

## Review Article

# Once-daily use of inhaled corticosteroids: A new regimen in the treatment of persistent asthma

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### ABSTRACT

Asthma is a disease of chronic airway inflammation that is characterized clinically by bronchial hyper-responsiveness and airflow limitation. Chronic inflammation, coupled with ongoing repair of airways damaged by the persistent inflammatory process in asthma, results in permanent structural and functional airway changes (remodeling) that can lead to irreversible airflow obstruction. Current guidelines emphasize treatment of the underlying inflammatory process in asthma and recommend early, long-term anti-inflammatory treatment to diminish or prevent the irreversible component of airflow obstruction. Furthermore, they recognize that inhaled corticosteroids are the most effective anti-inflammatory agents available for the treatment of asthma. Patient adherence to prescribed inhaled corticosteroid medication is associated with decreased airway inflammation, improved pulmonary function and symptom control. Moreover, marked declines in morbidity and mortality due to asthma have been attributed to appropriate use of inhaled corticosteroids.

Strict patient adherence with prescribed anti-inflammatory medication is crucial for obtaining optimal therapeutic benefit for patients with asthma. Despite the proven effectiveness of inhaled corticosteroids, patient adherence to prescribed therapy is often low, resulting in increased patient morbidity. Complex dosing regimens contribute greatly to patient non-adherence. Thus, new once-daily regimens of inhaled corticosteroid treatment have been introduced as

means to improve patient adherence and provide optimal therapeutic benefit. In the present review, the complex inflammatory and remodeling processes in asthma and their contributions to the clinical manifestations of the disease will be discussed. Currently available, once-daily inhaled corticosteroid treatment options and the advantages of these therapeutic options in the treatment of persistent asthma also will be discussed.

**Key words:** asthma, budesonide, inhaled corticosteroids, once daily, Pulmicort Respules<sup>®</sup>, Pulmicort Turbuhaler<sup>®</sup>.

### INTRODUCTION

Asthma is a chronic inflammatory disease of the airways involving the recruitment and activation of numerous inflammatory cell types.<sup>1,2</sup> The underlying inflammatory process in asthma and subsequent repair (remodeling) result in altered structure and function of the airways, demonstrated clinically by airway hyperresponsiveness and airway obstruction.<sup>1,3</sup> An irreversible component of airway obstruction has been associated with disease duration and may be a direct consequence of the ongoing remodeling process associated with uncontrolled chronic inflammation.<sup>4</sup>

International guidelines for the treatment of asthma recommend early, long-term treatment with anti-inflammatory agents to prevent possible irreversible airflow obstruction and recognize inhaled corticosteroids as the most effective anti-inflammatory agents currently available for the treatment of persistent asthma.<sup>5,6</sup> Worldwide trends in hospital admission rates and mortality due to asthma reflect the effectiveness of inhaled corticosteroid therapy. A marked underuse of inhaled corticosteroids in many countries has been associated with increasing

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morbidity and mortality due to asthma, whereas steady declines in morbidity and mortality in other countries have been attributed to more widespread symptom control through the use of inhaled corticosteroids.<sup>7</sup>

Optimal therapeutic benefit from the use of inhaled corticosteroids in asthma depends on strict adherence to prescribed therapy. New once-daily inhaled corticosteroid regimens have been introduced that may increase patient adherence to prescribed therapy and, thus, increase therapeutic efficacy.

## ASTHMA AS AN INFLAMMATORY DISEASE

Asthma is a disease of chronic airway inflammation.<sup>8</sup> Numerous inflammatory cell types, including mast cells, macrophages, eosinophils and lymphocytes, are involved in the inflammatory process.<sup>1,2</sup> These mediators of inflammation contribute to airway hyperresponsiveness, airflow obstruction and perpetuation of the inflammatory process.

Mast cell and macrophage activation is the initial response to the inciting trigger or inhaled allergen in asthma. Activated mast cells release several pro-inflammatory mediators, including histamine, leukotrienes and other lipid mediators (e.g. prostaglandins and platelet activating factor); eosinophil and neutrophil chemotactic factors;<sup>9</sup> and cytokines, which include interleukin (IL)-3, IL-4, IL-5 and granulocyte-macrophage colony stimulating factor (GM-CSF). These cytokines, in conjunction with IL-1 and tumor necrosis factor (TNF)- $\alpha$  released by activated macrophages, up-regulate expression of endothelial cell adhesion molecules and promote eosinophil recruitment and survival.<sup>1,10</sup> Endothelial cell adhesion molecules, such as intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1,

immobilize circulating inflammatory cells at the site of inflammation and help to regulate their entry into the airway mucosa.<sup>10,11</sup>

Eosinophils, the major effector cells in the inflammatory process,<sup>1</sup> are important for cytokine production and the release of mediators (e.g. leukotrienes and oxygen free radicals) and granular proteins, such as major basic protein. Leukotrienes contribute to airway obstruction by directly increasing airway smooth muscle tone (bronchoconstriction), mucus secretion and vascular permeability (edema), and by affecting mucociliary function.<sup>9</sup> Granular proteins, which cause damage to the airway epithelium,<sup>1,9</sup> and sensory neuropeptides, which are released through the actions of eosinophil-derived inflammatory mediators, also contribute to airway hyperresponsiveness.<sup>12</sup>

T lymphocytes may be essential for persistence of inflammation in chronic disease. Release of IL-4 (in atopic asthma) and IL-5, predominantly by the T helper (Th)2 subclass of T lymphocytes, contributes to IgE synthesis and eosinophil production, respectively.<sup>1,10</sup>

Similar to inflammatory cells, resident bronchial epithelial cells generate numerous cytokines, lipid mediators, peptides and reactive oxygen species (Table 1) that recruit circulating inflammatory cells to the airway lumen, modulate airway tone and regulate secretions.<sup>13,14</sup>

## Inflammation associated with reduced pulmonary function, disease severity and bronchial hyperreactivity

Airflow limitation is the result of various inflammatory features characteristic of asthma, including acute bronchoconstriction, airway edema and mucus plug formation (Fig. 1).<sup>8,15</sup> Forced expiratory volume in 1 s (FEV<sub>1</sub>), the most critical measure of airflow limitation, usually is

