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Budesonide Inhalation Suspension

A Review of its Use in Infants, Children and Adults with Inflammatory Respiratory Disorders

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Data Selection

Sources: Medical literature published in any language since 1983 on Budesonide, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand) and Medline. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'Budesonide' and 'inhaled-preparations' and ('asthma'or 'croup' or 'bronchopulmonary dysplasia' or 'bronchiolitis' or 'postbronchiolitic wheezing' or 'chronic obstructive pulmonary disease') and ('neonates' or 'infants' or 'children' or 'adolescents' or 'adults') and freetext searching on 'Budesonide and nebulisation' or 'Budesonide inhalation suspension' or 'Budesonide nebulizing suspension' or 'nebulized Budesonide' or 'Budesonide nebulizers'. Medline search terms were 'Budesonide' and 'nebulizers-and-vaporizers' and ('asthma'or 'croup' or 'bronchopulmonary dysplasia' or 'bronchiolitis' or 'chronic obstructive pulmonary disease') and ('infants' or 'children' or 'adolescents' or 'adults') or 'Budesonide and nebulisation' or 'Budesonide inhalation suspension' or Budesonide nebulising suspension' or 'Budesonide and inhalation suspension' or 'nebulized Budesonide'. Searches were last updated 18 October 2000.

Selection: Studies in patients with asthma, croup, bronchiolitis or postbronchiolitic wheezing, bronchopulmonary dysplasia or chronic obstructive pulmonary disease who received budesonide inhalation suspension. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: budesonide, asthma, croup, bronchiolitis, wheezing, bronchopulmonary dysplasia, chronic obstructive pulmonary disease, pharmacodynamics, pharmacokinetics, therapeutic use, infants, children, adults.

Contents

Summary

Abstract

Budesonide, a topically active corticosteroid, has a broad spectrum of clinically significant local anti-inflammatory effects in patients with inflammatory lung diseases including persistent asthma.

In infants and young children with persistent asthma, day- and night-time symptom scores, and the number of days in which β_2-agonist bronchodilators were required, were significantly lower during randomised, double-blind treatment with budesonide inhalation suspension 0.5 to 2 mg/day than placebo in 3 multicentre trials. Significantly fewer children discontinued therapy with budesonide inhalation suspension than with placebo because of worsening asthma symptoms in a study that included children who were receiving inhaled corticosteroids at baseline.

Recent evidence indicates that budesonide inhalation suspension is significantly more effective than nebulised sodium cromoglycate in improving control of asthma in young children with persistent asthma.

At a dosage of 2 mg/day, budesonide inhalation suspension significantly reduced the number of asthma exacerbations and requirements for systemic corticosteroids in preschool children with severe persistent asthma. In children with acute asthma or wheezing, the preparation was as effective as, or more effective than oral prednisolone in improving symptoms.

In children with croup, single 2 or 4mg dosages of budesonide inhalation suspension were significantly more effective than placebo and as effective as oral dexamethasone 0.6 mg/kg or nebulised L-epinephrine (adrenaline) 4mg in alleviating croup symptoms and preventing or reducing the duration of hospitalisation.

Early initiation of therapy with budesonide inhalation suspension 1 mg/day appears to reduce the need for mechanical ventilation and decrease overall cortico-

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steroid usage in preterm very low birthweight infants at risk for chronic lung disease.

In adults with persistent asthma, budesonide inhalation suspension ≤8 mg/day has been compared with inhaled budesonide 1.6 mg/day and fluticasone propionate 2 mg/day administered by metered dose inhaler. Greater improvements in asthma control occurred in patients during treatment with budesonide inhalation suspension than with budesonide via metered dose inhaler, whereas fluticasone propionate produced greater increases in morning peak expiratory flow rates than nebulised budesonide. Several small studies suggest that the preparation has an oral corticosteroid-sparing effect in adults with persistent asthma and that it may be as effective as oral corticosteroids during acute exacerbations of asthma or chronic obstructive pulmonary disease.

The frequency of adverse events was similar in children receiving budesonide inhalation suspension 0.25 to 2 mg/day or placebo in 12-week studies. During treatment with budesonide inhalation suspension 0.5 to 1 mg/day in 3 nonblind 52-week studies, growth velocity in children was generally unaffected; however, a small but statistically significant decrease in growth velocity was detected in children who were not using inhaled corticosteroids prior to the introduction of budesonide inhalation suspension. Hypothalamic-pituitary-adrenal axis function was not affected by short (12 weeks) or long (52 weeks) term treatment with nebulised budesonide.

In conclusion, budesonide inhalation suspension is the most widely available nebulised corticosteroid, and in the US is the only inhaled corticosteroid indicated in children aged ≥1 year with persistent asthma. The preparation is suitable for use in infants, children and adults with persistent asthma and in infants and children with croup.

Pharmacodynamic Properties

Budesonide is a topically active corticosteroid with anti-inflammatory properties. In patients with asthma, the drug suppresses the number of inflammatory cells in the lungs, inhibits synthesis and release of cytokines, reduces bronchial hyperresponsiveness to a variety of substances and attenuates both the early and late asthmatic response.

A single 4mg dose of nebulised budesonide inhalation suspension did not perturb serum cortisol levels in healthy adult volunteers. Similarly, budesonide inhalation suspension 1 to 4 mg/day had no significant effect on plasma markers of systemic corticosteroid activity in bone, blood or adrenal tissue in adult patients with asthma. In contrast, significant dose-related suppression of eosinophil counts and both osteocalcin and morning plasma cortisol levels occurred during treatment with oral prednisolone 5 to 20 mg/day in this randomised, double-blind, crossover study.

No pharmacodynamic studies have been conducted in children with asthma during treatment with budesonide inhalation suspension. However, when administered as a dry powder, inhaled budesonide produced significant improvement in markers of inflammation in inhaled corticosteroid-naive children that were correlated with reductions in use of as-needed β-agonist bronchodilators and improvements in asthma symptom scores and pulmonary function tests.

Pharmacokinetic Properties

The mass median aerodynamic diameter of the droplets in budesonide inhalation suspension is ≈3 to 5μm when the preparation is administered via jet nebuliser with compressor. In adults, the lung deposition of budesonide from the nebulised suspension was ≈15% of the nominal dose when delivered by 3 commonly used

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jet nebulisers. The systemic bioavailability of budesonide was 6% after a single 1000μg dose of budesonide inhalation suspension in children aged 3 to 6 years with persistent asthma; in adults, the systemic bioavailability of budesonide was 13%. The volume of distribution at steady state, terminal elimination half-life and clearance of budesonide were 3 L/kg, 2.3 hours and 32.2 L/h, respectively, in children and 2.7 L/kg, 2.3 hours and 80.4 L/h, respectively, in adults.

Therapeutic Use

In Children

Budesonide inhalation suspension has been evaluated in infants and young children aged 6 months to 8 years with symptomatic persistent asthma in 3 multicentre, randomised, double-blind, placebo-controlled, parallel-group trials. After 12 weeks of treatment, daytime and night-time asthma symptom scores, the primary efficacy variables in these studies, were significantly lower among infants and children treated with budesonide inhalation suspension 0.5 to 2 mg/day than among those receiving placebo. The number of days during which β_2-agonist bronchodilators were required for breakthrough asthma symptoms was also reduced significantly in children treated with budesonide compared with placebo. In 1 study, in which all children were receiving inhaled corticosteroids prior to enrolment, the proportion of children who discontinued therapy because of worsening of asthma symptoms was significantly greater in placebo than budesonide 0.5 to 2 mg/day recipients.

Budesonide inhalation suspension 1mg twice daily significantly reduced the number of asthma exacerbations and the requirements for systemic corticosteroids in preschool children with severe persistent asthma in 2 small, randomised, double-blind studies.

Recent data indicate that budesonide inhalation suspension is significantly more effective than nebulised sodium cromoglycate in improving control of asthma symptoms in young children with persistent asthma.

In randomised trials, nebulised budesonide was as effective as or more effective than oral prednisolone in improving symptoms in children with acute asthma or wheezing.

Budesonide inhalation suspension is an effective and well tolerated alternative to systemic corticosteroids in children with mild to severe croup. The formulation, given as a 2 or 4mg single dose, was more effective than placebo and as effective as oral dexamethasone 0.6 mg/kg in alleviating croup symptoms and reducing the duration of hospital stay in several studies. In 1 small study, budesonide inhalation suspension was as effective as nebulised L-epinephrine 4mg in young children with moderately severe croup.

Several published studies with budesonide have failed to demonstrate a beneficial effect on the symptoms of acute bronchiolitis or the prevention of postbronchiolitic wheezing during the 6-month to 1-year period after treatment. Two-year follow-up results from a recently published prospective, nonblind study suggests that administration of budesonide inhalation suspension during and for 2 months after respiratory syncytial virus-bronchiolitis may reduce the development of subsequent respiratory symptoms. Double-blind studies with long term follow-up (≥2 years) are needed to confirm these results.

In very low birthweight infants (median birthweight 805g) born prior to 30 weeks of gestation, nebulised budesonide 0.5mg twice daily for 14 days significantly reduced overall requirement for corticosteroids and facilitated discontinuation of mechanical ventilation compared with placebo. There was, however,

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no significant difference in supplemental oxygen requirements at 28 days of age between the 2 groups in this randomised, double-blind study.

In Adults

Improvements in asthma control were significantly greater in patients with asthma during treatment with budesonide inhalation suspension 2 or 8 mg/day than inhaled budesonide 1.6 mg/day administered by a metered dose inhaler plus spacer device in a randomised, double-blind, crossover study. Greater improvements in morning and evening peak expiratory flow and greater reductions in as-needed β_2-agonist use occurred in patients during treatment with budesonide 8 mg/day than budesonide via metered dose inhaler. Greater increases in evening peak expiratory flow rates were documented during treatment with a lower dosage of budesonide inhalation suspension (2 mg/day) than budesonide via metered dose inhaler in this 4-week crossover study.

High dosages of fluticasone propionate via metered dose inhaler provided greater improvements in asthma control than budesonide inhalation suspension 2 or 4 mg/day in a randomised, nonblind, multicentre, crossover trial. Morning peak expiratory flow rates increased by a significantly greater extent after switching from nebulised budesonide 2 or 4 mg/day to inhaled fluticasone propionate 2 mg/day. There were, however, no differences in the number of 24-hour symptom-free intervals during 4 weeks of treatment with fluticasone propionate or budesonide inhalation suspension. Systemic effects on hypothalamic-pituitary-adrenal axis function were not quantified in this study.

Several small studies suggest that budesonide inhalation suspension has an oral corticosteroid-sparing effect in some adults with persistent asthma. The mean dosage of prednisolone was reduced by 59% (from 12.6 mg/day) in 55% of patients after 12 weeks' treatment with budesonide inhalation suspension 2 mg/day in a noncomparative study.

Nebulised budesonide may be as effective as oral corticosteroids in the treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD). In a randomised, double-blind, multicentre study, forced expiratory volume in 1 second increased by a similar amount in 188 hospitalised patients with acute exacerbations of COPD during 3 days' treatment with budesonide inhalation suspension 2mg every 6 hours or oral prednisolone 30mg every 12 hours. Both active treatments were significantly more effective than placebo in increasing post-bronchodilator forced expiratory volume in 1 second.

Tolerability

Budesonide inhalation suspension was generally well tolerated in clinical studies in infants and children. The frequency of adverse events was similar in children receiving budesonide inhalation suspension 0.25 to 2 mg/day or placebo in 12-week studies. Growth velocity was generally unaffected in children who had prior exposure to inhaled corticosteroids during 3 nonblind 52-week studies in which patients received budesonide inhalation suspension 0.5 to 1 mg/day or standard asthma care. Children with persistent asthma who were not using inhaled corticosteroids prior to receiving budesonide inhalation suspension experienced a small but significant decrease in growth velocity compared with those who received standard asthma care. There was no evidence of hypothalamic-pituitary-adrenal axis suppression after 12 weeks' double-blind and 52 weeks' nonblind treatment with budesonide inhalation suspension.

In adults with oral and inhaled corticosteroid-dependent asthma, reduced dosages of oral prednisolone after the introduction of budesonide inhalation suspen-

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sion for 12 weeks resulted in the resolution of systemic adverse events in 24% of patients, and reduced the overall incidence of purpura, moon face, skin thinning and weight gain.

Dosage and Administration

In the US, budesonide inhalation suspension is indicated for the maintenance treatment of asthma and as prophylactic therapy in children aged 12 months to 8 years. In children receiving treatment with inhaled bronchodilators and/or inhaled corticosteroids, the recommended initial dosage is 0.5 mg/day. In those receiving oral corticosteroids, a higher initial dosage (1 mg/day) is recommended. The maximum recommended dosage in children is 0.5 mg/day in those previously receiving bronchodilators and 1 mg/day in those who were receiving inhaled or oral corticosteroids.

In the UK and elsewhere, budesonide inhalation suspension is indicated for use in children and adults with asthma. The recommended dosage in infants and children aged 3 months to 12 years with asthma is 1 to 2 mg/day when starting treatment, during an asthma exacerbation or during withdrawal of oral corticosteroids; maintenance doses are typically 50% lower than the starting dose. In adults and children aged >12 years, the starting dosage of budesonide inhalation suspension is 2 to 4 mg/day, although higher doses may be necessary in very severe cases of asthma.

In children with croup the usual dose of budesonide inhalation suspension is 2mg given as a single inhalation or as two 1mg doses 30 minutes apart.

1. Overview of Inflammatory Respiratory Disorders

Inflammatory disorders of the lung are important contributors to morbidity and mortality across the human lifespan. Asthma, as well as croup, bronchiolitis and bronchopulmonary dysplasia (BPD) are important pulmonary diseases in infants and children. In adults, asthma and chronic obstructive pulmonary disease (COPD), which may have an inflammatory component, are important.

