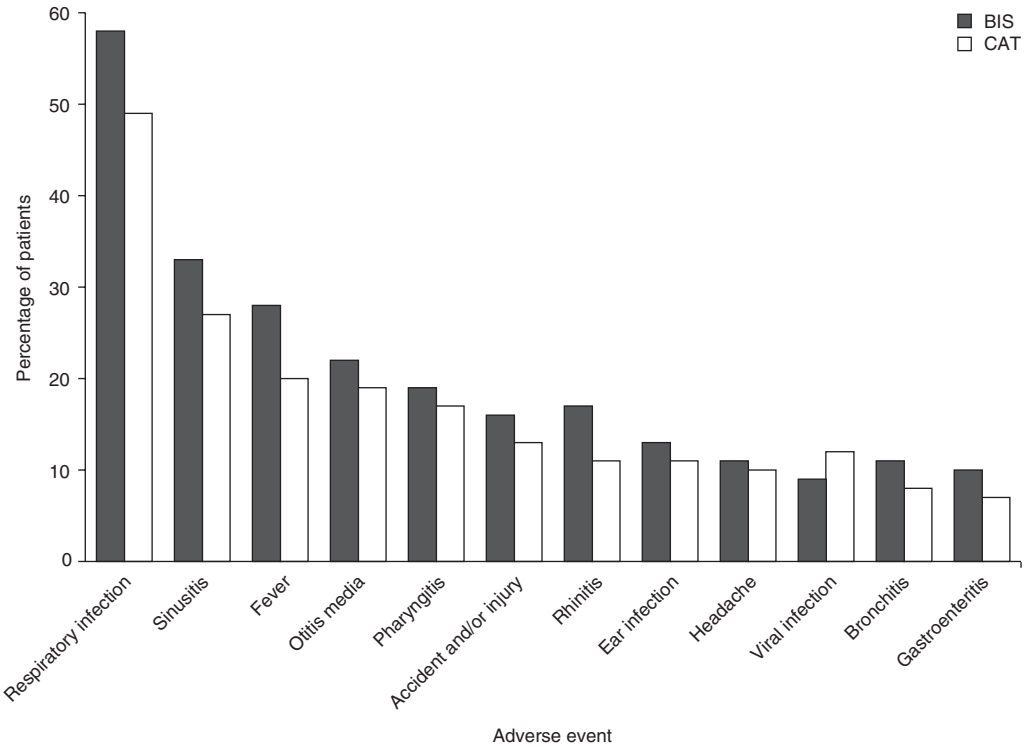

Fig. 3. Most common adverse events in children aged 6 months to 8 years receiving budesonide inhalation suspension (BIS) or conventional asthma therapy (CAT) [adverse events reported by ≥10% of children in any treatment group during the 1-year extensions of the BIS pivotal studies].[40]

tor trial conducted with sodium cromoglicate.[41] Only one case of dysphonia and three cases of hoarseness were reported in postmarketing surveillance of BIS.[41]

Tolerability of BIS in terms of adverse events was similar for the 670 patients who completed the 52-week open-label extensions of the 12-week studies.[21,40] After adjusting for the duration of drug exposure, there was no significant difference in the rates of adverse events between patients in the BIS (n = 447) and conventional asthma therapy (n = 223) groups (figure 3), with similar results across patient subpopulations (i.e. based on gender, race or age).[21,40] There was also no difference between the BIS and conventional asthma therapy groups in the percentage of patients who experienced a serious adverse event (8.3% vs 8.1%, respectively) or who discontinued treatment because of an adverse event (0.7% vs 0.4%, respectively).[40]

A recent 12-week, randomised, double-blind, placebo-controlled study assessed the safety of BIS 0.5 and 1.0mg administered once daily in 141 infants aged 6–12 months who had mild-to-moderate persistent asthma or recurrent wheeze.[42] In this study by Berger et al.,[42] the percentages of infants who experienced one or more adverse event while receiving BIS 0.5mg, BIS 1.0mg or placebo were 90%, 98% and 88%, respectively. The most frequently reported adverse events are shown in figure 4.[42] Overall, the types and frequencies of adverse events were similar across treatment groups. With the exception of rhinitis, the frequencies of adverse events also were similar in the age strata of 6 to <9 months and 9 to <12 months. Serious adverse events were reported in two patients who received BIS 1.0mg (asthma, pneumonia) and in three patients who received BIS 0.5mg (asthma, respiratory infection, viral infection); none was related to treat-

ment.[42] The number of positive nasal fungal cultures was low and similar between the treatment groups.[42]