**Table 1** Epithelial-derived cytokines

Colony-stimulating factors	Pleiotropic cytokines	Growth factors	Receptors/antagonists	Chemoattractant cytokines		
				Lymphocyte chemoattractant factor	C-X-C/ $\alpha$ chemokines	C-C/ $\beta$ chemokines
GM-CSF	IL-6	TGF- $\beta$	Type 1 TNFR	IL-16	IL-8	RANTES
G-CSF	IL-11	TGF- $\alpha$	icIL-1Ra Type 1		GRO- $\alpha$	MCP-1
M-CSF	IL-1	SCF			GRO- $\gamma$	MCP-4
CSF-1	IL-10	bFGF				Eotaxin
	TNF- $\alpha$					MIP-1 $\alpha$ (rat)

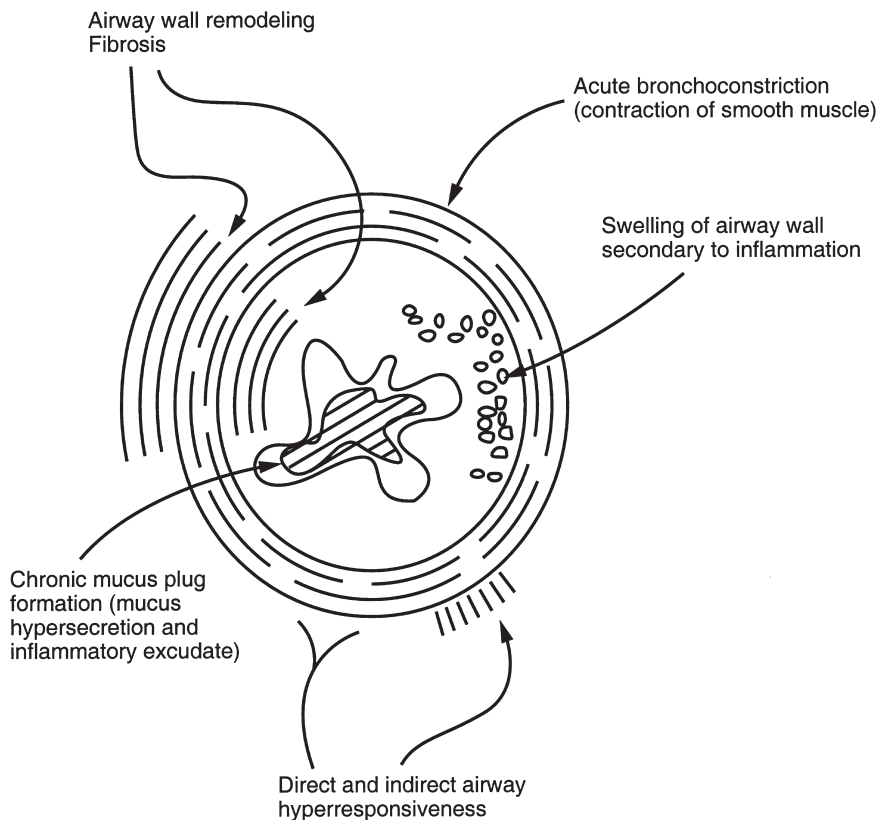
GM-CSF, granulocyte-macrophage colony stimulating factor; G-CSF, granulocyte colony stimulating factor; M-CSF, macrophage colony stimulating factor; CSF, colony stimulating factor; IL, interleukin; TNF, tumor necrosis factor; TGF, transforming growth factor; SCF, stem cell factor; bFGF, basic fibroblast growth factor; TNFR, tumor necrosis factor receptor; GRO, growth-related gene product; RANTES, regulated on activation, normal T cell expressed and secreted; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein. Reprinted with permission from: Politio AJ, Proud D. Epithelial cells as regulators of airway inflammation. *J. Allergy Clin. Immunol.* 1998; **102**: 714–18.

decreased in asthma.<sup>8</sup> Furthermore, percentage predicted FEV<sub>1</sub> in childhood is a significant predictor of adult pulmonary function level.<sup>16</sup>

Longitudinal studies have shown that children with frequent and persistent asthma have reduced pulmonary function in later life.<sup>16,17</sup> A significant correlation between asthma duration and reduced pulmonary function has been demonstrated by Zeiger *et al.*, using regression analysis of data obtained from 1041 children in the Childhood Asthma Management Program (CAMP) study. Asthma duration was significantly ( $P < 0.001$ ) associated with lower levels of several lung functions, including percentage predicted FEV<sub>1</sub>.<sup>18</sup> Weiss *et al.* have similarly reported reduced pulmonary function with time in a retrospective, 13-year population-based study. The authors predicted a 5% reduction in FEV<sub>1</sub> by age 10 and a 7% reduction by age 15 in females who develop asthma at the age of 7.<sup>19</sup>

In a detailed comparison of the extent of inflammation in mild intermittent and mild-to-moderate persistent asthma, Vignola *et al.* have compared several markers of inflammation in mucosal biopsies and bronchoalveolar lavage (BAL) fluid from 24 patients with mild

intermittent asthma, 18 patients with mild-to-moderate persistent asthma and 12 healthy control subjects.<sup>20</sup> Mucosal biopsies demonstrated significant ( $P = 0.001$ ) increases in the numbers of activated eosinophils and T lymphocytes in both asthma populations, with a significantly greater increase in patients with persistent asthma. The BAL analysis also revealed a significantly greater increase in eosinophil activation in persistent asthma than in mild intermittent asthma, compared to controls.<sup>20</sup> These data indicate that increased disease severity is associated with a greater degree of inflammation. Vignola *et al.* have also demonstrated increased epithelial shedding in mucosal biopsy specimens from the persistent asthma population compared with intermittent and control populations. Epithelial loss, a consequence of the inflammatory process, previously has been associated with hyperactivity in asthma.<sup>21–23</sup> Analysis of bronchial biopsy specimens from 11 adult patients with atopic asthma, reported by Jeffery *et al.*, has demonstrated a positive correlation between the extent of epithelial loss and the degree of bronchial hyperactivity.<sup>21</sup>



**Fig. 1** Inflammatory features that contribute to airflow limitation in asthma. Reprinted with permission from Stephen T Holgate MD.<sup>15</sup>