Asthma is the most common chronic illness of childhood; of the nearly 5 million children and adolescents in the US who are affected by the disease, 1.2 million are under the age of 4 years.[1] Asthma is responsible for more school absenteeism than any other chronic disease, and lost work productivity for parents who care for children with asthma is substantial.[2]

The worldwide prevalence of asthma among children has risen in the last few decades.[1,3-5] Between 1980 and 1994 the prevalence rate for asthma increased by 75% in the US; the largest increase (160%) occurred among children aged 0 to 4 years (from 22.2 to 57.8 per 1000; $p < 0.05$).[1] The highest prevalence rates of self-reported asthma in a survey of children aged 13 to 14 years in 56 countries were in the UK, New Zealand, Australia, the Republic of Ireland, Canada, Peru, Costa Rica, Brazil and the US (prevalence ranged from 36.8% in the UK to 24% in the US).[6]

Asthma symptoms often develop during the first years of life, although diagnosis of asthma can be difficult because infants with early-onset wheezing constitute a heterogeneous group. Upon initial presentation, infants with transient wheezing are clinically indistinguishable from those with early expression of asthma. Longitudinal studies suggest that approximately 40% of children who have lower respiratory tract illness with wheezing before age 3 still have wheezing episodes at 6 years of age.[7] Apparent risk factors for the development of asthma in children include a family history of asthma or atopy, maternal smoking during pregnancy, respiratory syncytial virus (RSV) bronchiolitis in the first year of life (particularly in children

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with a family history of atopy or asthma),[8] and exposure to tobacco smoke, allergens (i.e. house dust mites, animal dander, plant pollen) or high humidity in the home.[9-13]

Asthma is an inflammatory disease of the airways that is characterised by airway hyperresponsiveness, reversible airflow obstruction and airway remodelling. The intensity of inflammation is influenced by various inducers and provokers of asthma. Inhaled corticosteroids are the most effective anti-inflammatory agents for the long term management of asthma.[14] Clinical studies in school-aged children and adults suggest that early intervention with inhaled corticosteroids modifies the progressive nature of the disease process and prevents the development of chronic airway obstruction.[15,16] Other agents such as sodium cromoglycate, nedocromil and theophylline are generally less effective than inhaled corticosteroids in improving the clinical and inflammatory manifestations of asthma.[17] Hence, current treatment guidelines recommend inhaled corticosteroids as the cornerstone of asthma therapy in children and adults with persistent asthma.[14,18]

Several other respiratory illnesses of early childhood, including croup, bronchiolitis and BPD, may also have an inflammatory component to their pathophysiology. Croup (acute laryngotracheobronchitis) is a common cause of upper airway obstruction in infants and young children that is characterised by fever, a barking cough, hoarse voice, inspiratory stridor and varying degrees of respiratory distress.[19] These symptoms usually follow the onset of an upper respiratory tract infection by 1 to 2 days and are thought to result from laryngeal and tracheal oedema. Most cases of croup occur in children aged ≤3 years; it is estimated that 1 to 5% of children in their second year of life may require outpatient treatment for croup.[20] Parainfluenza virus type 1 accounts for ≈38% of cases with an identifiable viral cause; other etiological agents include RSV, other parainfluenza viruses, influenza virus and *Mycoplasma pneumoniae*.[21]

Bronchiolitis is the most common lower respiratory tract illness of infancy and is frequently associated with RSV infection.[22] It is estimated that 50 to 80% of hospitalisations for bronchiolitis are attributable to RSV.[22] Up to 2% of all infants are admitted to hospital for acute bronchiolitis in the first 12 months of life.[23] Most infants recover from the acute illness within several days; however, some patients develop persistent lower respiratory symptoms that require further medical attention. Approximately 75% of infants with bronchiolitis experience subsequent cough and wheezing that tend to subside as the patient grows older.[23] The pathophysiology of postbronchiolitic wheezing is unclear, but is thought to include airway inflammation caused by RSV, small airways or an atopic family history.[23]

Bronchopulmonary dysplasia is a chronic lung disease that affects premature infants who require supplemental oxygen and mechanical ventilation.[24] Its pathophysiology is complex, but is thought to include interstitial pulmonary fibrosis along with an inflammatory component. Treatment regimens for BPD consist of supplemental oxygen, bronchodilators, diuretics and corticosteroid therapy; inhaled corticosteroids are an attractive alternative to oral agents because of their improved tolerability profile.[24]

Despite the substantial evidence that anti-inflammatory agents, including inhaled corticosteroids and sodium cromoglycate, are effective in the treatment of asthma, these agents remain underprescribed for paediatric patients in some countries.[25,26] Factors that may contribute to underuse of these agents in paediatric patients include the lack of an inhaled corticosteroid formulation in the US that is suitable for use in children under the age of 4 years,[27-29] difficulty manipulating a pressurised metered dose inhaler with spacer device and facemask and poor patient acceptance of this system.[30] Nebuliser therapy allows drug delivery through passive inhalation, thus requiring less patient coordination and only passive cooperation by the paediatric patient.[31] The availability of budesonide inhalation suspension, a corticosteroid for administration using a compressed air driven jet nebuliser is a significant advance in the US for paediatric

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patients with asthma. Budesonide inhalation suspension has been approved by the US Food and Drug Administration (FDA) for use in children up to age 8 years; it is the only corticosteroid formulation approved by the FDA for use in children aged between 12 months and 4 years with persistent asthma.

Inhaled budesonide delivered via dry powder or pressurised metered dose inhaler has been studies extensively in children with asthma ranging in age from 3 through 18 years;[15,32-38] its therapeutic efficacy in asthma and rhinitis has been previously reviewed in *Drugs*.[39,40] This review focuses on the use of the nebulised formulation, budesonide inhalation suspension, in children and adults with inflammatory respiratory disorders. As the vast majority of published data, including the largest and most recent studies, have been conducted in children with asthma, most of this review pertains to this population.

2. Pharmacodynamic Properties

Budesonide is a topically active corticosteroid with anti-inflammatory properties. Corticosteroids including budesonide exert their anti-inflammatory effects by binding with specific receptors present in the cytoplasm of most cells. After binding, the drug-receptor complex is translocated to the nucleus, where it influences gene transcription, either directly through binding with glucocorticoid response elements in the promoter region of certain genes, or indirectly through interactions with other transcription factors (e.g. nuclear factor κB).[41] Budesonide has approximately 200-fold greater affinity for the glucocorticoid receptor and 1000-fold greater topical anti-inflammatory activity than cortisol, the natural ligand.[42]

Unlike fluticasone propionate and beclomethasone dipropionate, budesonide is reversibly conjugated with intracellular fatty acids in airway and lung tissue to form lipophilic budesonide esters; these esters are unable to bind with the glucocorticoid receptor, and instead serve to prolong the retention of budesonide within the airways.[43-45] Budesonide is released from the conjugates by the action of intracellular lipases which hydrolyse the ester bonds, thus making budesonide available to bind with the glucocorticoid receptor.[44] *In vitro* data suggest that the extended airway retention of budesonide contributes to the relatively long duration of local anti-inflammatory activity of the drug.[46]

In patients with asthma, inhaled corticosteroids have a broad spectrum of clinically significant anti-inflammatory effects. The number of inflammatory cells in the lungs is reduced and the synthesis and release of cytokines and other inflammatory mediators is inhibited. In studies in adults and children aged ≥7 years with asthma, bronchial hyperresponsiveness to a variety of substances and the early and late asthmatic responses to inhaled allergen were attenuated. Secretion of mucus and plasma exudation into the airways of patients are minimised. These drugs also prevent or reverse β_2-receptor down-regulation associated with long term β_2-agonist usage.[41,47,48]

Nebulised budesonide inhalation suspension did not perturb serum cortisol levels in healthy adult volunteers. After inhalation of a single 4mg dose of budesonide inhalation suspension, morning serum cortisol levels were similar to those obtained after inhalation of placebo on 2 occasions (687 *vs* 652 nmol/L, respectively, n = 16) in a randomised, double-blind, crossover study. Serum cortisol levels decreased to 204 nmol/L when the same volunteers received inhaled budesonide 4mg from a Turbuhaler (an inhalation-driven dry powder inhaler) and were even lower after inhalation of fluticasone propionate delivered by pressurised metered dose inhaler with spacer device (189 nmol/L) and 4mg (93 nmol/L).[49]

Similarly, budesonide inhalation suspension had no significant effect on plasma markers of systemic corticosteroid activity in bone, blood or adrenal tissue in adult patients with asthma [forced expiratory volume in 1 second (FEV_1) >70% predicted]. Compared with values obtained during 4 days of placebo administration, eosinophil counts and both osteocalcin and morning plasma cortisol levels were not significantly different after 4 days'

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treatment with budesonide inhalation suspension 1, 2 and 4 mg/day.[50] As expected, significant dose-related suppression of all 3 variables occurred during treatment with oral prednisolone 5 to 20 mg/day in this randomised, double-blind, crossover study ($p < 0.05$ *vs* placebo). Plasma cortisol levels were significantly lower after treatment with prednisolone 10 and 20 mg/day than with budesonide 2 and 4 mg/day, respectively.[50] Moreover, abnormal plasma cortisol values (<150 nmol/L) occurred in about one-third of individual assays (13 of 36) drawn during prednisolone treatment, but only once during treatment with budesonide.[50]

Budesonide inhalation suspension had no significant effects on various biochemical markers of systemic corticosteroid effects on bone turnover in adult patients with COPD. Budesonide-treated patients had higher mean urinary corticosteroid metabolite levels (2012 *vs* 1079 mg/24 hours for prednisolone; $p < 0.05$), higher mean serum osteocalcin levels (2.3 *vs* 0.6 ng/ml for prednisolone; $p < 0.05$) and significantly lower 24-hour urinary calcium to creatinine ratios (0.28 *vs* 0.53 for prednisolone; 95% confidence intervals 0.1 *vs* 0.2, respectively).[51] These result suggest that budesonide inhalation suspension 4 mg/day for 5 days may have less effect on bone turnover than predisolone 30 mg/day for 5 days.

Although no pharmacodynamic studies have been conducted in children with asthma during treatment with budesonide inhalation suspension, the anti-inflammatory properties of the drug administered by other devices (e.g. Turbuhaler, an inhalation-driven, dry powder inhaler) have been extensively investigated in adults and children with asthma. The anti-inflammatory effects of inhaled budesonide delivered via dry-powder or metered dose inhaler in adults with persistent asthma are presented in table I.

Inhaled budesonide produced significant improvements in markers of inflammation that correlated with improvement in asthma symptom scores and decreased use of as-needed β-agonist bronchodilators in 25 inhaled corticosteroid-naive children aged 7.5 to 15 years with moderate persistent asthma. Serum levels of eosinophilic cationic protein, a specific indicator of eosinophilic activation, and the soluble low affinity receptor for immunoglobulin (Ig)E (sCD23), which is involved in IgE-mediated activation, proliferation and differentiation of B lymphocytes, were reduced significantly ($p < 0.05$ *vs* baseline) after 3 months of treatment with inhaled budesonide (1200 μg/day during the first month, then 800 μg/day).[74]

Table I. Pharmacodynamic effects of inhaled budesonide 100 to 1600 μg/day (delivered via inhalation-driven dry powder or metered dose inhaler) in randomised, double-blind comparative studies in adults with persistent asthma

↓ early[52] and late asthmatic response to inhaled allergen[53,54]
↓ bronchial hyperresponsiveness[52,54-66] including reversal of subsensitivity to AMP produced by regular treatment with long-acting β_2-agonists[67]
↓ allergen-induced increases in eosinophils in induced sputum and blood[54]
↓ eosinophils in peripheral blood,[53,54,57,62,68] induced sputum,[53,55,56,59,66] BAL fluid,[69] and in airway epithelial[56,70] and submucosal tissue[56,58,71]
↓ mast cells in airway epithelial and submucosal tissue[58,61,71]
↓ $CD25^+$[61] and $CD3^+$[72] T lymphocyte numbers in bronchial mucosa
↓ inflammatory cells in airway epithelium[70]
↓ ECP and EPX in induced sputum[59] and blood[62,68]
↑ expression and release of IL-10, an anti-inflammatory cytokine, from alveolar macrophages in BAL fluid[69]
↓ release of pro-inflammatory cytokines (MIP-1α, GM-CSF and IFN-γ) from alveolar macrophages in BAL fluid[69]
↓ NO concentration in exhaled air[55,56,60]
↓ IL-5-responsive eosinophil/basophil progenitors and $CD34^+$ haemopoietic progenitors (including $CD34^+$IL-5Rα$^+$ cells) in bone marrow[53]
↓ expression of HLA-DR antigen in bronchial tissue[71]
↑ binding of GR to DNA in bronchial mucosa[73]
↓ binding of NFκB, but not CREB, to DNA in bronchial mucosa[73]
↑ β_2-receptors on lymphocytes after down-regulation by regular treatment with a long-acting β_2-agonist[67]
↑ ciliated epithelial cells and intraepithelial nerves in airways[70]
↓ tenascin immunoreactivity, an indicator of airway remodelling process[72]

AMP = adenosine monophosphate; **BAL** = bronchoalveolar lavage; **CREB** = cyclic AMP response element binding protein; **ECP** = eosinophil cationic protein; **EPX** = eosinophil protein X; **GM-CSF** = granulocyte-macrophage colony- stimulating factor; **GR** = corticoid receptor; **IFN-γ** = interferon-γ; **IL** = interleukin; **IL-5Rα$^+$** = α subunit of the IL-5 receptor; **MIP-1α** = macrophage inflammatory protein-1α; **NO** = nitric oxide; **NFκB** = nuclear factor kappa B; ↑ and ↓ indicate significant ($p < 0.05$) increases and decreases, respectively, versus baseline, placebo and/or other comparator.

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The ability of inhaled budesonide to reduce non-specific bronchial hyperresponsiveness in children with persistent asthma has been established in randomised, double-blind studies. Significant ($p < 0.05$) increases (approximately 1 to 2 doubling doses) in the concentrations of histamine or house dustmite antigen required to provoke a 20% decrease in FEV_1 [PC_{20}] were obtained in children aged ≥7 years receiving budesonide 400 or 600 μg/ day.[75-77] Importantly, bronchial hyperresponsiveness continued to decline throughout one study in which the PC_{20} of histamine was determined at 4-month intervals; no plateau was reached after 20 months of treatment with budesonide 400 μg/day.[78] Budesonide also attenuated both the early- and late-phase reactions to allergen challenge in adults with asthma after a single 200 or 800μg dose,[79] after 3 doses of 800μg given 2 hours apart[80] and after multiple doses of 400 μg/day for 7 days.[54]

Inhaled budesonide also protects against exercise-induced bronchoconstriction in children with asthma. In a randomised, double-blind study, significant improvements in exercise tolerance were observed in children with mild persistent asthma (mean FEV_1 103.7% predicted, reversibility in FEV_1 3.5% and fall in FEV_1 after exercise 12.2%) aged ≥7 years treated with budesonide 200μg daily. Moreover, the change from baseline in the mean maximum fall in FEV_1 (–7 to –8%) after exercise was sustained during 27 months of treatment with budesonide.[81]

3. Pharmacokinetic Properties

This section presents a general overview of the pharmacokinetic properties of budesonide, followed by a brief summary of the effects of drug delivery device on the pharmacokinetics of the drug. In addition, an overview of the results from a study with budesonide inhalation suspension in children with persistent asthma aged 3 to 6 years are presented. More extensive reviews of the pharmacokinetic properties of budesonide after inhalation from the Turbuhaler or metered dose inhaler[39,40,82] and on the topic of nebulised drug therapy[83] have been published elsewhere.

