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REVIEW

Inhaled budesonide in the management of acute worsenings and exacerbations of asthma: A review of the evidence

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Summary
The use of systemic corticosteroids, together with bronchodilators and oxygen therapy, has become established for the management of acute asthma. These agents are undoubtedly effective, but are also associated with problems such as metabolic adverse effects. Inhaled corticosteroids (ICS) offer potential benefit in the acute setting because they are delivered directly to the airways. They are also likely to reduce systemic exposure, which would lead in turn to reductions in rates of unwanted systemic effects. In order to evaluate the role of budesonide in the management of acute asthma exacerbations we conducted a review of the literature and critically evaluated the rationale for the use of ICS in general in this setting.
Trials in adults and children requiring treatment for acute exacerbation of asthma have shown clinical and/or spirometric benefit for budesonide when delivered via nebulizer, dry powder inhaler, or aerosol in the emergency department, hospital and follow-up settings. The efficacy seems to benefit from high doses given repeatedly during the initial phase of an acute exacerbation. These acute effects are likely to be linked to the drug's distinctive pharmacokinetic and pharmacodynamic profile. The current evidence base revealed encouraging results regarding the efficacy of the ICS budesonide in patients with wheeze and acute worsening of asthma. Future studies should focus on the efficacy of these agents in more severe asthma worsenings.

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Introduction

Asthma is a chronic inflammatory disease, characterized by reversible airway obstruction in response to various stimuli. Exacerbations, manifesting as the temporary worsening of symptoms, form part of the natural history of the disease, but may also represent failure of ongoing long-term therapy. They also commonly lead to emergency department presentation and hospitalization, and to complications in the longer term.[1]

Acute asthma exacerbations often present differently in children and adults. According to British guidelines, acute exacerbation of asthma in adults ranges from brittle asthma, or wide variation in peak expiratory flow rates (PEFRs) and sudden severe attacks against a background of apparently well controlled disease, to near fatal asthma where mechanical ventilation is necessary.[2]

Acute severe asthma in adults is characterized by reduced PEFR, raised respiratory and heart rates, and an inability to complete spoken sentences in one breath. In children, the definition of acute disease is much simpler, with acute severe asthma being described as an inability to complete sentences in one breath or being too breathless to talk or feed, with raised respiratory and heart rates.[2] The US National Institutes of Health (NIH) recommendations state simply that asthma exacerbations are acute or subacute episodes of progressively worsening shortness of breath, wheezing, and chest tightness or some combination of these symptoms, and that early treatment is the best management strategy.[3] This has been seen in studies such as that of Volovitz et al.,[4] in which an inhaled corticosteroid (ICS) was used for acute asthma in children in the home setting.

British and US guidelines address the issue of acute asthma exacerbation by recommending as the main therapeutic interventions oxygen, inhaled β_2-agonists and systemic corticosteroids.[2,3] The central role of systemic corticosteroid treatment is underlined by the observation from the literature that treatment within an hour of presentation reduces the need for subsequent hospitalization, with greatest benefit being seen in patients with severe exacerbations.[1] Moreover, the significant spirometric improvements seen after corticosteroid therapy are maintained for up to 3 days.[5] Despite its undoubted effectiveness, there are problems with the treatment approach currently recommended. Debate remains over which dosages of the systemic corticosteroids available should be used.[6] Questions relating to the optimum balance between corticosteroids and β_2-agonists also remain to be answered definitively,[7] with British and American guidelines differing on this point.[2,3]

In this review, we critically evaluate the rationale for the use of ICS in the management of acute asthma exacerbations and evaluate the role of budesonide in the management of such exacerbations in both adults and children.

Methods

Two Cochrane systematic reviews formed the basis for data collection, one of the early use of ICSs in the emergency department treatment of acute asthma[8] and one of inhaled steroids for episodic viral wheeze of childhood.[9] Additional

studies for review were identified by searching PubMed using search terms that included: budesonide, ICS, asthma exacerbations, asthma worsenings, acute asthma, systemic corticosteroids, wheeze, and children.

Adverse effects of short courses of systemic corticosteroids provide a rationale for the use of ICSs

Short courses of systemic corticosteroid therapy for acute asthma exacerbations are undoubtedly effective in providing lasting symptomatic relief, are relatively inexpensive and are associated with good compliance.[5] However, the adverse effects of long-term systemic corticosteroid therapy are well documented[10] and concerns persist over the long-term safety of repeated short courses of systemic corticosteroid therapy. Such concerns warrant clinical evaluation and require clinicians to undertake a risk:benefit assessment when considering systemic corticosteroid therapy given the availability of effective alternative treatment choices—ICS. Adverse effects associated with systemic corticosteroid therapy including bone loss, may be less pronounced with ICS, perhaps as a result of their delivery directly to the desired site of action.[11]

Serum osteocalcin measurements in patients receiving corticosteroids have indicated that even short, intermittent courses of systemic agents have undesirable effects on bone metabolism in patients with asthma, and that the use of inhaled rather than systemic corticosteroids reduces this risk substantially.[12]