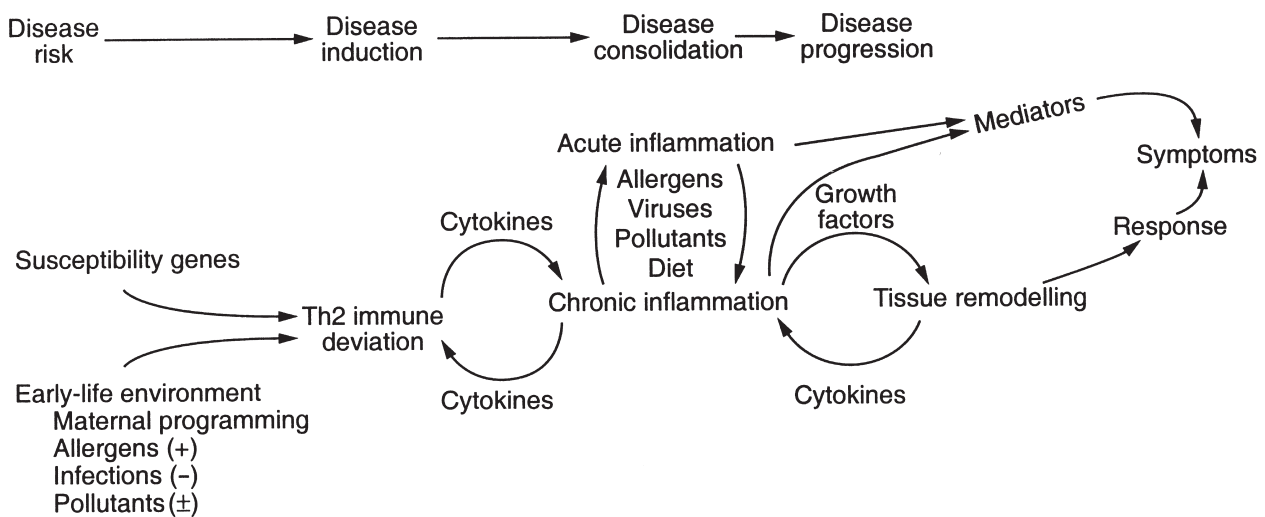
## AIRWAY REMODELING

Airway remodeling, observed in the lungs of even mildly affected asthmatics,<sup>24,25</sup> results from a continuous cycle of airway damage and repair associated with chronic inflammation (Fig. 2).<sup>3,26</sup> While the process is not well defined, release of growth factors and fibrogenic cytokines, activation of fibroblasts and myofibroblasts, increased synthesis and deposition of collagen and increased synthesis and release of extracellular matrix components are among the events proposed to be involved.<sup>27</sup> In addition, airway epithelial cells play a prominent role by producing growth factors and extracellular matrix proteins and influencing fibroblast recruitment and proliferation.<sup>13</sup> Typical pathologic findings of the remodeled airway wall include a thickened bronchial subepithelial basement membrane caused by collagen deposition<sup>24,25</sup> and increased airway smooth muscle mass.<sup>3</sup> These changes in the size and composition of the airway wall can have a negative impact on airway function by rendering the airways stiffer and more prone to airflow obstruction.<sup>28</sup> Mucous gland hyperplasia, another feature of the remodeled airway wall,<sup>29</sup> can contribute further to airflow obstruction through excess mucus production, and thickening of the airway wall can contribute to hyperresponsiveness by amplifying the narrowing produced by smooth muscle shortening.<sup>24,30</sup> Irreversible airflow obstruction due to remodeling has been reported in asthma<sup>4</sup> and has been related to disease severity.<sup>24,25</sup>

Current asthma treatment guidelines, which recognize the ongoing inflammatory process in asthma and the contribution of remodeling to irreversible loss of pulmonary function, emphasize early and long-term anti-inflammatory therapy.<sup>5,6</sup> Inhaled corticosteroids are the most potent anti-inflammatory agents available for the treatment of asthma<sup>31</sup> and are thus recognized as the mainstay of treatment.<sup>5,6</sup>

The benefit of early therapeutic intervention with inhaled corticosteroids has been supported by numerous clinical trials in asthma.<sup>32–38</sup> In one controlled prospective study,<sup>32</sup> 216 children with mild-to-moderate asthma were evaluated for 1–2 years before the initiation of treatment with inhaled budesonide and for an additional 3–6 years while receiving treatment. Sixty-two control subjects who received only theophylline,  $\beta_2$ -agonists and sodium cromoglycate also were evaluated over 3–7 years. Control subjects exhibited a 1–3% annual decrease in percentage predicted FEV<sub>1</sub> over time, whereas subjects receiving inhaled budesonide exhibited significant ( $P < 0.01$ ) improvements in FEV<sub>1</sub>. Furthermore, duration of asthma prior to inhaled corticosteroid treatment affected patient response. Children with asthma for 2 years demonstrated significantly greater increases in FEV<sub>1</sub> with treatment, compared with children with an asthma duration of 5 or more years.

In a study by Haahtela *et al.*,<sup>33</sup> 103 newly diagnosed adult asthmatics were randomized to receive treatment with an inhaled corticosteroid (budesonide) or inhaled



**Fig. 2** The underlying mechanisms of asthma and its clinical evolution are shown. A cycle of chronic inflammation and ongoing tissue remodeling culminates in disease progression and possible irreversible airflow obstruction. Reprinted with permission from Holgate ST; The cellular and mediator basis of asthma in relation to natural history. *Lancet* 1997; **350** (Suppl. 11): 5–9.<sup>26</sup>

terbutaline for 2 years. In a follow-up study,<sup>34</sup> patients who received budesonide for the first 2 years were randomized to either continue inhaled corticosteroid treatment or to receive placebo. Patients who received terbutaline for the first 2 years were crossed over to treatment with budesonide. After 1 year of treatment, those patients treated with budesonide from the onset of diagnosis demonstrated greater improvements in pulmonary function and decreased bronchial hyperreactivity compared with patients initially receiving terbutaline. These studies stress the importance of early intervention, before the onset of irreversible airflow obstruction, to achieve optimal therapeutic response. The study by Haahtela *et al.* has also demonstrated the importance of continuing inhaled corticosteroid therapy, because pulmonary function deteriorated in 67% of patients who were switched from budesonide to placebo.

