Review of the Unique Properties of Budesonide

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ABSTRACT

Background: The aim of inhaled corticosteroid (ICS) therapy for asthma is to attain high therapeutic activity in the airways while keeping the risk of systemic adverse effects relatively low. However, the physicochemical and pharmacokinetic properties of various ICSs affect this ratio, thereby influencing their ability to fulfill the requirements of an ideal agent.

Objective: This article reviews the physical and pharmacokinetic properties of budesonide, outlining how they, safety data, and use of different inhalation devices enable budesonide to meet many of the clinical requirements of an ideal ICS for the treatment of asthma.

Results: ICS efficacy is influenced by lipophilicity, lung deposition, and retention in airway tissue, whereas the rate of elimination determines systemic activity. Budesonide is retained in the airways to a greater extent than other ICSs because of an esterification process that increases its lipophilicity. The prolonged retention of budesonide in the airways may contribute to its efficacy when administered QD. In addition to a pressurized metered-dose inhaler, budesonide is available as a dry-powder inhaler and in nebulized form, which can be used by asthma patients aged ≥6 months.

Conclusions: When combined with delivery devices suitable for a spectrum of patient groups, the physical and pharmacokinetic properties of budesonide lend it many of the characteristics of an ideal ICS, including favorable efficacy and tolerability profiles. (Clin Ther. 2003;25[Suppl C]:C42–C60) Copyright © 2003 Excerpta Medica, Inc.

Key words: budesonide, airway selectivity, efficacy, safety.
INTRODUCTION
Asthma is a chronic inflammatory disorder of the airways, affecting ~5% of adults and ~10% of children worldwide. It remains a serious global health problem despite the introduction of effective new treatments. Since the discovery of the extensive inflammatory basis of the disease, inhaled corticosteroids (ICSs) have played a central role in the management of asthma. It is now widely accepted that they are effective in controlling inflammation and improving lung function and asthma symptoms. As a result, ICSs are recommended as first-line therapy for all patients with persistent asthma.

Over the past decade, our understanding of the molecular mechanisms involved in the control of inflammation has improved considerably. Glucocorticosteroids mediate their effects through cytoplasmic glucocorticoid (GC) receptors that are present on most cells, although to varying extents. After glucocorticosteroids bind to the GC receptors, the glucocorticosteroid GC receptor complex alters the transcription of a wide range of inflammatory mediators, thereby reducing inflammation. Because GC receptors are present throughout the body, the aim of ICS therapy is to achieve high local therapeutic activity in the airways while keeping the risk of systemic adverse effects relatively low. The airway selectivity of ICSs is determined by their physicochemical and pharmacokinetic properties, as well as by the drug formulation and the delivery device. Desirable features of an ICS include a high affinity and potency for GC receptors, and prolonged lung retention combined with low oral bioavailability, rapid clearance, and systemic elimination. In addition, an ICS should be clinically effective at low doses, suitable for patients of all ages and for all asthma severities when used with the appropriate delivery device, and have a favorable safety profile (ie, a good therapeutic margin with minimal systemic effects), particularly during long-term therapy.

The successful use of beclomethasone, a first-generation ICS, was initially reported in 1972. However, this ICS was not specifically developed for administration by inhalation. The search for a corticosteroid with an improved ratio of topical-to-systemic activity led to the development of budesonide.

The current article reviews the physical and pharmacokinetic properties of budesonide, outlining how these factors, the available safety data, and the use of different inhalation devices enable budesonide to meet many of the clinical requirements of an ideal ICS for the treatment of asthma.

INHERENT PROPERTIES OF ICSs
To optimize the topical-to-systemic ratio of ICSs, research has focused on their structure–activity relationship. It was found that lipophilic substitution at the 16α and 17α positions on the corticosteroid nucleus increases airway selectivity. In the case of budesonide, lipophilic acetal groups at the 16α and 17α positions enhance glucocorticosteroid receptor binding, prolong airway retention, and increase
systemic metabolism. Some ICSs (ie, fluticasone propionate) contain halogen groups; the absence of halogen atoms on the corticosteroid nucleus contributes to the optimal topical-to-systemic activity ratio of budesonide (Figure 11).5

Physical Properties

The physical properties of ICSs affect their airway selectivity. Although it is important for an ICS to have a high receptor-binding affinity, topical efficacy is also influenced by lipophilicity, lung deposition, and retention in airway tissue.