3.2 Adrenal Function

In the three pivotal US studies, BIS produced no clinically relevant changes in adrenal function at any dosage level. There were no clinically relevant differences in basal cortisol levels throughout the studies, and changes from baseline to week 12 were similar in children who received BIS at dosages of 0.25–2 mg/day and those who received placebo.[17-19] In the study by Shapiro et al.,[19] the highest BIS dosage (1.0mg twice daily) produced an approximate 10% decrease in corticotropin (ACTH)-stimulated plasma cortisol levels, but only one patient in this group shifted from a normal to abnormal stimulated response during the study.[19,43] Similarly to the 12-week studies, no significant difference in mean basal or ACTH-stimulated cortisol levels were observed between treatment groups during the 52-week open-label extensions (figure 5).[40,43] Overall, BIS therapy did not affect the proportion of children with shifts from normal responses to tetracosactide (cosyntropin) at baseline to abnormal responses at week 12 (9–13% for BIS vs 15% for placebo)[17-19,43] or week 52 (24% for BIS vs 21% for conventional asthma therapy).[40,43] In the comparator trial by Leflein et al.,[24] basal and ACTH-stimulated plasma cortisol levels at baseline and week 52 were similar for patients treated with BIS and those treated with sodium cromoglicate.

In the 12-week study by Berger et al.[42] conducted in infants aged 6–12 months, mean tetracosactide-stimulated plasma cortisol levels at study end were 674, 661 and 650 nmol/L for infants who received BIS 0.5mg, BIS 1.0mg or placebo, respectively. Changes from baseline in poststimulated

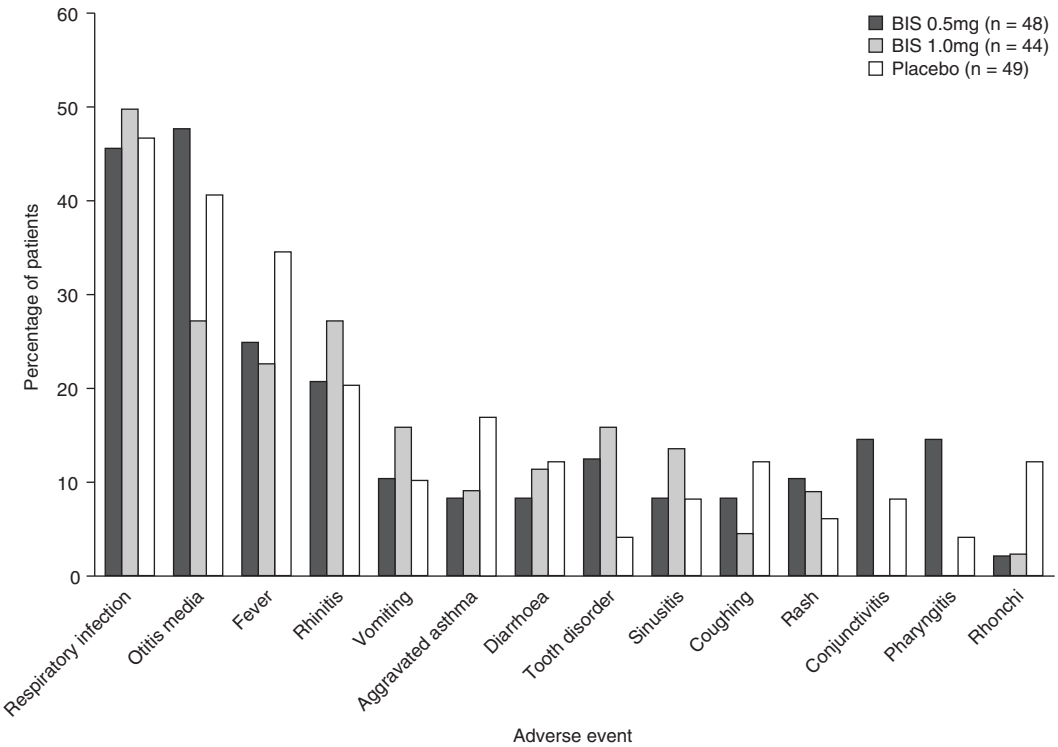

Fig. 4. Most common adverse events in infants aged 6–12 months with mild-to-moderate asthma receiving budesonide inhalation suspension (BIS) or placebo (adverse events reported by ≥10% of infants in any treatment group during 12 weeks of double-blind treatment).[42]