3.1 Overview

The bioavailability of orally administered budesonide in adults ranges from 6 to 11%.[82,84] Elimination of the drug appears to depend on hepatic blood flow, typical of a drug which undergoes extensive first-pass metabolism (85 to 95% of the orally absorbed portion of a dose).[85,86] Indeed, budesonide is rapidly and extensively metabolised in the liver by cytochrome P450 3A4 with a terminal elimination half-life of ≈1.5 to 3 hours.[84,86,87] The major metabolites of budesonide, 16α-hydroxyprednisolone and 6β-hydroxybudesonide, have <1% of the corticosteroid activity of the parent compound.[84] Most (≈70%) of an oral or inhaled dose of radiolabelled budesonide was eliminated via the kidneys, although the amount of unchanged drug in the urine was negligible.[84,86]

3.2 Effect of Delivery Device on Budesonide Pharmacokinetics

Systemic absorption of inhaled drugs occurs from the oropharynx, the lungs and the gastrointestinal tract, and the extent of absorption may be modified by metabolism of drugs in the lungs, liver or gut. Since there is negligible lung metabolism of budesonide, most of the drug that is deposited in the lungs becomes systemically available. However, as stated above, only 6 to 11% of the budesonide dose which is absorbed via the gastrointestinal tract is systemically available.

Lung deposition and systemic absorption of inhaled budesonide are therefore largely dependent on such factors as the type of device used (e.g. jet *vs* ultrasonic nebuliser or metered dose *vs* dry powder inhaler), the properties of the formulation (e.g. suspension *vs* solution) and the patient's inhalation technique. Inhalation devices are designed to deliver aerosolised drugs to the lower airways; however, a portion of the drug is inevitably deposited on the oropharynx and is subsequently swallowed.

When considering values of deposition and systemic availability of drugs from different inhaler systems, it is important to distinguish between nominal dose (the labelled dose), the metered dose

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(amount of drug that leaves the metering unit with each actuation) and the delivered dose (the amount of drug that reaches the patient). For example, the lung deposition of budesonide inhaled via Turbuhaler, metered dose inhaler with spacer device or metered dose inhaler without spacer device is ≈32, 34 and 15%, respectively, of the metered dose.[88] The lung deposition of budesonide from the nebulising suspension is ≈15% of the nominal dose when delivered by a Pari Inhalierboy, Pari LC Plus or the Maxin MA-2 nebuliser.[89]

For a nebulised drug, the nebuliser-compressor combination has a substantial effect on the amount of drug delivered to the patient, and consequently, on the amount of drug that is absorbed systemically. Nebulisers vary considerably in the size of droplet they produce, the nebulisation time and the amount of drug they deliver. These factors may also vary with a particular nebuliser depending on the source of compressed air and whether the drug being administered is in a solution or a suspension.[90] Typically a portable mechanical device is used, unless the patient is in hospital in which case continuous oxygen from a wall-mounted source may be used. The patient's breathing pattern and the use of a face mask or mouthpiece also influence both the dose delivered to the patient and the lung deposition of the drug.[91,92]

Droplet size [measured in mass median aerodynamic diameter (MMAD)] is potentially the most critical characteristic of a nebuliser/compressor system as it contributes significantly to the extent of aerosol deposition in the lungs.[92] Droplets <5μm in diameter are more likely to deliver medication to the small airways, whereas droplets larger than 10μm in diameter tend to deposit in the oropharynx.[83] *In vitro* cascade impaction studies of commercially available nebuliser/compressor systems, including the Pari LC and Pari LC Plus with either a Pari Master or DeVilbiss Pulmo-Aide compressor, found the MMAD of budesonide inhalation suspension droplets produced by these systems varied from 3.8 to 5.5μm.[92] Slight variation in the delivered dose, which ranged from ≈13 to 18% of the nominal dose, was seen under simulated paediatric conditions with these systems.[92] In contrast, a conventional ultrasonic nebuliser was found to be much less efficient than a jet nebuliser at nebulising a suspension; the ultrasonic nebuliser produced a median inhaled mass of 9.9% of the nominal budesonide dose compared with 31.4% of the nominal dose for the jet nebuliser. Hence, ultrasonic nebulisers should not be used with budesonide inhalation suspension.[93]

Table II. Mean pharmacokinetic parameters of single dose budesonide in 10 children aged 3 to 6 years[a][94]

V_{ss} (L/kg)	3
$t_{½}$ (h)	2.3
Cl (L/h)	32.2
F (%)[b]	6.1

a Budesonide inhalation suspension 1000μg was administered over 5 minutes with a Pari LC Plus™ nebuliser fitted with a mouthpiece.

b Systemic bioavailability as the proportion of the 1000μg nebulised dosage reaching the systemic circulation relative to a 117μg intravenous infusion of budesonide.

Cl = total body clearance; **F** = systemic bioavailability; $\mathbf{t_{½}}$ = terminal elimination half-life; $\mathbf{V_{ss}}$ = volume of distribution at steady state.

3.3 Pharmacokinetics of Budesonide Inhalation Suspension

The pharmacokinetic properties of budesonide inhalation suspension have been investigated in children aged 3 to 6 years with persistent asthma and are presented in table II.[94] In general, the pharmacokinetic profile of budesonide is similar in adults and children, except for total body clearance which is 2-fold higher in adults than in children (although total body clearance per kilogram of bodyweight is higher in children than in adults).[94,95]

Each child (n = 13) received an intravenous infusion of budesonide (mean dose 117μg) 3 hours before inhaling a single 1000μg dose of budesonide inhalation suspension over 5 minutes with a Pari LC Plus nebuliser fitted with a mouthpiece (10 children, mean age 4.7 years completed the study). The mean amount of inhaled drug delivered to the patient was 232μg (range 192 to 273μg), approximately 18% (≈42μg) of which was deposited in the lungs (as assessed by the plasma concentration

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method).[94] Budesonide was rapidly absorbed after oral inhalation, reaching peak plasma concentrations (≈2.6 nmol/L) ≈17 minutes after the start of nebulisation.[42] The area under the plasma concentration versus time curve (AUC) per milligram nominal budesonide dose (4.6 nmol/L·h/mg) was similar to that reported in adults (3.9 nmol/L·hour/mg) in another study;[95] however, the systemic bioavailability of nebulised budesonide in children (6% of the nominal dose) was less than half that in adults (≥13%).[94] These data suggest that systemic exposure to budesonide after inhalation of the same nominal dose from a Pari LC Plus jet nebuliser is similar in children and adults. These findings are in agreement with results of a separate study in which systemic exposure was similar in children aged 2 to 3 years and 4 to 5 years compared with that in adults aged ≥20 years after inhaling the same nominal dose (400μg) of budesonide from a metered dose inhaler and spacer device. The AUC was 144, 155 and 128 nmol/L, respectively, in the 3 groups.[96] Thus, based on similar systemic exposure in adults and children, dosage adjustments on a mg/kg basis to limit systemic effects of inhaled budesonide in children are unnecessary.[94]

4. Therapeutic Use in Infants and Children

Budesonide inhalation suspension has been compared with placebo[27,28,97-100] and sodium cromoglycate[101,102] in infants and young children with persistent asthma. It has been evaluated in combination[103] or in comparison[104-106] with an oral corticosteroid in children with acute asthma. In combination with nebulised terbutaline, the drug has been compared with an oral corticosteroid in infants (≤18 months of age) with acute wheezing;[107] budesonide inhalation suspension has also been compared with nebulised terbutaline in children (aged 5 to 18 years) with acute asthma.[108] The preparation has been compared with nebulised ipratropium bromide in infants with acute wheezing who also received nebulised fenoterol and an intravenous corticosteroid.[109] Results of these studies are presented in sections 4.1 and 4.2.

Budesonide inhalation suspension has been shown to be effective in the treatment of paediatric patients aged 3 months to 5 years with mild to moderate[110,111] and moderate to severe[112-114] croup. The drug was as effective as oral dexamethasone[115,116] and nebulised epinephrine,[117] but not intramuscular dexamethasone[118] in improving croup symptom scores in infants and young children with croup of varying severity (section 4.3). Furthermore, budesonide inhalation suspension has been evaluated in paediatric patients with acute bronchiolitis and postbronchiolitic wheezing (section 4.4)[23,119,120] and in premature infants at risk for the development of BPD (section 4.5).[121,122]

4.1 Persistent Asthma

Although asthma is the most prevalent chronic disease in children, until recently only a few well designed clinical trials of asthma medications had been conducted in large groups of infants and young children (section 4.1.1). The major challenges associated with clinical trials in this patient population include the indirect reporting of symptoms through a parent or guardian and the inability of patients aged <6 years to reliably perform pulmonary function tests.[123-125] Thus, the diagnosis of asthma and monitoring of response to asthma treatment in infants and young children rely on subjective assessments of symptoms by parents. In 1 epidemiological study which evaluated the extent of agreement between 139 parents reporting wheezing in their children and clinician diagnosis of wheeze and asthma, less than 50% agreement was noted between the 2 groups' reports of this symptom.[126] This underscores the difficulty in comparing results from clinical trials with varying definitions of asthma symptoms.

The first published evidence of the clinical efficacy of budesonide inhalation suspension in the treatment of infants and children with severe asthma was reported in case series.[127-130] Subsequent clinical trials compared the efficacy of the drug with that of placebo or sodium cromoglycate in paediatric patients aged 6 months to 8 years with mild to severe persistent asthma,[27,28,97-102] and

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dose response studies were conducted with budesonide inhalation suspension in children aged <5 years[131-133] or 6 to 15 years[134] with persistent asthma. These trials have examined different dosage regimens of budesonide inhalation suspension in children with persistent asthma of varying severity, and the results are the focus of this section.

4.1.1 Comparisons with Placebo

Recently, budesonide inhalation suspension was evaluated in 3 multicentre, randomised, double-blind, placebo-controlled US clinical trials that enrolled more than 1000 children aged 6 months to 8 years with persistent asthma of varying disease duration (2 to 107 months) and severity.[27,28,97] Dosages of budesonide inhalation suspension ranged from 0.25mg once daily to 1mg twice daily and were administered for 12 weeks.

Patients aged 6 months to 8 years with symptomatic persistent asthma who were treated daily with at least 1 chronic asthma medication (i.e. an inhaled corticosteroid,[27,97] sodium cromoglycate[27,28] and/or theophylline[27,28]) and had used as-needed bronchodilators for at least 3 months were eligible to participate in studies in which daytime and night-time asthma symptom scores were the primary end-points. All participants in 1 study, which enrolled children aged 4 to 8 years,[97] and those able to perform pulmonary function tests in trials that included infants aged ≥6 months,[27,28] were required to demonstrate an FEV_1 of ≥50% of the predicted normal value and ≥15% reversibility in FEV_1 after inhalation of a standard dose of the short-acting β_2-agonist bronchodilator salbutamol (albuterol). Infants and young children with a history of severe or unstable asthma or symptoms limited to seasonal allergen exposure were excluded from these studies, as were those who received recent (i.e. long term use in the preceding 12 weeks or intermittent use within 30 days of enrolment) systemic corticosteroid therapy.

During the 2- or 3-week baseline period and the double-blind treatment phase, parents recorded daytime and night-time asthma symptom scores, use of as-needed β_2-agonist bronchodilators, and morning and evening peak expiratory flow (PEF) rates (if applicable). Patients who experienced asthma symptoms and required breakthrough β_2-agonist bronchodilators on 5 of the last 7 days of the baseline period had their long term asthma medications withdrawn and were randomised to 12 weeks of double-blind treatment with budesonide inhalation suspension or placebo.[27,28,97] Budesonide inhalation suspension or placebo was administered once[27,28] or twice[27,97] daily over approximately 5 minutes with a Pari LC Plus nebuliser (MMAD 5μm[94]) and a Pari Master compressor with mouthpiece or facemask.

Use of a short-acting inhaled β_2-agonist bronchodilator on an as-needed basis was permitted for breakthrough asthma symptoms. Use of medications for rhinitis or allergy (i.e. antihistamines, intranasal or topical corticosteroids, sodium cromoglycate or immunotherapy) was allowed as long as the treatment was constant throughout the baseline and treatment phases of the study.[28,97]

The primary efficacy variables were the change from baseline in daytime and night-time asthma symptom scores which were rated on a 4-point scale (table III). Secondary efficacy variables included the number of days in which as-needed short-acting β_2-bronchodilators were used and morning and evening PEF. Spirometry was performed at enrolment, at randomisation and after 2, 4, 8 and 12 weeks of treatment in all patients in 1 study[97] and in a subset of patients in 2 studies.[27,28]

Patients enrolled in the three 12-week randomised, double-blind studies described above were eligible for enrolment in 3 subsequent nonblind studies to assess the long term (52 weeks) safety and tolerability of the lowest individual maintenance dose of budesonide inhalation suspension.[135] Although these studies were primarily safety trials, efficacy parameters were also evaluated. All patients who completed the double-blind treatment phase or those who withdrew because of worsening of asthma symptoms were randomised in a 2 to 1 ratio (n = 670) to further treatment with budesonide inhalation suspension or conventional asthma therapy (which included short-acting oral or inhaled

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Table III. Asthma symptom severity scale used in multicentre, randomised, double-blind studies of budesonide inhalation suspension[a][76,77,81]

Score	Severity	Description
0	None	No symptoms of asthma
1	Mild	Awareness of asthma symptoms and/or signs that were easily tolerated
2	Moderate	Asthma symptoms and/or signs with some discomfort, causing some interference of daily activities or sleep
3	Severe	Incapacitating asthma symptoms and/or signs, with inability to sleep or perform daily activities

a Daytime and night-time symptom severity scores were recorded each day. Baseline values were the mean scores recorded in the week prior to the start of treatment. Scores at end-point were the mean daytime and night-time scores recorded throughout 12 weeks of treatment.