Second-generation ICSs have a wide range of lipophilicities (Table I).16-21 High lipophilicity is an advantageous property associated with a high receptor affinity, but it also reduces water solubility and increases the likelihood of mucociliary clearance. Moreover, there is a strong correlation between lipophilicity and the volume of distribution of an ICS.22 Highly lipophilic compounds are readily partitioned into peripheral tissue, resulting in a large volume of distribution and leading to excessive systemic distribution and retention. Both fluticasone propionate21 and mometasone furoate16 have larger volumes of distribution than budesonide (Table I).18,19

After inhalation, ICSs enter the circulation by direct absorption from the lungs and by oropharyngeal deposition leading to the gastrointestinal tract. The oral bioavailability of a second-generation ICS is low—6% to 11% for budesonide23 and <1% for both fluticasone propionate24 and mometasone furoate.16 Therefore, the main systemic source of an ICS with a high first-pass metabolism in the liver is absorption from the lungs.25 Lung deposition of the ICS and its related systemic effects depend on the formulation and the inhaler device. For corticosteroids with low oral bioavailability, an inhaler that deposits a high proportion of the drug in the lungs may produce greater adverse systemic effects; however, in clinical practice, this risk of systemic effects can be reduced with lower doses.22 Budesonide is retained in the lungs to a greater extent than with other ICSs due to a unique esterification process described in the next section. This process increases the airway selectivity of budesonide.

Figure 1. Structure of budesonide. Reproduced with permission of Marcel Dekker from Brattsand and Axelsson.11 In: Schleimer et al, eds. Inhaled Glucocorticoids in Asthma: Mechanisms and Clinical Actions. 1997:351–379.
Table I. Physical and pharmacokinetic properties of inhaled corticosteroids (ICSs). Potency measures are given relative to budesonide. 16-21

<table>
<thead>
<tr>
<th>ICS</th>
<th>Halogenated</th>
<th>First-Pass Inactivation, % Delivered Dose</th>
<th>Elimination Half-Life, h</th>
<th>Volume of Distribution, L</th>
<th>Lipophilicity, log kₐ</th>
<th>Relative Receptor Binding Affinity</th>
<th>Relative Topical Blanching Potency</th>
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<tr>
<td>Budesonide</td>
<td>No</td>
<td>89</td>
<td>2.3</td>
<td>180</td>
<td>3.7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>BDP/BMP</td>
<td>No</td>
<td>NA</td>
<td>&lt;2/NA</td>
<td>NA</td>
<td>4.8/4.3</td>
<td>0.4/1.1</td>
<td>0.5/0.4</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>Yes</td>
<td>&gt;99</td>
<td>14.4</td>
<td>859</td>
<td>4.5</td>
<td>2.3</td>
<td>1</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>Yes</td>
<td>&gt;99</td>
<td>4.5</td>
<td>332</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

BDP = beclomethasone dipropionate; BMP = beclomethasone monopropionate (metabolite of BDP); NA = not available.
**Budesonide Pharmacokinetics**

The pharmacokinetic properties of budesonide have been extensively investigated and are well characterized. The rate of elimination of ICSs is important in determining their systemic activity and is expressed as the elimination half-life, derived from the systemic clearance and the volume of distribution. Budesonide has a shorter terminal half-life than fluticasone propionate and mometasone furoate (Table I). Thus, systemic accumulation of budesonide is more easily avoided, which is of particular importance during long-term treatment.

**Esterification**

As mentioned previously, budesonide is retained in airway tissue to a greater extent than other ICSs. After entering a cell in the airways, inhaled budesonide primarily binds to the GC receptor. Following dissociation of protein molecules that hold the receptor in an inactive state, the GC–receptor complex translocates to the nucleus. This complex acts as a transcription factor for upregulating anti-inflammatory mediators and downregulating proinflammatory mediators. In addition, the GC–receptor complex directly interacts with the transcription factors, activator protein 1, and nuclear factor-κB, blocking gene transcription at the level of DNA binding and counteracting the effects of proinflammatory cytokines. This mechanism is believed to be extremely important in the anti-inflammatory action of ICSs.