A direct comparison between nebulized budesonide (Pulmicort® Respules®), which has been used in many studies of inhaled steroids in acute asthma, and oral prednisolone shows a clear benefit for the former. Wilson et al.[13] compared the systemic activity of budesonide 1, 2 and 4 mg with oral prednisolone 5, 10, and 20 mg over 4 days in patients with mild asthma. For morning plasma cortisol, serum osteocalcin, and blood eosinophils, there was a significant dose-related suppression with prednisolone but not with budesonide.[1]

In acute settings the apparent difference between inhaled and systemic corticosteroids has also been documented in school children[14,15] as well as in infants[16] using markers of bone turnover and HPA-axis measurements. A dose-related effect on osteocalcin was seen for oral prednisolone 2.5 and 5 mg but not for inhaled budesonide 200 and 800 μg (pMDI and spacer) among prepubertal school children.[15] In smaller children (1–3 years), 10 days of inhaled budesonide (400 μg qid for 3 days and 400 μg bid for 7 days) did not influence serum or urinary cortisol or markers of bone turnover.[16]

Dolan et al.[17] investigated the adrenal dynamics through hypoglycemia and ACTH stimulation in asthmatic children 11–15 years old who during the previous year had received repeated "bursts" (less than 7 days) of short-term high-dose prednisone (1–2 mg/kg/day) for acute exacerbations. Most children had a normal adrenal response, however in those who received more than 4 "bursts" per year a subnormal response was seen.

There have also been concerns with respect to the acute psychiatric effects of systemic steroids.[18]

ICSs may give a faster effect

There is evidence that the inhaled route may provide an even faster onset of effect than systemic steroids. This apparent benefit has been documented in acute severe asthma in adults[19,20] and in children with moderately severe acute asthma.[21] There may also be a benefit for ICS with the concomitant use of inhaled beta-agonists. One study has suggested that ICS might enhance β_2-agonist responsiveness.[22] ICS have thus attracted attention as a potential alternative to systemic therapy in acute asthma.

ICSs in wheeze

An evidence-based and comprehensive review of the literature in children concluded that episodic treatment with a high dose of ICS is beneficial in children with mild, virally induced wheezing, whereas maintenance treatment with a low dose provides no benefit.[9] Five randomized controlled trials in children with mild viral episodic wheeze were identified by the reviewers: there were significant overall reductions in oral corticosteroid requirements in two double-blind crossover studies in which high doses of ICS were used, and a significant preference by parents for the active treatment over placebo. More recent studies further support the utility of ICS in the management of childhood wheeze.[23,24]

There are also more specific data to show efficacy of inhaled budesonide in children with wheezing induced by respiratory infections. Three double-blind studies have shown beneficial effects of budesonide in children aged from 1 to 10 years (Table 1). Connett and Lenney[25] showed a preference for budesonide over placebo in addition to reductions in day- and night-time wheezing. Svedmyr et al.[26] demonstrated notable reductions in acute healthcare resource consumption in terms of emergency room attendance and hospital admissions with budesonide in one study in which Turbuhaler® was used in children aged 3–10 years. The need for hospital care was not reduced by budesonide in another study by these authors that involved very young children (1–3 years), but reductions in symptom scores (cough, wheeze, noisy breathing, and breathlessness) as recorded by parents were reported.[27]

ICSs in acute worsenings

An Italian group[28] investigated the use of short-term increases in budesonide Turbuhaler® dosage to control asthma worsening in patients already receiving maintenance treatment with budesonide 100 μg twice daily. In 67 patients with moderate asthma receiving long-term therapy with budesonide 100 μg twice daily, budesonide 800 μg daily (to give a total daily dose of 1000 μg) or placebo was added to treatment for 7 days at the first sign of an asthma exacerbation (defined as a 30% fall in PEFR on 2 consecutive days); placebo inhalers were added for asthma worsening in the other two groups of patients in this trial (67 receiving budesonide 400 μg twice daily routinely and 75 receiving budesonide 100 μg twice daily). Both dosages of budesonide (800 and 200 μg/day) were effective in controlling symptoms and maintaining lung function over a period of several

Table 1 Studies of inhaled budesonide in children with acute wheezing.