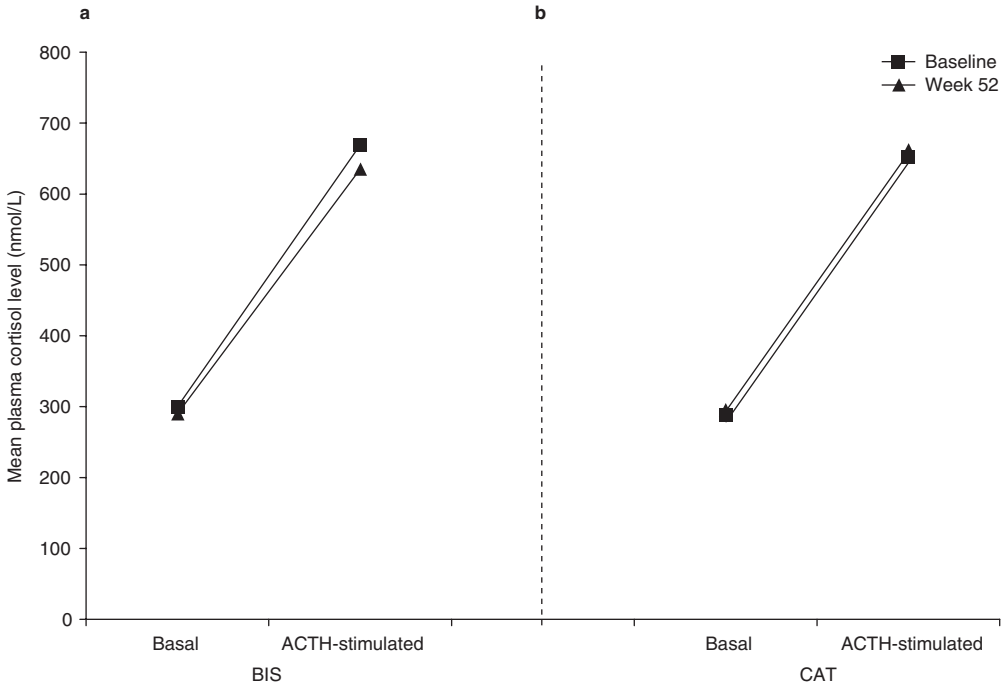

Fig. 5. Mean basal and corticotropin (ACTH)-stimulated plasma cortisol levels at baseline and after 52 weeks of treatment with (**a**) budesonide inhalation suspension (BIS) or (**b**) conventional asthma therapy (CAT) in children with persistent asthma (reproduced from Irani et al.,[43] with permission of the Annals of Allergy, Asthma, & Immunology. © 2002).

plasma cortisol levels were similar between groups. Seven patients had a shift in tetracosactide-stimulated plasma cortisol responses from normal at baseline to abnormal at week 12; four (14.3%) and two (11.8%) in the BIS 0.5 and 1.0mg treatment groups, respectively, and one (3.2%) in the placebo group.[42] Results in infants stratified by age (6 to <9 months and 9 to <12 months) were consistent with the overall results.[42]

3.3 Growth

Although the short-term pivotal trials of BIS were not prospectively designed to assess growth, data from the 52-week open-label extensions demonstrated a small effect of BIS on growth in one of the three studies.[40,44] In the 52-week follow-up study[40] of the trial by Kemp et al.[18] involving children with mild asthma and no prior exposure to inhaled corticosteroids, growth velocity was reduced by about 0.8 cm/year in children treated with BIS (0.25–1.0 mg/day) versus placebo (6.55 ± 2.08 vs 7.39 ± 2.52 cm/year; $p = 0.002$).[40] However, the pooled analysis (Kemp et al.,[18] Shapiro et al.[19] and Baker et al.[17]) showed a nonsignificant difference in growth velocity of 0.1cm between the BIS and conventional asthma therapy groups. The differences in growth observed among these three studies might be related to the severity of underlying asthma. Kemp et al.[18] included patients with mild asthma, whereas the patients in the studies by Baker et al.[17] and Shapiro et al.[19] had more severe asthma. Finally, in the studies by Baker et al.[17] and Shapiro et al.,[19] which evaluated skeletal age, mean differences between skeletal and chronological age were similar between children treated with BIS (0.25–2.0 mg/day) and those treated with conventional asthma therapy.[44] Although not designed as a prospective growth study, a small but significant reduction in growth velocity (–0.86 cm/year; $p < 0.001$) was reported with BIS in the 52-week

comparator study by Leflein et al.[24] In the aforementioned Berger et al.[42] study of infants aged 6–12 months, mean height increased from baseline in all treatment groups; baseline-adjusted increases in height were 0.2cm (95% CI −0.6, 1.0) and 0.6cm (95% CI −0.2, 1.4) in patients treated with BIS 0.5 and 1.0mg, respectively, compared with placebo.