Excess (unbound) budesonide forms esters with long-chain fatty acids, producing a depot of highly lipophilic inactive budesonide within the cell. Intra-cellular lipases then hydrolyze the ester conjugates, releasing the less lipophilic free budesonide into the cell. These processes, respectively called esterification and de-esterification, are reversible and concentration dependent, and have been demonstrated in human lung tissue. Furthermore, they are specific for the airways and are probably unique to budesonide because they are dependent on the ICS structure. Esterification increases the retention time of budesonide locally (Figure 2) and is associated with a greater prolongation of the anti-inflammatory effect compared with that of fluticasone propionate. The slow, continuous release of free budesonide into the airways supports its suitability for QD administration. The prolonged, selective airway retention and short plasma half-life of budesonide, as well as its esterification and low uptake in systemic tissues, increase its airway selectivity.

**PHYSICAL AND PHARMACOKINETIC EFFECTS ON CLINICAL EFFICACY OF Budesonide**

Logically, an ideal ICS must demonstrate a dose–response effect and should be clinically effective at low doses. In large, placebo-controlled studies of treatment
administered via dry-powder inhaler (DPI), the clinical efficacy of budesonide demonstrated a dose–response effect at 100 to 400 µg BID in adult patients with mild to moderate persistent asthma (Figure 3A) and at 100 to 800 µg BID in adults with moderate to severe persistent disease. In a 12-week, double-blind, randomized study in 473 adults with moderate to severe persistent asthma, budesonide administered via DPI (100, 200, 400, and 800 µg BID) improved lung function at low doses. All doses of budesonide significantly improved the mean change in morning peak expiratory flow compared with placebo (P < 0.001). Budesonide via DPI has similarly demonstrated a dose–response effect (100–400 µg BID) in children and adolescents aged 6 to 18 years with moderate to severe persistent asthma (Figure 3B; statistical significance not provided).

Trademark: Pulmicort Turbuhaler® (AstraZeneca Pharmaceuticals LP, Wilmington, Delaware).
Figure 3. Dose–response effect of budesonide showing the change in peak expiratory flow (PEF) from baseline (A) in adult patients with moderate persistent asthma35 (all doses significantly improved mean change vs placebo [P < 0.001]) and (B) in children and adolescent patients with moderate to severe asthma.36 Reprinted with permission of Elsevier from Busse et al,35 J Allergy Clin Immunol. 1998;101:457–463, and Shapiro et al,36 J Pediatr. 1998;132:976–982.
QD Versus BID Administration of Budesonide

Budesonide provides effective asthma control in most patients with stable asthma when administered BID. However, evidence suggests that compliance with treatment improves as the dosing frequency decreases; thus, QD administration of asthma therapy may lead to improved control. The efficacy of QD administration with budesonide via DPI has been investigated both in adults and children. The results of these studies suggest that QD budesonide effectively controls mild to moderate persistent asthma. Nebulized QD budesonide is also effective in infants and is approved in the United States for use in children aged ≥12 months with mild or moderate persistent asthma.

The effectiveness of QD budesonide is thought to be linked to the esterification process. Therefore, a QD treatment that produces continuous anti-inflammatory effects may have positive implications for increased patient compliance and better treatment outcomes in asthma therapy.

Quality of Life

In addition to its adverse effect on lung function, asthma has a marked impact on the health-related quality of life (HRQL) of patients. The effect of budesonide on patients’ HRQL has been investigated in several studies.

The long-term effects of ICSs on HRQL were examined for the first time in the Formoterol and Corticosteroids Establishing Therapy study. During the run-in period, there were significant improvements in HRQL, as assessed by Asthma Quality of Life Questionnaire (AQLQ) scores, in all patients who received budesonide via DPI 800 µg BID (P < 0.001).

The effect of maintenance treatment with budesonide via DPI was investigated in 309 adult patients with mild to moderate stable asthma in a placebo-controlled study. Patients were randomized to receive budesonide 200 or 400 µg once daily for 6 weeks. The dose of budesonide was then reduced to 200 µg for an additional 12 weeks in patients who had received the 400-µg dose, and was left unchanged in those who had received the 200-µg dose. Statistically significant and clinically relevant improvements in overall AQLQ score and in all domains were observed with the budesonide treatment groups at 6 and 18 weeks compared with the placebo group.

DELIVERY OF BUDESONIDE TO THE AIRWAYS

Various inhalation devices are available to deliver corticosteroids to the lungs. The principal systems are pressurized metered-dose inhalers (pMDIs), DPIs, and nebulizers. Because pMDIs require coordination between actuation and inhalation, they may be difficult for children to use correctly. However, using a pMDI in combination with a spacer can eliminate the need for such coordination. DPIs or nebulizers may be easier to manipulate in this patient group. In some DPIs, the pow-
der is contained in a compartment, small capsule, or disk. The pMDI and DPI may be inappropriate for very young children because they need to hold their breath for 10 seconds after inhalation. ICSs are recommended for the management of persistent asthma in infants and young children. However, some ICSs cannot be used to treat young children and infants with asthma because suitable delivery devices are not available.