Secondary efficacy variables included the number of days in which as-needed short-acting β_2-agonist bronchodilators were used and morning and evening peak expiratory flow. Spirometry was performed at enrolment, at randomisation and after 2, 4, 8 and 12 weeks of treatment in all patients in 1 study[76] and in a subset of patients in 2 studies.[77,81]

β_2-agonists, theophylline, sodium cromoglycate and/or inhaled corticosteroids).[135] The initial dosage of budesonide inhalation suspension was 0.5mg once or twice daily; the dosage was titrated on an individual basis to the lowest dosage that controlled asthma symptoms.[135] Asthma exacerbations in both groups were treated with intermittent courses of oral prednisone.[135]

The effect of budesonide inhalation suspension on hypothalamic-pituitary-adrenal (HPA) axis function was evaluated in a subset of the 670 patients enrolled in the long term studies. Assessment tools included reported adverse events, morning basal and corticotrophin-stimulated effects on plasma cortisol levels (section 6.1.1). Growth was measured via stadiometry, and skeletal age was assessed in 2 of the long term studies (section 6.1.2).[135]

Asthma Symptom Scores

Budesonide inhalation suspension consistently improved daytime and night-time asthma symptom scores in children with persistent asthma (table IV). After 12 weeks of treatment, reductions in daytime and night-time asthma symptom scores were significantly greater among infants and young children in all 3 studies who were treated with budesonide inhalation suspension 0.5 to 2 mg/day compared with placebo ($p \leq 0.05$). Overall reductions in symptom scores ranged from 29 to 41% in budesonide-treated patients and 7 to 20% among those receiving placebo.[27,28,97]

Daytime and night-time asthma symptom scores were also significantly ($p \leq 0.05$) lower among infants and young children with mild persistent asthma who received budesonide inhalation suspension 0.25 mg/day compared with placebo; reductions in symptom scores ranged from 37 to 40% in budesonide recipients and 15 to 20% among those receiving placebo in this study.[28]

Improvements in daytime and night-time asthma symptoms were generally evident within 2 weeks of starting budesonide therapy; the full therapeutic effect was reached after approximately 4 to 6 weeks of treatment and was sustained throughout 12 weeks of double-blind treatment with budesonide inhalation suspension. In contrast, mean changes in asthma symptom scores were minimal in placebo recipients during these studies.[27,28,97] In long term studies, children receiving budesonide maintained improvements in asthma symptom scores compared with baseline; the improvements were similar to those observed in the conventional therapy groups after 52 weeks.[135]

The efficacy of once and twice daily budesonide inhalation suspension was similar across different age groups. Mean changes from baseline in asthma symptom scores in patients with mild asthma aged <2, 2 to 4, or >4 years[28] or in patients with moderate asthma aged 0.5 to 4 or >4 years did not differ from the overall analyses.[27]

Budesonide inhalation suspension can be administered effectively by either face mask or mouthpiece. As expected, the mean age of children who used face masks during nebulisation was lower (36.4 months) than that for mouthpiece users (70 months).[136] Mean changes from baseline in daytime and night-time asthma symptom scores in children who received budesonide inhalation suspension administered via face mask or mouthpiece

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Table IV. Effect of budesonide inhalation suspension (BIS) or placebo (PLA) on asthma symptom scores in paediatric patients with asthma in multicentre, randomised, double-blind, parallel-group, 12-week trials[a]

Reference	Dosage [no. of patients]	Baseline characteristics		Results at end-point		LOE[d] (%)
		asthma symptom score[b]		asthma symptom score[b,c]		
		daytime	night-time	daytime	night-time	
In infants and young children (ages 6 months to 8 years) with mild persistent asthma[e,f]						
Kemp et al.[28]	BIS 0.25mg qd [91]	1.44	1.32	↓0.57*	↓0.49*	14
	BIS 0.5mg qd [83]	1.33	1.19	↓0.46*	↓0.42*	17
	BIS 1mg qd [93]	1.31	1.19	↓0.50*	↓0.42*	13
	PLA [92]	1.27	1.08	↓0.26	↓0.16	23
In infants and young children (ages 6 months to 8 years) with moderate persistent asthma[e,g,h]						
Baker et al.[27]	BIS 0.25mg qd [94]	1.21	1.13	↓0.28	↓0.28	16
	BIS 0.25mg bid [99]	1.31	1.33	↓0.40*	↓0.49***	13*
	BIS 0.5mg bid [98]	1.33	1.20	↓0.46**	↓0.42**	15
	BIS 1mg qd [95]	1.28	1.25	↓0.37*	↓0.40**	21
	PLA bid [95]	1.27	1.16	↓0.19	↓0.13	26
In young children (ages 4 to 8 years) with inhaled corticosteroid-dependent asthma						
Shapiro et al.[97]	BIS 0.25mg bid [47]	1.35	1.10	↓0.45*	↓0.36*	11*
	BIS 0.5mg bid [42]	1.33	1.04	↓0.53**	↓0.37*	2*
	BIS 1mg bid [45]	1.35	1.08	↓0.55**	↓0.36*	13*
	PLA bid [44]	1.33	1.18	↓0.11	↓0.08	36

a BIS and PLA were administered over approximately 5 minutes by a Pari LC Plus nebuliser with mouthpiece or facemask.

b Asthma symptom scores were recorded daily by parent or guardian (0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms). Baseline values are the mean scores recorded in the week prior to the start of treatment. Scores at end-point are the mean daily scores recorded throughout 12 weeks of treatment.

c Mean change from baseline.

d Lack of efficacy (LOE) defined as the percentage of patients who discontinued treatment because of worsening asthma symptoms.

e Based on diagnostic criteria from the US National Heart, Lung, and Blood Institute Guidelines for the Diagnosis and Management of Asthma.[14]

f Asthma not adequately controlled by bronchodilators or noncorticosteroid anti-inflammatory agents.

g Asthma not adequately controlled by other asthma medications. More than 99% of patients were using oral or inhaled albuterol, 72% were using sodium cromoglycate, 31% were using inhaled corticosteroids, and 10% were using theophylline prior to study enrolment.

h Loss of efficacy data obtained from Mellon, et al.[29]

bid = twice daily; **qd** = once daily; ↓ indicates decrease; * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs PLA.

were similar to those observed in the total patient population.[136]

Use of Bronchodilators for Breakthrough Symptoms

The number of days during which β_2-agonist bronchodilators were required for breakthrough asthma symptoms was reduced significantly in children treated with budesonide inhalation suspension 0.25 to 2 mg/day for 12 weeks ($p \leq 0.038$ *vs* placebo). Children who received budesonide used β_2-agonists on 4.4 to 6.8 fewer days per 2-week period during treatment compared with baseline.[27,28,97] In contrast, placebo recipients reduced their β_2-agonist usage by 2.4 to 4.2 days per 2-week treatment period compared with baseline. Bronchodilator usage in children with mild persistent asthma during 12 weeks of treatment with budesonide 0.25 to 1mg once daily or placebo is depicted in figure 1.[28]

The use of β_2-agonist bronchodilators for breakthrough symptoms was significantly reduced in children who received budesonide inhalation suspension via mouthpiece ($p \leq 0.008$ *vs* placebo).[136] Children who received budesonide through face masks also used less breakthrough medication than

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the placebo group; however, differences between the 2 groups did not reach statistical significance.[136]

Withdrawals Due to Worsening Asthma Symptoms

The number of children withdrawn from the 12-week studies because of worsening of asthma symptoms, which was defined as 1[28] or 2[97] asthma exacerbations requiring treatment with oral corticosteroids, ranged from 2 to 21% in children treated with budesonide inhalation suspension 0.25 to 2 mg/day and from 23 to 36% in placebo recipients (table IV).[27,28,97] In 1 study, in which all patients were receiving inhaled corticosteroids prior to enrolment,[97] the proportion of patients who discontinued therapy because of worsening asthma symptoms was significantly greater in the placebo than in the budesonide groups (36 *vs* 9%, $p \leq 0.015$).[97]

Pulmonary Function Tests

In general, morning and evening PEF increased during treatment with budesonide inhalation suspension. Statistically significant increases in morning and/or evening PEF were seen in patients with moderate asthma treated with budesonide inhalation suspension 0.25 to 1 mg/day ($p \leq 0.05$ *vs* placebo); in contrast, PEF changed little in placebo-treated patients (table V).[27]

Significant improvements in mean morning PEF were obtained in patients with inhaled corticosteroid-dependent asthma during treatment with budesonide 0.25 to 1mg twice daily ($p \leq 0.03$ *vs* placebo).[97] Improvements in morning PEF in children with mild asthma treated with budesonide 0.25, 0.5 or 1mg once daily were not statistically different from that in placebo recipients.[28]

FEV_1 generally increased during treatment with budesonide inhalation suspension (table V). Significant increases in FEV_1 were obtained in children with mild asthma who received budesonide inhalation suspension 0.5 ($p = 0.044$) or 1mg ($p = 0.033$) once daily[28] compared with placebo and in those with moderate ($p \leq 0.05$)[27] or inhaled corticosteroid-dependent ($p \leq 0.05$) asthma[97] who received budesonide 0.5mg twice daily.

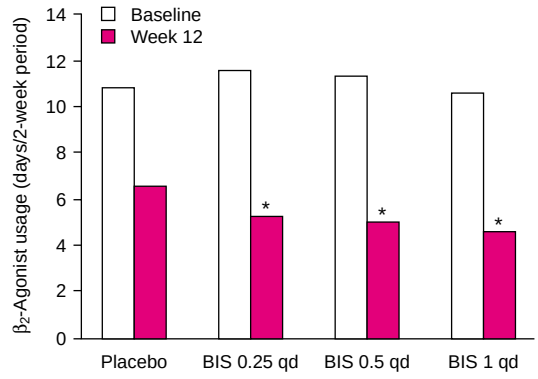

Fig. 1. As-needed β_2-agonist bronchodilator usage in paediatric patients treated with budesonide inhalation suspension (BIS). The frequency of as-needed β_2-agonist usage for asthma symptoms during 12 weeks of treatment compared with a 2-week baseline period. Data from the treatment period (weeks 0 through 12) were normalised to 2 weeks in order to allow comparison with the baseline period. Paediatric patients (aged 6 months to 8 years) with mild persistent asthma received BIS 0.25mg (BIS 0.25; n = 91), 0.5mg (BIS 0.5; n = 83) or 1mg (BIS 1; n = 93) or placebo (n = 92) once daily (qd) in a multicentre, randomised, double-blind, parallel-group trial.[28] * $p < 0.05$ *vs* placebo.

Once-Daily Administration

In keeping with results from studies of once daily budesonide via Turbuhaler in older children[34,35,81,137] and adults[138] with asthma, once daily nebulised budesonide provided effective asthma control in children aged ≥12 months with mild to moderate persistent asthma.[27,28] Among children enrolled in the above-mentioned studies, significant ($p \leq 0.05$ *vs* placebo) improvement in daytime and night-time asthma symptom scores was obtained in those with mild persistent asthma who received budesonide 0.25, 0.5 or 1mg once daily[28] and in patients with moderate persistent asthma who received 1mg once daily.[27] In the subset of patients with mild asthma who were consistently capable of performing spirometry, statistically significant improvements in FEV_1 were observed in patients who received nebulised budesonide 0.5mg (n = 28; $p = 0.044$ *vs* placebo) or 1mg (n = 33; $p = 0.033$ *vs* placebo) once daily.[28]

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Table V. Effect of budesonide inhalation suspension (BIS) or placebo (PLA) on lung function in paediatric patients with persistent asthma in multicentre, randomised, double-blind, parallel-group, 12-week trials[a]

Reference	Dosage	Baseline characteristics (mean) [no. of patients]			Results at end-point [no. of patients]		
		FEV_1 (% predicted)	PEF (L/min)		FEV_1 (L)[b]	PEF (L/min)[b]	
			am	pm		am	pm
In paediatric patients with mild persistent asthma[c]							
Kemp et al.[d,e][28]	BIS 0.25mg qd	83.8 [29]	142.4 [44]	151.5 [42]	↓0.01 [29]	↑14.4 [44]	NR
	BIS 0.5mg qd	81.9 [28]	137.5 [41]	149.2 [41]	↑0.03* [28]	↑6.5 [41]	NR
	BIS 1mg qd	78.3 [33]	130.8 [54]	136.9 [55]	↑0.03* [33]	↑10.9 [54]	NR
	PLA qd	81.6 [38]	143.9 [55]	150.7 [55]	↓0.07 [38]	↑7.1 [55]	NR
In paediatric patients with moderate persistent asthma[c]							
Baker et al.[d,f][27]	BIS 0.25mg qd	79 [33]	164 [33]	170 [33]	↑0.07 [31]	↑10.9 [32]	↑16.8* [32]
	BIS 0.25mg bid	83 [34]	157 [34]	169 [34]	↑0.08 [33]	↑23.0** [34]	↑19.2* [34]
	BIS 0.5mg bid	80 [30]	167 [30]	177 [30]	↑0.17* [29]	↑24.8** [29]	↑21.0** [29]
	BIS 1mg qd	78 [35]	157 [35]	166 [35]	↑0.11 [34]	↑17.1* [34]	↑14.1 [34]
	PLA bid	79 [32]	156 [32]	161 [32]	↑0.04 [28]	↓0.2 [32]	↑1.9 [32]
In paediatric patients with inhaled corticosteroid-dependent asthma							
Shapiro et al.[g][97]	BIS 0.25mg bid	80.5 [47]	155.6 [47]	160.9 [47]	↑0.05 [47]	↑15.3** [47]	↑14.9* [47]
	BIS 0.5mg bid	78.8 [42]	162.1 [42]	171.6 [42]	↑0.08* [42]	↑11.8* [42]	↑11.6 [42]
	BIS 1mg bid	80.2 [45]	167.6 [45]	169.9 [45]	↑0.07 [45]	↑10.4* [45]	↑13.2 [45]
	PLA bid	79.2 [44]	158.3 [44]	164.7 [44]	↓0.01 [44]	↓1.3 [44]	↑3.0 [44]

a BIS and PLA were administered over approximately 5 minutes with the Pari LC Plus nebuliser with a mouthpiece or facemask.

b Mean change from baseline.

c Based on diagnostic criteria from the US National Heart, Lung, and Blood Institute Guidelines for the Diagnosis and Management of Asthma.[14]

d Not all patients randomised to treatment in the studies by Kemp et al.[28] (n = 359) and Baker et al.[27] (n = 480) were capable of performing pulmonary function tests. The results pertain to the subset of patients capable of performing such tests.

e Percent reversibility of FEV_1 was 26.1, 31.6, 26.3 and 27 for the BIS 0.25, 0.5 and 1mg once daily and PLA groups, respectively.

f Percent reversibility of FEV_1 was 29, 30, 30, 27 and 29 for the BIS 0.25mg daily, 0.25mg twice daily, 0.5mg twice daily and 1mg daily and PLA groups, respectively.

g Percent reversibility of FEV_1 was 35.9, 36.2, 32.3 and 30.3 for the BIS 0.25, 0.5 and 1mg twice daily and PLA groups, respectively.

bid = twice daily; **FEV_1** = forced expiratory volume in 1 second; **NR** = not reported; **PEF** = peak expiratory flow rate; **qd** = once daily; ↑ indicates increase; ↓ indicates decrease; * $p \leq 0.05$, ** $p \leq 0.01$ *vs* PLA.

Age-Related Efficacy

Analysis of pooled data from 2 studies[27,28] suggests that once daily administration of budesonide inhalation suspension is equally effective in paediatric patients aged <4 (n = 259) and ≥4 (n = 384) years with persistent asthma.[139] Budesonide-treated patients who received 0.25, 0.5 or 1mg once daily for 12 weeks had improved daytime and night-time asthma symptom scores and required fewer days of β_2-agonist bronchodilator therapy compared with placebo recipients. Similar age-independent improvements in these parameters were seen with twice daily administration of budesonide inhalation suspension 0.25 and 0.5mg in paediatric patients aged <4 (n = 127) and ≥4 years (n = 164) with moderate persistent asthma.[140]

4.1.2 Severe Persistent Asthma

Infants and young children with severe asthma received budesonide inhalation suspension 2 mg/day in 2 randomised, double-blind, placebo-controlled studies.[98,100] Infants and children (n = 36) enrolled in 1 study were aged 10 months to 5 years (mean age 27 months) and had required a minimum of 0.75 mg/kg of oral prednisolone on alternate days for ≥4 weeks.[98] Infants (n = 40) aged 6 to 30 months (mean age 17 months) who had experienced asthma exacerbations requiring oral corticosteroid administration during each of the 3 previous months or had daily asthma symptoms for at least 15 consecutive days were included in a second study.[100] Concomitant oral salbutamol solution 100 μg/kg 3 times daily was administered in 1

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trial.[100] Asthma exacerbation rates, symptom scores and oral prednisolone requirements were recorded during 8[98] or 12[100] weeks' treatment with budesonide inhalation suspension.