Evidence suggests that predicted adult height is achieved irrespective of the short-term growth delay associated with inhaled corticosteroid therapy.[45-49] Data from the CAMP (Childhood Asthma Management Program) study indicated that while budesonide (delivered via a dry powder inhaler [DPI]) was associated with a smaller mean increase in height compared with placebo at the end of treatment (1.1cm), there was no difference between groups for mean projected final height.[48] This transient growth effect is supported by the results of a prospective cohort study in which children with mild-to-moderate asthma treated with an average daily dose of inhaled budesonide of 110–877μg (mean duration 9.2 years) attained normal predicted adult height.[49] These findings suggest that any effect on growth is transient, and that children receiving inhaled budesonide should reach their final predicted adult height.[4,48,49]

4. Dosage and Administration

Dose responses based on standard efficacy asthma outcomes are difficult to demonstrate for inhaled corticosteroids. Accordingly, there were no consistent dose-related trends with respect to efficacy parameters in the three large placebo-controlled trials,[17-19] except that the 0.25mg once-daily dosage appeared to be less effective compared with the higher dosages.[17] Although the effect of divided doses on the efficacy of BIS was not formally evaluated, BIS 0.5mg twice daily produced numerically superior results to BIS 1.0mg once daily in children with moderate asthma.[17] The evidence generally supports total daily BIS doses of 0.25–1.0mg as being effective in children with mild-to-moderate persistent asthma,[17,18,24,28] whereas patients with more severe disease may require the higher doses of 0.5–2.0 mg/day.[14-16,19,25,27] Moreover, in a case series of 56 infants and children with frequent severe asthma exacerbations, de Jongste and Duiverman[50] reported effective doses of up to 2.5 mg/day. In addition to the child's disease severity, the physician should also consider the manufacturer's recommendations when selecting appropriate dosages.

In the US, BIS is indicated for use in patients with asthma who are aged 12 months to 8 years. The recommended starting dose of BIS for patients previously receiving either bronchodilators alone or inhaled corticosteroids is 0.5 mg/day (either once daily or twice daily in divided doses). A starting dose of 0.25 mg/day may also be considered for children who are symptomatic whilst receiving nonsteroidal therapy. A higher starting dose (1.0 mg/day) is recommended for those patients previously receiving oral corticosteroids.[13] If once-daily administration does not provide adequate control of asthma symptoms, consideration should be given to either increasing the total dose or administering the drug in divided doses.[13] The maximum recommended daily dose is 0.5 mg/day for patients previously receiving bronchodilators alone and 1.0 mg/day for those receiving prior inhaled or oral corticosteroids.[13] In the UK, the recommended starting dose of BIS is 0.5–1.0mg twice daily for children aged 3 months to 12 years and 1.0–2.0mg twice daily for adolescents ≥12 years, with recommended maintenance doses being typically half the initial dose.[12]

The benefit of a high starting dosage of BIS was demonstrated in a relatively small study in infants and young children with recurrent wheeze (n = 42), in which BIS 1.0mg administered twice daily, followed by a stepwise decrease of 25% every second day for 1 week, was associated with significantly greater early improvement in asthma symptoms compared with a constant dose of 0.25mg administered twice daily.[39] A 12-week, randomised, double-blind, parallel-group study conducted in 64 children aged 6–40 months with three or more asthma exacerbations in the previous year similarly demonstrated greater efficacy with a higher BIS starting dose. BIS 2.0 mg/day resulted in significantly less daytime and night-time wheezing compared with a

starting dose of 0.5 mg/day. Although the percentage of children requiring oral corticosteroids to treat an exacerbation was lower in the 2.0 mg/day BIS group (37% vs 47%), the difference was not statistically significant ($p = 0.42$).[51] In contrast to these studies, results of another 12-week, randomised, double-blind study demonstrated no significant differences in symptom control, hospital visit frequency and rescue medication use in children with recurrent bronchial obstruction who were younger than 18 months of age and who received BIS 1.0 mg/day for 1 month followed by 0.25 mg/day for 2 months ($n = 24$) versus BIS 0.2 mg/day for 3 months ($n = 25$).[52]