### NEW REGIMEN OF ONCE-DAILY INHALED CORTICOSTEROIDS FOR ASTHMA

Poor adherence with prescribed therapeutic regimens is common in patients with chronic disease<sup>39</sup> and is an important factor in the failure to respond to prescribed therapy.<sup>40</sup> Numerous reports have documented poor adherence with medication in patients with asthma and chronic obstructive pulmonary disease.<sup>41–45</sup> In a study on adherence in a general practice setting, Dekker *et al.* have investigated adherence with prescribed cromoglycates,  $\beta_2$ -agonists, anticholinergics and theophyllines, corticosteroids and other pulmonary medications in 156 patients between 12 and 64 years of age. Adherence, defined as a reported daily intake of  $\geq 50\%$  of the prescribed amount of medication, was demonstrated in only 30% of patients overall and 58% of patients with daily symptoms.<sup>43</sup> Adherence to a once-daily dosing schedule was reportedly higher than that with multiple-daily dosing schedules.<sup>43</sup> Electronic monitoring of inhaler devices has been used in several studies to objectively monitor patient adherence with prescribed anti-asthma medications.<sup>41,42,45</sup> Results of these studies have demonstrated poor patient adherence, with both underuse and overuse of prescribed medications. In one such study, only one of 34 patients enrolled in either a 12-week clinical trial with four daily doses of a prescribed cromolyn-like agent (Lodoxamide) or a 28-day trial with four daily doses of a prescribed corticosteroid (tixocortol pivalate) was considered adherent. A patient was considered adherent if appropriate medication was used on  $\geq 75\%$  of days

studied; in both trials, patients took the study drug as prescribed on a mean of approximately 37% (range 0–77%) of days.<sup>45</sup>

Non-adherence with prescribed therapy has been associated with increased morbidity in both pediatric and adult asthmatics.<sup>41,44</sup> Bender *et al.* have reported an association between marked underuse of prescribed daily inhaled corticosteroid medication and treatment failure, urgent-care contact with a clinician and administration of systemic corticosteroids in 24 asthmatic children during a 3-month study period.<sup>41</sup> Moreover, Horn *et al.* have demonstrated an association between patient adherence with a standard, incremental regimen of inhaled salbutamol and decreased morbidity in a 9-month study of 160 adult asthmatics.<sup>44</sup> Urine salbutamol concentrations, used as a measure of patient adherence, increased with the incremental doses prescribed in patients with significantly improved FEV<sub>1</sub>. Both FEV<sub>1</sub> and peak expiratory flow rate (PEFR) deteriorated in those patients showing no increase in urine salbutamol concentration over the study period. These studies demonstrate a significant lack of adherence to prescribed medications in patients with asthma and further demonstrate that poor adherence is a cause of increased patient morbidity.

Complex dosing regimens have a negative impact on patient adherence with prescribed therapeutic regimens in asthma and other chronic diseases.<sup>40</sup> Eisen *et al.* have suggested that selecting medications that permit the lowest daily prescribed dose frequency may, in fact, be the single most important strategy to improve patient adherence.<sup>46</sup> Numerous studies have shown that patient adherence increases as drug-dosage frequency decreases<sup>46–49</sup> and improved adherence with inhaled corticosteroid therapy in asthma has been demonstrated with reduced daily dose frequencies.<sup>50</sup> In a study comparing patient adherence to schedules of two and four daily doses with the inhaled corticosteroid flunisolide, a significant ( $P < 0.001$ ) increase in non-adherence was observed in patients switched from four inhalations twice daily to two inhalations four times daily. The percentage of days in which patients were non-adherent rose from  $20.2 \pm 40.3$  with twice-daily dosing to  $57.1 \pm 49.6$  with four times daily dosing.<sup>50</sup>

Patient preference for once-daily dosing of inhaled corticosteroid therapy in asthma has been reported in a trial assessing the efficacy of budesonide dry powder administered via Turbuhaler® in 141 patients ( $\geq 12$  years of age) with mild asthma. Ninety-seven percent of patients enrolled in the study preferred once-daily dosing.<sup>51</sup>

Furthermore, using a decision-analysis approach to evaluating once-daily versus twice-daily dosing of theophylline, Jordan and Reichman have considered the effects of patient non-adherence on therapeutic efficacy. These authors have suggested that anticipated gains in efficacy obtained with multiple daily dosing might be eliminated by lower patient adherence and conclude that once-daily dosing is favorable to twice-daily dosing for most patients.<sup>52</sup>

In addition to improving patient adherence, once-daily administration of inhaled corticosteroids may reduce the potential for adverse systemic effects. In an assessment of the systemic effects of single and multiple doses of inhaled fluticasone propionate and inhaled budesonide in healthy volunteers, Lönnebo *et al.* have demonstrated increased systemic effects (i.e. changes in plasma cortisol and white blood cell counts) with multiple versus single drug doses.<sup>53</sup> Systemic accumulation, which is greater for those inhaled corticosteroids exhibiting a longer elimination half-life (e.g. fluticasone propionate), may explain the presence of increased systemic effects;<sup>54</sup> infrequent dosing regimens may reduce systemic accumulation and thus decrease the long-term risk for adverse effects.

### ONCE-DAILY BUDESONIDE INHALATION POWDER (PULMICORT TURBUHALER®) IN THE TREATMENT OF ASTHMA

Pulmicort Turbuhaler® (AstraZeneca, Wayne, PA, USA) is a dry powder inhaler that differs from conventional pressurized metered-dose inhalers (pMDI) in that it is breath actuated and optimal drug delivery does not rely on the coordination of inhaler actuation with inspiration. Because failure to properly coordinate actuation with inspiration has been reported as a frequent error in inhaler technique, regardless of age,<sup>55</sup> dry powder inhalers may improve drug delivery and increase therapeutic efficacy compared to conventional pMDI, in both adult and pediatric asthma patients.

Patient preference for Turbuhaler® over pMDI has been reported in two separate studies.<sup>56,57</sup> In a 10-week open-label, randomized, crossover study comparing the safety and efficacy of budesonide administered via pMDI with spacer to that of budesonide administered via Turbuhaler® in 28 patients with stable asthma, patient preference was assessed by questionnaire at the end of the study period. Turbuhaler® was rated significantly better than pMDI in every aspect addressed in the preference questionnaire, including general preference, ease

of inhalation, size of the device, taste, cough, hoarseness and other local irritation.<sup>56</sup> In a second multicenter, open-label, crossover study, inhalation device preferences were determined in 123 adult patients with stable asthma.<sup>57</sup> Patient preferences for administration of terbutaline (via pMDI or Turbuhaler®) and budesonide (via pMDI with Nebuhaler or Turbuhaler®) were determined by questionnaire following 14-day treatment periods with each inhalation device. Turbuhaler® was rated significantly ( $P < 0.001$ ) higher than pMDI (for terbutaline) and pMDI with Nebuhaler (for budesonide).