Budesonide inhalation suspension 1mg twice daily significantly reduced the number of asthma exacerbations, asthma symptom scores and the requirement for systemic corticosteroids in preschool children with severe asthma.[98,100] Asthma exacerbations occurred in 40% of budesonide-treated patients (n = 20) compared with 83% of placebo recipients (n = 18; $p < 0.01$) during the 12-week study.[100] During 12 weeks of treatment, 55% of budesonide recipients remained without an asthma exacerbation compared with 8% of placebo recipients ($p < 0.05$).[100] After 8 weeks of treatment during the other study, the dosage of oral prednisolone (mean dosage 1.32 mg/kg on alternate days at entry) was decreased by 80% among infants and young children treated with budesonide (n = 17) compared with a 41% dosage reduction in the placebo group (n = 14; $p < 0.05$).[98]

Significant reductions in the incidence of daytime ($p < 0.05$)[98,100] and night-time ($p < 0.01$)[100] wheezing were also noted among budesonide-treated children compared with placebo recipients.

4.1.3 Comparisons with Sodium Cromoglycate

According to preliminary results from 2 clinical trials, budesonide inhalation suspension is significantly more effective than nebulised sodium cromoglycate in improving control of asthma symptoms in young children with persistent asthma.[101,102] Children enrolled in one 52-week randomised, nonblind, multicentre study were aged ≈4 years and had mild to moderate persistent asthma (mean duration of asthma ≈2.7 years).[101] Infants aged 11.6 to 31.2 months (mean age 18 months) were included in a further single-blind, parallel-group study in which they received either budesonide inhalation suspension 0.5mg twice daily or nebulised sodium cromoglycate 20mg 3 times daily for 3 months, followed by a 6-month observation period.[102] During the 52-week study, dosages could be titrated up or down after 8 weeks of treatment with either budesonide inhalation suspension 0.5mg once daily (or in divided doses given twice daily) or sodium cromoglycate 20mg 4 times daily (mean dosages during the final 44 weeks of the study were not reported in the abstract).[101] Asthma exacerbation rates, the primary end-point, and symptom scores were recorded during 12[102] or 52[101] weeks of active treatment and after the whole study period of 9 months.[102]

Children treated with budesonide inhalation suspension (n = 168) had nearly a 4-fold lower mean asthma exacerbation rate over 52 weeks than those treated with sodium cromoglycate (n = 167) [1.23 *vs* 4.65 exacerbations per year, respectively; $p \leq 0.001$).[101] In addition, mean time to first asthma exacerbation was significantly ($p < 0.001$) longer for budesonide-treated patients (217 days) compared with those who received sodium cromoglycate (148 days). Mean time to first addition of chronic asthma therapy was also significantly ($p < 0.001$) longer for budesonide recipients (321 days) compared with sodium cromoglycate recipients (235 days).[101] Furthermore, mean improvements in daytime and night-time asthma symptom scores were significantly ($p < 0.001$) greater in the budesonide group than in the sodium cromoglycate group, and budesonide-treated patients experienced significantly more rescue medication-free days than the sodium cromoglycate group (–6.17 *vs* –4.14 days per 2 weeks, respectively; $p < 0.001$) from baseline to week 52.[101]

After 3 months of active treatment in the other study, the asthma exacerbation rate was significantly ($p = 0.0017$) lower in budesonide-treated children [2 of 37 (5.4%)] than in those who received sodium cromoglycate [13 of 41 (32%)].[102] Children in the budesonide group also had significantly more days ($p = 0.012$) and nights ($p = 0.002$) without cough and significantly ($p = 0.011$) more nights without awakening due to cough than the sodium cromoglycate group.[102] The positive effects of budesonide inhalation suspension on asthma symptoms and exacerbation rates were sustained during the 6-month follow-up period.[102]

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4.2 Acute Asthma or Wheezing

Paediatric patients with acute asthma or wheezing received varying dosages of budesonide inhalation suspension in several randomised, double-blind, comparative studies.[103-109] Three of these studies took place in hospital emergency departments[103,106,108] and the remaining studies enrolled paediatric patients after they were admitted to hospital.[104,105,107,109] Two of these studies are available only as abstract reports.[104,108]

Patients who presented with wheezing and shortness of breath were eligible for these studies if their symptoms failed to respond to at least 1 dose of nebulised bronchodilator,[103,109] they had a baseline FEV_1 <70% of predicted[104,108] or if they had an asthma symptom score of ≥3 on a 12-point scale.[107] Patients were excluded if they had received systemic corticosteroids within 7 days,[105] 1 month[103] or 24 hours[106] of enrolment. Children with chronic lung diseases such as cystic fibrosis or BPD were also excluded from the studies.[103,105,106] Two studies included only patients aged ≤18[107] or ≤24[109] months; 2 trials enrolled patients between the ages of 2 and 8[103] or 2 and 12[106] years. These trials in infants and young children used symptom scores and length of hospital or emergency department stay as primary efficacy variables.[103,107,109] The remaining trials included children aged 5 to 18 years and evaluated PEF and/or FEV_1 and symptom scores for assessing response to therapy.[104,105,108] Three studies included information on the type of nebuliser used to administer medications;[105-107] the 5 fully published trials were conducted in hospital and used continuous oxygen from a wall-mounted source at 5 to 8 L/min as the air source.[103,105-107,109]

Budesonide inhalation suspension has a rapid onset of action. Within 2 to 24 hours of administration in conjunction with a β_2-agonist bronchodilator, improvements from baseline in mean asthma symptom scores[105,106,109] and/or FEV_1 [104,105] and PEF[104] were apparent in budesonide recipients. Budesonide inhalation suspension 0.25mg every 6 hours and nebulised ipratropium bromide 0.1mg every 6 hours both decreased asthma symptom scores compared with baseline 12 hours after the first dose; however, a significantly greater reduction in symptom scores was reported in the budesonide group after 12 hours ($p < 0.01$ *vs* ipratropium bromide).[109] Decreases in mean symptom score, respiratory rate, heart rate and respiratory distress score were significantly larger in the budesonide group than in the prednisolone group ($p < 0.05$ for all parameters) in 1 study that included 80 children aged 2 to 12 years who were treated in a hospital emergency department;[106] a decrease in respiratory distress score by 1 grade occurred faster in the budesonide group than the prednisolone group (1.7 ± 0.6 *vs* 2.5 ± 1.2 hours, respectively; $p < 0.01$).[106]

Compared with nebulised budesonide, oral prednisolone produced similar mean improvements from baseline in FEV_1 and PEF in 1 study in children aged 7 to 13 years who were admitted to hospital for acute asthma.[104] Following 24 hours of treatment in another study, FEV_1 improved significantly in the budesonide group ($p = 0.0073$ *vs* baseline), but not in the prednisolone group.[105] In a separate study conducted in a hospital emergency department, mean percent changes in FEV_1 were higher in children who received 3 doses of nebulised budesonide 0.5mg plus nebulised terbutaline 2.5mg ($n = 33$) compared with those who received 3 doses of nebulised terbutaline 2.5mg ($n = 32$); however, the difference between the 2 groups was not significant.[108]

Mean length of hospital stay for budesonide-treated children who were admitted to hospital was similar to those who received prednisolone in 1 study (3.5 days in both groups).[107] The mean length of hospital stay in the budesonide group was significantly shorter than in the ipratropium bromide group (66.4 *vs* 93 hours; $p < 0.01$) in the only study that compared these 2 agents.[109]

In a separate study that took place in a hospital emergency department, mean length of stay was significantly shorter in the budesonide group than in the prednisolone group (2.9 ± 1.7 *vs* 5.5 ± 4.6 hours, respectively; $p < 0.001$).[106] 5 of 39 children in the prednisolone group were admitted to hospital

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because of asthma symptoms compared with 1 of 41 children in the budesonide group.[106]

4.3 Croup

According to the results of several randomised, double-blind studies, budesonide inhalation suspension is significantly more effective than placebo, as effective as oral dexamethasone and nebulised epinephrine (adrenaline), and less effective than intramuscular dexamethasone at reducing symptom scores in paediatric patients with croup (table VI).

Most studies enrolled infants as young as 3 months-of-age;[110,111,115,116,118] overall, these studies enrolled paediatric patients aged 3 months to 9 years.[110-118] Five studies enrolled patients who were admitted to hospital with a diagnosis of croup,[111-114,116] while the remaining studies were conducted in hospital emergency departments.[110,115,117,118]

The primary efficacy variable in these studies was the croup symptom score. Four of the studies used the 17-point croup scoring system developed by Westley et al.,[141] which is a valid, responsive and reliable outcome measure in children with croup.[110,111,115,118] Different scoring systems, including 1[113] based on the Westley et al.[141] scale and those developed by Husby et al.[114] and Liepzig et al.,[112] were used in the remaining studies,[112-114,116,117] which may explain the disparity between baseline severity scores in these studies (range 3.7[116] to 8[114]). The various scoring systems used in these studies are described in table VI.

In a randomised, double-blind, placebo-controlled trial, two 1mg doses of budesonide inhalation suspension administered 30 minutes apart were more effective than placebo in children aged 4 months to 5 years with moderate to severe croup [at 2 hours after treatment, mean modified croup score decreased from 8 to 4 in the budesonide group (n = 20) but remained unchanged at 8 in the placebo group (n = 16; p = 0.008] (table VI).[114] Overall disease severity, cough and stridor also decreased significantly in the budesonide group ($p < 0.05$ *vs* placebo for all parameters), whereas there were no significant differences in sternal retractions, dyspnoea or cyanosis.[114]

Single doses of budesonide inhalation suspension 2mg[111,115,116] or 4mg[118] given alone[111,115,116,118] or in combination with oral dexamethasone 0.6 mg/kg[115] produced a decrease in croup score of ≥2 points from baseline within 4 to 5 hours (table VI). Rapid symptom relief with nebulised budesonide with or without dexamethasone led to earlier hospital or emergency department discharge compared with placebo in children with mild to moderately severe croup.[110,111,115,118]

Relapse rates varied considerably in clinical studies of single dose corticosteroids in children with croup. In 1 study, 9 of 72 (12.5%) children contacted (3 budesonide 2mg, 4 placebo and 2 dexamethasone 0.6 mg/kg recipients) had visited a physician for persistent croup symptoms in the 7 to 10 days after hospital discharge.[116] In contrast, 15 of 27 (56%) patients who received nebulised budesonide 2mg and 21 of 27 (78%) placebo recipients had been treated with oral dexamethasone 0.6 mg/kg within 7 days of study commencement.[111] Within 1 week of treatment, 7 placebo recipients and 1 patient from the budesonide group were admitted to hospital with croup symptoms.[111]

Roberts et al.[112] evaluated the efficacy of multiple doses of budesonide inhalation suspension in hospitalised children with moderate to severe croup. 82 children aged 6 months to 8 years with a croup score ≥4 were randomised to receive nebulised budesonide 2mg (n = 42) or placebo (n = 40) administered every 12 hours to a maximum of 4 doses. Croup scores were assessed 2, 6 and 12 hours after the initial dose, then every 12 hours up to 48 hours if the patient remained in hospital. Parents were contacted 1 and 3 days after hospital discharge to assess relapse rates.

At 6, 12 and 24 hours, children in the budesonide group had significantly lower croup scores (as estimated from a graph) of ≈4.1, 4.0 and 3.9, respectively, than patients in the placebo group (croup scores ≈5.5, 5.0 and 4.8, respectively; $p < 0.001$).[112] Fourteen of 42 (33%) [p = 0.02 *vs* placebo] children in the budesonide group still had a

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Table VI. Overview of randomised, double-blind trials comparing budesonide inhalation suspension (BIS) with placebo (PLA) or other agents in paediatric patients with croup

Reference (disease severity, setting)	Treatment	No. of patients (mean age in y)	Mean baseline croup symptom score[a]	Croup symptom score at end-point (time of last observation)
Comparisons with PLA				
Husby et al.[114]	BIS 1mg every 30 min x 2 doses	20 (1.6)	8	4** (2h)
(mod-sev, H)	PLA every 30 min x 2 doses	16 (1.1)	8	8 (2h)
Klassen et al.[111] (mild-mod, ED)	BIS 2mg	27 (1.8)	4 (3,5)[b]	1** (4h)
	PLA	27 (2.2)	4 (3,5)[b]	3 (4h)
Klassen et al.[110]	BIS 2mg + oral DEX[c]	25 (1.2)	4.4	3 (4h)
(mild-mod, ED)	PLA + oral DEX[c]	25 (1.8)	4.1	2.3 (4h)
Roberts et al.[112]	BIS 2mg every 12h	42 (2.3)	6.4	3.9*** (24h)
(mod-sev, H)[d]	PLA every 12h	40 (2.2)	6.3	4.8 (24h)
Godden et al.[113]	BIS 2mg at entry & 1mg every 12h	46 (3)	5.3	1.2** (24h)
(mild-sev, H)				
	PLA at entry & every 12h	41 (3.1)	5.2	3 (24h)
Comparison with IM DEX [all patients received nebulised racemic epinephrine][e]				
Johnson et al.[118] (mod-sev, ED)	BIS 4mg	48[g]	3.8	1.8* (5h)
	IM DEX[f]	47[g]	4.0	1.1***[†](5h)
	PLA	49	3.8	2.5 (5h)
Comparisons with oral DEX				
Klassen et al.[115] (mild-mod, ED)	BIS 2mg	65 (1.5)	3.5	1.2 (4h)
	oral DEX[c]	69 (1.3)	3.6	1.2 (4h)
	BIS 2mg + oral DEX[c]	64 (1.6)	3.8	1.3 (4h)
Geelhoed et al.[116] (mod, H)[d]	BIS 2mg	27 (2.8)	3.7	1.5* (12h)
	oral DEX[c]	23 (1.9)	3.8	0.9* (12h)
	PLA	30 (2.5)	3.8	2.8 (12h)
Comparison with nebulised L-epinephrine				
Fitzgerald et al.[117] (mod-sev, ED)	BIS 2mg	35 (1.7)	7.2	3.4 (24h)
	L-epinephrine 4mg	31 (2.1)	7.7	3.4 (24h)

a In 4 studies,[110,111,115,118] the maximum croup symptom score was 17 and was based on degree of stridor (0 none; 1 audible with stethoscope at rest; 2 audible without stethoscope at rest), retractions (0 none; 1 mild; 2 moderate; 3 severe), air entry (0 normal; 1 decreased; 2 severely decreased), cyanosis (0 none; 4 with agitation; 5 at rest), and level of consciousness (0 normal; 5 altered). Roberts et al.[112] used a maximum croup score of 11 based on stridor (0 none; 1 inspiratory; 2 inspiratory and expiratory), sternal retractions (0 none; 1 present), dyspnoea (0-3 points, respiratory rate adjusted for weight), tachypnoea (0-3 points, pulse rate adjusted for age), cyanosis (0 none; 1 minimal; 2 obvious cyanosis or requires oxygen). Godden et al.[113] used a maximum croup score of 17 based on oxygen saturation (zero 95-100%; one 92-94%; two 89-91%; three 86-88%; four <86%), stridor (0 none; 1 when agitated; 2 mild at rest; 3 moderate at rest; 4 severe at rest), cough (0 none; 1 when agitated; 2 mild at rest; 3 moderate to severe at rest), retractions (0 none; 1 mild; 2 moderate; 3 severe) and respiratory distress (0 none; 1 mild; 2 moderate; 3 severe). Geelhoed et al.[116] used a maximum croup score of 6 based on stridor (0 none; 1 only when crying, exertion; 2 at rest; 3 severe biphasic) and retractions (0 none; 1 only on crying, exertion; 2 at rest; 3 severe biphasic). Fitzgerald et al.[117] used a maximum score of 17 based on inspiratory stridor (0 none; 1 audible with stethoscope; 2 when agitated; 3 at rest; 4 severe), cough (0 none; 1 when agitated; 2 croup-like at rest; 3 severe at rest), retractions (0 none; 1 mild; 2 moderate; 3 severe), dyspnea (0 none; 1 mild; 2 moderate; 3 marked) and colour (0 normal; 2 cyanosed in air; 4 cyanosis with oxygen). Husby et al[114] used a maximum croup score of 17 based on inspiratory stridor (0 to 4), cough (0 to 3), retractions (0 to 3), dyspnoea (0 to 3) and colour (0 to 4).

b Median croup score (25th, 75th percentile).

c Patients received oral DEX 0.6 mg/kg.

d Values estimated from graphs.

e All patients received 0.5ml of 2.25% nebulised racepinephrine combined with either BIS or PLA suspension, depending on study group assignment.

f Patients received IM DEX 0.6 mg/kg at randomisation.

g Mean age of all patients randomised was 24±18 months.