The choice of nebuliser affects the delivery of BIS. Conventional ultrasonic nebulisers inefficiently aerosolise BIS and, thus, are not suitable for administration of BIS.[53] Smaldone et al.[54] demonstrated that BIS can be successfully administered via several commercially available jet nebuliser/compressor systems. However, the study demonstrated a substantial variability in performance, with values for inhaled mass ranging from 2% to 18% of the nebuliser charge.[54] Among the 13 most efficient systems, the mass median aerodynamic diameter ranged from 3.8 to 5.5μm, which is considered within the respirable range.[54] One of the most efficient nebuliser/compressor systems was the Pari LC-Jet Plus® nebuliser with a Pari-Master® compressor. The pivotal studies evaluated BIS administered via this nebuliser/compressor system.[17-19] A randomised, single-blind, crossover study compared the clinical effect of budesonide administered via the Aiolos® or Pari LL® nebuliser in 38 children aged <4 years who had a chronic wheeze. Although this study demonstrated a 2-fold difference between nebulisers in the percentage of the nominal drug dose delivered to the patient, no significant effect on clinical outcomes or the minimal effective dose was observed in this study.[55] These studies highlight the differences in drug delivery based on different nebuliser designs. However, additional factors that affect aerosol delivery include patient characteristics (e.g. breathing pattern) and caregiver variables (i.e. facemask seal, blow-by technique).[54,56] For example, Geller et al.[57] recently demonstrated that use of the blow-by technique (1.5cm from the face) decreased lung deposition of budesonide by as much as 43%.

Retrospective analyses of the 12-week pivotal studies by Kemp et al.[18] and Baker et al.[17] demonstrated similar efficacy of BIS when delivered via a jet nebuliser using either a facemask or mouthpiece.[58,59] Retrospective safety analysis of the study by Baker et al.[17] demonstrated a similar incidence, type and severity of non-asthma-related adverse events among children in the BIS (facemask and mouthpiece) and placebo treatment groups. Moreover, no clinically significant between-group differences were observed in vital signs, physical findings or laboratory test results (including nasal or oral fungal cultures).[20]

In vitro, BIS has demonstrated chemical compatibility and physical stability over 30 minutes when admixed in a nebuliser cup with levalbuterol hydrochloride, salbutamol, sodium cromoglicate and ipratropium bromide.[60] These findings suggest that BIS may be mixed with any of these commonly nebulised asthma medications. While this approach to drug administration may increase the overall duration of nebulisation therapy, it may also allow for more convenient administration of multiple medications.

5. The Role of Budesonide Inhalation Suspension in the Treatment of Infants and Children with Asthma

Inhaled corticosteroids are the cornerstone treatment for persistent asthma in patients of all ages. According to the NAEPP, inhaled corticosteroids administered via nebuliser or metered-dose inhaler (MDI) with a holding chamber, with or without a facemask, or via DPI are the preferred agents for the long-term control of persistent asthma of any severity in infants and young children.[4] Previously, sodium cromoglicate and nedocromil were considered first-line treatment options for children aged ≤5 years who have mild persistent asthma; however, substantial evidence supporting inhaled corticosteroids as the preferred controller therapy in children

was provided by the CAMP study. In this trial, continuous long-term treatment with budesonide (mean follow-up 4.3 years) via DPI produced significant improvements in airway responsiveness, asthma symptoms and rescue medication use compared with placebo in 1041 children aged 5–12 years who had mild-to-moderate persistent asthma. Nedocromil provided little or no benefit with regard to these outcomes compared with placebo.[48]

The efficacy and safety of BIS in infants and children are well established. Among other studies, three US randomised, double-blind, placebo-controlled studies involving >1000 infants and children aged 6 months to 8 years have demonstrated that BIS improves daytime and night-time asthma symptoms, decreases rescue medication use and improves pulmonary function across all asthma severities.[17-19] In comparative trials in children with persistent asthma, BIS was superior to nebulised sodium cromoglicate[24-26] and as effective as nebulised beclometasone.[27,28]

BIS has a favourable long-term safety profile, with an incidence of adverse events that does not differ from that of placebo. Although concerns exist regarding the potential effects of inhaled corticosteroid use on adrenal function and growth, the NAEPP's evidence-based guidelines concluded that "the use of inhaled corticosteroids at recommended doses does not have long-term, clinically significant, or irreversible effects" on the adrenal/pituitary axis or vertical growth.[4]

Combined data from the three pivotal trials of BIS and their open-label extensions demonstrated no effect on adrenal function in children aged 6 months to 8 years, and an additional 12-week study demonstrated no adverse effects on adrenal function in infants aged 6–12 months. However, it should be noted that isolated cases of adrenal suppression have been reported in children receiving high-dose BIS therapy[61] or discontinuing long-term treatment with inhaled budesonide.[62] With respect to growth, children treated with BIS have demonstrated small but statistically significant reductions in growth velocity over 1 year in some studies. The class effect of corticosteroids on growth is well established; however, evidence suggests that these short-term effects do not typically prevent achievement of predicted adult height.[45-47] Nevertheless, growth should be monitored in all children who receive long-term inhaled corticosteroid treatment.