Clinical trials have demonstrated greater efficacy of budesonide inhalation powder when administered via Turbuhaler® compared with pMDI.<sup>56,58</sup> In a randomized, double-blind, parallel-group study conducted in 126 children with persistent asthma, Agertoft and Pedersen compared the effects of budesonide administered via Nebuhaler with those of half the dose of budesonide administered via Turbuhaler®.<sup>58</sup> To ensure that patients were not being overtreated prior to enrolment, their normal doses of budesonide administered via Nebuhaler were reduced by half; only those patients demonstrating deterioration in asthma control at the reduced doses were enrolled in the study. Following stabilization and a 2-week run-in period, patients were randomized to receive budesonide via Nebuhaler at their normal dose or via Turbuhaler® at half their normal dose for 9 weeks. Other than reduced  $\beta_2$ -agonist use in the Turbuhaler® group, no differences in effect were demonstrated between treatment via Nebuhaler and treatment at half the dose of budesonide via Turbuhaler®, indicating increased efficacy of budesonide via Turbuhaler®. A second open-label, randomized, crossover study conducted in 28 patients with stable asthma has similarly demonstrated that budesonide via Turbuhaler® was at least as effective as budesonide via pMDI at daily doses of 800 and 1600  $\mu\text{g}$ .<sup>59</sup>

The demonstration of equivalent efficacy at half the dose of budesonide administered via Turbuhaler® compared with pMDI, by Agertoft and Pedersen, confirmed previous reports of greater lung deposition of inhaled medication with Turbuhaler®.<sup>59,60</sup> Lung depositions of budesonide and terbutaline administered via Turbuhaler® are reportedly twice those following administration via pMDI. These data suggest that the same degree of asthma control can be achieved at a lower dose using Turbuhaler®, reducing the potential risk for adverse systemic effects.

Numerous trials have demonstrated the safety and efficacy of once-daily budesonide administered via Turbuhaler® in children and adults with persistent asthma

**Table 2** Published studies supporting the efficacy of once-daily budesonide inhalation powder via Turbuhaler®

Author (year)	Study design	Dose	Treatment		Age range (years)	Disease severity	Conclusions
			duration (weeks)	Patient number			
Campbell <i>et al.</i> <sup>61</sup> (1991)	d.b., p.c., p.g., r	400 µg QD	8	141	≥ 12	Mild	Significant improvements in PEF and bronchodilator use and improved symptoms in 53 of 65 patients compared to PBO. Twelve patients increased to 400 µg BID.
Campbell <i>et al.</i> <sup>61</sup> (1998)	d.b., p.g., r	400 µg QD 200 µg BID	8	167	5–12	Mild	Significant improvements in PEF, FEV <sub>1</sub> , FVC and asthma symptoms. Increase in evening PEF greater with 400 µg QD.
Chisholm <i>et al.</i> <sup>62</sup> (1998)	d.b., p.g., r	200 µg QD 100 µg BID	8	76	18–70	Mild to moderate	Minimal improvement in PEF; differences between treatment groups not significant.
Jónasson <i>et al.</i> <sup>69</sup> (1998)	d.b., p.c., p.g., r	200 µg QD 100 µg QD 100 µg BID	12	163	7–16	Mild	Significant reductions in exercise-induced bronchoconstriction in all treatment groups and in FEV <sub>1</sub> and methacholine hyperreactivity with 100 µg BID compared with PBO.
Jones <i>et al.</i> <sup>63</sup> (1994)	d.b., p.c., p.g., r	400 µg QD 200 µg BID	12	340	12–70	Mild to moderate	Significant improvements in PEF and improvements in asthma symptoms and bronchodilator use. Equal efficacy of QD and BID dosing.
McFadden <i>et al.</i> <sup>70</sup> (1999)	d.b., p.c., p.g., r	400 µg QD 200 µg QD	18	309	18–70	Mild to moderate	Significant improvements in FEV <sub>1</sub> , PEF, asthma symptoms, bronchodilator use and quality of life with 400 and 200 µg QD. Both doses appropriate in introductory and maintenance therapy.
Shapiro <sup>73</sup> (1999)	d.b., p.c., p.g., r	400 µg QD 200 µg QD	12	274	6–17	Inhaled corticosteroid dependent	Significant improvements in FEV <sub>1</sub> , PEF, asthma symptoms and bronchodilator use compared to PBO.
LaForce <sup>71</sup> (1999)	d.b., p.c., p.g., r	400 µg QD	12	177	18–70	Mild to moderate	Significant improvements in FEV <sub>1</sub> , FEF <sub>25–75%</sub> , PEF, asthma symptoms and bronchodilator use (puffs/day) compared to PBO.
Metzger <sup>72</sup> (1999)	d.b., p.c., p.g., r	400 µg QD	12	184	18–70	Inhaled corticosteroid dependent	Significant improvements in FEV <sub>1</sub> , PEF, asthma symptoms and bronchodilator use compared with PBO.

BID, twice daily; d.b., double-blind; FEF<sub>25–75%</sub>, forced expiratory flow after 25% to 75% of vital capacity has been expelled; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; PBO, placebo; p.c., placebo-controlled; PEF, peak expiratory flow; p.g., parallel group; QD, once daily; r, randomized.

(Table 2) and have further demonstrated equivalent efficacy of once-daily versus twice-daily administration.<sup>61–63</sup> Both Campbell *et al.*<sup>61</sup> and Jones *et al.*<sup>63</sup> have reported equivalent efficacy of budesonide 400 µg administered once daily via Turbuhaler® and 200 µg administered twice daily in the treatment of children from 5 to 12 years of age with mild asthma and in the treatment of patients from 12 to 70 years of age with mild-to-moderate asthma, respectively. Similarly, Chisholm *et al.*<sup>62</sup> have reported that 200 µg budesonide administered once daily via Turbuhaler® is as effective as 100 µg given twice daily in a randomized, double-blind, parallel-group study conducted in 76 adult asthmatics with mild-to-moderate disease severity. These studies support the efficacy of budesonide administered via Turbuhaler® in the treatment of persistent asthma in children and adults and further support the use of once-daily dosing regimens for the treatment of patients with mild-to-moderate asthma.