DEX = dexamethasone; **ED** = emergency department; **H** = admitted to hospital; **IM** = intramuscular; **mod** = moderate; **sev** = severe; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs* PLA, † $p = 0.003$ *vs* BIS.

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croup score ≥4 at 12 hours after the initial dose compared with 24 of 40 (60%) children in the placebo group.[112] Budesonide recipients also achieved clinically significant reductions in croup symptom scores (≥2 points) faster than patients treated with placebo.[112] Within 3 days of hospital discharge, 1 of 34 patients in the budesonide group and 7 of 32 placebo recipients who were contacted required further medical attention for croup symptoms as determined by the parents (p = 0.02).[112]

4.4 Acute Bronchiolitis and Postbronchiolitic Wheezing

Two early studies[119,120] suggested that budesonide inhalation suspension may reduce the number of wheezing episodes and decrease time in hospital in paediatric patients with acute bronchiolitis; however, 1 study was a retrospective, uncontrolled comparison of infants admitted to hospital during 2 different time periods spanning 10 years.[120] Results of the second study must be qualified by the fact that the investigators were not blinded to the treatment groups, the control group did not receive placebo and a foot pump rather than an air compressor was used to administer study medications.[119]

Recently published well controlled studies with budesonide have failed to demonstrate a beneficial effect on the symptoms of acute bronchiolitis or the prevention of postbronchiolitic wheezing.[23,142] These studies evaluated the short and long term effects of budesonide inhalation suspension compared with placebo in a total of 201 infants aged 4 to 41 weeks.[23,142] In the study by Richter et al.,[23] infants were randomised to receive nebulised placebo every 12 hours for 6 weeks or budesonide inhalation suspension 1mg every 12 hours for 5 days, followed by 0.5mg every 12 hours for a total of 6 weeks. Symptom scores were used to assess acute symptoms. After hospital discharge, parents used diary cards to record daytime and night-time symptoms and β_2-agonist bronchodilator usage over a 6-month[23] or 12-month[142] follow-up period. Cade et al.[142] randomised infants to either nebulised placebo or budesonide inhalation suspension 1mg twice daily from hospital admission until 2 weeks after discharge.

No significant differences were found between the budesonide and placebo groups in clinical scores 48 hours after the initial dose[23] or median time to hospital discharge[23,142] during the acute phase of the illness. Furthermore, at 6-[23] or 12-[142] month follow-up, there were no significant differences between the budesonide and placebo groups in the prevalence of wheeze, daytime or night-time respiratory symptom scores or use of β_2-agonist bronchodilators.[142]

According to a recent prospective, nonblind study, administration of budesonide inhalation suspension to infants during and after the acute phase of RSV bronchiolitis may reduce recurrent wheezing and, subsequently, the need for chronic asthma medications. 117 infants aged 0 to 9 months (mean age 2.6 months) who were hospitalised for treatment of RSV bronchiolitis were randomised to 1 of 3 groups: symptomatic treatment only (group I, n = 41) or symptomatic treatment plus nebulised budesonide administered via Spira nebuliser in dosages of either 500μg 3 times daily for 1 week (group II, n = 40) or 500μg 2 times daily for 2 months (group III, n = 36).[143] Symptomatic treatment consisted of supplemental oxygen, nebulised bronchodilators and inhaled racemic epinephrine. Six months after RSV infection, allergy skin tests to common antigens demonstrated atopy in 13, 28 and 25% of infants, respectively, in groups I, II and III.

Two years after RSV infection, parental interviews revealed that 14 of 38 infants in group I (37%) were receiving continuous inhalation treatment for asthma compared with 7 of 39 infants in group II (15%; p = 0.06 *vs* group I) and 4 of 32 infants in group III (12%; p = 0.01 *vs* group I).[143] The efficacy of nebulised budesonide could not be attributed to the atopic status of infants or to atopic heredity, both of which were more common in budesonide-treated infants compared with those who received symptomatic treatment only. Other variables such as smoke exposure at home and duration of breast-feeding were similar between the

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3 groups; however, maternal smoking during pregnancy was not reported.

These results suggest that double-blind studies with budesonide in infants with RSV bronchiolitis be designed to determine the appropriate dosage and duration of therapy and to assess the long term (≥2 years) effects of the drug on respiratory status in these patients.

4.5 Chronic Lung Disease of Prematurity

The results of a randomised, double-blind, placebo-controlled, multicentre trial suggest that inhaled corticosteroids reduce the need for systemic corticosteroids and decrease supplemental oxygen requirements in premature infants who are at increased risk for the development of BPD.[24] Treatment with an inhaled corticosteroid (beclomethasone dipropionate) did not, however, prevent BPD in this study.[24]

A recent study demonstrated reduced need for intubation in premature infants (median gestational age 26 weeks) with respiratory distress syndrome who received budesonide inhalation suspension as of day 7 of life.[121] Very low birthweight infants [median birth weight 805g (range 525 to 1227g)] who required mechanical ventilation on day 6 of life or were extubated and received nasal continuous positive airway pressure (NCPAP) with an inspired oxygen fraction (F_iO_2) ≥0.3 were evaluated in a randomised, double-blind, placebo-controlled trial. At study inclusion 8 and 9 infants, respectively, in the budesonide and placebo groups required mechanical ventilation, and 5 infants in each group were receiving NCPAP with F_iO_2 ≥0.3. Budesonide inhalation suspension 0.5mg (n = 13) or placebo (n = 14) was delivered twice daily using a dosimetric jet nebuliser (Spira Electro 4) with the output inserted into the inspiratory limb of the breathing circuit of intubated infants. A facemask was used to deliver medication to spontaneously breathing infants. This system synchronises nebulisation with inspiration and has been shown to deliver ≈1.1% of the nominal budesonide dose.[144]

After 14 days' treatment, there was no significant difference between the 2 groups in the primary efficacy variable (30% decrease in F_iO_2). However, significantly ($p < 0.01$) more infants in the budesonide group (7 of 8 infants) were extubated by the end of the study compared with the placebo group (2 of 9 infants).[121]

At 28 days of age, all 27 infants required supplemental oxygen, but 5 budesonide-treated infants were able to discontinue all corticosteroid therapy.[121] Only 1 infant in the budesonide group required intravenous dexamethasone, and the remaining 7 infants continued to receive budesonide inhalation suspension after the study period was over.[121] In contrast, all 14 placebo recipients continued to receive corticosteroids; 3 infants received intravenous dexamethasone followed by treatment with nebulised budesonide, and 11 infants in the placebo group received nebulised budesonide from age 28 days.[121] Calculation of the number of infants needed to treat with nebulised budesonide for 2 weeks was 7 to decrease intravenous dexamethasone usage [relative risk (RR) = 0.35, relative risk ratio (RRR) = 64.1%] and 3 to reduce the need for either inhaled or intravenous corticosteroids (RR = 0.61, RRR = 38.4%).[121]

In a separate study, reductions in systemic corticosteroid requirements were noted in premature infants with BPD who received corticosteroid therapy as of day 7 after birth. Very low birthweight infants (≤1500g at birth) born prior to 30 weeks of gestation and remaining ventilator-dependent at 7 days of age were evaluated in a randomised, double-blind, placebo-controlled study.[122] Patients in the active treatment group (n = 30) received intravenous dexamethasone 0.25 mg/kg every 12 hours for 3 days, followed by nebulised budesonide 0.5mg twice daily for 18 days; those in the control group received intravenous saline followed by nebulised saline solution on the same schedule. There were no significant differences between the 2 groups in the primary outcomes, which included survival rate, incidence of chronic lung disease at 28 days, duration of hospitalisation and postnatal age at time of extubation.[122] Lung compliance was significantly greater after 3 days' treatment with dexamethasone compared with placebo (1.85

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vs 0.86 ml/kg/cm H_2O; p = 0.01).[122] This increase was not sustained after 7 or 18 days of nebulised budesonide treatment.[122] However, at the end of the treatment period, fewer infants in the active treatment group than in the placebo group (7 *vs* 17 patients, respectively; p = 0.02) required systemic corticosteroid rescue for symptomatic disease.[122] Further studies are needed with budesonide inhalation suspension in order to define the role of the drug in infants at risk for BPD.

5. Therapeutic Use in Adults

5.1 Asthma

Budesonide inhalation suspension has been compared with fluticasone propionate in adults with persistent asthma[145] and with oral prednisolone in adults with acute asthma.[146] The drug has also been compared with budesonide administered via metered dose inhaler plus spacer device (Nebuhaler) in adult patients with moderate or severe persistent asthma.[147]

Evidence from a double-blind, double-dummy, crossover study suggests that budesonide inhalation suspension is effective in patients whose asthma is not controlled on moderate dosages of inhaled corticosteroids.[147] 26 adults (mean age 45 years) with moderate or severe unstable asthma (mean FEV_1 63% predicted; range 36 to 93% predicted) not controlled by inhaled corticosteroids and β_2-agonist bronchodilators were randomised to 4 weeks' double-blind treatment with budesonide inhalation suspension 1 and 4mg twice daily administered via jet nebuliser or budesonide 0.8mg twice daily delivered via a metered dose inhaler plus spacer device. Significant improvements were noted in the 4mg twice daily nebulised budesonide group compared with the metered dose inhaled group; patients reported significant decreases in cough, breathlessness, wheezing and β_2-agonist use ($p < 0.05$ for all parameters) and increases in morning and evening PEF ($p < 0.01$ for both parameters). Nebulised budesonide 1mg twice daily was significantly more effective than the metered dose inhaler for evening PEF ($p < 0.01$) and for 2 of 5 symptoms ($p < 0.05$) in this study.[147]

High dose budesonide inhalation suspension has been studied in 135 adult patients (mean age 33 years) who were hospitalised and required corticosteroid therapy to treat severe acute asthma (PEF 20 to 70% predicted).[146] An abstract report of this randomised, double-blind, double-dummy, 24-hour study demonstrated that nebulised budesonide 4mg administered at study entry and at 3, 6, 12 and 18 hours was as effective as a single dose of prednisolone 30 or 40mg administered at study entry and at 6, 12 and 18 hours. Mean PEF increased significantly from baseline (statistics not reported) in all 3 groups after 24 hours of treatment, and there was no significant difference between the 3 groups.[146]

There is 1 published comparative study of budesonide inhalation suspension and fluticasone propionate delivered via metered dose inhaler and Volumatic spacer in adult patients with asthma.[145] This was a randomised, nonblind, multicentre, crossover trial in 37 patients aged 18 to 70 years. During a 1 week run-in period, patients continued their usual asthma medications which included either 2 or 4 mg/day nebulised budesonide. Patients were randomised to continue their current treatment or to replace budesonide with fluticasone propionate 1mg twice daily. Each treatment arm lasted for 4 weeks with a 4-week washout period in between. Mean change in morning PEF was significantly greater in the fluticasone propionate group than in the 2 budesonide groups combined (+20.5 *vs* –0.6 L/min; p = 0.007 compared with budesonide). Fluticasone propionate also increased morning PEF significantly compared with the budesonide 4 mg/day group (+52 *vs* +9.1 L/min; p = 0.026), but not compared with the budesonide 2 mg/day group.[145]

There was no significant difference between the fluticasone propionate and budesonide groups in 24-hour symptom-free intervals. Overall patient preference was not significantly different; 66% preferred the fluticasone propionate metered dose inhaler with Volumatic spacer compared with 34%

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who preferred nebulised budesonide.[145] However, significantly more patients considered fluticasone propionate easier to administer (78 *vs* 22%; p = 0.007) and more convenient to use (76 *vs* 24%; p = 0.008) than nebulised budesonide. Unfortunately, systemic effects on HPA axis function were not quantified in the patients enrolled in this study.[145]

Several small studies suggest that budesonide inhalation suspension has an oral steroid-sparing effect in adult patients with persistent asthma.[148,149] A subsequent noncomparative 12-week study in 42 oral corticosteroid-dependent adults (eligible patients were receiving ≥10 mg/day of prednisolone or equivalent) with an FEV_1 ≤50% of predicted showed that the addition of nebulised budesonide 2 mg/day allowed 23 patients (55%) to reduce their prednisolone dose by a mean of 59%.[150] In addition to oral corticosteroids, these patients were also using inhaled corticosteroids 2 mg/day (budesonide or beclomethasone dipropionate) plus nebulised β_2-agonist bronchodilators at study enrolment. A reduction was seen in the prednisolone dose within 3 to 4 weeks of starting budesonide; most of the prednisolone dose reductions occurred by the fifth or sixth week of budesonide treatment and were maintained for the remainder of the 12 weeks.[150] Lung function as assessed by PEF was maintained throughout the 12-week study, and asthma symptom scores decreased significantly from baseline ($p < 0.01$). Use of β_2-agonist bronchodilators did not change during the study.[150]