Budesonide can be delivered via DPI, pMDI with spacer, or nebulizer as an inhalation suspension, and it can be used by asthma patients of all ages. Budesonide is the first ICS to be approved for administration with a nebulizer; this formulation was developed in response to the specific delivery needs of infants and young children. As mentioned previously, budesonide is the only ICS approved in the United States for use in children aged ≥12 months; it is also licensed for use in children aged ≤8 years when administered as an inhalation suspension. Nebulizers produce a water-based aerosol of the drug that is administered to the patient via mouthpiece or face mask. Although budesonide is more water soluble than some other ICSs, it is mainly in suspension in the aerosol rather than in the solution. Because beclomethasone dipropionate and fluticasone propionate are ~100 times less soluble than budesonide, they are less suitable for nebulization.

In clinical trials, budesonide inhalation suspension has been shown to be an effective treatment in infants aged ≥6 months and in young children with mild to severe persistent asthma. Furthermore, budesonide inhalation suspension is effective in the treatment of children with acute asthma. In a study of children aged 5 to 16 years randomized to treatment with budesonide inhalation suspension or oral prednisolone, change in forced expiratory volume in 1 second from baseline after 24 hours was significantly improved only in the budesonide group (P < 0.01), and the budesonide group had a greater improvement in breathlessness compared with the oral prednisolone group (P < 0.05). In another study, children aged 2 to 12 years were treated with 3 doses of nebulized budesonide and salbutamol at 30-minute intervals or a single dose of oral prednisolone followed by 3 doses of nebulized salbutamol. The budesonide/salbutamol group had greater improvements in respiratory rate, pulmonary index, and respiratory distress scores compared with the prednisolone/salbutamol group (all P < 0.01), and significantly more patients in the budesonide/salbutamol group were fit for discharge within 2 hours of treatment compared with the prednisolone/salbutamol group (P < 0.001). Currently, the recommended course of action to resolve acute exacerbations is to use rapid-acting inhaled beta₂-agonists with the addition of oral GCs if there is an inadequate response to beta₂-agonists. Therefore, the use of budesonide inhalation suspension may reduce the need for oral corticosteroid

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therapy in pediatric patients with acute asthma, but more evidence is required to assess the use of ICSs in this setting.

As discussed previously, the formulation of the drug and the type of inhaler device influence lung deposition and the therapeutic ratio of the ICS. A strong correlation between clinical efficacy and lung deposition has been demonstrated. Lung deposition of budesonide is twice as high when administered via DPI versus pMDI; this increase in lung deposition is associated with a 2-fold increase in the bronchodilatory effect. Moreover, there is less variability in lung deposition within subjects (coefficient of variation, 32.9% vs 64.7%, respectively) and between subjects (coefficient of variation, 28.4% vs 61.8%, respectively) with DPI compared with a pMDI in healthy volunteers; similar results have been found in patients with asthma (Table II). There is a good correlation between in vitro fine-particle dose (aerodynamic diameter <5 μm) and in vivo lung deposition. Budesonide via DPI produces a higher proportion of fine particles than other devices, and may lead to more effective lung deposition.

Because the flow of inspired air is responsible for the generation and delivery of the aerosol with a DPI, any impairment of airflow may limit efficacy. Drug delivery through DPIs is also affected by the intrinsic resistance of the inhaler. Budesonide via DPI has a relatively high intrinsic resistance (1.00 cm H₂O min⁻¹ vs 0.03 cm H₂O min⁻¹ for typical inspiratory airway resistance); therefore, impaired airflow has little effect on inspiratory flow. Most patients—even children aged 3 to 10 years or those with acute asthma—can generate sufficient inspiratory flow for effective therapy (>30 L/min) with the DPI.


<table>
<thead>
<tr>
<th>Comparison</th>
<th>Variability, CV%</th>
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<tr>
<td></td>
<td>DPI</td>
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<tr>
<td>Healthy volunteers</td>
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<tr>
<td>Within subjects</td>
<td>32.9</td>
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<td>Between subjects</td>
<td>28.4</td>
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<tr>
<td>Patients</td>
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<tr>
<td>Within patients</td>
<td>39.3</td>
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<td>Between patients</td>
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CV = coefficient of variation.