Study	Patients enrolled	Design	Treatments	Results
Connett and Lenney[25]	32 preschoolers with viral wheezing	R, DB, PC	BUD 800 μg bid via spacer or 1600 μg bid via spacer+mask × 7d. Treatment continued until one pair of active and PL inhalers used per patient	28 treatment pairs completed by 25 patients. 12 families preferred BUD; 6 PL; 7 no preference. Mean day and night time wheeze significantly reduced by BUD
Svedmyr et al.[26]	31 aged 3–10 y with URTI	R, DB, PC, CO	BUD TH 0.2 mg qid × 3d, then tid × 3d, then bid × 3d. 2 BUD and 2 PL courses given per patient	22 children completed 67 periods. Emergency room visits: 3 BUD, 8 PL. All hospital admissions associated with PL. Morning and evening PEFR higher with BUD ($P = 0.015$; $P = 0.022$), but symptom scores similar for BUD and PL
Svedmyr et al.[27]	55 aged 1–3 y with airway infection	R, DB, PC, PG	BUD 400 μg or PL qid × 3d, then bid × 7d via spacer+mask. Each child followed for 1 yr	BUD reduced symptom scores (especially cough) but not need for hospital care

Abbreviations: bid = twice daily; BUD = budesonide; CO = crossover; DB = double-blind; PC = placebo-controlled; PEFR = peak expiratory flow rate; PG = parallel groups; PL = placebo; qid = four times daily; R = randomized; TH = Turbuhaler; tid = three times daily; URTI = upper respiratory tract infection.

months, and that the addition of budesonide 800 μg daily at the onset of worsening was beneficial.

Volovitz et al.[4] investigated the efficacy of high dosages of budesonide in children aged 1–14 years with acute asthma exacerbations treated at home. Children received budesonide 200–400 μg four times daily in combination with a β_2-agonist at the first sign of an asthma exacerbation, and the budesonide dosage was decreased over 4–8 days. Overall, the children's parents were able to control 94% of the 1061 asthma exacerbations; in addition, high-dosage budesonide was associated with a reduced need for oral corticosteroid therapy and hospitalization.

ICSs in acute asthma

In view of the problems (most notably metabolic) with systemic corticosteroids, and the encouraging findings in patients with acute wheeze or worsening of asthma, the use of ICS formulations in patients with acute asthma has been investigated in a number of studies in the emergency department and hospital settings as well as following discharge from the emergency department. This has allowed a systematic review of the data.[8]

Edmonds et al.[8] investigated early use of ICS in the emergency department treatment of acute asthma and compared inhaled steroids vs. placebo and inhaled steroids vs. systemic steroids in 11 studies. The primary analysis compared inhaled steroids vs. placebo on hospitalization (5 studies), pulmonary function (4 adult studies) and clinical scores (2 studies in children). Five of these 7 studies compared inhaled steroids vs. placebo alone and 2 studies compared inhaled steroids plus systemic steroids vs. systemic steroids alone. A total of 191 patients received treatment with an ICS and 185 did not. The patients who were given ICS were less likely overall to be admitted to hospital (odds ratio [OR] 0.30; 95% confidence interval [CI] 0.16–0.57). Patients receiving concomitant systemic steroids showed a similar, but non-significant, trend towards reduced admissions compared with placebo (OR 0.45; 95% CI: 0.18–1.12). Patients who received ICS also showed small but nevertheless significant improvements in PEFR (8%; 95%CI: 3–13%) and FEV_1 (5%; 95%CI: 0.4–10%). The secondary analysis compared ICS alone with systemic treatment alone. Four such studies were identified and all involved pediatric patients. Of a total of 313 patients, 159 received inhaled steroids, and 154 systemic steroids. There was a marked heterogeneity between study results and meaningful pooling of results was not possible.[8]

Doses and dosing schedules

In the studies included by Edmonds et al.[8] there was a wide variety in doses and dosing schedules. Three of the studies included in the primary analysis gave a single dose of ICS (beclomethasone;[29] budesonide[30,31]), while the others gave multiple doses (from 3 doses [budesonide[32]] to 18 doses [flunisolide[19]]) over 3–8 h. Total doses ranged from low (beclomethasone 200 μg)[29] to very high (flunisolide 18 mg).[19] In the analysis of ICS vs. oral steroid, three studies gave a single dose of ICS,[14,21,33] and one gave three doses.[34] The doses of ICS were moderate to high (budesonide 1600 μg and dexamethasone 1.5 mg/kg).[14,21] All four used 2 mg/kg of

oral prednisolone or prednisone in the systemic steroid group.

It is notable that all studies in the primary analysis which used budesonide showed a favorable outcome[31,32] and this was also the case in the study by Sung et al.,[30] where budesonide was added to systemic steroids.

In the comparisons between ICS and systemic steroids in children the two studies with budesonide[14,34] showed better or equal efficacy. The study by Scarfone et al.[21] showed equal efficacy between inhaled dexamethasone and prednisone. The only study comparing fluticasone with a systemic steroid (prednisone) showed better outcomes (including improvements in the forced expiratory volume over 1 min [FEV_1] and the requirement for subsequent hospitalization) when patients received systemic steroid therapy.[33] The authors recommended that inhaled fluticasone should not be used to treat severe acute asthma.