5.2 Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Budesonide inhalation suspension has been evaluated as an alternative to oral prednisolone in a double-blind, multicentre trial in adult patients who required hospitalisation due to an acute exacerbation of COPD (mean pre- and post-bronchodilator FEV_1 1.10 and 1.16, respectively).[151] Patients who recently received systemic corticosteroids or used inhaled corticosteroid doses >1500 μg/day were excluded from the study. 188 patients (mean age 70 years) were randomised to receive 72 hours' treatment with budesonide inhalation suspension 2mg every 6 hours (n = 69), oral prednisolone 30mg every 12 hours (n = 58) or placebo (n = 61). All patients received standard medical care consisting of nebulised β_2-agonist bronchodilators and ipratropium bromide, oral antibiotics and supplemental oxygen. The primary efficacy variable was mean change in post-bronchodilator FEV_1 from baseline to 72 hours; secondary end-points included the Borg dyspnoea score and changes in pre-bronchodilator FEV_1.[151]

At study end-point, there was a greater improvement from baseline in post-bronchodilator FEV_1 with both active treatments compared with placebo. The mean and 95% confidence interval for the differences between active treatment and placebo were: budesonide *vs* placebo 0.11L (0.02-0.19) and prednisolone *vs* placebo 0.16L (0.08-0.25). Pre-bronchodilator FEV_1 was improved by prednisolone (statistics not reported in this abstract). There was no statistically significant difference in FEV_1 between the budesonide and prednisolone groups. Changes in the Borg dyspnoea score were similar between the 3 groups.[151]

In 1 small, 5-day, randomised, parallel-group study the effects of budesonide inhalation suspension 2mg twice daily (n = 10) were compared with those of oral prednisolone 30 mg/day (n = 10) in patients (mean age 50 years) with corticosteroid-responsive asthma or COPD.[51] This was primarily a pharmacodynamic study, but FEV_1 was also included as an efficacy variable. All patients were receiving inhaled corticosteroids (mean dose 0.85 mg/day) and inhaled β_2-agonist bronchodilators prior to study entry; nebulised albuterol was used 4 times daily during the study. Mean baseline FEV_1 was similar in both groups. After 5 days of treatment, mean FEV_1 increased from 1.8 to 2.1L in the prednisolone group and from 1.9 to 2.0L in the budesonide group.[51]

6. Tolerability

6.1 In Children

Budesonide inhalation suspension was generally well tolerated in randomised, double-blind,

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placebo-controlled studies. During 12-week clinical trials the frequency of adverse events in children treated with budesonide inhalation suspension 0.25 to 2 mg/day did not differ significantly from that in placebo recipients with respect to the overall incidence, severity and type of adverse events.[27,28,97] Respiratory infection, fever, sinusitis, rhinitis, accidental injury, headache, pharyngitis and otitis media were reported by ≥10% of patients treated with budesonide or placebo (fig. 2).[28] There were no significant differences in the number of patients with positive oral or nasal cultures for candidiasis during treatment with budesonide or placebo.[28,97] In 1 trial, oropharyngeal fungal cultures were positive in 18 of 470 (4%) budesonide-treated patients and 2 of 95 (2%) placebo recipients; the distribution of positive cultures between treatment groups was similar and was not dose related.[27]

The adverse event profile of budesonide inhalation suspension during the 52-week nonblind safety studies in 670 paediatric patients aged ≤8 years was similar to that in the 12-week studies. In addition, the incidence of adverse events and the percentage of patients whose treatment was discontinued because of an adverse event were similar between budesonide recipients (n = 447) and conventional asthma therapy recipients (n = 223).[135]

6.1.1 Hypothalamic-Pituitary-Adrenal Axis Function

Mean basal and adrenocorticotropic hormone (ACTH)-stimulated cortisol levels were not adversely affected by 12 weeks' treatment with budesonide inhalation suspension 0.25 to 2 mg/day.[27,28,97] Importantly, there was no difference in the number of individuals treated with budesonide or placebo who had a shift from a normal to abnormal ACTH-stimulated cortisol response between baseline and week 12.[27,28,97]

In both the 12- and 52-week studies, ACTH 0.125mg was administered intramuscularly in children aged ≤2 years, and ACTH 0.25mg was administered intravenously to children aged >2 years.[27,28,97,135] ACTH-stimulated cortisol levels at baseline and after 52 weeks' treatment were similar among patients treated with budesonide inhalation suspension 0.5 to 1 mg/day (n = 125) and did not differ from those in patients randomised to conventional asthma therapy (n = 55), which consisted of short-acting oral or inhaled β_2-agonists, theophylline, sodium cromoglycate and/or inhaled corticosteroids (34% of patients received other inhaled corticosteroids).[135]

6.1.2 Growth

Growth velocity was generally unaffected by 52 weeks' nonblind treatment with budesonide inhalation suspension 0.5 to 1 mg/day. Although these trials were not designed as prospective growth studies, growth velocity data were collected for 527 children who completed 1 year of treatment with budesonide inhalation suspension (n = 371) or conventional asthma therapy (n = 156; 37 patients (24%) received other inhaled corticosteroids).[135] Growth velocity was similar between the budesonide and conventional asthma therapy groups in 2 of three 52-week safety studies.[152] In a subset of patients with mild asthma who did not have prior exposure to inhaled corticosteroids, a small yet statistically significant reduction in growth velocity (–0.8 cm/year) was observed in patients who received budesonide (n = 150) compared with children who were treated with conventional asthma therapy (n = 58) [growth rates 6.55 ± 2.08 *vs* 7.39 ± 2.51 cm/year for budesonide and conventional therapy, respectively; p = 0.002].[152] However, twice as many patients in the conventional therapy group than the budesonide group withdrew from the study because of worsening asthma symptoms. Thus, patients in the conventional therapy group with more severe disease who may be affected by disease-related growth rate reductions were excluded from the analysis.

6.2 In Adults

In adult patients with both oral and inhaled corticosteroid-dependent asthma, 12-weeks' treatment with budesonide inhalation suspension as a substitute for the inhaled corticosteroid, in conjunction with reduced doses of oral prednisolone, resulted in the resolution of adverse effects in 9 of 37 (24%) patients studied.[150] The incidence of

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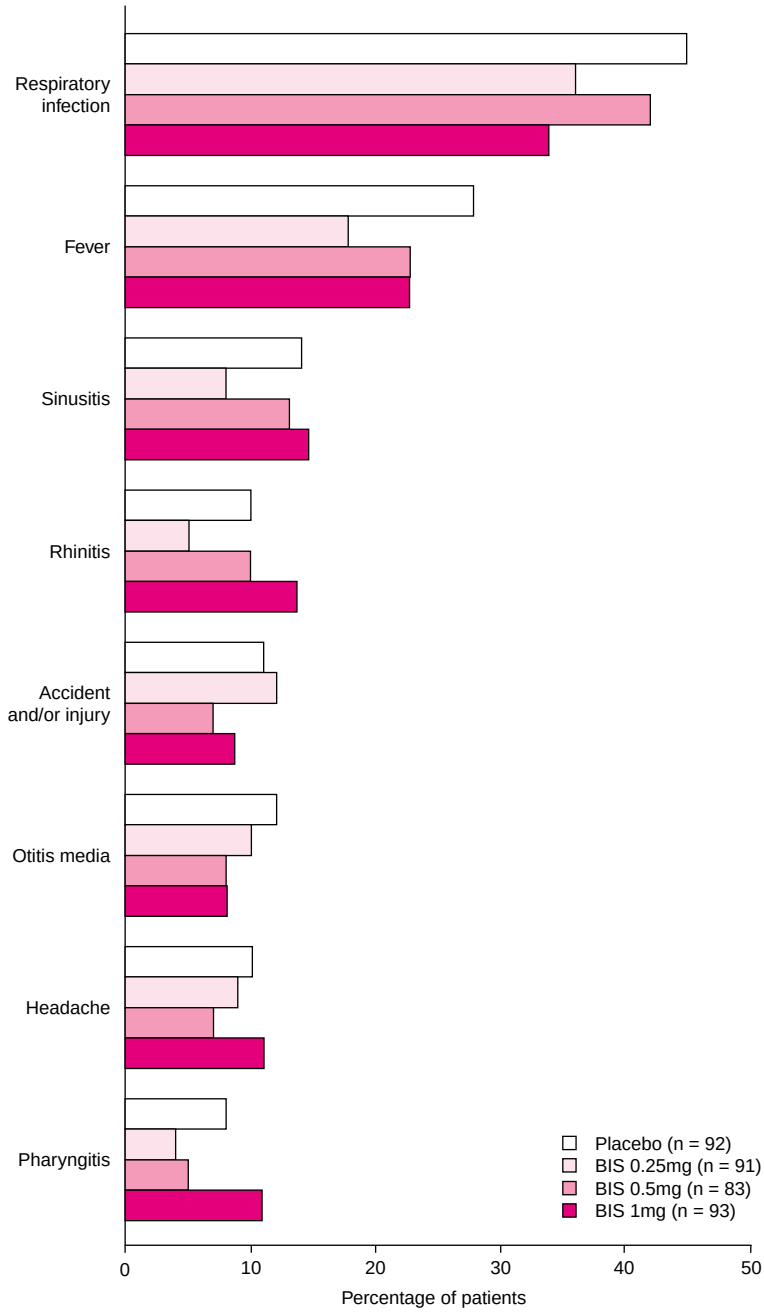

Fig. 2. Adverse events occurring in infants and young children who received once daily treatment with budesonide inhalation suspension (BIS) or placebo. Events included are those that were reported by ≥10% of patients in any 1 treatment group during a 12-week randomised, double-blind trial in 359 children aged 6 months to 8 years (mean age 56 months). There were no significant differences between the BIS and placebo groups.[28]

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purpura, moon face, skin thinning and weight gain were reduced overall. Treatment-emergent adverse events were reported in 23 of 37 patients (62%); the vast majority were musculoskeletal or respiratory in nature, which is consistent with systemic corticosteroid withdrawal.

7. Dosage and Administration

In the US, budesonide inhalation suspension is indicated for the maintenance treatment of asthma and as prophylactic therapy in children aged 12 months to 8 years.[153] In children receiving treatment with inhaled bronchodilators and/or inhaled corticosteroids, the recommended initial dosage is 0.5 mg/day. In those receiving oral corticosteroids, a higher initial dosage (1 mg/day) is recommended. The maximum recommended dosage in children is 0.5 mg/day in those previously receiving bronchodilators and 1 mg/day in those who were receiving inhaled or oral corticosteroids.[153] Children who are symptomatic despite receiving standard asthma care without corticosteroids may respond to budesonide dosages as low as 0.25mg once daily.[153]

In the UK and elsewhere, budesonide inhalation suspension is indicated for prophylaxis of asthma in children and adults especially if not fully controlled by β_2-agonist bronchodilators or sodium cromoglycate.[154] The recommended dosage of budesonide inhalation suspension in infants and children aged 3 months to 12 years with asthma is 0.5 to 1mg twice daily when starting treatment, during an asthma exacerbation or during withdrawal of oral corticosteroids; maintenance doses are typically 50% lower than the starting dosage. In adults and children aged >12 years, the starting dosage is 1 to 2mg twice daily, although higher doses may be necessary in very severe cases of asthma.[154] For the treatment of croup, the usual dose of budesonide inhalation suspension is 2mg given as a single inhalation or as two 1mg doses 30 minutes apart.[155]

Budesonide inhalation suspension is available as 0.25 and 0.5 mg/2ml in the US,[153] and as 0.25, 0.5 and 1 mg/2ml in other countries in which its use is indicated.[154] As with all drugs in its class, the dosage of budesonide inhalation suspension should be individualised and titrated to the lowest dosage that effectively controls asthma symptoms.[153,154]

Budesonide inhalation suspension is administered over approximately 5 minutes by a compressed air driven, breath-enhanced open vent jet nebuliser such as the Pari LC Plus nebuliser which was used in the 3 US clinical trials in paediatric patients with asthma.[27,28,97] Compared with conventional nebulisers which have a constant output throughout inspiration and expiration, breath-enhanced nebulisers have enhanced output during inspiration only, and thus decrease drug wastage during expiration.[153,156,157] The formulation should not be administered with an ultrasonic nebuliser as these devices have proven inefficient in nebulising budesonide inhalation suspension.[93]

Either a facemask or mouthpiece may be used to administer budesonide inhalation suspension, the choice of which is individualised and determined by patient age and acceptance.[156,158] Both delivery methods are effective; ideally the facemask should fit closely to the face, thus preventing air and medication from escaping around the mask.[156,159] The 'blow-by' technique of administration that is sometimes used with nebulised β_2-agonist bronchodilators should not be used with budesonide inhalation suspension. If a facemask is used for delivery of budesonide inhalation suspension, the face should be washed after each treatment to prevent facial skin irritation.[153,154] Mouth rinsing with water is recommended (in adults and in children who can be taught to spit out the rinse) after a dose of inhaled corticosteroid, including budesonide, in order to minimise the amount of drug swallowed.[153,156]

Admixture of nebulised drugs just prior to administration shortens the duration of each treatment and may have a positive effect on compliance. A compilation of compatibility data on commonly used nebulised agents in Australia indicates that budesonide inhalation suspension is compatible with ipratropium bromide (Atrovent® multiple dose and Atrovent® Unit Dose Vial), sin-

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gle dose salbutamol (Sterinebs® and Ventolin Nebules®), multiple dose salbutamol (Ventolin®, Respolin® and Delta-West salbutamol), multiple dose terbutaline (Bricanyl®) and single dose sodium cromoglycate (Intal Nebules®).[160] Budesonide inhalation suspension is also chemically compatible with the European formulations of ipratropium bromide (Atrovent®), fenoterol hydrobromide (Berotec®), ipratropium bromide with fenoterol hydrobromide (Duovent®) and acetylcysteine (Lysomucil®).[161]

Alterations in the final volume of the nebuliser charge as a result of admixing budesonide inhalation suspension with other nebulised drugs has the potential to change the output of budesonide from the nebuliser. Admixture of budesonide inhalation suspension 0.25 or 0.5 mg/2ml with normal saline to a final volume of 7ml produced an increase in the inhaled mass of drug that was not proportional to the volume.[162] The mean inhaled mass of budesonide increased from 73.1 to 109.3μg (50%) after dilution of budesonide inhalation suspension 0.25 mg/2ml to a final volume of 7ml. In contrast, dilution of the 0.5 mg/2ml budesonide formulation to a final volume of 7ml increased the inhaled mass of drug by only 35% (from 165.8 to 223μg). MMAD (range 3.5 to 3.7μm) and geometric standard deviation (2.5 for all concentrations), measures of the *in vitro* aerodynamic behaviour of an aerosolised budesonide, were not affected by dilution of budesonide inhalation suspension with normal saline.[162]

8. Place of Budesonide Inhalation Suspension in the Treatment of Inflammatory Respiratory Disorders

The goals of asthma therapy, as identified in contemporary guidelines, are to eliminate or minimise asthma symptoms, maintain optimal lung function and prevent the development of asthma exacerbations and fixed airflow obstruction. Ideally, these goals will be achieved with the minimum amount of medication and with minimal medication-related adverse events and absenteeism from school or work because of asthma.[14,18] Recent asthma guidelines[14,18] recognise the benefits of early intervention with inhaled corticosteroids and the need to minimise the use of rescue medications such as short-acting β_2-agonist bronchodilators. Furthermore, emphasis is placed on the importance of a graded approach to asthma therapy. Children with mild intermittent or exercise-induced asthma may require an inhaled β_2-agonist on an as-needed basis for symptom control. If these agents are needed more than 3 to 7 times per week, daily preventative therapy is recommended (i.e. an inhaled corticosteroid, or in mild cases, sodium cromoglycate).[14,163]

A number of studies of early intervention with inhaled corticosteroids have confirmed the place of these agents in the treatment of school-aged children[15,164] and adults[16,165] with mild to moderate persistent asthma. Indeed, there is a general consensus that early introduction of inhaled corticosteroids may prevent the structural changes which result from uncontrolled inflammation in the airways and may prevent the development of irreversible airway obstruction.[48] Whether these benefits also apply to infants and young children with asthma remain to be determined.