Selection of the most appropriate administration device for inhaled corticosteroids has the potential to influence the degree of asthma symptom control. Therefore, it is important for clinicians to assess the ability of a child to use the administration device when selecting a therapy. Children younger than 4 years are often unable to effectively use MDIs or DPIs; the availability of a nebulised inhaled corticosteroid formulation provides a valuable option for effective delivery of therapy to this age group.

6. Conclusions

In conclusion, BIS has well established efficacy and safety in the treatment of infants and children with all degrees of asthma severity. In the US, BIS is the only inhaled corticosteroid available for nebulisation, and it is the first and only inhaled corticosteroid approved by the US FDA for use in children aged <4 years. On the basis of its long-term efficacy and safety record, and its potential for greater ease of use compared with other inhaled corticosteroid formulations, especially for young patients, BIS represents a valuable first-line treatment option for infants and children with persistent asthma.

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References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. NIH Publication No. 02-3659. Issued January, 1995 (updated 2002). Management segment (chapter 7): updated 2003 from the 2002 document: 1-180 [online]. Available from URL: http://www.ginasthma.com [Accessed 2005 Aug 9]
2. AAAAI. Pediatric asthma: promoting best practice. Guide for managing asthma in children. Milwaukee (WI): American Academy of Allergy, Asthma & Immunology, 2004: 1-143
3. American Lung Association, Epidemiology & Statistics Unit, Research and Scientific Affairs. Trends in asthma morbidity and mortality. 2004 Apr [online]. Available from URL: http://

www.texaslung.org/educationalresources/diseases/asthma/2004asthmatrends.pdf [Accessed 2005 Jul 22]