The importance of high doses

Our understanding of the dose–effect relationship of inhaled steroids in acute and severe asthma has increased in recent years. Experience with patients who deteriorate during maintenance treatment have shown that, on the whole, a simple doubling of the usual maintenance ICS dose is unlikely to be sufficient in the acute setting.[35] In a study among 28 children with mild to moderate asthma failed to demonstrate a benefit for increasing ICS dose compared with placebo for morning or evening PEFRs, diurnal peak flow variability, symptom scores, spirometric function or the parents opinion of the effectiveness of asthma medication.[35] Most studies showing a beneficial effect of ICS during acute asthma attacks used doses at least five times those usually given by inhalation for maintenance therapy.[14,19,30,32,34,36,37] In the systematic review by Edmonds et al.[8] six randomized, double-blind and controlled studies compared treatment with oral corticosteroids with ICS; the high doses used in these studies included budesonide 2400 μg via nebulizer as three doses of 800 μg at 30-min intervals,[34] budesonide 2000 μg via nebulizer every 8 h,[37] budesonide 1600 μg via DPI,[14] dexamethasone 1.5 mg/kg via nebulizer,[21] budesonide via MDI with spacer as three 400 μg doses at 30-min intervals,[32] and fluticasone 1000 μg via nebulizer twice daily.[36] ICS were generally at least as effective as oral corticosteroids in controlling acute asthma attacks in the emergency setting; in only one study did ICS not prove to be as effective as the oral comparator in terms of all parameters measured.[35]

The high doses and the high frequency of administration may be requisites to provide both a rapid and an additive effect of inhaled steroids on top of a regimen already including systemic steroids. Such an approach would be especially valuable in acute severe asthma.[38] The high dose effects may involve non-genomic effect of inhaled steroids as recently suggested by Horvath and Wanner[39] and Rhen and Cidlowsky.[40] These effects may be more rapid than those corticosteroid effects than involve genomic transcription, but may be more transient as has been noticed for the acute vasoconstrictor effect studied by Mendes et al.,[41] which only lasted 2 h in spite of high doses of ICS. Clinical benefits may comprise effects on mucosal edema through a direct effect on mucosal blood vessels,[41] but may also comprise acute effects on plasma exudation and bronchial secretion as suggested by Urbach et al.[42] The relevance of these observations needs further study.

Clinical experience with budesonide in acute asthma

The efficacy of budesonide in the acute setting has been investigated in adults and in children in emergency departments, in hospitalized patients, and during the follow-up period after discharge.

Budesonide in acute asthma in adults

Two studies[43,44] have compared nebulized budesonide given in repeated high doses with oral steroids in adults with severe acute asthma undergoing treatment in the emergency department (Table 2). Both studies showed no relevant difference between nebulized budesonide and oral prednisolone in terms of improvement in FEV_1. However, nebulized budesonide significantly reduced severity of wheezing relative to prednisolone at 24 and 48 h.[43] During the follow-up phase, FEV_1 was significantly higher in the budesonide group than in the prednisolone group after 28 days, and coughing was reduced after 7 days. It should be noted that this study was incomplete because of difficulties with recruitment, and the trial did not have sufficient power to detect a difference between treatments in terms of FEV_1. Mitchell et al.[44] reported similar spirometric improvements after 24 h in patients treated with nebulized budesonide (five doses of 4 mg) and in those who received high- and low-dose oral prednisolone (four oral doses of 40 mg or a single 30 mg dose).

Inhaled budesonide has also been investigated in patients discharged from hospital after an acute attack of asthma[43,45–47] (Table 2). Two of these randomized double-blind studies[45,46] showed similar efficacy of systemic treatment and inhaled budesonide via Turbuhaler®. Fitzgerald et al.[45] studied 185 patients and found budesonide 600 μg four times daily for 7–10 days was as effective as prednisone 40 mg daily in terms of relapse rates, quality of life, symptoms, and spirometry (Table 2). High-dosage budesonide via DPI was recommended by the authors as a viable alternative to systemic prednisone as follow-up treatment in patients with acute asthma stabilized in the emergency department.

Nana et al.[46] reached similar conclusions in their study in 81 patients. These researchers used a higher dosage of budesonide (1600 μg twice daily) and compared this with a tapering course of prednisolone (Table 2). Increases in spirometry were similar between groups (Fig. 1), as were clinical improvement, and need for rescue medication.

In a further study, inhaled budesonide was added to a 21-day course of oral prednisolone after initial stabilization in the emergency department.[47] This trial showed a halving of relapse rates over 21 days of follow-up and reduced β_2-agonist usage when budesonide 1600 μg daily via Turbuhaler® was added to nontapering oral prednisone 50 mg/day for 7 days (Table 2). Addition of budesonide also resulted in better asthma quality of life (AQLQ) scores. Pulmonary function was similar between groups, and β_2-agonist

Table 2 Studies of inhaled budesonide in adult patients with acute asthma.