### ONCE-DAILY BUDESONIDE INHALATION SUSPENSION (PULMICORT RESPULES®) IN THE TREATMENT OF ASTHMA

Difficulties encountered in using conventional inhalation devices by young children and by caregivers in administering therapy to infants and young children may result in suboptimal drug delivery and reduced therapeutic efficacy.<sup>64</sup> Budesonide inhalation suspension is the first nebulized corticosteroid developed for pediatric asthma patients and is the first inhaled corticosteroid developed for use in children <4 years of age. It is now available commercially in 35 countries. For infants and very young

children who lack the coordination and knowledge to properly use other delivery devices, nebulization is the delivery method of choice.<sup>65,66</sup> Clinical trials have demonstrated the safety and efficacy of once-daily budesonide inhalation suspension in children with mild-to-moderate persistent asthma (Table 3).

### OTHER ONCE-DAILY INHALED CORTICOSTEROID REGIMENS

Whereas substantial evidence supports the safety and efficacy of once-daily administration of Pulmicort® in the treatment of pediatric and adult asthmatics, data supporting the safety and efficacy of other once-daily inhaled corticosteroid regimens are limited.<sup>67,68</sup> Only one study has been published on once-daily dosing of inhaled flunisolide, which was as effective as twice-daily dosing in 366 asthmatics (6–70 years of age) with well-controlled disease. Patients switched from two inhalations of flunisolide twice daily to four inhalations once daily of an equivalent dose (1000 µg) demonstrated similar changes in pulmonary function, asthma symptoms, and β-agonist use.<sup>68</sup> Similarly, only one comparative study of the safety and efficacy of once- or twice-daily administration of inhaled beclomethasone has demonstrated no significant differences in the control of asthma, based on pulmonary function tests, asthma symptoms and bronchodilator use, in 37 adults with moderate asthma.<sup>67</sup>

In conclusion, current asthma treatment guidelines, which are based on knowledge of the underlying inflammatory process in asthma and evidence that chronic inflammation leads to irreversible changes in airway

**Table 3** Published studies supporting the efficacy of once-daily budesonide inhalation suspension

Author (year)	Dose	Patient number	Age range (years)	Disease severity	Conclusions
Baker <i>et al.</i> <sup>74</sup> (1999)	0.25 mg QD 1.0 mg QD 0.25 mg BID 0.50 mg BID	480	0.5–8	Moderate	Results suggest that 0.50 mg is minimal effective dose; however, significant improvements in evening PEF and bronchodilator use with 0.25 mg QD compared to PBO. QD dosing efficacious relative to PBO.
Kemp <i>et al.</i> <sup>75</sup> (1999)	0.25 mg QD 0.50 mg QD 1.0 mg QD	359	0.5–8	Mild	Significant improvements in asthma symptoms and bronchodilator use with all doses and in FEV <sub>1</sub> with 0.50 mg and 1.0 mg QD, compared to PBO.

BID, twice daily; FEV<sub>1</sub>, forced expiratory volume in 1 s; PBO, placebo; PEF, peak expiratory flow; QD, once daily. Both studies were randomized, double-blind, placebo-controlled, parallel-group studies of 12 weeks duration.

structure and function, emphasize early and long-term anti-inflammatory treatment to diminish the irreversible component of airway obstruction.<sup>5,6</sup> Inhaled corticosteroids are the most effective anti-inflammatory agents available for the treatment of asthma and their use is associated with decreased airway inflammation, improved pulmonary function and symptom control. Poor patient adherence to prescribed therapy has been associated with increased morbidity in asthma<sup>41,44</sup> and evidence suggests that simple dosing regimens increase patient adherence.<sup>46</sup> New once-daily inhaled corticosteroid regimens for the treatment of asthma may improve patient adherence to prescribed medications and thereby optimize therapeutic efficacy.