4. National Asthma Education and Prevention Program. Expert panel report: guidelines for the diagnosis and management of asthma: update on selected topics 2002. J Allergy Clin Immunol 2002; 110 (5 Suppl.): S141-219
5. Jeffery PK. Remodeling and inflammation of bronchi in asthma and chronic obstructive pulmonary disease. Proc Am Thorac Soc 2004; 1: 176-83
6. Tasche MJA, Uijen JHJM, Bernsen RMD, et al. Inhaled disodium cromoglycate (DSCG) as maintenance therapy in children with asthma: a systemic review. Thorax 2000; 55: 913-20
7. Barnes PJ. Efficacy of inhaled corticosteroids in asthma. J Allergy Clin Immunol 1998 Oct; 102 (4): 531-8
8. Brogden RN, McTavish D. Budesonide: an updated review of its pharmacological properties and therapeutic efficacy in asthma and rhinitis. Drugs 1992 Sep; 44 (3): 375-407
9. Hvizdos KM, Jarvis B. Budesonide inhalation suspension: a review of its use in infants, children and adults with inflammatory respiratory disorders. Drugs 2000 Nov; 60 (5): 1141-78
10. Szefler SJ. Pharmacodynamics and pharmacokinetics of budesonide: a new nebulized corticosteroid. J Allergy Clin Immunol 1999 Oct; 104 (4): S175-83
11. Agertoft L, Andersen A, Weibull E, et al. Systemic availability and pharmacokinetics of nebulised budesonide in preschool children. Arch Dis Child 1999 Mar; 80 (3): 241-7
12. Pulmicort Respules [summary of product characteristics]. Luton: AstraZeneca UK Ltd, 2001 Jun 11
13. Pulmicort Respules (budesonide inhalation suspension) prescribing information. Wilmington (DE): AstraZeneca LP, 2004 Mar
14. de Blic J, Delacourt C, Le Bourgeois M, et al. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. J Allergy Clin Immunol 1996 Jul; 98 (1): 14-20
15. Ilangovan P, Pedersen S, Godfrey S, et al. Treatment of severe steroid dependent preschool asthma with nebulised budesonide suspension. Arch Dis Child 1993 Mar; 68 (3): 356-9
16. Wennergren G, Nordvall SL, Hedlin G, et al. Nebulized budesonide for the treatment of moderate to severe asthma in infants and toddlers. Acta Paediatr 1996; 85: 183-9
17. Baker JW, Mellon M, Wald J, et al. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. Pediatrics 1999 Feb; 103 (2): 414-21
18. Kemp JP, Skoner DP, Szefler SJ, et al. Once-daily budesonide inhalation suspension for the treatment of persistent asthma in infants and young children. Ann Allergy Asthma Immunol 1999 Sep; 83: 231-9
19. Shapiro G, Mendelson L, Kraemer MJ, et al. Efficacy and safety of budesonide inhalation suspension (Pulmicort Respules) in young children with inhaled steroid-dependent, persistent asthma. J Allergy Clin Immunol 1998 Nov; 102 (5): 789-96
20. Mellon M, on behalf of the Budesonide Inhalation Suspension Study Group. Efficacy of budesonide inhalation suspension in infants and young children with persistent asthma. J Allergy Clin Immunol 1999 Oct; 104: S191-9
21. Leflein JG, Gawchik SM, Galant SP, et al. Safety of budesonide inhalation suspension (Pulmicort Respules) after up to 52 weeks of treatment in infants and young children with persistent asthma. Allergy Asthma Proc 2001 Nov-Dec; 22 (6): 359-66
22. Scott MB, Ellis MH, Cruz-Rivera M, et al. Once-daily budesonide inhalation suspension in infants and children <4 and ≥4 years of age with persistent asthma. Ann Allergy Asthma Immunol 2001 Dec; 87 (6): 488-95
23. Mendelson L, Cook D, Cruz-Rivera M, et al. Twice-daily budesonide inhalation suspension in infants and children <4 and ≥4 years of age with persistent asthma. J Asthma 2002 May; 39 (3): 227-37
24. Leflein JG, Szefler SJ, Murphy KR, et al. Nebulized budesonide inhalation suspension compared with cromolyn sodium nebulizer solution for asthma in young children: results of a randomized outcomes trial. Pediatrics 2002 May; 109 (5): 866-72
25. Chipps BE, Schnepp CM, Briscoe M. Budesonide inhalation suspension reduces the need for emergency intervention in pediatric asthma: a named-patient case series. J Asthma 2003 Dec; 40 (8): 895-900
26. Murphy KR, Fitzpatrick S, Cruz-Rivera M, et al. Effects of budesonide inhalation suspension compared with cromolyn sodium nebulizer solution on health status and caregiver quality of life in childhood asthma. Pediatrics 2003 Sep; 112 (3): e212-9
27. Delacourt C, Dutau G, Lefrançois G, et al. Comparison of the efficacy and safety of nebulized beclometasone dipropionate and budesonide in severe persistent childhood asthma. Respir Med 2003 Feb; 97 Suppl. B: S27-33
28. Terzano C, Allegra L, Barkai L, et al. Beclomethasone dipropionate versus budesonide inhalation suspension in children with mild to moderate persistent asthma. Eur Rev Med Pharmacol Sci 2000; 4: 17-24
29. van Staa TP, Cooper C, Leufkens HG, et al. Children and the risk of fractures caused by oral corticosteroids. J Bone Miner Res 2003 May; 18 (5): 913-8
30. Kaye LD, Kalenak JW, Price RL, et al. Ocular implications of long-term prednisone therapy in children. J Pediatr Ophthalmol Strabismus 1993 May-Jun; 30 (3): 142-4
31. Abernathy-Carver KJ, Fan LL, Boguniewicz M, et al. *Legionella* and *Pneumocystis pneumonias* in asthmatic children on high doses of systemic steroids. Pediatr Pulmonol 1994 Sep; 18 (3): 135-8
32. Brown ES, Chandler PA. Mood and cognitive changes during systemic corticosteroid therapy. Prim Care Companion J Clin Psychiatry 2001 Feb; 3 (1): 17-21
33. Sung L, Osmond MH, Klassen TP. Randomized, controlled trial of inhaled budesonide as an adjunct to oral prednisone in acute asthma. Acad Emerg Med 1998 Mar; 5 (3): 209-13
34. Matthews EE, Curtis PD, McLain BI, et al. Nebulized budesonide versus oral steroid in severe exacerbations of childhood asthma. Acta Paediatr 1999 Aug; 88 (8): 841-3
35. Daugbjerg P, Brenoe E, Forchhammer H, et al. A comparison between nebulized terbutaline, nebulized corticosteroid and systemic corticosteroid for acute wheezing in children up to 18 months of age. Acta Paediatr 1993 Jun-Jul; 82 (6-7): 547-51
36. Devidayal D, Singhi S, Kumar L, et al. Efficacy of nebulized budesonide compared to oral prednisolone in acute bronchial asthma. Acta Paediatr 1999 Aug; 88 (8): 835-40
37. 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 Oct; 102: 605-9
38. Sano F, Cortez GK, Solé 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 Apr; 105 (4): 699-703

39. Volovitz B, Soferman R, Blau H, et al. Rapid induction of clinical response with a short-term high-dose starting schedule of budesonide nebulizing suspension in young children with recurrent wheezing episodes. J Allergy Clin Immunl 1998 Apr; 101 (4 Pt 1): 464-9

40. Scott MB, Skoner DP. Short-term and long-term safety of budesonide inhalation suspension in infants and young children with persistent asthma. J Allergy Clin Immunol 1999 Oct; 104 (4 Pt 2): S200-9