Study	Patients	Design	Treatments	Results
Hospitalized patients				
Higenbottam et al.[43]	13	R	BUD neb 4 mg q8h × 48–72 h; then BUD TH 1600 μg bid × 7 d; then BUD TH 800 μg bid × 2 d PRED 40 mg/d × 9–11 d; then BUD TH 800 μg bid × 21 d	Similar increases in FEV_1 between groups after 48 h; coughing reduced in BUD group after 7 days; FEV_1 higher in BUD group after 28 d
Mitchell et al.[44]	135	R	BUD neb 4 mg × 5 doses over 18 h PRED 40 mg × 4 doses over 18 h PRED 30 mg stat	Similar increases in PEFR in all groups
Follow-up after discharge from the emergency department				
Fitzgerald et al.[45]	185	R, DB	BUD TH 600 μg qid × 7–10 d PRED 40 mg/d × 7–10 d	Relapse rates 10% (BUD) and 11.8% (PRED); similar improvements between groups in FEV_1, symptoms, PEFR and QoL scores
Nana et al.[46]	81	R, DB	BUD TH 1600 μg bid × 7d PRED 40 mg, reducing to 5 mg over 7 d	Similar increases in FEV_1 and mean morning PEFR; also symptoms and use of rescue medication
Rowe et al.[47]	188	R, DB	BUD 1600 μg/d+PRED 50 mg × 21 d PL+PRED 50 mg × 21 d	Relapse rates: 12.8% (BUD) and 24.5% (PL); AQLQ scores higher and fewer β_2-agonist actuations with BUD

Abbreviations: AQLQ = Asthma Quality-of-Life Questionnaire; BUD = budesonide; DB = double-blind; FEV_1 = forced expiratory volume in 1 s; neb = nebulized; PEFR = peak expiratory flow rate; PL = placebo; PRED = oral prednisolone/prednisone; QoL = quality of life; R = randomized; TH = Turbuhaler.

actuations were 2.4 and 4.2/day ($P = 0.01$) in the budesonide and placebo groups, respectively. The authors point out that the number of patients that would need to be treated with budesonide to prevent relapse under these circumstances would be as low as nine.

Budesonide in acute asthma in children

Most studies in children have been performed in the emergency department setting,[14,30,32,34,48] but some data are also relevant to those who are ultimately hospitalized[37,49] and to those being followed up.[14,37] It should be noted that all pediatric studies to date show comparable efficacy for inhaled budesonide and oral corticosteroids in the control of acute asthma exacerbations. A feature of the results of studies in children has been the apparent potential for reduced consumption of healthcare resources as shown by reduced hospitalization times or accelerated discharge from hospital in patients treated with inhaled budesonide.[30,32,34,48]

An early study by Djaugberg et al.[49] showed benefit of addition of nebulized budesonide to systemic corticosteroid or inhaled terbutaline. Budesonide 0.5 mg was inhaled every 4 h for up to 5 days and was associated with significantly improved symptom scores relative to placebo in children with acute wheezing. Subsequent randomized and double-blind studies have shown at least as much clinical benefit with inhaled budesonide as with oral prednisolone/prednisone across a wide range of ages (Table 3).

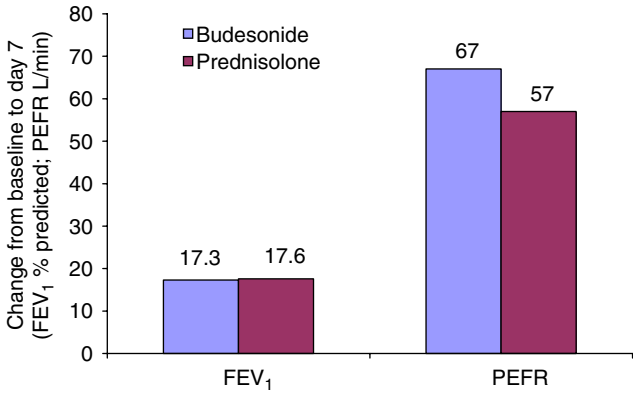

Figure 1 Mean changes in percentage predicted forced expiratory volume in 1 s (FEV_1) and peak expiratory flow (PEFR) from baseline to 7 days after emergency room treatment for an acute asthma attack with either budesonide 1600 μg twice daily via dry powder inhaler for 7 days or oral prednisolone tapering from 40 to 5 mg daily over 7 days.[46]

In the emergency department

Comparisons with placebo: single dose administration

A double-blind study by Tsai et al.[31] in children aged 6–17 years found acute treatment with budesonide inhalation suspension (up to 2 mg effective). A single dose of nebulized budesonide, but not nebulized terbutaline, rapidly decreased exhaled NO levels in 6 h. The decrease in exhaled

Table 3 Studies of inhaled budesonide in infants and children with acute asthma.