## REFERENCES

- Busse WW. Inflammation in asthma: The cornerstone of the disease and target of therapy. *J. Allergy Clin. Immunol.* 1998; **102**: S17–22.
- Djukanovic R, Roche WR, Wilson JW *et al.* Mucosal inflammation in asthma. *Am. Rev. Respir. Dis.* 1990; **142**: 434–57.
- Bento AM, Hershenson MB. Airway remodeling: Potential contributions of subepithelial fibrosis and airway smooth muscle hypertrophy/hyperplasia to airway narrowing in asthma. *Allergy Asthma Proc.* 1998; **19**: 353–8.
- Brown PJ, Greville HW, Finucane KE. Asthma and irreversible airflow obstruction. *Thorax* 1984; **39**: 131–6.
- British Thoracic Society. Guidelines for management of asthma. *Thorax* 1993; **48** (Suppl.): S1–24.
- National Asthma Education and Prevention Program. Expert panel report 2. Guidelines for the Diagnosis and Management of Asthma. Bethesda (MD): National Institutes of Health/National Heart, Lung, and Blood Institute; 1997 July. Publication no. 97-4051.
- Wennergren G, Kristjánsson S, Strannegård I-L. Decrease in hospitalization for treatment of childhood asthma with increased use of antiinflammatory treatment, despite an increase in the prevalence of asthma. *J. Allergy Clin. Immunol.* 1996; **97**: 742–8.
- Williams PV. Management of asthma. *Clin. Symposium* 1997; **49**: 1–32.
- Hill M, Szeffler SJ, Larsen GL. Asthma pathogenesis and the implications for therapy in children. *Pediatr. Clin. North Am.* 1992; **39**: 1205–24.
- Emanuel MB, Howarth PH. Asthma and anaphylaxis: A relevant model for chronic disease? An historical analysis of directions in asthma research. *Clin. Exp. Allergy* 1995; **25**: 15–26.
- Björnsdóttir US, Cypcar DM. Asthma: An inflammatory mediator soup. *Allergy* 1999; **54**: 55–61.
- Kraneveld AD, Folkerts G, Van Oosterhout AJ, Nijkamp FP. Airway hyperresponsiveness: First eosinophils and then neuro-peptides. *Int. J. Immunopharmacol.* 1997; **19**: 517–27.
- Larivée P. Airway inflammation and remodelling in asthma; airway epithelial cells. *Can. Respir. J.* 1998; **5**: 51–2.
- Polito AJ, Proud D. Epithelial cells as regulators of airway inflammation. *J. Allergy Clin. Immunol.* 1998; **102**: 714–18.
- NHLBI/WHO Workshop Report. Global strategy for asthma management and prevention. Bethesda (MD): National Institutes of Health, National Heart, Lung, and Blood Institute and the World Health Organization; 1995 Jan. Publication no. 95–3659.
- Roorda RJ, Gerritsen J, van Aalderen WMC *et al.* Follow-up of asthma from childhood to adulthood: Influence of potential childhood risk factors on the outcome of pulmonary function and bronchial responsiveness in adulthood. *J. Allergy Clin. Immunol.* 1994; **93**: 575–84.
- Oswald H, Phelan PD, Lanigan A *et al.* Childhood asthma and lung function in mid-adult life. *Pediatr. Pulmonol.* 1997; **23**: 14–20.
- Zeiger RS, Dawson C, Weiss S. Relationships between duration of asthma and asthma severity among children in the childhood asthma management program (CAMP). *J. Allergy Clin. Immunol.* 1999; **103**: 376–87.
- Weiss ST, Tosteson TD, Segal MR, Tager IB, Redline S, Speizer FE. Effects of asthma on pulmonary function in children. *Am. Rev. Respir. Dis.* 1992; **145**: 58–64.
- Vignola AM, Chanez P, Campbell AM *et al.* Airway inflammation in mild intermittent and in persistent asthma. *Am. J. Respir. Crit. Care Med.* 1998; **157**: 403–9.
- Jeffery PK, Wardlaw AJ, Nelson FC, Collins JV, Kay AB. Bronchial biopsies in asthma: An ultrastructural, quantitative study and correlation with hyperreactivity. *Am. Rev. Respir. Dis.* 1989; **140**: 1745–53.
- Laitinen LA, Heino M, Laitinen A, Kava T, Haahela T. Damage of the airway epithelium and bronchial reactivity in patients with asthma. *Am. Rev. Respir. Dis.* 1985; **131**: 599–606.
- Wardlaw AJ, Dunnette S, Gleich GJ, Collins JV, Kay AB. Eosinophils and mast cells in bronchoalveolar lavage in subjects with mild asthma. *Am. Rev. Respir. Dis.* 1988; **137**: 62–9.
- Awadh N, Müller NL, Park CS, Abboud RT, Fitzgerald JM. Airway wall thickness in patients with near fatal asthma and control groups: Assessment with high resolution computed tomographic scanning. *Thorax* 1998; **53**: 248–53.
- Chetta A, Foresi A, Del Donno M, Bertorelli G, Pesci A, Olivieri D. Airways remodeling is a distinctive feature of asthma and is related to severity of disease. *Chest* 1997; **111**: 852–7.
- Holgate ST. The cellular and mediator basis of asthma in relation to natural history. *Lancet* 1997; **350**: 5–9.
- Bousquet J, Vignola AM, Chanez P, Campbell AM, Bonsignore G, Michel FB. Airways remodelling in asthma: No doubt, no more? *Int. Arch. Allergy Immunol.* 1995; **107**: 211–14.
- Paré PD, Toberts CR, Bai TR, Wiggs BJ. The functional consequences of airway remodelling in asthma. *Monaldi Arch. Chest Dis.* 1997; **52**: 589–96.