41. Szefler SJ, Lyzell E, Fitzpatrick S, et al. Safety profile of budesonide inhalation suspension in the pediatric population: worldwide experience. Ann Allergy Asthma Immunol 2004 Jul; 93 (1): 83-90

42. Berger WE, Qaqundah PY, Blake K, et al. Safety of budesonide inhalation suspension in infants aged six to twelve months with mild to moderate persistent asthma or recurrent wheeze. J Pediatr 2005 Jan; 146 (1): 91-5

43. Irani A-M, Cruz-Rivera M, Fitzpatrick S, et al. Effects of budesonide inhalation suspension on hypothalamic-pituitary-adrenal-axis function in infants and young children with persistent asthma. Ann Allergy Asthma Immunol 2002 Mar; 88 (3): 306-12

44. Skoner DP, Szefler SJ, Welch M, et al. Longitudinal growth in infants and young children treated with budesonide inhalation suspension for persistent asthma. J Allergy Clin Immunol 2000 Feb; 105 (2): 259-68

45. Daley-Yates PT, Richards DH. Relationship between systemic corticosteroid exposure and growth velocity: development and validation of a pharmacokinetic/pharmacodynamic model. Clin Ther 2004 Nov; 26 (11): 1905-19

46. Doull IJM. The effect of asthma and its treatment on growth. Arch Dis Child 2004 Jan; 89 (1): 60-3

47. Creese KH, Doull IJ. Effects of inhaled corticosteroids on growth in asthmatic children. Curr Allergy Asthma Rep 2001 Mar; 1 (2): 122-6

48. Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. N Engl J Med 2000 Oct; 343 (15): 1054-63

49. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. N Engl J Med 2000 Oct; 343 (15): 1064-9

50. de Jongste JC, Duiverman EJ. Nebulized budesonide in severe childhood asthma [letter]. Lancet 1989; 333 (8651): 1388

51. Grimfeld A, Lesbros D, Ostinelli J, et al. Long-term study of nebulised budesonide in young children with moderate to severe asthma [abstract no. 0204]. Eur Respir J 1994; 7 Suppl. 18: 27S

52. Lødrup Carlsen CKC, Carlsen KH, Nikander K, et al. Nebulized budesonide after hospitalisation for recurrent bronchial obstruction in children younger than 18 months. Pediatr Allergy Immunol 2000; 12: 159-65

53. Nikander K, Turpeinen M, Wollmer P. The conventional ultrasonic nebulizer proved inefficient in nebulizing a suspension. J Aerosol Med 1999; 12 (2): 47-53

54. Smaldone GC, Cruz-Rivera M, Nikander K. In vitro determination of inhaled mass and particle distribution for budesonide nebulizing suspension. J Aerosol Med 1998; 11 (2): 113-25

55. Vikre-Jørgensen J, Agertoft L, Pedersen S. Dose titration of nebulized budesonide in young children. Pediatr Pulmonol 1997; 23: 270-7

56. Everard ML, Clark AR, Milner AD. Drug delivery from jet nebulisers. Arch Dis Child 1992; 67: 586-91

57. Geller DE, Kesser KC, Janssens HM, et al. Delivery of budesonide inhalation suspension (BIS) through an infant upper airway model [poster]. 99th International Conference of the American Thoracic Society; 2003 May 16-23; Seattle (WA)

58. Mellon M, Leflein J, Walton-Bowen K, et al. Comparable efficacy of administration with face mask or mouthpiece of nebulized budesonide inhalation suspension for infants and young children with persistent asthma. Am J Respir Crit Care Med 2000 Aug; 162 (2): 593-8

59. Georgitis JW, McWilliams B, Cruz-Rivera M, et al. Effective once-daily administration of budesonide inhalation suspension by nebulizer with facemasks or mouthpieces for persistent asthma in infants and young children. Pediatr Asthma Allergy Immunol 2001; 15 (1): 3-13

60. McKenzie JE, Cruz-Rivera M. Compatibility of budesonide inhalation suspension with four nebulizing solutions. Ann Pharmacother 2004 Jun; 38 (6): 967-72

61. Dunlop KA, Carson DJ, Shields MD. Hypoglycemia due to adrenal suppression secondary to high-dose nebulized corticosteroid. Pediatr Pulmonol 2002 Jul; 34 (1): 85-6

62. Zwaan CM, Odink RJH, Delemarre-van de Waal HA, et al. Acute adrenal insufficiency after discontinuation of inhaled corticosteroid therapy [letter]. Lancet 1992 Nov; 340 (8830): 1289-90

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