Study	Patients (age range)	Design	Treatments	Results
Emergency department				
Singhi et al.[32]	60 (3–12 yr)	R, DB	O_2+SAL neb+BUD pMDI q30min × 3 O_2+SAL neb+PL q30 min × 3	Hospitalization rates: BUD = 0%; PL = 23%. BUD also reduced O_2, aminophylline and systemic steroid requirements; improved PEFR and respiratory distress scores ($P<0.05$); reduced length of hospital stay
Devidayal et al.[34]	80 (2–12 yr)	R, DB	SAL neb 0.15 mg/kg+PL neb q30 min × 3+2 mg/kg PRED stat SAL neb+BUD neb 800 μg q30 min × 3+oral PL	Fit for discharge after 3 doses: BUD 54%, PRED 18% ($P<0.001$). O_2 saturation, pulmonary index and respiratory distress scores all significantly better with BUD ($P<0.01$)
Volovitz et al.[14]	22 (6–16 yr)	R, DB	BUD TH 1600 μg, then reducing doses after discharge × 1 wk PRED 2 mg/kg, then reducing doses after discharge × 1 wk	Treatments equivalent. During 4 h treatment both groups showed a similar improvement in: pulmonary index score including: oxygen saturation, respiratory rate, inspiratory expiratory ratio, accessory muscle use and wheezing; earlier response with BUD
Sung et al.[30]	44 (6 mo–18 yr)	R, DB	PRED 1 mg/kg+SAL neb 0.15 mg/kg q30 min × 3, then q4 h × 4+BUD neb 2 mg PRED 1 mg/kg+SAL neb 0.15 mg/kg q30 min × 3, then q4 h × 4+PL neb	Pulmonary index scores similar between groups (BUD vs PL). Patients discharged more rapidly from hospital overall after BUD treatment
Hospitalized children				
Sano et al.[48]	71 (3–24 mo)	NS	BUD neb 0.25 mg q6 h+IV fluids, hydrocortisone and formoterol neb Ipratropium 0.1 mg q6 h+IV fluids, hydrocortisone and formoterol neb	Significant reduction in clinical scores in both groups. Faster improvement with BUD, and hospitalization duration reduced (66.4 vs 93 h; $P<0.01$)
Matthews et al.[37]	46 (5–16 yr)	R, DB	BUD neb 2 mg/kg immediately and after 24 h PRED 2 mg/kg immediately and after 24 h	Significant increase in FEV_1 ($P<0.01$ vs baseline) with BUD only. PEFR and symptoms similar between treatments (also after 24 d follow-up with BUD TH 800 μg/d)

Abbreviations: BUD = budesonide; DB = double-blind; FEV_1 = forced expiratory volume in 1 s; neb = nebulized; NS = not stated;O_2 = humidified oxygen; PEFR = peak expiratory flow rate; PL = placebo; pMDI = pressurized metered-dose inhaler; PRED = oral prednisolone/prednisone; R = randomized; SAL = salbutamol; TH = Turbuhaler.

NO, a marker of inflammation, was correlated to an increase in PEFR.

Repeated dosing

Singhi et al.[32] showed elimination of the need for hospitalization when budesonide via pMDI and spacer was added to humidified oxygen and bronchodilator therapy (Table 3). Both groups showed significant improvements in respiratory status after 2 h, but budesonide was associated with considerable reductions in the proportion of children needing oxygen for more than 2 h (23% vs. 50%; $P<0.05$) and requirement for aminophylline infusion and systemic corticosteroid therapy (7% vs. 27%; $P<0.05$). The mean length of stay at the emergency department was more than halved by

the addition of budesonide to acute therapy (from 7.8 to 3.2 h; $P<0.01$).

Comparison to systemic steroids: single dose administration

Acceleration of recovery with the use of inhaled budesonide was demonstrated by Volovitz et al.[14] in their study in 22 older children (aged 6–16 years) who presented to the emergency department with moderately severe asthma attacks (Table 3). The children were either given a single dose of budesonide 1600 μg via DPI or 2 mg/kg prednisolone, followed by a tapering algorithm. Tapering budesonide conferred similar responses in terms of spirometry, pulmonary indices, wheezing, accessory muscle use, and oxygen saturation to those seen with tapering oral corticosteroid therapy (see also later discussion of onset of action). Asthma symptom scores improved more quickly with budesonide than with prednisolone during the first week after discharge, and budesonide treatment was not associated with the cortisol suppression seen at Week 3 in children who had received prednisolone.

Milani et al.[50] found that a single nebulized dose of budesonide provided comparable clinical improvement to a single oral dose of prednisone in children (aged 2–7 years) presenting with mild to moderate exacerbation of their asthma.

Comparison to systemic steroids: repeated dosing

Devidayal et al.,[34] in their study in 80 children aged 2–12 years, found that the rate of full recovery and subsequent discharge from the emergency department was increased threefold when a single oral dose of prednisolone 2 mg/kg was replaced with three doses of budesonide 800 μg given at 30-min intervals via nebulizer.

Inhaled budesonide in addition to systemic steroids

Sung et al.[30] failed to show benefit of addition of a single dose of nebulized budesonide to corticosteroid and bronchodilator therapy in terms of pulmonary index scores, but did note a nonsignificant tendency towards a lower median score (i.e. fewer/less severe symptoms) after 1 h in the budesonide group than with placebo ($P = 0.07$).