- 29 Carroll N, Elliot J, Morton A, James A. The structure of large and small airways in nonfatal and fatal asthma. *Am. Rev. Respir. Dis.* 1993; **147**: 405–10.
- 30 Kuwano K, Bosken CH, Paré PD, Bai TR, Wiggs BR, Hogg JC. Small airways dimensions in asthma and in chronic obstructive pulmonary disease. *Am. Rev. Respir. Dis.* 1993; **148**: 1220–5.
- 31 Barnes PJ. Efficacy of inhaled corticosteroids in asthma. *J. Allergy Clin. Immunol.* 1998; **102**: 531–8.
- 32 Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir. Med.* 1994; **88**: 373–81.
- 33 Haahtela T, Järvinen M, Kave T *et al.* Comparison of a  $\beta_2$ -agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N. Engl. J. Med.* 1991; **325**: 388–92.
- 34 Haahtela T, Järvinen M, Kava T *et al.* Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N. Engl. J. Med.* 1994; **331**: 700–5.
- 35 Kerstjens HA, Brand PL, Hughes MD *et al.* A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease. *N. Engl. J. Med.* 1992; **327**: 1413–19.
- 36 Overbeek SE, Kerstjens HAM, Bogaard JM, Mulder GH, Postma DS. Is delayed introduction of inhaled corticosteroids harmful in patients with obstructive airways disease (asthma and COPD)? *Chest* 1996; **110**: 35–41.
- 37 Selroos O, Pietinalho A, Löfroos AB, Riska H. Effect of early vs late intervention with inhaled corticosteroids in asthma. *Chest* 1995; **108**: 1228–34.
- 38 Van Essen-Zandvliet EE, Hughes MD, Waalkens HJ *et al.* Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-antagonists on lung function, airway responsiveness, and symptoms in children with asthma. *Am. Rev. Respir. Dis.* 1992; **146**: 547–54.
- 39 Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. *Psychiatr. Serv.* 1998; **49**: 196–201.
- 40 Bittar N. Maintaining long-term control of blood pressure: The role of improved compliance. *Clin. Cardiol.* 1995; **18** (Suppl. 3): III 12–16.
- 41 Bender B, Milgrom H, Rand C, Ackerson L. Psychological factors associated with medication nonadherence in asthmatic children. *J. Asthma* 1998; **35**: 347–53.
- 42 Chmelik F, Dougherty A. Objective measurements of compliance in asthma treatment. *Ann. Allergy* 1994; **73**: 527–32.
- 43 Dekker FW, Dieleman FE, Kaptein AA, Mulder JD. Compliance with pulmonary medication in general practice. *Eur. Respir. J.* 1993; **6**: 886–90.
- 44 Horn CR, Clark TJH, Cochrane GM. Compliance with inhaled therapy and morbidity from asthma. *Respir. Med.* 1990; **84**: 67–70.
- 45 Mawhinney H, Spector SL, Kinsman RA *et al.* Compliance in clinical trials of two nonbronchodilator, antiasthma medications. *Ann. Allergy* 1991; **66**: 294–9.
- 46 Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. *Arch. Intern. Med.* 1990; **150**: 1881–4.
- 47 Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. *JAMA* 1989; **261**: 3273–7.
- 48 Kruse W, Eggert-Kruse W, Ranpmaier J, Runnebaum B, Weber E. Dosage frequency and drug-compliance behaviour – A comparative study on compliance with a medication to be taken twice or four times daily. *Eur. J. Clin. Pharmacol.* 1991; **41**: 589–92.
- 49 Pullar T, Birtwell AJ, Wiles PG, Hay A, Feely MP. Use of a pharmacologic indicator to compare compliance with tablets prescribed to be taken once, twice, or three times daily. *Clin. Pharmacol. Ther.* 1988; **44**: 540–5.
- 50 Mann M, Eliasson O, Patel K, ZuWallack RL. A comparison of the effects of bid and qid dosing on compliance with inhaled flunisolide. *Chest* 1992; **101**: 496–9.
- 51 Campbell LM, Watson DG, Venables TL, Taylor MD, Richardson PDI. Once daily budesonide turbuhaler compared with placebo as initial prophylactic therapy for asthma. *Br. J. Clin. Res.* 1991; **2**: 111–22.
- 52 Jordan TJ, Reichman LB. Once-daily versus twice-daily dosing of theophylline. *Am. Rev. Respir. Dis.* 1989; **140**: 1573–7.
- 53 Lönnebo A, Grahnén A, Jansson B, Brundin RM, Ling-Anderson A, Eckernäs SÅ. An assessment of the systemic effects of single and repeated doses of inhaled fluticasone propionate and inhaled budesonide in healthy volunteers. *Eur. J. Clin. Pharmacol.* 1996; **49**: 459–63.
- 54 Thorsson L, Dahlström K, Edsbäcker S, Källén A, Paulson J, Wirén J-E. Pharmacokinetics and systemic effects of inhaled fluticasone propionate in healthy subjects. *Br. J. Clin. Pharmacol.* 1997; **43**: 155–61.
- 55 Larsen JS, Hahn M, Ekholm B, Wick KA. Evaluation of conventional press-and-breathe metered-dose inhaler technique in 501 patients. *J. Asthma* 1994; **31**: 193–9.
- 56 Engel T, Heinig JH, Malling H-J, Scharling B, Nikander K, Madsen F. Clinical comparison of inhaled budesonide delivered either via pressurized metered dose inhaler or Turbuhaler®. *Allergy* 1989; **44**: 220–5.
- 57 Boe J, Stiksa G, Svensson K, Åsbrink E. New method of evaluating patient preference different inhalation delivery systems. *Ann. Allergy* 1992; **68**: 255–60.
- 58 Agertoft L, Pedersen S. Importance of the inhalation device in the effect of budesonide. *Arch. Dis. Child.* 1993; **69**: 130–3.
- 59 Borgström L, Derom E, Stahl E, Wahlin-Boll E, Pauwels R. The inhalation device influences lung deposition and bronchodilating effect of terbutaline. *Am. J. Respir. Crit. Care Med.* 1996; **153**: 1636–40.
- 60 Thorsson L, Edsbäcker S, Conradson T-B. Lung deposition of budesonide from Turbuhaler® is twice that from a pressurized metered-dose inhaler P-MDI. *Eur. Respir. J.* 1994; **7**: 1839–44.
- 61 Campbell LM, Bodalia B, Gogbashian CA, Gunn SD, Humphreys PJ, Powell JP. Once-daily budesonide: 400  $\mu\text{g}$  once daily is as effective as 200  $\mu\text{g}$  twice daily in controlling childhood asthma. *Int. J. Clin. Pract.* 1998; **52**: 213–19.

- 62 Chisholm SL, Dekker FW, Knuistingh Neven A, Petri H. Once-daily budesonide in mild asthma. *Respir. Med.* 1998; **92**: 421–5.
- 63 Jones AH, Langdon CG, Lee PS *et al.* Pulmicort Turbohaler® once daily as initial prophylactic therapy for asthma. *Respir. Med.* 1994; **88**: 293–9.
- 64 Foucard T. Aggressive treatment of childhood asthma with local steroids. Good or bad? *Allergy* 1996; **51**: 367–71.
- 65 Bush A. Asthma in the child under five. *Br. J. Hosp. Med.* 1996; **55**: 110–14.
- 66 Szeffler SJ. Clinical need for a nebulized corticosteroid. *J. Allergy Clin. Immunol.* 1999; **104**: S162–8.
- 67 Gagnon M, Côte J, Milot J, Turcotte H, Boulet L-P. Comparative safety and efficacy of single or twice daily administration of inhaled beclomethasone in moderate asthma. *Chest* 1994; **105**: 1732–7.
- 68 ZuWallack RL, Rosen JP, Cohen L *et al.* The effectiveness of once-daily dosing of inhaled flunisolide in maintaining asthma control. *J. Allergy Clin. Immunol.* 1997; **99**: 278–85.
- 69 Jónasson G, Carlsen K-H, Blomqvist P. Clinical efficacy of low-dose inhaled budesonide once or twice daily in children with mild asthma not previously treated with steroids. *Eur. Respir. J.* 1998; **12**: 1099–104.
- 70 McFadden ER, Casale TB, Edwards TB *et al.* Administration of budesonide once daily by means of turbuhaler to subjects with stable asthma. *J. Allergy Clin. Immunol.* 1999; **104**: 46–52.
- 71 Laforce CF. Once-daily budesonide (Pulmicort Turbohaler®) is effective in asthmatic adults not maintained on corticosteroids. *Respir. Crit. Care Med.* 1999; **159**: A629.
- 72 Metzger WJ. Efficacy and safety of once-daily budesonide dry powder (Pulmicort Turbohaler®) in adults with inhaled steroid-dependent asthma. *J. Allergy Clin. Immunol.* 1999; **103**: A499.
- 73 Shapiro G. Once-daily budesonide dry powder (Pulmicort Turbohaler®) improves pulmonary function and symptoms in children with inhaled steroid-dependent asthma. *J. Allergy Clin. Immunol.* 1999; **103**: A500.
- 74 Baker JW, Mellon M, Wald J, Welch M, Cruz-Rivera M, Walton-Bowen K. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Pediatrics* 1999; **103**: 414–21.
- 75 Kemp J, Wanderer AA, Ramsdell J *et al.* Rapid onset of control with budesonide turbuhaler in patients with mild-to-moderate asthma. *Ann. Allergy Asthma Immunol.* 1999; **82**: 1–9.