Inhaled corticosteroids are the most effective long term therapy available for mild, moderate or severe persistent asthma.[14] Regular use of inhaled corticosteroids results in decreased hospitalisation rates,[15,166,167] reduced need for oral corticosteroids and β_2-agonist rescue therapy, improves pulmonary function and decreased bronchial hyperresponsiveness.[16,76,77,165] Inhaled corticosteroids are more effective in children with persistent asthma than inhaled sodium cromoglycate,[101,102,168,169] short-acting[77] and long-acting[170] β_2-agonists and combinations of nonsteroidal treatments including theophylline, sodium cromoglycate and oral β_2-agonists.[15] As demonstrated in adults with persistent asthma, inhaled corticosteroids are more effective than the oral leukotriene receptor antagonist montelukast.[171]

Unfortunately, many paediatric patients are unable to use metered dose or inhalation-driven dry powder inhalers reliably, and optimal drug delivery

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may not be achieved in those who lack the coordination or the controlled inhalation technique necessary to use these devices properly. Some children are unable or unwilling to cooperate with the use of a metered dose inhaler with tight-fitting facemask and spacer, in which case the dose delivered to a struggling or uncooperative child may be lower than that required for disease control. Finally, despite patient cooperation and adequate technique, metered dose inhalers with face mask and spacer may fail to control asthma symptoms in some children.[30,31,172] These issues, taken together, illustrate the need to consider the age and ability of the child when selecting a drug delivery device and suggest that an alternative method of delivering inhaled corticosteroids to infants and young children, other than metered dose inhalers with spacer devices, would be welcome.[14]

For infants and young children who will accept them, a pressurised metered dose inhaler plus spacer is the device of choice for drug delivery because of its relative ease of use, portability and cost-effectiveness. However, nebulisers offer several advantages for administering asthma medications, including corticosteroids, to children with persistent asthma whose parents are willing and able to comply with this method of delivering drug therapy. The dose is delivered over a period of 5 minutes and, importantly, drug administration requires minimal, albeit some, patient cooperation and coordination.[14] As such, the dose may be administered while the child is asleep, as long as the patient accepts the use of a close-fitting facemask.[30] For older children, a mouthpiece may be used.

Internationally developed guidelines for asthma management have recognised the efficacy of nebulised budesonide in the long term management of moderate to severe persistent asthma in children aged ≤5 years.[173] Nebulised budesonide ≤1 mg or >1mg twice daily, respectively, are recommended for children with moderate or severe persistent asthma as an alternative to inhaled corticosteroids delivered via pressurised metered dose inhaler with spacer device.[173] In addition, the US asthma treatment guidelines, which were developed before the availability of nebulised budesonide in that country, recommend that young children with moderate to severe asthma or a history of severe exacerbations of asthma have medications and a compressor-driven nebuliser at home for initiating β_2-agonist bronchodilators or anti-inflammatory agents during acute asthma attacks.[14] As seen in recently published studies with the drug in infants and young children with acute asthma, these patients may benefit from early initiation of budesonide inhalation suspension in conjunction with a β_2-agonist bronchodilator.[103,106,108]

Budesonide inhalation suspension is the most widely available corticosteroid for nebulisation and the only such formulation approved in the US. Moreover, it is the first inhaled corticosteroid formulation approved by the US FDA for use in children between the ages of 1 and 4 years. (Until the recent approval of the inhalation suspension, budesonide was only available in the US in an inhalation-driven dry powder inhaler that was indicated for use in adults and children aged ≥6 years.) Budesonide is well established as an effective inhaled corticosteroid with a high ratio of local effects in the lung to systemic corticosteroid effects, which result from extensive hepatic first-pass metabolism of orally absorbed budesonide and the low potency of metabolites.[47]

Recent studies have shown that once daily treatment with budesonide inhalation suspension is effective in infants and young children with mild to moderate persistent asthma.[27,28] Daily budesonide dosages of 0.25, 0.5 and 1mg produced significantly greater improvement in asthma symptom scores and reduced the need for bronchodilators compared with placebo. In children with moderate persistent asthma, equivalent improvement in asthma symptom scores was obtained with 1mg of budesonide administered once daily and 0.5mg administered twice daily.[27] These findings have important implications for children with a history of poor compliance, as once daily therapy with budesonide inhalation suspension is a simple, effective regimen for the treatment of persistent asthma.

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Anti-inflammatory agents, including inhaled corticosteroids, sodium cromoglycate or nedocromil, are recommended as first-line agents for long term control of symptoms in children with persistent asthma.[14,173] However, recent trials have demonstrated that 52-weeks' treatment with budesonide inhalation suspension 0.5mg once or twice daily was more effective than nebulised sodium cromoglycate 20mg 3 or 4 times daily in controlling asthma symptoms in young children with mild to moderate asthma.[101,102] The superior efficacy of budesonide in these studies is consistent with results of a separate randomised, double-blind, multicentre trial which enrolled 1041 children aged 5 to 12 years with mild to moderate persistent asthma.[169] Control of asthma symptoms was best in children who received budesonide 200μg via Turbuhaler than in those who received nedocromil 8mg via pressurised metered dose inhaler or placebo, all administered twice daily. In addition to fewer asthma symptoms, budesonide-treated children used fewer puffs per week of as-needed albuterol, had more episode-free days and improved airway responsiveness to methacholine than those who received nedocromil or placebo. Children who received budesonide had a 43% lower rate of hospitalisation for asthma, a 45% lower rate of urgent care visits for asthma and a 43% lower rate of prednisolone use compared with the placebo group during the treatment period (mean 4.3 years).[169]

In young children with moderate to severe persistent asthma, nebulised budesonide 0.25 to 1mg administered twice daily for 12 weeks decreased asthma symptom scores and reduced the use of as-needed β_2-agonist bronchodilators.[97,131] According to 2 trials, budesonide inhalation suspension 1mg twice daily for 8[98] to 12[100] weeks reduces the number of exacerbations and, more importantly, the requirement for systemic corticosteroids in young children with severe persistent asthma. Further long term studies would be necessary to confirm these results and to assess the long term effects of high dose nebulised budesonide on growth in children.

Nebulised budesonide may produce more rapid elimination of symptoms than oral prednisolone[106] or nebulised ipratropium[109] in young children with acute asthma or wheezing; when added to standard medical care, nebulised budesonide has the potential to reduce the requirement for systemic corticosteroids[106] and the duration of hospital or emergency department stay in this population.[106,107,109] These results are supported by a study which demonstrated equal efficacy of high dose budesonide via Turbuhaler 1600μg 4 times daily for 1 day with that of oral prednisolone 2 mg/kg/day × 2 doses, both followed by a 25% dose reduction every other day for 8 days, in 22 older children (6 to 16 years) with acute asthma exacerbations.[174] After 4 hours in the emergency department, both groups of children showed significant decreases from baseline in wheezing ($p < 0.05$) and accessory muscle use ($p < 0.001$) and an increase in oxygen saturation ($p < 0.05$), and none of these patients required admission to hospital.

Nebulised corticosteroids provide rapid symptom relief and prevent hospitalisation in children with mild to severe croup. A meta-analysis of well-designed trials, which included the trials presented in section 4.3, demonstrated that 1 hospital admission was prevented for every 3 to 8 children treated with nebulised corticosteroids in the emergency department.[175] Budesonide inhalation suspension 2 or 4mg is more effective than placebo,[111] as effective as nebulised epinephrine[117] and oral dexamethasone[115,116] and slightly less effective that intramuscular dexamethasone[118] in alleviating symptoms in children with croup. Clinically significant relief of croup symptoms may be achieved as early as 2 to 3 hours after administration of nebulised budesonide, which has important implications for decreasing length of stay in the emergency department.[110,114,116]

The role of budesonide inhalation suspension in the treatment of premature infants at risk for developing BPD is evolving. Recent evidence suggests that nebulised budesonide is an effective alternative to parenteral dexamethasone and, more specifically, that the drug facilitates the discontinuation

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of mechanical ventilation and decreases systemic corticosteroid requirements in this patient population. These results are in keeping with those from a similar study of 4 weeks' treatment with beclomethasone dipropionate administered by metered dose inhaler directly into the endotracheal tube of low birthweight premature infants.[24]

It is assumed that high dosages of inhaled corticosteroids have a better therapeutic index than oral corticosteroids such as prednisolone. Hence, budesonide inhalation suspension may be suitable as an alternative to oral corticosteroids[146,148,149] in adults with severe persistent asthma; nebulised budesonide may also be an effective alternative to oral corticosteroids in adults with acute exacerbations of COPD.[151] In adults with acute exacerbations of severe asthma, high dose budesonide inhalation suspension appears to be as effective as oral prednisolone, but further controlled trials would be needed to verify these results.[146]

Budesonide inhalation suspension may also have a role in the treatment of adult patients with asthma who cannot properly use metered dose or dry powder inhalers, or in adults whose disease is not controlled by medications delivered via these devices despite adequate inhalation technique.[14] Nebulised budesonide has been shown to be at least as effective as budesonide delivered via metered dose inhaler (not available in the US) with spacer device in adults with moderate to severe asthma. High dosages of fluticasone propionate (2 mg/day) delivered via metered dose inhaler with spacer device produced greater improvements in morning PEF than nebulised budesonide 2 or 4 mg/day in 1 short term, nonblind study in adults, but there was no difference between the fluticasone propionate and budesonide groups in 24-hour symptom-free intervals.[145] However, this study failed to standardise the nebuliser systems used and did not compare the effect high dose fluticasone propionate with that of nebulised budesonide on HPA axis function.

Budesonide inhalation suspension was generally well tolerated in clinical trials. In placebo-controlled trials, the type, incidence and severity of adverse effects, including oropharyngeal candidiasis, were similar between the budesonide and placebo groups.[27,28,97] Importantly, there was no evidence of HPA axis suppression in short term (12 weeks) studies in children with dosages of 0.25 to 2 mg/day[27,28,97] or long term (52 weeks) studies with budesonide inhalation suspension titrated to the lowest effective dosage, usually 0.25 to 0.5 mg/day or every other day.[135] Growth velocity was generally unaffected by long term treatment (15 months; 3 months' double-blind plus 12 months' nonblind treatment) with budesonide inhalation suspension in 2 studies;[135] however, in keeping with other studies of this drug class, growth velocity was slightly but statistically significantly lower in budesonide-treated patients compared with conventional asthma therapy in 1 study of infants and children with mild persistent asthma who did not have prior exposure to inhaled corticosteroids.[152]

There is general agreement that transient decreases in growth rates[176,177] and delayed puberty[177] are seen in children with asthma. However, until recently, the long term effects of inhaled corticosteroids, including budesonide inhalation suspension, on growth in children with asthma have not been clearly defined. Furthermore, the potential exists for 'catch up' growth after the onset of puberty or once inhaled corticosteroid doses are decreased or discontinued, but this topic also requires further evaluation.

The clinically relevant outcome with respect to growth is whether children treated with an inhaled corticosteroid attain their expected final height. Prospective studies involving many years of follow-up of a cohort are required to evaluate this endpoint. A recently published, prospective, cohort study found that children with asthma who received long-term treatment with inhaled budesonide had improved lung function and attained normal adult height.[38] In this study, the final height of children (n = 142) with mild to moderate persistent asthma was not adversely affected by 3 to 13 years' (mean duration 9.2 years) continuous treatment with inhaled budesonide 0.11 to 0.877

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mg/day [mean daily dose 0.412mg; mean cumulative budesonide dose 1.35 grams (range 0.41 to 3.99 grams)]. Consistent with results from shorter-term (≤1 year) studies with inhaled beclomethasone dipropionate[176,178,179] and nebulised budesonide,[152] the growth rate during the first year of budesonide treatment was ≈1cm less than during the run-in period; however, this growth reduction did not persist and had no relation to attained final height. The mean difference between measured and predicted final adult height was +0.3cm (95% confidence interval, –0.6 to +1.2) for budesonide-treated children, –0.2cm (95% confidence interval, –2.4 to +2.1) for control children with asthma, and +0.9cm (95% confidence interval, –0.4 to +2.2) for healthy siblings. Furthermore, there was no statistically significant correlation between the mean difference in measured and predicted final height and duration of budesonide treatment or mean daily or cumulative budesonide dose.[38] In a separate prospective trial which followed children during 4 to 6 years' treatment with inhaled budesonide, nedocromil or placebo, the effects of budesonide on growth were not sustained beyond the first year of treatment, and all 3 groups of children had similar growth velocity by the end of the trial.[169] These results are supported by retrospective cohort studies which also demonstrated that the final adult height of children who received inhaled corticosteroid therapy for asthma, after adjustment for average parental height, was not significantly different from that of age- and gender-matched control children.[180-184] Nevertheless, sensitivity to adverse effects on growth rate may vary between individual children, and growth should be monitored regularly in all paediatric patients using inhaled corticosteroids.[153]

To date, no data have been published regarding the susceptibility to childhood diseases (e.g. chicken pox, measles) or the immunogenicity of live-virus vaccines (e.g. varicella) in paediatric patients who are receiving maintenance doses of inhaled corticosteroids, including budesonide inhalation suspension.[14,185] Although high doses of inhaled corticosteroids theoretically present risks similar to systemic corticosteroids, it is not known how, or if, inhaled corticosteroid therapy influences the risk of developing severe infections in susceptible young children who have not been adequately vaccinated.[14,153,185] However, the American Academy of Pediatrics Report of the Committee on Infectious Diseases states that the administration of inhaled corticosteroids does not cause enough immunosuppression to contraindicate administration of live-virus vaccines.[186] If clinical or laboratory evidence of immunosuppression occurs with prolonged corticosteroid therapy, live-virus vaccines should not be administered until corticosteroid therapy has been discontinued for at least 1 month.[186] In rare instances, prophylaxis with immunoglobulins may be indicated upon exposure to measles or chicken pox in children receiving high dose inhaled corticosteroids who have not had these diseases or have yet to be vaccinated;[14,153] antiviral therapy may be considered in those children who develop chicken pox.[153]

In conclusion, budesonide inhalation suspension is the most widely available nebulised corticosteroid, and in the US is the only inhaled corticosteroid indicated in children ≥1 year of age with persistent asthma. The preparation is suitable for use in infants, children and adults with persistent asthma and in infants and children with croup.

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