Hospitalized patients

Sano et al.[48] used a pulmonary score that included wheezing and costal retraction, together with measurements of respiratory rate, and found significant improvements after 12 h when either nebulized budesonide or ipratropium was added to standard therapy with a bronchodilator, systemic corticosteroid and iv fluids, but with more rapid improvement with budesonide (Table 3). Of additional interest are the observations by Matthews et al.[37] in 46 hospitalized children aged 5–16 years with severe asthma exacerbations. After 24 h, although nebulized budesonide and oral prednisolone produced similar improvements in PEFR and symptoms, only patients treated with budesonide showed a significant mean change in FEV_1 from baseline. Oral corticosteroid treatment had no significant effect in this respect.

Differences between ICS in the acute setting

Budesonide seems to have a more consistent documentation in acute settings than steroids such as beclomethasone dipropionate (BDP) and fluticasone. There may be a difference on the pharmacokinetic level for these drugs that help explain these differences.

Dissolution and lipophilicity

Budesonide is readily dissolved in human bronchial secretions and is rapidly absorbed irrespective of the site of deposition, which contrasts with the dissolution profile of more lipophilic compounds, such as fluticasone.[51] This difference between corticosteroids becomes increasingly important in patients with pulmonary obstruction where there is greater central deposition of inhaled drugs and a faster clearance of lipophilic steroids.

Mortimer et al.[52] have shown that, in contrast to budesonide, the airway availability of fluticasone is severely restricted by methacholine challenge designed to decrease FEV_1 by over 25%. These authors measured AUCs for the two corticosteroids after single inhaled doses of fluticasone 1000 μg and budesonide 800 μg with and without the presence of methacholine. As shown in Fig. 2, the reduction in mean AUC of fluticasone after methacholine challenge was considerably greater (60%) than that seen with budesonide (21%).

An indication that such differences will have clinical importance in obstructed patients is the finding of a higher potency of budesonide vs. fluticasone and BDP in the study by Mendes et al.,[41] who studied the acute vasoconstrictor effects of these three ICS in healthy volunteers and asthmatic patients (Fig. 3).

Except for considerably lower airway availability of lipophilic steroids in acute obstructed patients, the rate of pulmonary absorption of budesonide appears to be an important factor determining the efficacy of the drug in

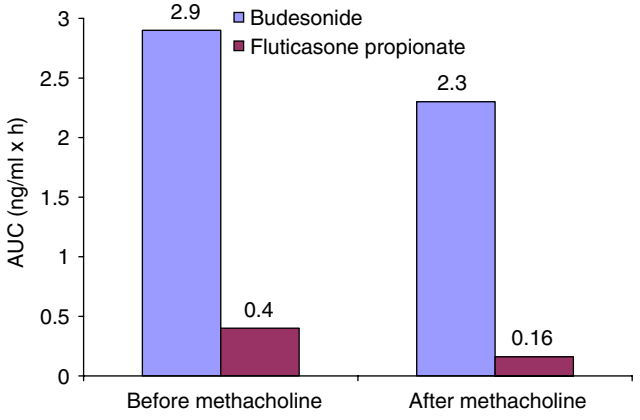

Figure 2 Mean areas under curves of plasma drug concentration vs. time (AUC) for single inhaled doses of budesonide (800 μg) and fluticasone (1000 μg) before and after challenge with methacholine.[52] The relative reduction in AUC caused by methacholine challenge was significantly greater for fluticasone than for budesonide ($P = 0.003$).

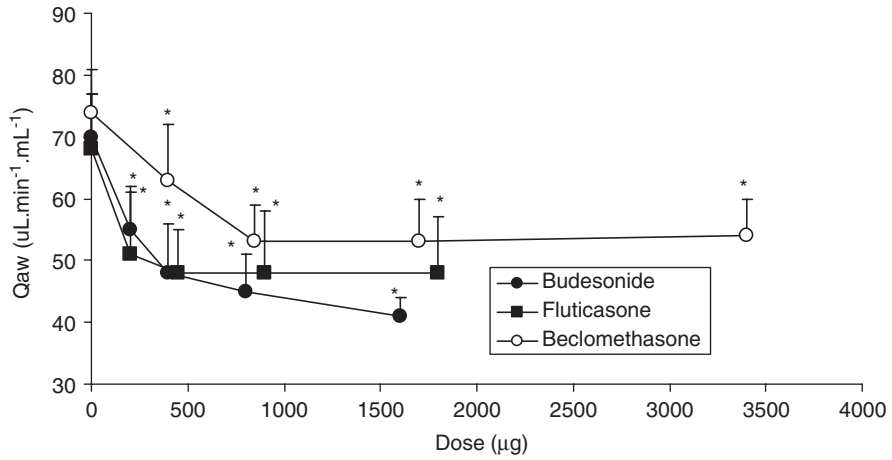

Figure 3 Comparative vasoconstrictor efficacy of three inhaled corticosteroids in 10 corticosteroid naïve patients with asthma.[41]

the acute setting. Budesonide has a mean absorption time of 0.8 h compared with, for example, the 5.9 h required by fluticasone.[53–56]

There is evidence to suggest that lipophilic inhaled steroids may be less than optimal for the treatment of acute airway obstruction.[33,57,58] Although there are no published head-to-head comparisons between budesonide and fluticasone in acute asthma, these two drugs have been used in our clinic.