*Trademark: Pulmicort Turbuhaler® (AstraZeneca Pharmaceuticals LP, Wilmington, Delaware).
SAFETY PROFILE OF BUDESONIDE
More than 580 clinical trials involving >38,000 patients and healthy volunteers—as well as >10 billion treatment days in clinical use—have confirmed that budesonide is well tolerated in patients of all ages with differing asthma severities (Periodic Safety Update Report, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware, October 2001).

Local Adverse Effects
Local adverse effects (eg, cough, hoarseness, sore throat) may be associated with ICS treatment. Because they are dose dependent, maximizing drug delivery to the lungs and minimizing oropharyngeal deposition with delivery devices such as the DPI could reduce these effects. The incidence of local adverse effects is lower when budesonide is administered via DPI rather than via pMDI: one study reported incidences of 5.8% versus 17%, respectively.69,70 Notably, among 90 patients using the budesonide DPI as their first ICS device, no cases of oropharyngeal candidiasis or hoarseness were reported after >2 years of use.70

Systemic Adverse Effects
Safety evaluations have revealed no evidence that administration of budesonide at the recommended doses is associated with any clinically relevant systemic adverse effects.

Short-term studies using sensitive markers of hypothalamic–pituitary–adrenal (HPA) axis function have been used to assess the systemic potency of ICS.71–74 However, the clinical relevance of such investigations is limited75; long-term studies that measure plasma cortisol concentrations after adrenocorticotropic hormone stimulation are now used more frequently.76,77 Treatment with budesonide for 1 year did not produce deteriorations in HPA axis function in adults78 or children.79

Although short-term studies have indicated that ICS can cause a transient reduction of growth rate in children with asthma,80,81 a long-term (>9 years), prospective study82 found no evidence that budesonide therapy (mean daily dose, 412 μg) in children with asthma affected the children’s expected final adult height. These data were supported by results from the Childhood Asthma Management Program Research Group study published in 200083 and are unique for budesonide—no long-term data are available for the final adult height of patients using other ICSs.

Studies with ICSs have shown conflicting results concerning their effects on bone metabolism and fracture rate.84–88 However, administration of budesonide (mean daily dose, 504 μg) for 3 to 6 years had no adverse effect on bone mineral density in children with chronic asthma,84 and 2 years of treatment with budesonide via DPI had no significant effects on bone mineral density compared with noncorticosteroid treatment in adults (0.1% vs 0.4% increase in lumbar
spine, 0.9% vs 0.4% reduction in neck of the femur). Data from the European Respiratory Society study on chronic obstructive pulmonary disease further support the findings that long-term treatment with budesonide has no statistically significant effect on fracture risk. Recent retrospective reviews of data from trials of asthma therapy have concluded that there is no evidence for an increased risk of loss of bone mineral density with ICS treatment.

Increased intraocular pressure and cataract formation are recognized adverse effects of oral corticosteroids. An analysis of pooled data from 4 prospective studies found no statistically significant increase in intraocular pressure in asthmatic patients aged 6 to 70 years who were treated with budesonide (200–1600 μg/d) for up to 20 weeks. Retrospective case-control and epidemiologic studies have suggested a link between use of ICSs and an increased risk of cataracts, although this effect may be confined to patients receiving high average daily doses (>1 mg for >2 years) and/or older adults. Studies of long-term treatment with budesonide have found no evidence of any association with an increased risk of cataract formation in adults (mean age, 53 years) or children.

Recent data from Sweden in mothers using budesonide during pregnancy suggested that there was no increase in the rate of congenital malformations or other clinically relevant effects associated with pregnancy outcomes. These data contributed to the US Food and Drug Administration's approval of budesonide as the only ICS with a category B pregnancy rating.

CONCLUSIONS

When combined with delivery devices suitable for the spectrum of patient groups, the physical and pharmacokinetic characteristics of budesonide lend it many of the characteristics of an ideal ICS. These include favorable efficacy and tolerability profiles and a high therapeutic index, which makes it acceptable for long-term treatment; the availability of QD administration; effective treatment of asthma in patients of all ages and asthma severities; and a positive impact on patients' quality of life. Thus, based on current knowledge, it appears that budesonide has the potential to be an ideal ICS.

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