Rapid onset of action

Systemic corticosteroids (oral or parenteral) have been found to be effective in controlling acute asthma attacks within 4 h in adults[59] and children.[60,61] Two studies[62,63] failed to show a benefit for early administration of IV corticosteroid in acute asthma, although the balance of subsequent pooled evidence favored corticosteroid use.[59]

For budesonide specifically, improvements in lung function may be apparent as early as 1–4 h after inhalation in patients with acute or stable asthma[14,64] and be accompanied by improvements in inflammatory markers after approximately 4–6 h.[65,66] Significant improvements in lung function were observed with ascending doses of budesonide (200, 800 and 1600 μg) within 4–5 h, with the highest dose producing a significant improvement in inflammatory marker status that was seen from the first day of treatment.[66] Vathenen et al.[65] showed that budesonide 800 μg twice daily increased FEV_1 and histamine reactivity from the first dose of budesonide, with maximal changes seen 6 h after inhalation. In a study of 41 adults with stable asthma who stopped ICS therapy for 4 days and then received a single dose either of budesonide 2400 μg or placebo via DPI, sputum eosinophil levels were significantly lower 6 h after budesonide (25%) than placebo (37%; $P<0.05$), and airway responsiveness improved with budesonide by a factor of 2.2.[67] In a study in children,[14] clinical activity of both inhaled budesonide (1600 μg via DPI) and oral prednisolone (2 mg/kg) was noted immediately after administration with similar effects over the first 4 h of treatment (Fig. 4). At 4 h, PEFR had improved ($P<0.01$) to the same extent in both groups, as had pulmonary index scores ($P<0.001$), wheezing ($P<0.05$), accessory muscle use ($P<0.001$), and oxygen saturation ($P<0.05$).

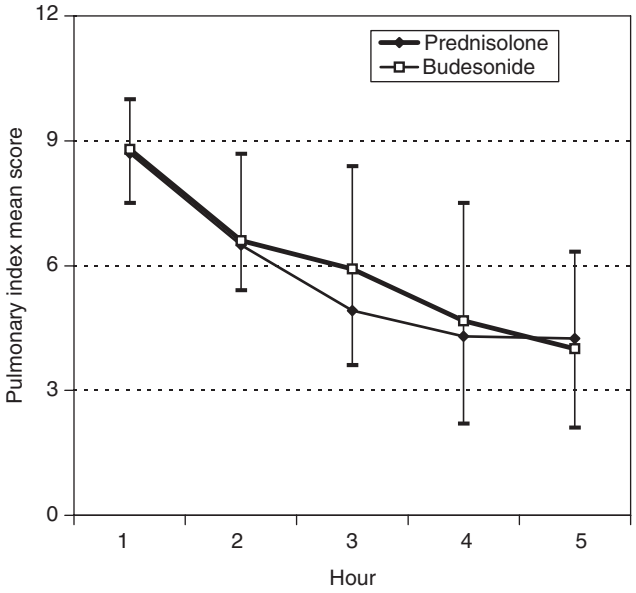

Figure 4 Time course of effect of inhaled budesonide (1600 μg via dry powder inhaler) and oral prednisolone (2 mg/kg) in children treated for acute asthma in the emergency department setting.[14]

A rapid effect of budesonide on late allergic responsiveness has also been reported.[68] Administration of budesonide 800 μg via DPI 4–6 h after allergen challenge resulted in a rapid (after 1–2 h; $P<0.001$ at 2 h) and sustained reduction in severity of late-onset allergic reactions when compared with placebo.

Conclusions

Data would suggest that inhaled budesonide has a role in the management of acute asthma exacerbation and pediatricians and primary care physicians are starting to recommend increases in dosage of ICS at home at the onset of an asthma

exacerbation.[69] Studies of inhaled budesonide have shown consistently positive results, with no indication that such therapy is inferior to oral corticosteroid therapy. These findings contrast with those for some other ICS dies of ICS and making cross study comparisons in the acute exacerbation setting given the difficulty in defining clinically relevant and measurable severity thresholds for asthma worsenings and exacerbations.

The apparent efficacy of inhaled budesonide in patients with acute asthma is most probably linked to the drug's pharmacokinetic profile, with key factors including rapid penetration of target tissues and fast onset of action.

In addition to further work to clarify clinically relevant severity thresholds of acute asthma exacerbations, further studies are now warranted in patients with more severe asthma exacerbations to more fully define the role of budesonide and other ICS in this setting.

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